Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Coronary Inflammation Is Associated With Plaque Progression in Men With HIV

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BACKGROUND: People with HIV are at elevated risk for atherosclerotic cardiovascular disease despite viral suppression, suggesting contributions from nontraditional mechanisms. Coronary vascular inflammation may play a role, but its relationship to plaque progression remains incompletely defined. The perivascular fat attenuation index (FAI) score, derived from coronary computed tomography angiography, is associated with vascular inflammation. We evaluated whether coronary inflammation is associated with the incidence and progression of coronary plaque and whether these relationships differ by HIV status.

METHODS: A total of 504 men (n=292 with HIV; n=212 without HIV) from the Multicenter AIDS Cohort Study underwent coronary computed tomography angiography over a median of 4.5 years (3.8–4.9). FAI measurements were performed on baseline scans. Changes in noncalcified, calcified, and total plaque volumes were categorized into tertiles of progression. Associations were estimated using multinomial logistic regression adjusted for interscan time and cardiovascular risk factors. Modified Poisson regression estimated incident plaque.

RESULTS: Higher FAI scores in the left anterior descending (LAD) and left circumflex were associated with greater odds of belonging to the highest tertile of noncalcified (LAD odds ratio [OR], 1.83 [1.27–2.64]; left circumflex OR, 2.55 [1.66–3.91]); calcified (LAD OR, 2.62 [1.64–4.18]; left circumflex OR, 3.92 [2.36–6.51]); and total plaque progression (LAD OR, 1.81 [1.25–2.62]; left circumflex OR, 2.65 [1.71–4.10]) among men with HIV, per SD increase in FAI score after adjusting for cardiovascular risk factors, and remained significant after adjustment for baseline plaque. Higher LAD FAI score was associated with incident calcified plaque in men with HIV (RR, 1.21 [1.01–1.46]). Associations for noncalcified and calcified plaque progression were stronger in men with HIV than in men without HIV.

CONCLUSIONS: Coronary inflammation, assessed by FAI, is independently associated with incident and progressive coronary plaque in men with HIV. These findings support a role for vascular inflammation in accelerated atherosclerosis in people with HIV and highlight FAI as a potential biomarker for risk stratification.

GRAPHICAL ABSTRACT: A graphical abstract is available for this article.

Key Words: atherosclerosis ■ biomarkers ■ computed tomography angiography ■ inflammation ■ risk assessment

People with HIV (PWH) are at increased risk for coronary artery disease despite effective antiretroviral therapy and viral suppression.[1,2] As HIV has transitioned to a chronic disease, coronary artery disease has become a major contributor to morbidity and premature mortality.[3,4] This excess risk is not fully captured by traditional cardiovascular risk factors and is thought to reflect persistent immune activation and inflammation, despite effective viral control.[5,6] Vascular inflammation is a key driver of atherosclerotic disease progression and

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This manuscript was sent to Todd C. Villines, Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCIMAGING.126.020165.
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CLINICAL PERSPECTIVE

Despite effective antiretroviral therapy, people with HIV remain at increased risk for atherosclerotic cardiovascular disease that is not fully explained by traditional risk factors. In this multicenter longitudinal study, higher coronary inflammation measured noninvasively by the coronary computed tomography angiography-derived fat attenuation index score was associated with greater progression of coronary plaque over a median follow-up of 4.5 years, particularly among men with HIV. Associations were observed across noncalcified, calcified, and total plaque phenotypes and remained significant after adjustment for traditional cardiovascular risk factors and baseline plaque burden, suggesting that fat attenuation index captures residual inflammatory risk not reflected by conventional risk assessment. Notably, coronary inflammation was also associated with incident calcified plaque among men with HIV. These findings support persistent vascular inflammation as a contributor to accelerated atherosclerosis in people with HIV and may help explain the excess cardiovascular risk observed despite contemporary HIV treatment. For practicing clinicians, these results highlight the potential value of coronary inflammation imaging as a complementary tool for cardiovascular risk assessment in individuals with HIV undergoing coronary computed tomography angiography. However, further prospective studies are needed to validate whether fat attenuation index-guided risk stratification predicts cardiovascular events and demonstrates incremental prognostic value beyond existing imaging markers.

Nonstandard Abbreviations and Acronyms

CCTA	coronary computed tomography angiography
FAI	fat attenuation index
LAD	left anterior descending
LCx	left circumflex
MACS	Multicenter AIDS Cohort Study
MWH	men with HIV
MWoH	men without HIV
OR	odds ratio
PWH	people with HIV
RCA	right coronary artery

cardiovascular events, even among individuals receiving guideline-directed lipid-lowering therapy.[7,8] These observations underscore the need for biomarkers that capture residual inflammatory risk and thus improve cardiovascular risk stratification in PWH.

The perivascular fat attenuation index (FAI) score derived from coronary computed tomography angiography (CCTA) is an emerging approach to noninvasively detect coronary inflammation.[9,10] In the large multicenter ORFAN study of patients without known HIV undergoing CCTA for suspected coronary artery disease, high FAI scores were associated with an increased risk of major adverse cardiovascular events and cardiac mortality over a median follow-up period of 2.7 years.[9] The FAI score improved risk prediction independent of traditional risk factors and plaque burden, capturing otherwise occult coronary inflammation and bridging a gap in risk assessment by identifying high-risk individuals who might not be otherwise identified.[9]

The presence of atherosclerotic plaque and total plaque burden and composition are strong predictors of future cardiovascular events.[11] Prior work from the MACS (Multicenter AIDS Cohort Study) demonstrated greater coronary plaque prevalence and accelerated progression among men with HIV (MWH) than in men without HIV (MWoH).[12,13] However, whether coronary inflammation, assessed by FAI, is associated with longitudinal changes in plaque burden and phenotype in PWH is not known.

Leveraging serial CCTA scans with quantitative plaque analysis in men with and without HIV, the MACS provides a unique opportunity to examine the relationship between coronary inflammation and plaque incidence and progression over time. Defining these relationships may improve our understanding of the importance of inflammation-driven atherosclerosis in PWH and identify individuals at heightened risk for progressive coronary disease who may not be recognized by conventional risk assessment alone.

METHODS

Study Population

The MACS, now part of the Multicenter AIDS Cohort Study/MWCCS (Women's Interagency HIV Study Combined Cohort Study), is an ongoing prospective multicenter cohort evaluating the impact of HIV-1 infection on cardiovascular and other health outcomes among men with and without HIV who have sex with men in Baltimore/Washington, DC, Chicago, Pittsburgh, and Los Angeles.[13] Participants undergo semiannual visits including standardized clinical interviews, physical examinations, laboratory testing, and biospecimen collection.

Eligible MACS participants were aged 40 to 70 years, weighed <300 lbs, and had no prior history of cardiac surgery or percutaneous coronary intervention. Institutional review board approval was obtained from all participating centers, and all participants provided written informed consent. Data available on reasonable request.

Plaque Quantification

Coronary plaque volume was quantified at baseline and follow-up using a standardized MACS CCTA protocol with a prespecified 4- to 5-year interscan interval, as previously described.[14] Images were analyzed at a central reading center (Lundquist Institute at Harbor-UCLA Medical Center) by investigators blinded to

participant data using semiautomated plaque analysis software (QAngioCT Research Edition, Medis Medical Imaging Systems).

The Society of Cardiovascular Computed Tomography 17-segment model was applied, including segments with a diameter ≥1.5 mm. Plaque volumes across the entire coronary tree were categorized as calcified plaque or noncalcified plaque, which included low-attenuation, fibrous-fatty, and fibrous components, and total plaque as the sum of all components.

FAI Score Measurement

Coronary inflammation was assessed at the University of Oxford using the perivascular FAI score derived from the CaRi-Heart platform (Caristo Diagnostics, Ltd, Oxford, United Kingdom). The FAI score is a validated, computed tomography-derived imaging biomarker associated with coronary inflammation. CCTA images were processed to segment the coronary arterial wall and surrounding perivascular adipose tissue along major epicardial vessels. Perivascular fat was defined as adipose tissue voxels located within a radial distance from the outer vessel wall equal to the local vessel diameter and with attenuation values between −190 and −30 Hounsfield units.[9]

FAI scores were generated using the proximal 40-mm segments of the left anterior descending (LAD), left circumflex (LCx), and right coronary (RCA) arteries using a proprietary algorithm that incorporates attenuation measures adjusted for age, sex, local coronary anatomy (including vessel branching patterns, surrounding anatomic structures, and background adipocyte characteristics), as well as technical factors related to the scanner, acquisition settings, and image reconstruction parameters. The specific correction procedures incorporated within the algorithm are proprietary and are not publicly disclosed by the vendor, consistent with standard practices for regulated medical devices operating under ISO 13485 quality management systems and regulatory oversight.[9,10] Prior validation studies demonstrated excellent reproducibility (intraclass correlation coefficient >0.98).[9]

HIV Status and Covariates

HIV serostatus was determined prospectively at each study visit using standardized serological testing.[13] Participants were classified based on HIV status at the time of the baseline CCTA.

Demographic and clinical data were collected using standardized protocols, including blood pressure, smoking status, and fasting lipids and glucose levels. Continuous time-varying covariates were averaged across visits between baseline and follow-up scans to reflect cumulative exposure during the interscan interval. FAI measurements and smoking status were assessed at baseline.

Medication use (antihypertensive, lipid-lowering, and glucose-lowering therapies) was assessed through structured interviews supplemented by pharmacy records and medication container review. Antihypertensive, glucose-lowering, and statin medication exposure was defined as use reported at ≥20% of interscan visits.

Statistical Analysis

Baseline characteristics were summarized as mean ± SD, median (interquartile range), or frequency (percentage), based on distribution assessed using the Shapiro-Wilk test.

Plaque progression was evaluated separately for noncalcified, calcified, and total plaque volumes. As the distribution of plaque progression was severely skewed, even after applying various transformations, and as there are no clinically recognized thresholds for plaque volume, we classified the progression outcome into tertiles of low, moderate, and high progression.[13] Noncalcified plaque progression tertiles were defined as <6.42 mm^3, 6.42 to 48.96 mm^3, and >48.96 mm^3; calcified plaque progression tertiles as <0.06 mm^3, 0.06 to 15.47 mm^3, and ≥15.47 mm^3; and total plaque progression tertiles as <11.75 mm^3, 11.75 to 73.07 mm^3, and ≥73.07 mm^3.

Associations between the baseline LAD, LCx, and RCA FAI scores and plaque progression categories were assessed using multivariable multinomial logistic regression, estimating ORs for the second and third tertiles relative to the lowest tertile.

Unadjusted models assessed total inflammatory cardiovascular risk, reflecting the association between FAI and plaque progression adjusted only for the duration of time between successive scans. To determine inflammation beyond that attributable to traditional cardiovascular risk factors, residual inflammatory cardiovascular risk was assessed. These models additionally included current smoking, low-density lipoprotein cholesterol, statin exposure, systolic blood pressure, antihypertensive medication use, fasting glucose, diabetes medication use, and education level. Stratified analyses by HIV status were performed and effect modification by HIV status was tested by multiplicative interaction terms.

To facilitate interpretation of the tertile-based analyses, descriptive analyses were also performed examining absolute plaque volume progression across baseline FAI-score tertiles.

Incident plaque analyses were restricted to participants without baseline plaque for each plaque type. Incident plaque was defined as the development of new measurable plaque at follow-up. Associations between baseline FAI scores and incident plaque were assessed using modified Poisson regression with robust variance estimation, including interscan time as an offset term and adjusting for the same cardiovascular risk factor covariates. Each imaging predictor was evaluated in separate models using the same covariate adjustments.

All tests were 2-sided, and a $P<0.05$ was considered statistically significant. Analyses were based on a prespecified hypothesis that coronary inflammation (FAI) is associated with coronary plaque progression. Given the limited number of biologically related and correlated outcomes and exposures examined, adjustment for multiple comparisons was not performed. Results were interpreted based on the consistency, direction, and magnitude of associations as well as P values. Analyses were performed in R, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

The study cohort included 504 men (292 MWH and 212 MWoH) after excluding 44 participants (21 MWH and 23 MWoH) due to missing covariate data. A CONSORT diagram is shown in Figure 1, and the study cohort characteristics are presented in Table 1. MWH were younger (52.4±6.5 versus 56.3±7.6 years), less

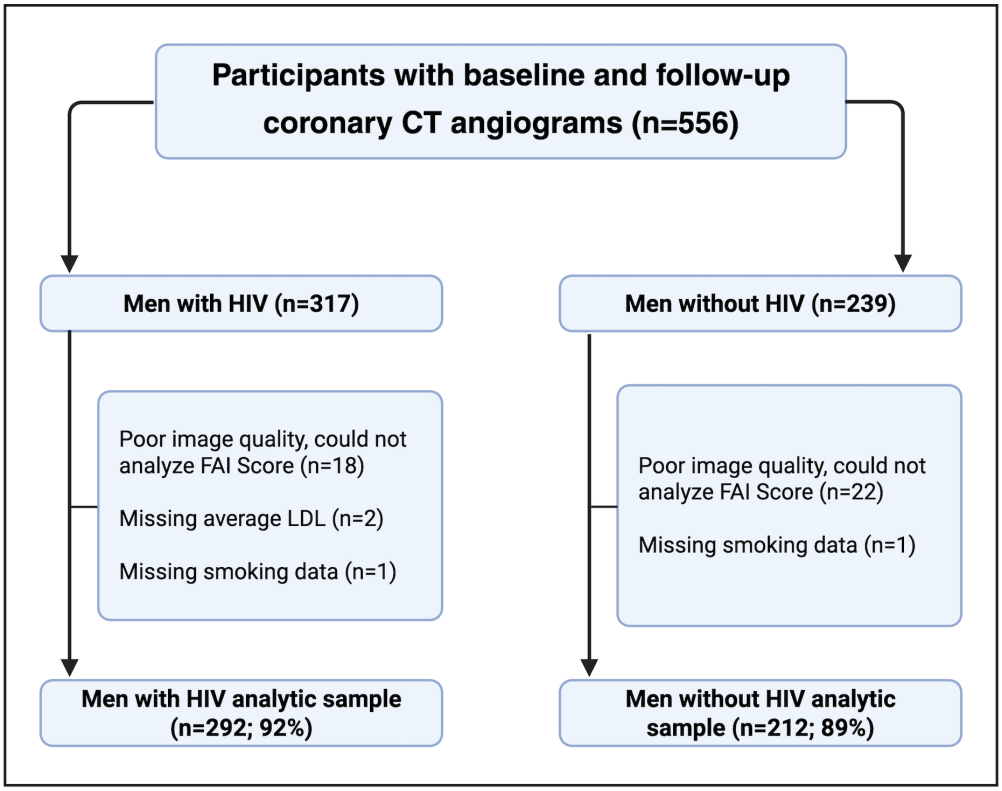


Figure 1. Flowchart of study participants.
CT indicates computed tomography; FAI, fat attenuation index; and LDL, low-density lipoprotein.

likely to be White (50.0% versus 71.0%), and more likely to have <12 years of education (25.0% versus 10.7%). Triglycerides were higher and HDL cholesterol lower in MWH.

Baseline plaque volumes were similar between groups, while baseline FAI scores were modestly lower in MWH (LAD, 6.9±5.1 versus 8.0±5.0; LCx, 6.4±3.4 versus 8.0±4.3; RCA, 7.1±6.1 versus 8.7±6.0).

Coronary Inflammation and Plaque Progression in MWH

Across plaque phenotypes, higher LAD and LCx FAI scores were consistently associated with greater plaque progression, particularly among MWH. Associations for RCA FAI were weaker and generally attenuated after multivariable adjustment.

Vessel-specific FAI score associations with plaque progression across phenotypes are shown in Figure 2. Tables S1 and S2 present absolute plaque volume change by FAI-score tertiles and demonstrate increasing median plaque progression across increasing FAI-score tertiles. In addition, analyses using the mean FAI-score of the 3 coronary arteries (Tables S3 through S5) and the FAI-score of the most inflamed coronary artery (Tables S6 through S8) were consistent with the results of the vessel-specific analyses.

Noncalcified Plaque

The FAI scores predicted noncalcified plaque progression in the overall cohort and in MWH across coronary territories in models adjusting only for interscan time. In MWH, each SD increase in FAI was associated with 83% higher odds of belonging to the highest tertile of progression in the LAD (odds ratio [OR], 1.83 [1.27–2.64]), 155% higher odds in the LCx [OR, 2.55 [1.66–3.91]), and 46% higher odds in the RCA (OR, 1.46 [1.03–2.07]), reflecting total inflammatory risk (Table 2).

Given that clinical cardiovascular risk factors contribute to atherogenesis partly through vascular inflammation, residual inflammatory risk independent of traditional cardiovascular risk factors was assessed. In these analyses, LAD and LCx FAI scores remained predictive of noncalcified plaque progression. Associations were observed for the highest tertile of progression in the overall cohort (LAD OR, 1.44 [1.11–1.86]; LCx OR, 1.54 [1.18–2.00]) and among MWH (LAD OR, 1.60 [1.10–2.32]; LCx OR, 2.02 [1.29–3.14]), but were not significant in MWoH. The associations between the FAI scores and noncalcified plaque are presented in Table 2.

The association of the LCx FAI score with the highest tertile of noncalcified plaque progression was stronger in MWH (OR, 2.01) than in MWoH (OR, 1.37; $P_{interaction}$=0.08).

Table 1. Characteristics of Study Participants

Variable	All (N=504)	Men with HIV (n=292)	Men without HIV (n=212)
Demographics			
Age, y	54.0±7.3	52.4±6.5	56.3±7.7
Interscan time, y	4.5 (3.8–4.9)	4.6 (4.0–5.0)	4.1 (3.6–4.9)
Education ≤12 y, %	19.0%	25.0%	10.8%
Ethnicity			
White	58.9%	50.0%	71.2%
Black	29.2%	33.9%	22.6%
Hispanic/other	11.9%	16.1%	6.2%
Cardiovascular risk factors			
SBP*, mm Hg	127.8±11.0	126.9±11.0	129.0±10.8
BMI*, kg/m^2	25.9 (23.5–28.9)	25.4 (23.2–28.4)	26.4 (23.9–29.5)
LDL cholesterol*, mg/dL	105.0±27.4	102.3±25.2	108.7±29.8
HDL cholesterol*, mg/dL	48.5 (41.8–58.0)	46.2 (39.6–55.2)	52.6 (44.6–60.4)
Total cholesterol*, mg/dL	182.1±31.1	180.8±29.2	183.6±33.7
Triglycerides*, mg/dL	118.1 (83.9–159.3)	134.4 (95.6–179.3)	102.2 (78.2, 128.6)
Antihypertensive therapy†, %	39.9%	39.7%	40.6%
Glucose-lowering therapy†, %	8.9%	8.9%	9.0%
Statin use†, %	42.5%	41.4%	44.3%
Smoking status			
Never, %	25.7%	28.1%	22.6%
Former, %	51.8%	44.9%	61.3%
Current, %	22.5%	27.0%	16.1%
Baseline plaque volumes			
Noncalcified plaque, mm^3	25.8 (0.0–88.4)	26.1 (0.0–86.1)	26.5 (0.0–90.7)
Calcified plaque, mm^3	0.9 (0.0–17.3)	0.8 (0.0–14.6)	1.5 (0.0–19.8)
Total plaque, mm^3	32.4 (0.0–104.8)	32.0 (0.0–102.8)	34.3 (0.0–107.9)
Follow-up plaque bolumes			
Noncalcified plaque, mm^3	63.9 (10.3–166.3)	66.4 (13.4–160.3)	59.3 (7.0–179.3)
Calcified plaque, mm^3	7.0 (0.0–48.8)	8.0 (0.0–43.8)	6.9 (0.0–56.9)
Total plaque, mm^3	77.9 (12.8–224.2)	84.8 (15.5–214.9)	75.1 (10.6–240.9)
Baseline FAI scores			
LAD FAI score	7.4±5.1	6.9±5.1	8.0±5.0
LCX FAI score	7.1±3.9	6.4±3.4	8.0±4.3
RCA FAI score	7.8±6.1	7.1±6.1	8.7±6.0
HIV-specific factors			
HIV RNA <50 copies/mL, %		82.1%	
CD4$^+$ T-cell count, cells/μL		655 (503–811)	
Cumulative ART use, y		9.4 (6.7–12.5)	
AIDS diagnosis, %		9.2%	
Baseline ART regimen			
PI-based		44.4%	
NNRTI-based		47.5%	
INSTI-based		11.3%	
Follow-up ART regimen			
PI-based		32.9%	
NNRTI-based		43.0%	
INSTI-based		29.3%	

Data are reported as mean ± SD, median (interquartile range) based on normality (assessed using Shapiro-Wilk), or percentage. ART indicates antiretroviral therapy; BMI, body mass index; FAI, fat attenuation index; HDL, high-density lipoprotein; INSTI, integrase strand transfer inhibitor; LAD, left anterior descending; LCX, left circumflex; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RCA, right coronary artery; and SBP, systolic blood pressure.

*Values are averaged across all interscan visits.

†Participants were defined as medication users if they reported medication use at least 20% of study visits between scans.

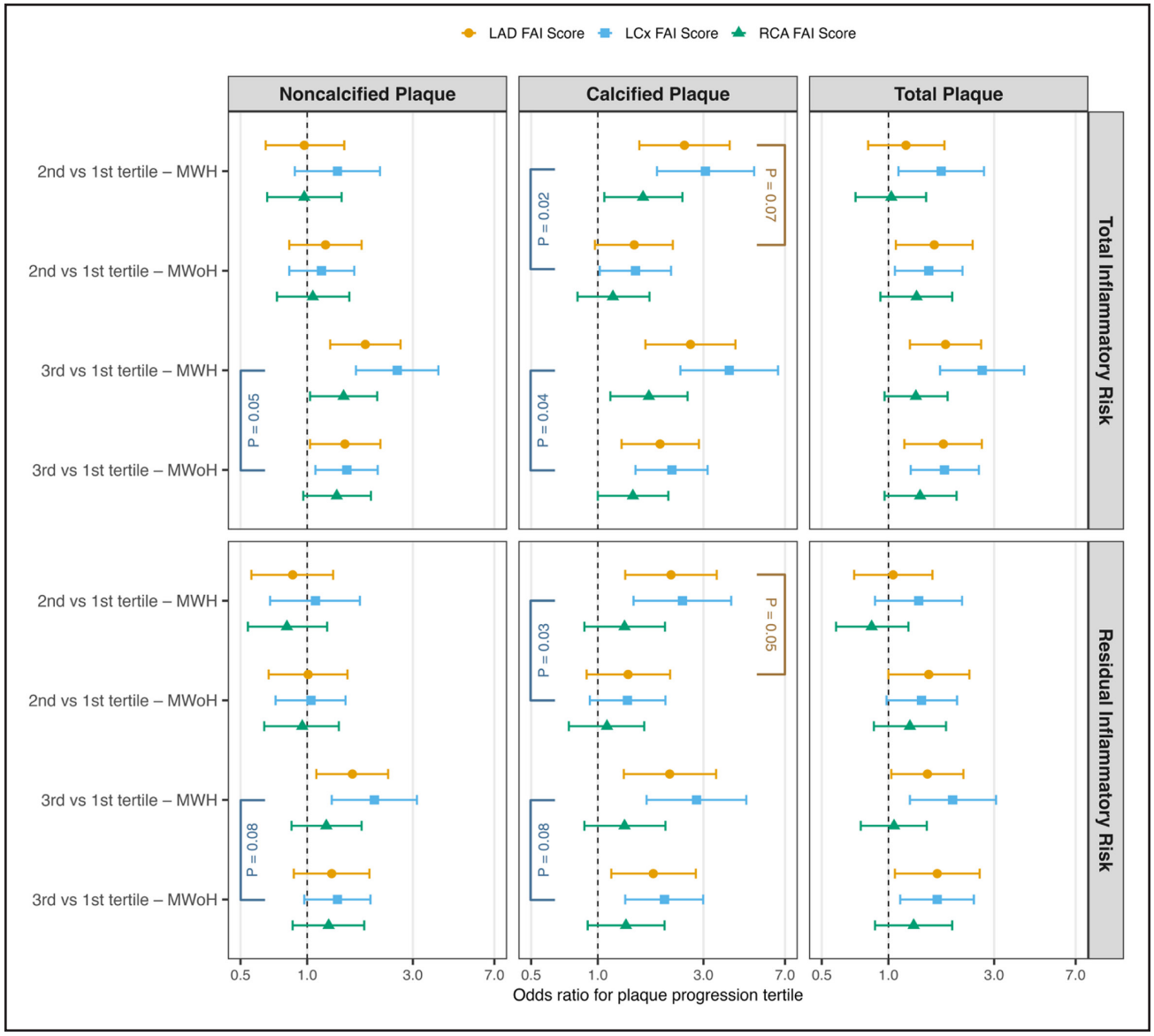


Figure 2. Forest plot showing total and residual inflammatory risk in men with HIV (MWH) and men without HIV (MWoH). Forest plot showing odds ratios for progression to the second and third tertiles of noncalcified, calcified, and total plaque progression per SD increase in left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA) fat attenuation index (FAI) scores, stratified by HIV status. Brackets with accompanying *P* values indicate interaction terms between FAI score and HIV status (shown for $P<0.10$), highlighting differences in associations between MWH and MWoH. Noncalcified plaque progression tertiles were defined as <6.42 mm³, 6.42 to 48.96 mm³, and >48.96 mm³; calcified plaque progression tertiles as <0.06 mm³, 0.06 to 15.47 mm³, and ≥15.47 mm³; and total plaque progression tertiles as <11.75 mm³, 11.75 to 73.07 mm³, and ≥73.07 mm³.

The RCA FAI score was not significantly associated with progression after adjustment.

Calcified Plaque

Across coronary territories, higher FAI scores reflected the total inflammatory cardiovascular risk and were associated with greater odds of belonging to the second and highest tertiles of calcified plaque progression in the overall cohort. Effect sizes were larger in MWH, corresponding to greater than 2-fold higher odds of belonging to the highest tertile of progression in the LAD, nearly 4-fold higher odds in the LCx, and 70% higher odds in the RCA, per SD increase in the respective FAI score. The results are shown in Table 3.

After multivariable adjustment, the LAD and LCx FAI scores were able to capture residual inflammatory risk and remained associated with the second and highest tertiles of calcified plaque progression (Table 3). RCA FAI score associations were not significant after adjustment.

Associations were stronger in MWH than in MWoH in the LAD and LCx for the second tertile of plaque progression ($P_{interaction}$=0.05 and 0.03, respectively), and in the LCx for the highest tertile of plaque progression ($P_{interaction}$=0.08).

Table 2. Association of Coronary Inflammation Imaging Scores With Noncalcified Plaque Progression Tertiles

Noncalcified plaque						
Group	LAD FAI score, second tertile OR (95% CI); *P* value	LAD FAI score, third tertile OR (95% CI); *P* value	LCx FAI score, second tertile OR (95% CI); *P* value	LCx FAI score, third tertile OR (95% CI); *P* value	RCA FAI score, second tertile OR (95% CI); *P* value	RCA FAI score, third tertile OR (95% CI); *P* value
Total inflammatory risk						
All participants	1.08 (0.82–1.41); *P*=0.59	1.63 (1.27–2.10); *P*<0.001	1.21 (0.93–1.57); *P*=0.15	1.80 (1.39–2.31); *P*<0.001	1.01 (0.77–1.31); *P*=0.96	1.40 (1.10–1.78); *P*=0.006
MWH	0.97 (0.65–1.47); *P*=0.90	1.83 (1.27–2.64); *P*=0.001	1.37 (0.88–2.13); *P*=0.16	2.55 (1.66–3.91); *P*<0.001	0.97 (0.66–1.43); *P*=0.88	1.46 (1.03–2.07); *P*=0.03
MWoH	1.21 (0.83–1.76); *P*=0.33	1.48 (1.03–2.14); *P*=0.04	1.16 (0.83–1.63); *P*=0.38	1.51 (1.09–2.08); *P*=0.01	1.06 (0.73–1.55); *P*=0.75	1.36 (0.96–1.94); *P*=0.09
P value for HIV × FAI interaction	0.41	0.39	0.62	0.05	0.68	0.74
Residual inflammatory risk						
All participants	0.94 (0.71–1.24); *P*=0.66	1.44 (1.11–1.86); *P*=0.006	1.04 (0.79–1.37); *P*=0.79	1.54 (1.18–2.00); *P*=0.001	0.89 (0.67–1.17); *P*=0.39	1.25 (0.97–1.59); *P*=0.08
MWH	0.86 (0.56–1.31); *P*=0.47	1.60 (1.10–2.32); *P*=0.01	1.09 (0.69–1.73); *P*=0.72	2.02 (1.29–3.14); *P*=0.002	0.82 (0.54–1.23); *P*=0.34	1.23 (0.85–1.77); *P*=0.27
MWoH	1.02 (0.68–1.52); *P*=0.94	1.32 (0.89–1.95); *P*=0.17	1.04 (0.72–1.49); *P*=0.84	1.39 (0.99–1.96); *P*=0.06	0.95 (0.64–1.40); *P*=0.80	1.26 (0.87–1.83); *P*=0.22
P value for HIV × FAI interaction	0.49	0.33	0.79	0.08	0.60	0.87
Residual inflammatory risk independent of baseline noncalcified plaque						
All participants	0.94 (0.71–1.24); *P*=0.65	1.43 (1.09–1.88); *P*=0.009	1.02 (0.77–1.35); *P*=0.88	1.38 (1.05–1.82); *P*=0.02	0.88 (0.67–1.16); *P*=0.35	1.21 (0.93–1.57); *P*=0.16
MWH	0.83 (0.54–1.27); *P*=0.39	1.67 (1.13–2.46); *P*=0.01	1.01 (0.64–1.62); *P*=0.95	1.79 (1.13–2.85); *P*=0.01	0.81 (0.54–1.23); *P*=0.32	1.23 (0.83–1.83); *P*=0.29
MWoH	1.05 (0.70–1.56); *P*=0.82	1.21 (0.80–1.83); *P*=0.37	1.06 (0.74–1.53); *P*=0.75	1.21 (0.83–1.75); *P*=0.32	0.97 (0.65–1.45); *P*=0.87	1.11 (0.73–1.68); *P*=0.62
P value for HIV × FAI interaction	0.42	0.16	0.92	0.07	0.65	0.44

Odds ratios and 95% CIs are derived from multivariable multinomial logistic regression models for the second and third tertiles of plaque progression compared with the first tertile. The specific set of covariates in each serially adjusted multivariable model are as follows: total inflammatory risk represents the association between baseline FAI score and plaque progression adjusted for interscan interval. Residual inflammatory risk models additionally adjust for traditional cardiovascular risk factors (current smoking, LDL cholesterol, statin exposure, systolic blood pressure, antihypertensive medication use, fasting glucose, diabetes medication use, and education level). Residual inflammatory risk independent of baseline noncalcified plaque additionally adjusts for baseline noncalcified plaque volume. The *P* values for the multiplicative interaction term between HIV serostatus and FAI are reported below the HIV-stratified results, indicating whether the difference in the association between FAI and plaque progression was statistically significantly different between those with and without HIV. Sample sizes: all participants (n=504), MWH (n=292), and MWoH (n=212). FAI indicates fat attenuation index; LAD, left anterior descending; LCx, left circumflex; LDL, low-density lipoprotein; MWH, men with HIV; MWoH, men without HIV; OR, odds ratio; and RCA, right coronary artery.

Total Plaque

Higher LAD and LCx FAI scores were associated with greater total plaque progression, particularly for the highest tertile. After adjustment, associations remained significant in the overall cohort (LAD OR, 1.54 [1.17–2.02]; LCx OR, 1.71 [1.29–2.26]) and in MWH (LAD OR, 1.50 [1.03–2.18]; LCx OR, 1.95 [1.25–3.06]).

Associations for RCA FAI were not significant after adjustment. The results are presented in Table 4.

HIV-Specific Clinical Factors

Among MWH, adjustment for HIV RNA ≥50 copies/mL, average CD4 count, history of AIDS, protease inhibitor exposure, and cumulative antiretroviral therapy duration (in separate models to avoid collinearity) did not significantly alter the associations between the FAI scores and plaque progression (Figure 3).

Results in Men Without HIV

In MWoH, associations were attenuated by multivariable adjustment and specific to plaque characterization. After adjustment, LAD FAI was associated with calcified and total plaque progression, but not with noncalcified plaque. RCA FAI was not associated with plaque progression (Tables 2 through 4).

Adjustment for Baseline Plaque

Among MWH, the FAI scores captured residual inflammatory cardiovascular risk independent of baseline plaque burden. Associations between LAD and LCx FAI and

Table 3. Association of Coronary Inflammation Imaging Scores With Calcified Plaque Progression Tertiles

Calcified plaque						
Group	LAD FAI score, second tertile OR (95% CI); *P* value	LAD FAI score, third tertile OR (95% CI); *P* value	LCx FAI score, second tertile OR (95% CI); *P* value	LCx FAI score, third tertile OR (95% CI); *P* value	RCA FAI score, second tertile OR (95% CI); *P* value	RCA FAI score, third tertile OR (95% CI); *P* value
Total inflammatory risk						
All participants	1.83 (1.36–2.47); *P*<0.001	2.11 (1.57–2.83); *P*<0.001	1.95 (1.46–2.62); *P*<0.001	2.59 (1.93–3.49); *P*<0.001	1.36 (1.04–1.78); *P*=0.023	1.52 (1.17–1.98); *P*=0.002
MWH	2.46 (1.54–3.94); *P*<0.001	2.62 (1.64–4.18); *P*<0.001	3.06 (1.85–5.08); *P*<0.001	3.92 (2.36–6.51); *P*<0.001	1.60 (1.07–2.41); *P*=0.023	1.70 (1.14–2.54); *P*=0.009
MWoH	1.46 (0.97–2.18); *P*=0.07	1.91 (1.28–2.86); *P*=0.002	1.48 (1.02–2.14); *P*=0.037	2.16 (1.48–3.13); *P*<0.001	1.17 (0.81–1.71); *P*=0.41	1.44 (1.00–2.08); *P*=0.05
P value for HIV × FAI interaction	0.07	0.18	0.02	0.04	0.21	0.38
Residual inflammatory risk						
All participants	1.63 (1.20–2.21); *P*=0.002	1.80 (1.33–2.44); *P*<0.001	1.71 (1.26–2.31); *P*=0.001	2.13 (1.57–2.90); *P*<0.001	1.21 (0.92–1.59); *P*=0.18	1.33 (1.01–1.75); *P*=0.04
MWH	2.14 (1.33–3.45); *P*=0.002	2.14 (1.32–3.45); *P*=0.002	2.42 (1.46–4.02); *P*=0.001	2.83 (1.69–4.74); *P*<0.001	1.34 (0.88–2.03); *P*=0.17	1.35 (0.89–2.06); *P*=0.16
MWoH	1.39 (0.90–2.14); *P*=0.14	1.83 (1.19–2.82); *P*=0.006	1.39 (0.94–2.06); *P*=0.10	2.05 (1.37–3.06); *P*<0.001	1.11 (0.75–1.64); *P*=0.60	1.36 (0.92–2.02); *P*=0.12
P value for HIV × FAI interaction	0.05	0.19	0.03	0.08	0.27	0.50
Residual inflammatory risk independent of baseline calcified plaque						
All participants	1.67 (1.23–2.26); *P*=0.001	1.64 (1.20–2.26); *P*=0.002	1.75 (1.29–2.37); *P*<0.001	1.81 (1.31–2.50); *P*<0.001	1.22 (0.92–1.61); *P*=0.16	1.22 (0.91–1.64); *P*=0.18
MWH	2.19 (1.36–3.54); *P*=0.001	2.12 (1.31–3.43); *P*=0.002	2.53 (1.52–4.21); *P*<0.001	2.61 (1.55–4.40); *P*<0.001	1.35 (0.88–2.06); *P*=0.17	1.38 (0.90–2.12); *P*=0.14
MWoH	1.44 (0.93–2.23); *P*=0.10	1.48 (0.89–2.47); *P*=0.13	1.36 (0.93–2.01); *P*=0.12	1.61 (1.02–2.53); *P*=0.04	1.15 (0.77–1.71); *P*=0.49	0.95 (0.57–1.59); *P*=0.84
P value for HIV × FAI interaction	0.09	0.12	0.03	0.07	0.33	0.16

Odds ratios and 95% CIs are derived from multivariable multinomial logistic regression models for the second and third tertiles of plaque progression compared with the first tertile. The specific set of covariates in each serially adjusted multivariable model are as follows: total inflammatory risk represents the association between baseline FAI score and plaque progression adjusted for interscan interval. Residual inflammatory risk models additionally adjust for traditional cardiovascular risk factors (current smoking, LDL cholesterol, statin exposure, systolic blood pressure, antihypertensive medication use, fasting glucose, diabetes medication use, and education level). Residual inflammatory risk independent of baseline calcified plaque additionally adjusts for baseline calcified plaque volume. The *P* values for the multiplicative interaction term between HIV serostatus and FAI are reported below the HIV-stratified results, indicating whether the difference in the association between FAI and plaque progression was statistically significantly different between those with and without HIV. Sample sizes: all participants (n=504), MWH (n=292), and MWoH (n=212). FAI indicates fat attenuation index; LAD, left anterior descending; LCx, left circumflex; LDL, low-density lipoprotein; MWH, men with HIV; MWoH, men without HIV; OR, odds ratio; and RCA, right coronary artery.

plaque progression remained significant after additional adjustment for baseline plaque volume, including noncalcified, calcified, and total plaque phenotypes. In contrast, associations in MWoH were no longer significant after adjustment for baseline plaque. RCA FAI remained nonsignificant after baseline plaque adjustment (Tables 2 through 4).

Plaque Incidence

Among participants without plaque at baseline, each SD increase in LAD FAI score was associated with a 21% higher risk of incident calcified plaque (RR, 1.21 [1.01–1.46]; *P*=0.042), with similar trends observed for LCx (RR, 1.27 [0.95–1.70]; *P*=0.102) and RCA (RR, 1.17 [0.98–1.39]; *P*=0.084), independent of traditional cardiovascular risk factors. No significant associations were observed in MWoH or in the overall cohort.

DISCUSSION

In this prospective multicenter study of men with and without HIV, higher coronary vascular FAI scores were associated with greater progression of coronary atherosclerotic plaque over time. These findings provide evidence that a noninvasive, computed tomography-derived marker of coronary inflammation predicts plaque development independent of traditional cardiovascular risk factors and baseline plaque burden. To our knowledge, this is among the first studies to link coronary inflammation assessed by FAI with plaque volume progression by phenotype, demonstrating particularly strong

Table 4. Association of Coronary Inflammation Imaging Scores With Total Plaque Progression Tertiles

Total plaque						
Group	LAD FAI score, second tertile OR (95% CI); *P* value	LAD FAI score, third tertile OR (95% CI); *P* value	LCx FAI score, second tertile OR (95% CI); *P* value	LCx FAI score, third tertile OR (95% CI); *P* value	RCA FAI score, second tertile OR (95% CI); *P* value	RCA FAI score, third tertile OR (95% CI); *P* value
Total inflammatory risk						
All participants	1.39 (1.05–1.82); *P*=0.02	1.76 (1.35–2.30); *P*<0.001	1.59 (1.21–2.08); *P*=0.001	2.03 (1.55–2.65); *P*<0.001	1.17 (0.91–1.51); *P*=0.22	1.35 (1.06–1.73); *P*=0.02
MWH	1.20 (0.81–1.79); *P*=0.37	1.81 (1.25–2.62); *P*=0.002	1.73 (1.11–2.70); *P*=0.02	2.65 (1.71–4.10); *P*<0.001	1.03 (0.71–1.48); *P*=0.89	1.33 (0.96–1.85); *P*=0.09
MWoH	1.61 (1.08–2.40); *P*=0.02	1.77 (1.18–2.64); *P*=0.006	1.52 (1.07–2.16); *P*=0.02	1.79 (1.26–2.56); *P*=0.001	1.34 (0.92–1.94); *P*=0.13	1.39 (0.96–2.03); *P*=0.08
P value for HIV × FAI interaction	0.29	0.85	0.71	0.16	0.30	0.93
Residual inflammatory risk						
All participants	1.23 (0.93–1.63); *P*=0.14	1.54 (1.17–2.02); *P*=0.002	1.40 (1.06–1.84); *P*=0.02	1.71 (1.29–2.26); *P*<0.001	1.05 (0.81–1.35); *P*=0.73	1.19 (0.92–1.53); *P*=0.18
MWH	1.06 (0.71–1.59); *P*=0.78	1.50 (1.03–2.19); *P*=0.03	1.39 (0.88–2.19); *P*=0.15	1.97 (1.26–3.08); *P*=0.003	0.85 (0.58–1.24); *P*=0.39	1.07 (0.77–1.51); *P*=0.68
MWoH	1.54 (1.01–2.35); *P*=0.04	1.71 (1.10–2.66); *P*=0.02	1.43 (0.99–2.06); *P*=0.06	1.70 (1.16–2.50); *P*=0.007	1.26 (0.87–1.83); *P*=0.23	1.33 (0.89–1.98); *P*=0.16
P value for HIV × FAI interaction	0.34	0.78	0.91	0.26	0.25	0.81
Residual inflammatory risk independent of baseline total plaque						
All participants	1.18 (0.90–1.57); *P*=0.24	1.46 (1.09–1.96); *P*=0.01	1.31 (0.99–1.73); *P*=0.06	1.40 (1.03–1.90); *P*=0.03	1.01 (0.77–1.31); *P*=0.95	1.08 (0.81–1.44); *P*=0.61
MWH	1.00 (0.67–1.51); *P*=0.99	1.50 (1.02–2.22); *P*=0.04	1.27 (0.80–2.01); *P*=0.31	1.65 (1.02–2.64); *P*=0.04	0.84 (0.57–1.23); *P*=0.37	1.07 (0.74–1.56); *P*=0.71
MWoH	1.49 (0.97–2.30); *P*=0.07	1.48 (0.88–2.49); *P*=0.14	1.35 (0.92–1.98); *P*=0.12	1.33 (0.84–2.12); *P*=0.22	1.17 (0.78–1.76); *P*=0.45	0.90 (0.54–1.52); *P*=0.70
P value for HIV × FAI interaction	0.27	0.47	0.90	0.22	0.35	0.36

Odds ratios and 95% CIs are derived from multivariable multinomial logistic regression models for the second and third tertiles of plaque progression compared with the first tertile. The specific set of covariates in each serially adjusted multivariable model are as follows: total inflammatory risk represents the association between baseline FAI score and plaque progression adjusted for interscan interval. Residual inflammatory risk models additionally adjust for traditional cardiovascular risk factors (current smoking, LDL cholesterol, statin exposure, systolic blood pressure, antihypertensive medication use, fasting glucose, diabetes medication use, and education level). Residual inflammatory risk independent of baseline total plaque additionally adjusts for baseline total plaque volume. The *P* values for the multiplicative interaction term between HIV serostatus and FAI are reported below the HIV-stratified results, indicating whether the difference in the association between FAI and plaque progression was statistically significantly different between those with and without HIV. Sample sizes: all participants (n=504), MWH (n=292), and MWoH (n=212). FAI indicates fat attenuation index; LAD, left anterior descending; LCx, left circumflex; LDL, low-density lipoprotein; MWH, men with HIV; MWoH, men without HIV; OR, odds ratio; and RCA, right coronary artery.

associations among MWH. These results support the potential role of coronary inflammation in the progression of coronary atherosclerosis in MWH and highlight FAI as a potential imaging biomarker to identify individuals at increased risk for disease progression.

PWH remain at elevated cardiovascular risk despite effective antiretroviral therapy, a phenomenon incompletely explained by conventional risk factors.[15] Persistent immune activation and chronic inflammation are thought to underlie this residual risk.[9,12,16] Prior work from the ORFAN study established the prognostic value of the FAI score for cardiovascular events independent of conventional risk assessment and obstructive coronary artery disease.[9] Our findings extend this concept by demonstrating that coronary inflammation is also associated with structural plaque progression, independent of traditional coronary artery disease risk factors and HIV clinical factors in MWH. Moreover, the association between LAD FAI score and calcified plaque progression was stronger in MWH compared with MWoH, suggesting that HIV-related inflammation may amplify the relationship between vascular inflammation and plaque progression. Persistent elevations in proinflammatory cytokines and monocyte activation despite viral suppression may promote endothelial dysfunction, vascular permeability, and inflammatory cell recruitment, mechanisms that plausibly link HIV to accelerated plaque progression.[17–21]

Prior studies in PWH assessed the associations of perivascular FAI with inflammatory markers and plaque characteristics in cross-sectional analyses.[22–24] The REPRIEVE imaging substudy related changes in FAI to concurrent changes in plaque composition but did not assess whether baseline coronary inflammation predicts future plaque progression and did not include a directly

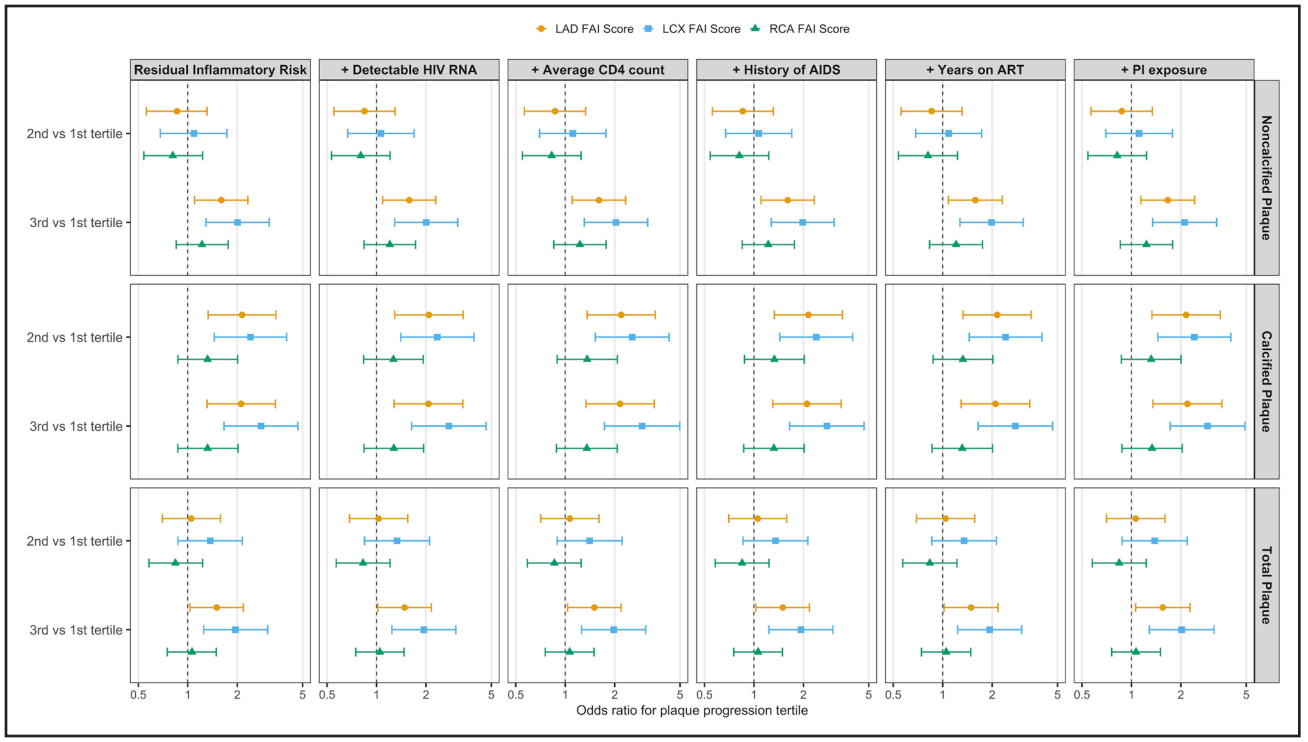


Figure 3. Forest plot showing residual inflammatory risk independent of HIV-related clinical factors.
Forest plot showing odds ratios for progression to the second and third tertiles of noncalcified, calcified, and total plaque per SD increase in left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA) fat attenuation index (FAI) scores among men with HIV (MWH; n=292). Rows represent the plaque phenotype being evaluated (from **top** to **bottom**: noncalcified, calcified, or total plaque progression), as indicated by the row headers on the right. The first column presents residual inflammatory risk models, which evaluate the association between baseline FAI score and plaque progression tertiles adjusted for interscan time and traditional cardiovascular risk factors (current smoking, low-density lipoprotein cholesterol, statin exposure, systolic blood pressure, antihypertensive medication use, fasting glucose, diabetes medication use, and education level). The subsequent columns present models additionally adjusted for HIV-specific factors, including detectable HIV RNA (≥50 copies/mL), average CD4 count, history of AIDS, cumulative years on antiretroviral therapy (ART), and protease inhibitor (PI) exposure, respectively. Noncalcified plaque progression tertiles were defined as <6.42 mm^3, 6.42 to 48.96 mm^3, and >48.96 mm^3; calcified plaque progression tertiles as <0.06 mm^3, 0.06 to 15.47 mm^3, and ≥15.47 mm^3; and total plaque progression tertiles as <11.75 mm^3, 11.75 to 73.07 mm^3, and ≥73.07 mm^3.

comparable HIV-uninfected group.[25] In addition, changes in inflammation and plaque volumes were modeled as concurrent, time-varying processes, limiting the ability to distinguish whether perivascular fat attenuation reflects or precedes structural plaque change. The analysis was also restricted to noncontrast measurements in the proximal RCA, without accounting for vessel-specific heterogeneity.[25] In contrast, our study evaluates baseline, vessel-specific FAI from contrast-enhanced CCTA and relates it to subsequent plaque progression by phenotype within a unified cohort, providing a direct and clinically interpretable assessment of inflammation-driven atherosclerotic progression.

A key observation was the association between the FAI score and calcified plaque progression compared with noncalcified plaque in MWH. Chronic vascular inflammation has been closely linked to arterial calcification, and prior imaging studies have shown that focal inflammation predicts subsequent calcification.[26] Inflammatory signaling can promote osteogenic differentiation of vascular smooth muscle cells and release of calcifying extracellular vesicles, processes that drive plaque mineralization.[27,28] Accordingly, elevated FAI score may reflect persistent inflammatory activity that promotes progression toward calcified plaque phenotypes. While calcified plaque is generally considered a more stable plaque phenotype than noncalcified plaque, progression of calcified plaque nevertheless reflects ongoing atherosclerotic remodeling and increasing plaque burden.[29] The stronger association between FAI and calcified plaque progression observed in MWH may therefore represent a distinct pattern of inflammation-associated plaque evolution.

Notably, baseline FAI scores were modestly lower among MWH in our cohort despite stronger associations with plaque progression. This finding was also reported in similar studies evaluating FAI in PWH and PWoH.[30,31] Although the reasons remain uncertain, the absolute difference in baseline FAI was small and may reflect differences in participant characteristics, including other measured or unmeasured factors related to imaging, treatment, or patient biology. As our study was observational and FAI was assessed only at baseline, we cannot

determine whether longitudinal changes in FAI differ by HIV status.

Effect estimates were directionally consistent in the RCA but attenuated compared with the LAD and LCx. This may reflect greater technical variability in the RCA FAI measurements related to proximity to the aortic wall and susceptibility to imaging artifact.[32] Additionally, greater atherosclerotic burden in the LAD may render LAD-derived FAI more sensitive to inflammation-related changes.[33] While ORFAN demonstrated the prognostic value of FAI across all major coronary vessels for cardiovascular events, the weaker RCA associations observed in our study may reflect limited power or follow-up duration to detect associations with plaque progression.[9]

These findings have important clinical implications, particularly in MWH. Cardiovascular risk prediction in PWH remains challenging, as conventional risk scores often underestimate risk and do not capture vascular inflammation.[34] While systemic inflammatory biomarkers reflect generalized inflammation, they lack specificity for coronary inflammation.[35,36] In contrast, FAI provides a noninvasive, vessel-specific measure of coronary inflammation derived from routine CCTA. By identifying individuals with active vascular inflammation, FAI may refine risk stratification and enable more precise targeting and monitoring of the effectiveness of anti-inflammatory therapies, though further studies are needed to determine its clinical utility, particularly in PWH. This concept is also supported by randomized trials demonstrating cardiovascular benefit from inflammation-modulating therapies, including statins, colchicine, and interleukin-1β inhibitors.[37–39]

Several limitations merit consideration. The cohort included only men, and as an observational study, residual confounding cannot be excluded. Although standardized protocols were used, measurement variability related to CCTA acquisition and technical factors may influence both plaque and FAI assessments, and since no clinically established thresholds exist for plaque progression, the clinical relevance of our data-driven tertile cut points remains uncertain. However, 93.4% of participants in the highest progression tertile demonstrated an absolute increase in total plaque volume exceeding 80 mm^3 (Figure S1), a value similar to the recently reported data-driven prognostic threshold for baseline total plaque volume identified in the PROMISE trial, which was associated with approximately a 2-fold higher risk of major adverse cardiovascular events.[40] Although our analyses were guided by prespecified hypotheses, interaction and secondary analyses should be interpreted in the context of the number of comparisons performed, which may increase the risk of a type I error, and would benefit from confirmation in independent cohorts. This study did not evaluate cardiovascular outcomes, and whether FAI-associated plaque progression translates into future cardiovascular events requires further investigation. Finally, sample size and follow-up duration may have limited the power to detect modest subgroup effects. Nonetheless, this study leveraged a large, well-characterized multicenter cohort with standardized imaging and inclusion of participants with and without HIV drawn from the same study population, enhancing internal validity and minimizing selection bias.

In summary, coronary inflammation assessed by the FAI score was associated with progression of coronary atherosclerotic plaque independent of traditional cardiovascular risk factors and baseline plaque burden, with stronger and more consistent associations observed among MWH compared with MWoH. These findings suggest that FAI captures inflammation-driven processes not reflected by conventional risk assessment and support further evaluation of coronary inflammation as a potential pathway and therapeutic target in HIV-associated atherosclerosis.

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Received June 15, 2026; accepted August 17, 2026.

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Acknowledgments

Data in this manuscript were collected by the MACS (Multicenter AIDS Cohort Study), now the MACS/MWCCS (WIHS Combined Cohort Study). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the NIH. MWCCS (Principal Investigators): Baltimore CRS (Todd Brown and Joseph Margolick), U01-HL146201; Data Analysis and Coordination Center (Gypsyamber D'Souza, Stephen Gange, and Elizabeth Topper), U01-HL146193; Chicago-Northwestern CRS (Steven Wolinsky, Frank Palella, and Valentina Stosor), U01-HL146240; Los Angeles CRS (Roger Detels and Matthew Mimiaga), U01-HL146333; Metropolitan Washington CRS (Seble Kassaye and Daniel Merenstein), U01-HL146205; Pittsburgh CRS (Jeremy Martinson and Charles Rinaldo), U01-HL146208. The MWCCS is funded primarily by the National Heart, Lung, and Blood Institute, with additional cofunding from the Eunice Kennedy Shriver National Institute of Child Health & Human Development, National Institute on Aging, National Institute of Dental & Craniofacial Research, National Institute of Allergy and Infectious Diseases, National Institute of Neurological Disorders and Stroke, National Institute of Mental Health, National Institute on Drug Abuse, National Institute of Nursing Research, National Cancer Institute, National Institute on Alcohol Abuse and Alcoholism, National Institute on Deafness and Other Communication Disorders, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Minority Health and Health Disparities, and in coordination and alignment with the research priorities of the National Institutes of Health, Office of AIDS Research. MWCCS data collection is also supported by UL1-TR000004 (UCSF CTSA), UL1-TR003098 (JHU ICTR), UL1-TR001881 (UCLA CTSI), P30-AI-050409 (Atlanta CFAR), P30-AI-073961 (Miami CFAR), P30-AI-050410 (UNC CFAR), P30-AI-027767 (UAB CFAR), P30-AI-124414 (ERC-CFAR), P30-MH-116867 (Miami CHARM), UL1-TR001409 (DC CTSA), KL2-TR001432 (DC CTSA), and TL1-TR001431 (DC

CTSA). The authors gratefully acknowledge the contributions of the study participants and dedication of the staff at the MWCCS sites.
Figure 1 created in BioRender.com. Dr Leucker had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Sources of Funding

Dr Antoniades is supported by British Heart Foundation (CH/F/21/90009, TG/19/2/34831, RE/24/130024, and RG/F/21/110040), Innovate UK (grant 104472), the National Consortium of Intelligent Medical Imaging through Innovate UK (grant 104688), the EU Horizon 2020 (MAESTRIA grant agreement ID: 965286), and the NIHR Oxford Biomedical Research Centre (Cardiac and Imaging themes). K. Chan is supported by the British Heart Foundation (FS/CRTF/24/24704). Dr Brown is supported in part by K24AI120834. Dr Hays is supported by the NIH/NHLBI (R35HL172680). Dr Leucker is supported by the NIH/NHLBI (R01HL176322) and was supported by an American Heart Association Career Development Award (19CDA34760040).

Disclosures

Dr Antoniades has a leadership role in the British Atherosclerosis Society, and has received honoraria/consulting fees from Amarin, Covance, Silence Therapeutics, AMGEN, Abcentra, Nodthera, Novartis, and Eli Lilly, and research grants from Sanofi, Novo Nordisk, AstraZeneca, and Lexicon. Drs Antoniades and Shirodaria are founders, shareholders, and nonexecutive directors of Caristo Diagnostics. Dr Brown has served as a consultant to Gilead Sciences, EMD-Serono, ViiV Healthcare, Jannsen, and Merck. Dr Leucker has received research grants from Amgen, Novartis, and Merck. The other authors report no conflicts.

Supplemental Material

Tables S1–S8
Figure S1

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