Presence, Characteristics, and Prognostic Associations of Carotid Plaque Among People Living With HIV

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Background—Data from broad populations have established associations between incidental carotid plaque and vascular events. Among people living with HIV (PLWHIV), the risk of vascular events is increased; however, whether incidental carotid plaque is increased and there is an association between incidental carotid plaque, plaque characteristics, and vascular events among PLWHIV is unclear.

Methods and Results—Data from the multi-institutional Research Patient Data Registry were used. Presence and characteristics (high-risk plaque, including spotty calcification and low attenuation) of carotid plaque by computerized tomography among PLWHIV without known vascular disease were described. Data were compared with uninfected controls similar in age, sex, and cardiovascular risk factors, including diabetes mellitus, hyperlipidemia, and cigarette smoking to cases. Primary outcome was an atherosclerotic cardiovascular disease event, and secondary outcome was ischemic stroke. Cohort consisted of 209 PLWHIV (45±10 years, 72% male) and 168 controls. Using computerized tomography, PLWHIV without vascular disease had higher rates of any carotid plaque (34% versus 25%; P=0.04), noncalcified (18% versus 5%; P<0.001) and high-risk plaque (25% versus 16%; P=0.03). Over a follow-up of 3 years, 19 atherosclerotic cardiovascular disease events (9 strokes) occurred. Carotid plaque was independently associated with a 3-fold increase in atherosclerotic cardiovascular disease events among PLWHIV (hazard ratio, 2.91; confidence interval, 1.10–7.7, P=0.03) and a 4-fold increased risk of stroke (hazard ratio, 4.43; confidence interval, 1.17–16.70; P=0.02); high-risk plaque was associated with a 3-fold increased risk of atherosclerotic cardiovascular disease events and a 4-fold increased risk of stroke.

Conclusions—There is an increase in incidental carotid plaque, noncalcified plaque, and high-risk plaque among PLWHIV, and the presence and characteristics of carotid plaque are associated with subsequent vascular events. **(*Circ Cardiovasc Imaging*. 2017;10:e005777. DOI: 10.1161/CIRCIMAGING.116.005777.)**

Key Words: atherosclerotic cardiovascular disease events ■ cardiovascular disease ■ carotid plaque ■ HIV ■ stroke

Among people living with HIV (PLWHIV), studies have shown a disproportionate vulnerability to select cardiovascular diseases, including myocardial infarction (MI) and stroke.[1,2] Specifically, PLWHIV face a more than 2-fold greater risk of vascular events, including both MI and ischemic stroke as compared with uninfected individuals.[3,4] The mechanisms involved in the increased risk of vascular events in HIV are incompletely understood,[5] and more effective means of identifying PLWHIV at highest risk of incurring atherosclerotic cardiovascular disease (ASCVD) events may be of value.

Computerized tomography (CT) allows for the detailed anatomic delineation of large- and medium-sized vessels and the reproducible early detection and characterization of atherosclerosis and atherosclerotic plaque.[6] Among PLWHIV, studies using CT focused on coronary imaging have established that PLWHIV have an increased prevalence of coronary atherosclerosis, noncalcified, and high-risk coronary atherosclerotic plaque, and studies have shown an association between coronary atherosclerosis and plaque features with subsequent ASCVD events.[7,8] Among PLWHIV, there are no data testing whether HIV status is associated with an increase in carotid plaque using CT and whether the presence or characteristics of carotid plaque using CT in HIV is associated with an increase in subsequent

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ASCVD events. Therefore, we compared the presence and characteristics of incidental carotid plaque among a population of PLWHIV without known vascular disease to an uninfected control group similar with regards to age, sex, and cardiovascular risk factors, including diabetes mellitus, hyperlipidemia, and cigarette smoking to cases and tested the association between the presence of plaque and plaque features with adverse outcomes.

Methods

Study Design and Patient Population

The study was retrospective in design, and our data set was developed from an established and validated research registry of PLWHIV and non-HIV controls.[1,9–12] In brief, PLWHIV were identified via a broad initial search, which included the *International Classification of Diseases* Ninth Revision codes for HIV (*International Classification of Diseases* Ninth Revision-clinical modification codes 042, 043, or V08) used in the research registry plus HIV-related diagnosis-related codes (diagnosis-related groups: diagnosis-related group 488, 489, 702, 705, 707, 708, 710, 711, 714, 790) and specific search terms (eg, HIV, antiretroviral therapy [ART], AIDS) generating a broad initial sample size of (n) 9375 (Figure 1A). From this data set, we confirmed a diagnosis of HIV on chart review and identified all PWLHIV who had a neck CT with contrast. Subjects with a prior history of ASCVD, including MI, coronary artery disease, cerebrovascular disease (stroke and transient ischemic attack), prior carotid or peripheral vascular disease, and prior atrial fibrillation were excluded. Subjects with nondiagnostic/unavailable neck CT scans and subjects in whom the indication for the CT scan was stroke were also excluded. Control subjects were derived from the same database. In brief, 441 subjects were noted to be erroneously coded under the extended search term HIV and served as the control group. A through chart review demonstrated that these subjects had the word HIV in the medical record typically because of HIV testing and did not have HIV. Non-HIV control subjects with a prior history of ASCVD, coronary artery disease, and cerebrovascular disease were excluded (stroke and transient ischemic attack). Data collection, image analysis, and event adjudication were performed by 3 independent and blinded groups. One team performed electronic medical record review to ascertain data on baseline cardiovascular risk factors and HIV-specific parameters, another adjudicated clinical outcomes, and a third performed image analysis of the neck CTs. Our study was approved by the Institutional Review Board.

Data Collection

Traditional Cardiovascular Risk Factors

Baseline covariates were collected within 1 year of the neck CT scan by electronic medical record review. Data were collected on traditional cardiovascular risk factors, including hypertension, dyslipidemia, diabetes mellitus, and family history of coronary heart disease.[13] The use of cardiovascular medications, body mass index, sleep apnea, creatinine levels, smoking, alcohol use, and illicit drug use were also collected.

HIV-Specific Parameters

Data were collected on duration since HIV diagnosis, duration of antiretroviral therapy, category of antiretroviral therapies, viral load, CD4 count, and nadir CD4 count as previously described.[11] All efforts were made to collect the HIV-specific parameters from the electronic medical record at a time point closest to the CT scan.

CT Neck Image Analysis

The types of CT scans included CT neck with contrast, CT angiography, and positron emission tomography-CT with contrast, performed for a variety of indications. Indications for neck CT included assessment for trauma (27%), neck mass (17%), neck cancer (13%), lymphadenopathy (8%), abscess (7%), neck pain (7%), headache (2%), dysphagia (1%), and varied (12%). We assessed the presence of plaque, plaque composition (calcified, mixed, and noncalcified), degree of stenosis based on North American Symptomatic Carotid Endarterectomy Trial (NASCET) evaluation (minimal, 1%–30%; mild, 31%–50%; moderate, 51%–69%; severe, 70%–99%), presence of high-risk plaque (HRP) features, including spotty calcification (size of calcification <3 mm in all directions) and low attenuation (if circular region of interest with diameter of 1 mm shows area with mean attenuation <40 HU).[14] A plaque score was computed by summing the maximum thickness of plaque in each segment (mm) on both sides according to Gupta et al.[15] The carotid images were analyzed by 3 experienced readers (S.J., P.S., R.T.), blinded to the clinical data, on a cardiac workstation (Tera Recon, Foster City, CA). All readers completed standardized CT training to assess interobserver variability and had excellent interobserver agreement for presence of plaque (kappa, 0.92), grade of stenosis (kappa, 0.77), type of calcification (kappa, 0.74), low attenuation (kappa, 0.95), and spotty calcification (kappa, 0.69).

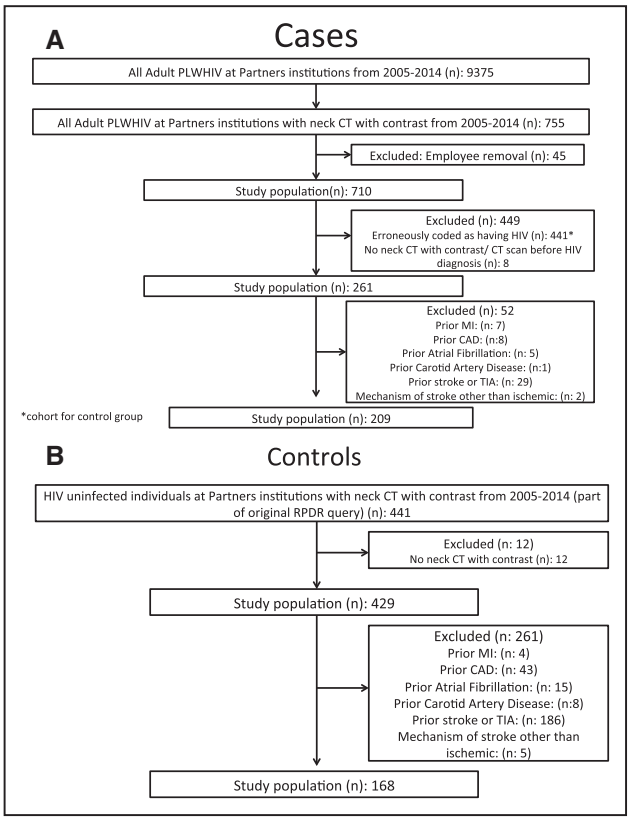

Figure 1. **A**, Consort diagram describing inclusion and exclusion criteria for the people living with HIV (PLWHIV) cohort. After excluding 52 subjects with prior cerebrovascular and cardiovascular disease, our eligible study population was 209. **B**, Consort diagram describing the inclusion and exclusion criteria for the uninfected cohort. After excluding 261 subjects with prior cerebrovascular and cardiovascular disease, our eligible study population was 168. CAD indicates coronary artery disease; CT, computed tomography; MI, myocardial infarction; RPDR, Research Patient Database Registry; and TIA, transient ischemic attack.

Outcomes

The primary outcome was an ASCVD event, defined as MI, coronary heart disease death, or ischemic stroke, in accordance with ASCVD end points defined in the 2013 American College of Cardiology/American Heart Association Risk Assessment Guidelines.[16] The secondary outcome was ischemic stroke as defined by the American Heart Association/American Stroke Association consensus document.[17] All events were adjudicated by blinded board-certified physicians using standardized definitions blinded to other variables.[18]

Statistical Analysis

Continuous variables were presented as mean±SD or median and interquartile range, whereas categorical variables were presented as

percentages. Parameters were compared between the 2 groups using Student's *t* test or Mann Whitney test for continuous variables and χ^2 or Fisher exact test for categorical variables, as appropriate. Univariate and multivariate Cox proportional hazard regression analyses were performed to determine the association between the presence of any carotid plaque or HRP and outcomes among the entire cohort and then just limited to PLWHIV. The multivariate models were adjusted for the number of traditional cardiovascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, current smoking, and family history of coronary artery disease. Hazard ratios (HR) are presented with 95% confidence interval (CI). Kaplan–Meier curves were generated to compare event-free survival among PLWHIV and uninfected individuals with and without plaque. Between-group differences were assessed using the log-rank test. A *P* value <0.05 was considered significant. Statistical calculations were performed using SPSS software (SPSS version 22; IBM Corp., Armonk, NY) and STATA software (Version 13, StataCorp LP., College Station, TX).

Results

Study flow diagrams for the derivation of both the PLWHIV and uninfected control individuals are presented in Figure 1A and 1B. After exclusion of subjects in each cohort for prior vascular disease, there were 209 PLWHIV and 168 controls. The distribution of type of CT scans included CT neck with contrast (65%), CT angiography (44%), and positron emission tomography-CT with contrast (4%). PLWHIV had a higher frequency of CT neck with contrast, while controls had a higher number of CT angiography. The indication categories in the 2 groups were similar for abscess, cancer, dysphagia, pain, mental status change (*P*<0.05 for all), whereas significant differences were found for the numbers in each group where the indication was lymphadenopathy, mass, and trauma (*P*>0.05 for all). Tables 1 and 2 describe the baseline characteristics of PLWHIV and uninfected controls. There were no significant differences in age (45±10 versus 43±17 years, HIV+ versus HIV−; *P*=0.07), sex (72% versus 65% male; *P*=0.18), prevalence of diabetes mellitus (10% versus 11%; *P*=0.61), hyperlipidemia (15% versus17%; *P*=0.67), and cigarette smoking (33% versus 30%; *P*=0.57). Cardiovascular medication use was similar between the 2 groups.

PLWHIV varied significantly with regards to race (more Black) and had increased illicit drug use, lower body mass index, and lower high-density lipoprotein as compared with uninfected controls. The mean duration of HIV was 14±7 years, 49% had an undetectable viral load, the mean CD4 count was 378±358 cells/mm^3, and 93% (n=194) of the PLWHIV were on ART. Variables including duration of ART, CD4 nadir, and CD4 count were present in 93% of the cases (missing 7%), absolute CD8 count for 69% of the cases (missing 31%), and undetectable viral load for 88% of the cases (missing 12%).

Carotid Plaque Characteristics

PLWHIV free of known vascular disease had an increased rate of any carotid plaque (34% versus 25%; *P*=0.04), noncalcified carotid plaque (18% versus 5%; *P*<0.001), and higher plaque score (1.8±3.4 versus 1.2±2.7; *P*=0.03). PLWHIV also had a significantly higher number of any HRP (25% versus 16%; *P*=0.03), higher number of HRP features per patient (*P*=0.03), and a higher number of low attenuation plaque (16% versus 7%; *P*=0.007; Table 3 and Figure 2).

Table 1. Baseline Characteristics of PLWHIV Versus Uninfected Individuals

	PLWHIV (n=209)	Uninfected (n=168)	*P* Value
Age (mean±SD)	45.6±10	43.1±17	0.07
Male sex	150 (72)	109 (65)	0.18
Race			0.02
White	106 (51)	30 (65)	
Black	73 (35)	5 (11)	
Asian	4 (2)	2 (1)	
Other	19 (9)	6 (13)	
Hispanic/Latino	27 (13)	3 (6)	0.35
Diabetes mellitus	20 (10)	19 (11)	0.61
Hypertension	46 (22)	53 (31)	0.04
Hyperlipidemia	31 (15)	28 (17)	0.67
Current smoker	71 (33)	51 (30)	0.57
Family history of CAD	10 (6)	2 (1)	0.07
Family history of stroke/TIA	11 (5)	7 (5)	1.00
Number of risk factors			
0	82 (21)	107 (28)	<0.001
1	93 (25)	30 (8)	
2	20 (5)	21 (6)	
3	12 (3)	10 (3)	
4	2 (1)	0 (0)	
IVDU			0.01
Current	17 (8)	0 (0)	
Past	19 (9)	0 (0)	
Cocaine use			<0.01
Current	17 (8)	0 (0)	
Past	35 (17)	2 (4)	
CV medications			
Aspirin	19 (9)	15 (9)	1.00
ACE inhibitor	19 (9)	15 (9)	1.00
ARB	5 (1)	2 (1)	0.46
Beta blocker	30 (14)	18 (11)	0.35
Statin	27 (12)	18 (11)	0.74

Values are mean±SD or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CV, cardiovascular; HDL, high-density lipoprotein; IVDU, intravenous drug use;

LDL, low-density lipoprotein; PLWHIV, people living with HIV; and TIA, transient ischemic attack.

Outcomes: ASCVD/Stroke

The primary outcome was an ASCVD event. Over a median follow-up of 3 years, there were 17 ASCVD (ischemic stroke, 9; MI, 6; coronary heart disease death, 2) events among 209 PLWHIV and 2 ASCVD events (coronary heart disease death, 2) among uninfected controls (*P*=0.002). The secondary outcome of interest was ischemic stroke. There were 9 ischemic strokes among

Table 2. Baseline Characteristics of PLWHIV Versus Uninfected Individuals

	PLWHIV (n=209) HIV	Uninfected (n=168)	*P* Value
Total cholesterol, mg/dL	170±48	182±42	0.09
Trigylcerides, mg/dL	172±148	148±104	0.09
HDL, mg/dL	44±22	52±19	0.01
LDL, mg/dL	92±38	101±37	0.14
BMI, kg/m^2	26±5.3	28±7.4	0.01
Systolic blood pressure, mm Hg	123±19	126±18	0.31
Diastolic blood pressure, mm Hg	75±11	74±11	0.42
Heart rate, bpm	83±17	83±16	0.99
Creatinine, mg/dL	1.1±1.2	1.1±1.2	0.85
HCV coinfection	38 (18)		
Duration since HIV, y	14±7 diagnosis		
Endocarditis	6 (3)		
CD4 count, cells/mm^3	378±358		
CD4 nadir, cells/mm^3	184±194		
CD8 count, cells/mm^3	825±550		
ART at time of CT	194 (93)		
NNRTI	67 (32)		
NRTI	159 (76)		
PI	87 (42)		
Integrase inhibitors	23 (11)		
Duration of ART, y	9.8 (4.9–15.0)		
Undetectable viral load, copies/mL	104 (49)		

Values are mean±SD, n (%), or median (IQR). ART indicates antiretroviral therapy; BMI, body mass index; CT, computed tomography; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, non-nucleotide reverse transcriptase inhibitors; NRTI, nucleotide reverse transcriptase inhibitors; PI, protease inhibitors; and PLWHIV, people living with HIV.

Table 3. Carotid Plaque Characteristics in PLWHIV Versus Uninfected Individuals

	PLWHIV (n=209)	Uninfected (n=168)	*P* Value
Any plaque	72 (34)	42 (25)	0.04
Plaque score	1.8±3	1.21±3	0.03
Composition			
Calcified plaque	6 (3)	8 (5)	0.33
Noncalcified plaque	38 (18)	8 (5)	<0.001
Partially calcified plaque	46 (22)	34 (20)	0.67
Stenosis			
Moderate (>50%)	10 (5)	2 (1)	0.07
Severe (>70%)	3 (1)	0 (0)	0.25
Any high risk plaque	53 (25)	27 (16)	0.03
Spotty calcification	25 (12)	13 (8)	0.22
Low attenuation	34 (16)	12 (7)	0.007
Number of high-risk plaque features			0.03
0	156 (75)	141 (82)	
1	42 (20)	22 (13)	
2	10 (5)	5 (3)	
3	1 (0.5)	0 (0)	

Values are mean±SD or n (%). PLWHIV indicates people living with HIV.

PLWHIV as compared with 0 strokes among controls (*P*=0.005). Among PLWHIV, there were 10 ASCVD events among the 72 PLWHIV with carotid plaque (14%) as compared with 7 events among the 137 PLWHIV without plaque (5%; *P*=0.027). Similarly, among PLWHIV, there were 6 ischemic stroke events among the 72 PLWHIV (8%) with any carotid plaque as compared with 3 events among 137 PLWHIV (2%) without any plaque (*P*=0.046).

Among PLWHIV, there were 8 ASCVD events among the 53 PLWHIV with any HRP (15%) as compared with 9 events among the 156 PLWHIV without HRP (6%; *P*=0.032), and there were 5 ischemic stroke events among the 53 PLWHIV (9%) with any HRP as compared with 4 events among 156 PLWHIV (2%) without any HRP (*P*=0.048).

Univariate and Multivariate Modeling for Outcomes

Entire Cohort

Among the whole cohort, there was an unadjusted association between HIV status and ASCVD events (HR, 5.81; CI, 1.34–25.2; *P*=0.02) and ischemic stroke and presence of any carotid plaque with ASCVD events (HR, 3.32; CI, 1.34–8.29; *P*=0.01) and ischemic stroke (HR, 4.89; CI, 1.22–19.60; *P*=0.03). After adjustment for the number of cardiovascular risk factors, HIV status (HR, 5.22; CI, 1.20–22.67; *P*=0.027) and carotid plaque (HR, 2.77; CI, 1.08–7.12; *P*=0.03) were independent predictors of ASCVD events (Table 4).

PLWHIV

In analysis confined to PLWHIV, the presence of any carotid plaque was associated with an almost 3-fold increased risk of ASCVD events (HR, 2.91; CI, 1.10–7.7; *P*=0.03) and a 4-fold increased risk of ischemic stroke (HR, 4.14; CI, 1.03–16.6; *P*=0.04). In multivariate analysis confined to PLWHIV, after adjustment for cardiovascular risk factors, the presence of any carotid plaque was associated with an increased risk for ASCVD events (HR, 2.84; CI, 1.05–7.63; *P*=0.03) and with a trend toward an increased risk for ischemic stroke (HR, 3.57; CI, 0.86–14.7; *P*=0.07; Table 5 and Figure 3A and 3B). Also among PLWHIV, the presence of any HRP was associated with an unadjusted 3-fold increased risk for ASCVD events (HR, 3.02; CI, 1.15–7.88; *P*=0.02) and a 4-fold increased risk of stroke (HR, 4.43; CI, 1.17–16.70; *P*=0.02). In multivariate analysis, after adjustment for number of cardiovascular risk factors, the presence of any HRP feature remained associated with an increased risk of ASCVD events (HR, 2.93; CI, 1.11–7.77; *P*=0.03) and with an increased risk of stroke (HR, 3.89; CI, 1.01–14.89; *P*=0.04; Table 6 and Figure 4A and 4B). We also evaluated the association of noncalcified plaque and events: the presence of noncalcified plaque was associated with an unadjusted 3-fold increased risk for ASCVD events (HR, 3.21; CI, 1.22–8.45;

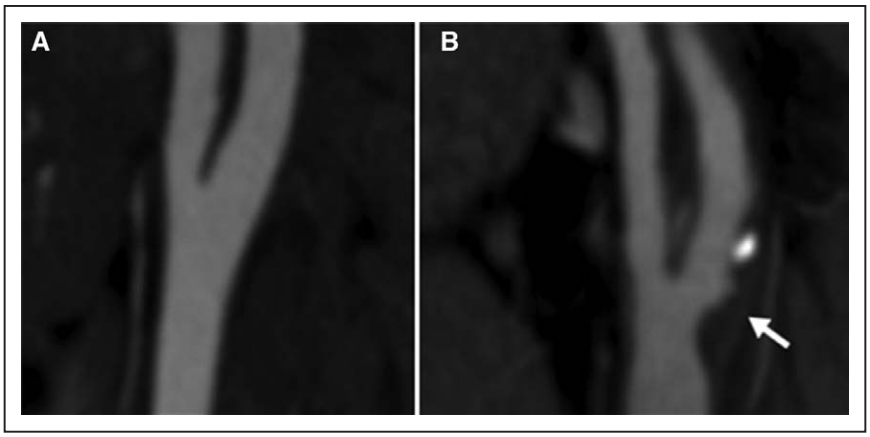

Figure 2. A computed tomography (CT) neck image of the right carotid artery in a uninfected individual free of carotid plaque (**A**) as compared with a neck CT image from a people living with HIV (PLWHIV) with carotid plaque with a non-calcified component (**B**, arrow).

P=0.02) and stroke (HR, 3.71; CI, 0.992–13.85; *P*=0.051). In multivariate analysis, the presence of any noncalcified plaque remained associated with an increased risk of ASCVD events (HR, 3.36; CI, 1.26–8.91; *P*=0.02) and an independent association with stroke (HR, 4.65; CI, 1.17–18.53; *P*=0.03).

Discussion

Leveraging data from a large US healthcare system, we tested, using CT, whether HIV status was associated with an increase in incidental carotid plaque, whether HIV status was associated with high risk and noncalcified plaque, and whether incidental carotid plaque and plaque characteristics were associated with subsequent vascular events among PLWHIV. In a cohort free of known vascular disease, we found that HIV status was associated with an increased rates of incidental carotid plaque, noncalcified plaque, and HRP as compared with uninfected controls. Additionally, in follow-up, among PLWHIV, the presence of carotid plaque, noncalcified plaque, and HRP was associated with an increased risk of both any atherosclerotic event and stroke after adjustment for cardiovascular risk factors.

Our hypothesis that there would be an increase in subclinical carotid plaque in HIV was based on prior data from several groups showing an increase in subclinical coronary plaque in HIV.[19,20] For example, Lo et al[19] showed in a study of 78 men living with HIV without a history of vascular disease that incidental coronary atherosclerosis by CT was almost 2-fold higher in men living with HIV as compared with demographic and risk factor uninfected men (59% versus 34%). Based on these findings, we hypothesized that there would be an increase in subclinical carotid plaque by CT among PLWHIV free of known vascular disease. The hypothesis was also supported by robust data using ultrasound for detection of carotid plaque in HIV and data from other inflammatory diseases associated with an increased risk of vascular events.[21,22] For example, in a study of 1822 PLWHIV using serial ultrasound, Hanna et al[21] showed that PLWHIV had a 61% greater risk of new focal carotid artery plaque formation over 7 years compared with uninfected controls, regardless of baseline vascular phenotype and after controlling for cardiometabolic risk factors. There are also significant data in other diseases that share pathophysiological overlap with HIV. Specifically, the mechanisms of increased vascular risk in HIV are likely related to immune activation and an increase in inflammation,[23,24] and in other diseases where an immune activation and inflammation play a key pathophysiological role, an increase in incidental carotid plaque has been reported.[25,26] For example, in rheumatoid arthritis and diabetes mellitus, data have described an increase in incidental carotid plaque.[27,28] We extend these findings to HIV and provide, to our knowledge, the first study characterizing carotid plaque by CT in HIV and demonstrate an increased number of incidental carotid artery plaque in PLWHIV as compared with an uninfected cohort.

Given its spatial resolution, CT is an excellent technique for characterizing atherosclerotic plaque composition, and data using CT in broad populations have shown that the association between atherosclerotic plaque in the coronaries and adverse outcomes is markedly influenced by plaque composition.[29,30] Among PLWHIV, data using CT have shown that there is a marked increase in the prevalence of both noncalcified plaque[31] and HRP in coronary arteries of PLWHIV.[8,32] For example, Post et al[20] showed in a study of 618 PLWHIV that the prevalence of any noncalcified coronary plaque was 63% as compared with 53% in uninfected controls. Similar, D'Ascenzo et al,[31] in a meta-analysis of 9 studies (1229 PLWHIV and 1029 controls), showed that the rates of noncalcified plaque were >3-fold higher in PLWHIV (58% versus 17%). Prior to this current work, there were no data testing the prognostic significance of noncalcified plaque or HRP in the carotid arteries among PLWHIV. However, there are data testing the prevalence and prognostic significance of noncalcified plaque and HRP in the carotid in non-HIV populations.[33] For example, Homburg et al evaluated the associations between carotid plaque ulceration and plaque characteristics in ischemic stroke patients and found that a lipid-rich core (noncalcified plaque) was associated with plaque ulceration, whereas calcification (plaque stability) was inversely

Table 4. Multivariate Regression Model for ASCVD Events in PLWHIV Versus Uninfected Individuals

	Univariate Analysis *P* Value	Multivariate Analysis *P* Value
HIV	5.80 (1.34–25.15) 0.01	5.22 (1.20–22.6) 0.03
Any carotid plaque	3.32 (1.33–8.28) 0.01	2.77 (1.08–7.12) 0.03
Number of CV factors*		1.12 (0.70–1.77) 0.62

ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; and PLWHIV, people living with HIV.

*Number of CV risk factors include DM, HTN, HLD, current smoker, and family history of CAD.

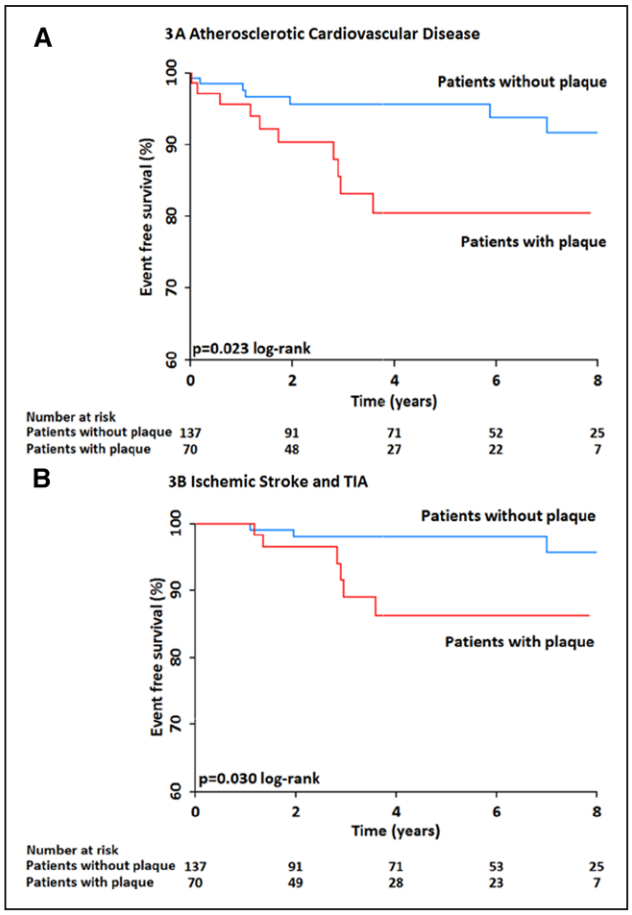

Figure 3. **A**, Kaplan–Meier event-free survival curve for atherosclerotic cardiovascular disease (ASCVD) events in people living with HIV (PLWHIV) with and without any carotid plaque showing that PLWHIV with any carotid plaque have a significantly increased risk for ASCVD events as opposed to those without plaque. **B**, Kaplan–Meier event-free survival curve for ischemic stroke in PLWHIV with and without any carotid plaque showing that PLWHIV with carotid plaque have an increased risk for stroke as opposed to those without plaque. TIA indicates transient ischemic attack.

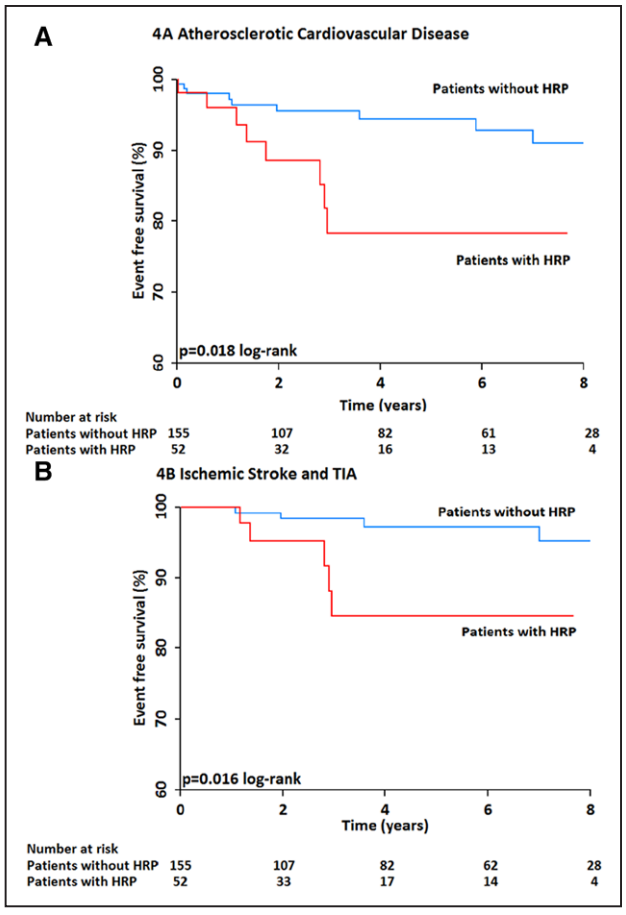

Figure 4. **A**, Kaplan–Meier event-free survival curve for atherosclerotic cardiovascular disease (ASCVD) events in people living with HIV (PLWHIV) with and without high-risk morphology carotid plaque showing that PLWHIV with any high-risk plaque (HRP) are at an increased risk for ASCVD events as opposed to those without any high risk plaque. **B**, Kaplan–Meier event-free survival curve for ischemic stroke in PLWHIV with and without high-risk morphology carotid plaque showing that HIV-infected individuals with any high-risk plaque have an increased risk for ischemic stroke as opposed to those without any high-risk plaque. TIA indicates transient ischemic attack.

associated with plaque ulceration. We extend these prior observations to PLWHIV and find that PLWHIV have an increase number of noncalcified carotid plaque and HRP and that these plaque characteristics are associated with an increase risk of subsequent clinical vascular events.

Data have established that the risk of vascular events is increased in HIV.[5] For example, Chow et al showed that the incidence rate of ischemic stroke was 5.27 per 1000 person years in PLWHIV compared with 3.75 in uninfected patients (adjusted HR of 1.40) and that HIV remained an independent predictor of stroke after controlling for demographics and stroke risk factor.[1] Additionally, studies in broad cohorts have demonstrated that the presence of carotid plaque is associated with an increased incidence of vascular events. For example, Gepner et al[34] reported that in 6779 subjects without prior cardiovascular disease from the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, carotid plaque presence by carotid ultrasound (c=0.782 to c=0.787; *P*=0.045) marginally improved prediction of stroke/transient ischemic attack, above the traditional cardiovascular risk factors. However, no prior study has connected carotid plaque to vascular events and stroke specifically in HIV. In this study, consistent with prior data, the baseline risk of a vascular event was higher in PLWHIV as compared with a uninfected cohort, and additively, we show that the adjusted risk for a vascular event in PLWHIV with carotid plaque or HRP was ≈3-fold higher than those without plaque.

Strengths of our study include the first ever CT-based assessment of the presence of incidental carotid plaque in HIV, as well as first reporting on quantitative and qualitative plaque carotid analysis in relation to events in this population. However, some limitations merit discussion. This was a retrospective study, and HIV-specific parameters were not recorded at the time of the CT but were gathered from the electronic medical record at a time close to the study. All efforts were made to collect the viral load assay data closest to the date of physician visit (ART data) if not on the same date. Nonadherence is a possible factor as well. We suspect that the majority of patients in whom detectable viral load was noted were experiencing blips–temporary low level, detectable viremia observed in the context of transient ART nonadherence. We consider it likely that transient

Table 5. Multivariate Regression Model for Carotid Plaque and Outcomes in PLWHIV

	Univariate Analysis *P* Value	Multivariate Analysis *P* Value
ASCVD		
Any carotid plaque	2.91 (1.10–7.67) 0.03	2.84 (1.05–7.63) 0.03
Number of CV factors*		1.06 (0.64–1.75) 0.79
Stroke/TIA		
Any carotid plaque	4.14 (1.03–16.6) 0.04	3.57 (0.86–14.7) 0.07
Number of CV factors*		1.42 (0.79–2.54) 0.23

ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; PLWHIV, people living with HIV; and TIA, transient ischemic attack.

*Number of CV risk factors include DM, HTN, HLD, current smoker, and family history of CAD.

nonadherence with ART is relatively common in this cohort, as it is in other contemporary cohorts. Indeed, a recent investigation published by the Swiss HIV Cohort team suggested that blips can be observed in ≤41% of HIV-infected patients to whom ART is prescribed. Because uninfected controls were generated from the original query, there may be an element of referral/selection bias. Additionally, cocaine use was only available for 65% of the subjects and its interpretation as significantly different between the cases and controls should be done with caution, and the observational nature precludes definitive determinations of causal drivers of outcomes. We also acknowledge that the type of CT was not prespecified and CT scans included arterial and venous phase CT studies, which differ in spatial resolution. However, CT angiography scans, with their higher resolution for plaque analysis, were more prevalent in the uninfected cohort.

Conclusions

PLWHIV without prior vascular disease have an increased number of carotid plaque, noncalcified plaque, and HRP as compared with uninfected controls, and in follow-up, the presence of carotid plaque, noncalcified plaque, and HRP is associated with an increased risk of adverse vascular outcomes. Further research is needed to identify the underlying mechanisms, both general or HIV specific, contributing to this increased risk and whether interventions, such as statins, can reduce risk in this vulnerable population.

Table 6. Multivariate Regression Model for High-Risk Plaque and Outcomes in PLWHIV

	Univariate Analysis *P* Value	Multivariate Analysis *P* Value
ASCVD		
Any high-risk plaque	3.02 (1.15–7.88) 0.024	2.93 (1.11–7.77) 0.03
Number of CV factors*		1.08 (0.65–1.79) 0.74
Stroke/TIA		
Any high-risk plaque	4.43 (1.17–16.70) 0.02	3.89 (1.01–14.89) 0.04
Number of CV factors*		1.47 (0.81–2.68) 0.204

ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; PLWHIV, people living with HIV; and TIA, transient ischemic attack.*Number of CV risk factors include DM, HTN, HLD, current smoker, and family history of CAD.

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Disclosures

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References

1. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007;92:2506–2512. doi: 10.1210/jc.2006-2190.
2. Sico JJ, Chang CC, So-Armah K, Justice AC, Hylek E, Skanderson M, McGinnis K, Kuller LH, Kraemer KL, Rimland D, Bidwell Goetz M, Butt AA, Rodriguez-Barradas MC, Gibert C, Leaf D, Brown ST, Samet J, Kazis L, Bryant K, Freiberg MS; Veterans Aging Cohort Study. HIV status and the risk of ischemic stroke among men. *Neurology*. 2015;84:1933–1940. doi: 10.1212/WNL.0000000000001560.
3. Marcus JL, Leyden WA, Chao CR, Chow FC, Horberg MA, Hurley LB, Klein DB, Quesenberry CP Jr, Towner WJ, Silverberg MJ. HIV infection and incidence of ischemic stroke. *AIDS*. 2014;28:1911–1919. doi: 10.1097/QAD.0000000000000352.
4. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, Moretti C, Omedè P, Sciuto F, Bollati M, Modena MG, Gaita F, Sheiban I. Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy. *Eur Heart J*. 2012;33:875–880. doi: 10.1093/eurheartj/ehr456.
5. Chow FC. HIV infection, vascular disease, and stroke. *Semin Neurol*. 2014;34:35–46. doi: 10.1055/s-0034-1372341.
6. Sanz J, Fayad ZA. Imaging of atherosclerotic cardiovascular disease. *Nature*. 2008;451:953–957. doi: 10.1038/nature06803.
7. Lo J, Lu MT, Ihenachor EJ, Wei J, Looby SE, Fitch KV, Oh J, Zimmerman CO, Hwang J, Abbara S, Plutzky J, Robbins G, Tawakol A, Hoffmann U, Grinspoon SK. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet HIV*. 2015;2:e52–e63. doi: 10.1016/S2352-3018(14)00032-0.
8. Zanni MV, Abbara S, Lo J, Wai B, Hark D, Marmarelis E, Grinspoon SK. Increased coronary atherosclerotic plaque vulnerability by coronary computed tomography angiography in HIV-infected men. *AIDS*. 2013;27:1263–1272. doi: 10.1097/QAD.0b013e32835eca9b.
9. Suchindran S, Regan S, Meigs JB, Grinspoon SK, Triant VA. Aspirin use for primary and secondary prevention in human immunodeficiency virus (HIV)-infected and HIV-uninfected patients. *Open Forum Infect Dis*. 2014;1:ofu076. doi: 10.1093/ofid/ofu076.
10. Chow FC, He W, Bacchetti P, Regan S, Feske SK, Meigs JB, Grinspoon SK, Triant VA. Elevated rates of intracerebral hemorrhage in individuals from a US clinical care HIV cohort. *Neurology*. 2014;83:1705–1711. doi: 10.1212/WNL.0000000000000958.
11. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. *J Acquir Immune Defic Syndr*. 2012;60:351–358. doi: 10.1097/QAI.0b013e31825c7f24.
12. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab*. 2008;93:3499–3504. doi: 10.1210/jc.2008-0828.
13. Triant VA, Lee H, Hadigan C, Grinspoon SK.Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007;92:2506–2512.

14. Walker LJ, Ismail A, McMeekin W, Lambert D, Mendelow AD, Birchall D. Computed tomography angiography for the evaluation of carotid atherosclerotic plaque: correlation with histopathology of endarterectomy specimens. *Stroke*. 2002;33:977–981.
15. Gupta A, Baradaran H, Kamel H, Pandya A, Mangla A, Dunning A, Marshall RS, Sanelli PC. Evaluation of computed tomography angiography plaque thickness measurements in high-grade carotid artery stenosis. *Stroke*. 2014;45:740–745. doi: 10.1161/STROKEAHA.113.003882.
16. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98.
17. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV, American Heart Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism.. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064–2089. doi: 10.1161/STR.0b013e318296aeca.
18. Kirwan BA, Lubsen J, de Brouwer S, Danchin N, Battler A, Bayes de Luna A, Dunselman PH, Glasser S, Koudstaal PJ, Sutton G, van Dalen FJ, Poole-Wilson PA; ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) Investigators. Diagnostic criteria and adjudication process both determine published event-rates: the ACTION trial experience. *Contemp Clin Trials*. 2007;28:720–729. doi: 10.1016/j.cct.2007.04.001.
19. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, Nasir K, Grinspoon SK. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. *AIDS*. 2010;24:243–253. doi: 10.1097/QAD.0b013e328333ea9e.
20. Post WS, George RT, Budoff M. HIV infection and subclinical coronary atherosclerosis. *Ann Intern Med*. 2014;161:923–924. doi: 10.7326/L14-5033-2.
21. Hanna DB, Post WS, Deal JA, Hodis HN, Jacobson LP, Mack WJ, Anastos K, Gange SJ, Landay AL, Lazar JM, Palella FJ, Tien PC, Witt MD, Xue X, Young MA, Kaplan RC, Kingsley LA. HIV infection is associated with progression of subclinical carotid atherosclerosis. *Clin Infect Dis*. 2015;61:640–650. doi: 10.1093/cid/civ325.
22. Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, Waters DD. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation*. 2004;109:1603–1608. doi: 10.1161/01.CIR.0000124480.32233.8A.
23. Hsu DC, Ma YF, Hur S, Li D, Rupert A, Scherzer R, Kalapus SC, Deeks S, Sereti I, Hsue PY. Plasma IL-6 levels are independently associated with atherosclerosis and mortality in HIV-infected individuals on suppressive antiretroviral therapy. *AIDS*. 2016;30:2065–2074. doi: 10.1097/QAD.0000000000001149.
24. Barbour JD, Jalbert EC, Chow DC, Gangcuangco LM, Norris PJ, Keating SM, Heitman J, Nagamine L, Seto T, Ndhlovu LC, Nakamoto BK, Hodis HN, Parikh NI, Shikuma CM. Reduced CD14 expression on classical monocytes and vascular endothelial adhesion markers independently associate with carotid artery intima media thickness in chronically HIV-1 infected adults on virologically suppressive anti-retroviral therapy. *Atherosclerosis*. 2014;232:52–58. doi: 10.1016/j.atherosclerosis.2013.10.021.
25. Kao AH, Lertratanakul A, Elliott JR, Sattar A, Santelices L, Shaw P, Birru M, Avram Z, Thompson T, Sutton-Tyrrell K, Ramsey-Goldman R, Manzi S. Relation of carotid intima-media thickness and plaque with incident cardiovascular events in women with systemic lupus erythematosus. *Am J Cardiol*. 2013;112:1025–1032. doi: 10.1016/j.amjcard.2013.05.040.
26. Orlandi M, Suvan J, Petrie A, Donos N, Masi S, Hingorani A, Deanfield J, D'Aiuto F. Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: a systematic review and meta-analysis. *Atherosclerosis*. 2014;236:39–46. doi: 10.1016/j.atherosclerosis.2014.06.002.
27. Rho YH, Chung CP, Oeser A, Solus J, Asanuma Y, Sokka T, Pincus T, Raggi P, Gebretsadik T, Shintani A, Stein CM. Inflammatory mediators and premature coronary atherosclerosis in rheumatoid arthritis. *Arthritis Rheum*. 2009;61:1580–1585. doi: 10.1002/art.25009.
28. Ostling G, Hedblad B, Berglund G, Gonçalves I. Increased echolucency of carotid plaques in patients with type 2 diabetes. *Stroke*. 2007;38:2074–2078. doi: 10.1161/STROKEAHA.106.480830.
29. Vazquez-Figueroa JG, Rinehart S, Qian Z, Joshi PH, Sharma A, Lee J, Anderson H, Murrieta L, Wilmer C, Carlson H, Taylor K, Ballard W, Karmpaliotis D, Kalynych A, Brown C III, Voros S. Prospective validation that vulnerable plaque associated with major adverse outcomes have larger plaque volume, less dense calcium, and more non-calcified plaque by quantitative, three-dimensional measurements using intravascular ultrasound with radiofrequency backscatter analysis: results from the ATLANTA I Study. *J Cardiovasc Transl Res*. 2013;6:762–771. doi: 10.1007/s12265-013-9473-0.
30. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hishida H, Narula J. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:319–326. doi: 10.1016/j.jacc.2007.03.044.
31. D'Ascenzo F, Cerrato E, Calcagno A, Grossomarra W, Ballocca F, Omedè P, Montefusco A, Veglia S, Barbero U, Gili S, Cannillo M, Pianelli M, Mistretta E, Raviola A, Salera D, Garabello D, Mancone M, Estrada V, Escaned J, De Marie D, Abbate A, Bonora S, Zoccai GB, Moretti C, Gaita F. High prevalence at computed coronary tomography of non-calcified plaques in asymptomatic HIV patients treated with HAART: a meta-analysis. *Atherosclerosis*. 2015;240:197–204. doi: 10.1016/j.atherosclerosis.2015.03.019.
32. Tawakol A, Lo J, Zanni MV, Marmarelis E, Ihenachor EJ, MacNabb M, Wai B, Hoffmann U, Abbara S, Grinspoon S. Increased arterial inflammation relates to high-risk coronary plaque morphology in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2014;66:164–171. doi: 10.1097/QAI.0000000000000138.
33. Homburg PJ, Rozie S, van Gils MJ, van den Bouwhuijsen QJ, Niessen WJ, Dippel DW, van der Lugt A. Association between carotid artery plaque ulceration and plaque composition evaluated with multidetector CT angiography. *Stroke*. 2011;42:367–372. doi: 10.1161/STROKEAHA.110.597369.
34. Gepner AD, Young R, Delaney JA, Tattersall MC, Blaha MJ, Post WS, Gottesman RF, Kronmal R, Budoff MJ, Burke GL, Folsom AR, Liu K, Kauvfman J, Stein JH. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima- media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8:e002262.

CLINICAL PERSPECTIVE

Our study aimed to provide insight into the prevalence, characteristics, and prognostic associations of CT-assessed carotid plaque among people living with HIV (PLWHIV) free of known vascular disease as compared with uninfected individuals. Using a large established and validated registry, we show that, as compared with uninfected controls, PLWHIV have an increased prevalence of carotid plaque, noncalcified plaque, and high-risk plaque. In the overall cohort, HIV status and any carotid plaque were independent predictors of cardiovascular and cerebrovascular events. Within PLWHIV, the presence and composition of carotid plaque was associated with a 3- to 4-fold increase in adverse vascular outcomes. This is the first study, to our knowledge, to report computed tomography–based assessment of presence of carotid plaque in HIV, as well as reporting on quantitative and qualitative carotid plaque analysis with relation to events in this population. With these data, we provide evidence of subclinical high-risk plaque in PLWHIV that is associated with worse cardiovascular outcomes as compared with uninfected controls. Although this is an observational data set and randomized control trials are needed to delineate causality, these data can help clinicians in identifying high-risk PLWHIV and provide aggressive risk factor modification.

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Presence, Characteristics, and Prognostic Associations of Carotid Plaque Among People Living With HIV

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