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Authors

Hsu, Denise C
Fei, Yi
Hur, Sophia
et al.

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Plasma IL-6 levels are independently associated with atherosclerosis and mortality in HIV-infected individuals on suppressive ART

Denise C HSU[1], **Yi Fei MA**[2], **Sophia HUR**[2], **Danny LI**[2], **Adam RUPERT**[3], **Rebecca SCHERZER**[4], **S.C. KALAPUS**[2], **Steven DEEKS**[2], **Irini SERETI**[1,*,+], and **Priscilla Y HSUE**[2,+]

[1]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

[2]University of California San Francisco (UCSF), San Francisco, CA, USA

[3]Leidos Biomedical Research, Inc, Frederick, MD, USA

[4]University of California and Veterans Affairs Medical Center, San Francisco, CA, USA

Abstract

Objective—To determine the associations of markers of immune activation with atherosclerosis and mortality, in participants with treated and suppressed HIV infection.

Design—Observational study of 149 HIV-infected participants with virologic suppression on antiretroviral therapy.

Methods—Cryopreserved mononuclear cells and plasma were used to evaluate markers of T cell and monocyte activation, inflammation and coagulopathy. Carotid artery intima-media thickness (CIMT) was measured by high-resolution ultrasound at the common, bifurcation and internal carotid regions. Associations of immunologic markers with CIMT and all-cause mortality were assessed using multivariable linear regression and Cox proportional hazards regression.

Results—The majority of participants were male (93%) and white (67%), median age of 48.5 years and median $CD4^+$ T cell count of 522 cells/μL. The median baseline IMT was 1.0 mm. Over a median of 8.3 years of follow-up, 12 deaths occurred.

In multivariate analysis, adjusted for traditional cardiovascular risk factors, higher monocyte CCR5 expression (5.4%, 95%CI [2.4–8.4], p=0.001) was associated with greater common carotid IMT. Higher plasma IL-6 was associated with greater bifurcation (8.0%, 95%CI [2.3–13.7], p=0.007) and overall mean IMT (5.2%, 95%CI [0.7–9.7], p=0.026).

Finally, higher plasma IL-6 (HR 1.9, 95%CI [1.0–3.7], p=0.030), internal carotid (HR 4.1, 95%CI [1.2–13.7], p=0.022) and mean IMT (HR 5.2, 95%CI [1.2–22.1], p=0.026) were individually associated with all-cause mortality.

[*]Corresponding author: Prof. Priscilla Y Hsue, Room 5G1 Cardiology SFGH, 1001 Potrero Avenue, San Francisco, CA 94110. Priscilla.Hsue@ucsf.edu.

[+]These 2 authors contributed equally to this work

Conflict of interests

We declare no conflict of interests.

Conclusions—Higher monocyte CCR5 expression and plasma IL-6 were associated with atherosclerosis, independent of traditional cardiovascular risk factors. IL-6 and CIMT were individually associated with all-cause mortality. The impact of therapies targeting immune activation in CVD in treated HIV infection merits additional investigation.

Keywords

Atherosclerosis; IL-6; CCR5; immune activation; HIV

Introduction

HIV-infected individuals are at increased risk of atherosclerosis [1–3] and cardiovascular disease (CVD) [4–6], when compared to the general population. In most studies, this difference persists even after adjustment for traditional CV risk factors, with CVD accounting for about 10% of deaths in this population [7, 8]. The increased risk of CVD in HIV-infected individuals is likely due to a combination of higher prevalence of traditional cardiovascular risk factors such as diabetes (DM), hypertension (HT), dyslipidemia and smoking [4, 9–12]; adverse effects from antiretroviral therapy (ART) including protease inhibitors [13–15]; and persistent inflammation [16, 17].

Inflammation is key to the process of atherogenesis [18, 19]. Multiple cellular (HLA-DR^+CD38^+ T cells) and soluble markers (Interleukin (IL)-6, C-reactive protein (CRP), soluble (s) CD14 and sCD163) of immune activation and coagulopathy (D-dimer) are elevated in HIV-infected individuals and do not fully normalize with ART [20–23]. Elevated IL-6, CRP and D-dimer levels have been associated with cardiovascular disease [17, 24], cardiovascular death [16] and overall mortality [25, 26] in HIV-infected individuals.

The mechanisms by which immune activation and chronic inflammation in HIV infection contribute to atherogenesis have not been clearly delineated. It has been postulated that HIV activated endothelial cells attract circulating monocytes and T cells via chemokines and adhesion molecules, resulting in atheroma formation. Persistent immune activation further contributes to this process, culminating in plaque rupture and triggering of the coagulation cascade [27].

Ultrasound measurement of carotid intima-media thickness (IMT) is one of the most widely used and validated atherosclerosis imaging techniques and has been shown to predict future CVD [28, 29]. Increased carotid IMT has been documented in HIV-infected persons in some [30–32] but not all studies [33]. Cross-sectional studies focusing on treated individuals with undetectable viral loads have found that T cell activation (% of HLA-DR^+CD38^+ T cells) and T cell senescence (% of $CD28^-CD57^+$ T cells) [34], monocyte CD11b and CX3CR1 expression [35], plasma sCD163 [36], sCD14 [37], soluble vascular cell adhesion molecule-1 (sVCAM) [38, 39] and TNF levels [38] are associated with atherosclerosis independent of CV risk factors. Furthermore, longitudinal studies on HIV-infected individuals have identified plasma CRP [40] and sCD14 levels [41], frequency of $CD16^+$ monocytes [42] and CCR5 expression on leukocytes [43] to be associated with atherosclerosis progression.

A better understanding of the factors involved in atherogenesis may lead to new therapeutic targets to reduce morbidity and mortality from CVD in HIV-infected individuals. In this study, we measured cellular markers of activation (T cell and monocytes), soluble markers of inflammation (IL-6, CRP, sCD14, sCD163) and coagulation (D-dimer, sTF) in order to determine which measures were independently associated with greater carotid IMT and overall mortality.

Methods

Study cohort

HIV-infected participants on ART with undetectable viral loads (plasma HIV RNA <75 copies/mL) were identified from the SCOPE cohort, a longitudinal observational cohort of HIV-infected individuals in San Francisco. The SCOPE study (NCT01519141) was approved by the UCSF Committee on Human Research and all participants provided written informed consent before study enrolment. Eligible subjects within the SCOPE cohort were invited to participate in a sub-study of cardiovascular function. Subjects were not recruited based on the presence or absence of cardiovascular risks.

At enrolment into the cardiology sub-study, we collected data on demographics, the presence of CVD risk factors, past and current medication usage, recreational drug use, and HIV disease characteristics (duration of HIV infection, nadir $CD4^+$ T cell count, and past and current ART regimen). Blood was also drawn to measure $CD4^+$ T cell count and HIV RNA levels as well as fasting glucose, total cholesterol, high-density lipoprotein (HDL) and triglycerides.

All participants were followed as part of the SCOPE study. For all-cause mortality, participants were followed through October 2015 or until the time of death. Vital status and date of death were determined using the National Death Index and the Social Security Death Index.

Carotid intima-media thickness measurement

CIMT was measured using high resolution B mode ultrasound in a total of 12 segments that included the near and far walls of the common carotid, bifurcation, and internal carotid regions on both the left and right sides, according to the standardized protocol of the Atherosclerosis Risk in Communities (ARIC) Study [44, 45] and has been previously described by our group [31, 40]. Within each segment (common, bifurcation, internal), IMT was calculated as the average of the near and far walls of the left and right carotid arteries. Overall mean CIMT was calculated as the average of the 12 segments. Plaque was defined as a focal region of CIMT >1.5mm. The reproducibility of our measurements using these techniques has been previously described and included a mean absolute difference of 0.04mm with a coefficient of variation of 3.4% and an intraclass correlation coefficient (ICC) of 0.98 [40].

Assessment of markers of immune activation, inflammation and coagulopathy

Cryopreserved peripheral blood mononuclear cells (PBMCs) from the time point closest to carotid IMT measurement, median 32 days (interquartile range, IQR 9–74), were thawed in batches. Cells were stained with viability dye LIVE/DEAD® Fixable Blue Dead Cell Stain Kit (Life technologies, NY, USA), washed then stained with fluorescent conjugated antibodies to cell surface markers. To measure bulk $CD4^+$ and $CD8^+$ T cell activation, PBMCs were stained with anti-CD3 PerCP (BD, NJ, USA), anti-CD8 pacific blue (BD), anti-CD4 eFluor 605 (eBioscience, CA, USA), anti-CX3CR1 PE (eBioscience), anti-CD28 PE-Cy7 (eBioscience), anti-CD57 FITC (BD), anti-CD38 APC (BD) and anti-HLA-DR APC-Cy7 (BD). PBMCs were stained with anti-CD2, anti-CD3, anti-CD19 and anti-CD20 efluor 450 (eBioscience), anti-CD56 V450 (BD), and anti-HLA-DR efluor 605 (eBioscience), to identify monocytes (lineage negative, HLA-DR^+ cells). PBMCs were also stained with anti-CD14 FITC (eBioscience), anti-CD16 PE-Cy7 (Biolegend, CA, USA), anti-CCR2 PerCP-Cy5.5 (Biolegend), anti-CX3CR1 APC (Biolegend), anti-TF PE (eBioscience) and anti-CCR5 APC-Cy7 (BD) to evaluate subpopulations of monocyte. Cellular markers were detected by flow cytometry using an LSRII flow cytometer (BD).

Soluble markers of inflammation (IL-6, CRP, sCD14, sCD163) and coagulopathy (D-dimer, sTF) were assessed in cryopreserved plasma samples, using a multiplex electrochemiluminescence assay (Meso Scale Discovery, MD, USA).

Statistical Analysis

We first summarized demographic and clinical characteristics as well as levels of IMT and biomarkers as median (IQR) for continuous variables and count (percentage) for categorical variables.

We used linear regression models with robust standard errors to estimate the unadjusted associations of each biomarker with IMT, using separate models for each segment (common, bifurcation, internal and overall mean). We also sought to identify combinations of biomarkers that were simultaneously predictive of IMT for each segment. We found that many of the markers of immune activation and inflammation were strongly correlated. Traditional variable selection methods have been shown to perform poorly in this setting. We therefore used the LASSO (Least Absolute Shrinkage and Selection Operator) procedure [46] that uses cross-validation to determine both the number of included predictors and the degree of shrinkage to avoid over-fitting. LASSO is well suited for so called high-dimensional data, where the number of predictors may be large relative to the sample size, and the predictors may be correlated. The final multivariate model retained only biomarkers showing significant associations with IMT at the 0.05 level.

Logistic regression was used to evaluate associations of markers of immune activation with the presence of plaque. Cox proportional hazards regression models were used to examine associations of IL-6 and CIMT with all-cause mortality.

In multivariable adjusted models, candidate covariates included demographics (age, race/ethnicity, and gender) and traditional CVD risk factors (smoking, presence of diabetes, hypertension and CVD, the levels of fasting glucose, HDL, LDL and triglyceride, BMI, the

use of antihypertensive medications and cholesterol lowering medications), as well as HIV-related characteristics (duration of HIV infection, duration of ART use, nadir $CD4^+$ T cell count, $CD4^+$ T cell count and CD4:CD8 ratio at CIMT measurement) and hepatitis C co-infection.

We implemented LASSO using the R package glmnet. All other analyses were conducted using the SAS system, version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Participant characteristics

Carotid IMT and markers of immune activation, inflammation and coagulopathy were measured in 149 HIV-infected participants on ART who had an undetectable viral load. The majority of the participants were male (93%) and white (67%) with a median age of 48.5 years (Table 1). The median duration of HIV infection was 15 years and the median nadir $CD4^+$ T cell count was 140 cells/μL. At the time of carotid IMT measurement, the participants had been on ART for a median of 8 years and had considerable immune restoration with a median $CD4^+$ T cell count of 522 cells/μL.

At the time of carotid IMT measurement, 43% of participants had hypercholesterolemia, 34% were hypertensive, 26% were current smokers, 7% were diabetic and 6% had a history of CVD (coronary artery disease and/or cerebral vascular disease). Over 60% of participants had at least 1 and over 30% had 2 or more traditional CVD risk factors.

Over a median follow-up of 8.3 years (IQR 6.8–11.9), there were 12 deaths. Four participants died of non-AIDS malignancies, 2 from sudden cardiac death, 2 from unnatural causes (accident/violent/overdose), 1 from end stage liver disease, 1 from intestinal perforation, 1 from bullous erythema multiforme and 1 from unknown cause.

CIMT and markers of immune activation measurements

The summary of IMT measurements at the different regions of the carotid arteries, markers of immune activation, inflammation and coagulopathy is included in Table 2. Overall, the median measurement of IMT ranged from 0.8 mm for the common carotid, 1.2 mm for the bifurcation, 0.9 mm for the internal carotid regions, and 1.0 mm for the overall mean carotid IMT. Plaque was present in 54% of participants.

Associations of biomarkers of immune activation with CIMT and plaque

In univariate unadjusted analyses higher monocyte CCR5 expression (18.3%, 95% CI [6.1–32.0], p=0.003) and higher plasma IL-6 levels (4.1%, 95% CI [0.5–7.7], p=0.027) were associated with greater common carotid IMT at the baseline visit. Higher proportion of $CD28^-CD57^+$ (senescent) $CD4^+$ T cells (2.4%, 95% CI [0.2–4.7], p=0.035) and higher plasma IL-6 levels (7.3%, 95% CI [1.9–13.0], p=0.008) were associated with greater IMT at the bifurcation region. Higher plasma IL-6 levels were also associated with greater overall mean IMT (5.9%, 95% CI [1.8–10.2], p=0.005). None of the markers of immune activation, inflammation and coagulopathy evaluated were significantly associated with internal carotid IMT (Table 3) or the presence of plaque (data not shown).

In the multivariable model with LASSO selection and adjustment for traditional cardiovascular risk factors and $CD4^+$ T cell count at time of CIMT, doubling of MFI in monocyte CCR5 expression was independently associated with 5.4% (95% CI [2.4–8.4], p=0.001) increase in common carotid IMT. Doubling of plasma IL-6 was independently associated with an increase in IMT of 8.0% (95% CI [2.3–13.7], p=0.007) and 5.2% (95% CI [0.7–9.7], p=0.026) at the bifurcation regions and overall mean IMT respectively (Fig 1).

Associations of demographics and traditional cardiovascular risk factors with CIMT

Each year increase in age was independently associated with greater IMT at the common, bifurcation, internal carotid regions and overall mean IMT (by 1.1 to 1.6%, p<0.001 to p=0.002, Fig 1). Male sex was independently associated with greater common carotid and overall mean IMT (by 16.3%, p=0.022 and 16.0%, p=0.031). Being of Latino origin was associated with reduced internal carotid IMT (by 28.2%, p=0.014). Each 10% increase in LDL was associated with increases in IMT at the common, bifurcation, internal regions and overall mean IMT (by 1.5 to 2.1%, p=0.002 to p=0.04, Fig 1). Each 10% increase in BMI was associated with 1.0% (p=0.007) increase in common carotid IMT. Longer duration of protease inhibitor use was associated with increase in overall mean IMT by 1.8% (95% CI [0.2–3.4], p=0.026, Fig 1).

Of all the demographic or HIV infection characteristics, CV risk factors and markers of immune activation, inflammation and coagulopathy examined, only older age was associated with increased risk of plaque (2%, 95% CI [0–5], p=0.039).

Associations of IL-6 and CIMT with all-cause mortality

In Cox proportional regression models adjusted for traditional cardiovascular risk factors, $CD4^+$ T cell count at time of CIMT measurement and hepatitis C co-infection, factors individually associated with increased mortality risk included IL-6 (hazard ratios (HR) 1.9 per doubling, 95% CI [1.0–3.7], p=0.030), internal carotid (HR 4.1 per doubling, 95% CI [1.2–13.7], p=0.022) and overall mean IMT (HR 5.2 per doubling, 95% CI [1.2–22.1], p=0.026).

DISCUSSION

HIV-infected individuals are at increased risk of atherosclerosis [1–3] and cardiovascular disease (CVD) [4–6], when compared to the general population even after adjustment for traditional CV risk factors. Immune activation is postulated to be a contributor to the excess risk. In this study we evaluated treated HIV-infected persons with suppressed plasma HIV viremia and found that higher levels of monocyte CCR5 expression and systemic inflammation (plasma IL-6) were associated with greater CIMT. As expected, we found that traditional and/or well-established risk factors (including age, male sex, obesity, hyperlipidemia and duration of PI use) were also associated with greater CIMT. Furthermore, higher levels of plasma IL-6 and greater internal carotid and mean IMT were individually associated with all-cause mortality.

IL-6 plays an important role in atherogenesis and pathogenesis of CVD. It can stimulate hepatic synthesis of acute-phase proteins, activate endothelial cells, promote lymphocyte

proliferation, neutrophil migration and macrophage differentiation [47, 48]. In the general population, higher plasma IL-6 levels have been associated with greater carotid IMT [49], atherosclerosis progression [50], coronary heart disease [51] and CV deaths [52]. Similarly, in HIV-infected individuals on ART, higher plasma IL-6 levels have been associated with CVD [17], CV deaths [16] and mortality [25]. There is also evidence to suggest that IL-6 is a stronger predictor of clinical events than hsCRP or D-Dimer in HIV infection [53]. Furthermore, a causal relationship between IL-6 signalling pathways and CVD was suggested from a meta-analysis involving over 120,000 participants [54]. Individuals with the Asp358Ala variant in the IL-6 receptor gene have reduced levels of the membrane bound form of the IL-6 receptor and thus attenuated IL-6 signalling. The presence of this allele was associated with lower levels of CRP and fibrinogen as well as reduced risk of CVD [54].

A number of studies exploring associations of markers of immune activation and inflammation (including IL-6) with atherosclerosis have been performed and results have been inconsistent (reviewed by Vos et al [55]). These contradictory findings are likely due in part to the heterogeneity of participant populations, with some studies including individuals who were not on ART [56, 57] or not virologically suppressed [37, 58]. Furthermore, the majority of prior studies measured CIMT in the common carotid region [55] rather than all 3 regions (common, bifurcation and internal) of the carotid arteries. Similar to our study, Longenecker et al found that IL-6 was positively associated with common carotid IMT in a study of 60 HIV+ subjects with a HIV-1 RNA < 400 copies/ml, but the association was no longer statistically significant after adjustment for traditional CV risk factors [59]. Recently, a study by Siedner et al found an association between plasma IL-6 levels at 6 months after ART initiation and common carotid IMT [58]. Thus far, ours is the only study in HIV-infected individuals who were on ART for a substantial period of time, with suppressed viremia that identified that IL-6 was independently associated with CIMT in the bifurcation region as well as overall mean CIMT even after adjustment for traditional cardiovascular risk factors.

The bifurcation region is particularly susceptible to the pro-atherogenic effect of chronic inflammation, because the low endothelial shear stress environment enables the attachment and infiltration of inflammatory cells [60–62]. Previously, we found that in HIV-infected individuals, higher plasma CRP was associated with more rapid CIMT progression in the bifurcation region [40]. Our current finding that higher plasma IL-6 is independently associated with greater CIMT in the bifurcation region further supports the role of chronic inflammation in the pathogenesis of atherosclerosis in treated HIV-infection.

In this study, higher monocyte CCR5 expression was associated with greater common carotid IMT. CCR5 is a chemokine receptor that is expressed on the surface of monocytes, macrophages and endothelial cells. CCR5 and its ligands CCL3, CCL4 and CCL5 have been implicated in the pathogenesis of atherosclerosis [63–65]. CCR5 antagonism or deletion was associated with reduced plaque size in murine models of atherosclerosis (reviewed by [63]). Furthermore, CCR5 mRNA expression was also associated with progression in carotid IMT in HIV-infected individuals [43]. Frequency of $CCR5^{+}$ monocytes has also been correlated with plasma IL-6 and D-dimer levels in HIV-infected individuals [66].

Even though therapeutic agents against IL-6 (tocilizumab) and CCR5 (maraviroc or cenicriviroc) are available or under investigation, their potential use to reduce risks of atherosclerosis is unclear at this stage. Tocilizumab use in individuals with rheumatoid arthritis was associated with significant adverse effects and worsening of lipid profile [67, 68]. Maraviroc intensification in HIV-infected individuals on ART with suppressed viral load has been associated with reduced immune activation [69], however increases in immune activation including $CD4^+$ and $CD8^+$ T cell activation and plasma sCD14 levels have also been found [70].

In our study, no independent associations were found between CIMT and markers of T cell activation and senescence, different monocyte subpopulations based on CD16 expression or other soluble markers of inflammation and coagulopathy such as CRP, D-dimer, sCD14, sCD163, in accordance with other studies that also noted similar negative results [35, 38, 59, 71].

Despite that only 2 of the 12 deaths in our cohort were due to CVD, higher plasma IL-6 and greater internal carotid and mean IMT were individually associated with all-cause mortality even after adjustment for traditional CVD risk factors, $CD4^+$ T cell count at CIMT measurement and hepatitis C co-infection. Higher IL-6 has been associated with all-cause mortality in HIV-infected individuals [25]. Our study incorporates non-invasive imaging, namely, carotid IMT as a predictor of mortality in HIV. To our knowledge, only one previous study has reported the association between carotid IMT and mortality in HIV-infected individuals [72]. Of note, this older study only evaluated hsCRP. Our finding that higher plasma IL-6 and greater internal carotid and mean IMT were individually associated with all-cause mortality likely reflects the important role of immune activation and inflammation in the pathogenesis of cardiovascular disease [18, 19] and malignancies [73, 74], major contributors to serious non-AIDS events (SNAEs) and mortality [75]. The associations between plasma IL-6, internal carotid and mean IMT and all-cause mortality have potential implications for the use of biomarkers and non-invasive imaging for identifying high-risk individuals in the future.

Given the cross-sectional nature of our study, causality cannot be established. Additionally, our cohort included a low proportion of women. However, our cohort is representative of the HIV-infected individuals who are in care in developed countries. Participants in our cohort had a long duration of HIV infection, significant CD4 depletion prior to ART initiation followed by a substantial period of time on ART and immune recovery, and had suppressed viral load at the time of carotid IMT and markers of immune activation measurement. Furthermore, over 60% of our participants had at least one CV risk factor and over 30% had two or more. This high prevalence of CV risk factors is consistent with other HIV-infected cohorts reported in the literature [4, 9], suggesting that our findings should be generalizable to male HIV populations in western countries.

In summary, we found that higher monocyte CCR5 expression was independently associated with greater common carotid IMT. Higher plasma IL-6 levels were also independently associated with greater IMT at the bifurcation region and overall mean IMT. Furthermore, higher plasma IL-6 levels, greater internal carotid and mean IMT were individually

associated with all-cause mortality, suggesting that innate immune activation and inflammation is important in atherogenesis and pathogenesis of SNAEs in HIV-infected individuals. The impact of therapies targeting immune activation and inflammation on CVD in HIV merits additional investigation.

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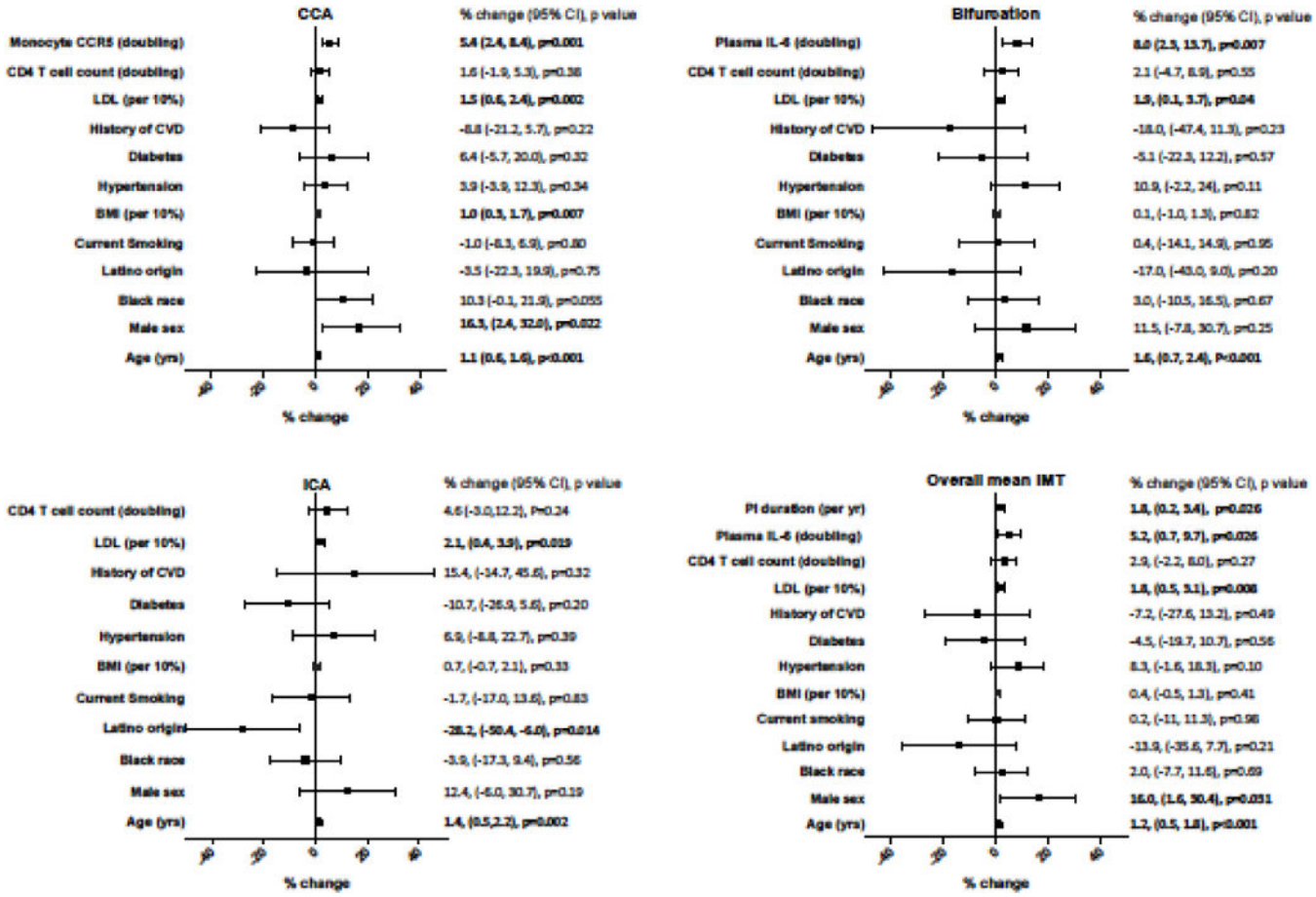

Figure 1.

Multivariate analysis of factors associated with IMT (intima media thickness) at the common carotid (CCA), bifurcation, internal carotid (ICA) and overall mean IMT. Estimates (95% CI, confidence interval) of % change in IMT were calculated from linear regression models with robust standard error. Candidates for the multivariable model were selected using the LASSO (Least Absolute Shrinkage and Selection Operator) procedure with adjustment for traditional cardiovascular risk factors including age, gender, race, current smoking, BMI (body mass index), hypertension, diabetes, history of CVD (cardiovascular disease, coronary artery disease and/or cerebrovascular disease) and LDL (low-density lipoprotein) as well as $CD4^+$ T cell count at time of CIMT measurement. Significant associations, P<0.05 are in bold.

Table 1

Demographic and clinical characteristics of HIV-infected participants.

Participants (n)	149
Age, median years (IQR)	48.5 (43.9–54.4)
Male (%)	138 (92.6)
Race	
White (%)	100 (67.1)
Black (%)	30 (20.1)
Latino (%)	9 (6)
Other (%)	10 (6.7)
Current Smoking (%)	38 (25.5)
History of CVD (%)	9 (6)
Diabetes (%)	10 (6.7)
Hypertension (%)	51 (34.2)
Anti-hypertensive drugs (%)	46 (30.9)
LDL, median mg/dL (IQR)	110 (90–134)
Triglyceride median mg/dL (IQR)	142.5 (95.5–242)
Hypercholesterolemia (%)	63 (42.6)
Cholesterol lowering drugs (%)	58 (39.2%)
BMI	24.7 (22.6–27.9)
Duration of HIV infection, median yrs (IQR)	15.2 (10.9–18.6)
Duration of ART, median yrs (IQR)	8.1 (4.6–11.4)
Nadir CD4 count, median cells/μL (IQR)	140 (32–250)
CD4 count at CIMT measurement, median cells/μL (IQR)	522 (325–726)
HIV VL <75 copies/mL at CIMT measurement (%)	149 (100%)

Data are presented as median (IQR) or numbers (percent).

IQR, interquartile range; CVD, cardiovascular disease (coronary artery disease and/or cerebrovascular disease); Hypertension, two consecutive blood pressure readings with either systolic >140 mmHg or diastolic >90 mmHg; LDL; low-density lipoprotein; Hypercholesterolemia, LDL>160 mg/dL; BMI, body mass index; HIV VL, HIV viral load; CIMT, carotid intima media thickness

Table 2

Summary of measurements of carotid IMT and markers of immune activation, inflammation and coagulopathy (n=149).

Carotid IMT measurements	**Median (IQR)**
Common Carotid IMT (mm)	0.8 (0.7–1.0)
Carotid bifurcation IMT (mm)	1.2 (1.0–1.6)
Internal Carotid IMT (mm)	0.9 (0.7–1.1)
Overall mean Carotid IMT (mm)	1.0 (0.8–1.2)
Presence of plaque (n, %)	80 (53.7)
Markers of T cell activation	
CD4:CD8 ratio	0.58 (0.35–0.78)
% HLA-DR^{+}CD38^{+} CD4^{+} T cells	2.40 (1.78–3.71)
% CD28^{-}CD57^{+} CD4^{+} T cells	3.02 (1.28–7.75)
% CX3CR1^{+} CD4^{+} T cells	3.92 (1.61–9.27)
% HLA-DR^{+}CD38^{+} CD8 T cells	6.90 (4.66–11.35)
% CD28^{-}CD57^{+} CD8 T cells	39.00 (30.05–46.50)
% CX3CR1^{+} CD8 T cells	41.20 (31.15–49.90)
Monocyte subsets	
% CD14^{++}CD16^{-} Monocytes	86.70 (83.6–89.95)
% CD14^{+}CD16^{+} Monocytes	5.78 (3.80–7.55)
% CD14^{dim} CD16^{+} Monocytes	3.60 (2.30–5.63)
% CX3CR1^{+} Monocytes	6.00 (4.04–8.63)
% CCR2^{+} Monocytes	91.00 (87.95–93.80)
% Tissue Factor^{+} Monocytes	0.30 (0.24–0.39)
CCR5 Median Fluorescent Intensity	614 (530–698)
Soluble (plasma) markers of inflammation and coagulopathy	
IL-6 (pg/mL)	1.02 (0.71–1.64)
CRP (mg/L)	1.57 (0.76–3.95)
sCD14 (μg/mL)	1.83 (1.55–2.16)
sCD163 (ng/mL)	475 (343–633)
D-dimer (mg/L)	0.32 (0.22–0.47)
sTissue Factor (pg/mL)	70.94 (51.28–95.66)

Data are presented as median (IQR) or numbers (percent).

IMT, intima media thickness; IQR interquartile range.

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Table 3

Univariate analysis of associations of markers of immune activation, inflammation and coagulopathy with IMT

	Common carotid IMT		Bifurcation region IMT		Internal carotid IMT		Overall mean IMT	
	% change (95% CI)	P value	% change (95% CI)	P value	% change (95% CI)	P value	% change (95% CI)	P value
T cell activation								
CD4:CD8 ratio[#]	0.11 (−0.7, 0.9)	0.80	0 (−1.1, 1.2)	0.96	0.4 (−0.8, 1.6)	0.55	0.2 (−0.7, 1.1)	0.62
HLA-DR$^+$CD38$^+$ CD4$^+$ T cells[§]	−2.4 (−7.7, 3.4)	0.41	−2.4 (−9.5, 5.3)	0.53	−5.8 (−12.5, 1.3)	0.11	−3.7 (−9.5, 2.6)	0.24
CD28$^-$CD57$^+$ CD4$^+$ T cells[§]	1.2 (−0.3, 2.6)	0.12	**2.4 (0.2, 4.7)**	**0.035**	1.5 (−0.9, 3.9)	0.23	1.7 (−0.1, 3.5)	0.065
CX3CR1$^+$ CD4$^+$ T cells[§]	0.7(−1.3, 2.8)	0.50	1.4 (−1.7, 4.6)	0.39	0.1 (−3.3, 3.7)	0.95	0.8 (−1.8, 3.4)	0.55
HLA-DR$^+$CD38$^+$ CD8$^+$ T cells[§]	2.1 (−2.3, 6.7)	0.36	−1.4 (−7.6, 5.2)	0.67	−0.2 (−6.4, 6.5)	0.95	0 (−5.2%, 5.4)	1.0
CD28$^-$CD57$^+$ CD8$^+$ T cells[§]	3.9 (−1.3, 9.4)	0.15	7.8 (−0.5, 16.9)	0.068	3.8 (−4.1, 12.5)	0.36	5.9 (−0.6, 12.7)	0.079
CX3CR1$^+$ CD8$^+$ T cells[§]	2.1 (−2.5, 6.9)	0.37	4.1 (−3.4, 12.2)	0.29	1.8 (−5.3, 9.4)	0.63	2.9 (−2.8, 8.9)	0.33
Monocyte subsets								
CD14^{++}CD16$^-$ Monocytes[§]	−14.1(−38.1, 19.2)	0.36	−18.2(−52.0, 39.5)	0.46	2.3 (−40.5, 75.9)	0.93	−11.1 (−43.8, 40.6)	0.62
CD14$^+$CD16$^+$ Monocytes[§]	0.6 (−4.0, 5.5)	0.80	−1.9 (−8.9, 5.7)	0.63	−6.0 (−12.3, 0.7)	0.08	−2.3 (−7.9, 3.6)	0.44
CD14^{dim} CD16$^+$ Monocytes[§]	1.6 (−2.5, 5.8)	0.45	0.7 (−5.5, 7.2)	0.83	0.1 (−6.5, 7.2)	0.98	0.5 (−4.7, 5.9)	0.86
CX3CR1$^+$ Monocytes[§]	1.2 (−3.4, 6.1)	0.61	0.3 (−6.4, 7.5)	0.93	0.3 (−6.9, 8.1)	0.93	0.0 (−5.6, 5.8)	0.99
CCR2$^+$ Monocytes[§]	−27.9 (−49.5, 2.9)	0.073	−30.9 (−62.4, 27)	0.24	−16.2 (−52.3, 48.8)	0.55	−24.6 (−54.3, 24.5)	0.27
Tissue Factor$^+$ Monocytes[§]	−1.6 (−8.0, 5.2)	0.63	−2.9 (−12.2, 7.3)	0.56	−7.8 (−16.5, 1.7)	0.11	−4.0 (−11.4, 3.9)	0.31
CCR5 MFI[§]	**18.3 (6.1, 32.0)**	**0.003**	5.7 (−11.3, 25.8)	0.54	−2.5 (−17.6, 15.5)	0.77	6.5 (−7.2, 22.3)	0.37
Soluble markers of inflammation and coagulopathy								
Plasma IL-6[§]	**4.1 (0.5, 7.7)**	**0.027**	**7.3 (1.9, 13.0)**	**0.008**	3.6 (−1.8, 9.2)	0.20	**5.9 (1.8, 10.2)**	**0.005**
Plasma CRP[§]	0.6 (−1.2, 2.4)	0.52	−0.3 (−2.9, 2.4)	0.82	−0.1 (−3.0, 2.9)	0.95	0 (−2.1, 2.2)	1.0
Plasma sCD14[§]	−6.6 (−15.6, 3.5)	0.2	−0.7 (−13.9, 14.6)	0.93	−4.9 (−19.5, 12.3)	0.55	−3.6 (−14.9, 9.2)	0.56
Plasma sCD163[§]	−1.6 (−6.7, 3.8)	0.56	1.1 (−5.8, 8.4)	0.77	−3.0 (−9.6, 4.2)	0.41	−0.4(−6.1, 5.6)	0.89
Plasma D-Dimer[§]	2.2 (−1.4, 5.9)	0.24	4.9 (−2.7, 13.1)	0.22	0.1 (−7.7, 8.7)	0.98	3.1 (−3.2, 9.8)	0.34
Plasma Tissue Factor[§]	4.6 (−0.9, 10.4)	0.11	6.8 (−0.5, 14.6)	0.07	0.9 (−7.1, 9.5)	0.84	4.7 (−1.6, 11.4)	0.15

Estimates (95% CI, confidence interval) of % change in IMT (intima media thickness) were calculated from linear regression models with robust standard error.

per 10% increase;

§ per doubling; MFI, median fluorescence intensity. Significant associations P<0.05 are in bold.