PRELIMINARY COMMUNICATION

Arterial Inflammation in Patients With HIV

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Context Cardiovascular disease is increased in patients with human immunodeficiency virus (HIV), but the specific mechanisms are unknown.

Objective To assess arterial wall inflammation in HIV, using ^{18}fluorine-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG-PET), in relationship to traditional and nontraditional risk markers, including soluble CD163 (sCD163), a marker of monocyte and macrophage activation.

Design, Setting, and Participants A cross-sectional study of 81 participants investigated between November 2009 and July 2011 at the Massachusetts General Hospital. Twenty-seven participants with HIV without known cardiac disease underwent cardiac ^{18}F-FDG-PET for assessment of arterial wall inflammation and coronary computed tomography scanning for coronary artery calcium. The HIV group was compared with 2 separate non-HIV control groups. One control group (n=27) was matched to the HIV group for age, sex, and Framingham risk score (FRS) and had no known atherosclerotic disease (non-HIV FRS-matched controls). The second control group (n=27) was matched on sex and selected based on the presence of known atherosclerotic disease (non-HIV atherosclerotic controls).

Main Outcome Measure Arterial inflammation was prospectively determined as the ratio of FDG uptake in the arterial wall of the ascending aorta to venous background as the target-to-background ratio (TBR).

Results Participants with HIV demonstrated well-controlled HIV disease (mean [SD] CD4 cell count, 641 [288] cells/μL; median [interquartile range] HIV-RNA level, <48 [<48 to <48] copies/mL). All were receiving antiretroviral therapy (mean [SD] duration, 12.3 [4.3] years). The mean FRS was low in both HIV and non-HIV FRS-matched control participants (6.4; 95% CI, 4.8-8.0 vs 6.6; 95% CI, 4.9-8.2; P=.87). Arterial inflammation in the aorta (aortic TBR) was higher in the HIV group vs the non-HIV FRS-matched control group (2.23; 95% CI, 2.07-2.40 vs 1.89; 95% CI, 1.80-1.97; P<.001), but was similar compared with the non-HIV atherosclerotic control group (2.23; 95% CI, 2.07-2.40 vs 2.13; 95% CI, 2.03-2.23; P=.29). Aortic TBR remained significantly higher in the HIV group vs the non-HIV FRS-matched control group after adjusting for traditional cardiovascular risk factors (P=.002) and in stratified analyses among participants with undetectable viral load, zero calcium, FRS of less than 10, a low-density lipoprotein cholesterol level of less than 100 mg/dL (<2.59 mmol/L), no statin use, and no smoking (all $P \leq .01$). Aortic TBR was associated with sCD163 level (P=.04) but not with C-reactive protein (P=.65) or D-dimer (P=.08) among patients with HIV.

Conclusion Participants infected with HIV vs noninfected control participants with similar cardiac risk factors had signs of increased arterial inflammation, which was associated with a circulating marker of monocyte and macrophage activation.

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Coronary artery disease (CAD) is significantly increased in patients infected with human immunodeficiency virus (HIV), but the specific mechanisms remain unknown.[1] Immunological modulations may play an important role in the pathogenesis of atherosclerosis in patients with HIV. Patients with HIV demonstrate a high prevalence of noncalcified coronary atherosclerotic lesions that are increased in association with markers of macrophage activation.[2] This is significant because infiltration of activated monocytes and macrophages into the endothelium contributes to the development of vulnerable atherosclerotic plaque susceptible to rupture.[3,4]

Positron emission tomography (PET) with ^{18}fluorine-2-deoxy-D-glucose (^{18}F-FDG-PET) is widely used for measurement of inflammation in the arterial wall. Accumulation of FDG in human atherosclerotic arteries correlates with the amount of immunohistochemical staining and gene expression for macrophage-specific markers, including CD68,[5-8] and is based on the fact that activated macrophages have an unusually high metabolic rate.[9-11]

Accordingly, we used ^{18}F-FDG-PET imaging to test the hypothesis that arterial wall inflammation is increased in

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patients with HIV compared with patients not infected with HIV with similar cardiac risk factors, in association with increased monocyte and macrophage activation.

METHODS

Study Participants

Eighty-one participants were investigated between November 2009 and July 2011. Twenty-seven participants infected with HIV without known cardiac disease underwent ^{18}F-FDG-PET and computed tomographic (CT) imaging. Data from patients with HIV infection were obtained as part of the screening process for NCT00965185. The participants with HIV were prospectively enrolled and had no known coronary disease at the time of imaging. Participants with HIV were receiving stable doses of antiretroviral therapy (ART) for at least 3 months before the time of the study. Exclusion criteria for the participants with HIV consisted of known cardiac disease or symptoms suggestive of cardiovascular or atherosclerotic disease (myocardial infarction, angina, arrhythmias, valvular heart disease, pericarditis, congestive heart failure, stroke, and peripheral vascular disease), use of statins, or recent acute infection.

Two separate non–HIV-infected control groups were selected prospectively for comparison with the HIV group from a large database of 15 587 participants and had undergone whole body PET-CT scans between 2005 and 2010, but in whom neither aortic FDG uptake nor coronary artery calcium (CAC) had been previously assessed. The primary indication for PET scan imaging for those patients was evaluation for neoplastic process. However, in both control groups, we excluded any patients with active malignancy, presence of active systemic inflammatory disease or use of systemic corticosteroid therapy at the time of PET scan imaging, or known HIV.

The first control group, which consisted of 27 participants not infected with HIV, was selected based on the absence of known atherosclerotic disease and matching to the HIV group for age, sex, and Framingham risk score (FRS) (non-HIV FRS-matched controls) using a 1:1 case matching technique. In this regard, the first patient with HIV was considered with respect to age, sex, and FRS. The database was examined to find the first patient of the same age and sex, with an FRS within ±4 points to the index patient. Matches were found for all participants within this range except for 1. Only participants in whom all data to establish FRS risk were available were eligible for selection. Participants with known cardiac or atherosclerotic disease were not eligible for selection. This process was repeated to obtain a match for each patient with HIV.

The second group of 27 control participants was selected based on the presence of known atherosclerotic disease and matching to the HIV group by sex (non-HIV atherosclerotic controls). Known atherosclerotic disease was defined as the presence of either (1) documented atherothrombotic events (such as prior stroke, myocardial infarction, or limb ischemia) or (2) documented presence of occlusive atherosclerotic disease (such as carotid stenosis or peripheral artery disease) using a 1:1 case matching technique. The sex of the first patient with HIV was considered and the database was examined to find the first non-HIV control participant of this sex with known atherosclerotic disease for selection. This process was repeated to obtain a match for each patient with HIV.

The selection of control participants was performed based on clinical and demographic matching criteria above, prior to, and independent of determination of the aortic FDG uptake. After matching and participant selection were completed, arterial inflammation and coronary calcium were prospectively determined between April and July 2011. Written informed consent was obtained from all participants infected with HIV. Non–HIV-infected controls underwent scanning for clinical purposes and were not consented for the study, but permission was received from the Partners Healthcare institutional review board to use the data from participants in the clinical database for comparison in our study. We used the data in full compliance with the institutional review board and Health Insurance Portability and Accountability Act regulations.

^{18}F-FDG-PET Imaging

Participants underwent PET imaging after an overnight fast to reduce myocardial FDG uptake. The PET imaging was performed 3 hours after administration of 13 mCi of ^{18}F-FDG (Siemens ECAT Exact HR+PET or biograph 64 system)[12] among participants with HIV and as per-clinical protocol using similar methodology among control participants. The system provides 63 planes, a 15.5-cm field of view, and a maximum 4.2-mm intrinsic resolution at the center of the field of view. Images were acquired in 3 dimensional mode over 20 minutes with an effective resolution of 5 mm.

Measurement of Aortic FDG Uptake With PET

All image analysis was performed while blinded to clinical data. Coregistration of the PET and CT scan images was performed using anatomical landmarks (such as ascending aorta, left atrium, spine). The ascending aorta was chosen for measurement. The target-to-background ratio (TBR) was calculated by dividing the mean arterial standardized uptake value (SUV) by the mean venous SUV (FIGURE 1). The mean arterial SUV is derived from the average of the maximum SUV values in serial axial measurements.

Measurement of CAC on CT Scan

For patients with HIV, coronary calcification was evaluated using standardized methods as previously described.[14,15] Participants without HIV underwent hybrid PET-CT scans, and CAC score was determined using similar parameters. Low attenuation CT scanning was performed using a pitch of 1.0, tube voltage of 120 kVp, tube current of 40 mAs, and slice thickness of 3 mm. Prior studies have demonstrated that CAC scores measured on CT scan im-

ages obtained from a hybrid PET-CT scanner are comparable with those obtained on a dedicated CT scanner.[16] For the purpose of our study, after CAC score was recorded, the status of CAC was dichotomously characterized as present or absent. Evaluation of CAC score was performed while investigators were blinded to clinical information or PET data, by a separate group of investigators (E.C. and S.A.) from those who performed the PET analyses.

HIV Parameters and Markers for Monocyte/Macrophage Activation, Inflammation, and Hemostasis

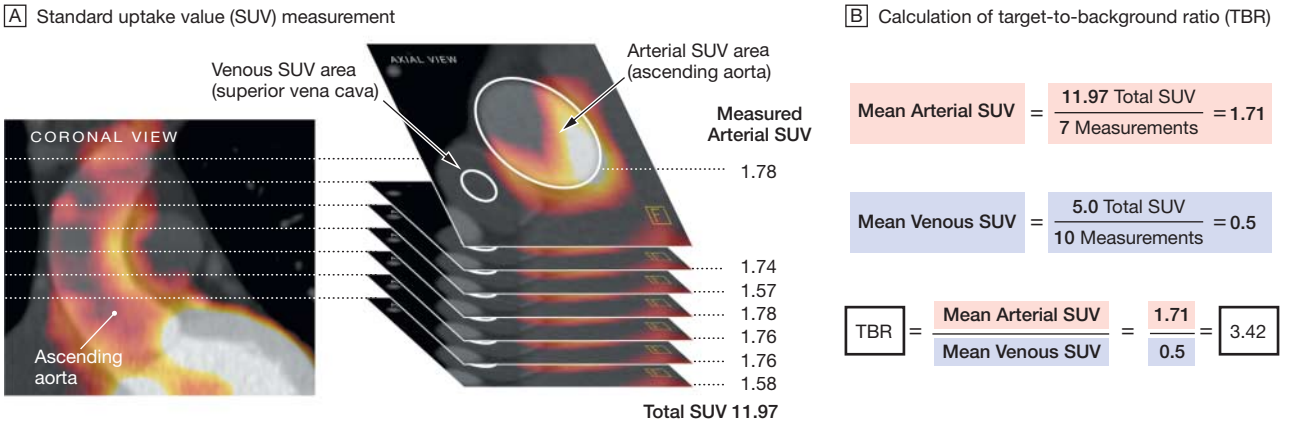
Participants infected with HIV were characterized in terms of immune function, inflammation, and monocyte and macrophage activation. HIV viral load was determined by ultrasensitive reverse transcriptase–polymerase chain reaction (Roche Amplicor Monitor; lower limit of detection = 48 copies/mL). HIV testing was performed by using enzyme-linked immunosorbent assay (Abbott) and confirmed by Western blot. CD4 cell count was assessed by flow cytometry. High-sensitivity C-reactive protein was measured by immunochemiluminometric assay (LabCorp). Soluble CD163 (sCD163) was measured from serum by enzyme-linked immunosorbent assay (Trillium Diagnostics).[2] D-dimer was measured using particle enhanced immunoturbidimetric assay (Roche Cobas).

Statistical Methods

Comparison of TBR with other variables in the 3 groups (HIV, non-HIV FRS-matched controls, and non-HIV atherosclerotic controls) was performed by using analysis of variance for normally distributed variables and the Kruskal-Wallis test for non–normally distributed variables. If the *P* value for the overall analysis of variance/Kruskal-Wallis test between groups was significant ($P < .05$), comparisons of variables between 2 groups were performed using *t* test for normally distributed continuous variables or the Wilcoxon rank sum test for non–normally distributed variables. For comparison of means, 95% confidence intervals are provided. Additional comparisons of TBR between the groups were performed in stratified analyses among those without CAC (calcium score of 0), low FRS (score, 0-10), a low-density lipoprotein cholesterol (LDL-C) level of less than 100 mg/dL (<2.59 mmol/L), not receiving a statin, not smoking, and limiting the HIV group for comparison to those with undetectable viral load. In addition, least squares multivariate regression modeling was performed to assess the differences in TBR between the HIV and non-HIV FRS-matched control groups simultaneously controlling for FRS, calcium score, smoking, statin use, and LDL-C in a single model among all patients in these 2 groups.

Pearson correlation coefficients were used to assess correlations for normally distributed data. For non–normally distributed variables, Spearman rho (ρ) was used to assess correlations and the *P* value was determined by the Hoeffdings D test. Two-tailed probability values are reported and statistical significance was assumed when $P < .05$. With 54 patients in each 2-group comparison, the study was powered at 85%, with a 2-sided significance level of .05, to detect a 0.83-SD difference between the groups. All statistical analyses were performed by using SAS JMP version 9.0.2 (SAS Institute). Complete data on all participants were available for PET-CT scans and cardiovascular disease (CVD) risk markers, as well as for CRP and sCD163 in the patients infected with HIV. D-dimer was available in a subset of patients with HIV (n = 14). No imputation was made for missing data.

Figure 1. Use of ^{18}F-FDG-PET/CT Imaging for Determination of Mean Arterial Target-to-Background Ratio (TBR)



^{18}F-FDG-PET indicates ^{18}fluorine-2-deoxy-D-glucose positron emission tomography; CT, computed tomography; SUV, standardized uptake value. The FDG uptake was measured from a point distal to the origin of coronary vessels to avoid myocardial spillover. ^{18}F-FDG-PET/CT imaging of the ascending thoracic aorta was performed according to validated, reproducible methods.[13] A, To determine the TBR of the aorta, regions of interest are drawn around the aorta in the axial position. This is repeated along the length of the aorta (every 5 mm along the long axis of the vessel). A mean arterial SUV is derived from the average of the maximum SUV values in serial axial measurements (1.71 in this example). The venous background SUV is derived from 10 measurements obtained in the superior vena cava. B, TBR is calculated by dividing the mean arterial SUV by the mean venous SUV (TBR = 3.42 in this example). The SUV is the decay-corrected tissue concentration of FDG (in kBq/mL) divided by the injected dose per body weight (kBq/g).

RESULTS

Participant Characteristics

The clinical characteristics of the HIV, non-HIV FRS-matched control, and non-HIV atherosclerotic control participants are shown in TABLE 1. Age was similar in the HIV and FRS-matched control groups and increased in the non-HIV atherosclerotic control group. All of the participants with HIV and all of the FRS-matched control participants demonstrated either low or intermediate FRS. Based on the matching, mean FRS was not significantly different between the HIV group and the FRS-matched control group (6.4; 95% CI, 4.8-8.0; vs 6.6; 95% CI, 4.9-8.2; $P=.87$). As expected, cardiovascular risk parameters were markedly increased and statin use was more prevalent in the non-HIV atherosclerotic control group. The majority of participants with HIV demonstrated well-controlled HIV disease (mean [SD] CD4 cell count, 641 [288] cells/μL) and virologic suppression (median [interquartile range {IQR}] HIV-viral RNA level, <48 [<48 to <48] copies/mL) (TABLE 2). The minimum duration of HIV infection was 5 years and mean (SD) duration of infection was 15.5 (5.7) years. The mean (SD) duration of treatment with ART was 12.3 (4.3) years (Table 2).

Arterial Inflammation in HIV and Non-HIV Control Groups

Arterial inflammation (TBR) in the aorta was higher in the HIV vs non-HIV FRS-matched controls (2.23; 95% CI, 2.07-2.40; vs 1.89; 95% CI, 1.80-1.97; $P<.001$) (Table 1 and FIGURE 2). In comparison, the arterial inflammation in the aorta was not significantly different between the HIV and the non-HIV atherosclerotic control group (2.23; 95% CI, 2.07-2.40; vs 2.13; 95% CI, 2.03-2.23; $P=.29$). The analysis was also repeated, limiting the comparison to those patients with HIV with undetectable viremia. The TBR of the aorta remained increased among the 21 patients with HIV with undetectable viremia (81%) compared with the 27 non-HIV FRS-matched control participants (2.24; 95% CI, 2.03-2.45; vs 1.89; 95% CI, 1.80-1.97; $P<.001$) (TABLE 3 and eTable 1, available at http://www.jama.com) and similar to that in the non-HIV atherosclerotic control group (2.24; 95% CI, 2.03-2.45; vs 2.13; 95% CI, 2.03-2.23; $P=.31$). The TBR of the aorta did not differ by use of ART class (protease inhibitor vs no protease inhibitor: 2.21; 95% CI, 2.03-2.39; vs 2.25; 95% CI, 1.98-2.52; $P=.81$; and nonnucleoside reverse transcriptase inhibitor vs no nonnucleoside reverse transcriptase inhibitor: 2.25; 95% CI, 1.94-2.56; vs 2.22; 95% CI, 2.07-2.37; $P=.84$). The TBR remained similar ($P=.82$) between the HIV group and the group with established CAD, controlling for age and statin use.

Stratified Analyses by Traditional Risk Factors

Calcium score was significantly higher in the non-HIV atherosclerotic control group compared with either the HIV or

Table 1. Demographic and Clinical Variables in the Study Groups[a]

Variables	Participants With HIV (n = 27)	Non-HIV FRS-Matched Control Participants (n = 27)	Non-HIV Atherosclerotic Control Participants (n = 27)	Overall *P* Value
Demographics				
Age, mean (95% CI), y	51.6 (49.5-53.6)	54.3 (51.1-57.5)	68.9 (65.3-72.6)[b,c]	<.001
Sex, male	25 (93)	25 (93)	25 (93)	>.99
FRS, mean (95% CI)	6.4 (4.8-8.0)	6.6 (4.9-8.2)	NA	.87
Current smoker	6 (22)	2 (7)	19 (70)[b,c]	<.001
Hypertension	5 (19)	4 (15)	24 (89)[b,c]	<.001
Hyperlipidemia	14 (52)	14 (52)	21 (88)[b,c] [n = 24]	.007
Statin use	0	7 (26)[b]	18 (67)[b,c]	<.001
Clinical atherosclerotic disease	0	0	27 (100)	
Traditional cardiovascular risk factors				
LDL-C, mean (95% CI), mg/dL	113 (103-123) [n = 26]	118 (106-131)	74 (62-86)[b,c] [n = 24]	<.001
HDL-C, mean (95% CI), mg/dL	48 (42-55)	53 (47-59)	44 (38-50)[c] [n = 17]	.14
Total cholesterol, mean (95% CI), mg/dL	192 (179-204)	194 (179-208)	147 (132-163)[b,c] [n = 17]	<.001
Triglycerides, median (IQR), mg/dL	121 (100-173)	96 (67-166) [n = 26]	80 (67-178)[b] [n = 17]	.07
Systolic BP, mean (95% CI), mm Hg	126 (120-131)	121 (114-127)	123 (117-129) [n = 26]	.45
Diastolic BP, mean (95% CI), mm Hg	79 (75-83)	76 (72-80)	72 (67-77)[b] [n = 21]	.04
Cardiac imaging parameters				
Target-to-background ratio, mean (95% CI)	2.23 (2.07-2.40)	1.89 (1.80-1.97)[b]	2.13 (2.03-2.23)[c]	<.001
Calcium score, median (IQR)	24.4 (0-92.6)	0 (0-4.8)[b] [n = 24]	425.2 (88.8-1234.3)[b,c] [n = 16]	<.001

Abbreviations: BP, blood pressure; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NA, not applicable.

SI conversions: To convert LDL-C, HDL-C, and total cholesterol to mmol/L, multiply by 0.0259; and triglycerides to mmol/L, multiply by 0.0113.

[a] Data are presented as No. (%) unless otherwise specified. For normally distributed variables, comparison among 3 groups performed using analysis of variance and comparison between 2 groups performed using *t* test. For non–normally distributed variables, comparison among 3 groups performed using Kruskal-Wallis test and comparison between 2 groups performed using Wilcoxon rank sum test. Hyperlipidemia was defined based on National Cholesterol Education Program Adult Treatment Panel III criteria.

[b] $P<.05$ vs participants with HIV.

[c] $P<.05$ vs non-HIV FRS-matched control participants.

non-HIV FRS-matched control groups (Table 1); however, the TBR of the aorta was not related to calcium score in univariate regression analysis among all participants ($P=.60$). Arterial inflammation in the aorta remained higher in the HIV group vs the non-HIV FRS-matched control group in stratified analyses limited to those participants with no coronary calcium ($P=.009$) (Table 3 and eTable 2), and separately among those participants with coronary calcium score of more than 0 ($P=.02$). Smoking rates were not significantly different between the HIV group and the non-HIV FRS-matched control group ($P=.12$). Moreover, aortic TBR was increased in the HIV group compared with the non-HIV FRS-matched control group in an analysis limited to nonsmokers (2.23; 95% CI, 2.04-2.43; vs 1.90; 95% CI, 1.81-1.99; $P=.001$) (Table 3; for additional smoking analysis, see eMethods and eTable 3). Similarly, arterial inflammation in the aorta remained higher in the HIV group vs the non-HIV FRS-matched control group in stratified analyses limited to participants with low FRS (score, 0-10), low LDL-C level (<100 mg/dL), and those patients not receiving statins (all $P \leq .01$) (Table 3, eTable 4, eTable 5, and eTable 6).

Table 2. HIV Disease–Related Parameters and Risk Factors in Participants With HIV[a]

Variables	Participants With HIV (n = 27)
HIV disease–related parameters	
Duration since HIV diagnosis, mean (SD), y	15.5 (5.7)
Currently taking ART	27 (100)
Duration of ART, mean (SD), y	12.3 (4.3) [n = 22]
Current PI treatment	11 (41)
Current NRTI treatment	26 (96)
Current NNRTI treatment	14 (52)
Current CD4 cell count, mean (SD), cells/μL	641 (288) [n = 26]
Nadir CD4 cell count, median (IQR), cells/μL	99 (50-250) [n = 25]
HIV-RNA level, median (IQR), copies/mL	<48 (<48 to <48) [n = 26]
Undetectable HIV-RNA level <48 copies/mL	21 (81) [n = 26]
Risk factors for HIV transmission[b]	
Men who have sex with men	17 (63)
Intravenous drug users	1 (4)
Heterosexual contact	2 (7)
Unknown	3 (11)
>1 Risk factor	4 (15)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.
[a] Data are presented as No. (%) unless otherwise specified.
[b] Risk factor data could be obtained from 24 patients (89% of the total 27 patients), 4 of whom had multiple risk factors for HIV transmission. More than 1 risk factor for HIV transmission included 2 for heterosexual contact and intravenous drug users, 1 for men who have sex with men and needlestick, and 1 for men who have sex with men and heterosexual contact.

Multivariate Regression Analysis of Cardiovascular Risk Factors

Adjusting simultaneously for traditional cardiovascular risk factors in a multivariate regression model, including FRS, statin use, calcium score, smoking, and LDL-C, aortic TBR remained higher in the HIV group compared with the non-HIV FRS-matched control group ($P=.002$). In contrast, traditional risk factors were not significant in the model (eTable 7).

Aortic TBR and Circulating Immune and Inflammatory Markers in Patients With HIV

The sCD163 level was higher in the HIV group in our study (median [IQR], 855 [451-1543] ng/mL; mean [SD], 1200 [988] ng/mL) than observed in a group of previously published comparable non-HIV control participants (median [IQR], 765 [572-1054] ng/mL; mean [SD], 883 [561] ng/mL).[2] The aortic arterial inflammation (TBR) significantly correlated with sCD163 levels ($P=.04$) (Table 4). In contrast with sCD163, high-sensitivity C-reactive protein and D-dimer were not significantly associated with aortic arterial inflammation (TBR) (Table 4). Limiting the analysis to the 21 patients with HIV with undetectable viral load (81%), sCD163 remained similarly and significantly associated with aortic TBR ($P=.03$) (Figure 3).

COMMENT

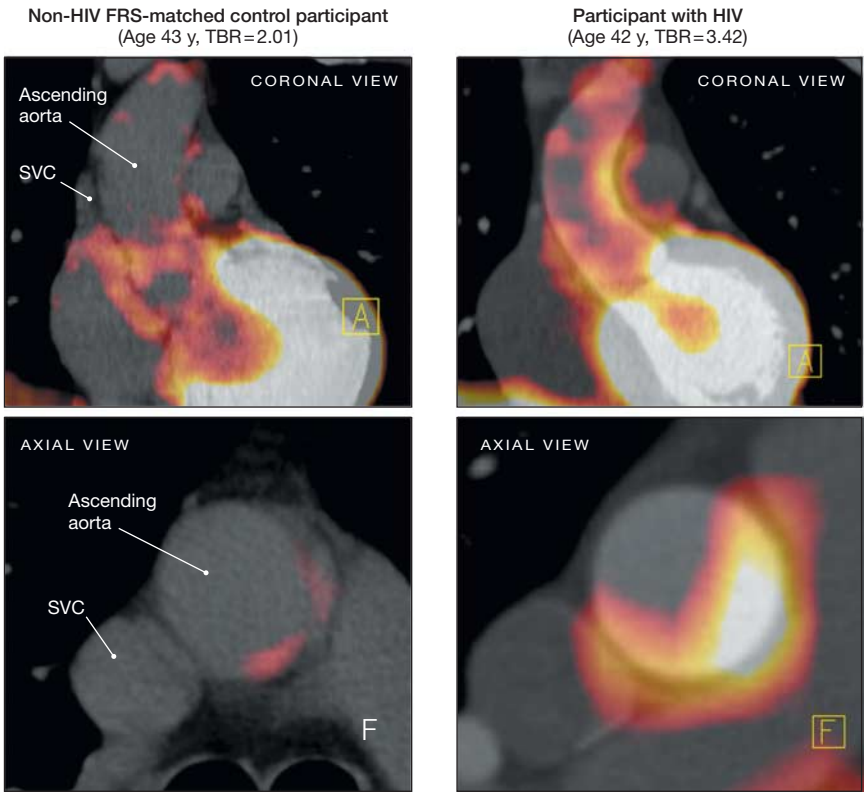
FDG accumulates within metabolically active macrophages infiltrating affected vessels such that increased FDG uptake reflects heightened vascular inflammation.[5-8] Indeed, through pathologic and histologic analyses of plaque specimens from participants with occlusive carotid disease who went on to receive carotid endarterectomy, studies have previously shown that arterial FDG uptake correlates closely with plaque macrophage infiltration characterized by increased CD68 staining.[5-8] Increased aortic FDG uptake is known to correlate with increased FDG uptake in the left main coronary artery.[17] Moreover, increased arterial FDG-PET uptake is associated with subsequent progression of atherosclerotic plaques[18] and identifies patients at risk for subsequent atherothrombotic events.[12,19] Hence, the signal that is observed likely reflects atherosclerotic inflammation with macrophage infiltration into arterial atheroma. The results from our study using the ^{18}F-FDG-PET technique suggest that macrophage infiltration and resulting arterial inflammation, measured here in the aorta, are increased among patients infected with HIV.

Our observation that HIV infection is associated with increased arterial inflammation, even among relatively young patients with HIV with low FRS and undetectable viremia, is concordant with the epidemiological observations that patients with HIV have a higher risk of stroke and myocardial infarction than patients without HIV[1,20] and demonstrates that this risk may not be measured adequately by traditional risk assessment tools, such as the FRS. Indeed, recent studies among patients

without HIV demonstrate that consideration of TBR can improve net reclassification index compared with use of FRS and traditional risk factors.[21] Moreover, these studies demonstrate that a TBR of more than 1.7 is associated with an approximate 40% reduction in CVD event-free survival over 3 years,[12] whereas a TBR of more than 2.25 (vs <1.84) is associated with a markedly increased risk of CVD events over 5 years.[21] These data suggest a clinically relevant degree of added CVD risk due to increased arterial inflammation in the HIV population studied herein.

One potential mechanistic link to this observation is suggested by our demonstration that a marker of monocyte and macrophage activation sCD163 was significantly associated with this inflammatory signal. CD163 is expressed specifically on the surface of monocytes and macrophages and has a known role as a scavenger receptor involved in the uptake of hemoglobin-haptoglobin complexes.[22] Soluble CD163 is shed via proteolytic cleavage at the cell surface and can be found in the circulation. Soluble CD163 has been previously shown as a circulating marker of atherosclerosis in patients without HIV.[23,24] Macrophages expressing CD163 have been found in human atherosclerotic plaques of patients without HIV[25] as well as within plaque lesions in simian immunodeficiency virus–infected monkey models.[26] In patients chronically infected with HIV, we have previously demonstrated sCD163 to be independently associated with increased noncalcified plaque among young, asymptomatic men.[2] We extend the observations further by observing a significant correlation between sCD163 and the extent of arterial inflammation. In contrast, markers of generalized inflammation (high-sensitivity C-reactive protein) and thrombosis (D-dimer) were not statistically significant in terms of their relationships to vascular inflammation in our study. Hence, in HIV, macrophage activation markers correlate with noncalcified plaques and arterial wall inflammation, 2 separate predictors of subsequent atherothrombosis. These observations suggest that sCD163 may be able to uniquely provide an index of risk of atherosclerotic disease in HIV. For example, in our study, we show that among patients infected with HIV, a sCD163 level of more than 800 ng/mL is associated with a markedly increased TBR of more than 2.3. Further studies are needed to determine if the

Figure 2. Representative ^{18}F-FDG-PET/CT Imaging of the Aorta



^{18}F-FDG-PET indicates ^{18}fluorine-2-deoxy-D-glucose positron emission tomography; CT, computed tomography; FRS, Framingham risk score; HIV, human immunodeficiency virus; SVC, superior vena cava; TBR, target-to-background ratio. There is increased aortic PET-FDG uptake (red coloration) in a participant infected with HIV compared with a non-HIV FRS-matched control participant. Neither participant had known heart disease. For each participant, the FRS was low with a score of 2 and calcium was not present on the cardiac CT scan. Neither participant was receiving a statin. A indicates anterior-posterior orientation and F, foot-head orientation.

Table 3. Target-to-Background Ratio in Stratified Analyses

	Participants With HIV		Non-HIV FRS-Matched Control Participants		
	Sample Size, No.	Mean (95% CI)	Sample Size, No.	Mean (95% CI)	*P* Value[a]
No coronary calcium	10	2.30 (1.92-2.69)	18	1.91 (1.81-2.01)	.009
Low FRS (0-10)	21	2.24 (2.05-2.43)	23	1.92 (1.83-2.00)	.002
Low LDL-C (<100 mg/dL)	8	2.30 (2.09-2.52)	6	1.91 (1.65-2.17)	.01
No statin use	27	2.23 (2.07-2.40)	20	1.88 (1.79-1.97)	.001
No smoking	21	2.23 (2.04-2.43)	25	1.90 (1.81-1.99)	.001
Undetectable viral load in the HIV-infected group	21	2.24 (2.03-2.45)	27	1.89 (1.80-1.97)	<.001

Abbreviations: FRS, Framingham risk score; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol.
[a] Comparison between 2 groups by *t* test.

demonstration of an increased sCD163 level in clinical practice will predict events and provide unique information to that of traditional risk indices.

One hundred percent of the patients with HIV studied were receiving ART and had been receiving such therapy for a long duration of approximately 12 years. A significant majority had undetectable HIV viral load. Viral load was not related to TBR and the observation of markedly increased TBR in HIV was confirmed in the subset with undetectable viremia. Thus, the observation of increased vascular inflammation by PET occurred in well-treated patients in whom significant detectable viremia was neither present nor likely to be a contributing factor. In contrast, increasing degrees of monocyte activation even within this well-controlled group were associated with increased arterial inflammation. The patients we studied are similar to the majority of patients undergoing treatment with ART today, with well-controlled virus and absent history of CVD. Such patients, particularly with low FRS, are not considered to be at high risk for CVD, yet such patients have increased arterial wall inflammation, equal to that of patients without HIV with established CAD.

Coronary artery calcium was higher in patients not infected with HIV with established CAD than in the HIV group. This difference may be due to the increased rate of traditional CVD risks in the atherosclerotic controls compared with the HIV group. The degree of inflammation is similar between the HIV group with very little CAC and low FRS and the established CAD group with significant CAC and traditional risks, suggesting that inflamed noncalcified plaque related more to nontraditional risk factors is likely to be present in the HIV group. Over time, the increased inflammation observed in the HIV group might itself induce an increase in CAC.

Our study design limits definitive conclusions regarding causality of increased inflammation, but our data suggest monocyte and macrophage activation may be contributing. We cannot completely rule out an effect of ART directly on arterial inflammation, but evidence from INSIGHT SMART[27] and STACCATO[28] study groups showing that ART decreases inflammation and endothelial activation, the lack of any ART class effect in our data, and the low traditional risk factors in our group on ART (ruling out an indirect effect) make this unlikely. We included a relatively small proportion of women; thus our findings may not be fully generalizable to women. Additionally, although the HIV population was prospectively identified, the control groups were subsequently selected from a database of imaged individuals. However, the analysis of aortic TBR was identical for all participants in the study, was performed only after matching and participant selection, and was performed blinded to clinical history. The study was adequately powered to detect a clinically relevant 0.83 SD difference between the study groups.

Our study demonstrates that HIV is associated with a high degree of inflam-

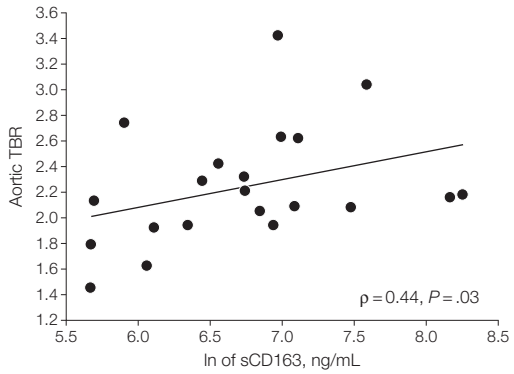
Table 4. Correlations of sCD163 and Other Inflammatory Parameters With Aortic TBR in Participants With HIV[a]

	Participants With HIV	Sample Size, No.	Correlation With Aortic TBR	*P* Value
HIV disease–related parameters				
Current CD4 cell count, mean (SD), cells/μL	641 (288)	26	r = –0.02	.91
Nadir CD4 cell count, median (IQR), cells/μL	99 (50-250)	25	ρ = –0.29	.12
HIV-RNA level, median (IQR), copies/mL	<48 (<48 to <48)	26	ρ = –0.04	>.99
Marker of monocyte/macrophage activation				
sCD163, median (IQR), ng/mL	855 (451-1543)	27	ρ = 0.31	.04
Markers of generalized inflammation and hemostasis				
hs-CRP, median (IQR), mg/L	1.2 (0.4-3.6)	27	ρ = –0.04	.65
D-dimer, mean (SD), ng/mL	246 (100)	14	r = 0.48	.08

Abbreviations: HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; sCD163, soluble CD163; TBR, target-to-background ratio.

[a]Relationships between continuous variables reported by Pearson correlation coefficient (r) for normally distributed variables and by Spearman ρ and Hoeffding D test for non–normally distributed variables.

Figure 3. Linear Regression of Aortic Target-to-Background Ratio (TBR) vs ln of sCD163 in 21 Patients With HIV With Undetectable Viral Load



HIV indicates human immunodeficiency virus; ln, natural logarithm; sCD163, soluble CD163. Solid line represents the linear regression fit across all 21 patients (aortic TBR = 0.8 + 0.22 × ln sCD163). A sCD163 level of more than 800 ng/mL corresponds with a ln of more than 6.7 and an aortic TBR of more than 2.3.

mation within the arterial wall, even in patients with low FRS and well-controlled viremia. These findings advance our understanding of the unique pathophysiology and predilection to early increased CVD among patients infected with HIV and suggest that monocyte and macrophage activation could play a critical role in the early expression of subclinical atherosclerosis in patients with HIV. These data have clinical relevance and suggest that patients with HIV with chronic infection have significant vascular inflammation, and thus added CVD risk, beyond that estimated by traditional risk factors. This information should now be considered in determining optimal monitoring and CVD prevention strategies for this group. Future studies will be useful to further investigate unique immune-based mechanisms of arterial inflammation and potential agents to reduce the proatherogenic activation of monocytes and macrophages with hopes of reducing risk of atherothrombosis in patients infected with HIV.

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Acquisition of data: Subramanian, Tawakol, Burdo, Abbara, Wei, Vijaykumar, Corsini, Hoffmann, Williams, Lo, Grinspoon.
Analysis and interpretation of data: Subramanian, Tawakol, Burdo, Abbara, Wei, Vijaykumar, Corsini, Abdelbaky, Zanni, Hoffmann, Williams, Lo, Grinspoon.
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