Association of HIV Viral Load with Monocyte Chemoattractant Protein-1 and Atherosclerosis Burden Measured by Magnetic Resonance Imaging

Michelle A. Floris-Moore, MD, MS[1], **Zahi A. Fayad, PhD**[2,3], **Joan W. Berman, PhD**[4], **Venkatesh Mani, MD**[2], **Ellie E. Schoenbaum, MD**[5,6], **Robert S. Klein, MD**[7,8], **Karen B Weinshelbaum, BA**[9], **Valentin Fuster, MD, PhD**[3], **Andrea A. Howard, MD, MS**[5,6], **Yungtai Lo, PhD**[8], and **Alison D. Schecter, MD**[3]

[1]Division of Infectious Diseases, University of North Carolina School of Medicine, Chapel Hill, NC

[2]Department of Radiology, Mount Sinai School of Medicine, New York, NY

[3]Department of Medicine, Mount Sinai School of Medicine, New York, NY

[4]Department of Pathology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

[5]Department of Epidemiology & Population Health, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

[6]Department of Medicine, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

[7]Division of Infectious Diseases, Mount Sinai School of Medicine, New York, NY

[8]Institute of Epidemiology, Biostatistics and Disease Prevention, Mount Sinai School of Medicine, New York, NY

[9]Mount Sinai School of Medicine, New York, NY

Introduction

Highly active antiretroviral therapy (HAART) has markedly increased life expectancy among persons infected with HIV. As HIV-infected persons age, chronic diseases like atherosclerosis have become increasingly important in their healthcare. Use of HAART has been linked to dyslipidemia and insulin resistance, well-established risk factors for atherosclerosis.[1-3] Individuals infected with HIV may also be at risk for vascular disease secondary to direct viral effects which induce chronic immune activation leading to increased expression of pro-inflammatory mediators by activated T cells and macrophages within the vasculature.[4,5]

Corresponding Author: Michelle Floris-Moore, MD, MS, Division of Infectious Diseases, University of North Carolina at Chapel Hill, 130 Mason Farm Road, CB 7030, Chapel Hill, NC 27599-7030. Tel: (919)966-4733; Fax: (919)966-6714; mfloris@med.unc.edu.

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Several pro-inflammatory cytokines and chemokines associated with HIV infection are linked to atherosclerosis, and may participate in vascular dysfunction in infected individuals. Monocyte chemoattractant protein-1 (MCP-1/CCL2) plays a crucial role in the pathogenesis of atherosclerosis, attracting monocytes into the arterial intima where they differentiate into macrophages, accumulate lipoproteins and become lipid-laden foam cells.[6] We previously demonstrated that human arterial smooth muscle cells (SMC) express the chemokine receptors CXCR4 and CCR5, and that HIV-infected SMC are themselves a source of MCP-1/CCL2, and have shown that MCP-1/CCL2 induces tissue factor, a major contributor to thrombosis associated with plaque rupture, in vascular SMC.[7,8] These findings suggest that HIV infection promotes an inflammatory response in the vessel wall and may thereby accelerate atherosclerosis.

Studies examining relationships of HIV infection and HAART with carotid artery intima-media thickness (IMT) as a surrogate marker for atherosclerosis have had conflicting results. Some have found little association with HIV infection or specific classes of antiretrovirals, whereas others have reported greater IMT among HIV-infected subjects but no association with antiretrovirals, and yet others have shown greater IMT associated with protease inhibitors (PIs). [9-12] Carotid artery ultrasound enables imaging of exophytic plaque on the carotid artery wall and measures IMT. However ultrasound may be unable to detect early atheromatous changes, cannot image the adventitial layer to gauge outward remodeling, and is unable to assess atherosclerosis in the thoracic aorta. Magnetic resonance imaging (MRI) is a noninvasive imaging modality that detects early atheroma formation and allows more global assessment of vascular structure, including the aorta.[13,14]

To assess whether HIV infected individuals have increased serum markers of inflammation and increased atherosclerosis plaque burden, we measured MCP-1/CCL2 levels and performed MRI of the thoracic aorta and carotid arteries in a well-characterized sample of HIV-infected and demographically similar uninfected individuals.

Methods

Study Participants and Design

We performed a cross-sectional analysis of MCP-1/CCL2 levels and thoracic aorta and carotid artery vessel wall parameters, as measured by high-resolution MRI, among participants in two parallel prospective observational studies of aging among men (CHAMPS study) and women (Menopause Study) who were either HIV-infected or at risk for infection because of injection drug use or high-risk sex (sex with a drug user; exchanging sex for money/drugs; unprotected sex with a man who has sex with men; or ≥5sexual partners in the past five years). Participants were recruited from the community in the Bronx, New York between September 2001 and July 2003. The study designs have been previously described in detail.[15,16] In brief, participants attended semi-annual research visits for standardized interviews, blood analysis, measurement of weight, height, and blood pressure, and carotid ultrasound to measure IMT.

From April 2005 to December 2006, participants with common carotid artery IMT of ≥0.7 mm (the minimum thickness required for optimal resolution of the vessel wall on MRI) were enrolled in a sub-study using MRI to characterize the vessel wall and detect atherosclerotic plaque in the carotid arteries and thoracic aorta. Participants eligible for the MRI sub-study were ≥45 years old and were not taking lipid-lowering medications. Individuals with metallic implants or claustrophobia, and women who were pregnant, were excluded. The study was approved by Institutional Review Boards at Montefiore Medical Center, Albert Einstein College of Medicine, and Mount Sinai School of Medicine. All participants gave written informed consent.

Research Visits

Standardized semi-annual interviews collected data on socio-demographics, medical history, HIV disease status, antiretroviral and other medications, physical activity, past/current illicit drug use (frequency/route of cocaine and heroin use), and cigarette smoking. Hypertension was defined as systolic blood pressure ≥130 mm Hg/diastolic blood pressure ≥85 mm Hg, using the average of two measurements taken while the participant was sitting. Participants with known hypertension and current use of anti-hypertensive medications were defined as hypertensive regardless of measured blood pressure. Limb and trunk fat were measured by dual X-ray absorptiometry (DEXA) scans using a GE Lunar Prodigy densitometer, Version 6.8 (Madison, Wisconsin, USA).

Assays

Blood was obtained for T-lymphocyte subset assays, HIV-1 viral load, MCP-1/CCL2 levels, hepatitis C virus antibody and RNA, and lipoprotein levels. Plasma was separated within 20 minutes of collection and stored at -70°C. Previously unthawed specimens were used for MCP-1/CCL2 assays. Levels of MCP-1/CCL2 were measured by sandwich enzyme-linked immunosorbent assay (Duoset ELISA, R & D Systems, Minneapolis, MN) with a sensitivity of 4 pg/mL. Blood was analyzed for CD4+ lymphocyte studies using flow cytometry and for HIV viral load by b-DNA assay (lower limit of detection 75 copies/ml). HIV serology was repeated at every visit for HIV-seronegative participants. Hepatitis C virus antibody testing was performed using enzyme immunoassay (ELISA 3.0, Ortho Diagnostic Systems, Rochester, NY). For HCV seropositive participants, HCV RNA was quantified by VERSANT HCV RNA assay (Bayer Corporation, Tarrytown, NY, lower limit of detection 615 IU/mL).

Lipoprotein levels were assayed by routine laboratory techniques using blood drawn following a 10-12 hour overnight fast.[17] Low-density cholesterol (LDL-C) levels were measured directly (Olympus Diagnostics, Olympus America Inc., Melville, NY). Participants without known diabetes underwent oral glucose tolerance testing, using a 75-g glucose beverage. Impaired glucose tolerance and diabetes mellitus were defined using American Diabetes Association criteria.[18]

Carotid Ultrasound

High-resolution B-mode carotid ultrasound scans were performed by a single technician with the participant supine. A Phillips ATL HDI 5000 ultrasound unit (Advanced Technology Laboratories, Bothell, Washington, USA) was used, with a linear L 7-4 broad band transducer and software optimized for carotid examinations. Right and left common carotid artery IMT measurements were obtained from the region of maximal wall thickness, within the distal 10mm of each common carotid artery. Three measurements of the far vessel wall were obtained on transverse cross-sectional views by a single radiologist using the instrument's electronic caliper, each measurement taken perpendicular to the curvature of the vessel wall. Three longitudinal views were also obtained. Mean IMT for each vessel was calculated by averaging the 3 measurements. The technician and radiologist were blinded to participants' HIV status.

MR Imaging

Non-contrast-enhanced MRI was performed on a 1.5T whole body MR system (Siemens Sonata, Erlangen Germany). A custom-built four-element phased array coil was used for carotid imaging. The six-element spine array and a two-channel anterior body coil were used for aortic imaging. After localization with a fast-gradient-echo sequence, all images were obtained by rapid extended coverage, double-inversion recovery (i.e., black-blood) turbo-spin-echo technique.[19] Carotid and abdominal aorta images were acquired without cardiac

triggering and free breathing; thoracic aorta images were acquired with ECG gating and breath hold where possible. Proton density (PD), T1 and T2 weighted images were acquired.

For carotid artery imaging, 24 transverse images centered at the carotid bifurcation were obtained with the following parameters: repetition time 2130ms/ 2130ms/900ms (PD/T2/ T1 images); echo time, 5.6/56/5.6ms (PD/T2/ T1 images); field of view, 12 cm; slice thickness, 3mm; 10% inter-slice gap; acquisition matrix, 256 x 256; no phase wrap; number of signal averages 2/4/3 (PD/T2/ T1 images); turbo factor (echo train length), 15/15/3 (PD/T2/ T1 images); receiver bandwidth, 488 Hz/pixel; no zero filling. 12 slices were acquired simultaneously with 4 dark-blood blocks. Inversion time was 157 ms. A chemical shift suppression pulse was used to suppress signal from fat. For the thoracic aorta, 16 to 32 transverse images were obtained from the origin of the left subclavian artery to the diaphragm. Imaging parameters were similar to carotid imaging, except: ECG gating was used; repetition time, 2RR intervals/ 2RR intervals/ 1RR interval (PD/T2/ T1 images); slice thickness, 5mm; 16 slices acquired simultaneously with 4 dark-blood blocks (above the level of the ventricles); 4 slices acquired simultaneously with 2 dark-blood blocks for mid-ventricular images; turbo factor, 31; inversion time, 450ms. The total examination lasted approximately 60 minutes.

The MR images were transferred to a dedicated computer for further planimetric analysis. Vessel wall dimensions were calculated by semi-automatic tracing, using computer-assisted morphometric analysis of cross-sectional MR images (Image Pro-Plus, Media Cybernetics, Carlsbad, CA). The tracing tool works by following an edge of significant contrast. Minimal, maximal and mean vessel wall thickness (VWT) and vessel wall area (VWA) were measured. Measurements were performed blinded to the participants' HIV status.

Data Analysis

Statistical analyses were performed using STATA® (Version 9, StataCorp, College Station, TX) and SPSS® (base 15.0, SPSS Inc., Chicago, IL) software. Univariate analyses were performed using Student's t-test or Mann-Whitney test, as appropriate. Regression analysis examined linear associations of MCP-1/CCL2 with HIV viral load, CD4+ cell count and vessel wall parameters, adjusting for age, body mass index (BMI) and current cigarette smoking. Linear regression models were constructed for thoracic aorta and common carotid artery mean VWT and VWA, measured by MRI. Carotid artery measurements used were the average of mean values for the left and right common carotid arteries. The outcome variables were log-transformed to meet normality criteria for linear regression. Covariates examined in multivariate analyses were HIV and viral load status, PI use, MCP-1/CCL2, age, race/ethnicity, hypertension, diabetes mellitus/impaired glucose tolerance, LDL-C, HDL-C, total cholesterol:HDL-C ratio, BMI, cigarette smoking, physical activity, trunk and limb fat, and HCV status. Interaction terms were tested and model fit examined. Based on data from the Framingham Heart Study offspring cohort, where MRI measured atherosclerotic plaque in asymptomatic adults, a sample size of 84 participants undergoing MRI would be necessary to achieve 90% power to detect a difference in vessel wall thickness between high- and low-risk participants in this study.[20] Significance was determined using 2-tailed tests with p <0.05 considered statistically significant.

Results

Study participants

One hundred ninety-one participants had carotid artery IMT of 0.7 mm or higher. Of these, 14 were on lipid-lowering medications and were therefore not eligible for this sub-study. All eligible participants had phlebotomy to measure MCP-1/CCL2. The first 120 of 177 eligible participants presenting for Menopause and CHAMPS study visits were screened for

participation in MRI testing. Of these, 36 had metallic implants or claustrophobia and were therefore excluded from undergoing MRI. A total of 177 participants are therefore included in this analysis, 84 of whom had MRI testing. The 84 MRI participants did not differ from the rest of the sample with respect to hypertension, diabetes mellitus, LDL-C, total cholesterol:HDL-C ratio, or cigarette smoking, nor in terms of the proportion that had detectable HIV viremia or currently used PI. A smaller proportion of the MRI group was male compared to the overall sample, largely because a higher proportion of men were ineligible for MRI due to retained metal from gunshot wounds.

Participants' characteristics

Of 177 participants, 98 (55%) were HIV-infected, of whom 60 (61%) had detectable HIV viremia (Table 1). Most (81%) of HIV-infected participants were antiretroviral-experienced and 67% were currently taking HAART, 48% of whom were taking PIs. Among PI-users the median duration of PI use was 66 months (IQR 42, 98) and 77% were on a ritonavir-boosted regimen. Antiretroviral use differed between HIV-infected participants with undetectable viral load and those with detectable viremia ($p = .04$). Of participants with detectable HIV viremia, 43% were not currently using antiretrovirals (*vs.* 16% of those with undetectable viral load) and 25% were antiretroviral-naive.

The majority of participants (68% of HIV-infected and 52% of HIV-uninfected) were Black. Differences in race/ethnicity by HIV and viral load status approached statistical significance ($p = .05$). Limb fat was highest among HIV-uninfected participants ($p = .04$); differences in trunk fat and BMI were not statistically significant. Compared to uninfected participants, HIV-infected participants had lower HDL-C ($p = .01$) but similar total cholesterol, LDL-C and triglyceride levels. Cigarette smoking was most prevalent among uninfected participants ($p = .02$), however the proportion smoking ≥1 pack per day did not differ by HIV or viral load status. Rates of hypertension and impaired glucose tolerance/diabetes mellitus were similar.

MCP-1/CCL2 levels

As shown in Table 1, mean MCP-1/CCL2 levels did not differ significantly between groups by HIV and viral load status ($p = .71$). However, analysis of linear relationships of MCP-1/CCL2 with HIV viral load among the HIV-infected participants (Figure 1A) showed a positive association, which remained significant after adjusting for age, BMI and current cigarette smoking ($p = .02$). Analysis of CD4+ cell count with MCP-1/CCL2 (Figure 1B) suggested a negative linear relationship, however this association did not reach statistical significance ($p = .07$). There was a positive association of MCP-1/CCL2 with both thoracic aorta VWA ($p = .01$) and VWT ($p < .01$), after adjusting for age, BMI and current cigarette smoking (Figure 2). There was no significant association of MCP-1/CCL-2 with carotid artery parameters.

Vessel wall parameters

Univariate Analysis—Upon univariate analysis, HIV infection was associated with higher mean thoracic aorta VWA (1.17 mm^2 among HIV-infected *vs.* 1.08, $p = .049$). Associations of thoracic aorta VWT with HIV status (mean =1.56 mm among HIV-infected *vs.* 1.51, $p = .07$) did not reach statistical significance. There was no association of any vessel wall parameter with viral load or antiretroviral group.

Other factors associated with thoracic aorta VWA on univariate analysis were male gender ($p < .01$), older age ($p = .01$), and smoking one or more packs of cigarettes/day ($p = .03$). Having an LDL-C ≥130 mg/dL had a borderline significant association with higher carotid artery VWA ($p = .05$). There was no association of any of the vessel wall parameters with hypertension, impaired glucose tolerance/diabetes, BMI, or hepatitis C status on univariate analysis.

Multivariate Analysis—Multivariate analyses of factors associated with vessel wall parameters are shown in Tables 2A and 2B. After adjusting for gender, cigarette smoking, PI use, MCP-1/CCL2, LDL-C, and total cholesterol:HDL-C ratio (Table 2A), being HIV infected was independently associated with having greater mean thoracic aorta VWA and VWT. Being HIV-infected was not significantly associated with carotid artery VWA or VWT. Higher MCP-1/CCL2 levels were independently associated with higher thoracic aorta VWA and VWT, but not with carotid artery measurements. Protease inhibitor use was not associated with any of the vessel wall parameters. Other factors independently associated with thoracic aorta VWA were male gender and cigarette smoking. Cigarette smoking was also associated with higher thoracic aorta VWT.

Inclusion of HIV viral load status in the multivariate analysis (Table 2B) showed that compared to being uninfected, being HIV infected with detectable viremia was independently associated with having greater mean thoracic aorta VWA and VWT. Compared to being uninfected, being HIV-infected with undetectable viral load was associated with increased thoracic aorta VWA, but not with VWT. Relationships between other covariates and outcome variables remained similar to those found in the models that included HIV status but not viral load. Race/ethnicity, age, limb and trunk fat, physical activity level, current cocaine use and hepatitis C status were explored in the multivariate models but were not significantly associated with any of the vessel wall parameters and did not alter relationships of other covariates with the outcome.

Discussion

In this study of a well-characterized group of HIV-infected participants and a demographically similar, high-risk, uninfected comparison group, HIV-infected individuals with higher viral load had higher MCP-1/CCL2 levels, which correlated with greater thoracic aorta atherosclerotic burden. There was also a positive linear relationship between HIV viral load and MCP-1/CCL2, suggesting that the amount of circulating virus may affect MCP-1/CCL2 levels. Although not statistically significant, there was a trend towards a negative correlation of CD4+ cell count with MCP-1/CCL2. Interestingly, even after adjustment for HIV status and viremia, MCP-1/CCL2 remained independently associated with atherosclerotic burden, suggesting that higher MCP-1/CCL2 levels may contribute additional risk for atherosclerosis, even after accounting for the effect of HIV infection, PI use, and traditional cardiovascular risk factors.

Weiss et al reported similar associations between HIV viremia and MCP-1/CCL2, showing higher MCP-1/CCL2 levels in HIV-infected individuals with higher viral loads compared with those with undetectable virus and healthy controls.[21] Similarly, in a study of 36 HIV-infected subjects, of whom 18 were viremic, investigators reported higher MCP-1/CCL2 mRNA expression and serum levels among viremic compared to aviremic subjects.[22] Coll et al have reported increased atherosclerosis in HIV-infected patients who have the MCP-1-2518 allele and found a correlation between MCP-1/CCL2 and IMT among HIV- infected patients who also had clinical evidence of lipodystrophy.[23][24]

Our analysis, adjusted for traditional cardiovascular risk factors, revealed greater thoracic aorta VWA and VWT associated with detectable HIV viremia. Having HIV infection, in the absence of detectable viremia, was associated with having greater VWA but not with increased VWT. Of note, corresponding analysis of carotid artery parameters revealed no significant associations with HIV infection or viral load status. It is possible that this reflects a differential impact of HIV infection and associated inflammation on different vascular sites. Both the aorta and the coronary arteries are derived from the embryonic mesoderm, while the carotid arteries develop from the ectoderm.[25] In addition, the magnitude of shear stress in the aorta differs considerably from that of the carotid arteries, potentially contributing to a differential effect

of inflammation on the vascular endothelium in these two locations.[26] Evidence suggests that the endothelial cell response to inflammatory stimuli is modulated by blood flow, and increased fluid shear stress has been shown to lead to increased MCP-1/CCL2 gene activation. [27,28] Our finding of associations of HIV/viral load status and MCP-1/CCL2 concentrations with thoracic aorta but not carotid artery parameters indicates the need for further investigation of mechanisms by which HIV infection promotes atherosclerosis, and perhaps different screening modalities for detecting subclinical vascular disease in HIV-infected individuals.

Other studies of subclinical atherosclerosis in the HIV-infected population have shown variable associations with HIV infection and antiretroviral therapy.[9,10,12] In a prospective cohort study of participants matched for age, sex, race, cigarette smoking, blood pressure and menopausal status, Currier et al reported no association of IMT with HIV infection or PIs, but found instead that age, BMI, and HDL-cholesterol predicted IMT.[9] In another longitudinal study that assessed both HIV-infected and uninfected participants, Hsue et al reported higher baseline carotid IMT and more rapid 1-year progression among HIV-infected patients versus age-matched controls, but no associations with PIs. In contrast, Johnsen et al found no association of IMT with HIV status, but increased IMT in HIV-infected subjects taking PIs versus those not on PIs.[11]

Many of these studies have not, however, included measures of inflammation and none have assessed atherosclerosis in the thoracic aorta. The use of MRI, which allows imaging of the thoracic aorta, is a major strength of our study. Although not in widespread clinical use for cardiovascular risk assessment, MRI is well-validated in cardiovascular research as a sensitive and reliable measure of atherosclerosis.[13,14,29] The fact that MRI allows visualization of the full-thickness of the vessel wall, as opposed to being limited to the intima and media, may be particularly advantageous when assessing atherosclerosis in the setting of HIV-infection. There is evidence suggesting that the mechanism of vascular disease in HIV-infected individuals may differ somewhat from typical atherosclerotic plaque formation. Early in the HIV epidemic, autopsies of young HIV-infected patients found a distinct arteriopathy with lesions intermediate in appearance between typical atherosclerosis and lesions seen with chronic rejection of cardiac transplants.[30] More recently, Regina et al reported two cases of HIV-infected patients who underwent surgery for carotid artery stenosis, describing extensive inflammatory infiltration of the vascular wall without typical atheromatous plaques.[31]

Our study is limited by its cross-sectional design. In addition, the relatively small number of participants with MRI results precludes a more detailed analysis of the impact of viral load and CD4+ cell count within the HIV-infected group. This study does, however, offer the advantage of including an HIV-uninfected comparison group with similar background cardiovascular risk, allowing us to better assess the impact of HIV infection and antiretroviral therapy. Although race/ethnicity was not found to be associated with vessel wall parameters in this study, the majority of participants in our study sample were Black, which may limit ability to generalize our findings to other HIV-infected populations with a different racial/ethnic composition.

In summary, our study finds that higher HIV viral load correlates with higher MCP-1/CCL2 levels, and shows an association of HIV infection and viral load status with atherosclerotic burden in the thoracic aorta. These findings highlight the need for further investigation focusing not only on traditional cardiovascular risk, but also on immunologic factors as potential contributors to atherosclerosis in the HIV-infected population.

Acknowledgments

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Fig. 1A
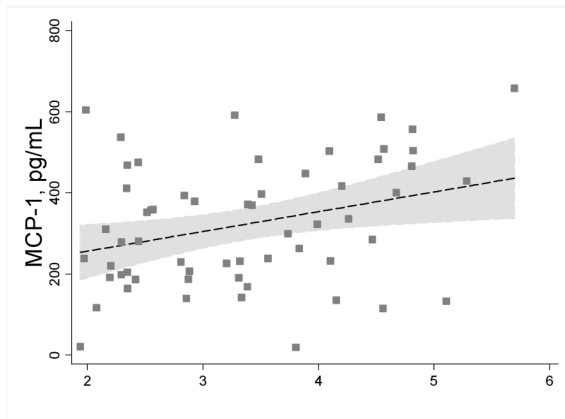
Log$_{10}$ HIV-1 Viral Load *

Fig. 1B
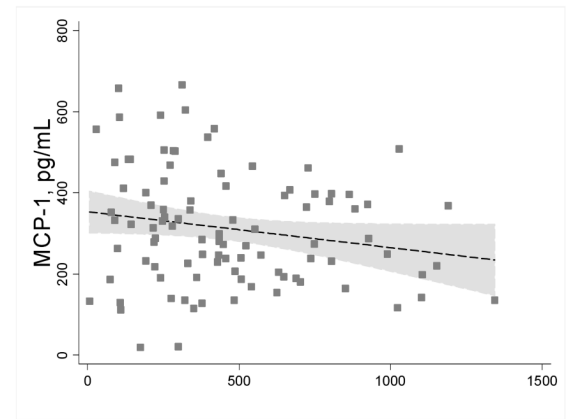
CD4+ Cell Count, cells/mm³

Figure 1.
Relationship of monocyte chemoattracted protein-1/chemokine (C-C motif) ligand 2 with HIV-1 viral load and CD4$^+$ cell count among HIV-infected participants. This figure shows the relationship of MCP-1/CCL2 with HIV-1 viral load (a) and CD4$^+$ cell count (b) among HIV-infected participants. Dashed line represents linear prediction from regression of MCP-1/CCL2 on viral load (P=0.02) and CD4$^+$ cell count, respectively (P=0.07), with 95%CIs shown in gray. *HIV-1 viral load was log-transformed to meet criteria for linear regression. CCL2, chemokine (C-C motif) ligand 2; CI, confidence interval; MCP-1, monocyte chemoattractant protein-1.

Fig. 2A

Fig. 2B

Figure 2.
Relationship of thoracic aorta mean vessel wall area and mean vessel wall thickness with monocyte chemoattractant protein-1/chemokine (C-C motif) ligand 2. The figure shows relationship of thoracic aorta mean VWA (a) and mean VWT (b) with MCP-1/CCL2. Dashed line represents linear prediction from regression on MCP-1/CCL2 of VWA (P=0.01) and VWT (P<0.01), respectively, with 95% CIs shown in gray. CCL2, chemokine (C-C motif) ligand 2; CI, confidence interval; MCP-1, monocyte chemoattractant protein-1; VWA, vessel wall area; VWT, vessel wall thickness.
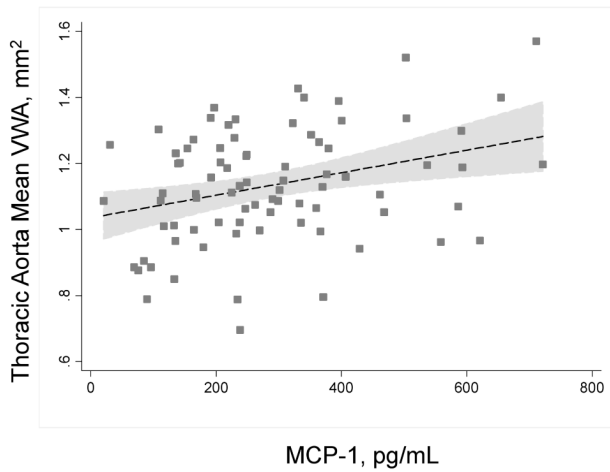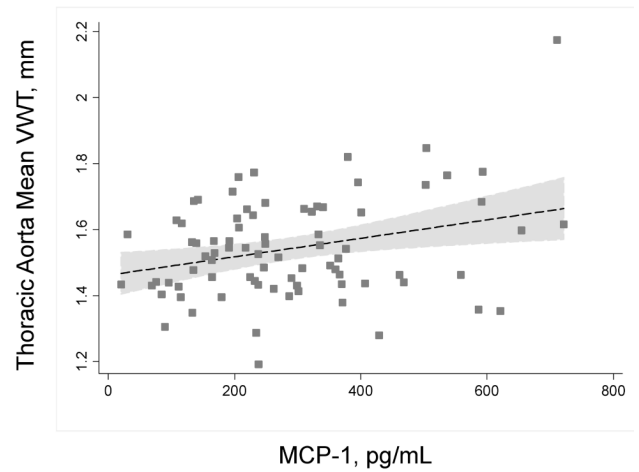
Table 1

Demographic and clinical characteristics of the study population (N = 177)

Characteristics	HIV-uninfected (N = 79)	HIV-infected, Viral Load <75 copies/mL (N = 38)	HIV-infected, Viral Load ≥75 copies/mL (N = 60)	p
Age, years, mean (S.E.)	55.3 (.7)	54.7 (1.0)	54.9 (.7)	.88
Male	49 (62.0)	21 (55.3)	39 (65.0)	.62
Race/Ethnicity				.05
Black	42(53.2)	25 (65.8)	42 (70.0)	
Latino	18 (22.8)	11 (28.9)	9 (15.0)	
White/Other Race	19 (24.1)	2(5.3)	9 (15.0)	
Detectable hepatitis C RNA	31 (39.2)	17 (44.7)	30 (50.0)	.45
MCP-1/CCL-2, pg/mL, mean (S.E.)	327.0 (18.9)	297.7 (19.9)	322.1 (19.9)	.71
BMI, kg/m², mean (S.E.)*	28.3 (.8)	25.2 (.7)	26.9 (.8)	.07
Limb fat, g, mean (S.E.)*	8735.8 (628.9)	6051.0 (617.0)	7599.8 (736.4)	**.04**
Trunk fat, g, mean (S.E.)*	12744.7 (781.4)	10090.8 (683.7)	11358.8 (913.3)	.15
Impaired Glucose Tolerance or DM*	19 (24.4)	11 (29.7)	10 (17.2)	.35
Hypertension†	53 (67.1)	23 (60.5)	36 (60.0)	.64
Total Cholesterol, mg/dL, mean (S.E.)	171.6(3.7)	168.9 (6.3)	159.5 (5.5)	.12
LDL-C, mg/dL, mean (S.E.)	99.9 (3.3)	95.1 (5.8)	91.4 (4.8)	.20
HDL-C, mg/dL, mean (S.E.)	50.5 (1.8)	46.9 (2.2)	43.1 (1.5)	**.01**
Triglycerides, mg/dL, mean (S.E.)	123.4 (11.1)	140.2 (14.1)	126.5 (10.8)	.27
Currently smoke cigarettes	58 (73.4)	18 (47.4)	41 (68.3)	**.02**
Smoke ≥ 1 pack/day	15 (19.2)	3 (7.9)	7 (11.7)	.20
Exercise at least once/week	51 (64.6)	21 (55.3)	39 (65.0)	.56
Watch > 4hrs TV/day*	37 (48.1)	22 (61.1)	27 (47.4)	.36
CD4 cell count, cells/mm3	---			.05
<200	---	3 (7.9)	15 (25.0)	
200–499	---	17 (44.7)	28 (46.7)	
≥500	---	18 (47.4)	17 (28.3)	
Antiretroviral use				**.04**
Naïve to antiretrovirals	---	4 (10.5)	15 (25.0)	
Used HAART in the past only	---	2 (5.3)	11 (18.3)	
Currently taking PI-based HAART	---	22 (57.9)	25 (41.7)	
Currently taking non-PI HAART	---	10 (26.3)	9 (15.0)	

Data are N(%), except where indicated. MCP-1/CCL-2 indicates monocyte chemoattractant protein-1; BMI, body mass index; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HAART, highly active antiretroviral therapy; and PI, protease inhibitor.

*
Data missing on BMI for 1 participant; on trunk and limb fat for 2 participants; on time spent watching TV for 7 participants; and on impaired glucose tolerance/diabetes mellitus for 4 participants.

†
Hypertension defined as systolic/diastolic blood pressure ≥ 130/85 or current use of antihypertensive medications.

Table 2

Table 2A. Multivariate linear regression of vessel wall parameters adjusted for HIV infection status.

Parameter	Log10 Mean Thoracic Aorta Vessel Wall Area		Log10 Mean Thoracic Aorta Vessel Wall Thickness		Log10 Mean Carotid Artery Vessel Wall Area		Log10 Mean Carotid Artery Vessel Wall Thickness	
	β Coefficient (95% CI)	p	β Coefficient (95% CI)	p	β Coefficient (95% CI)	p	β Coefficient (95% CI)	p
HIV infection	.048 (.016 - .080)	**<.01**	.023 (.002 - .043)	**.03**	.037 (-.015 - .089)	.17	.017 (-.017 - .051)	.29
PI-HAART [†]	-.029 (-.062 - -.005)	.08	-.010 (-.032 - .012)	.28	-.020 (-.069 - .029)	.29	-.016 (-.051 - .018)	.28
MCP-1 [†]	.018 (.005 - .032)	**.01**	.012 (.003 - .021)	**.01**	.015 (-.005 - .036)	.15	.005 (-.008 - .019)	.43
Male	.035 (.007 - .063)	**.02**	-.007 (-.025 - .011)	.41	.037 (-.005 - .079)	.07	.009 (-.020 - .037)	.57
Smoke ≥ 1 pack/day	.046 (.006 - .086)	**.02**	.040 (.014 - .066)	**<.01**	.030 (-.030 - .091)	.30	.017 (-.024 - .059)	.37
LDL-C ≥ 130 mg/dL	.035 (-.003 - .075)	.13	.020 (-.005 - .045)	.26	.087 (.021 - .153)	**.04**	.029 (-.015 - .073)	.34
Total Cholesterol: HDL-C ratio	.004 (-.009 - .016)	.55	.005 (-.003 - .013)	.23	.012 (-.008 - .033)	.24	.006 (-.007 - .018)	.37

Table 2B. Multivariate linear regression of vessel wall parameters adjusted for HIV infection and Viral Load status.

Parameter	Log₁₀ Mean Thoracic Aorta Vessel Wall Area		Log₁₀ Mean Thoracic Aorta Vessel Wall Thickness		Log₁₀ Mean Carotid Artery Vessel Wall Area		Log₁₀ Mean Carotid Artery Vessel Wall Thickness	
	β Coefficient (95% CI)	p	β Coefficient (95% CI)	p	β Coefficient (95% CI)	p	β Coefficient (95% CI)	p
HIV-infected, undetectable viral load [*]	.046 (.007 - .086)	**.02**	.019 (-.007 - .045)	.15	.023 (-.037 - .082)	.49	.014 (-.028 - .055)	.48
HIV-infected, viral load detectable [*]	.048 (.015 - .082)	**<.01**	.025 (.003 - .046)	**.02**	.047 (-.009 - .103)	.10	.019 (-.017 - .055)	.27
PI-HAART	-.028 (-.063 - .006)	.09	-.009 (-.031 - .013)	.33	-.019 (-.068 - .031)	.31	-.016 (-.051 - .020)	.31
MCP-1/CCL2 [†]	.018 (.005 - .032)	**.01**	.012 (.003 - .021)	**.01**	.015 (-.006 - .035)	.17	.005 (-.009 - .019)	.44
Male	.035 (.007 - .063)	**.02**	-.007 (-.026 - .011)	.41	.035 (-.007 - .077)	.08	.008 (-.021 - .037)	.59
Smoke ≥ 1 pack/day	.046 (.005 - .086)	**.03**	.039 (.012 - .066)	**<.01**	.032 (-.029 - .093)	.28	.018 (-.024 - .059)	.37
LDL-C ≥ 130 mg/dl	.036 (-.003 - .075)	.13	.020 (-.005 - .046)	.26	.086 (.020 - .151)	.05	.029 (-.016 - .073)	.36
Total Cholesterol: HDL-C ratio	.004 (-.009 - .016)	.55	.005 (-.003 - .013)	.23	.013 (-.008 - .034)	.22	.006 (-.007 - .019)	.90

NOTE: Thoracic aorta vessel wall area, vessel wall thickness, and carotid artery vessel wall area and vessel wall thickness log-transformed to meet normality criteria for linear regression. PI-HAART, protease inhibitor-based highly active antiretroviral therapy; MCP-1/CCL2, monocyte chemoattractant protein-1; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

[*] Reference group: HIV-uninfected. Detectable HIV-1 viral load indicates HIV-1 viral load ≥ 75 copies/ml.

[†] MCP-1/CCL2 measured in pg/mL, standardized (deviation from mean MCP-1/CCL2 value/standard deviation).