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T-cell Activation, Both Pre- and Post-HAART Levels, Correlates with Carotid Artery Stiffness over 6.5 years among HIV-infected Women in the WIHS

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Abstract

Objective—T-cell activation is a major pathway driving HIV disease progression. Little is known regarding the impact of T-cell activation on HIV-associated atherosclerosis and cardiovascular disease, a common co-morbidity in HIV infection. We hypothesized that T-cell activation will predict vascular stiffness, a measure of subclinical atherosclerosis.

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Design—Linear regression models evaluated the covariate-adjusted association of T-cell activation with vascular stiffness.

Methods—CD38 and HLA-DR expression on CD4+ and CD8+ T-cells was assessed by flow cytometry among 59 HIV-negative and 376 HIV-infected (185 hepatitis-C co-infected) women in the Women's Interagency HIV Study (WIHS). T-cell activation was defined by CD8+CD38+DR+ and CD4+CD38+DR+. Multiple activation assessments over 6.5 years were averaged. In 140 women, T-cell activation was measured before and after HAART initiation. Carotid artery ultrasounds were completed a median of 6.5 years after last measurement of T- cell activation and carotid artery stiffness including distensibility and elasticity were calculated.

Results—Percentages of CD4+ and CD8+ T-cell activation were significantly higher in HIV-infected compared to HIV-negative women. Among HIV-negative women, T-cell activation was not associated with carotid artery stiffness. Among HIV-infected women, higher CD4+ T-cell activation significantly predicted increased arterial stiffness independent of CD4 cell count and HIV RNA. The association was stronger among HIV/HCV co-infected compared to HIV-mono-infected women; however, the difference was not statistically significant (p-for interaction>0.05). Pre- and post-HAART levels of CD4+ T-cell activation significantly predicted carotid artery stiffness.

Conclusions—Persistent T-cell activation, even after HAART initiation, can contribute to structural and/or functional vascular damage accelerating atherogenesis in HIV infection. These results need to be confirmed in a longitudinal prospective study.

Keywords

T-cell activation; arterial stiffness; HIV-infection

Introduction

HIV-infected individuals have increased risk of atherosclerosis and cardiovascular disease (CVD)[1], which has been attributed to higher prevalence of traditional cardiovascular risk factors[2], HIV[3,4] as well as antiretroviral therapy (ART)[5]. The most investigated mechanisms for both HIV- and ART- associated increased cardiovascular risk include chronic inflammation[6], metabolic perturbations[7-9] and endothelial dysfunction[10]. However, the role of HIV-induced immune dysregulation in elevated cardiovascular risk among HIV-infected individuals is not fully understood. Consistent reports on the association between low CD4+ T-cell count and subclinical atherosclerosis[11-15] and CVD events[4,16] indicate a central role of immune dysregulation in accelerated CVD risk in HIV-infected subjects. While it is still not well defined whether low CD4+ T-cell count is an independent risk factor or a marker of some other mechanism, we hypothesize that T-cell activation or immune activation, a hallmark of HIV infection and the major driving force of CD4 decline[17,18], may partially explain the increased atherosclerotic burden in HIV-infected individuals.

Early T-cell activation predicts subsequent CD4 depletion, progression to AIDS, and survival in HIV-infected[17,19-21] and also in HIV and hepatitis C (HIV/HCV) co-infected subjects[22]. Currently, understanding the role of immune activation in HIV-associated atherosclerosis is of considerable interest. Majority of the published studies in this area

evaluated the role of markers of monocyte and macrophage activation, which are indicators of activation of innate immune system[23-25], while little is known regarding the impact of adaptive T-cell activation on HIV- associated atherosclerosis. To date, only two small scale, cross-sectional studies documented significant associations between T-cell activation and carotid artery stiffness[26], and atherosclerotic lesions[27,28]. In the current study, we evaluated if T-cell activation predicts future arterial stiffness measured after a median (IQR) 6.5 (3.5-8) years of the T-cell activation assessments in HIV-infected and HIV/HCV co-infected women in the WIHS.

Emerging evidence suggests that HIV-induced T-cell activation remains abnormally elevated even after viral suppression with highly active antiretroviral therapy (HAART)[29-31]. As shown in untreated patients years ago[17,20], data is compiling on the predictive value of T-cell activation for HIV disease progression and mortality among treated patients as well[32,33]. In the current study, we also evaluated if T-cell activation levels pre- and post-HAART equally predict future arterial stiffness.

Methods

Study Population

Details of the WIHS have been described previously[34]. In short, the WIHS is a multicenter, prospective study designed to examine the characteristics and course of HIV infection in US females. A total of 2059 HIV-infected and 569 uninfected women were enrolled between October 1994 and November 1995 at 6 different sites in the United States (Los Angeles, Calif; Northern California; Washington, DC; Bronx and Manhattan, NY; Brooklyn, NY; and Chicago, Ill). A second enrollment, between October 2001 and September 2002, added 737 HIV-infected and 406 HIV-uninfected women. Participants are assessed at baseline and every 6 months with an extensive battery of questionnaires and laboratory tests. The current study was limited to the initial enrollees. Written informed consent was obtained from study participants, and the study was approved by the institutional review boards at each site.

Measurements of T-cell activation levels were pooled from 3 substudies of the WIHS[6,35,36]. For each woman, activation markers were measured multiple times between WIHS visits 1 and 14. Eighty percent of participants had >1 assessment; the median (IQR (interquartile range)) number of assessments was 3 (1-5). The carotid artery ultrasound evaluations were completed between April 1, 2004 and September 30, 2005 (WIHS visits 20, 21, 22) as part of a cardiovascular substudy. The median (IQR) time difference between the last assessment of T-cell activation and carotid ultrasound evaluation was 6.5 (3.5-8) years. A total of 59 HIV-seronegative and 376 HIV-seropositive (185 HCV co-infected and 191 HIV monoinfected) women, who completed the carotid ultrasound evaluation and had at least one T-cell activation measurement were included in the current study. For 140 women, T-cell activation assessments were completed 6 months before and 6 months after initiation of HAART and the median (IQR) time differences between the pre- and post-HAART assessment of T-cell activation and carotid ultrasound evaluation were 7.5 (6.25, 8.25) and 6.5 (5.25, 7.25) years, respectively.

Outcome Variables

High resolution B-mode ultrasound with automated computerized edge detection software (Prowin, Patents, 2002, 2006, 2011) was used to assess the right distal common carotid artery far wall intima-media thickness (CIMT)[14] and stiffness[15]. Arterial stiffness was evaluated by measures of distensibility and elasticity of the arterial wall. Details of the methods have been described elsewhere[37]. Using carotid artery ultrasound, measurements of right common carotid artery diameters at systole (D_s) and diastole (D_D) were obtained. Systolic and diastolic blood pressure was measured concomitant with the carotid ultrasound and pulse pressure (PP) was calculated. Arterial distensibility and elasticity were calculated as:

$$\text{Distensibility} = [(2(D_s - D_D)/D_D) / PP] \times [10^6 / 133.3]$$

Distensibility index ($10^{-5}xNxm^{-2}$) is a continuous measure of arterial stiffness with lower distensibility indicating greater arterial stiffness.

$$\text{Elasticity (Young's Elastic Modulus)}: PP/DD \times 0.5 \times D_D/CIMT_D$$

PP = pulse pressure; DD= % arterial dilation over the cardiac cycle; D_D = arterial diameter at diastole; CIMTD = CIMT at diastole

Elasticity index ($10^{-6}xN^{-1}xm^2$) is a continuous measure of arterial stiffness with higher elasticity index indicating greater arterial stiffness. The coefficients of variation from a repeat-measures study were estimated as 1.8% for CIMT (intraclass correlation coefficient [ICC] = 0.98), 2.2% for $CIMT_D$ (ICC = 0.96) and 8.8% for blood pressure (ICC = 0.65 − 0.73)[26].

Laboratory Evaluations

CD4+ and CD8+ T-cell counts were measured by flow cytometry in laboratories participating in the National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS Flow Cytometry quality assurance program[34]. The fluorochrome-conjugated antibodies for three-color cytometry were anti -CD3, -CD4, -CD8, -HL-DR (DR), and -CD38 (Becton Dickinson, San Jose, CA and Pharmigen, San Diego, CA)[35,36,38]. Three WIHS substudies contributing to the T-cell activation assessments for the current study used comparable methods for flow cytometry. Activation of CD4+ and CD8+ T-cells was defined as percentages of T-cell subtypes expressing both CD38 and HLA-DR on the surface (CD4+CD38+DR+ and CD8+CD38+DR+, respectively). HIV-1 RNA quantification was performed every 6 months using real-time isothermal nucleic acid sequence-based amplification (Organon Teknika Corp., North Carolina)[39]. HCV antibody testing was done at baseline using Abbott EIA 2.0 or 3.0 assays[40].

Statistical analysis

The demographic and clinical characteristics of the study participants at the baseline immune activation marker assessment visit and carotid ultrasound visit were compared between the HIV- infected and -uninfected women using Wilcoxon rank sum and Chi-square test for continuous and categorical variables, respectively. Correlates of CD4+ and

CD8+ T-cell activation were evaluated by linear regression using generalized estimating equations (with an exchangeable correlation) to account for repeat measures of T-cell activation markers.

Linear regression model was used to evaluate the associations between measures of carotid arterial stiffness (distensibility, and elasticity; dependent variables) and T-cell activation (CD4+CD38+DR+, and CD8+CD38+DR+; independent variables) among the HIV-infected women. Repeat measures of T-cell activation markers were averaged for analysis involving total sample. Elasticity was log transformed to achieve normality; distensibility was normally distributed. Known risk factors of subclinical atherosclerosis including age, race, BMI, smoking, menopause, and ART (all at the time of carotid ultrasound evaluation) were included in the multivariate regression model as covariates. The models were also adjusted for the time difference between the last assessment of T-cell activation and carotid ultrasound evaluation. CD4 cell count and HIV viral load at the time of T-cell activation assessment were added to subsequent models individually and jointly. The multivariate model adjusted for both CD4 and HIV viral load was then stratified by HCV co-infection status. A test of interaction was performed by including the product term of T-cell activation and HIV/HCV co-infection status as a covariate in addition to the main effects terms.

Among 140 women with both pre- and post-HAART assessment of T-cell activation, differences in the levels of CD4+ and CD8+ T-cell activation 6 months before and after HAART initiation were tested using paired t-test. Pre- and post-HAART levels of T-cell activation were then correlated with arterial stiffness in linear regression models.

Results

At baseline immune activation assessment visit, HIV-infected women were younger, more likely to be HCV co-infected and have significantly higher CD4+ and CD8+ T-cell activation compared to HIV-negative women (Table 1). At the carotid ultrasound evaluation visit, similar differences were observed between the HIV-infected and –uninfected women in terms of age and HCV co-infection status. In addition, HIV-infected women had significantly lower BMI, and HDL-cholesterol at that time (Table 1). As the carotid ultrasound evaluation visit was much later in the WIHS follow-up period, both prevalence and duration of ART were greater at that time point compared to the baseline immune activation assessment visit. African-American race, low CD4+ T-cell count, CD4/CD8 ratio ≤ 1, higher HIV RNA, BMI <25 kg/m^2, and low HDL were associated with higher CD4+ and CD8+ T-cell activation and use of HAART, PIs, or NRTIs were associated with lower CD4+ and CD8+ T-cell activation (Table 2).

Athough the univariate associations of CD4+ and CD8+ T-cell activation with carotid artery distensibility and elasticity among the HIV-infected women were attenuated in the multivariate results, adjusted for age, race, BMI, smoking, ART, menopause, and time between activation marker and arterial stiffness assessment (model 1), both T-cell activation were significantly associated with decreased carotid arterial distensibility and increased elasticity, the direction of association for both stiffness outcomes indicating greater atherosclerosis with higher T-cell activation (Table 3). In subsequent models, CD4+ T-cell

count and HIV RNA was added separately (models 2, and 3, respectively) and jointly (model 4). In all models CD4+ T-cell activation remained significantly associated with distensibility and elasticity; whereas the strength of association of CD8 activation with elasticity was attenuated after controlling for CD4+ T-cell count and HIV RNA. CD8 activation was not significantly associated with distensibility in any multivariate model.

Stratified regression analysis by HIV/HCV co-infection status showed a stronger association of CD4+ T-cell activation with distensibility and elasticity among HIV/HCV co-infected women (n = 185) compared to the HIV monoinfected (n = 191) (Table 4). However, the interaction terms were not statistically significant (all p-value for interaction > 0.07). Levels of both T-cell activation markers were statistically significantly lower 6 months after HAART initiation compared to the levels 6 months before; mean (SD) pre- vs. post-HAART levels 14%(10.3) vs 11.4% (10.2) for CD4+ T-cell activation (p = 0.02), and 37.4%(15.5) vs. 29.7%(14.1) for CD8 activation (p<0.0001) (Supplementary Figure 1). However, the post-HAART levels of both T- cell activation were statistically significantly higher than the levels (average of the multiple assessments) in HIV-uninfected women (p<0.0001). Both pre- and post-HAART levels of CD4+ T-cell activation were significantly associated with arterial stiffness measures, decreased distensibility and increased elasticity (Table 5). CD8+ T-cell activation levels pre- or post- HAART were not associated with arterial stiffness. Among the HIV-uninfected women, neither CD4+ nor CD8+ T-cell activation levels were associated with carotid artery stiffness measures.

Discussion

This is the first report from a longitudinal study showing that early CD4+ T-cell activation levels, including levels both immediately before and after HAART initiation, can predict future carotid artery stiffness assessed by distensibility and elasticity of the common carotid artery over a median (IQR) of 6.5 (3.5 - 8) years. Our data show that increased CD4+ T-cell activation predicts future carotid artery stiffness independent of CD4+ T-cell count and HIV viral load. CD4+ T-cell activation levels 6 months before and after HAART initiation equally predicted future arterial stiffness over a median (IQR) of 7.5 (6.25, 8.25) and 6.5 (5.25, 7.25) years, respectively, also adjusted for CD4+ T-cell count and HIV RNA.

Binding of HIV to CCR5 or CXCR4 co-receptors induces *env*-mediated signals, which activate CD4 cells by inducing expression of immune markers such as CD25, CD38, CD57, CD69, CD70 and HLA-DR. Activated CD4 cells release soluble factors including cytokines which in turn activate CD8+ T-cells. HIV-induced T-cell activation is essential for viral replication, and activated T-cells that are not productively infected eventually die[41]. A decline in CD4+ T-cell count, which is the most important phenotypic characteristic of HIV disease progression, is due to a combination of factors including apoptosis of infected CD4+ cells, bystander activation of uninfected T-cells by HIV virions in tissue reservoirs, and cytokines which may cause global activation of the immune system[42-44]. Activation of T-cells is followed by expansion of the T-cell pool and death of a large number of T-cells through apoptosis. Since decline in CD4+ T-cell count is closely associated with T-cell activation, it is important to understand the effect of T-cell activation on arterial stiffness independent of CD4+ T-cell count.

Our results are consistent with a prior cross-sectional study in the WIHS that evaluated both T- cell activation markers and the carotid ultrasound at the same time point among 114 HIV-infected women. In that report, a significant association of higher levels of CD4+CD38+DR + T- cells were associated with lower carotid artery distensibility and increased elasticity; both associations indicating more stiffness associated with higher CD4+ T-cell activation[26]. Notably, both in our longitudinal analyses and in the cross-sectional study, the association of CD4+ T-cell activation with arterial stiffness was independent of CD4+ T-cell count, suggesting that the finding from multiple reports of an association between low CD4+ T-cell count and atherosclerosis[11-15] may be partially explained by CD4+ T-cell activation. In addition, results from the current study show that the association between CD4+ T-cell activation and arterial stiffness holds way out to more than 6 years, indicating a continued long term impact of persistent CD4+ T-cell activation on advancement of atherosclerosis. Activated immune cells may contribute to atherosclerosis by multiple pathways including upregulation of proinflammatory cytokines (e.g. IL-6, IL-10), INF-γ, granulocyte-macrophage colony stimulating factors (GM-CSF)[45] and leukocyte adhesion molecule[46]. Elevated T-cell activation is associated with higher circulating levels of sTNFR2, d-dimer, sICAM, and sVCAM[6,47], which play a critical role in atherogenesis. Consistent with cross-sectional study, we found only CD4+ T-cell activation, not CD8+ T-cell activation, was significantly associated with carotid artery stiffness independent of CD4+ T-cell count. While activation of both CD4+ and CD8+ T-cells may theoretically induce atherosclerotic changes in human arteries, Th1 response of activated CD4+ T-cells characterized by INF-γ production, has been particularly implicated in atherogenesis based on evidence from animal models and in vitro studies[48,49].

Our data confirmed a significant reduction in CD4+ and CD8+ T-cell activation within 6 month of HAART initiation; however, the post-HAART immune activation levels are remarkably higher than the levels in HIV-uninfected women as shown in supplementary figure 1. While the cause of persistent immune activation levels remain largely unknown, residual viral replication in the lymphoid tissue and microbial translocation have been implicated as possible mechanistic sources[50,51]. A number of studies have reported that HIV-induced T-cell activation remains abnormally elevated even after viral suppression with HAART[29,30] and post-HAART levels of T- cell activation can predict HIV disease progression and mortality[32,33] as does the activation levels in untreated patients[17,20]. Consistent with these disease outcome findings, our data show that both pre- and post-HAART CD4+ T-cell activation can equally predict carotid artery stiffness, which is a major strength of our study. A recent publication from the WIHS reported significant associations between carotid atherosclerosis and post-HAART levels of IL-6 and soluble IL-2 receptors; but pre-HAART levels of the same serum markers did not have such associations[52]. In contrast, both pre- and post-HAART levels of T-cell activation significantly predicted arterial stiffness in our results. In addition, HAART substantially reduces most inflammatory mediators at the levels of HIV-uninfected[52], but T-cell activation levels continues to remains elevated as shown in our data. Taken together, levels of T-cell activation is probably a more robust marker of atherosclerosis than serum inflammatory markers.

HIV-infected subjects are frequently co-infected with HCV. HIV/HCV co-infection is associated with a higher prevalence of CVD[53] and endothelial dysfunction[54] than HIV

monoinfection. HIV/HCV co-infected women had significantly higher levels of CD8 T-cell activation and HCV viremia was associated with CD4+ and CD8+ T-cell activation among the women in the WIHS[22,38]. HIV/HCV co-infection is also associated with increased levels of circulating soluble cellular adhesion molecules released by the vascular endothelium, including soluble intercellular adhesion molecule-1 (sICAM-1) and vascular adhesion molecule-1 (sVCAM-1)[54]. The increased inflammatory and cardiovascular burden in HIV/HCV co-infected women may be partially mediated by their elevated immune activation status. Among the 185 HIV/HCV co-infected women, CD4+ T-cell activation significantly predicted carotid artery distensibility and elasticity, whereas the association was not statistically significant among the 191 HIV monoinfected women. Although the interaction p-values did not reach statistical significance, the associated beta-estimates were remarkably stronger among the HIV/HCV co-infected group. However, these results should be interpreted with caution and more data is warranted to reach a conclusion on this regard.

In conclusion, our data showed that early CD4+ T-cell activation, measured before and after HAART initiation, can predict future carotid artery stiffness independent of CD4+ T-cell count. While the underlying mechanisms as to how activated CD4+ T-cells accelerate arterial stiffness is yet to be determined, it is possible that the activated T-cells are markers of inflammation and they contribute to structural and/or functional damage of arterial walls by adding to the elevated inflammatory status in HIV-infected individuals. Our results also suggest that HIV-induced activated CD4+ T-cells themselves can contribute to vascular stiffness as seen in our women before HAART initiation. Along with the proatherogenic complications of HAART, the sustained proinflammatory effects of immune activation post-HAART can accelerate atherogenesis despite restoration of CD4+ T-cell count and HIV viral load suppression. Findings from our study are of great significance because of the longitudinal nature of the data, reasonably large sample size, and also the fact that a much focused analysis of our data showed that immune cells remain activated after HAART treatment, which is predictive of future arterial stiffness.

However, a longitudinal prospective study is required to confirm our results. Knowledge gained from this study will have significant contribution in understanding the pathogenesis of accelerated risk of cardiovascular disease in HIV-infected subjects. Prevention strategies can be developed targeting activated CD4-cells and inflammation in order to reduce the burden of cardiovascular complications of HIV and HAART.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical characteristics of the study participants at baseline immune activation assessment visit and carotid ultrasound visit

	at baseline immune activation assessment visit					at carotid ultrasound evaluation visit				
	HIV-negative (n = 59)		HIV-positive (n = 376)			HIV-negative (n = 59)		HIV-positive (n = 376)		
	Median/%	IQR	Median/%	IQR	p[a]	Median/%	IQR	Median/%	IQR	p[a]
Age, years	36	8	38	9	.04	43	8	46	9	<.01
Race, %										
Black	49	…	59	…	.13					
Hispanic	37	…	25	…						
White or other	14	…	16	…						
BMI, kg/m^2	28	12	27	8	.44	30	14	27	8	.04
Current smoking, %	61	…	53	…	.25	54	…	49	…	.43
Diabetes, %	7	…	3	…	0.17	24	…	17	…	0.21
Menopause, %	7	…	14[b]	…	0.18	26	…	38	…	0.08
Hypertension, %	22	…	23	…	.89	25	…	27	…	.82
Hepatitis C antibody, %	31	…	49	…	<.01	31	…	49	…	<.01
CD8+CD38+DR+	7.0	12.0	35.0	26.5	<.01					
CD4+CD38+DR+	3.0	2.0	10.1	11.0	<.01					
HIV RNA, copies/mL	NA	…	9,700	30,700	NA	NA	…	160	7,520	NA
CD4 cell count, cells/μL	1077	580	399	333	<.01	907	430	408	352	<.01
LDL-C level, mg/dL						96	44	94	53	.57
HDL-C level, mg/dL						53	20	45	23	<.01
PI use, %	NA	…	10	…	NA	NA	…	40	…	NA
NRTI use, %	NA	…	46	…	NA	NA	…	67	…	NA
NNRTI use, %	NA	…	4	…	NA	NA	…	25	…	NA
PI use, months	NA	…		0[c]	6	NA	…	30[d]	60	NA
NRTI use, months	NA	…		18[c]	24	NA	…	72[d]	54	NA
NNRTI use, months	NA	…		0[c]	0	NA	…	12[d]	36	NA

[a] Kruskal-Wallis test for continuous variables and Chi-squared test for categorical variables.

[b] 41% of HIV positive women missing menopause data at first immune marker visit

[c] Number of months PI, NRTI, or NNRTI taken, between baseline visit and first immune marker visit.

[d] Number of months PI, NRTI, or NNRTI taken, between first immune marker visit and the carotid ultrasound visit

Note: Adherence was self reported. Hypertension was defined as any of: SBP >=140, DBP >=90, or self reported use of anti-hypertensive medication. Diabetes was defined as any of: Fasting glucose >=126, HgbA1C >=6.5%, self report, or self reported use of anti-diabetic medication. Women with no menstrual period over the past 12 months or more were defined as menopausal.

Table 2

CD4+ and CD8+ T-cell activation levels by baseline characteristics

		CD8+CD38+DR+		CD4+CD38+DR+†	
Variable		**LS Means (95% CI)**	**p*a***	**LS Means (95% CI)**	**p*a***
Age, years	<40	36.3 (34.2 – 38.3)	0.63	10.4 (9.6 – 11.2)	0.94
	40-44	36.3 (33.8 – 38.8)		10.5 (9.5 – 11.6)	
	45-49	38.7 (35.1 – 42.4)		10.2 (9.0 – 11.6)	
	50+	38.5 (33.8 – 43.2)		9.9 (8.4 – 11.6)	
CD4/CD8 ratio	≤ 1	37.6 (36.0 – 39.2)	**<.0001**	10.8 (10.1 – 11.5)	**<.0001**
	> 1	25.7 (22.6 – 28.9)		6.5 (5.7 – 7.4)	
CD4 cell count, cells/μL	<200	47.3 (44.4 – 50.2)	**<.0001**	18.4 (16.7 – 20.3)	**<.0001**
	200-349	40.5 (38.3 – 42.7)		12.3 (11.4 – 13.2)	
	350-499	36.3 (34.3 – 38.3)		10.1 (9.4 – 10.9)	
	500+	29.5 (27.7 – 31.4)		7.0 (6.5 – 7.6)	
HIV RNA, copies/mL	80	29.7 (27.6 – 31.7)	**<.0001**	7.8 (7.1 – 8.6)	**<.0001**
	81-3,999	33.1 (31.3 – 34.9)		8.8 (8.2 – 9.5)	
	4,000-49,999	41.2 (39.2 – 43.1)		12.0 (11.2 – 12.9)	
	50,000+	45.0 (42.8 – 47.3)		15.0 (13.8 – 16.3)	
Antiretroviral therapy	None	40.8 (38.9 – 42.8)	**<.0001**	11.8 (11.0 – 12.7)	**<.0001**
	Mono or combo	34.5 (32.3 – 36.7)		10.2 (9.3 – 11.1)	
	HAART	33.4 (31.4 – 35.4)		9.0 (8.3 – 9.7)	
PI use	Yes	34.0 (31.7 – 36.2)	**0.0005**	9.3 (8.6 – 10.2)	**0.0005**

Variable		CD8+CD38+DR+		CD4+CD38+DR+[†]	
		LS Means (95% CI)	p[a]	LS Means (95% CI)	p[a]
	No	37.7 (36.0 – 39.4)		10.8 (10.1 – 11.6)	
NRTI use	Yes	33.9 (32.1 – 35.7)	<**.0001**	9.5 (8.8 – 10.2)	<**.0001**
	No	40.6 (38.7 – 42.6)		11.8 (10.9 – 12.7)	
NNRTI use	Yes	32.0 (29.1 – 34.9)	**0.0005**	8.4 (7.4 – 9.4)	<**.0001**
	No	37.3 (35.7 – 39.0)		10.7 (10.0 – 11.4)	
Adherence to antiretroviral medications	Yes (≥95%)	38.3 (35.7 – 40.9)	**0.001**	9.3 (8.3 – 10.4)	**0.004**
	No	43.3 (39.9 – 46.7)		11.4 (9.9 – 13.2)	
Race/ethnicity	African American	38.8 (36.7 – 40.9)	**0.007**	11.1 (10.2 – 12.1)	**0.01**
	Hispanic	33.8 (30.6 – 36.9)		9.8 (8.6 – 11.2)	
	White or other	33.4 (29.7 – 37.1)		8.7 (7.7 – 9.9)	
Smoking	Current	37.8 (35.8 – 39.8)	0.22	10.5 (9.7 – 11.4)	0.32
	Past	36.6 (33.8 – 39.5)		9.6 (8.6 – 10.8)	
	Never	34.8 (31.8 – 37.8)		10.6 (9.4 – 12.1)	
Hepatitis C	Yes	36.9 (34.9 – 39.0)	0.06	10.5 (9.6 – 11.5)	0.70
	No	41.6 (37.3 – 46.0)		10.1 (8.4 – 12.1)	
Hypertension	Yes	38.1 (34.5 – 41.7)	0.95	10.0 (8.7 – 11.5)	0.61
	No	38.0 (35.9 – 40.0)		10.4 (9.5 – 11.2)	
Diabetes	Yes	32.3 (25.8 – 38.9)	0.20	9.3 (6.8 – 12.7)	0.49
	No	36.9 (35.3 – 38.5)		10.4 (9.7 – 11.1)	
BMI	< 25	38.2 (35.8 – 40.7)	**0.006**	11.0 (10.0 – 12.0)	**0.05**

Variable		CD8+CD38+DR+		CD4+CD38+DR+†	
		LS Means (95% CI)	p[a]	LS Means (95% CI)	p[a]
	25-29	34.7 (32.8 – 36.7)		9.8 (9.1 – 10.6)	
	30+	37.3 (35.0 – 39.7)		10.3 (9.4 – 11.3)	
HDL-C level, mg/dL	< 40	54.5 (48.0 – 60.9)	**0.003**	14.3 (11.9 – 17.2)	**0.001**
	≥40	39.7 (34.7 – 44.7)		8.8 (7.3 – 10.6)	
LDL-C level, mg/dL	≤130	45.6 (40.2 – 50.9)	0.68	10.3 (8.7 – 12.2)	0.55
	> 130	43.9 (38.1 – 49.7)		11.1 (8.8 – 14.1)	

†CD4+CD38+DR+ log transformed

[a]Generalized estimating equations with exchangeable correlation structure

Table 3

Association of early T-cell activation and carotid arterial stiffness

	Univariate		Multivariate							
			Model 1		Model 2 Model 1+CD4 count		Model 3 Model 1+HIV RNA		Model 4 Model 1+ CD4 count + HIV RNA	
	β estimate (SE)[b]	p-value	β estimate (SE)[b]	p-value	β estimate (SE)	p-value	β estimate (SE)	p-value	β estimate (SE)	p-value
Distensibility										
CD4+CD38+DR+	-0.12 (0.04)	0.002	-0.11 (0.04)	0.007	-0.10 (0.04)	0.02	-0.11 (0.04)	0.008	-0.10 (0.04)	0.02
CD8+CD38+DR+	-0.05 (0.02)	0.04	-0.04 (0.02)	0.08	-.04 (0.02)	0.11	-0.04 (0.02)	0.09	-0.04 (0.03)	0.12
Elasticity[a]										
CD4+CD38+DR+	0.004 (0.001)	0.002	0.003 (0.001)	0.004	0.003 (0.001)	0.02	0.003 (0.001)	0.006	0.003 (0.001)	0.02
CD8+CD38+DR+	0.002 (0.0007)	0.005	0.002 (0.0007)	0.03	0.001 (0.0007)	0.07	0.001 (0.0007)	0.05	0.001 (0.0007)	0.08

Model 1 adjusted for age, race, BMI, smoking, ART, menopause, time between activation marker and carotid ultrasound evaluations

[a] Elasticity is log transformed

[b] Units for distensibility 10^{-5}xNxm^{-2}, elasticity 10^{-6}xN^{-1}xm^{2}

Table 4

Association of early T-cell activation with carotid arterial stiffness parameters by HCV co-infection status

	HIV+HCV- (n = 191)		HIV+HCV+ (n = 185)		
	β estimate(SE)[a]	p-value	β estimate (SE)	p-value	*P* for interaction
Distensibility					
CD4+CD38+DR+	-0.06 (0.06)	0.31	-0.14 (0.06)	0.02	0.29
CD8+CD38+DR+	-0.04 (0.04)	0.26	-0.006 (0.04)	0.87	0.34
Elasticity					
CD4+CD38+DR+	0.001 (0.002)	0.55	0.005 (0.002)	0.01	0.08
CD8+CD38+DR+	0.0008 (0.001)	0.44	0.0009 (0.001)	0.42	0.90

Models adjusted for age, race, BMI, smoking, ART, CD4 count, HIV RNA, menopause, time between activation markers and carotid ultrasound evaluations

[a] Units for distensibility 10^{-5}xNxm^{-2}, elasticity 10^{-6}xN^{-1}xm^{2}

Table 5

Association of pre- and post-HAART T-cell activation with carotid arterial stiffness parameters (n = 140)

	Pre-HAART		Post-HAART	
	β estimate (SE)	**p-value**	**β estimate(SE)**	**p-value**
Distensibility				
CD4+CD38+DR+	-0.17 (0.06)	0.007	-0.20 (0.06)	0.002
CD8+CD38+DR+	-0.06 (0.04)	0.16	-0.04 (0.05)	0.42
Elasticity[a]				
CD4+CD38+DR+	0.005 (0.002)	0.003	0.005 (0.002)	0.005
CD8+CD38+DR+	0.001 (0.001)	0.19	-0.0003 (0.001)	0.86

Models adjusted for age, race, BMI, smoking, CD4 count, HIV RNA, menopause, time between activation markers and carotid ultrasound evaluations

[a] Elasticity is log transformed;

[b] Units for distensibility 10^{-5}xNxm^{-2}, elasticity 10^{-6}xN^{-1}xm^{2} Pre-HAART = 6 months preceding HAART initiation

Post-HAART = 6 months following HAART initiation