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Subclinical Cardiovascular Disease in HIV Controller and Long-Term Non-Progressor Populations

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Abstract

Objective: Elite controllers (EC), viremic controllers (VC), and long-term non-progressors (LTNP) control HIV viral replication or maintain $CD4^+$ T cell counts without antiretroviral therapy, but may have increased cardiovascular disease (CVD) risk compared to HIV-uninfected

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(HIV-) persons. We evaluated subclinical carotid and coronary atherosclerosis and inflammatory biomarker levels among HIV controllers, LTNP, HIV+ non-controllers and HIV- individuals in the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS).

Methods: We measured carotid plaque presence and common carotid artery intima-media thickness (IMT) in 1729 women and 1308 men, and coronary artery calcium and plaque in a subgroup of men. Associations between HIV control category and carotid and coronary plaque were assessed by multivariable regression analyses adjusting for demographics and CVD risk factors. Serum inflammatory biomarker concentrations (CD163, sCD14, Gal-3, Gal-3BP and IL-6) were measured and associations with HIV control categories assessed.

Results: We included 135 HIV controllers (30 EC) and 135 LTNP. Carotid plaque prevalence and carotid IMT were similar between HIV controllers, LTNP and HIV- individuals. HIV controllers and LTNP had lower prevalences of carotid plaque compared to viremic HIV+ individuals. Coronary atherosclerosis was similar in HIV controllers/LTNP compared to HIV- and viremic HIV+ men. Controllers and LTNP had higher concentrations of sCD163 and sCD14 compared to HIV- persons.

Conclusions: Subclinical CVD was similar in HIV controllers, LTNP and HIV- individuals despite elevated levels of some inflammatory biomarkers. Future studies of HIV controllers and LTNP are needed to characterize the risk of CVD among HIV+ persons.

Keywords

subclinical cardiovascular disease; carotid atherosclerosis; coronary atherosclerosis; human immunodeficiency virus; acquired immunodeficiency syndrome

INTRODUCTION

The widespread use of antiretroviral therapy (ART) to treat human immunodeficiency virus (HIV) is associated with extended survival,[1] which has resulted in greater age-related morbidity and mortality from noninfectious diseases, especially cardiovascular disease (CVD).[2–4] Traditional CVD risk factors, such as smoking,[5] contribute to increased CVD risk; however, adverse effects of ART[6,7] and elevated levels of inflammation and immune activation[8–11] are also implicated in higher CVD-associated morbidity and mortality among HIV-infected (HIV+) individuals.

HIV controllers are a rare subset of the HIV+ population who control viral replication in the absence of ART.[12,13] Long-term non-progressors (LTNP) are a related subset, classified by longitudinal stability of $CD4^+$ T-cell counts rather than by viral replication. HIV controllers and LTNP are overlapping phenotypes; however, important distinctions exist between the groups. While LTNP by definition do not show clinical progression of HIV infection in the absence of ART, they can have non-suppressed or even high-level viremia.[14] HIV controllers have chronic low-level viremia; however, they may demonstrate progression via decreasing $CD4^+$ T-cell counts over time.[14,15] The study of HIV controllers and LTNPs can help to elucidate the proportional contributions of ART, HIV replication, immunosuppression, and excess inflammation to subclinical CVD in HIV+ persons.

As with the broader HIV+ population, HIV controllers and LTNP exhibit increased levels of inflammation and immune activation/dysregulation compared to HIV-uninfected (HIV-) individuals.[16,17] Moreover, both HIV controllers and LTNP have increased T-cell activation compared to HIV+ non-controllers[18,19] even when compared to HIV+ non-controllers with ART-induced viral suppression.[20]. CVD risk among HIV controllers is less clear. Some smaller studies have shown a greater burden of subclinical carotid[21] and coronary[22] atherosclerosis among elite controllers compared to HIV- individuals. Although HIV infection may play a role in the development of atherosclerotic CVD, even when naturally controlled and independent of traditional CVD risk factors or ART, conclusive data among a larger sample of HIV controllers, including viremic controllers (VC) and LTNP, are lacking.

Carotid artery plaque and carotid intima-media thickness ([IMT], measured by carotid ultrasonography), and coronary artery plaque (measured by non-contrast computed tomography [CT] and coronary CT angiography [CTA]), are validated, non-invasive measures of subclinical atherosclerosis and vascular disease associated with increased risk for CVD events.[23–25] We performed carotid ultrasound in the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS), and cardiac CT scans in the MACS to assess subclinical CVD, and we measured inflammatory biomarker concentrations among a subset of MACS and WIHS participants. The purpose of this analysis is to compare the prevalence and extent of subclinical carotid and coronary atherosclerosis, as well as inflammatory biomarker levels, among HIV controllers, LTNP, HIV+ non-controllers, and HIV- individuals.

METHODS

Study Design and Inclusion Criteria

This study included participants from the MACS and WIHS, two ongoing prospective observational cohort studies of HIV+ and at-risk, HIV- men and women, respectively.[26,27] The MACS includes men who have sex with men and began enrollment in 1984, and the WIHS, which includes women, began in 1994. Each study includes semi-annual visits with structured interviews, physical examinations, and blood and urine collection. Participants with no known history of coronary artery disease were recruited in 2004 for participation in a vascular sub-study, which included carotid B mode ultrasound in MACS and WIHS[28] and non-contrast cardiac CT scans in MACS.[7] Additional MACS participants were recruited for a vascular sub-study in 2010 if they were between the ages of 40 to 70 years without a history of cardiac surgery or coronary revascularization. Some of these men also completed coronary CT angiography. The studies were approved by the institutional review boards of all participating sites. All participants provided informed consent.

Carotid Examination

Data were collected at a baseline visit from 2004–06 or from 2010–12. High resolution B-mode carotid artery ultrasound was performed to measure carotid plaque presence and mean far wall common carotid IMT as previously described.[28]

Cardiac CT Scans

Coronary artery calcium (CAC) was measured from non-contrast cardiac CT scans among MACS participants from 2010–13,[29,30] and coronary CT angiography was performed, as previously described.[31] Trained readers, blinded to participant characteristics and HIV serostatus, analyzed the CT images.[32] Each coronary segment was classified as normal or containing non-calcified, mixed (<50% of plaque area occupied by calcium) or calcified plaque. The coronary atherosclerosis measure used in analyses was coronary plaque presence, which was defined by the presence of one or more of any type of plaque in any coronary segment. Stenosis in each segment was defined as none, 1–29%, 30–49%, 50–69% or ≥70%.

HIV Control and Other Variables

HIV infection was determined by serologic testing (enzyme-linked immunosorbent assay [ELISA]) and confirmed using Western blot. The HIV control categories were HIV-, HIV controller, LTNP, HIV+ with undetectable viremia (viral load <50 copies/mL [MACS] or <80 copies/mL [WIHS]), and HIV+ with detectable viremia. For the two HIV+ non-controller categories, the viral load at the baseline carotid ultrasound visit was used to define undetectable versus detectable virema. HIV controllers were defined as elite controllers (EC) or viremic controllers (VC). Table 1 outlines these definitions. EC had undetectable viral load (as defined above), and VC had viral load <2000 copies/mL, each in the absence of ART. EC were included within the category of VC for the majority of analyses, unless otherwise specified, due to small numbers of EC. LTNP were defined as HIV+ individuals with $CD4^+$ T-cell counts ≥500 cells/μL for ≥5 years while not on ART. HIV controllers and LTNP who met criteria for multiple control definitions were included in each control category for the relevant analysis. Many HIV controllers and LTNP no longer met criteria at the time of the vascular study visit. For the primary analyses, participants who ever satisfied criteria for an HIV controller and/or LTNP category were included, even if they did not meet criteria at the time of the vascular study (see Discussion). HIV controllers and LTNP were combined for CT analyses due to small sample size.

Self-reported variables included age, race/ethnicity, income, education, history of injection drug use, current alcohol use, current cigarette smoking, history of diabetes mellitus (DM), and current use of antihypertensive and lipid-lowering medications. Measured CVD risk factors included body mass index (BMI), systolic blood pressure, total and high-density lipoprotein (HDL) cholesterol, and fasting glucose levels. In the MACS, DM was defined as a fasting serum glucose ≥126 mg/dL or self-reported use of DM medications. The WIHS expanded on this definition to also include DM self-report or hemoglobin A1c ≥6.5%, and confirmation by subsequent report of DM medication or laboratory parameter.[33] CVD risk factors were based on values recorded at the study visit closest to the vascular study visit. HIV clinical characteristics included baseline and nadir $CD4^+$ T-cell count, history of clinical AIDS, and cumulative duration of ART use.

Inflammatory Biomarker Measurements

Inflammatory biomarker concentrations were collected for an ancillary study among 1281 individuals from MACS and WIHS who had serial carotid ultrasound scans.[34]

Characteristics of this cohort have been previously described.[34] Biomarkers were chosen based on their established association with CVD risk.[9,10,34–37] Concentrations of soluble CD163 (sCD163), soluble CD14 (sCD14), interleukin-6 (IL-6), Galectin-3 (Gal-3) and Galectin-3BP (Gal-3BP) were measured using ELISA from stored frozen sera collected at the core study visit closest to the vascular study visit. All assays were performed at the University of Vermont in duplicate then averaged on single assay product lots. These analyses were restricted to HIV controllers and LTNP with biomarker measurements available who met exposure criteria at time of carotid ultrasound due to the variability of biomarker levels relative to ART use and viremia status.

Statistical Methods

Associations of HIV control category with presence of carotid and coronary plaque were assessed by estimation of prevalence ratios using modified Poisson regression.[38] Associations between HIV control category and extent of carotid IMT were assessed using linear regression. Models were adjusted for age, race/ethnicity, current cigarette smoking, MACS/WIHS center, education, current alcohol use and CVD risk factors (BMI, systolic blood pressure, total and HDL cholesterol, current use of antihypertensive or lipid-lowering medications, and DM). We used IVEware software to implement multiple imputation (5 imputation datasets) based on multivariate sequential regression separately for WIHS and MACS data, to account for the 1% of values that were missing.[39] Regression results for each imputation dataset were pooled using standard methods to account for increased variability due to the imputation process. Generalized gamma regression was performed in Stata to assess associations between HIV control categories and biomarker concentrations, adjusting for the same covariates as above. Shape and scale parameters were held constant, while the beta parameter was allowed to vary by exposure. Therefore, the percentage difference in biomarker concentrations associated with exposure category applies to all percentiles of the biomarker distribution.

RESULTS

Participant Characteristics

Our study included 210 HIV controllers and LTNP (31% female), including 30 EC, 105 VC, and 135 LTNP. There was overlap among HIV control categories, with 57 VC also meeting inclusion criteria for LTNP. Forty-three percent of LTNP had detectable viral load (median viral load 3220 copies/mL, interquartile range 453–13971). Fewer MACS participants satisfied control definitions at the time of carotid ultrasound compared to WIHS participants. Data on the timing of study visits relative to when participants met control definitions is shown in Supplementary Results.

Characteristics of the 1729 women in the WIHS and 1308 men in the MACS at the time of carotid ultrasound are shown in Table 2. Women in the WIHS tended to be younger, were more frequently African-American and tended to have lower blood pressure and lower total cholesterol compared to men in the MACS. A clinical AIDS diagnosis occurred in some controllers after they stopped satisfying the control definition. The median $CD4^+$ T-cell count was higher among HIV controllers and LTNP in the WIHS and MACS at the time of

the vascular study visit compared to HIV+ non-controllers, regardless of viral suppression among non-controllers. Fewer HIV controllers and LTNP in the WIHS were on ART at the time of carotid ultrasound compared to MACS participants (Supplementary Results).

Associations Between Carotid Plaque and HIV Control Status

The prevalence of carotid plaque and carotid IMT in each HIV control category are shown in Table 3. In adjusted analyses, there were no statistically significant differences between the prevalence of carotid plaque or extent of carotid IMT between HIV controllers or LTNP and HIV- individuals (Table 4 and Table 5, respectively). HIV+ individuals with detectable viremia had a 37% greater prevalence of carotid plaque compared to HIV- individuals (prevalence ratio [PR] 1.37, 95% confidence interval [CI] 1.11–1.68) after adjusting for demographics and CVD risk factors (Table 4). There were no statistically significant differences in carotid IMT among HIV control categories compared to HIV- individuals (Table 5).

In a secondary analysis comparing HIV controllers and LTNP to HIV+ individuals with detectable viremia, controllers and LTNP had a lower prevalence of carotid plaque (PR 0.73 (0.59–0.90), PR 0.72 (0.52–1.00), respectively, Supplementary Table 1). Another secondary analysis restricted the category of HIV controllers and LTNP to persons meeting the criteria at the time of carotid ultrasound. In adjusted analyses, there were no statistically significant associations between current HIV controller status and carotid plaque presence (Supplementary Table 2) or extent of carotid IMT (Supplementary Table 3) compared to HIV- individuals. Lastly, in secondary analyses limiting HIV controllers to only EC and when adjusting for duration of ART use, there were no significant differences in carotid plaque prevalence or extent of IMT compared to HIV- individuals (data not shown).

Associations Between Cardiac CT Findings and HIV Controller Status

We performed analyses of CAC (N=149 HIV controllers/LTNP) and coronary artery plaque on CT angiography (N=84 HIV controllers/LTNP) in the MACS. The prevalence of CAC in each HIV control category is shown in Supplementary Table 4. In adjusted analyses, there were no statistically significant differences in CAC prevalence between HIV controllers/LTNP and HIV- men (Supplementary Table 4). There were no substantial differences between control categories and coronary artery plaque presence on CT angiography among 84 HIV controllers/LTNP (including 8 EC and 41 VC) compared to HIV- men [adjusted PR 1.11 (0.85–1.47)]. There were also no statistically significant differences in the prevalence of coronary artery stenosis >50% or of specific plaque types (non-calcified, mixed, calcified; data not shown).

In a secondary analysis using HIV+ men with detectable viremia as the comparison group, HIV controllers/LTNP had similar CAC prevalence, prevalence of coronary artery stenosis and prevalence of specific plaque types (data not shown). Secondary analyses comparing HIV- individuals to EC only, and limiting categorization to current HIV controllers/LTNP at the time of CTA, also yielded statistically non-significant differences (data not shown).

Associations Between Inflammatory Biomarker Concentrations and HIV Control Status

Associations between inflammatory biomarker concentrations and HIV control category from 1281 individuals (including 33 HIV controllers/LTNP) who underwent carotid ultrasound are shown in Supplementary Figure 1. HIV controllers/LTNP had significantly higher concentrations ($p<0.05$) of sCD163 and sCD14 compared to HIV- individuals. HIV+ individuals with detectable viremia had higher concentrations ($p<0.05$) of all five biomarkers compared to HIV- individuals.

DISCUSSION

Subclinical cardiovascular disease is more prevalent among HIV+ than HIV- individuals.[28,40,41] Studying the rare HIV+ populations of HIV controllers and LTNP, using appropriate comparison groups, allows for better understanding of pathogenic factors contributing to CVD in the general HIV+ population. Studies have shown greater carotid IMT and coronary artery plaque prevalence among HIV controllers compared to HIV- individuals.[21,22] Our study is the largest study to date of HIV controllers and LTNP assessing carotid and coronary atherosclerosis using carotid ultrasound, non-contrast cardiac CT, and coronary CT angiography. There were no substantial differences in carotid plaque, carotid IMT, or coronary plaque between HIV controllers and LTNP and HIV- individuals; however, HIV controllers and LTNP had lower prevalence of carotid plaque compared to HIV+ individuals with detectable viremia. While the association between HIV serostatus and carotid IMT is complex,[42,43] Hanna et al. demonstrated an association between carotid plaque and mortality among HIV+ individuals.[44]

Prior studies by Hsue et al.[21] and Pereyra et al.[22] assessed the associations between elite controller status and subclinical carotid and coronary atherosclerosis, respectively. Hsue et al. demonstrated that EC (N=33, viral load <75 copies/mL) had greater carotid IMT compared to HIV- individuals (median 0.91 versus 0.72 mm).[21] Pereyra et al. demonstrated that EC (N=10, viral load <48 copies/mL) had a greater prevalence of coronary artery plaque on coronary CT angiography compared to HIV- individuals (78% versus 42%).[22] Neither study found substantial differences in subclinical atherosclerosis between HIV controllers and HIV+ non-controllers with suppressed viremia. While our study included EC, as well as VC and LTNP, we ran secondary analyses restricted to EC, in order to compare our work more directly to the previous studies.[21,22] We included a similar number of EC for the carotid analyses (N=30) as in the study by Hsue et al. (N=33)[21] and more EC for the analysis of coronary artery plaque than Pereyra et al. (N=10)[22]. When restricting to current EC, we had similar numbers (N=8) for the CTA analyses and fewer EC for the carotid analyses (N=16) compared to the prior work. Even in these sensitivity analyses, we showed similar prevalences of carotid plaque and CAC, and estimates of carotid IMT as in HIV- individuals.

Broadening our inclusion criteria to include VC and LTNP, in addition to EC, in both carotid and coronary analyses (N=210, N=149, respectively) improved the precision for estimating differences in subclinical atherosclerosis among these groups, HIV- individuals, and HIV+ non-controllers. Observational studies have shown that HIV controllers and LTNP often experience HIV disease progression over time; however, these individuals represent distinct

clinical phenotypes from HIV+ non-controllers.[45] In addition, carotid and coronary subclinical atherosclerosis generally develop slowly; therefore, the time spent virally exposed as an HIV controller or LTNP potentially has an impact on CVD risk.

There are some important clinical distinctions between HIV controllers and LTNP. LTNP often exhibit higher viral RNA levels compared to HIV controllers, despite high $CD4^+$ T-cell counts, while HIV controllers may have low $CD4^+$ T-cell counts despite low viremia.[45] Furthermore, Okulicz et al. showed steeper rates of $CD4^+$ T-cell decline among VC compared to EC, suggesting that even low-level viremia in VC may play a substantial role in clinical HIV progression.[14] In our study, the differences in viral load and T-cell activation appeared to be less marked among HIV controllers and LTNP. The median $CD4^+$ T-cell count was 506 cells/μL among VC and 763 cells/μL among EC, and 57% of LTNP had undetectable viral loads. Notably, among some HIV controllers and LTNP in the MACS especially, a substantial duration of time had elapsed between last satisfying criteria for a control category and the vascular study visit.

Elite controllers in prior studies were ART-naïve,[21,22] while over half of the HIV controllers and LTNP in the MACS who had previously met controller criteria were subsequently on ART. Prior work regarding CVD risk with ART use is not consistent. The SMART study demonstrated lower CVD risk among HIV+ individuals treated with continuous, rather than intermittent, ART, which was likely mediated by better viremic control,[46] while other studies have shown increased CVD risk with ART, although these studies generally included more clinically advanced HIV+ individuals and older drug formulations.[47,48] We performed sensitivity analyses adjusted for duration of ART that showed similar prevalence ratios of carotid plaque and extent of carotid IMT between HIV controllers, LTNP and HIV- individuals, suggesting that ART use was not a confounding variable with respect to CVD risk.

HIV controllers and LTNP had higher inflammatory biomarker concentrations compared to HIV- individuals. This study supports previous work demonstrating elevated concentrations of inflammatory biomarkers among HIV controllers and LTNP compared to HIV- individuals.[16,17,20,21] Levels of monocyte activation markers sCD163 and sCD14 have been associated with subclinical atherosclerosis in the MACS,[10] WIHS[35] and other cohorts.[9,34] Despite elevated concentrations of sCD163 and sCD14 in HIV controllers and LTNP compared to HIV- individuals, we found similar prevalences of carotid and coronary subclinical atherosclerosis. These findings could result from the complex interplay of host genetic and immunologic factors seen in HIV controllers.[12,17,49] T-cell activation among controllers is higher compared to ART-treated non-controllers,[12,49] and controllers have persistent low-level viremia, often greater than that seen with ART-treated HIV non-controllers.[50] Other contributing factors could include imprecision in our estimated differences in subclinical CVD or the duration of time between satisfying criteria for a control category and the vascular study visit.

The strengths of this study include the relatively large number of HIV controllers and LTNP included. Furthermore, the comparison groups were drawn from the same population as the HIV controllers and LTNP, in contrast to previous studies of subclinical CVD in HIV

controllers.[21,22] However, the absolute number of HIV controllers and LTNP included in this analysis remained limited. Particularly in the MACS, a significant proportion of HIV controllers and LTNP were on ART or no longer met the definition of controller at the time of the carotid ultrasound or CT scan, although we did perform sensitivity analyses adjusting for duration of ART use and restricting to current controllers. The cross-sectional observational study design limits our ability to assess causality. Our cohorts are well characterized, which allowed for adjustment for multiple confounding factors; however, there is always the possibility of unmeasured confounding variables.

In conclusion, there were similar prevalences of subclinical carotid and coronary atherosclerosis between HIV controllers and LTNP and HIV- individuals, and there was a lower prevalence of carotid plaque compared to HIV+ individuals with detectable viremia. Despite the similar prevalences of carotid and coronary atherosclerosis, HIV controllers and LTNP had higher concentrations of sCD14 and sCD163 compared to HIV- individuals. Future collaborative studies with large, well-characterized cohorts of HIV controllers and LTNP are needed to further characterize the risk of development of CVD among HIV+ persons, in order to design effective CVD screening, prevention and treatment strategies for this unique population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

HIV controller definitions

	MACS	WIHS
Elite controller	HIV-infected men with HIV-1 RNA <50 copies/mL tested on ≥2 occasions within 1.5 years for ≥2 years while not on ART *	HIV-infected women with HIV-1 RNA <80 copies/mL for ≥2 years while not on ART **
Viremic controller	HIV-infected men with HIV-1 RNA <2000 copies/mL and >50 copies/mL tested on ≥2 occasions within 1.5 years for ≥2 years while not on ART	HIV-infected women with HIV-1 RNA <2000 copies/mL and >80 copies/mL for ≥2 years while not on ART **

* Allowed one viral RNA measurement >50 copies/mL and <1000 copies/mL between HIV RNA levels <50 copies/mL.

** Allowed one viral RNA measurement between 2000 copies/mL and 20,000 copies/mL for VC and one viral RNA measurement between 80 copies/mL and 1000 copies/mL for EC, within the suppression episode, as long as it did not occur at either end of the suppression timeframe (time during which the individual met controller definition), and HIV RNA was measured at least once per calendar year.

Table 2.

Characteristics of carotid B-mode ultrasound study population

	WIHS				MACS			
	HIV controller/LTNP n=65	**HIV+ undetectable n=516**	**HIV+ detectable n=652**	**HIV- n=496**	**HIV controller/LTNP n=145**	**HIV+ undetectable n=439**	**HIV+ detectable n=225**	**HIV- n=499**
Age (years)	40.6 ± 9.2	41.1 ± 8.7	40.7 ± 8.8	37.0 ± 10.0	51.7 ± 6.4	49.1 ± 6.7	48.1 ± 6.6	53.1 ± 7.9
Black race (%)	66.2	50.4	63.0	61.3	22.8	28.0	42.2	24.4
BMI (kg/m^2)	31.2 ± 6.7	28.7 ± 7.1	27.9 ± 7.3	30.6 ± 8.2	25.6 ± 4.2	25.5 ± 4.9	25.2 ± 4.9	27.0 ± 5.0
Current smoker (%)	52.3	33.5	50.8	50.4	26.2	28.9	44.4	24.6
Former smoker (%)	20.0	26.6	20.2	20.8	49.0	44.6	32.9	48.3
Drinking 14+ drinks/week (%)	3.1	0.6	3.8	5.0	6.2	5.5	4.0	9.2
Income <$30,000/year (%)	73.8	79.8	85.1	81.5	33.8	50.8	64.4	36.3
Did not complete high school education (%)	40.0	35.3	44.9	33.3	4.1	6.6	10.7	4.8
Systolic blood pressure (mm Hg)	118 ± 15	117 ± 16	118 ± 18	118 ± 18	128 ± 14	125 ± 14	126 ± 15	129 ± 16
Blood pressure medication (%)	18.5	18.6	17.2	13.1	24.1	31.2	16.4	26.9
Total cholesterol (mg/dL)	174 ± 32	186 ± 42	164 ± 39	176 ± 38	193 ± 55	197± 46	182 ± 40	197 ± 42
HDL cholesterol (mg/dL)	47 ± 18	52 ± 18	43 ± 16	55 ± 16	45 ± 14	48 ± 16	43 ± 14	51 ± 14
Lipid-lowering medication (%)	6.2	10.1	3.2	1.6	26.9	33.7	17.8	22.2
Diabetes mellitus (%)	15.4	13.8	10.6	12.5	8.3	10.3	7.6	7.6
HIV Clinical Variables								
History of clinical AIDS (%)	4.6	35.7	40.5	-	13.1	13.9	14.2	-
Baseline ART use								
HAART use (%)	16.9	92.8	53.7	-	57.9	93.6	56.4	-
Combination therapy use (%)	1.5	0.6	2.0	-	9.7	5.7	5.3	-
Monotherapy use (%)	0.0	0.4	0.6	-	0.7	0.0	1.3	-
No ART use (%)	81.5	6.2	43.7	-	31.7	0.7	34.7	-
Years on HAART (years)	0 (0–0)	7 (5–14)	5 (2–10)	-	4 (0–7)	6 (4–9)	4 (1–7)	-
CD4$^+$ T-cell count (cells/μL)	626 ± 270	578 ± 291	364 ± 241	-	616 ± 273	612 ± 265	402 ± 232	-
Nadir CD4$^+$ T-cell count (cells/ μL)	364 ± 207	280 ± 195	297 ± 186	-	294 ± 169	293 ± 182	326 ± 365	-

	WIHS				MACS			
	HIV controller/LTNP n=65	**HIV+ undetectable n=516**	**HIV+ detectable n=652**	**HIV- n=496**	**HIV controller/LTNP n=145**	**HIV+ undetectable n=439**	**HIV+ detectable n=225**	**HIV- n=499**
Undetectable viral load *	35.4	100.0	0.0	-	62.5	100.0	0.0	-
HIV-1 viral load ** (copies/mL)	250 (<80–1500)	<80 (<80-<80)	6400 (990–29,000)	-	<40 (<40–599)	<40 (<10-<40)	5760 (623–34,900)	-

HIV controller definition includes viremic controllers and elite controllers. Undetectable, undetectable viral load; detectable, detectable viral load; HAART, highly-active antiretroviral therapy. Data are reported as mean (standard deviation) for normally distributed variables or percentage or median (interquartile range: 25%−75%) for non-normally distributed variables.

* Undetectable viral load: <50 copies/mL (MACS), <80 copies/mL (WIHS).

** among those with detectable viral load.

Table 3.

Unadjusted carotid artery plaque prevalence and common carotid intima media thickness by HIV control category

	WIHS		MACS	
	Carotid artery plaque prevalence	**CCA-IMT (μm)**	**Carotid artery plaque prevalence**	**CCA-IMT (μm)**
	N (%)	Median (IQR)	N (%)	Median (IQR)
HIV- (N=995 [496/499]) *	32 (6.5)	702 (642–769)	146 (29.3)	739 (676–831)
Elite controller (N=30 [19/11]) **	1 (5.3)	736 (682–787)	3 (27.3)	704 (674–775)
Viremic controller (N=105 [38/67])	1 (2.6)	715 (686–753)	20 (29.9)	759 (674–889)
Long-term non-progressor (N=135 [28/107])	1 (3.6)	720 (658–780)	30 (28.0)	746 (692–836)
HIV+, undetectable viremia (N=955 [516/439])	46 (8.9)	710 (646–778)	130 (26.9)	717 (659–810)
HIV+, detectable viremia (N=850 [652/225])	81 (12.3)	707 (654–775)	69 (27.8)	723 (662–786)

CCA-IMT = common carotid artery intima media thickness; IQR, interquartile range.

*N, total number of participants in HIV control category [number in WIHS/number in MACS].

**If HIV controllers/LTNP met criteria for multiple control definitions, they were included in each HIV control category.

Table 4.

Adjusted associations between HIV control category and carotid artery plaque prevalence

	WIHS (N=1724) PR (95% CI)	MACS (N=1308) PR (95% CI)	WIHS + MACS (N=3032) PR (95% CI)
HIV- (reference) (N=992 [493/499])*	1.00	1.00	1.00
HIV controller (N=135 [57/78])	0.44 (0.10, 1.85)	1.08 (0.76, 1.53)	0.96 (0.68, 1.35)
HIV+, undetectable (N=1000 [517/483])	1.07 (0.70, 1.64)	1.18 (0.96, 1.46)	1.17 (0.97, 1.42)
HIV+, detectable (N=905 [657/248])	1.33 (0.91, 1.95)	1.31 (1.02, 1.69)	1.37 (1.12, 1.69)
HIV- (reference) (N=992 [493/499])*	1.00	1.00	1.00
Long-term non-progressor (N=135 [28/107])	0.58 (0.08, 4.35)	1.04 (0.75, 1.43)	0.99 (0.73, 1.35)
HIV+, undetectable (N=993 [527/466])	1.03 (0.67, 1.58)	1.20 (0.98, 1.48)	1.18 (0.98, 1.42)
HIV+, detectable (N=912 [676/236])	1.32 (0.90, 1.93)	1.33 (1.02 (1.72)	1.38 (1.12, 1.70)

Prevalence Ratio (PR) adjusted for age, race/ethnicity, smoking, income, education, center, alcohol use, body mass index, diabetes mellitus, systolic blood pressure, use of hypertensive medications, total cholesterol, HDL-cholesterol, and use of cholesterol medications. Undetectable, undetectable viral load; detectable, detectable viral load.

*N, total number of participants in HIV control category [number in WIHS/number in MACS]. Separate models were performed for HIV controllers and for LTNP.

Table 5.

Adjusted associations between HIV control category and common carotid intima media thickness

	WIHS (N=1729) β (95% CI)	MACS (N=1308) β (95% CI)	WIHS + MACS (N=3037) β (95% CI)
HIV- (reference) (N=995 [496/499])*	0	0	0
HIV controller (N=135 [57/78])	−13 (−38, 13)	23 (−9, 55)	4 (−16, 25)
HIV+, undetectable (N=1001 [518/483])	−14 (−26, −2)	2 (−16, 20)	−9 (−19, 2)
HIV+, detectable (N=906 [658/248])	−15 (−27, −4)	12 (−10, 34)	−8 (−19, 3)
HIV- (reference) (N=995 [496/499])	0	0	0
Long-term non-progressor (N=135 [28/107])	−12 (−47, 24)	18 (−10, 46)	3 (−17, 24)
HIV+, undetectable (N=994 [528/466])	−14 (−26, −2)	1 (−17, 19)	−9 (−19, 1)
HIV+, detectable (N=913 [677/236])	−15 (−27, −3)	15 (−8, 37)	−7 (−18, 4)

Adjusted for age, race/ethnicity, smoking, income, education, center, alcohol use, body mass index, diabetes mellitus, systolic blood pressure, use of hypertensive medications, total cholesterol, HDL-cholesterol, and use of cholesterol medications. Undetectable, undetectable viral load; detectable, detectable viral load;

*N, total number of participants in HIV control category [number in WIHS/number in MACS]. Data are reported as β coefficient (95% confidence interval, μm). Separate models were performed for HIV controllers and for LTNP.