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Pre-Clinical Atherosclerosis due to HIV Infection: Carotid Intima-Medial Thickness Measurements from the FRAM Study

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Abstract

Background—Cardiovascular disease (CVD) is an increasing cause of morbidity and mortality in HIV-infected patients. However, it is controversial whether HIV infection contributes to accelerated atherosclerosis independent of traditional CVD risk factors.

Methods—Cross-sectional study of HIV-infected and control subjects without pre-existing CVD from the study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) and the Multi-Ethnic Study of Atherosclerosis (MESA). Pre-clinical atherosclerosis was assessed by carotid intima-medial thickness (IMT) measurements in the internal/bulb and common regions in HIV-infected and control subjects after adjusting for traditional CVD risk factors.

Results—For internal carotid, mean IMT was 1.17±0.50mm for HIV-infected participants and 1.06±0.58mm for controls ($p<0.0001$). After multivariable adjustment for demographic characteristics, the mean difference of HIV-infected vs. controls was +0.188mm (95%CI 0.113-0.263, $p<0.0001$). Further adjustment for traditional CVD risk factors modestly attenuated the HIV association (+0.148mm, 95%CI 0.072-0.224, $p=0.0001$). For the common carotid, HIV infection was independently associated with greater IMT (+0.033mm, 95%CI 0.010, 0.056, $p=0.005$). The association of HIV infection with IMT was similar to that of smoking which was also associated with greater IMT (internal +0.173mm, common +0.020mm).

Conclusions—Even after adjustment for traditional CVD risk factors, HIV infection was accompanied by more extensive atherosclerosis measured by IMT. The stronger association of HIV infection with IMT in the internal/bulb region compared to the common carotid may explain previous discrepancies in the literature. The association of HIV infection with IMT was similar to that of traditional CVD risk factors, such as smoking.

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Keywords

HIV; carotid IMT; smoking; cholesterol; diabetes; atherosclerosis

INTRODUCTION

The introduction of highly active antiretroviral therapy has led to a marked reduction in HIV/AIDS related mortality.[1-3] Accompanying this increased longevity, cardiovascular disease (CVD) has emerged as a significant cause of morbidity and mortality in those with treated HIV infection.[4-6]

Although continuous antiretroviral therapy appears to be associated with a lower rate of CVD than interrupted therapy[7,8], the extent to which CVD is accelerated due to HIV infection is not clear. In one review of a large registry, myocardial infarction (MI) hospitalization rates were increased 1.75 fold in those with HIV infection, with a stronger association seen in women (RR=2.98) than in men (RR=1.40).[9] In a study using MediCal claims data, coronary heart disease prevalence was significantly higher only in younger subjects with HIV infection compared to controls (men up to age 34 and women up to age 44).[10] In contrast, the adjusted risk of MI was lower in some older age groups of HIV-infected subjects compared to controls (>age 45). A third study of a health maintenance organization database found that the age-adjusted rates of hospitalization for coronary artery disease or MI were approximately 50-70% higher in HIV-infected men compared to control men.[11] One limitation of such studies is the inability to adjust adequately for traditional cardiovascular risk factors such as smoking.[9,11] Several studies have found that the prevalence of smoking is higher in those with HIV infection[11-14], which makes it difficult to the interpret studies that relied on registries and databases that did not have complete smoking data.

Furthermore, both HIV infection and the antiretroviral drugs used in HIV therapy have adverse effects on metabolic parameters that are known to contribute to CVD (reviewed in [15]). HIV infection is associated with decreased HDL and LDL, and increased triglycerides and VLDL. Some antiretroviral drugs induce hypertriglyceridemia, insulin resistance and diabetes. Most combination drug regimens restore LDL, but not HDL to normal levels.

Measurement of intima-medial thickness (IMT) in the carotid artery by ultrasound has been shown to be strongly associated with MI and coronary artery disease events.[16,17] While carotid IMT or presence of plaque has been used in many studies to assess factors contributing to atherosclerosis in HIV infection (reviewed in [18]), only a few studies have included control groups. Although some of those studies found an independent association of HIV infection with carotid IMT in the common carotid and the bulb region [19,20], most examined only the common carotid, not the internal or bulb region, and did not find a significant association of HIV infection with IMT after adjustment for other CVD risk factors.[21-25] For example, in a study of 168 HIV-infected and 68 HIV-uninfected participants, a 2-fold higher risk of lesions was found in the common carotid in HIV infection, but the risk ratio was reduced to 1.4 fold (p=0.32) after adjustment for gender, age, lipids and smoking.[21] However, a key limitation of many of these previous studies is the relatively small sample size of control participants, which limits the ability to detect independent associations with HIV infection. Of the two largest studies, one found an independent association of HIV infection with greater IMT in the common carotid and bulb after adjusting for demographics and traditional CVD risk factors[20], whereas the other found no evidence for an association of HIV infection with greater common carotid IMT

after adjusting for demographics, traditional CVD risk factors and a variety of non-traditional CVD risk factors[25].

Therefore, a major unanswered question is whether the effect of HIV infection on atherosclerosis is mediated by traditional CVD risk factors. A primary aim of the second examination of the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) was to evaluate this research question using carotid IMT.[26] To that end, we compared measurements of IMT in the common and internal/bulb regions of the carotid arteries in 433 HIV-infected participants from FRAM to 5749 control participants of similar age from FRAM and from the Multi-Ethnic Study of Atherosclerosis (MESA). We assessed the association of HIV Infection with carotid IMT after adjustment for demographics and traditional CVD risk factors (age, gender, race, smoking, diabetes, blood pressure and lipids).

METHODS

The FRAM study was initially designed to evaluate the prevalence and correlates of changes in fat distribution, insulin resistance, and dyslipidemia in a representative sample of HIV-infected participants and HIV-seronegative controls in the United States[26]. The second examination added measurements of carotid IMT to study pre-clinical atherosclerosis in HIV infection and incorporated data from the MESA study as additional controls. The methods of the FRAM study have been described in detail previously.[26] FRAM and MESA study protocols were approved by institutional review boards at all respective sites.

Study Population

The first FRAM exam enrolled 1183 HIV-infected and 297 HIV-uninfected controls from 2000-2. Control participants were recruited from two centers of the Coronary Artery Risk Development in Young Adults (CARDIA) study. The second exam, which included carotid IMT was conducted approximately five years later and examined 581 HIV-infected and 246 HIV-uninfected controls that had been seen at the first exam (three control participants were excluded, because they were found to be HIV-infected). Controls from the MESA study who had IMT preformed and matched inclusion criteria were also used for controls in this analysis. All three cohorts were nationally representative and the control groups were population-based.

FRAM HIV-Infected Study Sample—HIV-infected participants were initially recruited from 16 HIV or infectious disease clinics or cohorts, and were demographically nationally representative [26]. By the second exam, the FRAM HIV-infected participants were highly treated, with 97% having received some form of antiretroviral therapy and 94% having been on highly-active antiretroviral therapy.

FRAM CARDIA Study Sample—CARDIA participants were originally recruited in 1985-6 as a population-based sample of healthy 18-30 year old Caucasian and African-American women and men to longitudinally study cardiovascular risk factors.[27] At the time of the second FRAM exam, the CARDIA controls from the original FRAM study were 37-50 years old.

FRAM MESA Study Sample—An additional pool of control participants from the MESA study was included to supplement the control participant pool with individuals in the upper age range (45-78 years) of the HIV-infected FRAM participants. MESA was initiated in July 2000 to investigate the prevalence, correlates, and progression of cardiovascular

disease in a population-based sample of 6,814 men and women aged 45-84 free of clinical cardiovascular disease at enrollment, recruited from six U.S. field centers.[28]

To ensure comparability of the HIV-infected and control groups, participants included in this analysis were restricted to Caucasian, African-American, and Hispanic men and women aged 37-78 years who were free of clinical cardiovascular disease at the time of the ultrasound scan. All HIV-infected (n=433), MESA control (n=5521), and FRAM control (n=228) participants that met these criteria and had IMT measurements available were included in the analysis. Rather than age-matching participants from MESA, we used the entire cohort with available IMT measurements in this age range and adjusted for age as a covariate. Sensitivity analysis revealed similar findings for the association between HIV infection and IMT when the analysis was limited to HIV-infected and control participants matched on age, sex, and race/ethnicity (data not shown).

Data Collection

Demographic information, personal and family medical history, smoking and current medication use were assessed by structured questionnaires in the HIV-infected and control participants.[26,28]. Height, weight, and blood pressure were measured by standardized protocols. A fasting venous blood sample was collected from participants for measurement of glucose and lipids. We classified participants as having diabetes if they had a fasting blood glucose level of ≥126mg/dL (7.0mmol/L) or reported use of insulin or oral hypoglycemic medication.

Assessment of Carotid Intima-medial Wall Thickness

Trained sonographers at each field center performed B-mode ultrasonography of the right and left near and far walls of the common carotid and the internal carotid plus blub region of participants from MESA (Visit 1: 2002), FRAM HIV-infected participants (Visit 2: 2004-2007), and FRAM controls (Visit 2: 2005-2006). A standardized protocol for all 3 studies was developed by the Ultrasound Reading Center (Tufts Medical Center).[16,29] All sonographers were required to be trained and certified by the Tufts Ultrasound Reading Center, including review of scans. Manual tracings were used to compare segments. Ultrasound images were analyzed centrally at the Ultrasound Reading Center to calculate maximum near- and far-wall carotid intima-media thickness (cIMT) at each arterial site. The maximal wall thickness of the common carotid artery was computed as the mean of the maximum cIMT of the near and far walls of the right and left sides; available measurements of the common carotid ranged from 1-4 wall locations. Maximal cIMT of the internal carotid artery was computed in the same way and included the bulb region; available measurements ranged from 1-12 locations for FRAM HIV-infected and MESA participants and 1-16 locations for FRAM-Control participants. The greater number of measurements on FRAM-Control participants is due to a slightly different FRAM-Control reading protocol whereby separate measurements were attempted for the internal carotid artery and the carotid artery bulb (8 locations each), compared to MESA and FRAM HIV-infected which analyzed these anatomic sites as a single entity using 12 measurements.

Readers overlapped between both FRAM and MESA images and FRAM-Control and MESA images, which enabled us to adjust our statistical models for possible reader effects.[30] We had replicate readings (the same ultrasound scan read by 2 different readers) for a subset of HIV-infected (n=175) and control (n=134) participants; we included these replicates in the analysis, using generalized estimating equations (GEE) to account for the repeated measures. We tested for residual differences between study control populations in a combined MESA/FRAM-Control multivariable model for the participants who fell in the shared age range. This estimated adjusted differences between the two control groups of

-0.032mm (95%CI -0.138,0.074, p=0.56) for internal and -0.001mm (95%CI -0.044,0.042, p=0.96) for common. Although the confidence intervals are too wide to completely exclude a substantial difference between the two groups, the estimates suggest that any difference is likely to be too small to be of practical importance. We therefore combined the two control groups in the primary HIV vs. control multivariable models.

Statistical Analysis

We used linear GEE (with robust confidence intervals) to model the association between HIV infection and both common and internal/bulb cIMT. All models were adjusted for IMT reader. We applied a staged modeling approach for each cIMT outcome, first fitting a model with HIV infection alone, next fitting a model including HIV infection and demographic characteristics (age, gender, race/ethnicity), and finally fitting a model including demographics and traditional CVD risk factors (smoking status, diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, and HDL cholesterol). The small amount of missing data (~2%) was handled using a complete case approach. Non-linear age transformations were tested to confirm that a linear adjustment for age was adequate. All analyses were performed using PROC GENMOD in SAS version 9.1.3.

RESULTS

The characteristics of the participants studied are presented in Table 1. The age range of the participants in this analysis was restricted to 37-78 years, where there was overlap between the HIV-infected and control participants. The mean age of HIV-infected participants was 49 years and of controls was 61 years. Among HIV-infected participants, 70% were male, 51% Caucasian, 42% African-American and 7.2% Hispanic. Due to the design of the control cohorts, the controls were evenly divided by gender, and had a higher proportion of Hispanics that the HIV-infected cohort.

Current smoking was more common in HIV-infected participants (36%) than in controls (15%, p<0.0001). Prevalence of diabetes and use of medications for hypertension were similar in the HIV-infected and control participants. Differences in lipids and lipoproteins between HIV and controls are similar to previous reports.[31,32] HDL and total cholesterol levels were lower and triglyceride levels were higher in HIV infection.

Carotid IMT Measurements

Despite their younger age, mean unadjusted IMT for the internal carotid artery including the bulb region (Table 2) was higher in HIV-infected participants than in controls (1.17±0.50 vs. 1.06±0.58mm, p<0.0001). After multivariable adjustment for IMT reader and demographic factors (age, gender and race), the association of HIV infection with greater internal IMT was strengthened (+0.188mm, p<0.0001). This HIV association was somewhat attenuated after adjusting for the remaining traditional CVD risk factors (smoking, diabetes, blood pressure, total cholesterol and HDL-cholesterol), but the HIV-infected participants still had greater IMT (+0.148mm, p<0.0001). Although HIV infection was associated with greater internal carotid IMT in both women (+0.200mm) and men (+0.128mm), this association was stronger in women (p=0.046, test for interaction).

A similar pattern was seen in the common carotid artery, although the differences were smaller in magnitude (Table 2). Unadjusted mean common IMT levels were similar in HIV-infected participants and controls, but after adjustment for IMT reader and demographic characteristics, HIV infection was associated with 0.043mm greater IMT (p=0.0004). The HIV association was again somewhat attenuated after controlling for traditional risk factors to +0.033 mm, but remained statistically significant (p=0.005). The observed HIV

association was substantially stronger in women (+0.075mm) than in men for common carotid IMT (+0.013mm, test for interaction: p = 0.0034). The association of HIV infection with carotid IMT was similar when analysis was limited to either the MESA controls or the CARDIA controls and HIV-infected participants of the same age range (data not shown).

The multivariable adjusted associations of demographic factors, traditional CVD risk factors and HIV infection with both IMT measures are presented Table 3. For the internal carotid, the association of HIV infection (+0.148mm) was similar to that of current smoking (+0.173 mm), of diabetes (+0.117 mm) and of a 30mm higher systolic blood pressure (+0.162mm = 3x +0.054/10mm blood pressure). Similar results were found in the model for common carotid; the association of HIV infection (+0.033mm) with common carotid IMT was similar to that of smoking (+0.020mm), diabetes (+0.027mm), and a 10mm higher systolic blood pressure (+0.025mm). For both common and internal carotid IMT models, after systolic blood pressure entered the model, the diastolic blood pressure coefficient became negative, consistent with the known effects of pulse pressure on carotid IMT[33,34].

Although some effects, such as that of HIV infection, were stronger in one gender than the other (Supplemental Tables 1 and 2), we report results from the pooled model in Table 3 because the directions of their associations with IMT were the same in men and women for most factors. Within each gender, the magnitude of the HIV association was also similar to that of traditional risk factors such as smoking. Indeed, for the common carotid in women, the association with HIV infection (+0.077mm) with IMT was four times that of smoking (+0.01 mm). The weakest association of HIV infection with IMT was found in the common carotid for men (+0.013mm), where the association of HIV did not reach significance and was similar in magnitude to that of smoking (+0.017mm), but less than that of diabetes (+0.036mm).

Since IMT is known to be right-skewed, we performed a sensitivity analysis to address the question of whether a small group of individuals is driving the overall mean. We excluded participants with large dfbetas (a measure of how much impact each observation has on the predictor of interest). When we removed the 1% of individuals with the largest outliers (identified by the highest absolute value of cluster dfbeta), the HIV effect remained strong: 0.180 mm for internal cIMT (95%CI 0.111,0.249; p<0.0001) and 0.047 mm for common cIMT (95%CI 0.027,0.067; p<0.0001). Additionally, after removing outliers, the fully adjusted association between HIV and common cIMT remained statistically significant for both men (0.028 mm; 95%CI 0.004,0.053; p=0.0235) and women (0.080; 95%CI 0.046,0.115; p<0.0001).

We also considered the association of HIV infection with dichotomized IMT (internal or common IMT>1.5mm). Similar to the analysis considering IMT as a continuous measure, we found that the association of HIV infection with elevated cIMT was attenuated somewhat after adjustment for traditional CVD risk factors, but that it remained strong and statistically significant (RR=1.82; 95%CI 1.20,2.77; p=0.0047 for internal or common IMT>1.5). We also looked at the prevalence of stenosis and found that after adjustment for demographic and traditional risk factors, there was a higher risk of stenosis in HIV-infected participants compared with controls (RR=1.73; 95%CI 1.30,2.30; p=0.0002).

DISCUSSION

We have shown that pre-clinical atherosclerosis as quantified by ultrasound measurements of carotid IMT is increased in HIV-infected participants compared with controls, even after adjusting for demographics and traditional CVD risk factors. Thus while HIV infection and its therapies are associated with increases in several traditional CVD risk factors (e.g.,

decreased HDL cholesterol, increased non-HDL cholesterol and diabetes)[15], there is an additional effect of HIV infection beyond that on traditional CVD risk factors. The association of HIV infection with carotid IMT is similar in magnitude to that of traditional risk factors such as diabetes and smoking. The HIV association is of the magnitude of a 5-9 year increase in age. The association of HIV infection with carotid IMT was stronger in women than in men. These results have several implications for both research and clinical practice.

Previous findings from analyses of registries and administrative databases have suggested that the rates of CVD or MI are higher in HIV-infected patients than in uninfected patients.[9,11] Such studies, however, are unable to fully adjust for differences in the distribution of traditional CVD risk factors between HIV-infected and control participants. Given the many effects of HIV infection and antiretroviral drugs on metabolic parameters[15], the finding that there is an association of HIV infection with atherosclerosis beyond that explained by metabolic disturbances has important implications for risk assessment in patients. The residual increase in atherosclerosis as measured by IMT implies increased independent risk of coronary artery disease and stroke associated with HIV infection and/or its therapies. Now that patients with HIV infection are living longer, these data suggest that clinicians should consider HIV infection as a candidate CVD risk factor. This may be especially important for HIV-infected patients who have an intermediate level of risk as determined by predictive equations such as that from the Framingham Study.[35,36]

The finding that a stronger association of HIV infection with carotid IMT is seen in women compared to men is consistent with one registry study.[9] In that study, HIV-infected women had significantly more cardiovascular events than women controls, but the association in men was much smaller and did not reach statistical significance. Our data suggest that HIV infection may confer increased CVD risk in both sexes, but to a greater extent in women. In women, the association of HIV infection with IMT was greater than that of smoking; in men, the association of HIV infection with IMT was similar to that of smoking.

In the non-HIV-infected population, the effect of some risk factors, such as diabetes, on CVD are also more marked in women than men.[37] For example, after adjustment for other risk factors, diabetes was associated with a 70% higher risk of death from CVD in diabetic men compared to men without diabetes, and 230% higher risk in diabetic women compared to women without diabetes. Gender differences have also been observed for associations of risk factors with carotid IMT; for example, metabolic syndrome is more of an independent risk factor for greater carotid IMT in women than in men.[38]

Furthermore, we have previously shown that Caucasian women have the most atherogenic lipid profile among HIV-infected demographic groups, as LDL levels are not decreased by HIV infection[31,32] Those findings raise the possibility of additional increased risk in HIV-infected women relative to HIV-infected men mediated by traditional CVD risk factors.

We found that the HIV association was stronger with internal carotid IMT (including the bulb region) than with common carotid IMT. It is therefore of interest that the studies which found little association of HIV infection with IMT made those measurements only in the common carotid.[21-25] For example, one study of triads of 45 subjects, 89% male, found the common carotid to be 0.002 mm greater (95%CI -0.013,0.017; $p = 0.80$) in HIV-infected subjects not on protease inhibitors and 0.010 greater (95%CI -0.011,0.031; $p = 0.34$) in HIV-infected subjects continuously on protease inhibitors compared to controls.[23] A larger study of both men and women that included 1510 controls found evidence that HIV

infection was not associated with greater common carotid IMT after adjustment for demographic, traditional CVD risk factors and lifestyle factors, as the adjusted association was -0.007 mm for both HIV-infected men (95%CI -0.027,0.012, p=0.47) and women (95%CI -0.018,0.003, p=0.12) compared to controls.[25] However, the other large study that included 1168 controls did find an independent association of HIV infection with carotid IMT, with a much larger association seen at the bifurcation (HIV = +0.250mm, 95%CI, 0.198,1.303, p<0.0001) than in the common carotid (HIV = +0.044mm, 95%CI 0.021,0.066, p=0.0001).[20] The later results are comparable to our finding of an adjusted HIV association of 0.148mm (95%CI 0.072,0.224, p=0.0001) in the internal carotid including the bulb and 0.033mm (95%CI 0.010,0.056, p=0.005) in the common carotid. Furthermore, the earlier, smaller study finding an independent association of HIV infection with IMT also measured IMT in the bulb.[19] The reasons for the discrepancies among these reports deserve further study, but our results suggest that future studies in HIV infection should include the internal carotid and the bulb, which may be the locations where increased atherosclerosis due to HIV infection begins.

Limitations of our study include the use of cross-sectional data for both risk factors and carotid IMT. Given that the effects of HIV and anti-retroviral therapy on CVD risk factors are dynamic and cumulative, it might have been ideal to have longitudinal data for risk factors such as cholesterol, HDL and blood pressure. However, examination of the data from the first and second FRAM examinations shows surprisingly little change in metabolic parameters despite switches in antiretroviral therapy (data not shown). Controls ideally would have been identical except for the presence of HIV infection, but such a cohort would be impractical and perhaps impossible to develop. However, a major strength of this study was a large control group with extensive data on CVD risk factors that enabled us to adjust for relevant traditional CVD risk factors, including age, which was our major aim. Furthermore, we measured both the common carotid and the internal/bulb regions, which enabled us to explain the discrepancies in earlier reports.

Although we cannot rule out an association of HIV-related factors with IMT, we did not identify any HIV-related factor that could explain much of the HIV effect. The effects of HIV infection reported here include any effects of anti-retroviral drugs that are independent of their metabolic effects. Unlike in Maggi *et al*, who found a higher prevalence of lesions in those with PI therapy[39], we did not find a substantial association of PI exposure (or other antiretroviral drugs or classes) with increased IMT.

In summary, even after adjusting for traditional CVD risk factors, HIV infection is associated with increased pre-clinical atherosclerosis as measured by carotid IMT. The association of HIV infection with IMT is stronger in the internal and bulb region than in the common carotid. The association of HIV infection is more pronounced in women than in men. These results should be considered when clinicians assess CVD risk in HIV infected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Conflicts of Interest

All authors received funding from some of the supporting grants.

Role of the Funder

The funder played no role in the conduct of the study, collection of the data, management of the study, analysis of data, interpretation of the data or preparation of the manuscript. A representative of the funding agent participated in planning the protocol. As part of the standard operating procedures of CARDIA, the manuscript was reviewed at the NHLBI, but no revisions were requested.

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Table 1

Demographic and Clinical Characteristics of HIV-infected and Control Participants*

	FRAM HIV+	Controls
N	433	5749
Age in years	49 (7.7)†	61 (9.6)
Gender		
Female	30.5%	52.6%
Male	69.5%	47.4%
Race		
African-American	42.3%	31.9%
Caucasian	50.6%	44.0%
Hispanic	7.2%	24.1%
Smoking Status		
Current	36.3%	14.6%
Past	24.3%	38.1%
Never	39.5%	47.3%
Diabetic	8.7%	13.5%
Systolic BP (mmHg)	124.6 (7.6)	125.6 (20.8)
Diastolic BP (mmHg)	77.7 (10.1)	72.2 (10.2)
Lipid Lowering Medication Use	24.2%	16.0%
Antihypertensive Medication Use	27.3%	33.1%
Total Cholesterol (mg/dL)	188.2 (47.8)	194.8 (36.5)
HDL Cholesterol (mg/dL)	46.5 (16.8)	51.1 (15.0)
Triglycerides (mg/dL)	197.5 (161.9)	130.4 (91.5)
Family History of MI		
Parent	29.6%	35.9%
Sibling	5.1%	13.7%

Abbreviations: SD = standard deviation; BP = blood pressure; MI = myocardial infarction;

* Restricted on age (37-78 years) and race/ethnicity (African-American, Caucasian, Hispanic)

† Data for continuous variables are presented as mean (SD).

Table 2

Analysis of Common and Internal Carotid Intimal-Medial Thickness (cIMT) by HIV-infected and Control Participants.

IMT Measure	HIV-infected (N = 433*)	Controls (N = 5749*)	p-value†
Internal Carotid			
Internal carotid IMT (mm), Mean (SD)	1.17 (0.50)	1.06 (0.58)	<.0001
Mean difference of HIV-infected vs. Controls (95% CI)			
Adjusted for demographics‡	0.188 (0.113, 0.263)		<.0001
Adjusted for demographics and traditional CVD risk factors§	0.148 (0.072, 0.224)#		0.0001
Common Carotid			
Common cIMT (mm), Mean (SD)	0.88 (0.16)	0.86 (0.19)	0.17
Mean difference of HIV-infected vs. Controls (95% CI)			
Adjusted for demographics‡	0.043 (0.019, 0.066)		0.0004
Adjusted for demographics and traditional CVD risk factors§	0.033 (0.0010, 0.056)#		0.005

*N denotes number of participants included in analysis. Age restricted to 37-78 years and race restricted to include only African Americans, Caucasians, and Hispanics, to match the demographics of MESA and FRAM-controls.

†P-value for comparison of IMT levels in HIV+ vs. Control.

‡Adjusted for age, gender, race and reader.

§Adjusted for age, gender, race, reader, smoking status, diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, and HDL cholesterol.

#HIV association is stronger in women for common cIMT (p=0.003) and Internal cIMT (p=0.046)
HIV association in men for internal cIMT: 0.128 (95%CI 0.028, 0.228, p=0.012)
HIV association in women for internal cIMT: 0.200 (95%CI 0.082, 0.318, p=0.009)
HIV association in men for common cIMT: 0.013 (95%CI -0.032, 0.057, p=0.55)
HIV association in women for common cIMT: 0.077 (95%CI 0.035, 0.118, p=0.0003)

Table 3

Factors Associated with Carotid Intima-Medial Thickness in HIV Infected and Control Participants (demographics and traditional CVD risk factors)

	Internal Carotid IMT			Common Carotid IMT		
	Estimate	**95% CI**	**P-value**	**Estimate**	**95% CI**	**P-value**
HIV-infection	0.148	(0.072, 0.225)	0.0001	0.033	(0.010, 0.056)	0.005
Age (per 10 years)	0.162	(0.145, 0.180)	<.0001	0.073	(0.068, 0.078)	<.0001
Male	0.133	(0.101, 0.164)	<.0001	0.054	(0.045, 0.063)	<.0001
Black	-0.027	(-0.058, 0.005)	0.10	0.054	(0.045, 0.063)	<.0001
Hispanic	-0.083	(-0.117, -0.049)	<.0001	0.000	(-0.010,0.010)	0.93
Current smoker	0.173	(0.135, 0.210)	<.0001	0.020	(0.010, 0.031)	0.0002
Past smoker	0.091	(0.061, 0.121)	<.0001	0.020	(0.012, 0.028)	<.0001
Diabetes	0.117	(0.068, 0.165)	<.0001	0.026	(0.014, 0.039)	<.0001
Systolic BP (per 10 mmHg)	0.054	(0.043, 0.066)	<.0001	0.025	(0.022, 0.028)	<.0001
Diastolic BP (per 10 mmHg)	-0.065	(-0.086, -0.044)	<.0001	-0.026	(-0.032, -.020)	<.0001
Total Cholesterol (per 10 mg/dl)	0.009	(0.006, 0.013)	<.0001	0.004	(0.003, 0.005)	<.0001
HDL Cholesterol (per 10 mg/dl)	-0.022	(-0.032, -0.013)	<.0001	-0.011	(-0.014, -.008)	<.0001

Abbreviation: BP = Blood Pressure