Patients with Human Immunodeficiency Virus on Chronic Antiretroviral Treatment Have Increased Carotid Artery Wall Thickness on Magnetic Resonance Imaging in Comparison to Controls

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Concise Title: Carotid Artery Wall Thickness and HIV

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ABSTRACT

Objectives: While patients with human immunodeficiency virus (HIV) have an elevated stroke risk, ultrasound studies of carotid artery wall thickness have reported variable results. We hypothesized that subjects with HIV on chronic highly active antiretroviral therapy (HAART) would have increased carotid artery wall thickness by magnetic resonance imaging (MRI).

Methods: This cross-sectional study compared carotid artery wall thickness between 26 individuals infected with HIV on chronic HAART and 20 controls, without HIV but with similar cardiovascular risk factors, using 3.0-T non-contrast MRI. Inclusion criteria included males aged 35-55 years, and chronic HAART ($\geq$3 years) among HIV-seropositive subjects; those with known cardiovascular disease or diabetes were excluded.

Results: Between subjects with HIV and controls, there were no differences in age (47.8±5.0 vs. 47.8±4.7 years, p=0.19) or cardiovascular risk factors (p>0.05 for each). Mean wall thickness was increased in those with HIV versus controls for the left (0.88±0.08 vs. 0.83±0.08 mm, p=0.03) and right (0.90±0.10 vs. 0.85±0.07 mm, p=0.046) common carotid arteries. Among individuals with HIV, variables associated with

increased carotid artery wall thickness include lipoaccumulation [+0.09 mm, 95% confidence interval (CI) 0.03 to 0.14, p=0.003], Framingham risk score ⩾5% (+0.07 mm, 95% CI 0.01 to 0.12, p=0.02), and increased duration of protease inhibitor therapy (+0.03 mm per 5 years, 95% CI 0.01 to 0.06, p=0.02).

Conclusion: Individuals with HIV on chronic HAART have increased carotid artery wall thickness as compared to similar controls. In subjects with HIV, the presence of lipoaccumulation and duration of protease inhibitor therapy are associated with greater wall thickness.

Key Words: human immunodeficiency virus; stroke; carotid artery disease; magnetic resonance imaging; highly active antiretroviral therapy

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a leading cause of morbidity and mortality, with over 1 million persons infected and 55,000 new cases annually in the US alone (1). Since the introduction of highly active antiretroviral therapy (HAART), HIV has become a chronic, treatable disease similar to hypertension and hyperlipidemia, and life expectancy may approach those of uninfected persons in patients with durably suppressed virus (2-5). As the population with HIV ages, an excess of strokes (6-8) and myocardial infarctions (9,10) have been observed. Comparisons of the carotid artery utilizing ultrasound between individuals with and without HIV have provided disparate results, with some studies finding an increase in carotid artery intimal medial thickness among HIV patients as compared to controls (11-15), and other studies observing no difference (16,17). Existing studies have generally included untreated HIV-infected individuals, and it is not clear whether individuals with HIV on chronic, contemporary HAART have increased carotid wall thickness.

We hypothesized that individuals with HIV on chronic HAART would have increased carotid artery wall thickness. As carotid artery imaging by magnetic resonance imaging (MRI) may provide results similar to ultrasound with reduced inter-procedure variability (18), we utilized 3.0-T MRI to compare carotid artery wall thickness

between individuals with HIV on ⩾3 years of HAART with similar controls. We further evaluated the relationship between selected clinical variables and carotid artery wall thickness among subjects with HIV.

METHODS

The study recruited 26 HIV-infected (HIV+) subjects on HAART from a single academic medical center and 20 HIV-negative controls. Inclusion criteria were: male gender, age of 35-55 years, and (for cases only) continuous HAART for ⩾ 3 years. HAART was defined as the use of at least three different anti-HIV medications to achieve viral suppression. Exclusion criteria included history of cardiovascular disease (coronary artery disease, myocardial infarction, stroke, or prior revascularization), hepatitis C infection, diabetes, prior intravenous drug use, prolonged interruptions of HAART (⩾3 months), prior AIDS-defining illness, or contraindications to MRI. HIV-negative controls were recruited from the same community as the subjects. Control subjects were recruited via subjects' referral of friends and acquaintances in similar social circles, to approximate characteristics of those with HIV based upon age, race, sexual orientation, lifestyle factors, drug use, and medical history as previously done (19). This study was reviewed and approved by our Institutional Review Board and all subjects provided written informed consent.

Subjects with HIV had high medication compliance (mean 99±2%, range 90-100%) and 100% had an undetectable HIV RNA by PCR testing. The mean CD4+ T cell count was 682±468 cells/mm^3 (range 242 to 2597 cells/mm^3). Mean duration of HIV diagnosis was 16.8±8.1 years (range 4-30 years), and mean duration of HAART was 13.4±7.3 years (range 3-28 years). Protease inhibitors had been used in 24/26 patients during their treatment history; current protease inhibitors were used in 18/24 patients, with all 18 patients utilizing ritonavir as a "booster" PI.

An *a priori* power analysis was performed to determine the required sample size. To decrease the required sample size of the study, we *a priori* planned to evaluate the left and right carotid arteries in the same analysis to double our sample size, with a plan to adjust for the potential clustering effect. Based on prior estimates of carotid

intimal medial thickening of 0.62 ±0.11 mm and 0.70 ±0.10 between individuals without HIV and individuals with HIV on HAART (15), 25 subjects in each group with 2 carotids arteries each was determined to provide 85-89% power to detect a difference in mean carotid artery thickness between groups, using a two-tailed analysis, an alpha of 0.05, and after accounting for a clustering effect for the two arteries with a range of intra-cluster correlations from 0.50-0.70. During a pause in enrollment due to changes in study personnel, we performed an interim analysis when 46 of the 50 planned subjects were enrolled. At that time, we identified significant differences between groups, and we terminated subject enrollment early. As we observed significant differences for the separate left and right carotid arteries, a combined analysis that considered the left and right as independent arteries but attempted to correct for intra-subject clustering was no longer needed, and we instead performed separate analyses of the left and right carotid arteries. This eliminated the potential error and statistical assumptions required to estimate the clustering effect for a combined analysis.

All subjects and controls completed a detailed medical and social history questionnaire. For patients with HIV, medical records were reviewed to provide details regarding HIV medical and treatment history. A physical exam was performed by an experienced infectious disease specialist to assess anthropometric variables, including the presence of lipodystrophy, defined as the pathologic presence (lipoaccumulation) or absence (lipoatrophy) of adipose tissue in various anatomic locations consistent with HAART-associated side effects, consistent with previous literature (20). If lipodystrophy was present, further physical evaluation was performed to determine the presence of lipoaccumulation and/or lipoatrophy. Height, weight, waist circumference, and hip circumference were measured for each subject.

Subjects were instructed to abstain from caffeine, alcohol and vigorous exercise for at least 24 hours before all MRI procedures. A fasting, venous blood sample was obtained for measurement of glucose, lipids, complete blood count, and basic metabolic panel. In control subjects, HIV testing was performed to confirm the absence of HIV infection. All subjects with HIV had prior serologic testing that confirmed the diagnosis and justifying documented HIV treatment. Framingham cardiac risk factor scoring was

calculated according to standard criteria, accounting for age, cholesterol, smoking history, and blood pressure (21).

All magnetic resonance imaging was performed using a 3.0-Tesla whole body scanner (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany) and a bilateral four-channel carotid surface coil (Machnet BV, TD Eelde, The Netherlands). Subjects were scanned in a head first supine position. This study utilized images without the use of intravenous contrast. Multislice two-dimensional (2D) time-of-flight imaging was first performed to localize the left and right carotid artery bifurcation. The acquired images were also used to create minimal-intensity-projection images that were later used for positioning the vessel wall scan planes perpendicular to the axis of each common carotid artery. Typical scan parameters were as follows: repetition time / echo time = 22/5 msec; flip angle = 52°; slice thickness = 3 mm with an inter-slice gap of 3 mm; 30 slices; matrix size = 256x204; field of view 220x175 mm^2; in-plane spatial resolution = 0.86 x 0.86 mm^2.

Dedicated T1-weighted dark-blood imaging was performed separately for the left and right common carotid arteries, with imaging obtained over a 36 mm length in 2 mm increments proximal to the bifurcation of each common carotid artery. A multi-slice 2D T_1-weighted turbo spin echo sequence with spatial pre-saturation band-based dark-blood preparation was used. Sequence parameters were: axial imaging orientation; 18 slices; slice thickness = 2 mm; matrix size = 256x256; field of view = 160×160 mm^2; in-plane spatial resolution = 0.625×0.625 mm^2; repetition time / echo time = 800/12 msec; echo train length = 7; and echo train duration = 63 msec. Chemically selective fat suppression was applied to improve the definition of the outer wall boundary and avoid chemical shift artifacts.

As previously done, a short-axis image was selected for each common carotid artery immediately inferior to the carotid bulb and within 2 cm of the bifurcation (22). Existing literature has demonstrated good agreement between carotid intimal medial thickness and MRI utilizing semi-automated measurements of the carotid wall (18). Although proprietary automated tools have been developed, these are not commercially available or validated, so we averaged the diameter of the arterial wall from 8 evenly distributed sites manually measured on the short-axis image. In addition, the cross-

sectional external area and luminal area of each common carotid artery area were manually traced on the same short-axis images, with the difference of these representing cross-sectional wall area including the vessel wall and any plaque (**Figure 1**). The wall area was indexed to the external area (wall area / external area) as described previously (23). The presence of any visible carotid artery plaque was defined as visible wall thickening on any slice that was observed in at least two consecutive slices. Carotid artery distensibility was calculated in a manner consistent with prior literature, using the mean diameter derived from tracing the cross-sectional area of each artery at end-systole and end-diastole [distensibility coefficient = (2*change in diameter / end-diastolic diameter / pulse pressure] (22) using bright-blood cine images. A single blinded experienced reader performed all carotid measurements, using OsiriX version 5.8.1 for Mac OS X (OsiriX Foundation, Geneva, Switzerland). To minimize any bias, cases and controls were read in a random sequence, and the reader was blinded to all clinical variables including HIV status.

Our primary endpoint was a comparison in mean carotid artery thickness between groups. Secondary endpoints included comparisons of the cross-sectional wall area, indexed wall area, the presence of visible carotid artery plaque, and carotid artery distensibility. Comparisons of continuous variables were performed using the student's t-test for variables with normal distributions or the Mann-Whitney U test for variables without a normal distribution. Fisher's exact test was used for comparisons of categorical variables.

We further assessed clinical and laboratory characteristics among those with HIV to determine which of these variables might be associated with increased carotid artery wall thickness. These comparisons were performed using linear regression analysis that utilized the mean value of the left and right common carotid arteries for each patient. Statistical analyses were performed using IBM SPSS version 20 (IBM Corporation; Armonk, NY) for Mac OS X.

RESULTS

Patients with HIV (n=26) and controls (n=20) did not have statistically significant differences in regards to demographics, medical history, body mass index, medication

use (excluding anti-retrovirals), blood pressure, fasting cholesterol and glucose, and Framingham risk score (**Table 1**). HIV+ patients were more likely to report previous non-intravenous illicit drug use, had higher rates of clinical lipodystrophy, and greater resting heart rates.

HIV-seropositive subjects had increased bilateral common carotid artery wall thickness as compared to controls, while no differences were observed in external vessel area, luminal area, wall area, normalized wall area, or carotid distensibility index (**Table 2**).

The relationship between relevant clinical characteristics and carotid wall thickness in subjects with HIV is provided in Table 3. The presence of clinical lipodystrophy (specifically lipoaccumulation), an increased Framingham risk score, and greater duration of protease inhibitor therapy were each associated with increased carotid wall thickness.

There was a trend for increased duration of HIV diagnosis to be associated with greater carotid wall thickness on linear regression (p=0.08). In comparison to subjects with shorter diagnosis duration, those with an HIV diagnosis duration of ⩾10 years (⩾ 25th percentile) were observed to have a significant increase in carotid artery wall thickness [+0.07 mm, 95% confidence interval (CI) 0.01 to 0.13 mm, p=0.049], while no significant difference was observed in subjects with ⩾17 years (⩾50th percentile) of HIV diagnosis (+0.02 mm, 95% CI -0.03 to 0.08, p=0.40).

A longer duration of HAART was not associated with a difference in carotid artery wall thickness (p=0.29), and no significant differences were observed in subjects with ⩾ 6 years (⩾25th percentile) of HAART (+0.10 mm, 95% CI -0.01 to 0.11, p=0.10) or ⩾14 years (⩾50th percentile) of HAART (+0.01 mm, 95% CI -0.05 to 0.07, p=0.78) in comparison to those with shorter duration of HAART.

We further examined HIV+ subjects stratified by those with treatment with "high-risk antiretroviral agents. These "high-risk" agents are those previously noted to be associated with an increased risk of myocardial infarction, and include: protease inhibitors, including amprenavir, fosamprenavir, indinavir, lopinavir and nucleoside reverse transcriptase inhibitors including, abacavir and didanosine (9,24-26). Any use of "high-risk" protease inhibitors was observed in 77% (20/26) of subjects, and was not

associated with a significant difference in carotid artery wall thickness (+0.04 mm, 95% CI -0.03 to 0.10, p=0.31). Prior use of "high-risk" nucleoside reverse transcriptase inhibitors was noted in 46% (12/26) of HIV-seropositive subjects, and was also not associated with a difference in wall thickness (+0.03 mm, 95% CI -0.03 to 0.09, p=0.27).

DISCUSSION

This study finds that HIV-infected individuals receiving HAART for greater than three years have increased carotid artery wall thickness on MRI compared to HIV-negative controls, despite similar cardiovascular risk factors. Furthermore, among these HIV-seropositive subjects, increased wall thickness was associated with lipoaccumulation, elevated Framingham risk score, duration of protease inhibitor therapy, and an HIV diagnosis of ⩾10 years.

Several carotid artery ultrasound studies have reported an increase in carotid intimal medial thickness among subjects with HIV compared to controls (11,13-15), while other studies have reported no significant differences between groups (17,27). These studies examined heterogeneous populations, and generally included both treated and untreated. In comparison, this study examined patients with HIV on chronic HAART, as this represents a group of individuals more likely to survive to an older age and to have an increased risk of cardiovascular events. All of our HIV subjects had undetectable viral loads and high rates of medication adherence, suggesting an optimal HAART response. We further examined a relatively young population without known cardiovascular disease but with a significant duration of HIV diagnosis (mean 16.8 years) and HAART therapy (mean 13.4 years), which would be expected to have a low rate of carotid atherosclerosis absent HIV infection and concomitant use of HAART. These findings suggest that despite optimal medical management of HIV infection with contemporary HAART regimens a relatively young cohort of individuals with HIV may remain at increased risk for subclinical carotid artery atherosclerosis.

This study identifies a positive relationship between clinical lipodystrophy and carotid wall thickness in patients with HIV on chronic HAART, and may be related to metabolic alterations in this population(28). While these results contrast with a prior study using ultrasound(15), these discordant results may be explained by differences in

the examined populations, imaging modality, and measurement techniques. It is important to note that in comparison to ultrasound measurement of the intima and media, MRI measurement includes the adventitial layer, which may result in larger measurements. Nevertheless, in comparison to B-mode ultrasound, which only images two opposing points of the wall, MRI permits cross-sectional imaging; this has been demonstrated to correlate highly with ultrasound but with lower variability, potentially reducing the required sample size for clinical studies (18)

Prior studies that included individuals with untreated HIV have reported decreased arterial distensibility by carotid artery ultrasound (14,15,29). In contrast, the present study observed no change in carotid distensibility using MRI. It is possible that changes in distensibility are obviated in patients with well-controlled HIV on chronic HAART or with no evidence of systolic hypertension, although future study may be needed to investigate this issue further.

Increased carotid artery wall thickness was associated with prolonged exposure to protease inhibitors, while no significant relationship was observed with the overall duration of HAART. This is consistent with prior studies using carotid ultrasound (30), and reports of increased myocardial infarctions associated with exposure to protease inhibitors but not to other antiretroviral medication classes (31). It is also possible that increased duration of protease inhibitor use may be related to a longer duration of HIV diagnosis; a larger study would be needed to investigate this potential relationship.

Limitations of this study include its small size, and multivariable adjustments and comparisons between treatment regimens could not be adequately performed as a result. In addition, while observed differences in carotid artery wall thickness were statistically significant, the magnitude of these differences was small (as reported in ultrasound studies); additional study in larger populations is needed to confirm these results. Further, this study was limited to men, and future research in women may be warranted. In addition, men with HIV often have disproportionate rates of cardiovascular risk factors and substance abuse, and such variables may be incompletely accounted for in analyses comparing these patients with controls. Finally, lipodystrophy was diagnosed on physical exam by experienced infectious disease physicians experienced with assessing the presence of lipodystrophy in patients with HIV, but was not

quantitatively determined by imaging. Future studies should consider quantitative imaging measurement of lipodystrophy to validate these findings.

In conclusion, individuals with HIV infection receiving chronic HAART have increased carotid artery wall thickness on MRI as compared to controls with similar age, gender, and cardiovascular risk factors. Furthermore, we have demonstrated that the presence of lipoaccumulation and duration of exposure to protease inhibitors are associated with greater carotid wall thickness. Future studies are needed to determine whether increased carotid artery wall thickness is associated with an increased risk of stroke, and to determine the mechanism contributing to these findings.

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FIGURE CAPTIONS

Figure 1. Measurement of Common Carotid Artery Wall Thickness by Magnetic Resonance Angiography. Both patients are 45 year-old males with no cardiovascular

risk factors. The left common carotid mean wall thickness was 0.88 mm in the patient with HIV on chronic HAART (Figure 1A), and 0.82 mm in the control patient (Figure 1B). The external carotid area and luminal area are traced for each (labeled), and the wall thickness represents the mean of the 8 diameters (two are labeled).

Table 1. Patient Characteristics

	HIV+ (N=26)	HIV- (N=20)	p
Patient Demographics			
Caucasian	96%	90%	0.57
Age, years	47.8 ±5.0	47.8 ±4.7	0.19
Sex, male	100%	100%	1.0
Prior Male Sex with Male (MSM)	100%	100%	1.0
Past History			
Hypertension	19%	0%	0.06
Hyperlipidemia	38%	20%	0.21
Tobacco use (any)	23%	10%	0.44
Illicit drug use (any)	65%	20%	0.003
Exam Findings			
BMI, kg/m^2	25.4 ±3.9	23.9 ±3.5	0.19
Hip circumference, cm	96.2 ±7.2	95.9 ±8.2	0.93
Waist circumference, cm	90.8 ±11.8	86.0 ±13.6	0.22
Waist-to-hip ratio	0.94 ±0.09	0.89 ±0.10	0.10
Lipodystrophy (any)	81%	25%	<0.001
Lipoaccumulation	69%	20%	0.001
Lipoatrophy	65%	10%	<0.001
Medications			
Statin	38%	20%	0.21
Aspirin	15%	10%	0.37
Anti-hypertensive	15%	0%	0.12
Hemodynamics			
Systolic blood pressure, mmHg	115.4 ±15.4	120.4 ±14.4	0.27
Diastolic blood pressure, mmHg	70.7 ±9.3	67.2 ±7.1	0.17
Resting heart rate, beats/min	75.5 ±10.9	59.6 ±9.9	<0.001
Laboratory Tests (fasting)			
Glomerular filtration rate (ml/min)	83.2 ±21.0	85.1 ±15.2	0.74

Total cholesterol, mg/dL	172.4 ±32.7	185.0 ±36.4	0.24
HDL Cholesterol, mg/dL	49.6 ±11.8	56.0 ±14.8	0.12
LDL Cholesterol, mg/dL	96.2 ±26.4	93.3 ±31.3	0.75
Triglycerides, mg/dL	133.0 ±81.3	180.0 ±97.3	0.09
Glucose, mg/dL	90.3±10.3	97.2 ±14.4	0.07
Glucose ≥100 mg/dL	42%	7%	0.01
Risk Profiles			
Framingham risk score	3 (2-6)	3 (1-4)	0.81

Values provided as percentage, mean ± standard deviation, or median (interquartile range). HDL = high-density lipoprotein, HIV = human immunodeficiency virus, LDL = low-density lipoprotein. Cholesterol values, glucose, and Framingham risk scores were missing for one patient with HIV and one control.

Table 2. Carotid Artery Findings

	HIV (+) (n=26)	HIV (-) (n=20)	p
Mean wall thickness diameter (mm)			
Left (mm)	0.88±0.08	0.83±0.08	0.03
Right (mm)	0.90±0.10	0.85±0.07	0.046
External area (mm^2)			
Left	53.0±6.8	50.3±6.6	0.17
Right	55.3±6.0	51.9±9.3	0.14
Luminal area (mm^2)			
Left	32.7±5.5	31.2±4.9	0.34
Right	33.8±4.3	32.0±6.9	0.27
Wall area (mm^2)			
Left	20.3±2.2	19.1±2.2	0.06
Right	21.4±3.0	19.9±2.9	0.09
Normalized wall area			
Left	0.39±0.03	0.38±0.03	0.68
Right	0.39±0.04	0.39±0.03	0.86
Mean diameter change (systole – diastole in mm)			
Left	0.70±0.23	0.72±0.16	0.67
Right	0.70±0.17	0.73±0.20	0.60
Carotid distensibility Index (10$^-$3/kPa)			
Left (10$^-$3/kPa)	36.6±10.1	33.5±7.6	0.30
Right (10$^-$3/kPa)	36.6±10.1	32.9±9.6	0.21
Any visible carotid artery plaque			
Left	4%	0%	1.0
Right	0%	0%	1.0

Values provided as percentage or mean ± standard deviation. HIV = human immunodeficiency virus.

Table 3. Variables Associated with Mean Carotid Artery Wall Thickness in Patients with HIV

	Change in Wall Thickness (mm)		
	Estimate	**95% CI**	**p**
Patient Characteristics			
Age (per 10 years)	0.05	-0.01 to 0.11	0.06
Exercise level ≥2 (vs. <2)	-0.03	-0.09 to 0.04	0.42
Past History			
Hypertension	0.04	-0.03 to 0.11	0.27
Hyperlipidemia	0.01	-0.05 to 0.07	0.83
Tobacco use	0.01	-0.05 to 0.07	0.71
Illicit drug use	0.03	-0.03 to 0.09	0.28
Physical Exam Findings			
Body mass index (per 5 kg/m^2)	0.02	-0.02 to 0.06	0.27
Waist-to-hip ratio (per 1)	0.23	-0.08 to 0.55	0.14
Lipodystrophy (any)	0.07	0.01 to 0.14	0.047
Lipoaccumulation	0.09	0.03 to 0.14	0.003
Lipoatrophy	-0.01	-0.06 to 0.06	0.98
Medications			
Statin	0.01	-0.05 to 0.07	0.68
Aspirin	-0.04	-0.12 to 0.04	0.35
Anti-hypertensive	0.04	-0.04 to 0.12	0.29
Plasma metabolites (fasting)			
Total cholesterol (per 10 mg/dL)	0.01	-0.01 to 0.02	0.16
HDL Cholesterol (per 10 mg/dL)	-0.02	-0.04 to 0.01	0.18
LDL Cholesterol (per 10 mg/dL)	0.01	-0.01 to 0.02	0.12
Triglycerides (per 10 mg/dL)	0.01	-0.01 to 0.01	0.20
Glucose ≥100 mg/dL	0.01	-0.10 to 0.12	0.84
Risk Profiles			
Framingham risk score ≥5% (vs. <5%)	0.07	0.01 to 0.12	0.02
HIV History			

HIV diagnosis duration (per 5 years)	0.02	-0.01 to 0.03	0.08
Duration HAART therapy (per 5 years)	0.01	-0.01 to 0.03	0.29
Duration of PI therapy (per 5 years)	0.03	0.01 to 0.06	0.02
Duration of NRTI therapy (per 5 years)	0.01	-0.01 to 0.02	0.90

The mean value of the left and right common carotid wall thickness was used for each patient. CI = confidence interval, HAART = highly active antiretroviral therapy, HDL = high-density lipoprotein, HIV = human immunodeficiency virus, LDL = low-density lipoprotein, NRTI = nucleoside reverse-transcriptase inhibitor, PI = protease inhibitor. Cholesterol values, glucose, and Framingham risk scores were missing for one patient with HIV and one control.