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Atherosclerosis is evident in treated HIV-infected subjects with low cardiovascular risk by carotid cardiovascular magnetic resonance

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Abstract

Objective—Premature atherosclerosis has been observed among HIV-infected individuals with high cardiovascular risk using one-dimensional ultrasound carotid intima-media thickness (C-IMT). We evaluated the assessment of HIV-infected individuals with low traditional cardiovascular disease risk using cardiovascular magnetic resonance (CMR), which allows three-dimensional assessment of the carotid artery wall.

Methods—Carotid CMR was performed in 33 HIV-infected individuals (cases) (19 male, 14 female), and 35 HIV-negative controls (20 male, 15 female). Exclusion criteria included smoking, hypertension, hyperlipidaemia (total cholesterol/HDL ratio>5) or family history of premature atherosclerosis. Cases were stable on combination antiretroviral therapy (cART) with plasma HIV-1 RNA <50 copies/mL. Using computer modelling, the arterial wall, lumen, and total vessel volumes were calculated for a 4cm length of each carotid artery centered on the bifurcation. The wall/outer-wall ratio (W/OW), an index of vascular thickening, was compared between the groups.

Results—Cases had a median CD4 cell count of 690 cells/uL. Mean ($\pm$ SD) age and 10-year Framingham coronary risk scores were similar for cases and controls (45.2 $\pm$ 9.7years versus 46.9 $\pm$ 11.6years and 3.97 $\pm$ 3.9% versus 3.72 $\pm$ 3.5%, respectively). W/OW was significantly increased in cases compared with controls (36.7% versus 32.5%, $p<0.0001$); this was more

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Authors' contributions

AW and JHV conceived the study. DJP and KR advised on the study design. KR, JHV and PD were involved in data gathering. KR analysed CMR data. KR and JHV were involved with data analysis and interpretation as well as drafting the manuscript. WB performed the statistical analysis. KR drafted the initial manuscript. All authors were involved in the critical revision of the manuscript and approved it.

Conflicts of Interest

None of the other authors report any disclosures relevant to this work.

Ethics approval

Imperial College London NHS health care trust Ethics Committee

marked in HIV-infected females. HIV-status was significantly associated with increased W/OV after adjusting for age ($p<0.0001$). No significant association between antiretroviral type and W/OV was found – W/OV lowered comparing abacavir to zidovudine ($p=0.038$), but statistical model fits poorly.

Conclusions—In a cohort of treated HIV-infected individuals with low measurable cardiovascular risk, we have observed evidence of premature subclinical atherosclerosis.

Keywords

Human immunodeficiency virus; atherosclerosis; cardiovascular risk; magnetic resonance imaging; carotid intima-media thickness

INTRODUCTION

An estimated 35.3 million people are living with HIV worldwide.¹ An estimated 107,800 people in the UK were living with HIV in 2013, with one in four people living with HIV infection aged 50 years and over.² The introduction of effective combination anti-retroviral treatment (cART) in the mid-1990s has transformed HIV-infection from a fatal to a chronic lifelong condition in the developed world. Increasingly, this is also the case in low-to-middle income countries as access to treatment improves.¹ Despite this, mortality rates in HIV-infected patients are still higher than in the general population and non-AIDS related morbidity and mortality is increasing.^{3, 4} Cardiovascular disease, particularly ischaemic heart disease, is an important cause of morbidity and mortality among HIV-infected individuals.^{3, 5} Although traditional cardiovascular risk factors are highly prevalent and accepted to play a role in HIV-associated cardiovascular disease,^{6, 7} the role of long-term cART and HIV-infection itself remains controversial.

Atherosclerosis is a complex, active and progressive disease with inflammation involved at every stage. Chronic inflammatory diseases, such as rheumatoid arthritis,⁸ and infections, such as Chlamydia pneumonia and cytomegalovirus,⁹ have been shown to be associated with excess and premature cardiovascular risk. Assaults to the endothelium result in repair via up-regulation of innate and adaptive immune systems.¹⁰ If the endothelial insult is repeated or continuous, the inflammatory process is continued, amplified and becomes maladaptive, resulting in intimal proliferation¹¹ and eventually in atheroma. HIV-infection causes chronic inflammation with persistently increased inflammatory markers.¹² These increase with increasing viraemia^{13, 14} and predict mortality.¹⁵ HIV-infection is associated with raised markers of endothelial activation including VCAM-1, P-selectin and MCP-1, which decrease but may not normalise with antiretroviral treatment.¹⁴ Immune dysfunction may also contribute to the increased risk for atherosclerosis in HIV-infected individuals. Relative risk of ischaemic heart disease among patients with a CD4+ cell count 200 cells/uL was found to be greater than in those with a cell count >200 cells/uL at antiretroviral therapy initiation.¹⁶ Activated T-lymphocytes in HIV-infected individuals have been found to be associated with subclinical carotid artery disease.¹⁷

Carotid artery intima-media thickness (C-IMT) assessed with B-mode ultrasound has been shown to be predictive of future cardiovascular events in HIV-uninfected individuals.^{18, 19, 20}

C-IMT has been used in numerous studies to assess for the presence and rate of progression of subclinical atherosclerosis in HIV-infected individuals.^{21, 22} Findings have been conflicting due to variation in study design and ultrasound methodology. The presence of confounding variables, such as a high burden of traditional cardiovascular risk factors in the HIV-infected groups, and exposure to antiretroviral therapy, has made the effect of HIV-infection itself hard to ascertain.

Carotid vessel wall imaging by cardiovascular magnetic resonance (CMR) can overcome many of the limitations of C-IMT, which include one-dimensionality, variability of measurement site, and near field artefacts. It can be performed with constant resolution along the length of the artery and combined into a three-dimensional model giving the wall volume for the length of artery studied. CMR measurements of wall area and thickness have been shown to correlate well with measurements of C-IMT.²³ Reproducibility is good with interstudy coefficients of variation of 4.4%²⁴, allowing for a greatly reduced sample size in clinical studies. Inter-rater variability is low, with interobserver intraclass correlation coefficient of 0.96 at 1.5T field strength,²⁵ and 0.90-0.99 at 3T.²⁶

We report the first study using CMR to assess carotid wall thickness and determine the level of subclinical atherosclerosis in HIV-infected individuals with low cardiovascular risk, compared to a low cardiovascular risk, HIV-uninfected cohort.

METHODS

Patients and Setting

HIV-infected individuals (n=33) were recruited from the outpatient HIV unit at St Mary's Hospital, Imperial Healthcare NHS trust, London, United Kingdom. Inclusion criteria included HIV-infection (known HIV antibody positive for at least 2 years as we wanted to selected patients that have been living with HIV for more than 2 years), male or female sex, 20 to 70 years old, stable on cART and plasma HIV RNA<50 copies/mL (Quantiplex assayTM, Bayer, Emeryville, CA, USA). Exclusion criteria were current or previous history of cardiovascular disease or positive family history of premature vascular disease, current or previous history of major modifiable risk factors for atherosclerosis (current or former smoking, hypertension, hyperlipidaemia, diabetes), Framingham cardiovascular risk of more than 10% or DAD risk of more than 5%. The DAD risk equation is a cardiovascular risk score specifically developed for HIV-infected patients. It was based on the results of a large multicentre cohort study (The Data Collection on Adverse Effects on Anti-HIV Drugs Cohort-DAD), conducted mainly in Europe and North America). Other exclusion criteria included taking any cardiovascular medication (e.g. anti-platelet, antihypertensive, lipid-lowering medications), current alcohol abuse or recreational drug use of less than 6 months, or contraindication to CMR. The study was approved by the Imperial College London NHS health care trust Ethics Committee (reference number: 11/LO/1059) and all subjects provided written informed consent prior to enrolment. A control group comprising a historic cohort of HIV-uninfected healthy subjects (n=35) with no known cardiovascular disease, no current or previous history of major modifiable risk factors for atherosclerosis and low cardiovascular risk scores (<10%), matched for age, sex and where possible, ethnicity (self-reported for both groups) was used.²⁷ CMR was performed at the Cardiovascular

Biomedical Research Unit, Royal Brompton Hospital, London, United Kingdom. A single experienced investigator performed all HIV-infected subject analyses, blinded to all parameters other than HIV-status. All the CMR images were analysed using dedicated software (Atheroma Tools, a plug-in of CMR tools, Cardiovascular Imaging Solutions, London, UK).

Clinical procedures

A detailed assessment including age, height, weight, BMI, ethnicity as well as HIV-disease history and assessment of cardiac risk factors including family history of coronary artery disease and Framingham and DAD cardiovascular risk scoring was carried out at a screening visit. Blood pressure, ECG and blood tests (CD4 lymphocyte count, plasma HIV RNA, fasting lipids, glucose, electrolytes, urea and creatinine) were also performed. Subjects who reported no cardiovascular risk factors but were found to have elevated blood pressure (>140/90 mm Hg), elevated total cholesterol to HDL ratio (>5), triglycerides or glucose, or abnormal ECG were excluded from the study and referred to their physician for further management.

CMR

Carotid CMR was performed using a 3.0T scanner (Siemens Skyra, Erlangen, Germany) and a purpose-built bilateral four-channel phased-array carotid surface coil (Machnet BV, Eelde, the Netherlands), with the head and neck immobilized. A contiguous stack of 20 high-resolution T1-weighted fast spin echo (FSE) images, centred on the carotid bifurcation bilaterally, was acquired approximately perpendicular to the longitudinal axis of both common carotid arteries, giving 40 mm of longitudinal coverage per artery. Slice thickness was 2 mm. Typical T1-weighted FSE image sequence parameters were: field of view (FOV) read 110 mm, FOV phase 100%, TE 11ms, echo train length 9, readout time 90ms, bandwidth 230 Hz/pixel, 3 averages, pixel size 0.43mm×0.43mm (interpolated to 0.21mm×0.21mm), ECG-gated to each cardiac cycle with end-diastolic triggering. Dark blood preparation was used with the inversion time (TI) determined by average R-R interval.

The internal and external carotid artery surfaces were manually traced giving luminal and total vessel areas for each slice. 2D semi-automated modelling by the software assisted where flow suppression was incomplete. The lumen and wall volume was automatically calculated for each 2mm slice and summated to create a 3D model from which total lumen volume, wall volume and vessel volume were derived. Total wall volume was expressed as a percentage of the total vessel volume (wall/outer wall or W/OW ratio – an index of vascular thickening). A cine image perpendicular to the common carotid artery was manually contoured at end diastole and end systole for each side, and the percentage distensibility calculated.

The historic non-HIV infected cohort had been previously scanned on a 1.5T scanner using a similar protocol. Images had been previously analysed using the same standard methods as employed in this study to provide 'normative' data and a control group for future studies.²⁷ Previously, measures of carotid wall volume have been compared between 1.5T and 3.0T

magnetic field strengths with no significant differences reported, allowing comparison between scans acquired at the different field strengths to be made.²⁸

Sample Size

In a previous study by Keenan,²⁷ the age-group with the highest change in wall volume (60 to 69 years old) showed a mean wall volume of 1083mm³ with an estimated standard deviation (SD) of 189. Assuming an increase of 25% in wall volume among HIV-infected individuals a sample size of 22 patients (11 cases and 11 controls) would be required, to detect differences between groups. We aimed to recruit an age and sex matched sample of 5 subjects per age group (20 to 39 years, 40 to 49 years, 50+ years) per sex.

Statistical Analyses

Categorical data were presented as number (percentage) and comparisons undertaken using the chi-squared or Fishers Exact test. Numeric data were presented as a mean (SD) or 95% confidence interval if the data were normally distributed and analysed using a 2-sample independent t-test. Where data were not normally distributed as determined by using visual inspection of graphical data and test for normality. Median (IQR) was presented and comparisons done using the Mann-Whitney (Wilcoxon rank-sum) test. Linear regression analysis was performed to assess the strength of association between measured variables (W/OW, carotid artery wall volume, carotid artery lumen volume, total carotid artery volume) and age. The association of demographic and HIV-specific parameters with W/OW was analysed using linear regression.

Results

Patient Characteristics

Demographics, blood pressure and laboratory values, and coronary risk scores in HIV-infected subjects and age- and sex-matched control subjects are shown in Table 1. Age, sex distribution, total cholesterol levels, blood pressure, BSA, age and 10-year coronary risk were similar between both groups.

HIV-infected subjects had a mean age of 45.2±9.7 years. Mean duration of known HIV-infection was 8.8±4.4 years. All subjects were stable on cART with a median duration of treatment of 7 years (2-21 years); 24 were on a non-nucleoside reverse transcriptase inhibitors (NNRTI) based regimen and 9 on a protease inhibitor (PI) based regimen. All subjects were receiving an NRTI backbone that comprised of tenofovir, abacavir and zidovudine in 24, 6 and 3 subjects, respectively. Of those on a PI based regimen, 5 were on darunavir, 3 were on atazanavir and 1 was on lopinavir. All patients on PIs were on a boosted combination with ritonavir.

Carotid CMR Measurements

Carotid artery walls were significantly thicker in HIV-infected individuals compared to controls (Table 2). W/OW was significantly greater ($p<0.0001$) in HIV-infected subjects (36.7±3.7%) compared with the control group (32.5±2.8%); this was more marked in HIV-infected females (Table 3). There were no significant differences between total carotid

lumen volume, total carotid artery volume and total carotid wall volume between the study groups, although the total wall volume was increased in HIV-infected individuals ($1712 \pm 317 \text{ mm}^3$) compared with the control group ($1575 \pm 418 \text{ mm}^3$). There was no statistically significant difference in carotid artery distensibility between the two groups, although values were lower in HIV-infected patients (22.9% versus 24.2%, $p=0.35$). Univariate regression analysis revealed HIV-infection to be positively associated with W/OW (coefficient 5.28, $P=0.0001$). Multivariate regression analyses were performed to assess the relationship between demographic and HIV-disease parameters and W/OW ratio. Parameters included: age, ethnicity, CD4 cell count, nadir CD4 cell count, years since HIV diagnosis, years on cART and usage of NRTI or PIs – no significant associations were found other than a lower W/OW ratio of 5.48 ($p=0.038$) when comparing the NRTI abacavir to zidovudine. In the multivariate analysis, W/OW remained significantly associated with HIV status, independently of age, ($r=4.37$, $p=0.001$). There was no significant association between any other demographic or HIV-specific parameters and W/OW.

Carotid artery aging in HIV-infected individuals

Carotid artery lumen volume, total wall volume, total vessel volume, W/OW ratio and average distensibility for all subjects according to age group and divided by sex are presented in Table 4. Wall volume, total vessel volume and W/OW increased with age in both the HIV-infected and HIV-uninfected groups (Figure 1). No carotid plaques were detected in either group.

As with the HIV-uninfected controls, predictors of increased W/OW, wall volume and total vessel volume in the HIV-infected group were age and male sex. In HIV-infected males, wall volume and total vessel volume were positively associated with age. However after the third decade, there is an accelerated increase of vessel wall thickening (W/OW ratio) compared to control group males (Figure 1b). In HIV-infected females, a significantly increased W/OW was observed compared to female controls (36.4% versus 31.3%, $P=0.0002$). The increase in W/OW was more marked in HIV-infected females than in HIV-infected males when compared with their respective controls (36.2% versus 33.4% $p=0.0019$). Of note, in HIV-infected females the increase in W/OW was present from the third decade, with very little change throughout. This trend is different from the one observed in the female control group where W/OW significantly increased with age (Figure 1c).

Discussion

This carotid CMR study demonstrates that subjects with treated HIV-infection and low cardiovascular risk exhibit early atherosclerosis at a younger age compared to controls. As increased C-IMT is an independent predictor of myocardial infarction and stroke,^{18,19,20} the rate of vascular events is therefore likely to remain elevated despite aggressive control of traditional cardiovascular risk factors in HIV-infected patients.

The antiretroviral agents indinavir, abacavir and lopinavir are reported to be independently associated with increased cardiovascular disease risk in the DAD study.²⁹ Other studies have produced conflicting results with regards to the contribution of HIV-infection, type of antiretroviral therapy and traditional risk factors to increased vascular wall thickening using

a variety of US measurement techniques. Protease inhibitors have been associated with increased carotid plaques³⁰ and C-IMT,³¹ but larger and more recent studies have found no association with increased C-IMT.^{32, 33} Our study has not shown an association between PI-containing antiretroviral regimens and increased vascular wall thickness when compared with non PI-containing antiretroviral regimens but was not powered to do so and contains few patients on PI-containing therapy. The lower W/OW ratio when comparing the NRTI abacavir to zidovudine in this study is contrary to the increased cardiovascular risk generally associated with abacavir.¹⁶ The large confidence interval ($-10.63, -0.34$), low sample size (6 abacavir, 3 zidovudine) and overall poor fit of the model, with low R-squared of 0.14, make this finding unlikely to be of real significance. This result may also reflect a channeling bias whereby clinicians only use abacavir in subjects they consider to have very low cardiovascular risk.

Increased C-IMT and its progression over time have been shown to be associated with traditional cardiovascular risk factors.³² Our study included HIV-infected and HIV-uninfected cohorts with no traditional cardiovascular risk factors. Although our study has not followed up patients or controls longitudinally, the diverging lines between the groups with increasing age (Figure 1a) suggests that HIV-infection and/or its treatment may be associated with progression of vascular wall thickening beyond that normally seen with age.²⁷ Moreover, risk does not appear to be abolished by viral suppression, although the virus is not eradicated: chronic, low-grade inflammation and T-cell activation has been shown to persist.^{17, 34, 35} Exposure to HIV-infection and/or the toxic effects of cART are possible causative factors in the increased cardiovascular disease risk seen in HIV. If the increased vascular thickening solely reflected a historic period of untreated HIV-infection or suboptimal viral suppression, one might expect the difference between the groups would not increase with age. However, as a cross-sectional study, there may be unmeasured differences between the younger and older HIV-infected subjects – for example, immunosenescence in older subjects may allow the effects of HIV-infection and/or the toxic effects of cART to be more marked, resulting in the observed divergence of the lines with age in Figure 1a.

Hsue et al found that, in their HIV-infected cohort, C-IMT was higher, progressed more rapidly, and was associated with a nadir CD4+ count $<200\text{cells}/\mu\text{L}$, suggesting that HIV-infection itself is a predictor of increased C-IMT.³³ A recent study following two large cohorts of HIV-infected and HIV-uninfected individuals using B-mode ultrasound, however, has found no association of increased C-IMT over time with HIV-infection, beyond that seen with age.²² Carotid plaque development however, was significantly higher in the HIV-infected cohort when there was a CD4+ count $<500\text{cells}/\mu\text{L}$ at baseline, the risk rising the lower the CD4+ count. No association of plaque formation and nadir CD4+ level was found. Our study measured wall volume, which would incorporate the various locations measured for C-IMT as well as the separate areas of thickening defined as plaques in the ultrasound studies. In our study, multivariate analysis showed a trend to increased wall volume and increased W/OW with baseline CD4+ counts $<500\text{cells}/\mu\text{L}$; no such trend was seen with nadir CD4+ counts. As our numbers are small and only 8 of our cohort had baseline CD4+ counts $<500\text{cells}/\mu\text{L}$, and none $<200\text{cells}/\mu\text{L}$, it is not however possible to draw any firm conclusions; indeed, our study was not powered to detect these.

We observed a markedly increased W/OW in HIV-infected females. A possible explanation for this finding may be related to sex hormones. Oestrogen and androgen receptors are found in vascular tissue, with androgens mediating a variety of actions on endothelial and smooth muscle cells.³⁶ Oestrogen's cardioprotective role is well established. Oestrogen has been shown to protect against HIV Tat protein-induced inflammatory reactions in human vascular endothelium.³⁷ Progesterone, used in many hormonal contraceptives, exerts an immunosuppressive effect that may result in susceptibility to HIV progression³⁸ and hence possible vascular damage. HIV-infection can also cause premature ovarian insufficiency and menopause,³⁵ reducing oestrogen levels. Therefore, HIV-infection may cause excess atherosclerosis in HIV-infected females via changes in sex hormones relative to controls. However, information about contraception method, levels of sex hormones and numbers of females who were peri- or postmenopausal in our study are unknown.

The assessment of carotid vascular wall thickening and plaque quantification using CMR has been studied in a variety of patient groups including those at high risk of and with known CVD,^{23,25} as well as in those with chronic inflammatory diseases associated with accelerated atherosclerosis.³⁹ CMR has also been used in longitudinal studies to assess the effect of drugs, such as the cholesterol-lowering statins⁴⁰ or immunomodulatory drugs,⁴¹ on carotid vascular disease progression/regression. Carotid CMR would therefore also be applicable in the study of HIV-infected individuals with traditional CVD risk factors such as hypertension, hyperlipidaemia or smoking, or in those with markers of sub-optimally treated HIV-infection, treated with either established cardiovascular or anti-retroviral drugs, or with novel treatments. It is likely that the degree of atherosclerosis is greater in individuals with CVD risk factors. The results of this study may provide a baseline against which the contribution of other risk factors and their treatments can be measured.

Study limitations

This study has a number of limitations. Although adequately powered overall, the low numbers of older female HIV-infected subjects may be a reason why we observed a less marked difference in W/OW in older females compared with controls (Figure 1c). The HIV-infected group had a higher proportion of black individuals than the control group (Table 1) so possible racial variation in W/OW cannot be excluded. Previous studies have shown that in adults of black ethnicity, C-IMT is higher than in white adults at the level of the common carotid, but not the internal carotid arteries.^{42, 43} However, the results in those studies could have been affected by differences in traditional cardiovascular risk factor profiles between the racial groups (despite being adjusted for statistically).⁴² The use of a length of the common and internal carotid arteries in our study should reduce the effect of race in our results. In view of this, we believe the increased W/OW in HIV-infected subjects in our study is unlikely due solely to the different racial profile between the groups.

No significant association between W/OW and the use of abacavir or PIs has been found in our study. This may be due to the study not being powered to detect this effect or the exclusion of patients who are susceptible to and clinically manifesting the deleterious metabolic effects of cART, namely abnormal lipid profile and hyperglycaemia.

As a cross-sectional cohort study it is not possible to attribute the observed carotid vascular thickening to HIV-infection itself, as all the individuals were on cART.

Clinical implications and conclusion

This carotid CMR study has shown evidence of premature subclinical atherosclerosis in a cohort of treated HIV-infected individuals with low measurable cardiovascular risk factors. Despite being stable on cART with good viral suppression, they still exhibit early and greater carotid vascular thickening compared to HIV-uninfected controls. As increasing C-IMT has been found to be independently predictive of future stroke and myocardial infarction in HIV-uninfected populations, 18,19,20 the findings of this study suggest that the rate of vascular events is likely to remain elevated in HIV-patients despite aggressive treatment of cardiovascular risk factors, highlighting the need for improved patient and healthcare provider education to detect and manage aggressively early signs of cardiovascular disease. Given the known low-grade inflammation and immune activation associated with HIV-infection¹² and the known deleterious metabolic effects of existing cART regimens,²⁸ the presence of premature subclinical atherosclerosis in spite of the exclusion of all traditional cardiovascular risk factors highlights the need for the development of novel antiretroviral treatments.

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a)

b)

c)

Figure 1.

Graphs of carotid artery wall volume normalized to total vessel volume (W/OV ratio) plotted against age with regression line.

- a) HIV-infected (red) and HIV-negative controls (black).
- b) HIV-infected males (red) and HIV-negative control males (black).
- c) HIV-infected females (red) and HIV-negative control females (black).

Table 1

Baseline characteristics including clinical and laboratory parameters

	HIV-infected subjects (n=33)	Control Subjects (n=35)	<i>p</i>
Age (years)	45.2 (41.8, 48.7)	46.9 (42.9, 50.9)	0.52
Sex n (%)			
Male	19 (57)	19(55)	0.97
Female	14(43)	16(45)	0.89
Ethnicity n(%)			
White	16(48)	30(85)	<0.0001
Black	14(42)	2(5)	
Other	3(3)	3(8)	
Body surface area (m ²)	1.81 (1.76, 1.87)	1.88 (1.79,1.96)	0.22
Blood pressure (mmHg)			
Systolic	123.7 (120.0, 127.4)	121.3 (117.5, 125.2)	0.38
Diastolic	76.1 (73.3, 79.0)	76.2 (73.8, 78.6)	0.97
Total Cholesterol (mmol/L)	4.7 (4.5, 4.9)	4.9 (4.6, 5.2)	0.34
10-year coronary risk (%)	3.97 (2.58, 5.36)	3.72 (2.5, 4.9)	0.78
HIV disease related parameters			
Baseline CD4 cell count (cells/uL)	638.48 (556.72, 720.25)	N/A	
Nadir CD4 cell count (cells/uL)	276.36 (207.40, 345.33)	N/A	
Baseline plasma HIV RNA level <50 copies/mL n(%)	33 (100)	N/A	
Years since HIV diagnosis	8.82 (7.27, 10.37)	N/A	
Years on cART	7.5 (6.0, 9.0)	N/A	
cART therapy at screening n(%)			
NNRTI based	24 (72)	N/A	
PI based	9 (28)	N/A	
NRTI therapy at screening n(%)			
Tenofovir based	24 (72)	N/A	
Abacavir based	6(18)	N/A	
Zidovudine based	3 (9)	N/A	

Values are numbers for categorical variables or mean (95% confidence interval) for continuous variables. cART indicates combine antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2

Carotid CMR measurements in HIV-infected and control subjects

	HIV-infected subjects (n=33)	Control subjects (n=35)	p
Total Lumen Volume (mm ³)	2966.6 (2763.5, 3169.7)	3277.5 (2988.4, 3566.7)	0.079
Total Wall Volume (mm ³)	1712.1 (1599.4, 1824.8)	1574.8 (1431.3, 1718.3)	0.13
Total Vessel Volume (mm ³)	4678.7 (4391.7, 4965.8)	4852.3 (4433.3, 5271.4)	0.49
W/OV Ratio (%)	36.7 (35.4, 38.0)	32.5 (31.5, 33.5)	< 0.0001
Distensibility (%)	22.9 (20.6, 25.1)	24.2 (22.4, 26.1)	0.35

Values are mean (95% confidence interval). Significant values are shown in bold text.

Table 3

Difference in W/OV between male and female HIV-infected subjects compared to male and female controls using the Z-score.

	HIV-infected subjects - median (IQR)	Control subjects - median (IQR)	<i>p</i>
Males	1.36 (0.21,2.75)	0.39 (−0.52, 0.91)	0.024
Females	1.77 (0.14, 2.39)	−0.50 (−1.00, 0.32)	0.008

Significant values are shown in bold text.

Table 4

Carotid artery parameters by age group showing mean and 95% confidence intervals

	20-39 years	40-49 years	50-69 years	<i>p</i>
HIV-Males	n= 6	n=8	n=5	
Total Lumen Volume (mm ³)	2786.8 (2371.0, 3202.6)	3443.6 (3015.8, 3871.4)	3372.5 (2786.2, 3958.9)	0.047
Total Wall Volume (mm ³)	1673.8 (1267.5, 2080.0)	1919.3 (1759.9, 2078.8)	2052.8 (1723.7, 2381.9)	0.11
Total Vessel Volume (mm ³)	4460.6 (3804.5, 5116.7)	5362.9 (4831.1, 5894.8)	5425.3 (4598.8, 6251.9)	0.032
Average Distensibility (%)	22.5 (17.5, 27.5)	24.8 (19.3, 30.4)	21.2 (15.0, 27.4)	0.52
W/OW Ratio (%)	37.3 (31.9, 42.8)	36.0 (33.6, 38.4)	37.9 (34.3, 41.6)	0.63
HIV-Females	n=4	n=5	n=5	
Total Lumen Volume (mm ³)	2733.0 (1501.7,	2571.0 (2313.7, 2828.2)	2601.9 (2046.3, 3157.6)	0.86
Total Wall Volume (mm ³)	1424.1 (1292.0, 1556.6)	1460.5 (1252.6, 1668.4)	1594.8 (1434.0, 1755.5)	0.27
Total Vessel Volume (mm ³)	4157.1 (2813.0, 5501.1)	4031.5 (3640.0, 4423.1)	4196.7 (3761.3, 4632.1)	0.87
Average Distensibility (%)	22.8 (17.8, 27.9)	23.1 (17.9, 28.2)	21.6 (−0.04, 43.1)	0.96
W/OW Ratio (%)	35.0 (27.3, 42.7)	36.2 (32.9, 39.5)	38.1 (31.2, 45.2)	0.54