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BRIEF COMMUNICATION

Association of HIV Serostatus and Inflammation With Ascending Aortic Size

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BACKGROUND: The prevalence and extent of subclinical large vessel vasculopathy is not well defined among people living with HIV. We aimed to evaluate associations between aortic root and ascending aortic sizes measured by 2-dimensional transthoracic echocardiography and HIV serostatus, and to identify risk factors for larger aortic sizes among men with HIV, including levels of circulating inflammatory markers.

METHODS AND RESULTS: Using clinical and echocardiographic data from the MACS (Multicenter AIDS Cohort Study), adjusted multivariable linear and logistic regression was performed. Four segments of the proximal aorta were measured: aortic annulus, aortic root at the sinuses of Valsalva, sinotubular junction, and ascending aorta. HIV infection was associated with significantly larger aortic root (0.03 cm [95% CI, 0.002–0.06 cm]) and ascending aorta (0.04 cm [95% CI, 0.01–0.06 cm]) diameters. Higher standardized nadir CD4 (cluster of differentiation 4) T-cell count was significantly associated with smaller aortic root (–0.03 cm [95% CI, –0.05 to –0.01 cm]), sinotubular junction (–0.03 cm [95% CI, –0.05 to –0.01 cm]), and ascending aorta (–0.03 cm [95% CI, –0.05 to –0.004 cm]) diameters. Higher levels of standardized TNF-α (tumor necrosis factor-α) were associated with larger diameters of the aortic annulus (0.02 cm [95% CI, 0.003–0.04 cm]) and sinotubular junction (0.02 cm [95% CI, 0.002–0.04 cm]). There were no other cardiovascular or HIV disease severity–related risk factors associated with the aortic dimensions.

CONCLUSIONS: HIV infection is an independent risk factor for greater ascending aortic sizes. Lower nadir CD4 T-cell count and higher TNF-α levels are associated with larger aortic sizes in men with HIV.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00046280.

Key Words: aneurysm ■ aorta ■ echocardiography ■ HIV ■ inflammation ■ vascular disease

With the advent of combination antiretroviral therapy, cardiovascular disease has become more prevalent among people living with HIV.[1] Previously, HIV vasculopathy was described in rare case reports; the extent of large vessel vasculopathy has been less well defined in the modern combination antiretroviral therapy era.[2,3] Ascending aortic dilatation can lead to aortic aneurysms, dissection, and death, and predicts incident heart failure, stroke, and cardiovascular mortality.[4]

Known causes of ascending aortic dilatation include connective tissue diseases, cystic medial degeneration, and inflammatory diseases (eg, syphilis).[5] Atherosclerosis is typically associated with descending, not ascending, aortic aneurysms.[5] It is postulated that HIV-associated inflammation could trigger endothelial dysfunction and smooth muscle cell proliferation, leading to vascular injury.[2] We thus hypothesized that HIV infection is an independent risk factor for subclinical aortic dilatation. We aimed (1) to compare the

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associations between aortic sizes and HIV serostatus in men with HIV (MWH) and without HIV (MWOH) in the MACS (Multicenter AIDS Cohort Study) and (2) to identify risk factors for larger aortic sizes, including elevated inflammatory biomarker levels, among MWH.

METHODS

Access to the data set can be obtained for qualified researchers trained in human subject confidentiality protocols upon request via the https://statepi.jhsph.edu/mwccs/ website or email address MWCCS@jhu.edu.

MACS is a prospective observational study of men who have sex with men, with and without HIV, in the United States.[6] This study was approved by the institutional review boards from each field center and the coordinating center, and all participants provided written, informed consent. For this study, all participants with complete transthoracic echocardiograms between October 2017 and January 2019 were initially considered (n=1195).[7] Echocardiogram measurements were performed according to the American Society of Echocardiography guidelines.[8] Aortic measurements were performed at the levels of the aortic annulus, aortic root (level of the sinuses of Valsalva), sinotubular junction, and proximal ascending aorta, and indexed to body surface area. For the aortic annulus, measurements were made in midsystole from the inner edge to inner edge.[8] For the other aortic diameters, measurements were made in end-diastole, using leading edge to leading edge convention (or from the outer edge of the anterior aorta to the inner edge of the posterior aortic wall).[8] Interreader and intrareader reproducibility for all aortic measurements was high (0.95–0.97), as previously described.[7] Participants with missing data for all 4 aortic measurements (n=26) or with a history of aortic surgery (n=5, all attributable to concomitant aortic valve replacement) were excluded. Aortic diameters are reported standardized around mean age, given significant difference in age between MWH and MWOH.

We assayed 3 serum inflammatory biomarkers: TNF-α (tumor necrosis factor-α), IL-6 (interleukin-6), and hs-CRP (high-sensitivity C-reactive protein). Measurement methods for TNF-α levels, using the Meso Scale Discovery (MSD, Gaithersburg, MD) system, have been described previously.[9] For IL-6 levels, the Luminex platform (Luminex, Austin, TX) was used according to the manufacturer's protocol using a single lot of assay kits to eliminate lot-to-lot variability. Luminex assay data were collected and analyzed using a BioPlex 200 apparatus and BioPlex Manager software (Bio-Rad, Hercules, CA). hs-CRP measurement was performed using a high-sensitivity immunonephelometric assay (Quest Diagnostics).

Statistical Analysis

Demographic and clinical characteristics were compared using *t* tests and Wilcoxon rank sum tests for continuous variables and Pearson χ^2 test for categorical variables. Adjusted multivariable linear regression was performed to determine the associations between HIV serostatus and each aortic measurement, with adjustment for age, race and ethnicity, education level, MACS site, enrollment period (pre/post 2001), cardiovascular risk factors (heart rate, systolic blood pressure, antihypertensive medication use, diabetes, dyslipidemia, smoking history, alcohol use, cocaine use, and statin use), and prior cardiovascular events. Variables in the adjusted model were selected to account for potential factors that could affect the association between HIV serostatus and aortic diameters. Analyses restricted to MWH were performed using multivariable linear regression (same covariates as above) to study the association of nadir CD4 (cluster of differentiation 4) cell count (standardized around the mean), detectable HIV viral load (≥50 copies/mL) at the time of echocardiogram, undetectable viral load for the 5 years preceding the echocardiogram, and inflammatory marker levels (hs-CRP, TNF-α, and IL-6, each standardized around their means for analysis) with aortic sizes. Statistical analyses were performed using Stata version 16 (StataCorp, College Station, TX).

RESULTS

Baseline characteristics of the 1164 participants are listed in the Table. MWH in our cohort were 5 to 6 years younger than the MWOH, but both groups had similar cardiovascular risk profiles except for a higher prevalence of dyslipidemia among MWH. Among MWH, 84% were HIV virally suppressed at the time of the echo visit, with 53% virally suppressed in the preceding 5 years. In multivariable models that controlled for baseline demographic differences between the MWH and MWOH, HIV infection was associated with significantly larger aortic root and ascending aortic diameters, with a near significant association with larger sinotubular junction size (Figure 1). In subgroup analyses of MWH (Figure 2), lower nadir CD4 T-cell count was significantly associated with larger aortic root, sinotubular junction, and ascending aorta diameters after covariate adjustment, whereas HIV viral load was not. Levels of TNF-α were associated with larger aortic annular and sinotubular junction diameters among MWH (Figure 2). None of the other cardiovascular or HIV disease severity risk factors included in the multivariable models (Table) were associated with aortic diameters.

Table. Study Participant Demographics, Clinical Characteristics, and Echocardiographic Parameters

	Men without HIV, n=519	Men with HIV, n=645
Age, y	61.9 (54.8–68.7)	55.4 (48.9–62.5)
Race and ethnicity		
White, non-Hispanic	353 (68%)	304 (47%)
Black, non-Hispanic	117 (23%)	214 (33%)
Hispanic or other	49 (9%)	127 (20%)
Education <12th grade	83 (16%)	182 (28%)
History of cardiovascular events	33 (6%)	31 (5%)
Diabetes*	67 (13%)	96 (15%)
Antihypertensive medication use	217 (42%)	247 (38%)
Systolic blood pressure, mm Hg	132±17	128±16
Heart rate, beats per min	63 (58–72)	68 (61–75)
Dyslipidemia†	360 (73%)	447 (76%)
Total cholesterol, mg/dL	178 (153–202)	176 (150–204)
High-density lipoprotein cholesterol, mg/dL	53 (45–64)	49 (41–59)
Smoking status		
Never	173 (33%)	189 (29%)
Former and current	344 (67%)	455 (71%)
Cocaine use, active	35 (7%)	61 (10%)
Cocaine use, ever	230 (44%)	357 (55%)
Current alcohol use	419 (81%)	479 (74%)
Statin use	205 (40%)	235 (37%)
Undetectable viral load, <20 copies/mL) at visit	N/A	545 (84%)
Persistently undetectable viral load in the 5-y preceding echocardiogram	N/A	341 (53%)
Nadir CD4 count, cells/mm^3		
≤200	N/A	173 (27%)
201–350	N/A	191 (30%)
351–500	N/A	151 (23%)
>500	N/A	130 (20%)
Enrollment		
Before 2001	324 (62%)	195 (38%)
After 2001	215 (33%)	430 (67%)
Inflammatory markers		
hs-CRP, pg/mL	1.2 (0.6–2.7)	1.6 (0.9–3.3)
IL-6, pg/mL	2.7 (1.8–4.0)	3.1 (2.2–4.4)
TNF-α, pg/mL	1.1 (0.9–1.5)	1.2 (0.9–1.7)
Aortic diameters, age standardized		
Aortic annulus, cm	2.93±0.48	2.91±0.45
Aortic root, cm	3.59±0.35	3.60±0.34
Sinotubular junction, cm	3.24±0.37	3.25±0.34
Ascending aorta, cm	3.40±0.38	3.42±0.34
Indexed aortic diameters, age standardized		
Aortic annulus, cm/m^2	1.46±0.25	1.46±0.24
Aortic root, cm/m^2	1.79±0.22	1.81±0.21
Sinotubular junction, cm/m^2	1.62±0.22	1.63±0.20
Ascending aorta, cm/m^2	1.69±0.22	1.72±0.21
Aortic stenosis	5 (1%)	3 (0.5%)
Mild	3 (0.6%)	2 (0.3%)
Moderate	2 (0.4%)	1 (0.2%)
Aortic regurgitation	70 (13%)	70 (13%)
Trace	111 (21%)	136 (21%)
Mild	59 (11%)	63 (10%)
Mild/moderate	8 (1.5%)	6 (0.9%)
Moderate	3 (0.6%)	1 (0.2%)
Bicuspid aortic valve	2 (<0.1%)	1 (<0.1%)

CD4 indicates cluster of differentiation 4; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; N/A, not applicable; and TNF-α, tumor necrosis factor-α.

*Diabetes is defined as glycosylated hemoglobin ≥6.5% or fasting glucose ≥126 mg/dL or use of diabetes medications.

†Dyslipidemia is defined as fasting total cholesterol ≥200 mg/dL or low-density lipoprotein ≥130 mg/dL or high-density lipoprotein ≤40 mg/dL or use of lipid-lowering medication.

DISCUSSION

In a large cohort study of MWH and concurrently enrolled MWOH with similar risk factors for HIV acquisition, we found that HIV infection is an independent risk factor for greater aortic sizes, even among virally suppressed MWH and after adjusting for traditional cardiovascular risk factors. Moreover, lower nadir CD4 T-cell count was associated with larger aortic sizes. Nadir CD4 T-cell count may better reflect the duration and extent of past unregulated inflammation occurring in MWH. Recent, shorter-term, nonspecific measurements of inflammation (IL-6 and hs-CRP) may be less informative in chronic processes such as aortic dilatation. The association between elevated TNF-α and aortic dimensions signals a possible contribution of decreased collagen synthesis via cytokine-driven inflammation in the observed increase in aortic sizes among MWH.

Prior studies among people without HIV reported associations between abdominal (but not ascending) aortic aneurysms and TNF-α levels.[10] A recent Danish study by Høgh et al of predominantly men living with and without HIV found differences in prevalent aortic aneurysms detected by computed tomography imaging by HIV serostatus.[11] Aneurysms of the ascending aorta and infrarenal aorta were more common among MWH, with no aneurysms detected in women. Using the Danish definition of ascending aorta dilation by

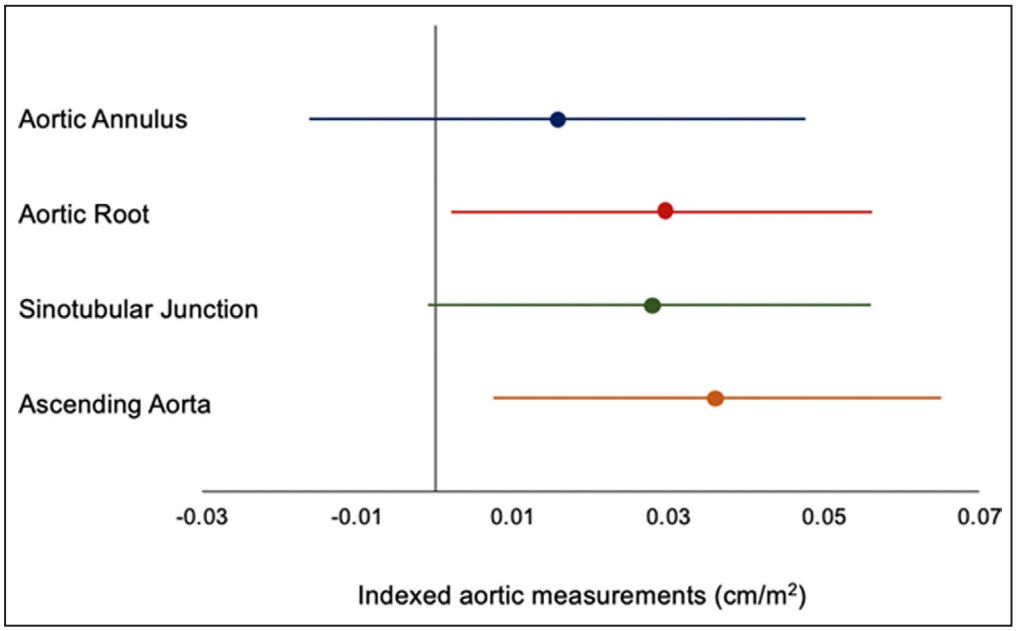

Figure 1. Adjusted associations between HIV serostatus and aortic sizes.
Adjusted for age, race and ethnicity, education level, MACS (Multicenter AIDS Cohort Study) site, enrollment period (pre/post 2001), and cardiovascular disease risk factors (heart rate, systolic blood pressure, hypertensive medication use, diabetes, dyslipidemia, smoking history, alcohol use, ever cocaine use, statin use, and history of cardiovascular events). Diabetes is defined as glycosylated hemoglobin ≥6.5% or fasting glucose ≥126 mg/dL or use of diabetes medications. Dyslipidemia is defined as fasting total cholesterol ≥200 mg/dL or low-density lipoprotein ≥130 mg/dL or high-density lipoprotein ≤40 mg/dL or use of lipid-lowering medication. History of cardiovascular events is defined as personal history of heart failure, myocardial infarction, cerebrovascular accident, or atrial fibrillation.

computed tomography of ≥4.5 cm to define aneurysm, the rate of ascending aortic aneurysm in that study was low at 2.4%.[11] Høgh et al found no significant associations between non-HIV and HIV-related disease-severity risk factors and aortic aneurysms including nadir CD4 count and inflammatory biomarker levels.[11] In contrast to the Danish study, our cohort was racially diverse and older, with lower rates of HIV viral suppression. Cardiac risk factor prevalence between the MWH and MWOH in our cohort was generally similar except for a higher rate of dyslipidemia and resultant statin therapy. Cohort differences may have contributed to the differences in results between the 2 studies. Notably, our study uses transthoracic echocardiography, which is often the primary modality used for screening and evaluating aortic dimensions.[12,13] Finding abnormal aortic root and ascending aorta diameters by echocardiography support subsequent full aortic imaging by computed tomography scanning or magnetic resonance imaging as suggested by current clinical guidelines.[14] This strategy is further substantiated by a recent study among people without HIV showing that a strong predictor of having aortic dilation at any level is the presence of dilation elsewhere.[15]

Limitations of the current study include the cross-sectional design, lack of data on infectious causes such as syphilis, and an emphasis on proximal aorta diameters using echocardiography. Strengths include the concurrent enrollment of MWOH as the comparator group, with similar risk factors for HIV acquisition as the MWH. This allows for more robust adjustment of potential confounders. Our cohort is characterized by extensive covariate ascertainment. We performed detailed assessment of all clinically relevant segments of the aortic root and ascending aorta, extending the findings from other studies. Our echo protocol minimizes measurement variability by its use of a single ultrasound machine vendor, extensive prestudy training of the technologists, and strict adherence to standardized acquisition and core laboratory image analysis protocols.

In conclusion, although recent attention has focused on increased risk for atherosclerosis among people living with HIV, our findings underscore the importance of a thorough assessment and consideration for other forms of cardiovascular disease, such as aortic enlargement, that may be presenting in people living with HIV.

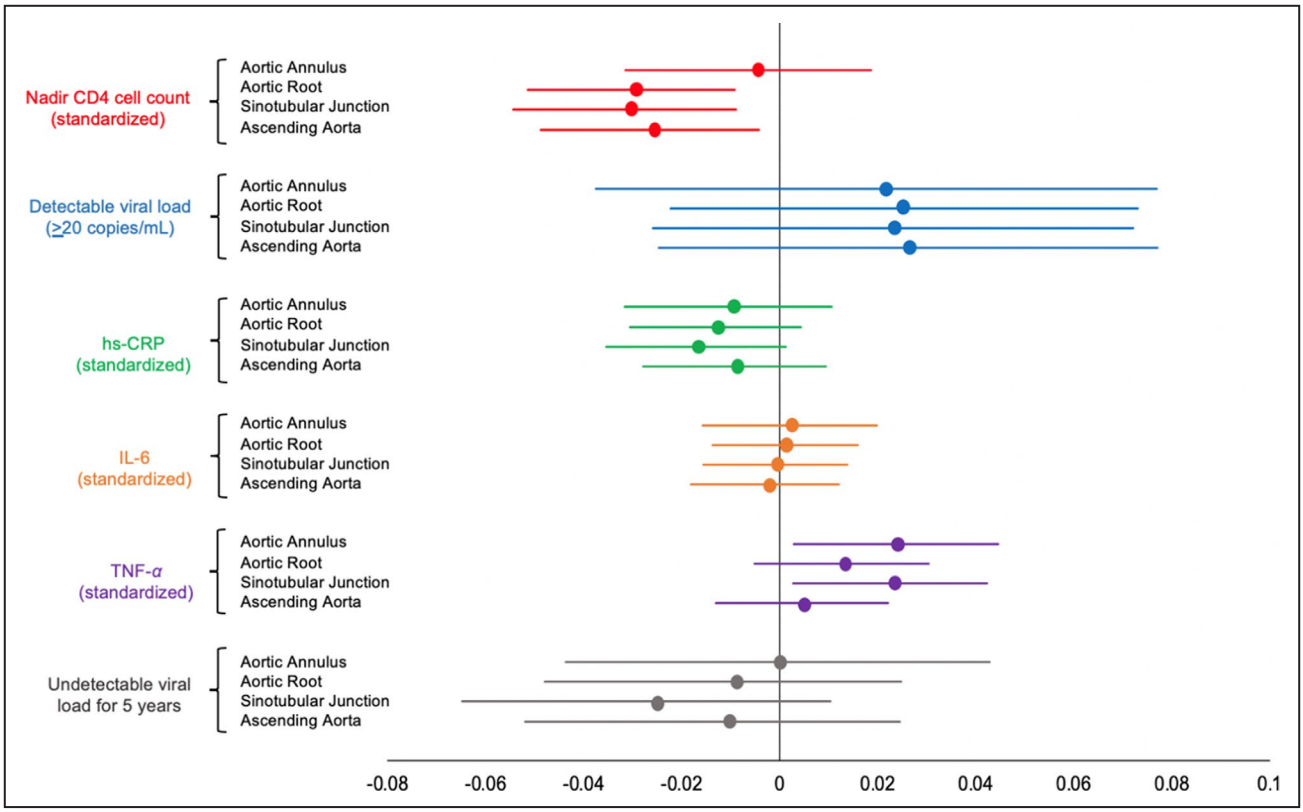

Figure 2. Adjusted associations between CD4 (cluster of differentiation 4) count, viral load, and inflammatory biomarker levels with aortic sizes among men with HIV (MWH).
Figure shows adjusted associations (regression coefficients, 95% CI) of nadir CD4 cell count, undetectable viral load at the visit, persistently undetectable viral load within the preceding 5 years of echocardiogram, and inflammatory markers, with aortic sizes among MWH. Adjusted for age, race and ethnicity, education level, MACS (Multicenter AIDS Cohort Study) site, enrollment period (pre/post 2001), and cardiovascular disease risk factors (heart rate, systolic blood pressure, hypertensive medication use, diabetes, dyslipidemia, smoking history, alcohol use, ever cocaine use, statin use, and history of cardiovascular events). Diabetes is defined as glycosylated hemoglobin ≥6.5% or fasting glucose ≥126 mg/dL or use of diabetes medications. Dyslipidemia is defined as fasting total cholesterol ≥200 mg/dL or low-density lipoprotein ≥130 mg/dL or high-density lipoprotein ≤40 mg/dL or use of lipid lowering medication. History of cardiovascular events is defined as personal history of heart failure, myocardial infarction, cerebrovascular accident, or atrial fibrillation. hs-CRP indicates high-sensitivity C-reactive protein; IL-6, interleukin-6; and TNF-α, tumor necrosis factor-α.

ARTICLE INFORMATION

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Disclosures

None.

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