Published in final edited form as:

J Acquir Immune Defic Syndr. 2020 October 01; 85(2): 233–238. doi:10.1097/QAI.0000000000002419.

Vascular Dysfunction and Monocyte Activation Among Women With HIV

Mabel Toribio, MD^a, Magid Awadalla, MD^b, Madeline Cetlin, BA^a, Evelynne S. Fulda, BA^a, Takara L. Stanley, MD^a, Zsofia D. Drobni, MD^b, Lidia S. Szczepaniak, PhD^c, Michael D. Nelson, PhD^d, Michael Jerosch-Herold, PhD^e, Tricia H. Burdo, PhD^f, Tomas G. Neilan, MD, MPH^b, Markella V Zanni, MD^a

^aMetabolism Unit, Division of Endocrinology, Massachusetts General Hospital and Harvard Medical School, Boston, MA;

^bDepartment of Radiology and Division of Cardiology, Cardiovascular Imaging Research Center (CIRC), Massachusetts General Hospital, Harvard Medical School, Boston, MA;

^cMRS Consulting in Biomedical Research, Albuquerque, NM;

^dDepartment of Kinesiology, Applied Physiology and Advanced Imaging Laboratory, University of Texas at Arlington, Arlington, TX;

^eDepartment of Radiology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA;

^fDepartment of Neuroscience, Temple University Lewis Katz School of Medicine, Philadelphia, PA.

Abstract

Objective: Women with HIV (WHIV) on antiretroviral therapy (ART) face an increased risk of cardiovascular disease (CVD) in the context of heightened systemic immune activation. Aortic stiffness, a measure of vascular dysfunction and a robust predictor of CVD outcomes, is highly influenced by immune activation. We compared aortic stiffness among women with and without HIV and examined interrelationships between aortic stiffness and key indices of systemic immune activation.

Correspondence to: Markella V. Zanni, MD, Metabolism Unit, Division of Endocrinology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, 5 LON 207, Boston, MA 02114 (mzanni@mgh.harvard.edu). M.T. was involved in study recruitment, data acquisition, data analysis, data interpretation, figure and table preparation, and manuscript writing. M.A. was involved in data acquisition, data analysis, data interpretation, figure preparation, and manuscript writing. E.S.F. and M.C. were involved in data analysis, data interpretation, figure preparation, table preparation, and manuscript writing. T.L.S. and Z.D.D. were involved in data interpretation and data analysis. L.S.S., M.D.N., M.J.H., and T.H.B. were involved in data acquisition, data analysis, and data interpretation. T.G.N. and M.V.Z. were involved in study design, data acquisition, data analysis, data interpretation, figure and table preparation, and manuscript writing. All authors contributed to critical revision of this manuscript.

M.T. and M.A. cofirst authors contributed equally.

T.G.N. and M.V.Z. cosenior authors contributed equally.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Methods: Twenty WHIV on ART and 14 women without HIV group-matched on age and body mass index (BMI) were prospectively recruited and underwent cardiovascular magnetic resonance imaging, as well as metabolic and immune phenotyping.

Results: Age and BMI did not differ significantly across groups (age: 52 ± 4 vs. 53 ± 6 years; BMI: 32 ± 7 vs. 32 ± 7 kg/m²). Aortic pulse wave velocity (aPWV) was higher among WHIV (8.6 ± 1.3 vs. 6.5 ± 1.3 m/s, $P < 0.0001$), reflecting increased aortic stiffness. Among the whole group and among WHIV, aPWV related to sCD163 levels (whole group: $R = 0.65$, $P < 0.0001$; WHIV: $R = 0.73$, $P = 0.0003$) and to myocardial fibrosis (extracellular volume; whole group: $R = 0.54$, $P = 0.001$; WHIV: $R = 0.47$, $P = 0.04$). Both HIV status and sCD163 levels independently predicted aPWV, controlling for age, BMI, cigarette smoking status, and systolic blood pressure (HIV status: β -estimate = 0.69, 95% CI [0.1 to 1.3], $P = 0.02$; sCD163: β -estimate = 0.002, 95% CI [0.0006 to 0.004], $P = 0.01$). Among WHIV, sCD163 levels independently predicted aPWV, controlling for duration of HIV, CD4 count, and HIV viral load (sCD163: β -estimate = 0.004, 95% CI [0.002 to 0.005], $P = 0.0005$).

Conclusions: Asymptomatic WHIV on ART have increased aortic stiffness as compared to matched control subjects. Among WHIV, aPWV related to heightened monocyte activation (sCD163) and to downstream CVD pathology (myocardial fibrosis).

ClinicalTrials.gov Registration: [NCT02874703](https://clinicaltrials.gov/ct2/show/study/NCT02874703).

Keywords

HIV; women; vascular dysfunction; cardiovascular disease; cardiac magnetic resonance imaging; monocyte activation; soluble CD163; immune activation

INTRODUCTION

Women with HIV (WHIV) on antiretroviral therapy (ART) face an increased risk of myocardial infarction (MI) and heart failure (HF) as compared to women without HIV.^{1–6} Accelerated vascular aging manifested as increased arterial stiffness may represent a pathophysiologic intermediary predisposing to MI and HF in this population. In the general population, aortic stiffness [reflected by increased aortic pulse wave velocity (aPWV)] has been shown to relate to systemic immune activation/inflammation^{7–9} and to predict both cardiovascular disease (CVD) events and all-cause mortality.^{10–12} Among WHIV, persistently increased systemic immune activation and inflammation represent a hallmark of ART-treated disease.¹³ Indeed, WHIV—as compared to women without HIV—exhibit markedly higher levels of systemic immune activation/inflammatory markers, including monocyte activation markers such as soluble CD 163 (sCD163).¹ Thus, it is plausible that WHIV may also exhibit higher aPWV in relation to select markers of systemic immune activation/inflammation.

Previous studies among predominately male cohorts examining the influence of HIV infection on large vessel arterial stiffness have yielded conflicting findings.^{14–18} Given that there are clear sex-based differences in immune activation^{1,19} and in manifestations of CVD²⁰ among people with HIV, we sought to investigate the role of HIV infection and systemic immune activation on arterial stiffness specifically among a cohort of

asymptomatic women with and without HIV. We hypothesized that WHIV would have a higher degree of arterial stiffness—quantified through aPWV on cardiovascular magnetic resonance imaging (MRI)^{21–24}—in relation to indices of systemic monocyte activation.

METHODS

Study Design and Participants

WHIV on ART aged 40–75 years without known CVD or diabetes were prospectively recruited. Women without HIV were group-matched based on age and body mass index (BMI). The study was approved through the Partners Institutional Review Board, and participants provided informed consent. Recruitment took place between August 2016 to November 2017 in the Greater Boston area, as previously described.^{25,26} Twenty WHIV and 14 women without HIV completed study procedures including cardiovascular MRI, yielding interpretable data on aPWV. Women without HIV were recruited through the Partners clinical research recruitment web site (rally.partners.org) and through flyer advertisements at the hospital and clinics in Boston and surrounding areas from which WHIV were recruited. From this cohort, data on myocardial fibrosis²⁵ and intramyocardial triglyceride content²⁶ were previously published, but data on aPWV—a powerful risk surrogate for both MI and HF^{10–12}—have never before been examined.

Laboratory Procedures

HIV viral load was measured using ultrasensitive RT-PCR (Roche Diagnostics/Cobas AmpliPrep/Cobas TaqMan HIV-1 test version 2.0). Systemic plasma levels of the inflammatory markers c-c motif ligand 2 (CCL2), soluble CD14 (sCD14), sCD163, and c-x-c motif chemokine ligand 10 (CXCL10) were measured using commercial enzyme-linked immunosorbent assay kits, as previously described.²⁵

Cardiovascular MRI-Mediated Assessment of aPWV

Participants underwent cardiovascular MRI using a 3.0-T system (Siemens, Erlangen, Germany). The aPWV was assessed as follows: Phase-contrast cine imaging was applied to assess aPWV between the ascending aorta and descending aorta at the level of the right pulmonary artery with slice orientation perpendicular to the aorta (Fig. 1).²⁷ The following sequence parameters were used: field of view, 270 × 270 mm; voxel size, 1.64 × 1.4 × 7 mm; repetition time/echo time, 8.8/2.7 ms; velocity encoding, 200 cm/s, retrospective ECG gating, and 80 acquired phases. The aPWV was determined from the time delay of the aortic flow-versus-time curves at locations in the ascending aorta and proximal descending aorta, using a cross-correlation method on the systolic upstroke part of the flow curves.²⁸ The aPWV was calculated as x/t , where x is the aortic path length along a midline in the vessel lumen, and t is the transit time (Fig. 1).²⁷ Myocardial fibrosis was quantified by measuring extracellular volume (ECV) on cardiovascular MRI, as previously described.²⁵

Statistical Analysis

Normally distributed data were presented as mean ± SD, whereas non-normally distributed data were presented as median (interquartile range). Between-group comparisons were made using the Student *t* test for normally distributed variables, the Wilcoxon rank-sum test for

non-normally distributed variables, or the Fisher exact test for categorical variables. Bivariate analyses were performed using a Pearson correlation coefficient or Spearman's ρ correlation coefficient, as appropriate. Among the whole group, linear least squares multivariable regression modeling was performed with aPWV as the dependent variable and HIV status, sCD163 levels, age, BMI, systolic blood pressure, and smoking status as covariates. These covariates were selected based on the existing literature, highlighting age, cigarette smoking, and select comorbidities (obesity and hypertension) as risk factors for vascular dysfunction.^{7,29,30} Among WHIV, linear least squares multivariable regression modeling was performed with aPWV as the dependent variable and plasma sCD163 levels, CD4⁺ T-cell count, HIV viral load, and duration since HIV diagnosis as covariates. JMP Pro software (version 12.0; SAS Institute) was used for statistical analyses, with $P < 0.05$ considered significant.

RESULTS

Baseline Demographics

Baseline characteristics of the groups of women with vs. without HIV are presented in Supplemental Table 1, Supplemental Digital Content, <http://links.lww.com/QAI/B490>, as previously published.²⁵ Notably, the 2 groups were well-matched on age and BMI (age 52 ± 4 years vs. 53 ± 6 years, $P = 0.61$; BMI 32 ± 7 kg/m² vs. 32 ± 7 kg/m², $P = 0.73$). WHIV had longstanding HIV (mean duration since HIV diagnosis 19 ± 8 years) and suppressed viremia [median viral load 19 (19, 19)]. Ninety percent of WHIV reported unprotected sex with men as a risk factor for HIV transmission, whereas 30% reported previous intravenous drug use as a risk factor. As previously published, plasma levels of select markers of systemic immune activation—including CCL2, soluble CD14, and soluble CD163—were higher among women with vs. without HIV.²⁵

aPWV and Relationship to Cardiac Structure

Compared to women without HIV, WHIV exhibited higher aPWV (8.6 ± 1.3 vs. 6.5 ± 1.3 m/s, $P < 0.0001$; Fig. 2A). The aPWV related directly to myocardial fibrosis (ECV) both among the whole group ($R = 0.54$, $P = 0.001$) and among WHIV ($R = 0.47$, $P = 0.04$) but did not relate to this measure in the subgroup of women without HIV.

Relationship Between aPWV and Immune Parameters

Among the whole group and among WHIV (and not among women without HIV), sCD163 related directly to aPWV (whole group: $R = 0.65$, $P < 0.0001$ and WHIV: $R = 0.73$, $P = 0.0003$; Fig. 2B). Levels of CCL2, CXCL10, and sCD14 did not relate directly to aPWV among the whole group and among WHIV (data not shown).

Predictors of aPWV

Among the whole group, after controlling for age, BMI, smoking status, and systolic blood pressure, both HIV status and sCD163 independently predicted aPWV (HIV status: (β -estimate = 0.69, 95% CI: [0.1 to 1.3], $P = 0.02$; sCD163: (β -estimate = 0.002, 95% CI: [0.0006 to 0.004], $P = 0.01$; see Supplemental Table 2, Supplemental Digital Content, <http://links.lww.com/QAI/B490>). Among WHIV, when controlling for duration since HIV

diagnosis, CD4⁺ T-cell count, and HIV viral load, levels of sCD163 independently predicted aPWV (sCD163: (β -estimate = 0.004, 95% CI: [0.002 to 0.005], P = 0.0005; see Supplemental Table 3, Supplemental Digital Content, <http://hnks.lww.com/QAI/B490>).

DISCUSSION

We determined that asymptomatic WHIV (versus age- and BMI-matched women without HIV) had significantly higher aPWV—a measure of aortic stiffness/vascular dysfunction and a powerful predictor of CVD events and mortality.^{10–12} We further demonstrated that among our full cohort, HIV infection and levels of a systemic marker of monocyte activation, sCD163, were independent predictors of aPWV, even when accounting for traditional CVD risk factors such as age, smoking, and blood pressure. Among WHIV, levels of sCD163 also remained a significant predictor of arterial pulse wave velocity even when accounting for HIV-specific parameters, including duration of HIV diagnosis and CD4⁺ T-cell count. These findings provide novel data with respect to vascular aging and associated predictors among women with vs. without HIV.

Immune activation and inflammation are believed to contribute to vascular aging and arterial stiffness in several ways—impairing endothelial function, accelerating vascular smooth muscle proliferation and fibrosis, and promoting the degradation of vascular wall elastin and collagen (see Supplemental Figure 1, Supplemental Digital Content, <http://links.lww.com/QAI/B490>).^{8,9,31} WHIV have higher levels of monocyte activation markers compared to men with HIV (MHIV)^{1,32} as well as higher levels of T-cell activation.¹⁹ Sex-specific differences in systemic immune activation between WHIV and MHIV may contribute to differences in CVD manifestations between these 2 groups^{20,33}—including a predilection to type II MI and HF with preserved ejection fraction among WHIV (vs. MHIV) who have experienced MI or HF, respectively.^{2,6,34,35} Thus, our focus specifically on immune activation and vascular function among women with versus without HIV permitted an investigation of sex-specific pathways potentially influencing vascular aging among WHIV. Moreover, despite our small sample size, our study revealed a strong relationship between monocyte activation and vascular function—laying an important foundation for future studies on vascular aging among WHIV.

In applying advanced cardiovascular imaging with cardiovascular MRI, we determined that the aPWV—an index of arterial stiffness and a powerful predictor of MI and HF^{10–12}—is higher among women with vs. without HIV. The aPWV determines when aortic pressure wave reflections arrive at the proximal aorta during the cardiac cycle. Normally, in young, healthy adults, reflected waves arrive during diastole, augmenting diastolic pressure and subsequently coronary perfusion. When the aPWV is higher, reflected waves arrive during systole rather than during diastole, resulting in loss of diastolic pressure augmentation and an increase in mid-to-late systolic load (see Supplemental Figure 1, Supplemental Digital Content, <http://links.lww.com/QAI/B490>). When diastolic pressure augmentation is lower, coronary perfusion is lower, which results in a reduction in the myocardial oxygen supply/demand ratio (see Supplemental Figure 1, Supplemental Digital Content, <http://links.lww.com/QAI/B490>).²⁹ Lower coronary perfusion and an altered myocardial oxygen supply/demand ratio are of significant relevance for women, in general, because of the

arrival of reflection waves earlier in the cardiac cycle in this population.²⁹ Moreover, this phenomenon is of particular relevance to WHIV, who, as noted, have a predilection to type II MI, precipitated by myocardial oxygen supply/demand mismatch.³⁴ Furthermore, among individuals with increased aPWV, the increase in mid-to-late systolic load precipitated by the arrival of reflected waves during systole can result in left ventricular remodeling, impaired left ventricular relaxation, and impaired systolic-diastolic coupling—all of which may contribute to the development of HF (see Supplemental Figure 1, Supplemental Digital Content, <http://links.lww.com/QAI/B490>).²⁹ Indeed, in our study, we demonstrated a significant relationship between aPWV and a measure of myocardial fibrosis (ECV), which is a precursor to diastolic dysfunction and HF, among WHIV.^{36,37}

In our study, we also noted a strong relationship between plasma sCD163 and aPWV even after controlling for traditional CVD risk factors. Soluble CD 163 is a systemic marker of monocyte activation, which is related to aortic inflammation in people with HIV (PHIV)³⁸ and which may plausibly contribute to vascular aging among WHIV. Of note, a previous study by Kooij et al did not find a significant relationship between levels of sCD163 and aPHIV among a predominantly male cohort of chronically infected PHIV (cohort >89% males).³⁹ These differences in study findings highlight the need for sex-specific studies or sex-stratified analyses of immune pathways contributing to vascular aging because these may differ across sexes. Given that HIV infection, in addition to sCD163 levels, was an independent predictor of aPWV in our cohort of women, our findings suggest that HIV infection may affect arterial stiffness through mechanisms other than monocyte activation. A recent proteomic study among people with versus without HIV, for example, revealed between-group differences in the circulating concentration of proteins involved in processes, such as endothelial permeability, which are relevant to arterial stiffness.⁴⁰ Future studies examining the effect of these biological processes on arterial stiffness among women with versus without HIV may provide insights into other HIV-specific effects on arterial aging among women.

Our study was limited by the cross-sectional study design. A significant proportion of WHIV in our study were obese, and approximately 40% were black/African American from the Boston and surrounding areas. Thus, our results may not be generalizable to other populations. However, our study did include participants from diverse racial/ethnic backgrounds and reflective of the demographic of WHIV in the Greater Boston area. Differences in aPWV between women with versus without HIV in our study may have been influenced by unmeasured confounders and differences in historical risk behaviors. Our relatively small size may also have affected our ability to adjust for measured confounders in multivariable modeling. Our study was strengthened by the prospective collection of data using comprehensive cardiovascular imaging techniques and metabolic/immune phenotyping procedures to investigate predictors of arterial stiffness among an at-risk and relatively understudied population in cardiovascular research—WHIV.

In conclusion, ART-treated women aging with HIV had higher aPWV as compared to matched women without HIV. Moreover, aPWV related to a systemic marker of monocyte activation, sCD163, among WHIV but not among women without HIV. Soluble CD 163 levels were an independent predictor of aPWV even after controlling for HIV-specific

parameters among WHIV and traditional CVD risk factors among the whole group. Additional studies are now needed to investigate whether monocyte activation contributes to higher arterial stiffness among WHIV and whether interventions that mitigate and/or target monocyte activation in this group forestall the progression from arterial stiffness to MI and HF in this group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank the participants in this study and the Nursing Staff of the Massachusetts General Hospital (MGH) Translational and Clinical Research Center. The authors also thank Jacob Calkins, Mary O'Hara, and Larry White from the MGH Martinos Center for Biomedical Imaging.

Supported by a Collaborative Feasibility Award from the NIH/Harvard Center for AIDS Research P30AI060354 to M.V.Z. and T.G.N. This project was also supported by National Institutes of Health (NIH) grants M01RR01066, 1UL1RR025758, and 8UL1TR000170 to the Harvard Translational and Clinical Research Center. Support was also received from the NIH grant P30DK040561 to the Nutrition Obesity Research Center at Harvard. M.T. is supported by the NIH/National Heart, Lung, and Blood Institute (NHLBI) grant 1K23HL147799-01. T.G.N. is supported by a gift from A. Curt Greer and Pamela Kohlberg and grants from the NIH/NHLBI R01HL130539 and K24HL150238. M.V.Z. and T.G.N. received support from the NIH/NHLBI grant R01HL137562. T.H.B. has received support from the NIH/NHLBI grant R01HL141132. The sponsor funded the study but had no role in the analysis of the data nor in the decision to publish the data.

T.L.S. has grant funding to her institution for an investigator-initiated grant from Novo Nordisk. T.H.B. is a coinvestigator on a study sponsored by Excision BioTherapeutics and has received equity from Excision BioTherapeutics. T.G.N. has been a consultant to and received fees from Parexel Imaging, Intrinsic Imaging, BMS, H3-biomedicine, and Syros Pharmaceuticals. M.V.Z. is a principal investigator of an investigator-initiated research grant from Gilead Sciences, Inc. to her institution. All disclosures are unrelated to the current work. The remaining authors have no conflicts of interest to disclose.

REFERENCES

1. Fitch KV, Srinivasa S, Abbara S, et al. Noncalcified coronary atherosclerotic plaque and immune activation in HIV-infected women. *J Infect Dis*. 2013;208:1737–1746. [PubMed: 24041790]
2. Triant VA, Lee H, Hadigan C, et al. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007; 92:2506–2512. [PubMed: 17456578]
3. Lang S, Mary-Krause M, Cotte L, et al. Increased risk of myocardial infarction in HIV-infected patients in France, relative to the general population. *AIDS*. 2010;24:1228–1230. [PubMed: 20400883]
4. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013;173:614–622. [PubMed: 23459863]
5. Womack JA, Chang CC, So-Armah KA, et al. HIV infection and cardiovascular disease in women. *J Am Heart Assoc*. 2014;3:e001035. [PubMed: 25324353]
6. Janjua SA, Triant VA, Addison D, et al. HIV infection and heart failure outcomes in women. *J Am Coll Cardiol*. 2017;69:107–108. [PubMed: 28057235]
7. Payne RA, Wilkinson IB, Webb DJ. Arterial stiffness and hypertension: emerging concepts. *Hypertension*. 2010;55:9–14. [PubMed: 19948990]
8. Park S, Lakatta EG. Role of inflammation in the pathogenesis of arterial stiffness. *Yonsei Med J*. 2012;53:258–261. [PubMed: 22318811]
9. Mozos I, Malainer C, Horbanczuk J, et al. Inflammatory markers for arterial stiffness in cardiovascular diseases. *Front Immunol*. 2017;8:1058. [PubMed: 28912780]

10. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55:1318–1327. [PubMed: 20338492]
11. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010; 121:505–511. [PubMed: 20083680]
12. Ohyama Y, Ambale-Venkatesh B, Noda C, et al. Aortic arch pulse wave velocity assessed by magnetic resonance imaging as a predictor of incident cardiovascular events: the MESA (Multi-Ethnic study of atherosclerosis). *Hypertension*. 2017;70:524–530. [PubMed: 28674039]
13. Hunt PW. Very early ART and persistent inflammation in treated HIV. *Clin Infect Dis*. 2017;64:132–133. [PubMed: 27965300]
14. Leite LHM, Cohen A, Boccara F. HIV infection and aortic stiffness. *Arch Cardiovasc Dis*. 2017;110:495–502. [PubMed: 28416296]
15. Moreira RC, Mill JG, Grinsztejn B, et al. HIV infection is not associated with aortic stiffness. Traditional cardiovascular risk factors are the main determinants-cross-sectional results of INI-ELSA-BRASIL. *J Acquir Immune Defic Syndr*. 2018;78:73–81. [PubMed: 29624545]
16. Msoka TF, Van Guilder GP, Smulders YM, et al. Association of HIV-infection, antiretroviral treatment and metabolic syndrome with large artery stiffness: a cross-sectional study. *BMC Infect Dis*. 2018;18:708. [PubMed: 30594160]
17. Rider OJ, Asaad M, Ntusi N, et al. HIV is an independent predictor of aortic stiffness. *J Cardiovasc Magn Reson*. 2014;16:57. [PubMed: 25187084]
18. Fourie CM, Schutte AE, Smith W, et al. Endothelial activation and cardiometabolic profiles of treated and never-treated HIV infected Africans. *Atherosclerosis*. 2015;240:154–160. [PubMed: 25795556]
19. Alcaide ML, Parmigiani A, Pallikkuth S, et al. Immune activation in HIV-infected aging women on antiretrovirals-implications for age-associated comorbidities: a cross-sectional pilot study. *PLoS One*. 2013;8:e63804. [PubMed: 23724003]
20. Abelman RA, Mugo BM, Zanni MV. Conceptualizing the risks of coronary heart disease and heart failure among people aging with HIV: sex-specific considerations. *Curr Treat Options Cardiovasc Med*. 2019;21:41. [PubMed: 31309321]
21. Suever JD, Oshinski J, Rojas-Campos E, et al. Reproducibility of pulse wave velocity measurements with phase contrast magnetic resonance and applanation tonometry. *Int J Cardiovasc Imaging*. 2012;28:1141–1146. [PubMed: 21805314]
22. Rogers WJ, Hu YL, Coast D, et al. Age-associated changes in regional aortic pulse wave velocity. *J Am Coll Cardiol*. 2001;38:1123–1129. [PubMed: 11583892]
23. Grotenhuis HB, Westenberg JJ, Steendijk P, et al. Validation and reproducibility of aortic pulse wave velocity as assessed with velocity-encoded MRI. *J Magn Reson Imaging*. 2009;30:521–526. [PubMed: 19711407]
24. Westenberg JJ, van Poelgeest EP, Steendijk P, et al. Bramwell-Hill modeling for local aortic pulse wave velocity estimation: a validation study with velocity-encoded cardiovascular magnetic resonance and invasive pressure assessment. *J Cardiovasc Magn Reson*. 2012;14:2. [PubMed: 22230116]
25. Zanni MV, Awadalla M, Toribio M, et al. Immune correlates of diffuse myocardial fibrosis and diastolic dysfunction among aging women with human immunodeficiency virus. *J Infect Dis*. 2019; 221:1315–1320.
26. Toribio M, Neilan TG, Awadalla M, et al. Intramyocardial triglycerides among women with vs. without HIV: hormonal correlates and functional consequences. *J Clin Endocrinol Metab*. 2019; 104:6090–6100. [PubMed: 31393564]
27. Voges I, Jerosch-Herold M, Hedderich J, et al. Maladaptive aortic properties in children after palliation of hypoplastic left heart syndrome assessed by cardiovascular magnetic resonance imaging. *Circulation*. 2010;122:1068–1076. [PubMed: 20805434]
28. Fielden SW, Fomwalt BK, Jerosch-Herold M, et al. A new method for the determination of aortic pulse wave velocity using cross-correlation on 2D PCMR velocity data. *J Magn Reson Imaging*. 2008;27:1382–1387. [PubMed: 18504758]

29. Chirinos JA, Segers P, Hughes T, et al. Large-artery stiffness in Health and disease: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;74: 1237–1263. [PubMed: 31466622]
30. Donato AJ, Machin DR, Lesniewski LA. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. *Circ Res*. 2018;123: 825–848. [PubMed: 30355078]
31. Vlachopoulos C, Dima I, Aznaouridis K, et al. Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals. *Circulation*. 2005;112:2193–2200. [PubMed: 16186422]
32. Ticona E, Bull ME, Soria J, et al. Biomarkers of inflammation in HIV-infected Peruvian men and women before and during suppressive antiretroviral therapy. *AIDS*. 2015;29:1617–1622. [PubMed: 26372272]
33. Raghavan A, Rimmelin DE, Fitch KV, et al. Sex differences in select non-communicable HIV-associated comorbidities: exploring the role of systemic immune activation/inflammation. *Curr HIV/AIDS Rep*. 2017;14:220–228. [PubMed: 29080122]
34. Crane HM, Paramsothy P, Drozd DR, et al. Types of myocardial infarction among human immunodeficiency virus-infected individuals in the United States. *JAMA Cardiol*. 2017;2:260–267. [PubMed: 28052152]
35. Feinstein MJ, Steverson AB, Ning H, et al. Adjudicated heart failure in HIV-infected and uninfected men and women. *J Am Heart Assoc*. 2018;7:e009985. [PubMed: 30571387]
36. Stone L, Looby SE, Zanni MV. Cardiovascular disease risk among women living with HIV in North America and Europe. *Curr Opin HIV AIDS*. 2017;126:585–593.
37. Toribio M, Neilan TG, Zanni MV. Heart failure among people with HIV: evolving risks, mechanisms, and preventive considerations. *Curr HIV/AIDS Rep*. 2019;16:371–380. [PubMed: 31482297]
38. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. *JAMA*. 2012;308:379–386. [PubMed: 22820791]
39. Kooij KW, Schouten J, Wit FW, et al. Difference in aortic stiffness between treated middle-aged HIV type 1-infected and uninfected individuals largely explained by traditional cardiovascular risk factors, with an additional contribution of prior advanced immunodeficiency. *J Acquir Immune Defic Syndr*. 2016;73:55–62. [PubMed: 27513572]
40. deFilippi C, Toribio M, Wong LP, et al. Differential plasma protein regulation and statin effects in HIV-infected and non-HIV-infected patients utilizing a proteomics approach protein regulation and statin effects in HIV. *J Infect Dis*. 2020.

FIGURE 1.

Assessment of aortic arch pulse wave velocity: (A) Image of the thoracic aorta (oblique parasagittal/candy cane view). The solid white line, which is perpendicular to the ascending aorta (1) and divides the proximal descending aorta (2), represents the acquisition planes for the pulse wave velocity assessment on cardiovascular MRI. B, Aortic flow-versus-time curves: aPWV is determined from the time delay of the representative aortic flow-versus-time curves recorded at the ascending aorta (location 1 (blue) in A and red velocity-time curve in B) and the descending aorta (location 2 (red) in A and blue velocity-time curve in B) using a cross-correlation method on the systolic upstroke part of the flow curves. Pulse wave velocity is defined as $\Delta x / \Delta t$, where Δx is the aortic path length along a midline in the vessel lumen (dashed white line in A), and Δt is the transit time (distance between systolic upstroke of ascending and descending aorta flow curves shown in B).

FIGURE 2.

aPWV and monocyte activation. A, aPWV among women with versus without HIV. aPWV was significantly higher among WHIV versus women without HIV. [Data are graphically shown as median (interquartile range).] B, Relationship between aPWV and systemic monocyte activation among WHIV. Among WHIV, aPWV related directly to a marker of systemic monocyte activation, soluble CD163.