HIV Infection Is Not Associated With Aortic Stiffness. Traditional Cardiovascular Risk Factors Are the Main Determinants—Cross-sectional Results of INI-ELSA-BRASIL

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Introduction: Aortic stiffness measured by carotid-femoral pulse wave velocity (cf-PWV) is a marker of subclinical atherosclerosis. We propose to assess whether HIV infection is associated with arterial stiffness and their determinants in HIV-infected subjects.

Methods: We compared data from an HIV cohort (644 patients, HIV+) in Rio de Janeiro with 2 groups: 105 HIV-negative (HIV−) individuals and 14,873 participants of the ELSA-Brasil study. We used multivariable linear regression to investigate factors associated with cf-PWV and whether HIV was independently associated with aortic stiffness and propensity score weighting to control for imbalances between groups.

Results: From 15,860 participants, cf-PWV was obtained in 15,622 (98.5%). Median age was 51 (interquartile range 45–58), 44.41 (35.73, 54.72), and 43.60 (36.01, 50.79) years ($P < 0.001$), and median cf-PWV (m/s; interquartile range) was 9.0 (8.10, 10.20), 8.70 (7.90, 10.20), and 8.48 (7.66, 9.40) for ELSA-Brasil, HIV− and HIV+, respectively ($P < 0.001$). In the final weighted multivariable models, HIV group was not associated with cf-PWV when compared either with ELSA-Brasil [β = −0.05; 95% confidence interval (CI) = −0.23; $P = 0.12$; $P = 0.52$] or with the HIV- groups (β = 0.10; 95% CI = −0.10; 0, 31; $P = 0.32$). Traditional risk factors were associated with higher cf-PWV levels in the HIV+ group, particularly waist-to-hip ratio (β = 0.20; 95% CI = 0.10; 0.30; $P < 0.001$, result per one SD change).

Conclusions: HIV infection was not associated with higher aortic stiffness according to our study. In HIV-infected subjects, the stiffness of large arteries is mainly associated with traditional risk factors and not to the HIV infection per se.

Key Words: people living with HIV, cardiovascular risk factors, arterial stiffness

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INTRODUCTION

After widespread use of antiretroviral (ARV) therapy, the decreasing incidence of opportunistic diseases has been followed by the emergence of diseases not traditionally linked to HIV infection, especially cardiovascular diseases (CVDs), which have become important causes of morbidity and mortality among people living with HIV/AIDS (PLWHA) either in developed or in developing countries, including Brazil.[1,2] Epidemiologic studies suggest that PLWHA are at increased risk of CVD when compared with the general population.[3–5] Current understanding of the etiology involves a complex interplay between inflammation and endothelial dysfunction, eventually leading to the process of atherosclerosis.

In this particular scenario, a higher prevalence of traditional CV risk factors followed by persistent viral activity resulting in immune activation and systemic inflammation has been observed.[6,7] Moreover, despite certain regimens of ARV therapy, which have been initially implicated with an excess risk of CVD throughout deregulation of lipid and glucose metabolism, recent studies showed that earlier initiation and

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continuous use of ART could actually improve CV outcomes.[8–10] These findings indicate that nontraditional factors such as viral replication might explain a higher CV risk in PLWHA.

To investigate subclinical atherosclerosis and the pathogenesis of CVD, several methods have been used. Arterial stiffness, measured as the aortic pulse wave velocity between the carotid and femoral arteries (cf-PWV), is a noninvasive and reproducible technique, which has shown to predict CV events in healthy subjects.[11,12] Preliminary investigations showed that HIV infection and certain classes of ARV therapies were associated with an increased cf-PWV. However, these results are inconsistent and a limited number of those studies have been conducted in large adult population settings.[13–15]

Although data from Brazil about the transition of the morbi-mortality profile in PLWHA are scarce, we recently demonstrated a significant decrease in the global mortality rates driven by AIDS-related causes with an increased indication of CVD conditions as causes of death in HIV-infected subjects.[16–18]

Moreover, there is a lack of studies and methods evaluating subclinical atherosclerosis in PLWHA in middle-income countries. Recently, we characterized the risk factors for carotid intima media thickness (cIMT) in a significant sample of a Brazilian PLWHA cohort,[19] and later, we found no association between HIV infection and early atherosclerosis, also measured by cIMT.[20]

Hence, in this study, we propose to compare cf-PWV among 3 groups of subjects: one infected with HIV and 2 non-HIV–infected and to determine variables associated with arterial stiffness in HIV-infected individuals.

METHODS

Study Design and Participants

We conducted a cross-sectional study comparing data from 3 different groups of individuals. The first group, herein after referred as HIV+ group, was a sample of 649 HIV-infected patients prospectively followed in the Instituto Nacional de Infectologia Evandro Chagas (INI) cohort in Rio de Janeiro, a national reference center for infectious diseases, especially for care, research, and training related to HIV/AIDS since 1986. An observational and clinical database available in electronic and paper records is maintained, with PLWHA receiving primary, specialty, and tertiary HIV care at its facilities. Participants were invited to join this study while waiting for their consultations (clarifying that their consultation and treatment follow-up would not depend on their participation), if they were between ages of 25 and 75 and underactive follow-up at INI outpatient clinic.[18] The second group consisted of 106 individuals who were HIV negative (HIV−) recruited based on HIV+ participant's nomination at the day of the main study procedures. The eligibility criteria were age 25–75 years, partner, spouse, relative, coworker, or someone in the neighborhood of the HIV+ participant who had an anti-HIV rapid screen test negative at study entry. The third group was composed by participants of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil study), a prospective cohort of 15.105 active or retired public servants of both sexes with ages between 35 and 74 years from 5 universities and one research institution. Its aim is to investigate the incidence and risk factors for chronic diseases, in particular, CVDs and diabetes.[21] Baseline data for the ELSA-Brasil group were collected from 2008 to 2010,[22] whereas data for the other 2 groups were collected using the same protocols, equipment, and technical staff between January 2011 and January 2012. The study was approved by the Comitê de Ética em Pesquisa from INI, the local institutional review board.

Data Collection

After participants had signed an informed consent form, all 3 groups went through the same baseline examination of the ELSA-Brasil study. This included detailed questionnaires' interviews, covering sociodemographics, family history, medication exposure, and comorbidity characteristics. In addition, clinical and anthropometric examinations, oral glucose tolerance test, and blood samples were collected for a complete laboratory evaluation.[23] HIV cohort–specific information was also obtained, including use of combined ART (cART), regimens, and the time in years on each regimen, current CD4 counts, viral loads, and cytomegalovirus. Nadir CD4 counts and previous HIV viral load measurement were obtained from the medical charts in the cohort's database. Aortic stiffness was measured using cf-PWV with a validated and noninvasive automatic device (Complior SP; Artech Medical, Paris, France). Systolic and diastolic blood pressures were recorded at the day of cf-PWV examination. More detailed description of procedures can be found elsewhere.[21,22,24–26]

Variables were defined or calculated as follows. Race/ethnicity was self-referred and categorized into black, brown, white, and others. The last category comprises indigenous (native Brazilian) and Asiatic participants. Diabetes mellitus (DM) was defined as having glycated hemoglobin $>6.5\%$ or fasting glucose >126 mg/dL, or oral glucose-tolerance test levels >200 mg/dL or current use of a hypoglycemic drug. Resting blood pressure was measured 3 times in the nondominant arm in the sitting position, and hypertension was ascertained if the mean of the last 2 measurements showed systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or if in use of antihypertensive drugs. Dyslipidemia was defined as low-density lipoprotein levels ≥ 130 mg/dL or use of lipid-lowering drugs. Cumulative smoking was calculated as pack-years, by multiplying the number of packs of cigarettes smoked per day by the number of years of smoking and a heavy smoker a person who has smoked >10 pack-year. Family history of sudden death and family history of acute myocardial infarction (AMI) or stroke were defined as the informed occurrence of any episode of those conditions among parents or brothers younger than 65 years of age. History of CVD was defined as informed past occurrence of angina, AMI, or stroke. Body mass index was calculated as the ratio of measured weight in kilograms and squared height in meters. Cumulative viral load (viremia copy-years) was defined

as the area under the curve for 2 consecutive viral load measurements over time, in years.[27] Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation.[28] A variable to capture poor clinical management of hypertension, DM, or dislipidemia was defined as if a participant or patient reported no history of any one of these conditions and was taking no medication for them but was diagnosed with any of those conditions at the time of entry in the study.

Statistical Analysis

Descriptive comparisons of general characteristics among HIV+, HIV−, and ELSA-Brasil groups and general characteristics of HIV-infected participants, compared according to terciles of cf-PWV were performed with Kruskal–Wallis tests for continuous and χ^2 or Fisher exact tests for categorical variables. Data were expressed as median [interquartile range (IQR)] or frequency (%) where applicable.

To evaluate the association between cf-PWV and HIV +, linear regression models were used. We made 2 comparisons separately: (1) HIV+ group with the ELSA-Brasil group and (2) HIV+ group with the HIV- group. To choose the best multivariable model explaining cf-PWV values, we used an exhaustive procedure implemented by a genetic algorithm.[29] The procedure was also replicated 20 times and the overall best model was chosen.

To account for imbalances between comparison groups, we implemented propensity scores (PSs) to identify control units (ELSA-Brasil and HIV− groups) that were similar to treated units (HIV+ group). As method of estimation, we used the effect of the treatment on the treated (average treatment effects on the treated). Hence, for the first comparison (HIV+ and ELSA-Brasil groups), we chose the nearest neighbor-matching algorithm, without replacement using caliper width equal to 0.05 of the PS logit SD. For the outcome analysis, we created a matched data set to run the cf-PWV regression. In the second comparison (HIV+ and HIV− groups), generalized boosted modeling (GBM) was used as a nonparametric estimation of the PS. The number of GBM interaction trees was added until SMD in covariates was minimized while working with the maximum SMD as stopping rule. The average treatment effects on the treated weights were saved as variable into the original data set and then applied as probability weights in the final linear weighted regression model.[30,31] In both analysis, the quality of covariable balance was checked graphically with Q–Q plots and through standardized mean difference (SMD) below 0.25 after PS application, adding Kolmogorov–Smirnov statistics for the second comparison, (see Table 6, Supplemental Digital Content 1, http://links.lww.com/QAI/B122—Summary of balance metrics for propensity score matching between HIV+ and ELSA-Brasil groups and Table 7, Supplemental Digital Content 1, http://links.lww.com/QAI/B122—Summary of balance metrics for propensity score estimated with GBM between HIV+ and HIV− groups), with all variables reaching balance with the exception of age, income, and triglycerides in the parametric procedure, so these covariables were included in the final weighted linear model to take into account the residual confounding.

For the first analysis, we have generated 4 models for comparison: (1) a naive univariable model, for reference; (2) a full model with all the covariables chosen by the genetic algorithm, described above, which yielded different sets of variables for each comparison; (3) a univariable propensity-scores weighted model; (4) a full model with the variables that did not reach balance graphically for the first comparison and for the second comparison, the same variables used to calculate the propensity scores, to control for residual confounding.

Finally, to study factors associated with arterial stiffness in the HIV+ group, the best multivariate linear model was also chosen using the genetic algorithm described before.

All analyses were performed with the R environment version 3.2.2. For the parametric and nonparametric estimation, we adopted the MatchIt and twang packages, respectively.[32]

RESULTS

We included 15,860 subjects. Arterial stiffness was measured in 14,873, 105, and 644 from ELSA-Brasil, HIV−, and HIV+ groups, respectively. Overall, 45.69%, 35.24%, and 57.92% of subjects were men ($P < 0.001$); median age (IQR) was 51 (45–58), 44.41 (35.7, 54.7), and 43.6 (36.0, 50.78) years ($P < 0.001$); and median cf-PWV in m/s was 9.0 (8.1, 10.2), 8.70 (7.9, 10.2), and 8.48 (7.7, 9.4) for ELSA-Brasil, HIV−, and HIV+, respectively ($P < 0.001$).

Regarding characteristics of the HIV+ group, they were younger, had a higher proportion of schooling <9 years, and were predominantly men and blacks. Although they presented higher proportion of current and heavy (>10 pack-years) smokers and family history of sudden death, they also exhibited a better lipid profile and less frequently dyslipidemia and hypertension, and lower body mass index, although there is overlap among confidence intervals and lower C-reactive protein levels with better renal function and improved management of CVD-related conditions than the other 2 groups. The ELSA-Brasil group presented older age, higher median income and schooling years, higher proportion of dyslipidemia as well as increased lipid profile and median high-sensitivity C-reactive protein but lower CKD-epi median. Although prevalences were not adjusted for age, it is worth mentioning that individuals from ELSA-Brasil exhibited a lower percentage of DM, albeit they were older (Table 1).

Information about ART use, specific regimens, and HIV-specific laboratory tests are shown in Table 4. At enrollment, 569 (88.63%) participants were under ART for an average of 4.91 years (IQR: 2.28–11.02), most commonly on a regimen containing nonnucleoside reverse transcriptase inhibitors (65.01%). Median current CD4 cell count was 579.86 (IQR: 370–740) cells per milliliter, with a nadir of 214 (IQR: 95.25–315.75) cells per milliliter and undetectable viral load in 452 (71.07%) individuals.

Comparison of cf-PWV Between HIV+ With ELSA-Brasil and HIV+ with HIV− Groups

Univariable and multivariable linear models revealed higher levels of cf-PWV in the ELSA-Brasil group when compared with the HIV+ group (Table 2). In the unweighted

TABLE 1. General Characteristics of Participants Stratified by Groups*

	Groups				
	ELSA-Brasil	**HIV−**	**HIV+**	**Total**	***P*†**
Total	14,873	105	644	15,622	
Sex: male	6795 (45.69)	37 (35.24)	373 (57.92)	7205 (46.12)	<0.001
Age in yr, median (IQR)	51 (45–58)	44.41 (35.73–54.72)	43.60 (36.01–50.79)	51 (45–58)	<0.001
Schooling <9 yrs	1887 (12.69)	59 (56.19)	308 (47.83)	2254 (14.43)	<0.001
Race					<0.001
Black	2357 (16.04)	23 (21.90)	147 (22.83)	2527 (16.36)	
Brown	4134 (28.13)	39 (37.14)	258 (40.06)	4431 (28.69)	
White	7680 (52.27)	38 (36.19)	212 (32.92)	7930 (51.35)	
Others	523 (3.56)	5 (4.76)	27 (4.19)	555 (3.59)	
Smoking					<0.001
Never	8483 (57.04)	60 (57.14)	320 (49.69)	8863 (56.74)	
Former	4449 (29.92)	24 (22.86)	172 (26.71)	4645 (29.74)	
Current	1940 (13.04)	21 (20)	152 (23.60)	2113 (13.53)	
Pack yr (10+)	3454 (23.33)	22 (20.95)	175 (27.22)	3651 (23.47)	0.0622
Income (R$), median (IQR)	1347.12 (725.38–2279.75)	414.50 (207.25–639.02)	414.50 (207.25–1036.25)	1312.58 (690.83–2072.50)	<0.001
Family history of sudden death	2223 (14.95)	15 (14.29)	120 (18.63)	2358 (15.09)	0.0369
Family history of AMI or stroke	4008 (26.95)	36 (34.29)	175 (27.17)	4219 (27.01)	0.2397
History of CVD	805 (5.41)	8 (7.62)	49 (7.61)	862 (5.52)	0.0368
Total cholesterol (mg/dL), median (IQR)	211 (186–239)	186 (162–214)	182 (156–211)	210 (185–238)	<0.001
HDL (mg/dL), median (IQR)	54 (46–65)	44 (37–53)	42 (35–51)	54 (46–64)	<0.001
LDL (mg/dL), median (IQR)	129 (107–152)	114 (95–136)	106 (87–133)	128 (106–151)	<0.001
Triglycerides (mg/dL), median (IQR)	114 (81–165)	100 (69–135)	120 (85–185)	115 (81–166)	<0.001
Dyslipidemia	8601 (57.85)	40 (38.10)	235 (37.24)	8876 (56.89)	<0.001
Use of lipid-lowering drugs	1915 (12.88)	8 (7.62)	88 (13.66)	2011 (12.87)	0.2295
Hypertension	5598 (37.64)	45 (42.86)	201 (31.21)	5844 (37.41)	0.0022
Antihypertensive medication use	4357 (29.29)	31 (29.52)	143 (22.20)	4531 (29)	<0.001
DM	2690 (18.09)	40 (38.10)	165 (25.62)	2895 (18.53)	<0.001
Use of antidiabetic drugs	1210 (8.14)	10 (9.52)	35 (5.43)	1255 (8.03)	0.0405
Poor management	7933 (53.36)	58 (55.24)	281 (43.97)	8272 (52.99)	<0.001
Waist/hip ratio, median (IQR)	0.90 (0.83–0.96)	0.89 (0.84–0.94)	0.90 (0.84–0.96)	0.90 (0.83–0.96)	0.1178
BMI, median (IQR)	26.49 (23.84–29.68)	27.68 (24.09–30.58)	24.43 (21.92–27.51)	26.41 (23.75–29.61)	<0.001
hs-CRP (mg/dL), median (IQR)	1.45 (0.72–3.28)	0.31 (0.20–0.60)	0.29 (0.17–0.65)	1.37 (0.66–3.16)	<0.001
CKD-Epi, median (IQR)	88.41 (76.24–101.27)	99.10 (81.82–108.86)	106.78 (92.57–120.91)	89.04 (76.68–102.45)	<0.001
SBP, median (IQR)	124 (114–136)	127 (118–141)	124 (115.75–134)	124 (114–136)	0.0797
DBP, median (IQR)	76 (69–83)	78 (71–84)	75 (70–83)	76 (69–83)	0.0896
cf-PWV (m/s), median (IQR)	9 (8.10–10.20)	8.70 (7.90–10.20)	8.48 (7.66–9.40)	9 (8.10–10.20)	<0.001

*Columns provide numbers (%) and IQR where applicable.
†Kruskal–Wallis and χ^2 tests.
cf-PWV, carotid-femoral pulse wave velocity; CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

model age, being male, presenting hypertension, DM, or dyslipidemia, use of antidiabetic drugs, serum creatinine, triglycerides, C-reactive protein, systolic blood pressure, and diastolic blood pressure had a positive association with cf-PWV levels. The magnitude of association was higher for waist-to-hip ratio ($\beta = 0.10$; 95% CI = 0.07; 0.14; $P < 0.001$, result per one SD change). Protective factors were schooling >9 years, being an ex-smoking, family history of CVD, antihypertensive, and lipid-lowering medication use.

When the HIV− group was used as control (Table 3), no association was seen between the HIV+ group and cf-PWV either in unweighted or weighted multivariable models. In this case, the unweighted model yielded age, female gender, hypertension, systolic blood pressure and diastolic blood pressure as predictive of increased cf-PWV. Once more, the association was stronger for waist-to-hip ratio ($\beta = 0.17$; 95% CI = 0.07; 0.27; $P < 0.001$, result per one SD change).

Determinants of cf-PWV in the HIV-Infected Population

In the crude analysis, age, smoking 10+ pack-years, family history of AMI or stroke, and other traditional CVD

TABLE 2. Comparison of cf-PWV (m/s) Between HIV+ and ELSA-Brasil Groups

Univariable Models	Unweighted			Weighted*		
Variable	**Estimate**	**95% CI**	***P***	**Estimate**	**95% CI**	***P***
Group: HIV	−0.68	−0.82 to −0.53	<0.001	−0.04	−0.24 to 0.16	<0.668
Multiple Models	**Unweighted**			**Weighted***		
Variable	**Estimate**	**95% CI**	***P***	**Estimate**	**95% CI**	***P***
Group: HIV	−0.14	−0.26 to −0.02	0.02628	−0.05	−0.23 to 0.12	0.5212
Age (yrs)	0.06	0.06 to 0.07	<0.001	0.07	0.06 to 0.08	<0.001
Sex: female	−0.13	−0.19 to −0.06	<0.001	—	—	—
Income (R$) × 10^4	−0.05	−0.22 to 0.11	0.5308	−0.89	−1.71 to −0.07	0.0324
Schooling: >9 yrs	−0.09	−0.16 to −0.02	0.0148	——	—	—
Smoking: former	−0.08	−0.13 to −0.02	0.003	—	—	—
Smoking: current	−0.01	−0.08 to 0.06	0.746	—	—	—
Family history of CVD	−0.17	−0.27 to −0.07	0.001	—	—	—
Hypertension	0.31	0.21 to 0.42	<0.001	—	—	—
Antihypertensive medication use	−0.27	−0.38 to −0.17	<0.001	—	—	—
DM	0.30	0.21 to 0.40	<0.001	—	—	—
Use of antidiabetic drugs	0.37	0.25 to 0.49	<0.001	—	—	—
Dyslipidemia	0.14	0.03 to 0.26	0.016	—	—	—
Use of lipid-lowering drugs	−0.14	−0.27, −0.01	0.033	—	—	—
Poor management	−0.15	−0.26 to −0.04	0.009			
Waist/hip ratio†	0.10	0.07 to 0.14	<0.001	—	—	—
Serum creatinine	0.25	0.16 to 0.34	0.013	—	—	—
LDL (mg/dL) × 10^2	−0.06	−0.15 to 0.04	0.233	—	—	—
Triglycerides ×10^2 (mg/dL)	0.03	0.01 to 0.05	0.010	0.24	0.15 to 0.33	<0.001
hs-CRP (mg/dL)	0.01	0.01 to 0.02	<0.001	—	—	—
SBP	0.03	0.03 to 0.04	<0.001	—	—	—
DBP	0.01	0.01 to 0.02	<0.001	—	—	—

*Estimated using a logistic regression model.
†Result expressed per SD change.
DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

risk factors were associated with higher terciles of cf-PWV, whereas HIV-specific characteristics were ART use, particularly with a protease inhibitor–containing regimen, time under ART in years, increased current CD4 cell count, lower nadir of CD4 cell count, and higher cumulative viral load (Table 4). Nevertheless, in the multivariable regression analysis, age, family history of sudden death, hypertension, antihypertensive medication use, waist-to-hip ratio, triglycerides, and systolic and diastolic blood pressure were predictors of increased cf-PWV (Table 5).

DISCUSSION

In our study, we have found no difference of cf-PWV when we compared either ELSA-Brasil with the HIV+ groups or the HIV+ with the HIV− groups, both in unweighted and weighted multivariable models. Moreover, traditional CV risk factors were the main determinants of arterial stiffness in HIV-infected participants. To our knowledge, this is the first study to compare arterial stiffness in a considerably large sample of participants in a middle-income country using a rich set of covariables.

Authors from different countries have reported increased cf-PWV in HIV-infected when compared with HIV-uninfected participants.[33–36] By contrast, results from several other studies revealed no association between arterial stiffness and HIV infection.[37,38] In Brazil, a study performed by Monteiro et al in 2 HIV-/AIDS-referral centers did not find significant differences in cf-PWV between PLWHA and uninfected controls, divergent from Eira et al who found increased cf-PWV in HIV-infected patients under cART, particularly among women.[39,40]

Still, our findings are in conformity with the latest evidence, which demonstrates no association between HIV infection and cf-PWV. For instance, Ho et al showed that initiation of ARV therapy at higher nadir $CD4^+$ T-cell counts was associated with reduced arterial stiffness in PLWHA.[15] In addition, Echeverria et al demonstrated similar arterial stiffness in PLWHA compared with non–HIV-infected participants.[37] In this scenario, roughly 90% of PLWHA were currently under ART with a high median CD4 cell count, similar to our results.

States of immune activation with chronic inflammation are linked to endothelial dysfunction and increased arterial stiffness through vessel loss of collagen and elastin.[41] The better management of CVD-related conditions as a result of free access to health care system in combination with regular visits to specialists and cART use might have mitigated the detrimental effects of HIV infection, likewise the inflammation

TABLE 3. Final Model for cf-PWV (m/s) on HIV+ and HIV− Participants

Univariable Models	Unweighted			Weighted*		
Variable	**Estimate**	**95% CI**	***P***	**Estimate**	**95% CI**	***P***
Group: HIV	−0.37	−0.67 to −0.07	0.016	0.03	−0.30 to 0.35	0.8743
Multiple Models	**Unweighted**			**Weighted***		
Variable	**Estimate**	**95% IC**	***P***	**Estimate**	**95% IC**	***P***
Group: HIV+	−0.06	−0.28 to −0.17	0.6724	0.10	−0.10 to 0.31	0.3199
Age (yrs)	0.05	0.04 to 0.06	<0.001	0.05	0.04 to 0.06	<0.001
Sex: female	0.265	0.08 to 0.45	0.0053	0.29	0.10 to 0.48	0.0030
Family history of sudden death	−0.24	−0.45 to −0.03	0.0231	−0.27	−0.46 to −0,09	0.0033
Hypertension	0.46	0.16 to 0.76	0.0028	0.59	0.24 to 0.95	0.0010
Antihypertensive medication use	−0.41	−0.72 to −0.10	0.0097	−0.62	−0.99 to −0.26	0.0008
Dyslipidemia	−0.16	−0.37 to 0.06	0.1538	−0.1629	−0.38 to 0.07	0.1737
Waist/hip ratio†	0.16	0.07 to 0.26	<0.001	0.17	0.07 to 0.27	0.0009
Income (R$) × 10^3	0.06	−0.02 to 0.14	0.1721	0.0566	−0.02 to 0.14	0.1743
LDL × 10^2 (mg/dL)	0.20	−0.02 to 0.56	0.0704	0.24	−0.08 to 0.56	0.1413
Triglycerides (mg/dL) ×10^3	0.86	−0.16 to 1.90	0.0980	1.19	0.10 to 2.27	0.0318
Serum creatinine (mg/dL)	0.08	−0.24 to 0.40	0.6251	0.08	−0.25 to 0.40	0.6422
SBP	0.02	0.01 to 0.03	<0.001	0.02	0.01 to 0.03	<0.001
DBP	0.02	0.01 to 0.04	<0.001	0.03	0.01 to 0.04	<0.001

*Estimated by generalized boosted modeling.
†Results are expressed per SD change.
DBP, diastolic blood pressure; LDL, low-density lipoprotein; SBP, systolic blood pressure.

in the vascular wall whereby we have demonstrated before.[20] This is an important piece of information to be explored in further studies aiming primary prevention.

Furthermore, being black is a well-known established risk factor for CVD.[42] The mechanism seems to involve endothelial dysfunction with reduced bioavailability of nitric oxide.[43] There is evidence pointing an association of black race with impaired microvascular function and greater arterial stiffness,[43] but we did not find racial differences in cf-PWV.

After adjustment for traditional CV risk factors, education, which is usually adopted as a proxy for socioeconomic status, was an important characteristic to explain cf-PWV variation, with lower levels of education expressed in years associated with higher arterial stiffness. The mechanism is closely related to disadvantaged trajectory of life with higher exposure to infections, toxins and pollution, tobacco use, physical inactivity, diet rich in saturated fats, and other exposures associated with the occurrence of CVD.[44]

With respect to traditional CVD risk factors, our results are in consonance with the findings of the great majority of the main determinants of arterial stiffness found in the literature.[45] We observed older age, sex, hypertension, DM, dyslipidemia, serum creatinine, triglycerides, C-reactive protein, and systolic and diastolic blood pressure being positively associated with cf-PWV levels, with the greatest magnitude of association for waist-to-hip ratio in both comparison groups. Abdominal adiposity has been recognized as an independent risk factor for CVD in addition to other anthropometric measures, and overweight has become epidemic in many middle-income countries, which calls urgent attention to preventive measures targeting weight reduction.[46]

Concerning HIV-related factors of arterial stiffness, previous work indicated profound immunodeficiency by a nadir CD4 cell count less than 200 cells per milliliter as an independent predictor of increased cf-PWV,[38] which calls for early initiation of ART. In multivariable analysis, the association between nadir of CD4 and cf-PWV was marginal.

ART also plays a pivotal role on this topic. Toxicity of some regimens, mainly by its metabolic effects, such as insulin resistance, dyslipidemia, and fat redistribution, has been linked to an increased arterial stiffness and CV risk, particularly with protease inhibitors. However, recent data point out beneficial CV effects of continuous and early initiation of ART mediated by the control of immune activation inducing vascular health.[9,10] In this article, our HIV-infected participants had almost 90 percent use of ART. Despite lack of information about adherence, it helps explain the good virologic control of this population.

In our results, the contribution of HIV-related covariables when present in the final adjusted model was nonsignificant.[36] Moreover, using similar methodology and comparing data from the same population, we previously reported no relationship between cIMT and HIV infection.[20]

In general, (1) cf-PWV might be a weak surrogate for CVD in this setting because it has better predictive ability for subjects with higher baseline risk when compared with the general population.[12] (2) HIV association with CVD has been exaggerated in the literature by the inclusion of HIV− control groups with lower prevalences of CV risk factors when compared with the HIV group, unmeasured confounding, and competing risks such as HIV-related deaths, which represent limitations in the analysis.[47] (3) The association between CVD and HIV has been attenuated by the use of less toxic ARV therapy regimens and control of comorbidities.[48] In our

TABLE 4. Characteristics of HIV+ Participants by Terciles of cf-PWV*

	(5.49, 7.95)	(7.95, 9)	(9, 15.4)	Total	*P*
Total	215	216	212	644	
Sex: female	91 (42.33)	84 (38.89)	96 (45.28)	271 (42.15)	0.4069
Age in yrs, median (IQR)	36.31 (29.81–43.41)	43.25 (38.34–49.51)	49.62 (44.66–56.73)	43.60 (36.01–50.79)	<0.001
Schooling: <9 yrs	96 (44.65)	102 (47.22)	110 (51.89)	308 (47.90)	0.3167
Race					0.1859
Black	42 (19.53)	57 (26.39)	48 (22.64)	147 (22.86)	
Brown	87 (40.47)	85 (39.35)	86 (40.57)	258 (40.12)	
White	71 (33.02)	67 (31.02)	73 (34.43)	211 (32.81)	
Others	15 (6.98)	7 (3.24)	5 (2.36)	27 (4.20)	
Smoking					0.005
Never	121 (56.28)	112 (51.85)	87 (41.04)	320 (49.77)	
Former	45 (20.93)	51 (23.61)	75 (35.38)	171 (26.59)	
Current	49 (22.79)	53 (24.54)	50 (23.58)	152 (23.64)	
Pack yr (10+)	35 (16.28)	61 (28.37)	78 (36.79)	174 (27.10)	<0.001
Income (R$), median (IQR)	414.50 (207.25–1021.45)	414.50 (207.25–1036.25)	414.50 (248.70–1036.25)	414.50 (207.25–1036.25)	0.3811
Family history of sudden death	34 (15.81)	45 (20.83)	41 (19.34)	120 (18.66)	0.3899
Family history of AMI or stroke	43 (20)	65 (30.09)	67 (31.60)	175 (27.22)	0.0135
History of CVD	13 (6.05)	13 (6.02)	23 (10.85)	49 (7.62)	0.0962
Total cholesterol (mg/dL), median (IQR)	166 (145.50–197.50)	183.50 (157.75–210.25)	192.50 (166–224.50)	182 (155–211)	<0.001
HDL (mg/dL), median (IQR)	42 (35–49)	41 (34–51)	44 (35.50–53.50)	42 (35–51.75)	0.1201
LDL (mg/dL), median (IQR)	100 (85–124)	107 (89–133)	110.50 (92.25–140.75)	106 (87–133)	<0.001
Triglycerides (mg/dL), median (IQR)	107 (73.50–143)	120 (82.75–185.25)	141 (104.75–201)	120 (85–185)	<0.001
CMV: IgG positive	209 (99.52)	212 (99.53)	205 (99.03)	626 (99.37)	0.7002
Dyslipidemia	54 (25.71)	84 (39.62)	96 (46.15)	234 (37.14)	<0.001
Use of lipid-lowering drugs	13 (6.05)	31 (14.35)	44 (20.75)	88 (13.69)	<0.001
Hypertension	29 (13.49)	64 (29.63)	107 (50.47)	200 (31.10)	<0.001
Antihypertensive medication use	26 (12.09)	43 (19.91)	73 (34.43)	142 (22.08)	<0.001
DM	33 (15.35)	55 (25.46)	77 (36.32)	165 (25.66)	<0.001
Use of antidiabetic drugs	3 (1.40)	8 (3.70)	24 (11.32)	35 (5.44)	<0.001
Poor management	68 (31.92)	99 (46.26)	113 (53.55)	280 (43.89)	<0.001
Waist/hip ratio, median (IQR)	0.87 (0.82–0.93)	0.90 (0.85–0.96)	0.94 (0.88–1.01)	0.90 (0.84–0.96)	<0.001
BMI, median (IQR)	24.10 (3.92)	25.18 (4.69)	26.23 (5.28)	25.18 (4.74)	<0.001
hs-CRP (mg/dL), median (IQR)	0.26 (0.15–0.48)	0.27 (0.18–0.61)	0.36 (0.18–0.81)	0.29 (0.17–0.65)	0.0128
CKD-Epi, median (IQR)	109.69 (96.25–130.50)	107.85 (92.55–119.50)	103.35 (89.18–114.38)	106.78 (92.57–120.91)	<0.001
SBP	118 (111, 126.50)	122.50 (115, 132)	131.50 (124, 145)	124 (115.75, 134)	<0.001
DBP	71 (66, 76)	75 (71, 81)	82 (76, 88)	75 (70, 83)	<0.001
ART use: yes	183 (85.12)	188 (87.04)	198 (93.84)	569 (88.63)	0.0119
PI-containing regimen	94 (43.72)	112 (51.85)	130 (61.32)	336 (52.26)	0.0013
NNRTI-containing regimen	146 (67.91)	133 (61.57)	139 (65.57)	418 (65.01)	0.3785
Cumulative viral load, median (IQR)	12.44 (6.57–27.11)	14.09 (5.8–29.7)	18.77 (10.7–31.78)	15.07 (6.96–29.73)	0.0012
Current CD4 counts (cells/mL), median (IQR)	514 (368.25–678.25)	539.50 (334.50–741.75)	595 (405.50–820)	579.86 (370–740)	<0.001
Nadir CD4 counts (cells/mL), median (IQR)	234.50 (122–319.75)	226 (76.50–335)	184 (87–296)	214 (95.25–315.75)	0.0334
Undetectable viral load: yes	137 (64.62)	146 (67.91)	169 (80.86)	452 (71.07)	<0.001
Time on cART (yr), median (IQR)	4.29 (1.82–10.19)	5.33 (2.17–10.71)	6.45 (3.45–11.57)	4.91 (2.28–11.02)	0.0063
Time on PI (yr), median (IQR)	4.91 (1.82–12.06)	6.12 (2.42–10.61)	6.16 (1.97–11.75)	5.83 (2–11.50)	0.8346
Time on NNRTI (yr), median (IQR)	2.65 (0.75–4.46)	2.92 (1.32–5.16)	3.3 (1.57–5.59)	2.86 (1.21–4.76)	0.0323

*Columns provide numbers (%) and IQR where applicable.

BMI, body mass index; CMV, cytomegalovirus; DBP, diastolic blood pressure; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; NNRTI, Nonnucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; SBP, systolic blood pressure.

scenario, nonnucleoside reverse transcriptase inhibitors were the most commonly used regimen, which usually have fewer toxicities concerns than Pis.[49]

The cross-sectional nature of the study imposes some limitations; first, if PLWHA with higher cf-PWV values have died from CVD and only persons with better prognosis who

TABLE 5. Final Linear Model for Clinical and HIV-Related Predictors of cf-PWV

Variable	Coefficient	95% CI	*P*
Sex: male	−0.23	−0.45 to −0.02	0.04
Age in yrs	0.05	0.04 to 0.06	<0.001
Race*			
White	−0.11	−0.37 to 0.11	0.2980
Brown	−0.03	−0.26 to 0.19	0.7576
Others	−0.31	−0.80 to 0.13	0.1597
Family history of sudden death	−0.30	−0.54 to −0.06	0.0137
Family history of AMI or stroke	0.16	−0.04 to 0.37	0.1145
Hypertension	0.51	0.16 to 0.84	0.0036
Antihypertensive medication use	−0.55	−0.90 to −0.19	0.0023
CMV: IgG positive	0.24	−0.73 to 1.36	0.5590
Dyslipidemia	−0.22	−0.46 to 0.03	0.0871
Waist/hip ratio†	0.18	0.08 to 0.29	<0.001
Income (R$) × 10^3	0.07	−0.01 to 0.15	0.0935
Serum creatinine × 10	0.07	−0.32 to 0.34	0.9552
LDL (mg/dL) × 10^2	0.19	−0.13 to 0.52	0.2446
Triglycerides (mg/dL) × 10^2	0.10	0.02 to 2.24	0.0457
Cumulative viral load × 10^2	−0.30	−0.96 to 0.36	0.3769
Current CD4 counts × 10^3(cells/mL)‡	0.33	−0.05 to 0.67	0.0539
Nadir CD4 counts × 10^3 (cells/mL)‡	0.23	−0.91 to 0.44	0.4940
Time on cART × 10 (yr)‡	0.09	−0.03 to 0.01	0.4344
No cART use	−0.08	−0.42 to 0.24	0.6117
PI-containing regimen	0.17	−0.03 to 0.32	0.1084
SBP	0.01	0.01 to 0.03	<0.001
DBP	0.02	0.01 to 0.04	<0.001

*Reference category = Black.
†Result expressed per a one SD change.
‡Included in the final model only for illustration.
CMV, cytomegalovirus; DBP, diastolic blood pressure; LDL, low-density lipoprotein; PIs, protease inhibitors; SBP, systolic blood pressure.

survived enough would have been enrolled into the study, this would lead to an underestimation in the relationship between arterial stiffness and HIV infection. However, as many years are necessary to develop arterial stiffness and the manifestation of a clinical CVD, it is unlikely that this fact have played a major role in our findings.

Another potential limitation was the selection of friend controls as HIV− group. This strategy was aimed at comparing a group with similar characteristics of PLWHA. However, we actually found elevated heterogeneity among the 3 groups (Table 1) and, to create a valid comparison, we implemented the propensity score analysis, which yielded similar results for comparisons between HIV+ and HIV− groups. In addition, HIV serostatus for the ELSA-Brasil study participants is unknown. Nevertheless, we expect a limited impact on the results since HIV prevalence in Brazilian population is low (0.4%),[50] and this sample comprised public workers, who tend to be healthier than the general population.

In conclusion, HIV infection was not associated with higher aortic stiffness in a large sample of participants in Brazil. Traditional risk factors were the main determinants of increased cf-PWV in the HIV-infected population. Based on ours and previous results, public policies aiming at offering careful attention to the management of traditional CV risk factors, especially among those with low socioeconomic position, with an emphasis to strategies targeting those overweight or presenting abdominal adiposity, are key to prevent CVD in the HIV-infected population.

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