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Potent Antiretroviral Therapy for Human Immunodeficiency Virus Infection Increases Aortic Stiffness

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Abstract

Background: Highly active antiretroviral therapy for AIDS is known to increase cardiovascular risk, but the effects of potent antiretroviral agents according to gender are unknown.

Objective: The present study evaluated the impact of HIV infection treatment on aortic stiffness according to gender.

Methods: From university-affiliated hospitals, we recruited 28 AIDS patients undergoing highly active antiretroviral treatment (HAART), 28 treatment-naïve HIV-infected patients, 44 patients with type 2 diabetes, and 30 controls. Aortic stiffness was determined by measuring pulse wave velocity (PWV) using a validated and non-invasive automatic device.

Results: The crude mean PWV values and 95% confidence intervals (95% CI) for HAART, diabetics, and controls were 9.77 m/s (95% CI 9.17-10.36), , 9.00 m/s (95% CI 8.37-9.63), 9.90 m/s (95% CI 9.32-10.49), and 9.28 m/s (95% CI 8.61-9.95), respectively, for men (P-value for trend = 0.14), and 9.61 m/s (95% CI 8.56-10.66), 8.45 m/s (95% CI 7.51-9.39), 9.83 (95% CI 9.21-10.44), and 7.79 m/s (95% CI 6.99-8.58), respectively, for women (P-value for trend <0.001). Post-hoc analysis revealed a significant difference between the mean PWV values in the HAART group and controls in women (P-value <0.01). After adjusting for other potential covariates, including systolic blood pressure and diabetes, these results did not change. The findings indicate that the impact of HAART treatment on aortic stiffness was amplified in women with hypertension, dyslipidemia, and metabolic syndrome.

Conclusion: Potent anti-retroviral agents used in the treatment of HIV infection increases aortic stiffness, mainly among women with higher cardiovascular risk. (Arq Bras Cardiol 2012;99(6):1100-1107)

Keywords: Anti Retroviral Agents; Acquired Immunosyndrome / therapy; HIV Infections / complications; Vascular Stiffness / drug effects.

Introduction

Highly active antiretroviral treatment (HAART) of HIV infection dramatically changed patient survival[1]. However, the treatment may be associated with a higher incidence of myocardial infarction mediated by an adverse cardiovascular risk factor profile[2-9] and other conditions, such as high arterial stiffness, which could be affected by HIV infection or its treatment[10, 11].

Age, diabetes, hypertension, and kidney failure have been independently associated with increased aortic stiffness measured by pulse wave velocity (PWV)[12]; and subjects with higher values have double the risk of a cardiovascular event, death, and all-cause mortality[13, 14].

Some studies have addressed the effect of HIV infection or its treatment with HAART on arterial stiffness and aortic augmentation showing a positive association[15-22]. No differences were found in PWV in a cohort of women in Rwanda when comparing HIV-infected women undergoing HAART and others not using HAART[23].

All studies described above are heterogeneous considering the population studied, time since infection, duration of treatment, and device used to measure PWV. Only six studies analyzed women[16,17, 21-23], totaling 39 females, as the cohort of women in Rwanda did not have a long HAART exposure to permit comparisons[23]. The search for gender differences is justified by a large registry of myocardial infarction in the United States that found a risk of 40% for HIV-positive men compared to HIV-free men, in contrast to a three-fold risk for HIV-infected women compared to HIV-free females[24].

In Brazil, AIDS mortality has decreased significantly since 1997 when HAART became available at the public health system free of costs. During the past decade, the profile of infected Brazilians has shifted from urban middle/upper class men to poor women[25].

We recruited a sample of HIV-infected subjects undergoing HAART without opportunistic infections and previous cardiovascular disease to verify the impact of HIV treatment on aortic stiffness according to gender. We compared these

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subjects with type 2 diabetes patients as they also present a higher cardiovascular risk.

Methods

The AGATA (from the Portuguese, "**A**valiação **G**eral da **AT**erosclerose em Adultos" General Evaluation of Atherosclerosis in Adults) is a cross-sectional study designed to evaluate the impact of HIV infection and its treatment on the cardiovascular system.

Subjects

At the outpatient clinic of a university-affiliated hospital in São Paulo, Brazil, we identified 56 consecutive patients with HIV infection, 28 using HAART and 28 patients with a recent diagnosis of HIV infection but not using HAART. Causes of infection were heterosexual contact (40.3%), homosexual contact (45.6%), injection drug use (12.3%), and unknown (1.8%). None of the patients had current or recent opportunistic infections or hepatitis B or C. Forty-four patients with type 2 diabetes were recruited consecutively from the outpatient clinic of our hospital. Thirty controls were invited from a worksite for periodic health examinations in the same hospital and matched for age (10-year) and sex with both HIV groups.

Enrollment Criteria

Inclusion criteria were age ranging from 20 to 69 years, at least 12 months of follow-up, and good compliance with HAART and type 2 diabetes treatment. Exclusion criteria were coronary heart disease (history of myocardial infarction, unstable angina, coronary revascularization), an electrocardiogram suggestive of past myocardial infarction, past history of cerebrovascular disease, peripheral artery disease, type 1 diabetes, creatinine clearance under 40 ml/min/1.73 m^2, and use of prescribed statins or fibrates.

Parameter Evaluation

All participants were examined in the morning after a 12-hour fasting. Weight, height, and waist circumference were measured using standard techniques. Resting blood pressure was measured using an oscillometric sphygmomanometer (Omron 705CP) with standard techniques. All participants, except those who reported a diagnosis of type 2 diabetes, were submitted to a glucose tolerance test.

Pulse Wave Velocity (PWV)

PWV was measured using a Complior-SP (Artech Medical, France). The transducers were placed over the suprasternal notch and femoral arteries. PWV was calculated by dividing the suprasternal notch -femoral distance by the difference in the transit time of the pulse waves digitally recorded in the carotid and right femoral artery (sampling rate 500 Hz). The PWV measurements were read by two researchers (RSC/JGM) blinded to the status of the participant.

Risk Factors

A participant was classified as hypertensive based on self-reported medical diagnosis, current treatment, office systolic blood pressure ≥ 140 mmHg, or diastolic ≥ 90 mmHg[13]; as diabetic based on self-reported medical diagnosis, current treatment, or a positive glucose tolerance test (glucose levels > 200 mg/dl after two hours); as dyslipidemic based on self-reported medical diagnosis or a LDL-cholesterol ≥ 130 mg/dl. We did not apply specific blood pressure cut-offs for diabetics, and metabolic syndrome was defined according to standard criteria[26]. Glomerular filtration rate was calculated from serum creatinine applying the CKD-Epi formula[27]

Statistical Analysis

Data are expressed as mean and 95% confidence interval (95% CI). Statistical analyses were performed using SPSS 16.0. Chi-square was used to compare categorical variables. The Spearman correlation coefficient was used to examine the association between PWV and other variables. Continuous variables were expressed as mean and standard error of the mean (SEM) and compared using Generalized Linear Models with a *post hoc* test of least square differences for multiple comparisons. PWV values were shown after adjusting for age using a generalized linear model.

All analyses were adjusted firstly for age and sex, and secondly for systolic blood pressure. The full multivariate model was adjusted for age, sex, systolic blood pressure, glucose tolerance, waist circumference, glomerular filtration rate, and triglycerides (log) for all participants, and differently for men and women according to the univariate analysis. Because PWV was highly right-skewed, generalized linear models using maximum likelihood optimization were constructed to assess the association between risk factors and PWV. We present the exponential beta-parameter estimates of PWV values calculated by the Wald test with 95% CI.

Ethical Issues

This study was approved by the Institutional Review Boards of the two hospitals, and all participants provided written informed consent.

Results

The mean time since diagnosis of HIV infection was greater for HAART patients than treatment-naïve HIV patients (10.4±3.7 vs. 6.5±4.8 years, $p<0.001$). The mean and standard deviation (SD) time of exposure to HAART was 7.7 (3.4) years. The mean (SD) nadir of CD4+ T-lymphocyte count was 207 (190) cells/mm^3 for the HAART group and 448(176) cells/mm^3 for the treatment-naïve HIV-group; the current CD4+ cell count was 701(400) cells/mm^3 for the HAART group and 609(307) cells/mm^3 for treatment-naïve HIV patients. The median (SD) highest viral load during the course of infection was 3,741 (10,312) copies/ml for the HAART group and 16,430 (27,151) copies/ml for the treatment-naïve group. Most of the HAART subjects had a well-controlled viral load (<50 copies/mL) compared to none in the treatment-naïve HIV group ($p<0.0001$). No difference was found between the groups regarding C-reactive protein values. Four patients in the HAART group and one patient in the treatment-naïve group were identified as type 2 diabetics.

The general characteristics of the subjects are shown in Table 1. Diabetic patients were older compared to HIV-

Table 1 - General Characteristics and Cardiovascular Risk Factors According to Group and Gender

	HIV HAART	HIV treatment-naive	Type 2 Diabetes	Controls	p-value from Analysis of Variance
			MEN		
	N = 20	N =18	N = 21	N = 16	
Age* (years)	45.0 ± 2.0‡	41.7 ± 1.7‡	46.2±1.1	41.6 ± 1.8‡	0.13
Race (%)					0.23
White	12 (60)	10 (56)	10 (48)	6 (38)	
Mixed	6 (30)	6 (33)	9 (42)	9 (56)	
Black	2 (10)	2 (11)	2 (10)	1 (6)	
Former/current smokers (%)	13 (65)	9 (50)	15 (71.4)	9 (56.3)	0.06
Body mass index* (kg/m^2)	25.2 ± 0.6 §.‖	25.3 ± 0.8§	30.1±1.0	31.6 ± 3.4	< 0.05
Waist circumference * (cm)	91.1 ± 2.1‡	87.3 ± 2.2‡. ¶	101.7±2.1	96.1 ± 2.8	< 0.001
Systolic blood pressure * (mm Hg)	127.4 ± 3.3#	117.4 ± 3.6‡	131.9±10.9¶	123.4 ± 7.4	< 0.01
High blood pressure† (%)	9 (45)	4 (22.2)	15 (71.4)	5 (31.3)	
Fasting blood glucose* (mg/dl)	113.8 ± 4.2‡	97.1 ± 2.6‡	154.9 ±7.6	101.8 ± 2.0‡	< 0.001
Glycated hemoglobin* (g %)	5.2 ± 0.2	5.6 ± 0.1	7.5±0.4	6.0 ± 0.1	< 0.001
Metabolic syndrome † (%)	6	3	N/A	6	
LDL-cholesterol* (mg/dl)	116.9 ± 5.3	110.4 ± 7.8	112.4±11.0	109.5 ± 7.6	0.153
Dyslipidemia † (%)	19 (95.0)	17 (94.4)	15 (75.0)	13 (81.3)	
eGFR* (ml/min/1.73 m^2)	82.1 ± 3.5	± 87.6 ± 4.0	80.3± 3.3	76.9 ± 3.4	0.24
			WOMEN		
	N = 8	N = 10	N = 23	N = 14	
Age* (years)	41.9 ± 2.1‡	42.6 ± 2.0‡	51.8 ± 1.1	43.3 ± 2.3‡	< 0.001
Race (%)					0.23
White	1 (12.5)	4 (40.0)	13 (56.6)	7 (50.0)	
Mixed	4 (50)	6 (60.0)	5 (21.7)	5 (35.7)	
Black	3 (37.5)	0 (0)	5 (21.7)	2 (14.3)	
Former/current smokers (%)	5(62.5)	5(50.0)	11(47.8)	6(42.9)	0.15
Body mass index* (kg/m^2)	25.5 ± 3.7§	28.0 ± 6.8	31.1 ± 5.1	26.6 ± 5.2§	< 0.05
Waist circumference * (cm)	85.5 ± 3.6§	86.2 ± 4.8§	97.6 ± 2.3‖	81.3 ± 3.4	< 0.001
Systolic blood pressure* (mm Hg)	119.4 ± 2.5	119. 5±4.2	124.2 ± 2.6	115.4 ± 5.7	0.38
High blood pressure† (%)	3 (37.5)	4 (40.0)	21 (91.3)	3 (21.4)	
Fasting blood glucose* (mg/dl)	98.5 ± 2.4‡	99.7 ± 2.6‡	139.5 ± 8.1	97,6 ± 1.9‡	< 0.001
Glycated hemoglobin* (g%)	5.0 ± 0.2	5.65 ± 0.2	6.8 ± 0.2	5.9 ± 0.1	< 0.001
Metabolic syndrome † (%)	2	3	3	---	
LDL-cholesterol* (mg/dl)	125.4 ± 36.3	120 ± 28.2	118.4 ± 32.7	129.0 ± 26.6	0.77
Dyslipidemia † (%)	7 (87.5)	5 (50.0)	21 (91.3)	6 (42.9)	
eGFR* (ml/min/1.73 m^2)	93.7 ± 5.6§	97.9 ± 6.0‡	76.4 ± 2.9	108.4 ± 6.3‡	< 0.001

HAART means highly active antiretroviral treatment for AIDS.

** Mean ± standard error of the mean.*

† The following definitions were adopted: (1) High blood pressure defined by self-reported medical history of hypertension, current treatment for hypertension, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg; (2) Dyslipidemia defined as LDL-cholesterol ≥ 130 mg/dl or current treatment for dyslipidemia; (3) Metabolic syndrome was defined according to the 3rd Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. [24] ; (4) Glomerular filtration rate (eGFR) was calculated by the CKD-EPI formula. [25]

‡ p <0.01 versus type 2 diabetes; § p <0.05 versus type 2 diabetes ; ‖ p <0.01 versus controls ,¶ p <0.05 versus controls

 # p <0.05 versus treatment-naïve.

infected patients and controls. Men with diabetes and controls had higher BMI and greater waist circumference compared to HIV-infected patients; only women with diabetes had a higher mean body mass index than the HAART group. High blood pressure was more common among diabetics in both sexes, but the mean systolic blood pressure was higher only among men with diabetes. Kidney function was impaired only in diabetic women.

Table 2 shows Spearman's correlation coefficients for variables associated with PWV. The variables associated with PWV for both sexes were age, systolic blood pressure, waist circumference, and fasting blood glucose. For women, a correlation was identified between PWV and glycated hemoglobin and the glomerular filtration rate.

An upward trend of the crude means for PWV is shown in Figure 1. Table 3 shows the crude values of PWV for all participants according to gender; the odds ratio for each category was calculated using the control group as the reference.

Adding other variables associated with PWV (Table 2) did not change the previous age-adjusted means for PWV. An important difference was observed between sexes in the pattern of mean PWV according to category. Among men, no differences were detectable between the groups. In contrast, among women, a significant upward trend was observed with higher values for women with diabetes and those undergoing HAART. *Post-hoc* analysis revealed a significant difference in the mean PWV between

Table 2 – Spearman Rank Correlation Coefficient for Pulse Wave Velocity

	Age	Body mass index	Waist circumference	Systolic blood pressure	LDL	Fasting blood glucose	Glycated hemoglobin	Leukocytes	C-reactive protein	Glomerular filtration rate
Men	0.610†	0.216	0.375†	0.451†	0.05	0.301†	0.126	0.306†	0.227	-0.165
Women	0.546†	0.127	0.283*	0.516†	0.02	0.485†	0.337*	0.019	0.139	-0.409†

** p < 0.05; † p < 0.01*

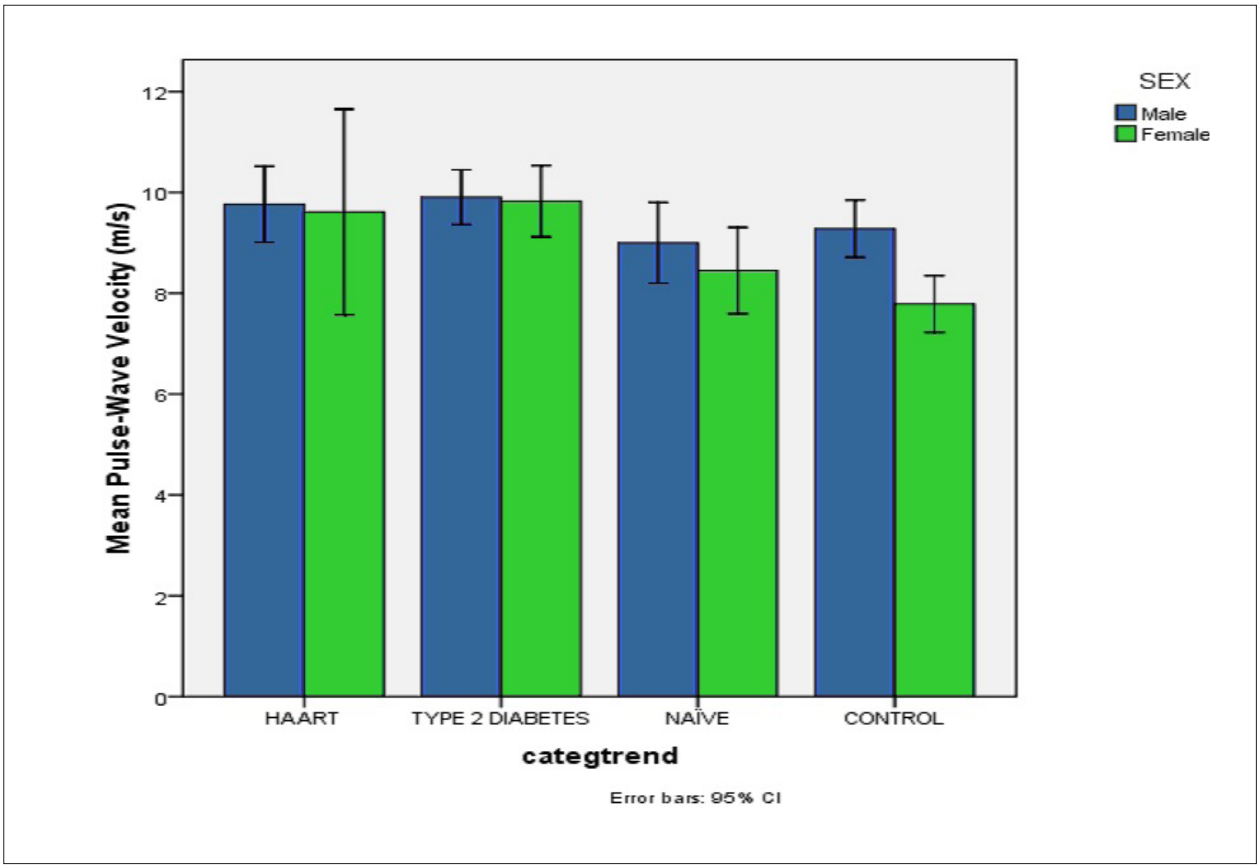

Figure 1 – *Mean pulse wave velocity of HIV-infected patients undergoing Highly active antiretroviral treatment (HAART), HIV treatment-naïve patients, and controls. The error bars indicate 95% confidence interval*

Table 3 – Mean Pulse Wave Velocity (95% Confidence Interval) and the exponential of the β parameter obtained from the generalized linear models according to groups and gender

	Controls	HIV Treatment-naive	Type 2 Diabetes	HIV HAART	p for trend
All participants					
	(n = 30)	(n = 28)	(n = 44)	(n = 28)	
Crude PWV (m/s)	8.58 (8.05 - 9.11)	8.80 (8.26 - 9.35)	9.86 (9.43 - 10.30) **,‖	9.72 (9.17 - 10.27) ‖,#	
Exp β parameter (age-adjusted)	1.00 (reference)	1.25 (0.58 - 2.67)	3.60 (1.81 - 7.14)	3.12 (1.46 - 6.68)	< 0.001
Exp β parameter (multi-adjusted)	1.00 (reference)	1.25 (0.58 - 2.67)	3.60 (1.81 - 7.14)	3.12 (1.46 - 6.68)	< 0.001
Men					
	(n = 16)	(n = 18)	(n = 21)	(n = 20)	
Crude PWV(m/s)	9.28 (8.61 - 9.95)	9.00 (8.37 - 9.63§	9.90 (9.32 - 10.49)	9.77 (9.17 - 10.36)	
Exp β parameter (age-adjusted)	1.00 (reference)	0.76 (0.30 - 1.89)	1.87 (0.77 - 4.52)	1.62 (0.66 - 3.97)	0.142
Exp β parameter (multi-adjusted)	1.00 (reference)	0.76 (0.30 - 1.89)	1.87 (0.77 - 4.52)	1.62 (0.66 - 3.97)	0.142
Women					
	(n = 14)	(n = 10)	(n = 23)	(n = 8)	
Crude PWV(m/s)	7.79 (6.99 - 8.58)	8.45 (7.51 - 9.39)	9.83 (9.21 - 10.44) ‖,#	9.61 (8.56 - 10.66) ‖	
Exp β parameter (age-adjusted)	1.00 (reference)	1.94 (0.57 - 6.64)	7.69 (2.81 - 21.03)	6.21 (1.67 - 23.14)	< 0.001
Exp β parameter (multi-adjusted)	1.00 (reference)	1.94 (0.57 - 6.79)	7.69 (2.76 - 22.19)	6.21 (1.62 - 23.10)	< 0.001
All participants without type 2 diabetes					
	(n = 30)	(n = 27)		(n = 23)	
Exp β parameter (age-adjusted)	1.00 (reference)	1.10 (0.52 - 2.35)	N/A	2.56 (1.16 - 5.61) ‖, #	< 0.05
Men without type 2 diabetes					
	(n = 16)	(n = 17)		(n = 15)	
Exp β parameter (age and sex-adjusted)	1.00 (reference)	0.63 (0.26 - 1.56)	-	1.21 (0.48 - 3.07)	0.35
Women without type 2 diabetes					
	(n = 14)	(n = 10)		(n = 8)	
Exp β parameter (age-adjusted)	1.00 (reference)	1.94 (0.60 - 6.27)	N/A	6.21 (1.77 - 21.79) ‖	< 0.02

HAART means highly active antiretroviral treatment for AIDS; The full multivariate model was adjusted for age, sex, systolic blood pressure, glucose tolerance, waist circumference, glomerular filtration rate, and triglycerides (log); ‡ p <0.01 versus type 2 diabetes; § p <0.05 versus type 2 diabetes; ‖ p <0.01 versus controls; ¶ p <0.05 versus controls

participants receiving HAART and controls. The results were similar when we excluded all participants with diabetes from the analysis.

Finally, we analyzed the effect modification of other risk factors associated with aortic stiffness (Table 4). The impact of HAART on PWV was more pronounced among Caucasians compared to Non-Caucasians, and among nonsmokers compared to ex- and current smokers. The presence of hypertension significantly increased the mean values of PWV for patients undergoing HAART and diabetics compared to subjects without hypertension. A glomerular filtration rate < 80 ml/min blurred the effect of HAART on PWV. Metabolic syndrome altered the association of the HAART group compared to controls and the treatment-naïve group.

Discussion

The results indicated increased PWV in HIV-infected patients undergoing HAART, mainly among women. HIV treatment-naïve patients did not have significantly higher PWV compared to controls. These results suggest that HAART, and not the HIV infection, is associated with increased arterial stiffness. The mean PWV values in HIV-infected patients undergoing HAART were similar to the values obtained for diabetics of both sexes. The presence of hypertension, dyslipidemia, or metabolic syndrome amplified the association between HAART and PWV.

Arterial stiffness has been recognized as a relevant predictor of hypertension and cardiovascular events. PWV is measured using a non-invasive, reproducible technique available in epidemiological studies[11-15]. Higher PWV values

Table 4 – Effect of Modification on Mean Pulse Wave Velocity and 95% Confidence Interval Adjusted for Age and Sex According to Conditions Associated with Aortic Stiffness. Comparisons are shown by the age and sex-adjusted exponential β parameter of the generalized equation with 95% Confidence Interval

		Controls	HIV Treatment-naive	Type 2 Diabetes	HIV HAART	p for trend
Race	White (n = 40)	(n = 13) 1,00 (reference)	(n = 14) 1.14 (0.43 - 3.06) §	(n = 23) 2.82 (1.16 - 6.86) ||	(n =13) 4.28 (1.57 - 11.67) ||.**	< 0.01
	Non-White (n = 46)	(n = 17) 1,00 (reference)	(n = 14) 1.38 (0.45 - 4.25) ||. §	(n = 21) 4.79 (1.73 - 13.25)	(n = 15) 2.39 (0.79 - 7.22)	< 0.05
Smoking habit	Never (n = 47)	(n = 15) 1,00 (reference)	(n = 14) 0.85 (0.26 - 2.72) ‡	(n = 18) 3.86 (1.29 - 11.5) ¶	(n = 18) 4.53 (1.26 - 16.3) ¶.#	< 0.01
	Former/current (n = 39)	(n = 15) 1,00 (reference)	(n = 14) 1.83 (0.69 - 4.85)	(n = 26) 3.34 (1.43 - 7.81) ||	(n = 10) 2.45 (0.98 - 6.11)	< 0.05
Hypertension	No (n = 58)	(n = 22) 1,00 (reference)	(n = 20) 0.89 (0.41 - 1.95)	(n = 8) 1.95 (0.69 - 5.53)	(n = 16) 1.95 (0.85 - 4.47)	0.046
	Yes (n = 28)	(n = 8) 1,00 (reference)	(n = 8) 2.82 (0.63 - 12.61)	(n = 36) 3.62 (1.12 - 11.66) ¶	(n = 12) 5.43 (1.38 - 21.29) ¶	0.001
Egfr (<80 ml/min)	No (n = 57)	(n = 19) 1,00 (reference)	(n = 19) 1.53 (0.64 - 3.67)	(n = 21) 3.63 (1.55 - 8.50) ||	(n = 19) 3.46 (1.45 - 8.30) ||	0.001
	Yes (n = 27)	(n = 10) 1,00 (reference)	(n = 8) 0.75 (0.17 - 3.31)	(n = 21) 2.72 (0.82 - 9.09)	(n = 9) 2.62 (0.62 - 11.10)	0.023
Metabolic syndrome	No (n = 57)	(n = 21) 1,00 (reference)	(n = 21) 1.25 (0.52 - 2.98)	N/A	(n = 15) 2.01 (0.78 - 5.23)	0.35
	Yes (n = 20)	(n = 6) 1,00 (reference)	(n = 6) 0.95 (0.26 - 3.47)	N/A	(n = 8) 3.62 (1.09 - 12.00) ¶. #	0.06
Dyslipidemia	No (n = 37)	(n = 11) 1,00 (reference)	(n = 6) 1.15 (0.37 - 3.58)	(n = 7) 3.41 (1.15 - 10.08) ¶	(n = 2) 1.11 (0.20 - 6.23)	0.14
	Yes (n = 39)	(n = 19) 1,00 (reference)	(n = 22) 1.15 (0.45 - 2.94) ‡	(n = 36) 3.22 (1.38 - 7.53) ¶	(n = 26) 2.85 (1.15 - 7.05) ¶ #	< 0.01

HAART means highly active antiretroviral treatment for AIDS; ‡ p <0.01 versus type 2 diabetes; § p <0.05 versus type 2 diabetes; || p <0.01 versus controls; ¶p <0.05 versus controls

suggest augmented arterial stiffness indicative of impaired elasticity of the artery wall that can be linked to future cardiovascular events[14-16]. Our results showing higher PWV values in patients undergoing HAART confirm previous data; however, this is the first study to show a significant impact among women.

Few studies have evaluated large groups of treatment-naïve HIV patients. Our results suggest that the treatment of HIV-infected patients with HAART has a greater impact on PWV than HIV infection itself. These data highlight the effect of HAART on the pathogenesis of arterial stiffness, in contrast with previously published results[5, 19, 22]. Wijk et al.[5] evaluated PWV in 37 HIV-infected patients, 14 diabetics, and 13 controls, finding increased PWV only among type 2 diabetics. [5] The study also showed a correlation between the duration of HAART and increased PWV and inflammatory parameters. The authors concluded that both HIV infection and HAART are involved in the progression of arterial stiffness and atherosclerotic changes. Regarding the correlation of PWV with the duration of HAART, we showed similar results.[5]

However, in our study, the HIV-infected patients had been using HAART for a mean of 8 years compared to 4.5 years in the other study. Possibly, the longer duration of HAART in our study better demonstrated the impact on PWV. One difference is that we did not find any association between PWV and C-reactive protein, even with a similar proportion of participants with viral load < 50 copies/ml.

Schillaci et al. showed increased aortic stiffness in HIV-infected subjects in the absence of antiretroviral therapy[22]. In our study, subjects were older, with a higher BMI and included more women than the Peruggia study, and HIV-infected treatment-naïve patients had PWV values very similar to controls. The assessment of arterial stiffness using applanation tonometry among HIV-infected Rwandan women (with or without HAART) did not show any differences in arterial wave reflection among the groups[23]. However, the duration of treatment was shorter and the women apparently had fewer cardiovascular risk factors than the women in our cohort. Analyzing the variables associated with increased PWV, age and systolic blood pressure were factors present in all groups. In previous studies, the duration of HAART was associated with greater PWV, but this was not confirmed in our analysis.

The most relevant finding in the present study was that PWV values in the presence of HIV infection and HAART treatment were different according to gender. We analyzed 24 women, whereas all previously published studies

analyzed only 39 females[16-17, 21, 22], as the cohort of women in Rwanda did not have a long HAART exposure to permit comparisons[20]. Importantly, although the number of women was lower compared to the number of men, we were able to show differences regarding the effect of HAART on aortic stiffness. We did not find other factors that could explain the sex differences.

Hormonal changes could be investigated using animal studies. A study in LDL-null mice examined the effects of ritonavir and amprenavir on cholesterol accumulation in macrophages, showing that females had lowers levels than males. The protective effect was lost after genetically removing estrogen receptor-alpha[28].

The significant difference in mean PWV among participants with metabolic syndrome in our sample was different from previous results[5]. Although we were able to classify subjects according to glucose tolerance as normal or impaired, we did not detect a higher PWV among HAART patients with impaired glucose tolerance. We also observed the impact of dyslipidemia as increased PWV in the HAART group. These data disagree with a small clinical trial that did not report any aortic stiffness alterations in subjects using pravastatin compared to placebo[29].

This analysis has several strengths. Most studies included only men, whereas we have an adequate proportion of women in all groups. The diagnosis of diabetes was based on an oral glucose tolerance test, a gold standard for type 2 diabetes diagnosis in epidemiological studies. The number of treatment-naïve HIV patients was higher compared to previous studies. The limitations are due to the cross-sectional design and proportion of males in the control group with body mass index > 25 kg/m^2.

Although these results were different compared to the general population, they are representative of men in this worksite facility, and the skewed mean body mass index observed in the control group did not blur the comparison of PWV between HAART and control groups.

Concluding, our results suggest that increased arterial stiffness in HIV-infected patients is associated more with the use of HAART than HIV infection itself, especially among women.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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