Risk factors related to hypertension among patients in a cohort living with HIV/AIDS

ABSTRACT

Introduction: Studies disagree as to whether there is a greater prevalence of hypertension among HIV/AIDS patients and the role of antiretroviral therapy. **Objective**: Evaluate the prevalence of hypertension and risk factors in a cohort of HIV-infected patients, with emphasis on antiretroviral therapy. **Method**: Case-control study conducted at baseline of a cohort, between June/2007 and December/2008 in Pernambuco/Brazil. Blood pressure was classified as normal, prehypertension, and hypertension. **Results**: Of 958 patients, 245 (25.6%) had hypertension (cases), 325 (33.9%) had prehypertension, and 388 (40.5%) were normotensive (controls). Comparison between hypertensive and normotensive patients showed that traditional factors, such as age > 40 (OR = 3.06, CI = 1.91-4.97), male gender (OR = 1.85, CI = 1.15-3.01), BMI > 25 (OR = 5.51, CI = 3.36-9.17), and triglycerides > 150 mg/dL (OR = 1.69, CI = 1.05-2.71), were independently associated with hypertension. Duration of antiretroviral therapy and CD4 > 200 cells/mm³ were associated with hypertension in univariate analysis, but did not remain in final model. Type of antiretroviral schema and lipodystrophy showed no association with hypertension. **Conclusion**: Hypertension in HIV/AIDS patients is partially linked to invariable factors, such as age and sex. Efforts should be directed toward controlling reversible factors, particularly excessive weight gain and unsuitable diet.

Keywords: HIV/AIDS, hypertension, antiretroviral therapy, cardiovascular risk.

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INTRODUCTION

Potent antiretroviral therapy (HAART) has resulted in lasting suppression of HIV replication, reduction of opportunistic infections and malignancies associated with AIDS, and has had a substantial impact on the survival rate and quality of life of infected individuals.[1] However, the potential to keep these patients under treatment for decades may be limited by a variety of metabolic and cardiovascular abnormalities observed in patients on HAART, including dyslipidemia, fat redistribution, insulin resistance,[2] hypertension,[3] and coronary ischemia.[4]

Two large prospective studies[4,5] showed that the HIV infected population is at increased risk of cardiovascular disease in the long term. However, individual cardiovascular risk is determined by a complex overlapping of several risk factors that include age, family history, smoking, hypertension, diabetes, and high blood lipids.[6] In the period prior to HAART, high blood pressure in infected patients was often associated with complications related to HIV, such as renal failure and vasculopathy.[7] In post-HAART period, some studies have raised the possibility that HAART may also induce hypertension[8-15] through the acceleration of atherogenesis and subsequent hardening of the vessel wall.[16]

Studies on blood pressure in HIV infected patients show conflicting results regarding the increased prevalence of disease among patients on HAART and the role of different treatment regimens in its genesis.[3,13,17,18] Given the importance of the subject and the urgency in adopting preventive measures for cardiovascular damage among patients with HIV/AIDS on antiretroviral treatment, this study was conducted to assess the prevalence of hypertension and possible risk factors in a cohort of 1,000 HIV patients, paying particular attention to the role of antiretrovirals in the development of the disease.

METHODS

A case-control study was conducted at baseline assessment of a cohort of outpatients with HIV/AIDS treated at the Infectious Diseases Unit, Oswaldo Cruz Medical College, University of Pernambuco and Correia Picanço Hospital of the Pernambuco State Department of Health, Brazil, from June 2007 to December 2008, and evaluated consecutively. After receiving the information, patients signed the informed consent form, answered a questionnaire and were submitted to measurement of anthropometric data, blood pressure and collection of blood samples to assess fasting blood glucose and lipids. Data on HIV infection and antiretroviral therapy were obtained from medical records. The study was approved by the Ethics Committee (protocol number 052/05). All participants were aged 18 years or over. Pregnant women and patients with signs of active AIDS or hospitalization in the previous three months were excluded.

Diagnosis of hypertension was confirmed on a second visit, not more than two months later, when two BP measurements were taken in an upper limb, and mean systolic and diastolic pressures were calculated. Patients were classified according to the criteria of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),[19] which considers the following classifications of blood pressure: normal (systolic BP < 120 mmHg and diastolic BP < 80 mmHg); prehypertension (systolic BP between 120-139 mmHg or diastolic BP between 80-89 mmHg); and hypertension (systolic BP > 140 mmHg and diastolic BP > 90 mmHg).

Cases were defined as patients with systolic BP > 140 mmHg and diastolic BP > 90 mmHg, measured on at least two occasions, or a previous diagnosis of hypertension and blood pressure levels controlled with an antihypertensive drug. Patients with normal blood pressure (systolic BP < 120 mmHg and diastolic BP < 80 mmHg) were considered controls.

DATA ANALYSIS

All univariate and multivariate analyses were carried out using the R statistical program (R Project for Statistical Computing www.r-project.org).

To test the assumption of normality for continuous variables involved in the study, the Shapiro Wilk test was used. In the comparative analysis of quantitative variables we used Student t-test. Chi-square and, when necessary, Fisher's test was used to test the association between dependent variable and potential risk factors. All conclusions were drawn at a 5% level of significance.

All the variables that, in the univariate analysis, showed a p-value < 0.25 for association with the dependent variable were introduced in a multivariate model (multiple logistic regression), by block, and those that remained in the model had a p-value of < 0.05. Then there was a final multivariate analysis that included the variables selected in each block, using as a cutoff point a p-value < 0.05.

RESULTS

Of the 1,000 HIV-positive patients eligible for the study, 958 agreed to participate and attended two or more visits. Hypertension was detected in 245 patients (25.6%), 36 (14.8%) of which were controlled with an antihypertensive drug. A total of 325 (33.9%) had pre-hypertension and 388 (40.5%) were normotensive (controls). In the univariate analysis, the mean age of hypertensive patients (Figure 1) was significantly higher than that of prehypertensive and hypertensive ones (43.4 + 9.2 years X 40.4 + 9.8 years X 36.9 + 8.9 years (p < 0.0001). The average duration of antiretroviral drugs use (Figure 2) was higher in hypertensive patients than in controls (1,742.6 + 1,211.5 X 1,389.2 + 1,182.6 days) (p = 0.0088), and waist circumference was also higher in hypertensive patients than in prehypertensive and normotensive ones (80.7 + 8.7 cm X 86.6 + 10.1 cm X 90.2 + 10.5 cm) (p < 0.0001).

In the univariate analysis of biological factors, age, male gender, and a family history of hypertension were associated with hypertension (Table 1); and among living habits, the consumption of vegetables and level of physical activity were associated with the presence of disease (Table 2). Of the metabolic characteristics, BMI > 25, high waist circumference (NCEP criteria)[20], level of cholesterol > 200 mg/dL, blood glucose levels > 100 mg/dL, and triglyceride values of > 150 mg/dL were associated with hypertension. In contrast, lipodystrophy was not associated with the disease (Table 3).

On assessing the factors associated with infection and antiretroviral treatment, we observed that CD4-lymphocyte count < 200 cells/mm^3, time elapsed since the diagnosis of HIV infection > 5 years, time elapsed since the diagnosis of AIDS, and duration of antiretroviral treatment > 1 year were all associated with the presence of hypertension. In this same analysis, the use of antiretroviral regimens containing protease inhibitors was not associated with hypertension (Table 4).

Figure 3 presents the results of multivariate logistic regression and show that age > 40 years (OR = 3.06, CI = 1.91-4.97), male gender (OR = 1.85, CI = 1.15-3.01), body mass index > 25 (OR = 5.51, CI = 3.36-9.17), and triglycerides > 150 mg/dL (OR = 1.69, CI = 1.05-2.71) were independently and significantly associated with hypertension.

**Figure 1:** Mean and standard deviation of age of patients with HIV/AIDS with hypertension (cases), prehypertension and normotensive (controls).
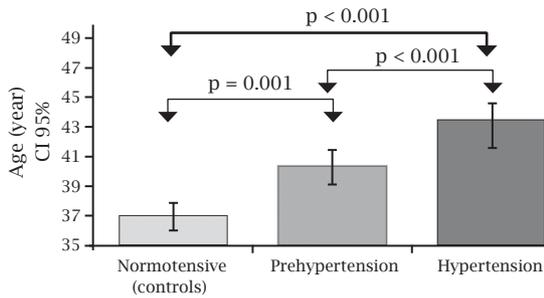
Figure 2: Mean and standard deviation of duration of therapy (in days) in patients with HIV/AIDS with hypertension (cases), prehypertension and normotensive (controls).
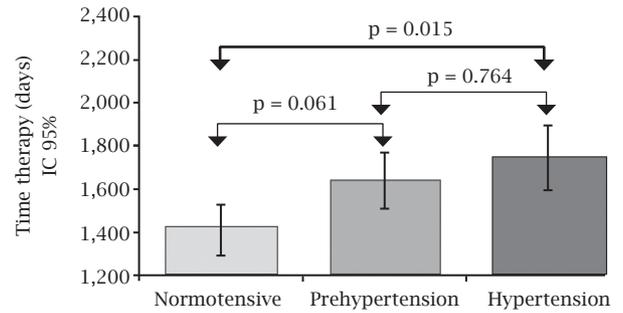
Figure 3: Model of the final multivariate analysis of association between hypertension and biological characteristics, living habits, metabolic and anthropometric factors related to HIV infection and antiretroviral therapy.
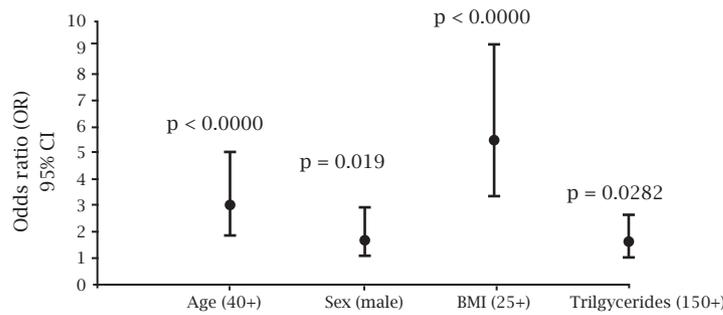
Table 1. Comparison of biological characteristics of 245 hypertensive patients (cases) and 388 normotensives (controls) in a cohort of individuals living with HIV/AIDS in Pernambuco, Brazil

Biological factors	Hypertensive		Normotensive		OR	95% CI		p-value
	n	%	n	%		lower	upper	
Age								
< 40	89/245	36.33	241/388	62.11	1.00	-	-	-
40 +	156/245	63.67	147/388	37.89	2.87	2.06	4.01	< 0.0001
Sex								
Female	89/245	36.33	175/388	45.10	1.00	-	-	-
Male	156/245	63.67	213/388	54.90	1.44	1.04	2.00	0.0292
Ethnicity								
White	63/245	25.71	106/388	27.32	1.00	-	-	-
Black	28/245	11.43	43/388	11.08	1.1	0.62	1.94	0.7531
Yellow	4/245	1.63	5/388	1.29	1.35	0.31	5.49	0.7305
Brown	145/245	59.18	227/388	58.51	1.07	0.74	1.57	0.7063
Indigenous	5/245	2.04	7/388	1.8	1.21	0.34	4.05	0.7656
Family history of hypertension								
No	174/245	71.02	231/388	60.31	1.00	-	-	-
Yes	52/245	21.22	116/388	30.29	1.68	1.15	2.47	0.0077
Not known	19/245	7.76	36/388	9.4	1.18	0.61	2.23	0.6197

$\chi 2$, chi-square; OR, odds ratio.

Table 2. Comparison of lifestyle of 245 hypertensive and 388 normotensive patients in a cohort of individuals with HIV/AIDS in Pernambuco, Brazil

Lifestyle	Hypertensive		Normotensive		OR	95% CI		p-value
	n	%	n	%		lower	upper	
Smoking history								
Never smoked	109/242	45.04	167/384	43.49	1.00	-	-	-
Former smoker	77/242	31.82	111/384	28.91	1.06	0.73	1.55	0.7520
Current smoker	56/242	23.14	106/384	27.6	0.81	0.54	1.21	0.3048
Cocaine								
Never used	227/244	93.03	348/388	89.69	1.00	-	-	-
Already used	17/244	6.97	40/388	10.31	0.65	0.86	2.83	0.1533
Consumption of alcohol								
Teetotaler / Light drinker	201/228	88.16	304/348	87.36	1.00	-	-	-
Heavy / Dependent drinker	27/228	11.84	44/348	12.64	0.93	0.55	1.54	0.7747
Consumption of vegetables								
Yes	171/240	71.25	242/383	63.19	1.00	-	-	-
No	69/240	28.75	141/383	36.81	0.69	0.49	0.98	0.0387
Consumption of fruits								
Yes	139	57.68	193	50.79	1.00	-	-	-
No	102/241	42.32	187/380	49.21	0.77	0.56	1.06	0.1150
Physical activity								
High	60/245	24.49	105/388	27.06	1.00	-	-	-
Moderate	56/245	18.37	58/388	7.99	1.89	1.14	3.14	0.0133
Low	141/245	53.88	236/388	56.96	1.17	0.78	1.76	0.4478

χ2, chi-square; OR, Odds Ratio.

Table 3. Comparison of anthropometric and metabolic characteristics of 245 hypertensive and 388 normotensive patients in a cohort of individuals with HIV/AIDS in Pernambuco, Brazil

Metabolic factors	Hypertensive		Normotensive		OR	95% CI		p-value
	n	%	n	%		lower	upper	
BMI								
< 25	116/245	47.35	312/382	81.68	1.00	-	-	-
25 +	129/245	52.65	70/382	18.32	4.95	3.47	7.14	< 0.0001
Abdominal circumference (NCEP)								
Normal	172/244	70.49	350/387	90.44	1.00	-	-	-
Altered *	72/244	29.51	37/387	9.56	3.96	2.57	6.18	< 0.0001
Total cholesterol (mg/dL)								
≤ 200	96/139	69.06	208/258	80.62	1.00	-	-	-
> 200	43/139	30.94	50/258	19.38	1.86	1.15	2.99	0.0101
HDL-cholesterol (mg/dL)								
> 40	69/144	47.92	117/255	45.88	1.00	-	-	-
≤ 40	75/144	52.08	138/255	54.12	0.92	0.61	1.39	0.6956
LDL-cholesterol (mg/dL)								
< 130	85/109	77.98	167/196	85.2	1.00	-	-	-
130 +	24/109	22.02	29/196	14.8	1.62	0.88	2.97	0.1130
Triglycerides (mg/dL)								
< 150	58/142	40.85	168/265	63.4	1.00	-	-	-
150 +	84/142	59.15	97/265	36.6	2.51	1.65	3.82	< 0.0001
Glycemia (mg/dL)								
< 100	111/140	79.29	236/253	93.28	1.00	-	-	-
100 +	29/140	20.71	17/253	6.27	3.62	1.93	7.00	< 0.0001
Lipodystrophy								
No	111/206	53.88	139/291	47.77	1.00	-	-	-
Yes	95/206	46.12	152/291	52.23	0.78	0.54	1.11	0.1794

χ2, chi-square; OR, odds ratio.
 * Altered = Women > 88 cm; Men > 102 cm.

Table 4. Comparison of factors related to HIV infection and antiretroviral therapy in 245 hypertensive and 388 normotensive patients in a cohort of individuals with HIV/AIDS in Pernambuco, Brazil

Factors related to HIV infection	Hypertensive		Normotensive		OR	95% CI		p-value
	n	%	n	%		lower	upper	
Use of HAART								
No	38/217	17.51	71/343	20.7	1.00	-	-	-
Yes	179/217	82.49	272/343	79.3	1.23	0.80	1.92	0.3537
Current HAART status								
Without HAART	30/214	13.62	61/327	18.65	1.00	-	-	-
With PI	89/214	41.78	141/327	43.12	1.28	0.77	2.16	0.3388
Without PI	95/214	44.60	125/327	38.23	1.55	0.93	2.60	0.0957
Duration of HAART exposure								
Up to 1 year	21/169	12.43	68/254	26.77	1.00	-	-	-
1 to 5 years	80/169	47.34	102/254	40.16	2.53	1.46	4.51	0.0014
5 + years	68/169	40.23	84/254	33.07	2.62	1.49	4.72	0.0013
Time of diagnosis of HIV								
Up to 1 year	19/153	12.42	49/253	19.37	1.00	-	-	-
1 to 5 years	61/153	39.87	113/253	44.66	1.39	0.76	2.62	0.2912
5 + years	73/153	47.71	91/253	35.97	2.07	1.14	3.89	0.0200
CD4 Nadir								
200 +	119/188	66.30	168/290	57.93	1.00	-	-	-
100 – 200	33/188	17.55	56/290	19.31	0.83	0.59	1.15	0.2750
< 100	36/188	19.15	66/290	22.76	1.04	0.70	1.56	0.8310
Current CD4 lymphocyte count								
500 +	49/126	38.89	63/200	31.50	1.00	-	-	-
200 – 500	61/126	48.41	98/200	49.00	0.80	0.49	1.31	0.3743
< 200	16/126	12.70	39/200	19.50	0.53	0.26	1.04	0.0698
Current viral load								
< 10,000	54/67	80.60	92/119	77.31	1.00	-	-	-
10,000 – 100,000	8/67	11.94	22/119	18.49	0.62	0.24	1.44	0.2841
100,000 +	5/67	7.46	5/119	4.20	1.42	0.39	4.93	0.5776

DISCUSSION

Although blood pressure levels are usually considered in studies of cardiovascular disease risk in populations of HIV-infected patients, the prevalence of hypertension, the focus of this study, has received little attention, and data are controversial and vary widely.[3,13,14,21] Possible explanations for these discrepant results include differences in study design, methodological aspects, the cut values for hypertension and differences in the populations studied. Using the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) criteria,[19] 25.6% of 958 patients with HIV/AIDS are hypertensive, a proportion similar to that found in the region, and in Brazil as a whole, in uninfected individuals.[22,23]

The comparison between HIV/AIDS non-hypertensive and hypertensive patients showed that traditional risk factors were associated with the presence of hypertension, such as older age, male gender, overweight/obesity, family history of hypertension, and increased levels of triglycerides. Lipodystrophy was not associated with the presence of hypertension. The duration of HAART exposure was associated with hypertension and the levels of CD4 lymphocytes below 200 cells/mm^3 showed a tendency to be protective against hypertension in univariate analysis; nevertheless, none of them remained in the final model. The type of antiretroviral schema was not associated with the onset of hypertension.

The findings of this study reinforce the hypothesis that HIV/AIDS and/or antiretroviral therapy, despite significantly increase the risk of atherosclerosis and cardiovascular disease,[4,17] do not appear to have a significant impact on the prevalence and genesis of hypertension compared with the factors traditionally associated with the disease, which is in agreement with the findings of Baekken *et al.*,[3] Bergensen *et al.*,[13] and Khalsa *et al.*[21]

There are, however, a number of aspects that deserve special mention: while the presence of lipodystrophy, hypercholesterolemia, and low levels of HDL fraction of cholesterol were not associated with hypertension, the increase in triglycerides was associated with the disease. Considering that the serum triglycerides are the lipids that most frequently undergo change with the use of anti-retrovirals,[24] the question arises as to whether this increase does not reflect the association of hypertension with the use of HAART for long periods or the use of some specifically antiretroviral schema, especially a schema containing Protease Inhibitors (PI), as suggested by Baekken et al.,[3] Crane et al.[18] The rise in triglyceride levels related to antiretroviral treatment is higher for the first generation of non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine) than for the protease inhibitors (PI), although the rise in LDL cholesterol is similar in both groups.[24] Moreover, the drugs of the group of nucleoside reverse transcriptase inhibitors, such as stavudine and zidovudine, may also play a role in these changes.[24] As for the PI, the highest rises in triglycerides are associated with booster regimens containing ritonavir.[24] Bearing in mind that preferred antiretroviral regimens suggested by the National STD/AIDS Program in Brazil is composed of zidovudine and lamivudine associated with efavirenz or one boosted PI (lopinavir or atazanavir both boosted with ritonavir),[25] the increase in triglycerides could signal the use of HAART in its different treatment regimens, without any preferential schema. On the other hand, as mentioned above, the duration of antiretroviral therapy was associated with hypertension in the univariate analysis, but this factor was no longer present in the multivariate analysis. Furthermore, the combination of an increase in triglycerides and hypertension could merely reflect a dietary disorder, or a diet rich in carbohydrates, so common among the obese.

As for obesity, this was a risk factor strongly associated with hypertension in this study, as in all studies that deal with hypertension in the general population.[19,22] Obesity of individuals with HIV/AIDS may be associated with excessive weight gain during treatment with HAART and should be avoided. However, while uninfected individuals often have the desire and strive to lose weight, among the infected patients, particularly those who already had symptoms of AIDS, the loss of weight enhances the fantasy of appearing ill and this is a "taboo" among the infected. Thus, it is not only lipodystrophy that merits attention. A recent Brazilian study showed that the majority of adults living with HIV/AIDS have a diet that needs improvement, and obesity was associated with a poorer quality of diet.[26] Nutritional interventions aimed at maintaining a healthy weight should be emphasized in the care of HIV patients[25] and may offer protection against the onset of hypertension in this group.

Moreover, in subjects with CD4 < 200, the risk of hypertension was lower. Certainly, loss of weight, and lower levels of triglycerides, most frequently found in patients with CD4 lymphocyte counts of less than 200 cells/mm^3,[24,27] could be reflected in the lower prevalence of hypertension in this group.

This study has the limitations inherent in a case control study, i.e., it does not determine the origin but the combination of factors, and data reflect a specific population (young and predominantly male). However, it has the advantage of being a study in which patients were prospectively selected based on the criteria of JNC 7 and of having excluded prehypertensive patients from the analysis, thereby highlighting the differences between the groups.

Finally, hypertension in patients with HIV/AIDS is associated with factors such as age > 40 years, BMI > 25, high triglyceride level, and male gender. Therefore, the control of the reversible factors associated with hypertension, particularly the reinforcement of dietary advice guidance and prevention of excessive weight gain, may represent an important advance in the prevention of cardiovascular morbidity among people living with HIV/AIDS.

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