



## SYSTEMIC ARTERIAL HYPERTENSION AND ASSOCIATED FACTORS IN PEOPLE WITH HIV/AIDS ON ANTIRETROVIRAL THERAPY

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### ARTICLE INFO

#### Article History:

Received 19<sup>th</sup> July, 2018

Received in revised form

09<sup>th</sup> August, 2018

Accepted 18<sup>th</sup> September, 2018

Published online 29<sup>th</sup> October, 2018

#### Key Words:

HIV Infections;

Antiretroviral Therapy;

Hypertension.

### ABSTRACT

This article aims at verifying the cumulative incidence of systemic arterial hypertension and associated factors in people with HIV/AIDS undergoing high-potency antiretroviral treatment. Epidemiological study of a retrospective cohort performed to patients with HIV/AIDS, attended at the Specialized Attention Service (SAE) in Ponta Grossa – Paraná, Brazil. The data were obtained by notification the records of diseases, injuries and medical records from 538 patients attended from January 2002 to December 2014. Most of the subjects were male, married, with 1-7 years of schooling, mean age at diagnosis of 36.6 years, and almost all of them were sexually infected and used some drug treatment. The mean incidence of hypertension was 24.4%. Subjects on antiretroviral therapy with a therapeutic regimen of association among Nucleotide Reverse Transcriptase Inhibitors, Non-Nucleotide Reverse Transcriptase Inhibitors and Protease Inhibitors showed a higher percentage of arterial hypertension. Age at diagnosis, weight, time, and the therapeutic regimen were able to explain 20.4% of blood pressure variability. It is concluded that hypertension in patients with HIV / AIDS and under antiretroviral therapy was associated with age at diagnosis, weight, time of treatment and therapeutic regimen.

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Citation: Erildo Vicente Muller, Suely Godoy Agostinho Gimeno, Pollyanna Kássia de Oliveira Borges, Daniele Bordin and Cloris Regina Blanski Grden. 2018. "Systemic arterial hypertension and associated factors in people with HIV/AIDS on antiretroviral therapy", *International Journal of Development Research*, 8, (10), 23308-23314.

### INTRODUCTION

AIDS is considered a global epidemic, with characteristics of instability and dynamicity in its epidemiological profile and, consequently, an important global public health problem and also in Brazil. According to UNAIDS there were 36.7 million people with HIV/AIDS (PLHA) in the world. Of these, 1.8 million were recently contaminated (UNAIDS, 2016). In Brazil the estimates indicate there are 830,000 people with HIV, and the number of AIDS-related deaths in the country in 2015 was 15,000 people. In Paraná state, up to 2015, 44,460 HIV/AIDS cases were recorded, with unstable mortality rates in the last 9 years, ranging from 5.0 to 5.9 deaths per 100,000 people (SESA, 2015). With the antiretroviral therapy introduction (ART) in Brazil in 1996, changes in the national epidemic profile were observed, with a reduction in mortality

and an improvement in PLHA life quality. There is a change in the natural history of the disease with chronic characteristics and prolonged evolution (Lima, Freitas, 2012). With increased survival and longer treatment time, severe adverse effects associated with therapy were observed, such as: metabolic changes, body fat redistribution, and increased lipid levels. These associations were studied in another study carried out with the same population of the present research and there was triglycerides increase, total cholesterol, LDL cholesterol, and HDL cholesterol decrease (Muller, Gimeno, 2017). Some studies have also suggested the prevalence of systemic arterial hypertension (SAH) increase, which leads to a higher risk to cardiovascular diseases (Correia et al., 2017). However, there is a paucity of studies on the arterial hypertension incidence in PLHA, which reduces the scientific evidence strength of the association between HAART and hypertension and opens up space for further research that may clarify this association in logistic studies. SAH is a multifactorial clinical condition characterized by pressure levels sustained elevation. The main

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known risk factors for SAH are: age, gender, ethnicity, overweight and obesity, hypersodic diet, sedentary lifestyle, alcohol and tobacco abusive consumption and unfavorable socioeconomic factors. The disease can be further aggravated by the presence of dyslipidemia, glucose intolerance and diabetes mellitus (DM) (Malachias *et al.*, 2016; Gus *et al.*, 2016). Since the metabolic factors (lipodystrophy, DM, glucose intolerance, etc.) are more altered in patients undergoing HAART, compared to non-HAART patients, the present study started with the hypothesis which subjects taking HAART would have higher blood pressure levels, given all other metabolic parameters would be increased because of medication, in association with inadequate lifestyle habits, as reported in the literature (Muller, Gimeno, 2017). In view of the above, the objective of the present study was to verify the systemic arterial hypertension cumulative incidence and associated factors in people with HIV / AIDS undergoing high-potency antiretroviral treatment (HAART).

## MATERIALS AND METHODS

Epidemiological study of a retrospective cohort performed to patients with HIV / AIDS, attended at the Specialized Attention Service (SAE) in Ponta Grossa, Paraná, Brazil. This service is a reference for the South Central Region of Paraná, and serves patients from 12 towns belonging to the Paraná's third Regional Health Service. A total of 753 records of patients attended by SAE from January 2002 to December 2014 were analyzed. Patients who had already had a diagnosis of arterial hypertension before the start of antiretroviral treatment ( $n = 215$ ) were excluded. Thus, 538 medical records were included in the study. Data were collected considering: weight (kg), systemic arterial blood pressure (SBP), antiretroviral treatment regimen, information was collected during six months. The classification criteria of pressure levels proposed in the VII Brazilian Guidelines for Hypertension (Malachias *et al.*, 2016) were used. Antiretroviral treatment regimens were divided into four groups: group A – Other associations that did not fit into groups B, C and D; group B – Nucleotide Reverse Transcriptase Inhibitors + Protease Inhibitors; group C – Nucleotide Reverse Transcriptase Inhibitors + Non Nucleotide Reverse Transcriptase Inhibitors; group D – Nucleotide Reverse Transcriptase Inhibitors + Non Nucleotide Reverse Transcriptase Inhibitors + Protease Inhibitors. The sociodemographic interest variables for the study were obtained through the notification of diseases and injuries records, namely: date of birth, gender, race/color; schooling, occupation, likely transmission way, and sexual behavior. In order to explore descriptively the effect of independent variables over time on blood pressure change, non-parametric regression adjustment diagrams were constructed using the LOWESS methods. To verify the factors influencing the change in blood pressure over time, the Marginal Logistic Regression was used. Generalized Equations Estimating (GEE) can be considered an extension of Generalized Linear Models that allow incorporating the expected correlation between the measurements performed in the same individual. Marginal Regressions by their ease in interpretation and absence of distributional assumptions have been preferred as an extension of Generalized Linear Models for dependent data. To select the variables able to explain the changes in blood pressure occurrence, the Stepwise method (union of Forward and Backward methods) was used. In this method the variables gender, race, schooling, marital status, transmission way, sexual behavior, schema, age at diagnosis and

weight were selected. The interactions of all variables over time were also tested since, because it was a longitudinal study, it was expected that the interactions existed. For the Forward method, a significance level of 25% was adopted. The selected variables and interactions were then inserted into a multivariate logistic marginal regression model, where the Backward method was applied. To Backward method a level of 5% of significance was adopted. It should be noted that, when the presence of interactions with time was verified, it was chosen to perform the comparisons fixing the times 0,995, 2,940 and 5,507, which corresponded to the first, second and third quartiles of the time, respectively. Statistical package R, version 3.2.2 was used. The research was conducted within ethical standards and approved by the Research Ethics Committee from Federal University of São Paulo (UNIFESP), under number 44227515.6.0000.5505 / 2015. Because it is a study that analyzed secondary and retrospective data, there was a dispensation by the Research Ethics Committee to the signing in the Informed Consent Form by the patients.

## RESULTS

The study followed over time 538 PLHA in the south central region from Paraná state. Of these, 56.1% ( $n = 302$ ) were males, 82.2% ( $n = 439$ ) whites, 17.4% ( $n = 93$ ) browns and blacks. The average age at diagnosis was 36.33 years, with a standard deviation of 10.88 years. Regarding to education, 7.8% ( $n = 35$ ) had not attended a school, 47.4% ( $n = 213$ ) of the patients had 1 to 7 years of schooling and 44.8% ( $n = 290$ ) had 8 or more years of study. It was observed that 49.2% ( $n = 242$ ) of the patients were married. Regarding to the transmission way, 98.5% of the individuals had sexual transmission, 89.0% of the PLHA declared to be heterosexual. Only 3.5% of the patients did not use any treatment. It was verified that during the studied period, the hypertension incidence was on average of 24.4%. The image 1 shows the arterial hypertension (BP) frequency among the categories of variables: gender, race, schooling, marital status, sexual orientation, age, weight and therapeutic regimen. It was verified that the male patients had a higher arterial hypertension percentage, and over time the difference between the categories remained practically constant. White patients had a higher percentage of arterial hypertension, with a difference between the categories. It is observed that white-colored PLWH showed an increasing tendency to increase BP over time.

The arterial hypertension percentage was very similar at all levels of schooling. It was observed that patients who had a partner had a higher arterial hypertension percentage and the difference between the categories showed an increasing trend over time. It was also found that people with HIV / AIDS (PLHA) who declared themselves to be homosexual showed a higher arterial hypertension percentage. Regarding to the therapeutic regimen, it was observed that antiretroviral therapy (ART) with antiretroviral therapy (DAT) (Nucleotide Reverse Transcriptase Inhibitors + Non Nucleotide Reverse Transcriptase Inhibitors + Protease Inhibitors) showed a higher arterial hypertension percentage. Patients older than the average at the time of diagnosis showed a higher arterial hypertension percentage and, after time, the difference between the categories remained practically constant. It is also observed that the group of PLHA with greater than average weight had a higher arterial hypertension percentage (Image 02).

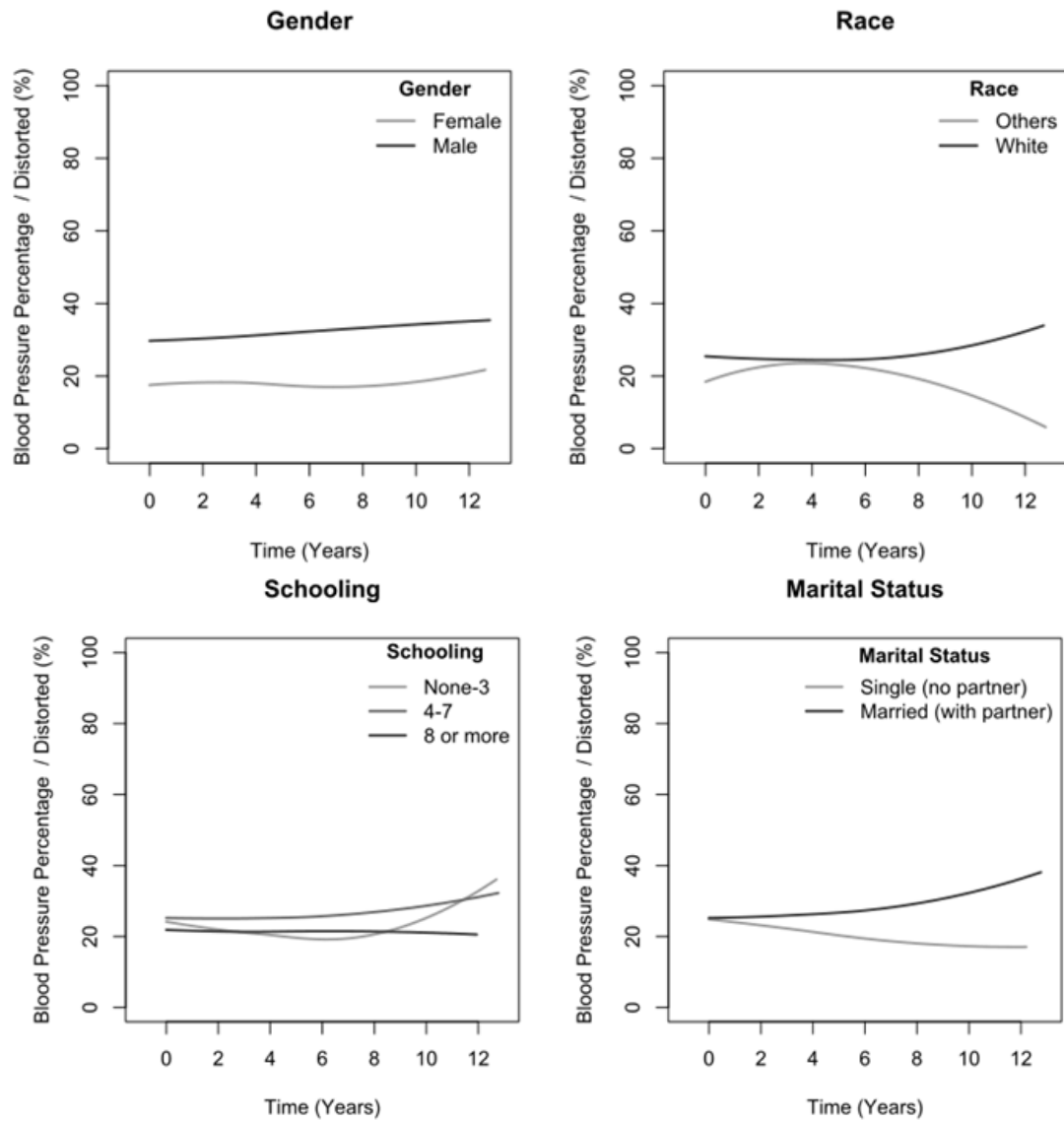
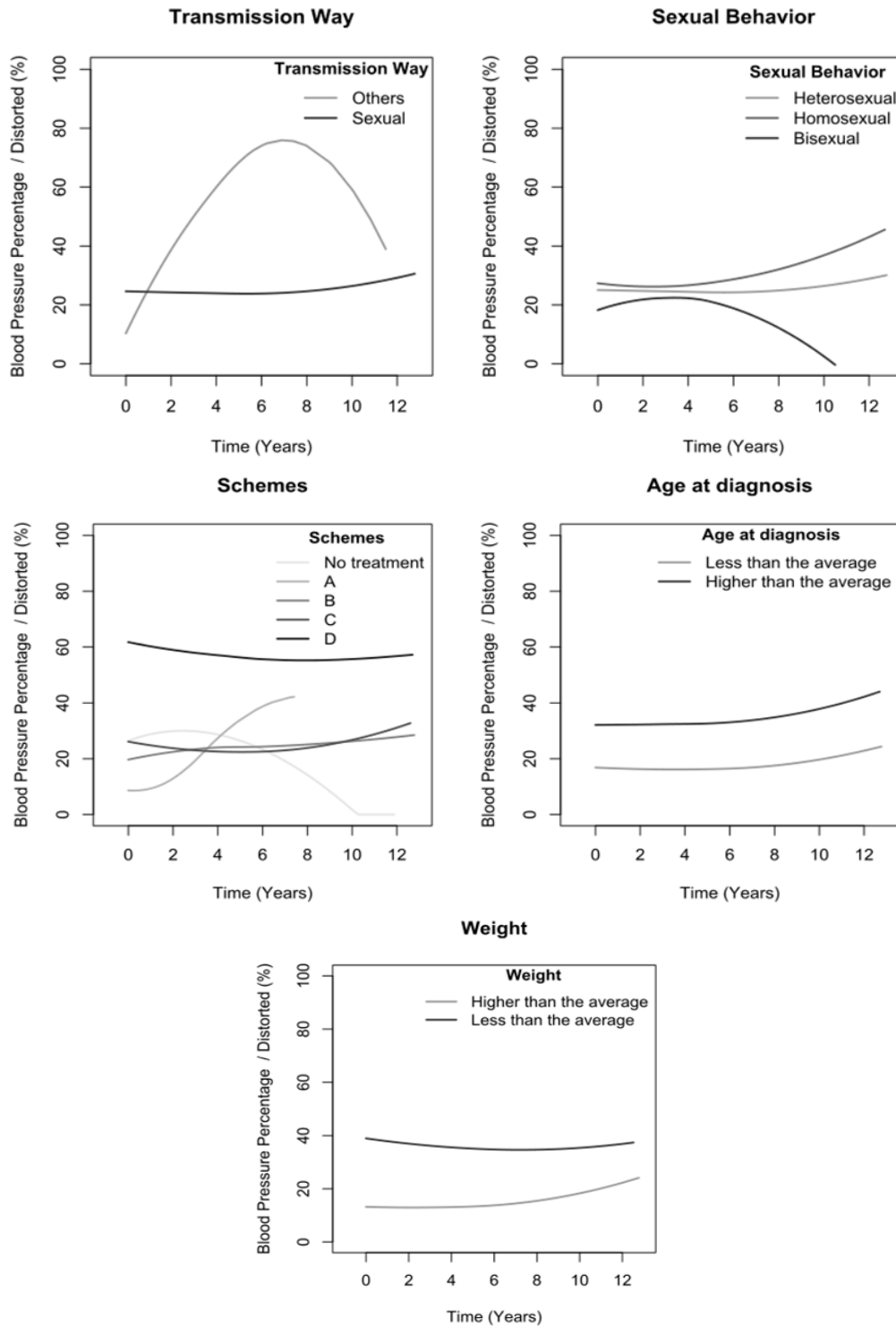


IMAGE 1. Percentage of people with HIV / AIDS and high blood pressure, according to time and variables categories of gender, race, education, marital status. South Center Region of Paraná, 2002-2014

Table 1. Univariate logistic regression analysis among sociodemographic, behavioral and health conditions of people with HIV / AIDS, and the outcome of hypertension. Central-South Region, Paraná, 2002-2014

	Variables	$\beta$	EP* ( $\beta$ )	P-Value	OR	IC(95%)
Gender	Female				1,00	-
	Male	0,666	0,143	0,000	1,95	[1,47; 2,58]
Race	Others				1,00	-
	White	0,063	0,177	0,721	1,07	[0,75; 1,51]
Marital Status	Single / No partner	-0,076	0,066	0,247	0,93	[0,81; 1,05]
	Married / With partner	0,164	0,145	0,259	1,18	[0,89; 1,56]
Transmission way	Others				1,00	-
	Sexual	-0,716	0,484	0,139	0,49	[0,19; 1,26]
Sexual Behavior	Heterosexual				1,00	-
	Bisexual	-0,017	0,320	0,958	0,98	[0,53; 1,84]
	Homosexual	0,043	0,246	0,863	1,04	[0,64; 1,69]
Therapeutic scheme	No treatment				1,00	-
	A	-0,241	0,395	0,542	0,79	[0,36; 1,70]
	B	-0,094	0,146	0,521	0,91	[0,68; 1,21]
	C	-0,090	0,139	0,519	0,91	[0,70; 1,20]
	D	0,539	0,477	0,259	1,71	[0,67; 4,36]
	Age at diagnosis	0,045	0,006	0,000	1,05	[1,03; 1,06]
	Weight	0,054	0,005	0,000	1,06	[1,05; 1,07]

\*standard error.



**IMAGE 2. People with HIV / AIDS and high blood pressure percentage, according to time and transmission way, sexual behavior, therapeutic schemes, age at diagnosis and weight. South Center Region of Paraná, 2002-2014**

Chart 1 presents the analysis about the factors that exerted influence on blood pressure univariate. The variable gender, schooling, transmission way, age at diagnosis and weight were selected as predictive powers for the multivariate model ( $p < 0.25$ ). Through this univariate analysis, it can be affirmed that there was gender influence on blood pressure ( $p < 0,001$ ), men had a chance of having hypertension 1.95 times higher than women. There was a significant influence ( $p = 0,000$ ) of age at diagnosis on blood pressure ( $p < 0,001$ ). It is noted that with each year increased in age, there was a 1.05-fold increase in the chance of having hypertension.

The influence of weight on blood pressure ( $p < 0,001$ ) was also observed, with an increase of 1.06 times in the chance of having arterial hypertension in each kilogram of body weight increase. When it was verified the interaction possibility among time and sociodemographic and health conditions of people with HIV / AIDS in antiretroviral therapy on blood pressure, it was observed that there was interaction among time and schooling, marital status and therapeutic regimen – indicating the effect of these variables on the change in blood pressure throughout the follow-up time (Chart 2). Chart 3 presents the age variable interaction in diagnosis, weight, time and treatment schedule.

**Table 2. Interaction among time and variables gender, race, schooling, marital status, transmission way, sexual behavior, therapeutic scheme, age at diagnosis, on blood pressure of people with HIV / AIDS on antiretroviral therapy. Central-South Region, Paraná, 2002-2014**

Variables tested in relation to the interaction with time	G. L.*	$\chi^2$	P-Value
Gender	1	0,220	0,639
Race	1	0,240	0,625
Schooling	1	4,450	0,035
Marital Status	1	3,870	0,049
Transmission Way	1	0,860	0,355
Sexual Behavior	2	0,430	0,809
Therapeutic scheme	4	15,390	0,004
Age at Diagnosis	1	0,440	0,508
Weight	1	2,380	0,123

\*Liberty Degrees.

**Chart 3. Influence of the age at diagnosis, weight, therapeutic regimen and time of treatment on blood pressure in people with HIV / AIDS in antiretroviral therapy. Central-South Region, Paraná, 2002-2014**

Variables	$\beta$	E.P ( $\beta$ )	P-Value	OR	IC (95%)
Age at Diagnosis	0,048	0,006	0,000	1,05	[1,04; 1,06]
Weight	0,056	0,004	0,000	1,06	[1,05; 1,07]
Time: 1 year					
Therapeutic scheme Without treatment					
A	-0,427	0,765	0,577	0,65	[0,15; 2,92]
B	-0,260	0,170	0,127	0,77	[0,55; 1,08]
C	-0,260	0,170	0,127	0,77	[0,55; 1,08]
D	-0,226	0,499	0,651	0,80	[0,30; 2,12]
Time: 3 years					
Therapeutic scheme Without treatment					
A	0,204	0,508	0,688	1,23	[0,45; 3,32]
B	-0,017	0,169	0,918	0,98	[0,71; 1,37]
C	-0,017	0,169	0,918	0,98	[0,71; 1,37]
D	0,239	0,449	0,595	1,27	[0,53; 3,06]
Time: 5,5 years					
Therapeutic scheme Without treatment					
A	1,040	0,480	0,031	2,83	[1,10; 7,25]
B	0,302	0,241	0,209	1,35	[0,84; 2,17]
C	0,302	0,241	0,209	1,35	[0,84; 2,17]
D	0,852	0,503	0,090	2,34	[0,87; 6,28]
Therapeutic scheme Without treatment	-0,068	0,047	0,146	0,93	[0,85; 1,02]
A	0,256	0,187	0,170	1,29	[0,90; 1,86]
B	0,057	0,022	0,011	1,06	[1,01; 1,11]
C	-0,006	0,024	0,805	0,99	[0,95; 1,04]
D	0,171	0,088	0,052	1,19	[1,01; 1,41]

R<sup>2</sup> = 20,4%

There was a significant influence of age on blood pressure diagnosis ( $p > 0,001$ ), with each year of elevation in age, a 1.05-fold increase in the chance of having arterial hypertension. A significant influence of weight on blood pressure ( $p > 0,001$ ) was observed, with each kilogram of increase in weight, a 1.06-fold increase in the chance of having arterial hypertension. It was found that the PLHA in ART with treatment time of 5.5 years showed a significant difference between the A scheme and the patients without treatment ( $p = 0,031$ ). Those patients on ART scheme showed a chance of having hypertension 2.83 times higher than that of the untreated group. In treatment regimen B, significant influence of time on pressure ( $p = 0,011$ ), was observed, with each year increased over time, and the patient's chance of having hypertension increased by 1.29 times. It was also observed that age at diagnosis, weight, time and scheme were able to explain 20.4% of blood pressure variability (Chart 3).

## DISCUSSION

Regarding to sociodemographic and behavioral conditions, the present study showed that the diagnosis average age of PLHA was 36.3 years, more frequently in male gender, white individuals with low schooling and the main transmission way was sexual.

These findings are corroborated by other authors (Pereira *et al.*, 2016), who found a mean age of PLHA of 36.6 years and a prevalence among men. The Ministry of Health also points out that in Brazil the average age of HIV / AIDS individuals is between 25 and 39 years old (Brazil, 2014). Researchers (Grangeiro *et al.*, 2014), in a Brazilian cohort study, report a predominance of AIDS among men with an average age of 36.9 years, data similar to those shown in this study. This epidemiological profile indicates that, although HIV infection and AIDS are manifested among women or young people, men are still the most affected and that the sexual pathway, schooling and age should continue to be considered in the public policies of HIV / AIDS intervention and prevention. Authors report the risk of AIDS occurrence in the male population is about 2 to 3 times higher than that observed among women (Rodrigues *et al.*, 2015). The predominance of the white race found in the present study can be explained by the European colonization of the southern region where the study was conducted. The literature also indicates that individuals with a lower schooling level have a greater burden of chronic diseases; in addition, low schooling may lead to a decrease in the understanding of health-related information, leading to even lower medication adherence with worse outcomes in these patients (Giroto *et al.* 2013). In the present study, it was not possible to obtain income from PLHA,

however, authors infer that people with low schooling have lower income, and it seems to be greater vulnerability in these individuals to spread the disease (Holanda *et al.*, 2015). In this study, it was verified that the cumulative incidence of systemic arterial hypertension (SAH) was 24.4% over time. There are few studies in the Brazilian follow-up about PLHA that verified the HA incidence, researchers from Rio de Janeiro, in a cohort study, found a HA incidence of 27% in ART patients (Arruda Junior *et al.*, 2010). In another study carried out in Spain, the authors pointed out that prior to the use of HAART, 7% of patients had hypertension and after 48 weeks of treatment 26% of patients in HAART had high blood pressure, thus showing a possible association between the usage of antiretrovirals and increased pressure levels (Palacius, *et al.*, 2006). In the present study, a higher SAH percentage was observed in men, a higher SAH percentage was also observed in white HPAEP, with a diagnosis age and weight above the average. A systematic review with publications from 35 countries showed a global hypertension prevalence of 37.8% for men and 32.1% for women (Pereira *et al.*, 2009). Overweight can be considered as one of the main risk factors to the SAH development. It is found that PLHA have marked weight loss prior to ART therapy. However, in order not to appear ill, they generally increase their food intake, associated to unhealthy lifestyle habits. With this, many patients become fat, leading to chronic diseases development, among them the SAH (Giroto *et al.*, 2013).

Regarding to the therapeutic regimen, it was observed that the PLHA in ART with a therapeutic regimen D (Nucleotide Reverse Transcriptase Inhibitors + Non-Nucleotide Reverse Transcriptase Inhibitors + Protease Inhibitors) showed a higher arterial hypertension percentage, as well as the time of treatment. Patients on ARV therapy, especially antiretroviral treatment regimens, are at increased risk of developing hypertension, lipodystrophy, increased insulin resistance and elevated serum lipids, and may develop metabolic syndrome. In addition to the aforementioned effects, medications as inhibitors of reverse transcriptase may have drug interaction with antihypertensives, thus contributing to the increase of blood pressure indices in patients with prior HA (Furini *et al.*, 2015). There is no consensus on the relationship between hypertension and HAART. However, recent studies have indicated a higher HA prevalence in subjects with high-potency antiretroviral therapy (HAART) (Havlir, Currier, 2015, Xu, Chen, Wang, 2017). In addition to HAART, other factors may contribute to an AH increase, such as overweight, obesity, age, gender, family history, hyperlipidemia, as well as eating habits and physical activity, but these data for logistical reasons could not be brought up in the present study.

A meta-analysis showed that exposure to HAART is significantly associated with hypertension increased risk, regardless of sociodemographic differences. From the results obtained, the authors describe that there is a need for strategies to reduce the risk of arterial hypertension among HAART in PLHA (Bigna *et al.*, 2017). Autores relatam que a TARV pode estar associada ao aumento de fatores de risco cardiovasculares, com maior possibilidade de esses eventos ocorrerem no primeiro semestre de tratamento (Eluwa, Badru, Akpoigbe, 2012). Nesse sentido se faz necessária a elaboração de uma linha de cuidado para acompanhamento das PVHA pelas equipes de saúde, tanto da atenção primária em saúde quanto dos centros de acompanhamento, visando a integralidade do cuidado que é um dos princípios norteadores

do SUS, para garantir aos PVHA horizontalidade e a verticalidade do cuidado. Authors report that HAART may be associated to an increase in cardiovascular risk factors, with a higher chance of these events occurring in the first half of treatment (Eluwa, Badru, Akpoigbe, 2012). In this sense, it is necessary to prepare a line of care for the PLHA monitoring by health teams, both primary health care and follow-up centers, aiming at the integral care that is one of the SUS guiding principles, in order to guarantee PLHA horizontality and verticality of care. This study presented some limitations, such as the lack of information in patients' charts regarding to height, smoking, alcoholic beverages consumption and physical activity. However, the lack of interest information to the research is an inherent limitation to studies that collect data in medical charts. One of the strengths to the present research was the results shown that nucleotide reverse transcriptase inhibitors (B and D regimens) would have a greater influence on the increase in blood pressure and that the longer treatment with this antiretrovirals group favors HA, fact not described in other studies. In view of the results found in the study, it is suggested that health professionals be attentive beyond the PLHA health conditions orientation. It is essential to keep up with these individuals in relation to the hypertension risk factors studied here (time and type of treatment, weight gain and the age of the treated subjects), making people exposed to such risk factors can be cared for a greater meeting routine, specific therapeutic projects establishment for cases and health education investment in order to minimize the hypertension incidence. It is also recommended that a hypertensive PLHA care network be established among the various points of health care, aiming at comprehensive and resolute assistance to these patients.

## Conclusion

Considering the aspects addressed in this article, it is concluded that the systemic arterial hypertension incidence in patients with HIV / AIDS was high when under antiretroviral therapy, and was associated with age at diagnosis, weight, time of treatment and therapeutic regimen.

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