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Original Article

Evaluation of cardiovascular risk factors in people living with HIV in São Paulo, Brazil

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Abstract

Introduction: HIV infection as a chronic disease has emerged from treatment advances over the past three decades. From this perspective, the diseases associated with AIDS are not a main threat for patients who use Antiretroviral Therapy (ART). A new set of HIV associated complications have emerged resulting in comorbidities related to aging and ART exposure as cardiovascular disease (CVD). This study aimed to evaluate the cardiovascular risk factors in people living with HIV (PLWH) in Brazil.

Methodology: This was a cross-sectional study carried out at all Specialized Care Services for people living with HIV in the Southeast of Brazil. A sociodemographic and clinical questionnaire was used and cardiovascular risk assessed through the Framingham Score. Data analysis was performed by Chi-square, Fisher's exact test and logistic regression.

Results: The majority were male, over 40 years old and they showed a mean age of 44 years. Current hypertension, diabetes, altered body mass index, presence of metabolic syndrome and altered abdominal circumference were also associated with cardiovascular risk. After regression analysis, male sex, older age, smoking, diabetes, hypertension and metabolic syndrome were related as predictive factors for a higher cardiovascular risk.

Conclusions: The results demonstrate that combination of the prevention of modifiable risk factors with considerable changes in lifestyle are determining factors for success in the therapeutic of PLWH. High levels of motivation are essential for behavioral changes, and nurses are ideally positioned to provide safe care with nonpharmacological strategies for CVD risk reduction.

Key words: HIV; cardiovascular disease; risk factors.

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Introduction

HIV infection as a chronic disease has emerged from treatment advances over the past three decades. Antiretroviral Therapy (ART) improves health and life expectancy and decreases substantially the risk of HIV transmission [1].

According to The Joint United Nations Programme on HIV/AIDS [2], almost 36.7 million people were living with HIV in the world until December 2015. Of these, 17 million had utilized ART [2].

From this perspective, the diseases associated with AIDS are not a main threat for patients who consistently use ART. A new set of HIV associated complications have emerged resulting in comorbidities related to aging and ART exposure, as neurocognitive decline, osteoporosis, metabolic disorders, liver and renal disorders and mainly cardiovascular disease (CVD) [1].

The usual metabolic disorders, such as hypertension, diabetes, dyslipidemia and obesity, are

known as modifiable risk factors and decrease life expectancy and lower individuals' quality of life. They have also been linked to changes induced by HIV infection and the use of ARV drugs, such as chronic inflammation, immune activation, immune deficiency, plasma lipid imbalances, and insulin resistance [3].

HIV-specific immune dysregulation may have atherogenic effects such as activation of endothelial and immune cells, enhancement of the percentage of circulating atherogenic immune cell subsets and modification of lipid function [4].

In this context, cytokines such as IL-6, TNF- α and C-reactive protein have been shown to be prevalent in people living with HIV (PLWH) and are related to the development of atherosclerosis, cardiovascular disease, immunosenescence and death [5].

The paradigm that explains the increased risk to cardiovascular diseases in PLWH includes the effects of HIV infection. In this stage, the persistent immune

activation and the endothelial inflammation, in addition to the effects of the exposure of ART, trigger a cascade of potential disorders such as dyslipidemia, ectopic accumulation of fat, diabetes or insulin resistance. Drug use, smoking, coinfections and lifestyle are also significant factors of risk in the development of cardiovascular diseases [6]. Furthermore, all these factors contribute to the buildup of calcified coronary plaque resulting in unwelcome coronary events [7].

Therefore, a cardiovascular risk assessment in PLWH is needed in the initiation of infection as well as during treatment of ART. The reduction of cardiovascular risk factors becomes vital in the provided care of this population [8].

These factors should be evaluated in the entire care process of PLWH. A multicentric study evidenced that cardiovascular risk factors are common in this population, but it is possible to have significant regional differences in the distribution of cardiovascular risk factors and risk scores [9].

Aiming to improve the provided care to this population under the perspective of health prevention and promotion, this study aimed to evaluate the cardiovascular risk factors in people living with HIV in Brazil.

Methodology

Study setting and participants

This is a cross-sectional study. Patients were enrolled from all outpatient specialized services in HIV care in a city of Southeast region of Brazil.

Patients were selected according to the inclusion criteria: age above 18 years, knowledge of their HIV positive status, being treated with ART prescribed for more than six months. Patients who had a history of CVD (acute myocardial infarction, stroke, angina pectoris, past heart surgery, coronary angioplasty), as well as pregnant women, patients with mental illness, and individuals in confinement situations were excluded.

Ethical approval

The study was approved by the Research Ethics Committee on Research of the Ribeirão Preto College of Nursing, Protocol 794.563/2014. It is important to highlight that all participants signed the consent form.

Measures

All participants completed a survey with demographic data, as sex, age, skin color, education, monthly income, sexual orientation and life habits as sedentary lifestyle, tobacco and alcohol use. Personal

and family history were also asked of the patient. Anthropometric data - weight, height and waist circumference and blood pressure were measured after the interview.

Research nurses were trained for measured height, weight, and vital signs of participants. Each one's height was measured to the nearest 0.1 cm by asking him/her to stand straight up against a stadiometer platform without shoes. After removing everything but using only light clothing, the participant stepped on a scale and weight was measured. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared.

Participants also consented to review medical records to collect data on ART, the type of ARV prescribed, date of initiation of therapy, date of diagnosis, date and values of the last CD4, viral load, Cholesterol, High Density Lipoproteins (HDL), Low Density Lipoproteins (LDL), triglycerides and glucose exams.

The cardiovascular risk score was calculated using software, available online, produced by The Framingham Heart Study (<https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php>) based on the observation of 8491 Framingham study participants (mean age, 49 years; 4522 women) who attended a routine examination between 30 and 74 years of age and were free of CVD in order to predict risk of developing CVD and its constituents (the Framingham Heart Study).

The variables included in calculating the Framingham Risk Score are age, sex, systolic blood pressure, use of antihypertensive, HDL and cholesterol dosage, smoking and diabetes. The risk for the occurrence of a cardiovascular event in the next ten years is classified as low (< 10%) or medium / high ($\geq 10\%$ to 20%) [10].

For the evaluation of Metabolic Syndrome, the criteria of International Diabetes Federation were used (IDF). The IDF criterion evaluates the values of Hypertension (HTN), triglycerides, glucose exams and HDL, abdominal circumference (CA) (women ≥ 80 cm and men ≥ 90 cm) [11]. By the IDF criterion the presence of change in the CA is mandatory, in addition to two other criteria, and ethnic parameters must be respected. [11]

Statistical Analysis

All analyses were conducted using SPSS 22. We used descriptive statistics to characterize the study population. Categorical variables were summarized

using frequencies and percentages and means and standard deviations were calculated for continuous data.

To test the association between the Framingham risk score with sociodemographic and general clinic or clinical variables related to HIV, the Pearson's Chi-Square test or the Fisher's exact test were used.

For the logistic regression, the medium and high response categories of the Framingham score were used in the same group as high risk. The interest in logistic regression is to model the probability of occurrence of the middle / high class, that is, what factors contribute to increase the probability of a higher risk. Thus, from

the resulting final model, the Odds Ratio (OR) and the predicted probabilities of the median / high score of the Framingham Score were calculated.

Results

A total of 340 PLWH were enrolled in the study. The majority were male, over 40 years old and they showed a mean age of 44 years as seen in Table 1.

Among the sociodemographic and behavioral variables, gender, age, skin color, marital status, schooling, and sexual orientation were associated with cardiovascular risk.

Table 1. Association between demographic and behavioral variables and Framingham score of PLWH in the city of Ribeirão Preto – São Paulo State, Brazil, 2014 – 2016.

Variables	Framingham risk score			p
	Low n (%)	Medium/High n (%)	Total n = 340 (%)	
Sex				
Male	137 (69.5)	60 (30.5)	197 (100.0)	0.002*
Female	120 (83.9)	23 (16.1)	143 (100.0)	
Age (years)				
≤ 39	111 (99.1)	01 (0.9)	112 (100.0)	< 0.001*
40 - 59	141 (71.6)	56 (28.4)	197 (100.0)	
≥ 60	08 (25.8)	23 (74.2)	31 (100.0)	
Skin color				
White	114 (72.2)	44 (27.8)	158 (100.0)	0.046†
Black	31 (67.4)	15 (32.6)	46 (100.0)	
Yellow	13 (92.9)	01 (7.1)	14 (100.0)	
Brown	98 (81.0)	23 (19.0)	121 (100.0)	
Indigenous	01 (100)	00 (00)	01 (100.0)	
Marital status				
Married	89 (74.2)	31 (25.8)	120 (100.0)	0.018*
Not married	123 (83.7)	24 (16.3)	147 (100.0)	
Widow	24 (70.6)	10 (29.4)	34 (100.0)	
Separate	24 (61.5)	15 (38.5)	39 (100.0)	
Education (years of study)				
< 8	117 (70.1)	50 (29.9)	167 (100.0)	0.006*
≥ 8	143 (82.7)	30 (17.3)	173 (100.0)	
Income (minimum wages)				
Up to 3	211 (75.4)	69 (24.6)	280 (100.0)	0.296*
More than 3	49 (81.7)	11 (18.3)	60 (100.0)	
Sexual orientation				
Heterosexual	176 (73.6)	63 (26.4)	239 (100.0)	0.012*
Homosexual	72 (87.8)	10 (12.2)	82 (100.0)	
Bisexual	12 (63.2)	07 (36.8)	19 (100.0)	
Sedentary lifestyle				
Yes	165 (75.7)	53 (24.3)	218 (100.0)	0.954*
No	92 (75.4)	30 (24.6)	122 (100.0)	
Smoking				
Yes	76 (69.7)	33 (30.3)	109 (100.0)	0.084*
No	181 (78.4)	50 (21.6)	231 (100.0)	
Alcohol use				
Yes	102 (75.0)	34 (25.0)	136 (100.0)	0.837*
No	155 (76.0)	49 (24.0)	204 (100.0)	

* Chi-square test; † Fisher's exact test.

Table 2. Association between general and HIV-related clinical variables and Framingham score of PLWH in the city of Ribeirão Preto, São Paulo State, Brazil, 2014-2016.

Variables	Framingham risk score			p*
	Low n (%)	Medium/High n (%)	Total n (%)	
Family history for HTN				
No	100 (81.3)	23 (18.7)	123 (100.0)	0.005
1st order relative	135 (70.7)	56 (29.3)	191 (100.0)	
2nd order relative	25 (96.2)	01 (3.8)	26 (100.0)	
Family history for Diabetes				
No	142 (78.0)	40 (22.0)	182 (100.0)	0.003
1st order relative	82 (68.3)	38 (31.7)	120 (100.0)	
2nd order relative	36 (94.7)	02 (5.3)	38 (100.0)	
Family history for MI				
No	174 (79.5)	45 (20.5)	219 (100.0)	0.009
1st order relative	44 (62.0)	27 (38.0)	71 (100.0)	
2nd order relative	25 (80.6)	06 (19.4)	31 (100.0)	
Family history for stroke				
No	163 (82.3)	35 (17.7)	198 (100.0)	0.003
1st order relative	57 (64.0)	32 (36.0)	89 (100.0)	
2nd order relative	28 (73.7)	10 (26.3)	38 (100.0)	
HTN				
Yes	47 (55.3)	38 (44.7)	85 (100.0)	< 0.001
No	210 (82.4)	45 (17.6)	255 (100.0)	
Diabetes				
Yes	08 (26.7)	22 (73.3)	30 (100.0)	< 0.001
No	249 (80.3)	61 (19.6)	310 (100.0)	
Dyslipidaemia				
Yes	60 (68.2)	28 (31.8)	88 (100.0)	0.067
No	197 (78.1)	55(21.8)	252 (100.0)	
BMI				
≤ 24.9 kg/m ²	146 (82.0)	32 (18.0)	178 (100.0)	0.011
≥ 25 kg/m ²	114 (70.4)	48 (29.6)	162 (100.0)	
Metabolic syndrome				
Yes	86 (62.3)	52 (37.7)	138 (100.0)	< 0.001
No	167 (82.6)	35 (17.3)	202 (100.0)	
Abdominal circumference				
Normal	186 (80.5)	45 (19.5)	231 (100.0)	0.002
Altered	71 (65.1)	38 (34.9)	109 (100.0)	
HIV time (years)				
≤ 10	154 (84.2)	29 (15.8)	183 (100.0)	>0.001
> 10	106 (67.5)	51 (32.5)	157 (100.0)	
HAART time (years)				
≤ 10	180 (81.4)	41 (18.6)	221 (100.0)	0.003
> 10	80 (67.2)	39 (32.8)	119 (100.0)	
TCD4+ cells (cells/mm³)				
< 200	19 (86.4)	03 (13.6)	22 (100.0)	0.258
≥ 200	241 (75.8)	77 (24.2)	318 (100.0)	
Viral load (copies/ml)				
≤ 40	209 (76.0)	66 (24.0)	275 (100.0)	0.674
> 40	51 (78.5)	14 (21.5)	65 (100.0)	

Table 2 (continued). Association between general and HIV-related clinical variables and Framingham score of PLWH in the city of Ribeirão Preto, São Paulo State, Brazil, 2014-2016.

Variables	Framingham risk score			p*
	Low n (%)	Medium/High n (%)	Total n (%)	
Use of protease inhibitor				
Ritonavir				
Yes	98 (77.8)	28 (22.2)	126 (100.0)	0.471
No	159 (74.3)	55 (25.7)	214 (100.0)	
Lopinavir				
Yes	41 (77.4)	12 (22.6)	53 (100.0)	0.744
No	216 (75.3)	71 (24.7)	287 (100.0)	
Fusamperenavir				
Yes	05 (62.5)	03 (37.5)	08 (100.0)	0.383
No	252 (75.9)	80 (24.1)	332 (100.0)	
Use of nucleoside reverse transcriptase inhibitors				
Didanosine				
Yes	01 (100)	00 (00)	01 (100.0)	0.569†
No	256 (75.5)	83 (24.5)	339 (100.0)	

* Chi-square test; † Fisher's exact test; HTN, hypertension; MI, myocardial infarction; BMI, body mass index; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy.

Also, the association between general and HIV-related clinical variables with cardiovascular risk according to the Framingham score was analyzed (Table 2).

The analysis of the general clinical variables showed an association between family history for HTN, diabetes, myocardial infarction, stroke and cardiovascular risk. In addition, the variables current HTN, current diabetes, altered BMI, presence of metabolic syndrome and altered abdominal

circumference were also associated with cardiovascular risk.

Among HIV-related clinical variables, only HIV diagnosis time and time of ART were associated with cardiovascular risk. After regression analysis, sex, age, smoking, current diabetes, HTN, and metabolic syndrome variables were related as predictive factors for a higher cardiovascular risk, according to Table 3. Even at a younger age, men are at greater risk than women and when only age is observed, it is noticed that those with more advanced age are at increased risk.

Table 3. Multiple logistic regression analysis of variables associated with cardiovascular risk, Ribeirão Preto, São Paulo State, Brazil, 2014-2016.

Variables	OR unadjusted (95% CI)	β	SE (β)	OR adjusted (95% CI)	p
Sex					
Male	2.27 (1.2 – 4.1)	3.15	0.56	23.47 (7.6 – 71.7)	< 0.0001
Age					
≥ 60 years	5.94 (44.7 – 3238.6)	8.09	1.32	3288.87 (245.2 – 44104.6)	< 0.0001
40 a 59 years	3.83 (6.3 – 339.6)	4.44	1.08	85.46 (10.2 – 713.3)	< 0.0001
Smoking					
Yes	1.56 (0.9 – 2.7)	2.38	0.49	10.87 (4.1 – 28.6)	< 0.0001
Diabetes					
Yes	11.02 (4.4 – 30.1)	3.25	0.76	25.98 (5.7 – 117.0)	< 0.0001
Hypertension					
Yes	3.75 (2.1 – 6.6)	1.13	0.44	3.10 (1.2 – 7.4)	0.0116
Metabolic syndrome					
Yes	3.24 (1.8 – 5.6)	1.06	0.46	2.91 (1.1 – 7.2)	0.0210

OR, Odds Ratio.

Discussion

This analysis shows that non-modifiable risk factors, male and elderly, and modifiable risk factors such as tobacco user, diabetes status, hypertension and metabolic syndrome, predisposes a higher cardiovascular risk in PLWH. Recent studies confirm that cardiovascular risk in this group is higher than in the general population [12-14]. This may be due to a combination of traditional risk and specific HIV factors [15].

In Brazil, the epidemiology of HIV infection reflects its regional heterogeneity, and the social and economic context in which they are inserted can produce situations of multiple vulnerabilities [16].

The Southeast region of Brazil is considered the most developed, populous, with the highest average income in the country and harbors almost half the number of reported HIV infections in Brazil [16].

From the results it was identified that being male was a predictor for greater cardiovascular risk. The increased number of HIV infection among men makes them vulnerable to illness due to CVD.

In general, men die twice as often due to coronary disease, have a higher incidence of infarction and, unlike women, have fewer protective hormonal factors, from which atherogenesis and thrombogenesis may emerge [17].

PLWH are actors in the epidemiological and demographic transition experienced by the Brazilian population. It is important to be aware of the aging process of this population, since cardiovascular risk increases substantially with HIV progression, more exposure to ART and the patient's age [18].

In this context, it is emphasized that the increase in age is related to the risk for CVD, since the presence of HIV in the body induces an intestinal microbial translocation that activates monocytes and promotes the release of cytokines that are associated with pro-inflammatory biomarkers, which may evolve into CVD [19].

Social and economic changes and globalization have impacted the lifestyle of PLWH. Therefore, the change in living habits are direct determinants for the occurrence of chronic diseases, such as CVD [20].

It is well known that smoking is a classic risk factor for CVD because it activates the inflammatory state. Thus, it increases the progression to AIDS, decreasing overall survival [21].

The prevalence of smoking in PLWH has been reported as high compared to the general population [15]. It is also worth noting that the proportion of deaths due to tobacco-related disease, including lung disease

and non-HIV-related cancer, has increased in this population [22], which raises treatment concerns.

The context of care for PLWH has changed over time, which has led to a change in their clinical profile. Initially the attention was focused on immunological control, with viral load and CD4 cell count control. Over the years it has been realized that other needs have resulted from the lifestyle changes adopted by PLWH.

As a result, there was a considerable increase in non-communicable chronic diseases in PLWH, such as hypertension (HTN) and diabetes. Currently, CVD is the main cause of death or disability, with hypertension being the comorbidity that represents more than half of the deaths worldwide [23].

Studies show different values of the prevalence of HTN in PLWH [5,24-25], and the evidence indicates that the control of HTN in this population can improve the patient's health conditions and affect other potential comorbidities [26].

Pre-existing comorbidities such as HTN and obesity are also strong predictors of DM [18]. In addition, the use of HAART, especially protease inhibitors, increases insulin resistance, favoring a prevalence increase of DM in PLWH [27].

The condition of hyperglycemia and hyperinsulinemia induce a higher production of triglycerides and low density lipoprotein cholesterol (LDL-c), generating systemic pro-thrombotic and pro-inflammatory conditions, which predisposes to cardiovascular events [28-29].

HTN and DM are multifactorial clinical conditions that are associated with metabolic disorders. In addition, the prolonged use of antiretroviral drugs, can modify cellular functioning patterns, altering glucose and lipid metabolism [30-31].

These metabolic alterations fit the criteria of Metabolic Syndrome (SM) [32], which aggregates several cardiovascular risk factors [28,33], implying a risk two times higher for myocardial infarction [34].

In this sense, health professionals should pay attention to the evaluation of new clinical disorders in PLWH, due to prolonged exposure to ART and greater survival [18]. To reduce cardiovascular risk, care should be directed toward adopting a healthy lifestyle [35].

Our study has some notable limitations. First, as a cross-sectional study, we are unable to infer causality, and we do not know if the metabolic disorders were there before HIV status. Finally, this is a single-site study, and although we had a representative sample from an important region of Brazil, with statistically significant relationships, our findings should be

examined in a multisite sample before implementing clinical changes based on our findings.

In this context, variables such as HIV diagnosis time, ART and time of ART were not independent predictors of cardiovascular risk in PLWH in regression analysis of this study. It is believed that this occurs because of the selection with only individuals with confirmed diagnosis, in use of the ART for more than 6 months and with good adhesion of treatment, making it difficult to compare them with another group with different characteristics and confirming the idea that HIV infection should be treated as a multifactorial phenomenon. It is evident that many additional studies will be needed for a complete understanding of this.

This research contributes to the body of knowledge on nursing care for people living with HIV. The results demonstrate that combination of the prevention of modifiable risk factors with considerable changes in lifestyle are determining factors for success in the therapeutic of PLWH. High levels of motivation are essential for behavioral changes, and nurses are ideally positioned to provide safe care with nonpharmacological strategies for CVD risk reduction.

Conclusion

This research contributes to the body of knowledge on nursing care for people living with HIV. The results demonstrate that combination of the prevention of modifiable risk factors with considerable changes in lifestyle are determining factors for success in the therapeutic of PLWH. High levels of motivation are essential for behavioral changes, and nurses are ideally positioned to provide safe care with nonpharmacological strategies for CVD risk reduction.

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