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Myocardial ischemia and left ventricular diastolic dysfunction in HIV infected patients and asymptomatic for coronary artery disease

Isquemia miocárdica e disfunção diastólica do ventrículo esquerdo em pacientes infectados pelo HIV e assintomáticos para doença arterial coronariana

Isquemia miocárdica y disfunción diastólica del ventrículo izquierdo en pacientes infectados por el VIH asintomáticos por enfermedad arterial coronaria

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Abstract
Highly active antiretroviral therapy (HAART) allows chronicity of AIDS evolution, leading to association of other pathologies such as coronary artery disease (CAD). Myocardial ischemia (MI) and left ventricular diastolic dysfunction (LVDD) evaluation in HIV-infected patients may favor primary prevention of CAD. The study aimed to evaluate frequencies of MI and LVDD in the population living with the human immunodeficiency virus (PLHIV) and asymptomatic for CAD. We analyzed data from 110 HIV-infected patients who underwent clinical and laboratory evaluation, treadmill exercise stress test, and transthoracic echocardiogram, and compared it with 2,619 healthy individuals from the control group (non-HIV and non-CAD), selected from the database. HIV-infected patients presented lower average age (51.5 ± 7.7), systemic arterial hypertension (28.0%) and dyslipidemia frequencies (32.0%). On the other hand, their MI frequency was twice as high (14.7%); and diastolic dysfunction (DD) percentage was higher in ischemic patients (45.5%). In the HIV-infected group, MI frequency was 10.0%, while that of DD was 18.2%. MI was twice as frequent among HIV infected patients compared to uninfected, despite lower frequency of risk factors for CAD. Non-ischemic patients living with HIV had a frequency of DD more than twice compared to the control individuals.
Keywords: HIV; Coronary artery disease; Myocardial ischemia; Left ventricular dysfunction; Highly active antiretroviral therapy.

Resumo
A terapia antirretroviral altamente eficaz (HAART) permite a cronicidade da evolução da AIDS, levando à associação de outras patologias, como a doença arterial coronariana (DAC). A avaliação da isquemia miocárdica (IM) e da disfunção diastólica do ventrículo esquerdo (DDVE) em pacientes infectados pelo HIV pode favorecer a prevenção primária de DAC. O estudo teve como objetivo avaliar as frequências de IM e DDVE na população vivendo com o vírus da imunodeficiência humana (PVHIV) e assintomática para DAC. Analisamos dados de 110 pacientes infectados pelo HIV submetidos a avaliação clínica e laboratorial, teste ergométrico em esteira e ecocardiograma transtorácico, e comparamos com 2.619 indivíduos saudáveis do grupo controle (sem HIV e sem DAC), selecionados da base de dados. Pacientes infectados pelo HIV apresentaram menores média de idade (51,5 ± 7,7) e frequência de hipertensão arterial sistêmica (28,0%) e de dislipidemia (32,0%). Por outro lado, sua frequência de IM foi duas vezes maior (14,7%); e o percentual de disfunção diastólica (DD) foi maior nos pacientes isquêmicos (45,5%). No grupo infectado pelo HIV, a frequência de IM foi de 10,0%, enquanto a de DD foi de 18,2%. O IM foi duas vezes mais frequente entre os pacientes infectados pelo HIV em comparação com os não infectados, apesar da menor frequência de fatores de risco para DAC. Pacientes não isquêmicos que vivem com HIV tiveram uma frequência de DD mais de duas vezes maior em comparação com os indivíduos controle.
Palavras-chave: HIV; Doença da artéria coronariana; Isquemia miocárdica; Disfunção ventricular esquerda; Terapia antirretroviral de alta atividade.

Resumen
La terapia antirretroviral de gran actividad (TARGA) permite la cronicidad de la evolución del SIDA, lo que lleva a la asociación de otras patologias, como la enfermedad de las arterias coronarias (EAC). La evaluación de isquemia miocárdica (IM) y disfunción diastólica del ventrículo izquierdo (DDVI) en pacientes infectados por VIH puede favorecer la prevención primaria de la EAC. El objetivo fue evaluar las frecuencias de IM y DDVI en la población que vive con el virus de la inmunodeficiencia humana (PVVIH) y asintomática de EAC. Analizamos datos de 110 pacientes infectados por VIH que se sometieron a evaluación clínica y de laboratorio, prueba de esfuerzo y ecocardiograma transtorácica y los comparamos con 2.619 individuos sanos del grupo control (sin VIH y sin EAC), seleccionados del base de datos. Los pacientes infectados por VIH presentaron menor edad promedio (51,5 ± 7,7) y frecuencias de hipertensión arterial sistémica (28,0%) y de dislipidemias (32,0%). Por otro lado, su frecuencia de IM fue dos veces mayor (14,7%); y el porcentaje de disfunción diastólica (DD) fue mayor en los pacientes isquémicos (45,5%). En el grupo infectado por VIH, las frecuencias de IM fueron 10%, mientras que la DD fue 18,2%. La IM fue dos veces más frecuente entre los pacientes infectados por VIH en comparación con los no infectados, a pesar de la menor frecuencia de factores de riesgo de EAC. Los pacientes no isquémicos que vivían con VIH tenían una frecuencia de DD de más del doble en comparación con los individuos de control.
Palabras clave: VIH; Enfermedad de la artéria coronária; Isquemia miocárdica; Disfunción ventricular izquierda; Terapia antirretroviral altamente activa.

1. Introduction

In 2020, the population living with the human immunodeficiency virus (PLHIV) was estimated at 37.7 million people worldwide, 73% of PLHIV received antiretroviral therapy (ART), and approximately 1,5000,000 were newly infected in 2020 (WHO, 2021). From 1997 onwards, the advent of highly effective or highly active antiretroviral therapy (HAART) brought a new perspective to the course of HIV infection as it provided control of viral load (VL) and consequent increase in life expectancy of these patients, transforming it into a chronic medical condition.

In parallel to longer longevity, other non-HIV related diseases start to increase, especially cardiovascular disease (CVD) (Thienemann, Sliwa & Rockstroh, 2013). Studies have shown a higher incidence of cardiovascular abnormalities in patients with HIV, including coronary artery disease (CAD), which is more prevalent and extensive in these individuals (Mangili *et al*., 2006; Post *et al*., 2014; Subramanian *et al*., 2012). As the incidence of opportunistic infections declines, prevalence of non-HIV/AIDS-related comorbidities, including CVD, continues to rise among HIV-infected patients compared to uninfected (Toribio *et al*., 2017).

Pathogenesis of this disorder encompasses complicated interactions between effects of chronic HIV infection, antiretroviral use, and patient's own factors, including genetic susceptibility.

Since the HIV-infected population has reached older ages, there has been an inherent increase in cardiovascular risk, over-added by effects of infection and its therapy. Knowledge and early management of this condition, including studying asymptomatic ones, are imperative.

The study aimed to evaluate frequencies of myocardial ischemia (MI) and left ventricular diastolic dysfunction (LVDD) in the PLHIV and asymptomatic for CAD. It also aimed to evaluate MI occurrence in this sample, besides to evaluate left ventricular (LV) systolic and diastolic functions in PLHIV on HAART and to compare the groups of HIV-infected and non-HIV-infected patients for the frequency of MI and diastolic dysfunction (DD).

2. Methodology

2.1 Study design and population

An observational, cross-sectional, analytical study with a quantitative approach was conducted with prospectively collected data (Pereira *et al*., 2018). 110 PLHIV were selected consecutively and non-randomly, with non-established CVD, from the Infectious Disease Outpatient Clinic of the University Hospital of Federal University of Sergipe (HU-UFS) and the Outpatient Clinic Center of Aracaju (CEMAR).

2.2 Inclusion criteria

Patients were included independent of gender, with HIV infection diagnosed, 10 years old or older (due to the possibility of vertical transmission of HIV), asymptomatic for cardiovascular diseases, and who signed the Informed Consent Form (ICF). Patients under 10 years old, with established coronary artery disease, as well as those with clinical signs of opportunistic infections, with recent hospitalization, debilitated patients, and pregnant women were excluded.

2.3 Ethics

This study is approved by the Research and Ethics Committee from Federal University of Sergipe following the Brazil regulation for research with human subjects and the Declaration of Helsinki. Reference number: 2.244.171

2.4 Statistical analysis

To estimate sample size, prevalence of atherosclerosis in HIV-infected patients, as documented in literature, was 48 to 63%. The 95% confidence interval and an acceptable difference of about 5% were also considered. This estimate used WinPepi software version 10.5 of April 22, 2010, reaching a sample size of at least 90 patients.

Seropositive individuals were invited to participate voluntarily in the present study, from October 2017 to March 2019. 168 HIV patients from the Infectious Diseases outpatient clinics were interviewed from October 2017 to November 2018, who underwent tests until March 2019. However, 16 patients refused to have exams and 42 patients missed schedule to perform at least one of exams (living too far from the capital's urban center); Thus, the final sample counted 110 patients who completed all study design steps.

Findings in this sample were compared to meet one of specific objectives with a database of 2,619 non-HIV-infected individuals without prior CAD and asymptomatic from cardiovascular symptoms admitted to the Cardiology methods service of a Hospital at Aracaju-Sergipe, for elective transthoracic echocardiography (TTE), exercise test (ET) and laboratory tests. Despite aforementioned losses, analyzes of different aspects were possible (sub analysis) and those variables based on TTE and ET exams were chosen, since these determine the investigative power of main outcome variables, LVDD and MI, respectively.

3. Results

3.1 Clinical characteristics of HIV-infected patients

The sample of HIV-infected patients consisted of 110 individuals with a mean age of 45.3 ± 11.7 years old, minimum age of 19 years old and maximum of 73 years old. There was a higher frequency of males with 69.1%. Among traditional risk factors for CAD, lower frequencies of diabetes mellitus (DM) (6.4%), obesity (14.5%), family history of early CAD (FHECAD) (14.5%), Systemic Arterial Hypertension (SAH) (21.8%) and dyslipidemia (DLP) (27.3%), and higher frequencies of smoking (37.3%) and sedentary lifestyle (59.1%) were found. Half of patients are infected with HIV greater than 7.0 years, 25% greater than 11.3 years, and 25% had less than 3.0 years. Treatment time was over 6.0 years in half of sample, 25% of patients reached values over 9.5 years, and 25% less than 2.0 years (Table 1).

Table 1. Clinical characteristics of HIV-infected patients undergoing highly active antiretroviral therapy at the HU and CEMAR outpatient clinics from October 2017 to March 2019.

Basal characteristic	**N = 110**
Age (years)	45.3 ± 11.7
Male Gender	76 (69.1)
Systemic Arterial Hypertension	24 (21.8)
Diabetes Mellitus	07 (6.4)
Dyslipidemia	30 (27.3)
Obesity	16 (14.5)
Smoking	41 (37.3)
Sedentary Lifestyle	65 (59.1)
Family History of Early Coronary Artery Disease	16 (14.5)
Time of Infection (years)	7.0 (3.0; 11.3)
Treatment Time (years)	6.0 (2.0; 9.5)
Myocardial Ischemia	11 (10.0)
Diastolic Dysfunction	20 (18.2)
Systolic Dysfunction	03 (2.7)
Highly Active Antiretroviral Therapy with Protease Inhibitor	50 (45.5)
CD4+ Count (cells / mm³)	511.5 (349.5; 737.8)
Undetectable Viral Load	91 (82.7)
CD4+ Count > 200cels. / mm³	102 (92.7)

Age expressed as average and standard deviation; disease and treatment times, and CD4+ counts expressed as median and interquartile range; other variables expressed in number of patients and percentage in parentheses. Source: Authors.

Frequencies of MI were 10.0% (CI 95%: 4.5 to 16.4), DD was 18.2% (CI 95%: 10.9 to 26.4), undetectable VL (< 40 copies/ml) was 82.7% and the CD4 + count above 200 cels/mm³ was 92.7% (95% CI: 87.3-97.2) (approximately 75% with values above 350 cels/mm³) were relevant; while systolic dysfunction was only 2.7% (CI 95%: 0.0 to 6.4).

3.2 HIV-infected patients with and without myocardial ischemia (MI)

Ischemic patients had an average age (55.4 ± 8.1 years) higher than non-ischemic patients (44.2 ± 11.6 years) with p = 0.002, with a difference between means of 11.2 ± 3.6 (95% CI: 4.1 to 18.3 years). There was also a higher females' frequency (54.5%) and following values for risk factors: SAH (45.5%), DLP (54.5%) and physical inactivity (90.9%) but with statistical significance only in the latter (p = 0.026).

There was a statistically significant difference between ischemic and non-ischemic subgroups' percentages (45.5% vs 15.2%; p = 0.027), over three times more occurrence of diastolic dysfunction among ischemic individuals; and a lower hypertension's frequency of hypertension in the non-ischemic group (19.2% vs 45.5%; p = 0.06), with difference between

averages of 26.3 ± 15.5 (95% CI -9.2 at 61.7) (Table 2).

Table 2. Comparison between ischemic and nonischemic patients living with HIV.

Characteristic	With ischemia (n=11)	Without ischemia (n=99)	P	Effect size
Age (years)	55.4±8.1	44.2±11.6	0.002	0.965
Women	06 (54.5)	28 (28.3)	0.091	0.245
Systemic Arterial Hypertension	05 (45.5)	19 (19.2)	0.060	0.275
Diabetes Mellitus	02 (18.2)	05 (5.1)	0.145	0.231
Dyslipidemia	06 (54.5)	24 (24.2)	0.067	0.295
Obesity	02 (18.2)	14 (14.1)	0.661	0.049
Smoking	04 (36.4)	37 (37.3)	1.000	0.009
Sedentary Lifestyle	10 (90.9)	55 (55.6)	0.026	0.312
Family History of Early Coronary Artery Disease	02 (18.2)	14 (14.1)	0.661	0.049
Left Ventricular Diastolic Dysfunction	05 (45.5)	15 (15.2)	0.027	0.343
CD4 + Count > 200 cells/mm³	591 (298-678)	506 (361-740)	0.670	0.286
Undetectable Viral Load	10 (90.9)	91 (92.9)	1.000	0.016

Age expressed as mean and standard deviation; other data expressed in absolute numbers and percentage in parentheses; p: statistical significance (Fisher's exact test, chi-square test and Student's t test). Source: Authors.

Analysis of factors associated with presence of MI in PLHIV was performed by logistic regression, at the beginning not adjusted, considering MI as dependent variable, with age, female gender, SAH, DM, DLP, obesity, FHECAD and occurrence of DD as independent variables (Table 3). These independent variables were listed either by fulfilling statistical criteria or by researcher's choice. Unadjusted odds ratio showed age is associated with presence of MI, as well as DLP. However, female sex, hypertension and sedentary lifestyle, whose odds ratios did not reach p less than 0.05, presented odds ratios and respective p values fulfilling criteria for entry into model to be adjusted (p-value less than or equal to 0.30 and odds ratio greater than or equal to 1.30). Likewise, it fulfilled the above criteria and included LVDD's occurrence.

Table 3. Unadjusted odds ratio for factors associated with presence of myocardial ischemia in patients with HIV.

Characteristic	Odds ratio	CI 95%	p
Age (years)	1.10	1.03 – 1.18	0.005
Women	3.04	0.86 – 10.8	0.085
Systemic Arterial Hypertension	3.51	0.97 – 12.7	0.056
Diabetes Mellitus	4.18	0.71 – 24.7	0.115
Dyslipidemia	3.75	1.05 – 13.4	0.042
Obesity	1.35	0.26 – 6.91	0.719
Family History of Early Coronary Artery Disease	1.35	0.26 – 6.91	0.719
Sedentary lifestyle	8.00	0.98 – 64.9	0.052
Smoking	0.94	0.258-3.44	0.928
Diastolic Dysfunction	4.85	0.40 – 58.3	0.213

Logistic regression, which the dependent variable is myocardial ischemia and other variables are independent; p: statistical significance (Fisher's exact test, chi-square test and Student's t test). Source: Authors.

In adjusted models, after the first one, independent variables were excluded at a time, generating different logistic regression models, to establish for which association with MI was suggested. It was observed only age variable presented a significant relation with MI, with an odds ratio of 1.1 (Table 4).

Table 4. Adjusted odds ratio for factors associated with myocardial ischemia in HIV patients.

Characteristic	Odds ratio	CI 95%	p
Age	1.10	1.03 – 1.18	0.005

Logistic regression, which the dependent variable is myocardial ischemia and other variables are independent; p: statistical significance (Fisher's exact test, chi-square test and Student's t test). Source: Authors.

3.3 HIV-infected patients with and without left ventricular diastolic dysfunction (LVDD)

Patients with HIV and DD had an average age (54.9 ± 9.5 years) higher than non-affected by this condition (43.2 ± 11.1 years) with p <0.0001, with difference between means of 11.7 ± 2.7 95% (CI 6.4 to 17.0 years); and greater participation of hypertensive (45%), diabetic (20%), obese (30%) and dyslipidemic (45%), but without significance for the last two cardiovascular risk factors (Table 5).

Table 5. Comparison between patients with and without diastolic dysfunction with HIV.

Characteristic	With diastolic dysfunction (n=20)	Without diastolic dysfunction (n=90)	p	Effect size
Age (years)	54.9 ± 9.5	43.2 ± 11.1	<0.0001	0.361
Male Gender	11 (55.0)	65 (72.2)	0.180	0.205
Systemic Arterial Hypertension	09 (45.0)	15 (16.7)	0.013	0.388
Diabetes Mellitus	04 (20.0)	03 (3.3)	0.020	0.386
Dyslipidemia	09 (45.0)	21 (23.3)	0.058	0.270
Obesity	06 (30.0)	10 (11.1)	0.072	0.299
Smoking	09 (45.0)	32 (35.5)	0.452	0.107
Sedentary Lifestyle	13 (65.0)	52 (57.8)	0.622	0.080
Family History of Early Coronary Artery Disease	03 (15.0)	13 (14.4)	1.000	0.009
Myocardial Ischemia	05 (25.0)	06 (6.7)	0.027	0.343
CD4 + Count > 200cels. / mm³	581 (388-673)	506 (328-798)	0.970	0.175
Undetectable Viral Load	20 (100)	81 (91)	0.208	0.201

Age expressed as average and standard deviation; other data expressed in absolute numbers and percentage in parentheses; p: statistical significance (Fisher's exact test, chi-square test and Student's t test). Source: Authors.

Considering DD as dependent variable and age, male gender, SAH, DM, DLP, obesity, FHECAD and occurrence of MI as independent variables, association between independent variables and presence of DD in HIV-infected patients was analyzed by logistic regression, initially not adjusted (Table 6). These independent variables were listed either by fulfilling statistical criteria or by the researcher's choice. Unadjusted odds ratio showed age is associated with the presence of DD, as well as hypertension, DM, obesity and MI. On the other hand, DLP, whose odds ratio did not reach p less than 0.05, presented an odds ratio and its p-value fulfilling criteria for entry into the model to be adjusted (p-value less than or equal to 0.30 and odds ratio greater than or equal to 1.30).

Table 6. Unadjusted odds ratio for factors associated with presence of diastolic dysfunction in HIV patients.

Characteristic	Odds ratio	CI 95%	p
Age (years)	1.11	1.05 – 1.18	<0.0001
Women	2.13	0.79 – 5.75	0.137
Systemic Arterial Hypertension	4.09	1.44 – 11.6	0.008
Diabetes Mellitus	7.25	1.48 – 35.5	0.015
Dyslipidemia	2.69	0.98 – 7.36	0.054
Obesity	3.43	1.07 – 10.9	0.037
Family History of Early CAD	1.03	0.26 - 4.02	0.96
Smoking	1.48	0.56-3.95	0.431
Highly Active Antiretroviral Therapy with Protease Inhibitor	2.05	0.76-5.51	0.154
Myocardial ischemia	4.67	1.26 – 17.3	0.021

Logistic regression, which the dependent variable is diastolic dysfunction and the other independent variables; p: statistical significance (Fisher's exact test, chi-square test and Student's t test). Source: Authors.

In adjusted models, after the first one, independent variables were excluded at a time, generating different logistic regression models, to establish an association with DD was suggested. There was a significant relationship of DD only with variables age and obesity, which presented odds ratios of 1.12 and 5.00, respectively (Table 7).

Table 7. Adjusted odds ratio for factors associated with diastolic dysfunction in patients with HIV.

Characteristic	Odds ratio	CI 95%	p
Age	1.12	1.06 – 1.20	<0.0001
Obesity	5.00	1.24 – 20.1	0.023

Logistic regression, which the dependent variable is diastolic dysfunction and the other independent variables; p: statistical significance (Fisher's exact test, chi-square test and Student's t test). Source: Authors.

Higher frequency of MI (14.7% vs 7.0%; p = 0.020) was observed when comparing the subgroup of seropositive patients over 40 years of age (total of 75 patients aged 41 to 73 years old) with the group of uninfected patients also aged over 40 years (total of 2,691 patients, ranging in age from 41 to 91 years), male gender (69.3% vs 48.9%; p = 0.001), and smoking (39.7% vs 4.40%; p <0.0001). However, there was a lower frequency of the following risk factors: SAH (28.0% vs 50.3%; p <0.0001) and DLP (32.0% vs 48.3%; p = 0.007) (Table 8).

Table 8. Comparative analysis of HIV patients and non-HIV individuals aged over 40 years.

Feature	HIV+ (n=75)	HIV- (n=2619)	p	Effect size
Age (years)	51.55 ± 7.75	58.8 ± 9.8	0.003	0.800
Male Gender	52 (69.3)	1282 (48.9)	0.001	0.095
Systemic Arterial Hypertension	21 (28.0)	1317 (50.3)	<0.0001	0.104
Diabetes Mellitus	07 (9.3)	279 (10.7)	0.850	0.010
Dyslipidemia	24 (32.0)	1265 (48.3)	0.007	0.076
Obesity	09 (12.0)	459 (17.5)	0.221	0.034
Smoking	30(39.7)	115 (4.4)	<0.0001	0.380
Myocardial Ischemia	11 (14.7)	183 (7.0)	0.021	0.069

Age expressed as mean and standard deviation; other data expressed in absolute numbers and percentage in parentheses; p: statistical significance (Fisher's exact test, chi-square test and Student's t test); HIV +: people living with HIV; HIV-: non-HIV-infected patients. Source: Authors.

3.4 Baseline clinical characteristics of people living with HIV

Laboratory data are shown in table 9. HIV infection is suppressed in most of patients evaluated. This was expressed by undetectable VL (< 40copy/ml) and lymphocytes CD4 + count above 200 cells/mm³. Furthermore, regarding metabolic profile of PLHIV group, it is evident significant majority of this sample shows a reduction of blood glucose, total cholesterol, LDL-cholesterol and triglyceride levels (by 60.0%), and an increase in HDL-cholesterol level (in 73.2%).

Table 9. Laboratory data of patients living with HIV.

Exams		n (%)
CD4+	**≥350**	82 (75.0)
	<350	28 (25.0)
Viral load	**Undetectable**	91 (82.7)
	Detectable	19 (17.3)
Blood glucose	**<100**	84 (76.4)
	≥100	26 (23.6)
Total Cholesterol	**≤200**	70 (63.6)
	>200	40 (36.4)
LDL	**≤130**	78 (70.9)
	>130	32 (29.1)
HDL	**≥40**	79 (71.8)
	<40	31 (28.2)
Triglycerides	**<150**	66 (60.0)
	≥150	44 (40.0)

Data expressed as number of patients and percentage in parentheses. Source: Authors.

3.5 Baseline clinical characteristics of non-HIV-infected patients

Sample of seronegative HIV patients consisted of 2,619 asymptomatic individuals with an average age of 58.8 ± 9.8 years, a minimum of 41 and a maximum of 91 years. There was a discreet higher frequency of females with 51.1%. Among the traditional risk factors for CAD, we found higher frequencies of hypertension (50.3%) and of DLP (48.3%) in practically half of the individuals; and lower frequency for smoking (4.4%) (Table 10).

Table 10. Characterization of non-HIV-infected patients (seronegative HIV).

Basal Characteristics	**N = 2.619**
Age (years)	58.8 ± 9,8
Women	1,337 (51.1)
Systemic arterial hypertension	1,317 (50.3)
Diabetes Mellitus	279 (10.7)
Dyslipidemia	1,265 (48.3)
Obesity	459 (17.5)
Smoking	115 (4.4)
Myocardial ischemia	183 (7.0)

Age expressed as mean and standard deviation; risk factors expressed as number of patients and percentage in parentheses. Source: Authors.

In another words, we observed that the frequencies of MI and DD are equally high in the group of patients with HIV, even at a lower average age and a lower frequency of risk factors for CAD, when compared to the other uninfected individuals. While logistic regression analysis, adjusted for factors associated with MI, shows a strong association only with age. In addition, regarding the dependent variable DD, it is suggested that age and obesity are the only associated factors, with caveats the sample size.

4. Discussion

The present study reveals HIV-infected patients had a lower average age (51.5 ± 7.7 vs 58.8 ± 9.8 years; p = 0.003) and lower frequencies of classic risk factors for CAD, especially hypertension (28.0% vs 50.3%; p <0.0001) and DLP (32% vs 48.3; p = 0.007). However, higher frequency was found for MI (14.7% vs 7.0%; p = 0.021) in relation to non-HIV-infected individuals. These findings are present even if HIV infection is under reasonable control (CD4 + count above 200 cells/mm³ and undetectable VL in most patients, besides use of HAART regimen). There are significant differences between the PLHIV group and the non-HIV-infected group. It suggests there is something more in HIV patients, which raises potential risk for coronary events, in contrast to the non-HIV group. However, it was observed a favorable adjusted odds ratio only for age. Literature really points to the fact such behavior is due to HIV infection and its treatment - ART use (Koenig, 2017; Lang *et al*., 2015; Vilela *et al*., 2011)-, with inflammation and immunological activation widely proven as HIV infection part, contributing to CAD emergence (Boettiger *et al*., 2020; Freiberg *et al*., 2013; Vachiat *et al*., 2017). In fact, a large cohort found a strong association of HIV-positive individuals along increased risk of MI, regardless of traditional risk factors (Katoto *et al*.,

2018; Silverberg *et al*., 2014).

Higher prevalence of smoking, DM, SAH and DLP in HIV patients is known to contribute to inflammation, as are co-infections that, in addition to this immune activation leading to inflammation, account for coagulation disorders (Freiberg *et al*., 2013). In this study, a high frequency of smoking (39.7% vs 4.4%; p <0.0001) among individuals living with HIV was found. Challenge for current medicine is to promote cardiovascular risk prevention in these patients, especially to reinforce the need for smoking cessation, taking into account genesis linked to multiple factors (Boettiger *et al*., 2020; Lang *et al*., 2015).

Evidence of satisfactory VL control (without treatment interruption), in parallel with elevation in blood glucose, total cholesterol, LDL-cholesterol and triglyceride levels, besides HDL-cholesterol level reduce, confirm the premise that HAART controls HIV infection at the expense of a worsening metabolic profile. However, the opposite was found in this study, with low blood glucose, total cholesterol, LDL-cholesterol and triglyceride levels, and high HDL-cholesterol level. In this respect, a question arises - studies such as SMART (Strategies for Management of Antiretroviral Therapy) show a large increase (in the range of 70%) in the risk of CVD in ART interruption, suggesting the need for continuous treatment to prevent HIV-associated inflammation and to reduce cardiovascular risk (Chihana *et al*., 2012; Longo-Mbenza *et al*., 1998). This fact also explains the reduced frequency of LV Systolic Dysfunction (only 2.7%) in our study for the group of patients with HIV, compared to prevalence of 35% in pre-HAART era (SMART, 2006).

Literature establishes HIV infection as a chronic condition in areas of wide HAART coverage (Baldassarre *et al*., 2007), allowing its association with an increase in non-immunodeficiency complications, notably CAD. High prevalence of traditional risk factors increases overall risk for CVD. Some studies estimate around 1.5 to 2.0 times general risk for this population (Triant *et al*., 2007; WHO, 2018).

Among HIV-infected patients, those with DD had a higher average age (54.9 ± 9.5 vs 43.2 ± 11.1 years; p <0.0001) and higher frequencies of risk factors for CAD, notably SAH (45%), DLP (45%), DM (20%) and obesity (30%) compared to those without DD, but with adjusted odds ratios favorable only for age and obesity. This fact suggests a probable participation also of metabolic syndrome in DD genesis, and not only MI process (Tavares *et al*., 2012), which in our study was present in a quarter of patients with DD.

Meanwhile, the subgroup of patients with HIV and without MI had a significant frequency of DD (15.2%) compared to low prevalence (1 to 7%) for DD in the general population (Almeida *et al*., 2018; Nagueh *et al*., 2016).

Long period of infection and HAART use seen in this population of HIV-infected patients reveals extensive exposure not only for the virus, but also to HAART regimens, which has been implicated in a more aggressive profile for development of atherosclerosis. Ninety-seven percent of patients in this study were using HAART, with 45.5% using Protease Inhibitors (PI), the class that most interfered with patients' metabolic profile (Gilbert, Fitch & Grinspoon, 2015). Prevalence of subclinical atherosclerosis in contrast to seronegative people, were not uniform, apart from there's an enormous absence of information about developing countries' situation. Previous studies imply HAART can cause DLP, SAH, endothelial dysfunction, particularly PI drugs (Ingle *et al*., 2014).

Regions of the globe with greatest poverty are still most affected, demanding a confrontation permeates production of scientific information (Senoner *et al*., 2019; Sinha & Feinstein, 2019). The evaluation of HIV infection in patients from northeast region of Brazil is essential to carry out public policy actions with elaboration, for example, of clinical protocols providing advanced preventive medical care for this particular population.

4.1 Study limitations

Patients' inclusion and, consequently, the sample size were limited due to spontaneous demand in outpatient clinics -

both due to availability and impossibility caused by health status. Socioeconomic condition was an impediment to displacement of many of these patients. Most of them are from Sergipe countryside; and even though they were Aracaju metropolitan area's residents, many patients were economically vulnerable. The fear of disclosing his identity was also a barrier to recruitment. In addition, it was seen a great resistance in successive stages, from questionnaires to exams. In order to contour these limitations, a satisfactory reception of patients was offer, including explanation about the ICF, confidentiality maintenance and benefits offered to them, especially to CVD prevention. Another limitation was several confounders' presence (such as DLP, which has ART itself as one of possible causes), which it will bring difficulties in defining atherosclerosis genesis in the PLHIV. Anyway, such limitations have been pointed out in other studies in same research area, complex interaction of factors in aforementioned genesis being a common argument, which still needs further clarification.

5. Conclusion

Myocardial ischemia occurred in HIV-infected patients with acceptable infection control and lower frequencies of the main risk factors for CAD, approximately twice as high as in non-HIV-infected individuals. Non-ischemic patients with HIV had a significant frequency of LVDD (more than twice) compared to healthy control individuals.

Moreover, additional and prospective studies that can follow PLHIV for a longer time are suggested to longitudinally verify the frequency of cardiovascular disorders, in addition to studies that can refine the presence of atherosclerosis in HIV-infected patients, without the presence of confounding events.

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