ORIGINAL ARTICLE

Self-reported HIV/HAART-associated Lipodystrophy and Modifiable Risk Factors for Cardiovascular Disease

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Abstract

Background: Patient self-report is the most common diagnostic tool in the literature to detect HIV/HAART-associated lipodystrophy. However, data on the association of cardiovascular risk factors with HIV/HAART-associated lipodystrophy assessed by self-report are still missing.

Objectives: To determine the prevalence of self-reported HIV/HAART-associated lipodystrophy and to identify independent associations between traditional modifiable cardiovascular risk factors and self-reported lipodystrophy.

Methods: We conducted a retrospective observational study at an outpatient infectious disease clinic in the Central-West of Brazil to identify the association between traditional modifiable cardiovascular risk factors and self-reported lipodystrophy. Sedentary lifestyle, smoking status, family history of cardiovascular disease, hypertension, diabetes, dyslipidemia, increased waist circumference and overweight were the cardiovascular risk factors assessed. Self-reported HIV/HART-associated lipodystrophy was categorized as: mild (noticeable by patients' close inspection), moderate (easily noticeable by patient and physician) or severe (readily noticeable by a casual observer). Prevalence ratio (PR) and 95% confidence interval (CI95%) were calculated. Multivariate Poisson's regression was used to analyze factors associated to HIV/HAART-associated lipodystrophy assessed by self-report considering a significance level of 5%.

Results: A total of 183 patients were included, with a mean age of 39.3±10.9 years. Most of the sample were male (77.6%), non-white (50.8%) and single (53.0%). The overall prevalence of HIV/HAART-associated lipodystrophy was 52.5% (95% CI 44.96 - 59.88). Severe lipodystrophy was observed in more than half patients (55.2%). No traditional modifiable cardiovascular risk factor was independently associated with lipodystrophy. Female sex (PR 1.49; 95% CI 1.15 – 1.95; p=0.003), time of HIV infection diagnosis of 1-3 years (PR 1.83; 95% CI 1.09 - 3.08; p=0.002) and a positive family history of CVD (PR 1.62; 95% CI 1.11 - 2.36; p<0.001) were independently associated with lipodystrophy.

Conclusion: HIV/HAART-associated lipodystrophy assessed by patient self-report was not associated with traditional modifiable cardiovascular risk factors. (Int J Cardiovasc Sci. 2020; 33(6):606-615)

Keywords: Retroviridae; Antivirals/therapeutic use; Cardiovascular Diseases/complications; Risk Factors; Metabolic Diseases/complications; Lipodystrophy.

Introduction

Antiretroviral therapy (ART) has significantly increased the survival and quality of life of people living with HIV/AIDS. Since the introduction and widespread use of combination ART, referred to as highly active antiretroviral therapy (HAART), HIV-related mortality has been reduced from 50 to 80%.[1] However, the long-term use of ARTs has been associated with metabolic abnormalities, including increased serum lipids, glucose, and insulin resistance. The combination of these disorders leads

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to a highly atherogenic profile, increasing the risk of cardiovascular disease (CVD).[2]

The interaction between host factors, HIV, and HAART is strongly associated with the accumulation or loss of body fat in specific body sites,[3] which has been identified as lipodystrophy.[4] Lipodystrophy is characterized by fat redistribution, with subcutaneous fat loss (lipoatrophy), mainly in the face, limbs, and buttocks, or fat accumulation (lipohypertrophy) in the abdomen, breast or posterior neck, or a combination of both.[4] The HIV-associated body fat redistribution in individuals receiving ART (HIV/HAART-associated lipodystrophy) by itself is associated to dyslipidemia and hypertriglyceridemia, low-HDL-cholesterol, reduced insulin sensitivity, and diabetes.[5] Subjects with HIV/HAART-associated lipodystrophy may have increased Framingham risk scores and higher coronary calcium scores and thus are at increased risk of coronary heart disease.[6,7]

The most common diagnostic tool reported in the literature to detect HIV/HAART-associated lipodystrophy is the self-reported body fat distribution.[8-10] It is an accurate, reproducible and easy-to-implement method, adding almost no costs to the usual care of HIV/AIDS patients.[10-12] Despite the common use of patients' self-reported methods to identify lipodystrophy, to our knowledge, there are no available data on the association of cardiovascular risk factors and HIV/HAART-associated lipodystrophy assessed exclusively by this method. Therefore, we assessed subjects attending an HIV/AIDS outpatient care center of a capital city in Brazil (a middle-income country) to determine the prevalence of self-reported HIV/HAART-associated lipodystrophy and possible independent associations between traditional modifiable cardiovascular risk factors and self-reported lipodystrophy.

Materials and methods

Study design and ethical aspects

This is a retrospective observational study conducted at the Outpatient Clinic of Infectious and Parasitic Diseases in Goias State, Brazil. Methodological details have been published elsewhere, since this is part of a large epidemiological study.[13-15] Data collection occurred between October 2009 and July 2011. The study was approved by the Research Ethics Committee under the approval number 163/2009.

Inclusion and exclusion criteria

Inclusion criteria were age ≥ 19 years, HIV infection and HAART. All patients willing to participate signed the informed consent form.

Pregnant and lactating women, subjects with an opportunistic infection diagnosed less than two months before recruitment or longer but without clinical resolution within that period, and those with cognitive incapacity to fulfill the self-perception instrument were excluded.

Data collection

Patients who met eligibility criteria to participate in the study were invited to participate. A multidisciplinary team with cardiologist, nutritionists, and undergraduate students of health sciences composed the research group. Data collection on sociodemographic, clinical and smoking status variables occurred during the interview with the cardiologist. Subsequently, the cardiologist referred the patients to a nutritionist, who applied an interview on self-perception of changes in body composition, alcohol consumption and physical activity level. Finally, trained investigators performed the anthropometric assessment of the patients.

Sociodemographic data collection

Sociodemographic variables (age, gender, skin color, income, marital status and schooling years) were assessed using a pre-tested standardized questionnaire.

Age was stratified in four categories: 19-29, 30-39, 40-49 and ≥ 50 years. Skin color was defined as white or non-white. Number of schooling years was divided in four groups: ≤ 4 years, 5-8 years, 9-11 years and ≥ 12 years. Marital status was defined as single, married and widow/divorced.

The income in the previous month was clustered into quartiles (1st quartile ≤ U$ 170.00; 2nd quartile from U$ 170.01 to U$ 240.00; 3rd quartile from U$ 240.01 to U$ 400.00 and 4th quartile ≥ U$ 400.01).

HIV-related clinical and laboratorial data

Clinical characteristics were time since diagnosis of HIV infection, duration of ART use and class of antiretroviral drug (nucleoside reverse-transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI).

The time since HIV diagnosis and the time of ART use were calculated based on the difference in years from the date of data collection and both events dates informed by the patient. Both variables were categorized in: <1 year, 1-3 years and >3 years. Information on CD4 T + lymphocytes count and viral load were obtained from the patient's medical chart, as these tests are performed routinely in the outpatient clinic. CD4 count was determined by flow cytometry and viral load by branched DNA (bDNA) assays for HIV-1 (Versante HIV-1 RNA 3.0 assay). CD4+ lymphocyte count (cells/mm3) was classified as ≤350 and >350.[14]

Biochemical tests

Biochemical tests were performed after 12 hours fasting and no alcohol consumption for at least three days. The enzymatic colorimetric method was used to determine total cholesterol (TC), HDL-cholesterol (HDL), serum triglycerides (TG) and blood glucose. The LDL-cholesterol (LDL) level was estimated with the Friedewald formula: LDL = TC - (HDL + TG/5)[16].

Anthropometric measurements

Anthropometric measurements were collected following standardized techniques,[16,17] and researchers were trained to make precise and accurate measurements.[18] To measure body weight, a digital scale with 150 kg capacity and 100 g accuracy was used (Tanita BC-558 Ironman). Height was measured to the nearest 0.1 cm with a 150 cm length non-elastic tape, at 50 cm from the ground, fixed to a wall without a baseboard. Patients were instructed to be barefooted during weight and height measurements.

BMI was calculated as weight (kg) divided by the square of height (m^2). Nutritional status was classified as: 1) underweight or normal weight (BMI < 18.5 kg/m^2 and between 18.5–24.9 kg/m^2, respectively); 2) overweight (BMI between 25.0-29.9 kg/m^2); and 3) obesity (BMI ≥ 30.0 kg/m^2).

Waist circumference (WC) was measured at the largest extension of the abdomen in a horizontal plane with a non-elastic measuring tape. Values of less than 80 cm for women and 94 cm for men were considered normal.

Cardiovascular risk factors

The short version of the International Physical Activity Questionnaire (IPAQ) was used to assess physical activity level. Subjects who reached ≥ 600 MET-min/week score were considered physically active, corresponding to 30 minutes of moderate physical activity five days a week, a total of 150 min/week. Subjects with score <600 MET-min/week were considered sedentary.[19]

Smoking status was investigated according to the Pan American Health Organization (OPAS—Organización Panamericana de la Salud)[20]. "Smoker" was defined as a current smoker or who had quit smoking for less than six months; "former smoker" who had quit smoking for more than six months; and "nonsmoker" who had never smoked.

Family history of cardiovascular disease is a non-modifiable risk factor for CVD. It was assessed by patient report and considered positive if an early event has happened in a first-degree relative (males before 55 years and females before 65 years)[21].

Subjects with systolic blood pressure (BP) ≥ 140 mmHg and diastolic BP ≥ 90 mmHg (mean of three office measurements) and/or on treatment were considered hypertensive.[22]

Diabetes was defined when fasting blood glucose was ≥ 126 mg/dl and/or on treatment.[23]

Dyslipidemia was defined when the cutoff points for TC, LDL-c, TG and/or HDL-c were met and/or on lipid lowering drugs. The cutoff points were: TC ≥ 200 mg/dL, LDL-c ≥ 160 mg/dL, TG ≥ 150 mg/dL, and HDL-c <40 mg/dL in men and <50 mg/dL in women.[24]

Increased WC was defined as ≥ 80 and <88 cm for females and ≥ 94 and <102 cm for males; and greatly increased when ≥ 88 cm in women and ≥ 102 cm in males.[21] These two categories were grouped for analysis.

BMI ≥ 25.0 kg/m^2 was considered as a cardiovascular risk factor.[21]

HIV/HART-associated lipodystrophy

A standardized, self-reported questionnaire was used to evaluate lipodystrophy.[13,25,26] First, patients were asked if their body appearance changed since the initiation of HIV treatment. If not, the degree of body fat redistribution was rated as absent and, if the answer was positive, HIV/HART-associated lipodystrophy was rated as present. Lipodystrophy was than categorized as: mild (noticeable by patients' close inspection), moderate (easily noticeable by patient and physician) or severe (readily noticeable to a casual observer).

Sample calculation and statistical analyses

The sample size was calculated with the software Epi-Info 3.0, with a confidence level of 95% and 80% power; 150 patients would be required to study the associations between lipodystrophy and cardiovascular risk factors.

The dataset was structured in Epi-Data 3.1 with double entrance to avoid inconsistencies. Statistical analyses were performed with the software Stata 12.0. Absolute and relative frequencies were estimated. Pearson's chi-squared test was used to study sex differences regarding the prevalence of lipodystrophy and its severity. The simple Poisson regression was used to calculate prevalence ratio (PR), 95% confidence interval (CI95%) and *p* values. All variables with a p-value ≤ 0.20 in simple regression were included in multivariate Poisson's regression analyses in three hierarchical levels as follow: 1st level – sociodemographic data; 2nd level - HIV-related clinical and laboratorial data; 3rd level – cardiovascular risk factors; and 4th level – anthropometric data. Variables that remained with a p < 5% after the adjustments were kept in the final regression model. The Wald`s test was used to measure the significance level of each Poisson coefficient, in both simple and multivariate regressions. It is a test similar to the chi-squared test and is the standard test of the Poisson regressions in the statistical package used. Statistical significance was established at 5%.

Results

A total of 183 patients met eligibility criteria and were included in this study, with a mean age of 39.3 ± 10.9 years. The prevalence of HIV/HAART-associated lipodystrophy in the overall sample was 52.5% (96/183). Most of the sample was male (77.6%), non-white (50.82%) and single (53.0%); sociodemographic characteristics of the sample as well as the prevalence of lipodystrophy by subgroups are described in Table 1. There was a significantly higher percentage of female subjects with lipodystrophy (*p*=0.003).

The distribution of the different levels of lipodystrophy is presented in Figure 1. No differences were observed between males and females (Table 1). Severe lipodystrophy was observed in more than half of the individuals (55.2%).

When we assessed the prevalence of HIV/HAART-associated lipodystrophy by HIV-related clinical and laboratorial variables, a higher prevalence of lipodystrophy (66.7% - PR 1.88; 95% CI 1.12 – 3.14; *p*=0.025) was observed among those with a time of diagnosis of HIV infection between 1 and 3 years. No other HIV-related clinical or laboratorial data evaluated were associated with lipodystrophy. All patients were using NRTI (Table 2).

The prevalence of HIV/HAART-associated lipodystrophy was assessed by the presence of cardiovascular risk factors. In this analysis, lipodystrophy was associated with a family history of CVD (PR 1.70; 95% CI 1.22 – 2.39; *p*=0.002) and increased/greatly increased WC (PR 1.39; 95% CI 1.06 – 1.82; *p*=0.018), as shown in Table 3.

After including the clinical and laboratorial HIV-related variables, and the cardiovascular risk factors in the model, female sex, 1-3 years of HIV infection diagnosis and a positive family history of CVD remained associated with lipodystrophy in the multiple regression analysis (Table 4).

Discussion

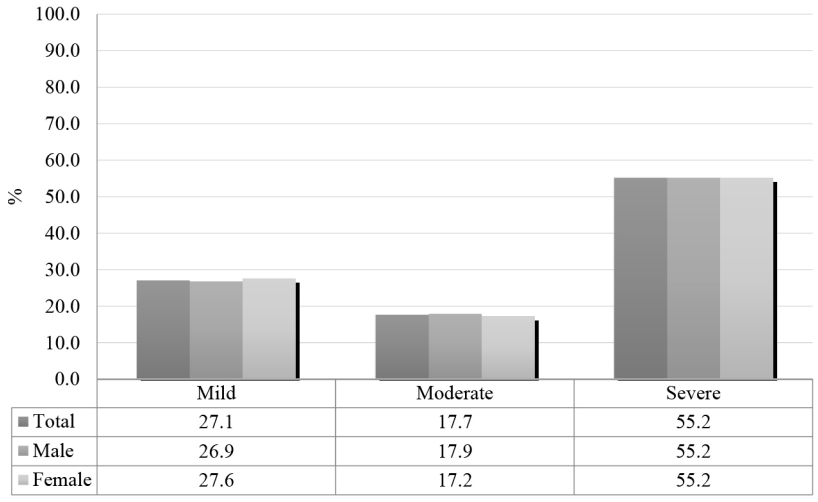
In a relatively large group of patients living with HIV/AIDS receiving HAART, the prevalence of HIV/HAART-associated lipodystrophy assessed exclusively by patient self-report was 52.5%. Most of these patients (55.2%) reported their lipodystrophy as severe, as opposed to mild or moderate. HIV/HAART-associated lipodystrophy was independently associated with female sex, 1-3 years of HIV infection diagnosis and a positive family history of CVD.

No association was found between self-reported HIV/HAART-associated lipodystrophy with traditional modifiable cardiovascular risk factors. In contrast, marked elevation of cardiovascular risk factors in HIV-infected patients with fat redistribution was previously reported by Hadigan *et al.*,[27] Some differences between the two studies need to be discussed. In the study by Hadigan *et al.*,[27] the population was older, had a longer time of HIV infection diagnosis and longer ART exposure. Additionally, and most importantly, the presence of lipodystrophy was determined by examiners rather than self-report. A difference in time course, considering ART prescriptions, between the two studies needs to be highlighted as well. In the last decade efforts have been made to reduce the use of drugs that are more strongly related to lipodystrophy such as stavudine and zidovudine and increase prescriptions of better tolerated drugs,[12] changing the

Table 1 – Prevalence of HIV/HAART-associated lipodystrophy assessed by self-report and associated sociodemographic factors

Variables	Total		Lipodystrophy prevalence				p-value*
	n	%	n	%	PR	95% CI	
Sex							0.003
Male	142	77.60	67	47.18	1.00		
Female	41	22.40	29	70.73	1.50	1.15 – 1.95	
Age							0.952
19-29 years	35	19.13	18	51.43	1.01	0.67 – 1.52	
30-39 years	61	33.33	32	52.46	1.03	0.73 – 1.46	
40-49 years	59	32.24	30	50.85	1.00		
≥50 years	28	15.30	16	57.14	0.51	0.75 – 1.69	
Skin color							0.598
White	90	49.18	49	54.44	1.07	0.82 – 1.42	
Non-white	93	50.82	47	50.54	1.00		
Schooling (years)							0.808
≤4 years	30	16.39	18	60.00	1.20	0.79 – 1.81	
5-8 years	42	22.95	22	52.38	1.05	0.70 – 1.58	
9-11 years	65	35.52	33	50.77	1.01	0.70 – 1.48	
≥12 years	46	25.14	23	50.00	1.00		
Marital Status							0.434
Single	97	53.01	50	51.55	1.07	0.76 – 1.52	
Married	50	27.32	24	48.00	1.00		
Widowed/Divorced	36	19.67	22	61.11	1.27	0.86 – 1.88	
Monthly income							0.864
1st quartile	59	32.24	31	52.54	1.07	0.74 – 1.55	
2nd quartile	35	19.13	18	51.43	1.05	0.68 – 1.61	
3rd quartile	51	27.87	25	49.02	1.00		
4th quartile	38	20.77	22	57.89	1.18	0.79 – 1.74	

*PR: prevalence ratio; 95% CI: 95% confidence interval. *Wald's Test.*



	Mild	Moderate	Severe
Total	27.1	17.7	55.2
Male	26.9	17.9	55.2
Female	27.6	17.2	55.2

Figure 1 – Distribution of patients with HIV/HAART-associated lipodystrophy by severity levels assessed by self-report (n=96)

lipodystrophy patterns over time.[28,29] Individuals in the study by Hadigan et al.,[27] were assessed in 2000, therefore not subject to this new prescription pattern, while our study was conducted in 2009.

The decision to use a self-report method alone instead of using evaluations performed by healthcare providers or combined methods relied on the fact that body changes related to HIV/HAART-associated lipodystrophy are more likely to be noticed by the patients themselves and their families, then by third parties.[30] This situation is particularly relevant in the HIV/AIDS clinics of Brazil and other developing countries, where the healthcare provided is mainly public, with high staff rotation in different work shifts. Therefore, the patient is rarely followed by the same physician throughout time. Moreover, the self-report method plays an important role in lipodystrophy diagnosing, since it is validated, low-cost for implementation, and widely applicable, especially in low-income countries.[10]

This study shared similarities with other studies regarding HIV/HAART lipodystrophy. The prevalence of HIV/HAART-associated lipodystrophy can range from 9% to 83%,[31] and depends on the criteria adopted for the diagnosis and on the characteristics of the studied population. Studies where lipodystrophy was assessed, either by a self-report method alone or by a combination of self-report method and observer evaluation, found a prevalence ranging from 45.9% to 64.3%,[11,12,32,33] which is similar to the 52.5% found in the present study.

Other similarities in the clinical characteristics of our population compared with other studies on HIV/HAART-associated lipodystrophy were found, such as a higher prevalence of lipodystrophy in females and patients living with HIV for a relatively longer time.[34-37] The higher prevalence of lipodystrophy among women might be explained by the higher body fat percentage in females when compared to males,[38] enabling a more noticeable fat redistribution related to the HAART. Additionally, women may have a better self-perception of body changes[39] than men.

Lipodystrophy prevalence was higher in patients living with HIV for 1 to 3 years. Since there is a dose-response relationship between the time of ART and lipodystrophy,[40] one would expect that the longer the HIV infection time, the higher the prevalence of lipodystrophy. Since the time of diagnosis does not necessarily coincide with treatment initiation, and ART time was not shown to be associated with lipodystrophy prevalence in our analysis, further investigations addressing exclusively the initiation time of ART are necessary.

Our study has some limitations. Despite the fact that lipodystrophy represents a continuum of fat redistribution over time, the study had a cross-sectional design, which allowed this temporal perspective. No control group was used for comparison. Also, no other method for the diagnosis of lipodystrophy was used for comparison with the self-reported method.

This study provides an important contribution to the knowledge of HIV/HAART-associated lipodystrophy identified by patient self-report. To our knowledge, this is the first time that this diagnostic approach was assessed focusing on associations between lipodystrophy and

Table 2 – Prevalence of HIV/HAART-associated lipodystrophy assessed by self-report and HIV-related clinical and laboratorial variables

Variables	Total		Lipodystrophy prevalence				p-value*
	n	%	n	%	PR	95% CI	
CD4 lymphocyte count							0.564
≤ 350 cells/mm^3	64	36.36	36	56.25	1.09	0.82 – 1.44	
> 350 cells/mm^3	112	63.64	58	51.79	1.00		
Time of HIV infection diagnosis							0.025
< 1 year	31	18.24	11	35.48	1.00		
1 - 3 years	51	30.00	34	66.67	1.88	1.12 – 3.14	
> 3 years	88	51.76	45	51.14	1.44	0.86 – 2.42	
ART time							0.131
< 1 year	58	35.58	25	43.10	1.00		
1 - 3 years	41	25.15	26	63.41	1.88	1.01 – 2.14	
> 3 years	64	39.26	36	56.25	1.31	0.90 – 1.88	
Drug classes							
NRTI							-
Yes	173	100.00	93	53.76		-	
No	0	0.00	0	0.00			
NNRTI							0.436
Yes	133	76.88	69	51.88	1.00		
No	40	23.12	24	60.00	1.16	0.85 – 1.56	
PI							0.799
Yes	47	27.17	26	55.32	1.04	0.77 – 1.41	
No	126	72.83	67	53.17	1.00		

*PR: prevalence ratio; 95% CI: 95% confidence interval; ART: antiretroviral therapy. *Wald's Test. NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor*

traditional cardiovascular risk factors. Future studies using the same methodology in different clinical contexts are necessary to continue developing this accessible, accurate, reproducible and easy-to-implement tool.[10-13]

Conclusion

HIV/HAART-associated lipodystrophy assessed by patient self-report was not associated with traditional modifiable cardiovascular risk factors in HIV/AIDS patients attending an outpatient care center in a capital city of a middle-income country.

Author contributions

Conception and design of the research: Jardim T, Cardoso RC, Silveira EA. Acquisition of data: Cardoso RC, Santos ASAC, Falco MO, Silveira EA. Analysis and interpretation of the data: Jardim T, Cardoso RC, Santos ASAC. Statistical analysis: Santos ASAC, Silveira EA. Obtaining financing: Falco MO, Silveira EA. Writing of the manuscript: Jardim T, Cardoso RC, Santos ASAC, Falco MO, Silveira EA. Critical revision of the manuscript for intellectual content: Jardim T, Cardoso RC, Santos ASAC, Falco MO, Silveira EA.

Table 3 – Prevalence of HIV/HAART-associated lipodystrophy assessed by self-report and cardiovascular risk factors

Variables	Total		Lipodystrophy prevalence				p-value*
	n	%	n	%	PR	CI 95%	
Sedentary lifestyle							0.087
No	105	57.38	61	58.10	1.29	0.96 – 1.74	
Yes	78	42.62	35	44.87	1.00		
Smoking							0.646
No	89	48.63	44	49.44	1.00		
Yes	49	26.78	26	53.06	1.07	0.77 – 1.50	
Former smoker	45	24.59	26	57.78	1.17	0.84 – 1.62	
Family history of CVD							0.002
No	173	96.11	87	50.29	1.00		
Yes	7	3.89	6	85.71	1.70	1.22 – 2.39	
Hypertension							0.230
No	166	90.71	85	51.20	1.00		
Yes	17	17	11	64.71	1.26	0.86 – 1.85	
Diabetes							0.905
No	177	96.72	93	52.54	1.05	0.46 – 2.37	
Yes	6	3.28	3	50.00	1.00		
Dyslipidemia							0.132
No	65	35.52	29	44.62	1.00		
Yes	118	64.48	67	56.78	1.27	0.93 – 1.74	
Waist circumference							0.018
Normal	123	71.93			1.00		
Increased or very increased	48	28.07			1.39	1.06 -1.82	
Overweight							0.306
No	122	71.35	62	50.82	1.00		
Yes	49	28.65	29	59.18	1.16	0.87 – 1.56	

*PR: prevalence ratio; 95% CI: 95% confidence interval. CVD: cardiovascular disease. *Wald's Test.*

Table 4 – Multivariate Poisson's regression analysis of factors associated with HIV/HAART-associated lipodystrophy assessed by self-report

Variables	Lipodystrophy		p-value*
	[a]PR	95% CI	
Sex			0.003
Male	1.00		
Female	1.49	1.15 – 1.95	
Time of HIV infection diagnosis			0.002
< 1 year	1.00		
1 - 3 years	1.83	1.09 – 3.08	
> 3 years	1.39	0.83 – 2.33	
Family history of CVD			<0.001
No	1.00		
Yes	1.62	1.11 – 2.36	

*[a]PR: adjusted prevalence ratio; 95% CI: 95% confidence interval; CVD: cardiovascular disease. *Wald's Test.*

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Rodrigo de Castro Cardoso, from *Universidade Federal de Goiás*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital de Clínicas da Universidade Federal de Goiás* under the protocol number 163/2009. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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