Anthropometric measures of central adiposity are highly concordant with predictors of cardiovascular disease risk in HIV patients

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ABSTRACT

Background: Body fat redistribution and metabolic abnormalities found in HIV patients receiving highly active antiretroviral therapy (HAART) contribute to an atherogenic profile, increasing cardiovascular disease risk.

Objective: We aimed to evaluate adiposity measures/indexes and propose cutoffs associated with predictors of cardiovascular disease risk in HIV patients on HAART.

Design: To evaluate cardiovascular disease risk in this cross-sectional study, we conducted electrocardiogram exams and stress electrocardiography, measured the ankle brachial index and blood pressure arterial hypertension, conducted lipid biochemical tests, and measured blood glucose. We measured circumferences [waist (WC), hip, thigh, calf, neck, trunk] and skinfold thicknesses (biceps, triceps, subscapular, suprailiac), conducted bioelectrical impedance analysis (BIA), and calculated indexes [body mass index, waist-to-hip ratio, waist-to-thigh ratio, waist-to-calf ratio, waist-to-height ratio (WHtR), trunk-to-arm ratio, body mass index corrected for body fat mass, Body Adiposity Index, conicity index, body shape index, fat mass (percentage), and phase angle]. For evaluating the performance of all adiposity measures/indexes, we used receiver operating characteristic (ROC) curves.

Results: Measures of central adiposity WC and WHtR showed the best performances—WC area under the curve (AUC) for men: 0.83 (95% CI: 0.78, 0.89; $P < 0.05$); WC AUC for women: 0.86 (95% CI: 0.81, 0.91; $P < 0.05$); WHtR AUC for men: 0.83 (95% CI: 0.78, 0.88; $P < 0.05$); and WHtR AUC for women: 0.85 (95% CI: 0.80, 0.91; $P < 0.05$). All adiposity measures/indexes presented different cutoffs from those proposed for the HIV seronegative population. The cutoffs for WC were 87.75 cm (sensitivity: 82.2%; specificity: 75.5%) for men and 90.5 cm (sensitivity: 84.0%; specificity: 73.0%) for women.

Conclusions: The measures/indexes of central adiposity presented excellent associations with predictors of cardiovascular disease risk, and the use of the cutoffs proposed in the present study aims to contribute to the early identification of increasing risk of cardiovascular diseases, enabling interventions. This trial was registered at the Brazilian clinical trials registry Registro brasileiro de ensaios clínicos (Rebec) as RBR-9rcxbq. *Am J Clin Nutr* 2018;107:883–893.

Keywords: cardiovascular disease risk, HIV, lipodystrophy, anthropometry, adiposity indexes, cutoffs

INTRODUCTION

Highly active antiretroviral therapy (HAART) brings unquestionable benefits to HIV patients, increasing their survival rates (1). However, there are some specific toxicities of this therapy, including morphologic changes (central adiposity increase and peripheral adiposity loss) and lipid and glucose metabolism alterations (2). The set of metabolic changes characterizes an atherogenic profile, contributing to the development of cardiovascular diseases (3).

Cardiovascular diseases are the causes of death for many patients currently. The D:A:D study (Data Collection on Adverse Events of Anti-HIV Drugs) is one of the largest databases of cardiovascular disease risk factors with 33,308 HIV patients. During the 10-y period, 289 of 2482 deaths were related to cardiovascular disease (rate of 1.60 deaths/1000 person-years) (4).

Adipose tissue is the major trigger of metabolic changes and development of chronic diseases and its redistribution is the key to the metabolic changes. The determination of body composition/distribution is broadly important in clinical practice, mainly due to the association of body fat and risk of cardiovascular diseases. Thus, this is crucial in the HIV population (5, 6).

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Abbreviations used: ABI, ankle brachial index; ABSI, A Body Shape Index; ART, antiretroviral therapy; BAI, Body Adiposity Index; BIA, bioelectrical impedance analysis; FRS, Framingham risk score; HAART, highly active antiretroviral therapy; NC, neck circumference; TAR, trunk-to-arm ratio; TC, total cholesterol; TrC, trunk circumference; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WTR, waist-to-thigh ratio.

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Anthropometry and bioelectrical impedance analysis (BIA) are simple, affordable, and noninvasive methods that can be used in clinical practice to classify patients according to their risk of diseases related to fat excess/redistribution (7). The adiposity indexes are divided between total fat evaluation and fat distribution evaluation (8).

Currently BMI is globally the most widely used adiposity index in the body composition area. However, it is an imperfect measure of adiposity (9). Seeking to overcome the limitations of the BMI, the Body Adiposity Index (BAI) and A Body Shape Index (ABSI) have been proposed (10, 11).

The measures/indexes of central adiposity include: waist circumference (WC), waist-to-height ratio (WHtR), and conicity index (calculated from the waist circumference (meters), divided by the square root of the body weight ratio (kilograms) divided by height (meters), multiplied by the factor 0.109] (12). And the anthropometric tools that assess body fat redistribution include the waist-to-hip ratio (WHR), waist-to-thigh ratio (WTR), trunk-to-arm ratio (TAR), and waist-to-calf ratio (13).

There is a positive correlation between neck circumference (NC) and trunk circumference (TrC) with factors related to metabolic syndrome (14).

Several researchers have studied the use of fat measures/indexes and associated cutoffs for their specific populations to evaluate metabolic changes/cardiovascular disease risk, but their use in the HIV patient population is still understudied (15–18). The studies have found different cutoff values from those proposed by the WHO and the International Diabetes Federation. However, no previous study to our knowledge has evaluated the performance of adiposity indexes in identifying cardiovascular disease risk in HIV patients.

As gain and changes in the distribution of body fat significantly increase morbidity and mortality risk in HIV patients on HAART, early identification of risk for cardiovascular disease development through the use of available, reliable, and practical methods is fundamental. On this basis, the aim of this study was to compare the effectiveness of all adiposity measures/indexes to associate it with predictors of cardiovascular disease risk in HIV patients on HAART and to propose specific cutoffs.

METHODS

This is an analytical cross-sectional study. It was conducted at the Outpatients Clinics of Ribeirão Preto Medical School (HC/FMRP) University Hospital, Sao Paulo, Brazil.

Inclusion criteria were as follows: age between 18 and 60 y, stable HIV patients (no signs or symptoms of opportunistic infections), use of HAART, and stable weight (<10% change during the last year).

Exclusion criteria were as follows: presence of edema, thyroid disease, chronic renal insufficiency, pulmonary disease, hepatic alterations, signs or symptoms of opportunistic infections, and presence of a pacemaker or a metal prosthesis.

All individuals who fulfilled the inclusion criteria from April 2014 to January 2016 were invited to participate in the study.

The Research Ethics Committee of the institution (HCRP protocol no. 17484/2013) approved the study and all volunteers gave written informed consent to participate.

Information about use of hypolipidemic and hypoglycemic drugs, currently used antiretroviral medications, and biochemical examinations was obtained (viral load and T CD4 cells).

Anthropometric indicators

At the same meeting all body composition evaluation was performed by a trained staff of 3 researchers. Patients removed all metal accessories and wore light clothing. They emptied the bladder and avoided the practice of rigorous physical activity in the previous 12 h and consumption of alcohol in the 24 h before the assessment.

Body weight was measured with an electronic Filizola scale of the platform type with a maximum capacity of 300 kg and precision of 0.1 kg. A stadiometer with 0.1-cm precision was used to measure height. BMI was calculated as kg/m^2.

The circumference measurements were performed with the use of a metal measuring tape (Sanny Brazil), accurate to 0.1 cm and maximum length of 2 m.

WC was performed midway between the inferior margin of the last rib and the ilium crest in a horizontal plane. Hip circumference was performed in the region of largest circumference between the waist and the thigh. Thigh circumference was performed at the end of the right gluteus (19). Calf circumference was measured at the height of the largest circumference of the right calf with the individual sitting and the legs flexed at 90 degrees (19). NC was measured on the upper margin of the thyroid cartilage (20). TrC was measured from the back of the trunk, 3 cm below the armpit, with the arms attached to the body. The tape measure was positioned on a horizontal line, and the entire circumference around the chest was measured (21).

The skin folds were measured with the Lange Skinfold Caliper (Beta Technology Incorporated, Cambridge, MD) adipometer in triplicate on the right side.

Bicipital skinfold was performed at the same midpoint used for the measurement of arm circumference: the arm fold was separated slightly, detached from muscle tissue, and the caliper was applied at a right angle. The subject's arm remained relaxed and hung by the side of the body (19). Tricipital skinfold was performed with the palm of the hand turned outwards; the measurement site was marked 1 cm above the site marked for the triceps fold. The calibrator was applied at the marked location, holding the fold vertically (19). Suprailiac skinfold was detached in the oblique position, on the axillary midline at the point where it lies above the iliac crest (19). To measure the subscapular skinfold the skin was raised 1 cm below the lower angle of the scapula, observing a 45-degree angle between the scapula and the vertebral column. The caliper was applied to the individual with their arms and shoulders relaxed (19).

Calculation of the indexes BMI, WHR, WTR, waist-to-calf ratio, TAR (13), WHtR, BMI corrected by fat mass (22), BAI (10), and conicity index (23) was performed according to definitions present in previous studies.

BIA was performed with the RJL SYSTEM (RJL Systems, Detroit, MI) instrument, applying a current of 50 kHz. The values of Resistance (R) and Reactance (Xc) in ohms were used to calculate fat mass and fat free mass by the Kotler equation (24). We also calculated the phase angle by the equation: $(Xc/R) \times (180°/\Pi)$ (25).

Blood analysis

Lipid [triglyceride, total cholesterol (TC), and HDL cholesterol] concentrations were measured by the enzymatic colorimetric method on a COBAS INTEGRA 400 instrument (Roche

Diagnostics, Indianapolis, IN) in the blood. LDL cholesterol was calculated with the Friedewald formula [LDL = TC – (TGs/5 + HDL)]. Plasma glucose was analyzed with a Yellow Springs Instruments 2300 STAT Glucose Analyzer (Yellow Springs Instruments Inc., Yellow Springs, OH).

Metabolic changes

For evaluating the metabolic changes, we used the criteria proposed by the National Cholesterol Education Program III (NCEP-ATP III) (TC ≥220 mg/dL, TGs ≥150 mg/dL, HDL cholesterol ≤40 mg/dL, LDL cholesterol ≥130 mg/dL or treatment for dyslipidemia; fasting glycemia ≥100 mg/dL or treatment; systolic blood pressure ≥130 mm Hg and diastolic blood pressure ≥85 mm Hg or treatment for hypertension; WC ≥88 cm for women and ≥102 cm for men) (26).

Electrocardiogram and stress electrocardiography

The resting electrocardiogram and stress electrocardiography tests were performed at the Cardiology Department of the Outpatients Clinics of Ribeirão Preto Medical School—USP. The ramp treadmill test was performed according to a standard protocol (27). This protocol allows adjustments in the inclination and velocity of the treadmill based on age in order to achieve a submaximal heart rate in ≥90% of the exams. A Micromed M200 treadmill controlled by a computerized system ERGO PC 13 (Micromed, Brazil) was used in all patients. Resting heart rate, blood pressure, and electrocardiography were recorded in the supine and upright positions before the test. Heart rate, blood pressure, and electrocardiography were recorded every minute throughout the test. The exercise protocol was discontinued if exertional hypotension, malignant ventricular arrhythmias, marked ST depression, or limiting chest pain were reported or at exhaustion. A single cardiologist analyzed all tests. The Duke treadmill score was calculated as previously reported (28).

Ankle brachial index

With an adequate-sized cuff and a portable 8-MHz Doppler instrument, systolic arterial pressures in the upper and lower limbs, right and left, were measured in topography of the brachial artery, posterior tibial, and dorsal foot. The cuff was positioned at arm and calf level, respectively. When the cuff was deflated, the systolic blood pressure was measured after auscultation of the first sound captured by the Doppler device. In order to calculate right and left ankle brachial index (ABI), a division was made between the highest systolic pressure in each lower limb (posterior tibial or dorsal foot) and higher systolic pressure in the upper limbs. A diagnosis of peripheral vasculopathy is considered to be <0.9 on either side (29).

Framingham risk score

We calculated the Framingham risk score (FRS) to evaluate the absolute risk of stroke and death in 10 y (30).

Cardiovascular disease risk classification

Patients with 1 of the following conditions were classified as having cardiovascular disease risk: *1*) cardiovascular changes identified by stress electrocardiography (positive result or Duke treadmill score <4) (28); *2*) two of the following criteria: ABI <0.9 (29); FRS >10% (30); cardiovascular disease risk criteria suggested by NCEP-ATP III (26); *3*) occurrence of some cardiovascular event (acute myocardial infarction, stroke, and deep venous thrombosis).

Statistical analysis

The continuous variables are reported as means ± SDs, and the categorical variables as frequencies and percentages.

Receiver operating characteristic curves were designed for each adiposity measure/index with the use of predictors of cardiovascular disease risk classification to identify sensitivity and specificity. The determination of the cutoffs was based on the values that maximized simultaneously both sensitivity and specificity.

For each adiposity measure/index, logistic regression analysis was conducted to obtain the OR for cardiovascular disease risk through the use of the cutoffs. In this analysis, adjustment was made for age, smoking, alcohol consumption, HAART duration, type of HAART, physical activity, and menopause (women).

Finally, individuals were divided into different groups with (+) or without (–) adiposity alteration for each adiposity index, according to the proposed cutoffs. Comparisons between patients (+) and (–) were made by Student's *t* test (continuous variables) and a χ^2-test (categorical variables).

Analyses were carried out with the SPSS 17.0 (Statistical Product and Service Solutions; IBM Corp.) program. A 5% significance level was considered in all analysis.

RESULTS

Of the 448 stable HIV patients undergoing HAART, 53.6% were men and 46.4% were women. The mean age of the total sample was 44.13 ± 9.93 y. The patients' mean time of positive serology was 10.27 ± 6.78 y and the HAART mean use time was 8.43 ± 6.17 y.

Regarding the ethnic breakdown of the evaluated group, the majority (70.5%) were white, whereas the others were black (11.8%) and mixed race (17.6%).

Almost half of the patients (49.8%) were using a combination of 2 nucleoside analog reverse transcriptase inhibitors with a nonnucleoside analog reverse transcriptase inhibitor; followed by a combination of 2 NRTIs with a protease inhibitor (42.3%). A minority of patients were taking a combination including the new classes: integrase inhibitor (II) and fusion inhibitor (4.8% and 0.7%, respectively).

The most prevalent metabolic alterations were reduced HDL (66.3%) and hypertriglyceridemia (46.0%), and there were differences in the mean values of these parameters between genders (**Table 1**). Systemic arterial hypertension diagnosis was present in 24.8% of the patients. Regarding the changes of glucose metabolism, 28.6% had altered fasting glycemia and 12.5% had the diagnosis of diabetes mellitus.

A considerable number of patients (27.68%) had peripheral atheromatous disease according to ABI (<0.9). According to FRS, 59 (13.16%) patients were at an absolute risk of infarction in 10 y between 10% and 15%. Finally, most (59.15%) of the patients presented increased cardiovascular disease risk

TABLE 1
Metabolic profile of the study group[1]

	All ($n = 448$)	Women ($n = 208$)	Men ($n = 240$)
Total cholesterol, mg/dL	193.03 ± 47.91	19494 ± 44.95	191.89 ± 50.41
Triglycerides, mg/dL	171.74 ± 111.56	158.59 ± 99.89	183.13 ± 119.80*
HDL cholesterol, mg/dL	41.41 ± 11.97	43.56 ± 12.98	39.55 ± 10.70**
LDL cholesterol, mg/dL	117.41 ± 38.52	120.41 ± 36.61	114.83 ± 40.00
Fasting glycemia, mg/dL	96.27 ± 23.82	95.25 ± 24.09	97.15 ± 23.70
Systolic blood pressure, mm Hg	122.61 ± 18.81	119.76 ± 18.11	125.07 ± 19.10
Diastolic blood pressure, mm Hg	79.04 ± 12.76	76.86 ± 12.30	80.91 ± 12.87

[1]Values are means ± SD. Student's t test; $*P < 0.05$; $**P < 0.001$ comparison between women and men.

(146 men and 116 women) according to the present study criteria.

The cutoffs proposed in the present study are different from those proposed for the HIV seronegative population and differ between the genders (**Table 2**).

Central fat indicators (WC and WHtR) were more efficient to identify metabolic changes and cardiovascular disease risk than total fat and fat distribution indexes for both genders (**Tables 3** and **4**). As expected, these measures also showed higher adjusted ORs (**Table 5**).

WC and WHtR showed the best performance to identify cardiovascular disease risk in both genders (AUCs: 0.86 and 0.85 for women; 0.83 and 0.83 for men), whereas phase angle proved to be an inadequate indicator (AUCs: 0.48 and 0.60 for men and women, respectively) for identifying cardiovascular disease risk in this population (**Figures 1** and **2**).

TABLE 2
Area under the ROC curve, cutoff, sensitivity, and specificity of the adiposity measures/indexes to identify cardiovascular disease risk[1]

		Area under the ROC curve (95% CI)	Cutoff	Sensitivity, %	Specificity, %
BMI, kg/m^2	Men	0.79 (0.73, 0.84)*	23.5	74.7	69.1
	Women	0.82 (0.76, 0.88)*	24.4	81.5	64.0
Waist circumference, cm	Men	0.83 (0.78, 0.89)*	87.75	82.2	75.5
	Women	0.86 (0.81, 0.91)*	90.5	84.0	73.0
Neck circumference, cm	Men	0.79 (0.73, 0.84)*	36.75	74.7	72.3
	Women	0.84 (0.78, 0.89)*	33.75	69.7	87.6
Trunk circumference, cm	Men	0.76 (0.70, 0.83)*	96.75	69.2	69.1
	Women	0.83 (0.77, 0.88)*	95.75	71.4	83.1
Waist-to-hip ratio	Men	0.83 (0.78, 0.88)*	0.93	80.7	70.2
	Women	0.80 (0.74, 0.86)*	0.90	79.8	68.5
Waist-to-thigh ratio	Men	0.80 (0.74, 0.86)*	1.72	78.8	69.1
	Women	0.74 (0.68, 0.81)*	1.61	73.1	66.3
Waist-to-calf ratio	Men	0.73 (0.66, 0.79)*	2.51	70.5	61.7
	Women	0.76 (0.69, 0.82)*	2.63	66.4	69.7
Trunk-to-arm ratio	Men	0.55 (0.48, 0.63)	1.82	53.4	51.1
	Women	0.62 (0.54, 0.70)*	1.43	56.9	59.6
Waist-to-height ratio	Men	0.83 (0.78, 0.88)*	0.52	74.0	81.9
	Women	0.85 (0.80, 0.91)*	0.57	87.4	70.8
Body Adiposity Index	Men	0.65 (0.59, 0.72)*	23.9	65.5	59.6
	Women	0.66 (0.58, 0.74)*	30.7	68.9	61.8
Conicity index	Men	0.80 (0.75, 0.86)*	1.27	77.4	70.2
	Women	0.78 (0.72, 0.85)*	1.32	72.3	69.7
A Body Shape Index	Men	0.68 (0.61, 0.75)*	0.14	70.5	54.3
	Women	0.59 (0.52, 0.67)*	0.13	59.7	59.6
BMI corrected by fat	Men	0.77 (0.71, 0.83)*	1.57	77.5	64.4
	Women	0.81 (0.76, 0.87)*	2.00	73.7	70.1
Fat mass, %	Men	0.74 (0.67, 0.80)*	17.9	67.4	72.2
	Women	0.79 (0.73, 0.85)*	31.5	74.6	64.7
Phase angle, ohm	Men	0.48 (0.40, 0.55)	—	—	—
	Women	0.60 (0.52, 0.68)*	5.8	58.8	52.9

[1]ROC curves; $*P < 0.05$. Phase angle for men: AUC < 0.50 (it is not possible to define a cutoff). ROC, receiver operating characteristic.

TABLE 3

Metabolic parameters and frequency of metabolic alterations according to each adiposity measure/index and cutoff for the men[1]

		Cholesterol		Triglycerides		HDL cholesterol		LDL cholesterol		Glycemia		
		mg/dL	%	mg/dL	%	mg/dL	%	mg/dL	%	mg/dL	%	CVDR, %
BMI	− (*n* = 99)	184.1 ± 47.2	17.1	157.1 ± 87.7	39.3	41.2 ± 11.6	49.4	112.3 ± 45.4	25.2	91.8 ± 15.3	26.2	36.3
	+ (*n* = 141)	197.3 ± 51.9*	26.9	200.6 ± 135.5*	60.9**	38.3 ± 9.8*	64.5*	128.4 ± 56.5*	38.2*	100.8 ± 27.4*	36.8	78.7**
Waist circumference	− (*n* = 97)	176.4 ± 48.0	12.3	149.8 ± 90.6	31.9	40.8 ± 11.6	49.4	108.2 ± 51.6	21.6	92.7 ± 17.3	26.8	26.8
	+ (*n* = 143)	202.3 ± 49.4**	30.0*	205.7 ± 131.2**	65.7**	38.6 ± 9.9	64.3*	130.9 ± 54.8*	40.5*	100.1 ± 26.6*	36.3	84.6**
Neck circumference	− (*n* = 105)	183.7 ± 47.4	16.1	156.2 ± 95.2	39.0	41.1 ± 11.7	51.4	114.1 ± 475	24.7	93.3 ± 16.7	28.5	35.2
	+ (*n* = 135)	198.2 ± 51.8*	28.1*	204.0 ± 192.1*	62.2**	38.2 ± 9.5*	63.7*	127.7 ± 55.9*	39.2*	100.1 ± 27.4*	33.5	81.4**
Trunk circumference	− (*n* = 110)	183.1 ± 45.5	17.2	161.0 ± 86.2	44.5	40.4 ± 11.6	53.9	111.2 ± 42.9	24.5	92.3 ± 15.2	22.7	40.9
	+ (*n* = 130)	199.2 ± 53.2*	27.6*	201.8 ± 139.7*	58.4*	38.8 ± 9.7	62.3	130.7 ± 58.4*	40.0*	101.2 ± 28.2*	40.7*	78.4**
Waist-to-hip ratio	− (*n* = 88)	170.4 ± 43.5	11.3	147.2 ± 92.8	34.0	39.1 ± 10.2	53.4	104.3 ± 41.5	18.1	92.4 ± 16.9	23.8	29.5
	+ (*n* = 152)	204.3 ± 50.0**	29.6**	203.9 ± 128.7**	62.5**	39.7 ± 10.9	61.1	131.8 ± 55.9**	41.4**	99.8 ± 26.3*	37.5*	79.6**
Waist-to-thigh ratio	− (*n* = 95)	174.3 ± 42.5	12.6	152.7 ± 90.2	38.9	39.3 ± 10.3	53.6	108.2 ± 39.9	20.0	92.0 ± 15.3	24.2	32.6
	+ (*n* = 145)	203.4 ± 51.9**	29.6*	203.0 ± 132.2*	60.6**	39.7 ± 10.9	61.3	130.6 ± 58.1*	41.3**	100.4 ± 27.2*	37.9*	80.0**
Waist-to-calf ratio	− (*n* = 99)	178.1 ± 14.5	14.1	169.4 ± 128.0	39.3	39.3 ± 10.0	53.5	113.5 ± 50.9	24.2	95.5 ± 24.9	29.2	42.4
	+ (*n* = 141)	201.5 ± 51.2*	29.0*	192.7 ± 113.1	60.9**	39.7 ± 11.1	61.7	127.5 ± 53.3*	39.0*	98.2 ± 22.6	34.7	74.4**
Trunk to arm ratio	− (*n* = 113)	181.2 ± 46.4	17.6	159.7 ± 85.5	43.3	38.4 ± 11.5	62.3	114.2 ± 43.7	28.3	94.8 ± 16.4	34.5	58.4
	+ (*n* = 127)	202.3 ± 52.0*	27.5*	203.9 ± 140.7*	59.8*	40.5 ± 9.8	54.3	128.4 ± 59.0*	37.0	99.1 ± 28.4	30.7	63.7
Waist-to-height ratio	− (*n* = 105)	174.7 ± 45.6	12.3	152.5 ± 84.6	37.1	40.9 ± 11.7	47.6	105.4 ± 41.5	20.0	93.2 ± 17.0	27.6	32.3
	+ (*n* = 135)	205.2 ± 50.0**	31.1**	206.9 ± 136.8*	63.7**	38.4 ± 9.7*	66.6*	134.4 ± 59.3**	42.9**	100.2 ± 27.3*	36.2	83.7**
Body Adiposity Index	− (*n* = 104)	188.7 ± 54.5	21.1	180.5 ± 126.5	47.1	40.4 ± 12.1	53.8	119.8 ± 57.7	26.9	98.1 ± 27.7	34.6	49.0
	+ (*n* = 136)	194.3 ± 47.0	24.2	185.1 ± 114.7	55.8	38.8 ± 9.3	61.7	123.2 ± 48.7	37.5	96.4 ± 19.8	30.8	70.5**
Conicity index	− (*n* = 94)	174.6 ± 43.3	12.7	148.2 ± 91.3	32.9	39.5 ± 10.1	51.0	107.8 ± 40.9	22.3	92.3 ± 15.3	25.5	31.9
	+ (*n* = 146)	203.0 ± 51.6**	29.4*	205.6 ± 130.4*	64.3**	39.5 ± 11.0	63.0	130.7 ± 57.4*	39.7*	99.5 ± 29.8*	36.9	80.1**
A Body Shape Index	− (*n* = 60)	182.4 ± 52.6	25.0	156.1 ± 91.5	40.0	39.5 ± 10.2	55.0	113.9 ± 45.4	38.3	93.1 ± 17.6	26.6	41.6
	+ (*n* = 180)	195.0 ± 49.3	22.2	192.1 ± 126.7*	56.1*	39.5 ± 10.8	59.4	124.3 ± 54.8	30.5	98.5 ± 25.1*	34.4	67.7**
BMI corrected by fat	− (*n* = 87)	184.4 ± 47.8	18.3	158.9 ± 95.6	36.7	41.0 ± 11.2	49.4	114.4 ± 48.3	26.4	92.1 ± 15.6	25.2	35.6
	+ (*n* = 153)	196.1 ± 51.4*	25.4	196.9 ± 129.8*	60.7*	38.6 ± 10.2	63.3	125.9 ± 54.7	34.6	99.9 ± 26.7*	36.6	75.8**
% Fat mass	− (*n* = 107)	181.8 ± 45.2	14.9	157.3 ± 93.2	37.3	40.7 ± 10.7	51.4	111.1 ± 46.0	23.3	93.2 ± 15.5	28.9	42.9
	+ (*n* = 133)	199.9 ± 52.9*	29.3*	203.8 ± 134.2*	63.9**	38.5 ± 10.5	63.9*	130.3 ± 56.2*	40.6*	100.2 ± 28.1*	35.3	75.9**

[1] Student's *t* test (continuous variables) and χ^2-test (categorical variables). *$P < 0.05$; **$P < 0.001$. Cutoffs used: BMI: 23.5 kg/m^2; waist circumference: 87.75 cm; neck circumference: 36.75 cm; trunk circumference: 96.75 cm; waist-to-hip ratio: 0.93; waist-to-thigh ratio: 1.72; waist-to-calf ratio: 2.51; trunk-to-arm ratio: 1.82; waist-to-height ratio: 0.52; Body Adiposity Index: 23.9; conicity index: 1.27; A Body Shape Index: 0.14; BMI fat: 1.57; body fat obtained by the bioelectrical impedance analysis: 17.9%. −, individuals without alteration of the adiposity measurement/index; +, individuals with alteration of the adiposity measurement/index of adiposity; CVDR, cardiovascular disease risk.

TABLE 4
Metabolic parameters and frequency of metabolic alterations according to each adiposity measure/index and cutoff for the women[1]

		Cholesterol		Triglycerides		HDL cholesterol		LDL cholesterol		Glycemia		
		mg/dL	%	mg/dL	%	mg/dL	%	mg/dL	%	mg/dL	%	CVDR, %
BMI	− (n = 79)	191.6 ± 48.7	27.8	156.1 ± 108	37.9	45.2 ± 12.9	64.5	122.9 ± 53.2	32.9	92.3 ± 21.0	16.4	27.8
	+ (n = 129)	195.9 ± 42.5	27.1	170.0 ± 94.9	39.5	42.5 ± 12.9	82.1*	131.4 ± 49.8	42.6	97.0 ± 25.6	28.6*	75.1**
Waist circumference	− (n = 84)	185.9 ± 45.8	22.6	134.8 ± 79.3	30.9	45.8 ± 13.4	65.4	115.3 ± 43.0	28.5	92.1 ± 21.4	15.4	22.6
	+ (n = 124)	200.0 ± 43.5*	30.6	174.7 ± 109*	44.3*	42.0 ± 12.4*	82.2*	136.9 ± 54.5*	45.9*	97.3 ± 25.5*	29.8*	80.6**
Neck circumference	− (n = 114)	191.0 ± 45.2	25.4	143.9 ± 102.0	29.8	45.9 ± 13.8	70.1	123.0 ± 47.6	36.8	91.9 ± 18.2	16.6	31.5
	+ (n = 94)	198.4 ± 44.4	29.7	176.3 ± 94.5*	50.0*	41.8 ± 11.6*	81.9*	137.5 ± 71.0*	41.4	99.2 ± 29.2*	32.9*	88.2**
Trunk circumference	− (n = 108)	186.7 ± 46.7	23.1	141.7 ± 93.2	31.4	45.3 ± 13.8	69.4	119.1 ± 44.3	33.3	90.4 ± 17.8	14.8	31.4
	+ (n = 100)	200.5 ± 41.6*	32.0	176.7 ± 104.0*	47.0*	41.6 ± 11.7*	82.0*	137.9 ± 56.3*	45.0	100.4 ± 28.5*	34.0*	85.0**
Waist-to-hip ratio	− (n = 73)	186.0 ± 43.7	36.9*	127.1 ± 73.7	26.0	46.3 ± 13.9	68.4	114.3 ± 36.9	35.6	87.7 ± 9.4	12.3	27.3
	+ (n = 135)	198.8 ± 45.1	22.2	175.6 ± 108.0*	45.9*	42.0 ± 12.2*	79.2	135.6 ± 56.2*	40.7	99.3 ± 28.2**	30.3*	73.3**
Waist-to-thigh ratio	− (n = 88)	187.5 ± 43.1	37.5*	130.1 ± 82.1	25.0	45.8 ± 13.2	69.3	117.8 ± 49.5	35.2	88.9 ± 13.1	11.3	35.2
	+ (n = 120)	199.3 ± 45.7	20.0	179.4 ± 106.0**	49.1*	41.8 ± 12.5*	80.0*	135.7 ± 56.7*	41.6	99.9 ± 28.8**	33.3*	73.3**
Waist-to-calf ratio	− (n = 99)	185.1 ± 40.7	32.3	140.0 ± 96.7	29.2	43.8 ± 12.1	72.7	121.7 ± 49.6	30.3	92.4 ± 25.0	15.1	39.3
	+ (n = 109)	202.6 ± 47.1*	22.9	175.4 ± 100.1*	47.7*	43.2 ± 13.7	77.9	134.0 ± 52.1	46.7*	97.7 ± 23.0	32.1*	73.3**
Trunk-to-arm ratio	− (n = 95)	191.8 ± 45.5	23.1	141.8 ± 90.3	27.3	45.1 ± 12.1	69.4	123.2 ± 49.4	34.7	91.0 ± 16.0	16.8	46.3
	+ (n = 113)	196.3 ± 44.4	30.9	172.6 ± 105.6*	48.6*	42.2 ± 13.4	80.5*	132.3 ± 52.4	42.4	98.7 ± 28.7*	30.0*	66.3*
Waist-to-height ratio	− (n = 73)	184.1 ± 45.3	30.1	132.8 ± 79.5	28.7	45.9 ± 14.3	63.0	114.2 ± 43.7	26.0	90.4 ± 18.6	12.3	19.1
	+ (n = 135)	199.8 ± 43.7*	25.9	172.5 ± 107.0*	44.4*	42.3 ± 12.0	82.2*	135.7 ± 53.5*	45.9*	97.8 ± 26.2*	30.3*	77.7**
Body Adiposity Index	− (n = 91)	190.3 ± 45.5	37.3*	164.8 ± 110.0	41.7	43.2 ± 12.2	74.7	125.1 ± 55.0	30.7	95.6 ± 31.1	18.6	40.6
	+ (n = 117)	197.4 ± 44.4	19.6	153.7 ± 91.4	36.7	43.8 ± 13.6	76.0	130.5 ± 48.0	45.2*	94.2 ± 16.7	28.2	70.0**
Conicity index	− (n = 92)	188.0 ± 42.8	36.9*	135.7 ± 75.9	32.6	45.3 ± 13.9	68.4	118.3 ± 39.5	32.6	89.9 ± 11.7	14.1	33.6
	+ (n = 116)	199.2 ± 46.1	19.8	176.7 ± 112.4*	43.9	42.1 ± 12.0	81.0*	135.7 ± 57.8*	43.9	99.5 ± 29.8*	31.8*	76.8**
A Body Shape Index	− (n = 38)	204.4 ± 38.9	52.3*	145.1 ± 92.6	31.5	47.6 ± 15.0	65.7	137.8 ± 51.4	50.0	91.5 ± 15.5	13.1	50.0
	+ (n = 170)	192.0 ± 45.9	21.7	161.6 ± 101.4	40.5	42.6 ± 12.3*	77.6	126.0 ± 51.0	36.4	96.0 ± 25.5	26.4	58.8
BMI corrected by fat	− (n = 89)	194.9 ± 48.1	42.6*	154.8 ± 104.2	38.2	45.0 ± 13.4	66.2	125.1 ± 51.3	35.9	93.5 ± 21.4	19.1	33.7
	+ (n = 119)	193.8 ± 42.5	15.9	161.3 ± 96.8	39.4	42.4 ± 12.5	82.3*	130.4 ± 51.2	41.1	96.5 ± 25.9	27.7	74.7**
% Fat mass	− (n = 83)	193.7 ± 47.0	40.9*	157.9 ± 105.0	39.7	44.3 ± 13.1	69.8	124.8 ± 51.2	36.1	93.6 ± 22.4	20.4	36.1
	+ (n = 125)	194.7 ± 43.6	18.4	159.0 ± 96.5	38.4	43.0 ± 12.8	79.2	130.3 ± 51.2	40.8	96.3 ± 25.1	26.4	71.2**

[1] Student's t test (continuous variables) and χ^2-test (categorical variables). *$P < 0.05$; **$P < 0.001$. Cutoffs used: BMI: 24.4 kg/m^2; waist circumference: 90.5 cm; neck circumference: 33.75 cm; trunk circumference: 95.75 cm; waist-to-hip ratio: 0.90; waist-to-thigh ratio: 1.61; waist-to-calf ratio: 2.63; trunk-to-arm ratio: 1.43; waist-to-height ratio: 0.57; Body Adiposity Index: 30.7; conicity index: 1.32; A Body Shape Index: 0.13; BMI fat: 2.00; body fat obtained by bioelectrical impedance analysis: 30.5%. –, individuals without alteration of the adiposity measurement/index; +, individuals with alteration of the adiposity measurement/index of adiposity; CVDR, cardiovascular disease risk.

TABLE 5
ORs of the adiposity measures/indexes for cardiovascular disease risk with the proposed cutoffs[1]

		OR (95% CI)	OR adjusted (95% CI)
BMI	Men	6.56 (3.69, 11.67)**	8.70 (4.16, 18.19)**
	Women	7.85 (4.17, 14.90)**	8.41 (4.24, 16.70)**
Waist circumference	Men	15.01 (7.93, 28.45)**	21.87 (9.32, 51.86)**
	Women	14.25 (7.24, 28.08)**	15.25 (7.33, 31.76)*
Neck circumference	Men	7.80 (4.33, 14.06)**	8.02 (3.92, 16.44)**
	Women	16.34 (7.78, 34.46)**	24.97 (10.40, 60.0)**
Trunk circumference	Men	5.26 (2.99, 9.26)**	7.23 (3.47, 15.07)**
	Women	12.33 (6.23, 24.41)**	13.81 (6.57, 29.03)**
Waist-to-hip ratio	Men	0.83 (0.78, 0.88)	0.83 (0.78, 0.88)
	Women	6.87 (3.65, 12.95)**	7.25 (3.68, 14.33)**
Waist-to-thigh ratio	Men	7.93 (4.40, 14.28)**	3.69 (1.86, 7.34)*
	Women	5.62 (3.09, 10.26)**	5.83 (3.04, 11.21)**
Waist-to-calf ratio	Men	4.00 (2.31, 6.95)**	2.23 (1.17, 4.27)*
	Women	4.14 (2.31, 7.45)**	4.03 (2.16, 7.53)*
Trunk-to-arm ratio	Men	1.25 (0.75, 2.11)	1.42 (0.75, 2.69)
	Women	1.63 (0.93, 2.87)	1.59 (0.87, 2.93)
Waist-to-height ratio	Men	10.11 (5.51, 18.57)**	8.56 (4.21, 17.42)**
	Women	16.80 (8.27, 34.12)**	19.20 (8.74, 42.12)**
Body Adiposity Index	Men	2.68 (1.57, 4.59)*	2.76 (1.45, 5.27)*
	Women	3.28 (1.85, 5.84)*	3.44 (1.84, 6.45)*
Conicity index	Men	8.19 (4.53, 14.80)**	5.78 (2.86, 11.70)*
	Women	5.67 (3.11, 10.36)**	6.75 (3.48, 13.10)**
A Body Shape Index	Men	3.08 (1.69, 5.61)*	3.25 (1.59, 6.68)*
	Women	1.30 (0.61, 2.80)	1.49 (0.65, 3.45)
BMI corrected by fat	Men	5.44 (3.04, 9.77)**	7.93 (3.69, 17.05)**
	Women	6.26 (3.38, 11.58)**	7.28 (3.67, 14.45)**
% Fat mass	Men	4.84 (2.73, 8.60)**	7.66 (3.57, 16.48)**
	Women	4.94 (2.69, 9.08)**	6.23 (3.13, 12.44)**

[1]Logistic regression analysis. OR adjusted: adjusted for age, ART type, ART time, smoking, alcohol consumption, physical activity, and menopause (women). *$P < 0.05$; **$P < 0.001$. ART, antiretroviral therapy.

DISCUSSION

This study presents as its main results the proposals of adiposity measure/index cutoffs associated with predictors of cardiovascular disease risk in HIV patients. This is the first study, to our knowledge, that has suggested indexes using anthropometric measures as tools to concur with cardiovascular disease risk in this group of patients, thus we believe that our work is of great relevance in clinical practice. In addition, the methodology used is rigorous, including stress electrocardiography that had not been introduced in other studies with the same purpose.

The Outpatients Clinics of Ribeirão Preto Medical School (HC/FMRP) University Hospital assist 800 HIV patients from the entire Brazilian population, so the sample evaluated (more than half) is considered representative of the country's ethnic component.

A cross-sectional study analyzed 666 HIV patients in the "Fat Redistribution and Metabolic Change in HIV Infection" (FRAM) study and found that simple anthropometric measures had good correlations with HOMA, TGs, and HDL cholesterol. However, this study questioned whether its findings would be validated with other obesity-associated health risks, rather than metabolic risk indicators. Considering this, we included in our study the methodology of stress electrocardiography, ABI, and evaluation of cardiovascular events. In addition, we proposed specific cutoffs for the adiposity measures/indexes to make the study broader (31).

Several recent studies have found an association of HIV with increased FRS. One study found that 38% of the 2005 participants from the United States in the HIV Outpatient Study (HOPS) were at moderate or high risk for cardiovascular disease (32), resembling the results of the present study. The identification of altered ABI in many patients corroborates data from studies supporting a role of HIV in conferring risk for peripheral arterial disease (33).

The higher incidence of acute myocardial infarction and atherosclerosis in the HIV population compared with the HIV seronegative population (ORs between 1.5 and 2) remained significant for all age groups, and even after viral suppression (HIV 1 RNA < 500 and CD4 ≥ 200) (34–38). In our study, we observed an atherogenic metabolic profile in most of our patients; this is in accordance with the risk pattern for metabolic and cardiovascular disease associated with fat redistribution in HIV patients on antiretroviral therapy (ART).

Thus, it is interesting to detect minimal changes in body fat with objective tools to assist health professionals and to prevent and minimize future cardiovascular complications (39). Owing to

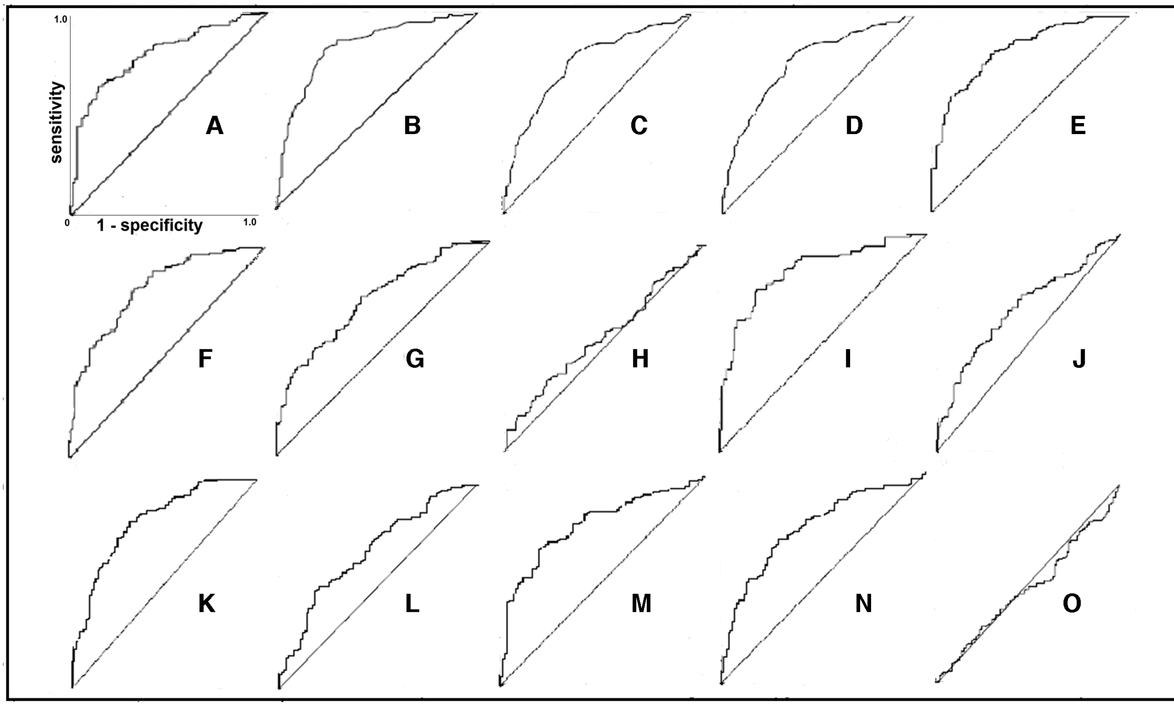

FIGURE 1 Receiver operating characteristic curves for the performance evaluations of adiposity measurements/indexes in identifying cardiovascular disease risk for men ($n = 240$). (A) BMI; (B) waist circumference; (C) neck circumference; (D) trunk circumference; (E) waist-to-hip ratio; (F) waist-to-thigh ratio; (G) waist-to-calf ratio; (H) trunk-to-arm ratio; (I) waist-to-height ratio; (J) Body Adiposity Index; (K) conicity index; (L) A Body Shape Index; (M) BMI corrected by fat; (N) fat mass (percentage); (O) phase angle.

the lack of studies in this field for this population, all adiposity measures/indexes were evaluated.

The present study confirms the hypothesis that the accumulation of intra-abdominal adipose tissue is associated with metabolic and neuroendocrine disorders (40), since WC and WHtR presented the best performances to predict cardiovascular disease risk in both genders.

Bennasar-Veny et al. (41) analyzed the correlation between adiposity indexes with cardiovascular and metabolic risk factors, using a sample of 50,254 individuals, from 20 to 68 y of age, and affirmed that WC is a simple and accurate method for assessing cardiovascular disease risk. A meta-analysis that gathered 15 prospective studies that included 25,114 individuals found that the risk of a cardiovascular disease incident increases 2% in men and women with a 1-cm increase in WC (42).

WHtR is also considered an indicator of abdominal obesity. Numerous studies, in non-HIV patients, have pointed out that WHtR, allied to WC, seems to be one of the best predictors of cardiovascular disease risk factors, due to the fact of evaluating central obesity (43). WC, when corrected for height, allows reliable results even in populations with a large variation in height (44). Evidence also indicates that another advantage of WHtR is its greater applicability in distinct populations (45). In a Brazilian study, when correlating the anthropometric indexes with trunk fat obtained by dual-energy X-ray absorptiometry in HIV patients, it was found that WHtR was the index with the best correlation coefficients (0.80 for men and 0.87 for women), suggesting that this would be the best index to evaluate the abdominal fat distribution of this specific group of patients (12).

Increased visceral adipose tissue and loss of gluteus femoral adipose tissue contribute to worsen the metabolic profile, making it more atherogenic. Thereat, Beraldo et al. (13) have proposed the WTR, which evaluates the relation between central (waist) and peripheral (thigh) fat. The results for WHR and WTR were similar, since both evaluated the same distribution of fat (central-peripheral). A better performance of the WTR was expected owing to 2 facts: *1*) these patients present a greater loss of adipose tissue in the thighs than in the hip and *2*) the thigh is not affected by variations in the pelvic architecture, such as the hip (46). However, a slightly better performance was found for WHR.

NC and TrC showed good performances, but lower than the measurements of central adiposity.

Currently, BMI is globally the most used adiposity index in the body composition area. However, it is an imperfect measurement of adiposity for not considering the composition and distribution of body fat. As in the present study, several studies have found the superiority of measures/indexes of central adiposity in relation to BMI in identifying metabolic alterations and cardiovascular disease risk (47–53).

BAI, ABSI, and BMI fat were proposed with the intention of overcoming the limitations of the BMI. Despite this purpose, these new indexes presented worse performances than the BMI in the present study. No previous study had evaluated the use of these new indexes in the HIV population, with the exception of BAI to identify metabolic syndrome. In other studies evaluating several populations with different ethnicities, it was found that BAI is not a very precise index.

Body fat (percentage) evaluated by BIA is considered the best double-indirect estimate of body fat and predictor of

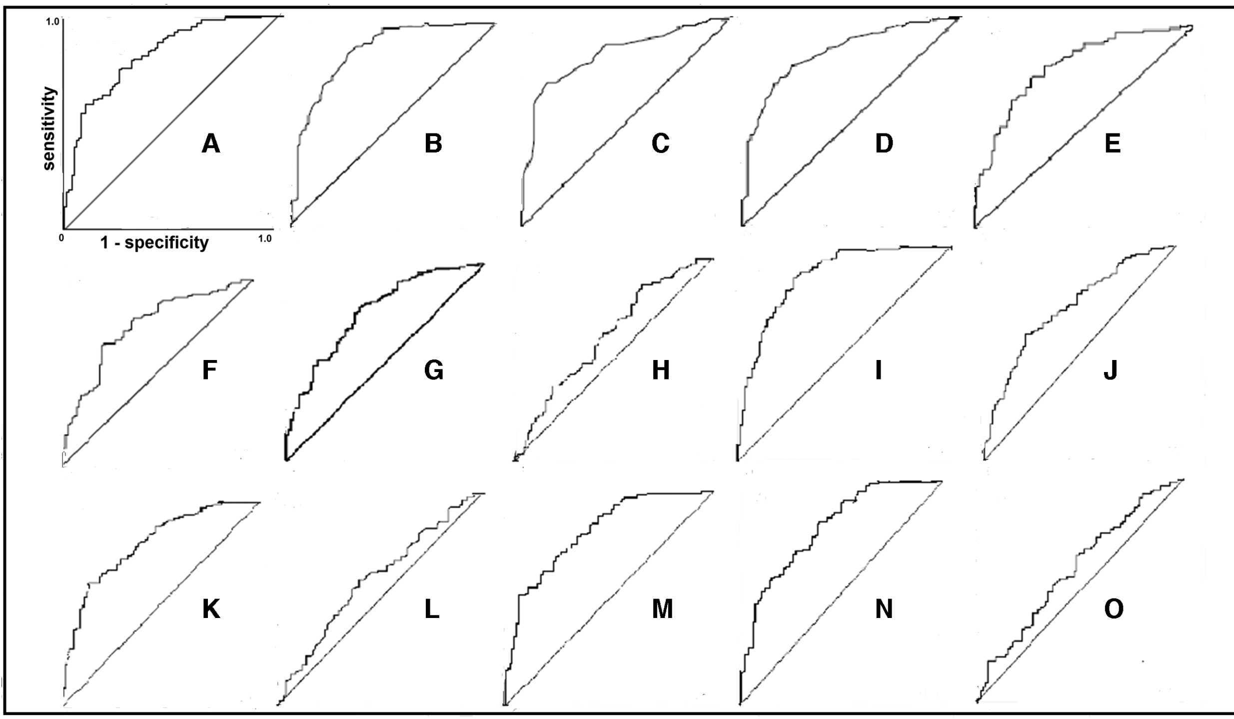

FIGURE 2 Receiver operating characteristic curves for the performance evaluations of adiposity measurements/indexes in identifying cardiovascular disease risk for women ($n = 208$). (A) BMI; (B) waist circumference; (C) neck circumference; (D) trunk circumference; (E) waist-to-hip ratio; (F) waist-to-thigh ratio; (G) waist-to-calf ratio; (H) trunk-to-arm ratio; (I) waist-to-height ratio; (J) Body Adiposity Index; (K) conicity index; (L) A Body Shape Index; (M) BMI corrected by fat; (N) fat mass (percentage); (O) phase angle.

cardiovascular disease risk (54). In the present study, it presented a satisfactory performance; however, not one exceeding the measures of central adiposity. It is important to note that monitoring of total body fat may not be sufficient to accompany HIV patients, since these individuals can gain and lose fat in segments maintaining the same total fat value over time, and the method does not detect specific changes by body segments (5).

Logistic regression analysis was performed to verify if the cutoffs proposed for adiposity measures/indexes independently reflect (confounding factors: age, ART, type of ART, smoking, alcohol consumption, physical activity, and menopause) increased cardiovascular disease risk. With the exception of ABSI for women, WHR for men, and TAR for both genders, all measures/indexes of adiposity were shown to reflect cardiovascular disease risk independently of the other confounding factors.

In the present study, all adiposity measures/indexes presented different cutoffs from those proposed for the seronegative HIV population.

The cutoffs found were lower than those proposed for the general population, except for WC and WHR in women (90.5 cm and 0.90 compared with 88 cm and 0.85). This can be explained by the fact that HIV-positive women have a greater accumulation of central adipose tissue than HIV negatives, unlike men who do not differ from the control group in relation to central fat accumulation, but with a lower amount of peripheral fat (29).

Discrepancies in the cutoffs for total and central adiposity have a profound effect on prevalence estimates from the public health point of view. Compared with the cutoffs described in this study, the current WHO and International Diabetes Federation cutoffs (55, 56) inadequately predict the cardiovascular disease risk of Brazilian HIV patients on HAART.

In summary, the adiposity measures/indexes presented good performances. WC and WHtR presented the best abilities, proving the hypothesis that abdominal obesity is more associated with cardiovascular disease risk than general obesity, even in the HIV patient population.

Training of multiprofessional teams is of great importance to carry out some measures that are simple and that can be used routinely even in institutions that do not have high-cost equipment. The use of anthropometry and its cutoffs proposed in the present study aims to contribute to the early identification of increased risk for cardiovascular diseases, allowing for interventions.

Among the limitations, it is a cross-sectional study but not prospective. We cannot state that the adiposity measures/indexes predict cardiovascular disease risk, but rather that they are highly associated with predictors of cardiovascular disease risk. In addition, the measures/indexes do not allow the differentiation of subcutaneous and visceral fat.

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The authors' contributions were as follows—RAB: designed and conducted the research; GCM and BRS: contributed to the acquisition of the data; AMN, VRB, and AS: provided essential reagents or materials; MCF-F: designed the research; RAB and MCF-F: analyzed data or performed statistical analysis, wrote the paper, and had primary responsibility for final content; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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