










Testosterone Deficiency and Changes in Body Composition in Men Living with HIV

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Abstract:

Introduction: Testosterone Deficiency (TD) is common in men living with HIV (MLWHIV) and is associated with worse clinical outcomes. This study aimed to evaluate the frequency of TD in MLWHIV and factors potentially associated with this condition.

Methodology: This observational cross-sectional study included MLWHIV aged > 18 years receiving Antiretroviral Therapy (ART). Clinical and laboratory data were collected, and body composition, Bone Mass (BM), Lean Mass (LM), and Fat Mass (FM), were assessed using Dual-energy X-ray Absorptiometry (DXA). TD was defined as Total Testosterone (TT) <300 ng/dL and/or calculated Free Testosterone (cFT) <6.4 ng/dL (Vermeulen's formula). Data are presented as median (interquartile range, IQR) and n (%).

Results: Eighty-four participants were included from May 2014 to August 2015. Median TT was 396.5 ng/dL (IQR 314.8–490.2), Sex Hormone-Binding Globulin (SHBG) 45.4 nmol/L (IQR 35.1–60.2), and cFT 6.6 ng/dL (IQR 5.3–7.4). TD prevalence was 22.6% by TT and 44% by cFT ($p < 0.001$). Using the cFT criterion, participants with TD were older (50 vs 45 years, $p < 0.01$), had higher prevalence of metabolic syndrome (27% vs 4.3%, $p < 0.01$), increased waist circumference (21.6% vs 4.3%, $p < 0.05$), and lower frequency of normal BM (37.5% vs 67.5%, $p < 0.05$). No differences were observed in CD4 count, ART duration or type, LM, FM, or lipodystrophy.

Conclusion: In MLWHIV, the cFT criterion identified more cases of TD than TT alone. TD in this population is associated with altered bone mass, increased waist circumference, and a higher prevalence of metabolic syndrome, highlighting the importance of systematic evaluation using cFT.

Keywords: Human immunodeficiency virus, Testosterone deficiency, Calculated free testosterone, Body composition, Bone mass, Lean mass, Fat mass.

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1. INTRODUCTION

The effectiveness of Antiretroviral Therapy (ART) has prolonged the disease-free life of people living with the Human Immunodeficiency Virus (HIV). On the other hand, HIV treated with ART is associated with a series of comorbidities unrelated to Acquired Immunodeficiency Syndrome (AIDS), characterizing the HIV infection as a chronic condition [1, 2].

Low testosterone levels are commonly seen in men living with HIV (MLWHIV). It is associated with higher mortality, frailty, osteoporosis, worse quality of life, and sexual performance [3, 4]. The prevalence depends on the population studied and the diagnostic criteria used, varying from 3 to 60% in the post-ART era [4].

Testosterone circulates in plasma in free (unbound) and protein-bound form. Only 1-4% is found in free form, while the majority is bound to albumin and Sex Hormone Binding Globulin (SHBG) [5]. HIV infection is associated with an increase in SHBG levels, which leads to normal levels of total testosterone and low levels of the free form [6]. The Endocrine Society recommends the calculation of Free Testosterone (cFT) or direct measurement using a balance dialysis assay for laboratory diagnosis of hypogonadism in MLWHIV. Measurements using immunoassays are not recommended as they are less accurate [6].

Testosterone Deficiency (TD) screening in MLWHIV is recommended by the Infectious Diseases Society of America (IDSA) in the presence of reduced libido, erectile dysfunction, reduced bone mass, or fragility fracture. The Endocrine Society also includes cases of weight loss [6, 7].

The pathophysiology of low testosterone levels in this population is multifactorial, and there is controversy regarding the associated predictive factors [8, 9]. Clinical factors such as age, body mass index, waist circumference, metabolic syndrome, smoking, diabetes, duration of illness, and duration of ART appear to be associated with an increased risk of testosterone deficiency [4].

This study aimed to evaluate the frequency of TD in MLWHIV, the factors, and changes in body composition potentially associated with this condition.

2. MATERIALS AND METHODS

2.1. Study Design and Participants

2.1.1. Inclusion and Exclusion Criteria

This observational cross-sectional study included MLWHIV aged over 18 years, recruited from the Infectious Diseases Outpatient Clinic of a tertiary care university hospital in the metropolitan region of Rio de Janeiro, Brazil. Participants were selected through convenience sampling. The exclusion criteria included previous use of anabolic steroids, androgenic agents, psychotropic drugs, opioids, or other substances that interfere with gonadal function, the presence of severe chronic or acute illness, endocrinopathies such as pituitary, thyroid, gonadal, or adrenal diseases, chronic kidney disease with a glomerular

filtration rate below 60 mL/min/1.73 m² according to CKD-EPI, and any changes in the ART regimen within the last six weeks.

The study was approved by the Research Ethics Committee of the University Hospital CAAE 17322613.9.0000.5243 and all participants signed an informed consent form before entering the study.

2.1.2. Clinical Assessment

Clinical data (gender, age, smoking, and alcohol consumption, duration of ART and HIV diagnosis) and anthropometric data (weight, height, cervical and abdominal circumference) were collected. The clinical assessment was carried out by the same examiner. Body weight was measured using a Filizola anthropometric scale (São Paulo, SP, Brazil) calibrated by the Brazilian National Metrology Institute. Height was assessed using a stadiometer, with the patient standing upright, arms extended along the body, head raised, and looking at a fixed point at eye level, with feet together and legs forming a right angle. Waist Circumference (WC) was measured with an inelastic SANNY measuring tape (São Bernardo do Campo, SP, Brazil), at the midpoint between the iliac crests and the last ribs, with the patient in an upright position at the end of the expiratory respiratory movement [11]. Neck Circumference (NC) was measured in the middle of the neck, immediately below the laryngeal prominence, with the participant in an upright position, looking forward, and with shoulders down. Body Mass Index (BMI) was calculated by dividing the weight, expressed in kilograms, by the square of the height in meters (kg/m²). Participants were classified according to Body Mass Index (BMI) as underweight, eutrophic, overweight, and obese [12]. The waist-to-height ratio (WHtR) was calculated by dividing the waist by height, with a cutoff point of 0.50 [13]. WC ≥ 102 cm was considered increased and Metabolic Syndrome (MS) was defined by the NCEP ATPIII (National Cholesterol Education Program Adult Treatment Panel III) diagnostic criteria and included 3 of the following 5 criteria: WC ≥ 102 cm in men, triglycerides ≥ 150 mg/dl or specific treatment, HDL-cholesterol < 40 mg/dl, Systolic Blood Pressure (SBP) ≥ 130 mmHg or Diastolic Blood Pressure (DBP) ≥ 85 mmHg or treatment with antihypertensives, and fasting blood glucose ≥ 100 mg/dL or taking medication for glycemic control [14]. Diabetes Mellitus (DM) was defined according to the American Diabetes Association (ADA, 2024) criteria, as two fasting blood glucose levels ≥ 126 mg/dL or an HbA1c level ≥ 6.5%, or the use of medication for glycemic control. Hypovitaminosis D was defined as 25-OH vitamin D TOTAL (25 (OH)D3) levels <30 ng/dL, as recommended in patients using ART [15].

2.1.3. Laboratory Assessment

Blood samples were collected in the morning after an overnight fast. Total testosterone and SHBG were measured using the Immulite 2000 Kit (Siemens). The reference values for SHBG are 10.0 to 57.0 nmol/L, and

for Total Testosterone (TT), they are 129 to 767 ng/dL. Free testosterone was calculated according to Vermeulen's formula [16], available at <https://www.issam.ch/freetesto.htm>.

The diagnosis of TD was verified by two criteria: serum TT levels < 300 ng/dL and/or cFT < 6.4 ng/dL (64 pg/mL) [6].

The 25(OH)D3 was measured using the LIAISON® 25 OH vitamin D TOTAL assay using the chemiluminescent immunoassay technology. Total Cholesterol, Triglyceride, HDL, and Glycemia were evaluated using an automated enzymatic/colorimetric method. LDL was calculated using the Friedewald equation (Total Cholesterol Col - (Triglycerides / 5) - HDL). Creatinine was assessed using the modified Jaffé kinetic method.

2.1.3.1. Assessment of Body Composition using the Dual-energy X-ray Absorptiometry (DXA) Technique

Whole-body DXA was performed using the Lunar iDXA model - General Electric Healthcare, Madison, WI (Encore 2010 software - version 13.40). DXA was performed in the supine position, with standard limb positioning, and the subject was fasting for at least 2 hours.

2.1.3.2. Bone Mass

Bone Mineral Density (BMD), in g/cm², was measured in the Total Femur (TF), Femoral Neck (FN), lumbar spine (L1-L4), and forearm [distal radius third (radius 33%) and Ultradistal Radius (UD)]. For individuals aged ≥ 50 years, BMD was assessed using T-scores at thresholds: T-score ≥ -1.0 for normal BMD, T-score ≤ -1.1 and > -2.5 for osteopenia, and T-score ≤ -2.5 for osteoporosis. For men aged < 50 years, age-adjusted Z-scores were calculated, with a Z-score ≤ -2.0 being considered low bone mass for age, as recommended by the World Health Organization (WHO) and the International Society of Clinical Densitometry (ISCD) [17, 18].

2.1.3.3. Lean Mass

Lean Mass Was Assessed Using The Appendicular lean mass index (ALM), which is the sum of the lean mass of the upper and lower limbs. Low lean mass was defined using the criteria established by Baumgartner and the Foundation for the National Institutes of Health (FNIH). The first is the relationship between the ALM and the square of the height in meters. Results < 7.26 kg/m² in men define low lean mass [19]. The second is the relationship between ALM and BMI, with low lean mass being defined as a value < 0.789 in men [20].

2.1.3.4. Fat Mass

Fat mass was assessed using the Fat Mass Index (FMI), Fat Mass Ratio (FMR), and Android Gynoid ratio (A/G). FMI is the relationship between total body fat in kilograms and the square of height in meters [21]. Values greater than 6 kg/m² were considered high [22]. The FMR is the ratio between the percentage of fat mass in the trunk and the percentage of fat mass in the lower limbs [23]. The A/G ratio is the relationship between body fat in

the android region (located between the ribs and the pelvis, with a demarcation greater than 20% of the distance between the iliac crest and the neck and a lower demarcation at the top of the pelvis) and the body fat of the gynoid region (area located between the hips and the upper thighs, with an upper demarcation below the top of the iliac crest at a distance of 1.5 times that of the android height). Values ≥ 1 were considered increased [22].

2.1.3.5. Lipodystrophy

Lipodystrophy was defined as the presence of Lipohypertrophy (LH) and/or Lipoatrophy (LA). LH was defined as the presence of increased WC (≥ 102 cm) and increased WHtR (≥ 0.5). LA was defined by the relationship between the percentage of leg fat and BMI < 0.65 [23, 24].

2.1.3.6. Statistical Analysis

Statistical analysis was performed using the statistical software R version 3.3.2 for Windows. Continuous variables are presented as medians and Interquartile Ranges (IQRs). Categorical variables are presented as absolute frequencies (n) and percentages (%). Data were subjected to the student's t-test and ANOVA (for normal distribution) or the Mann-Whitney or Kruskal-Wallis test (for non-parametric data) according to the sample characteristics. The Pearson or Spearman correlation was used for continuous variables. The chi-square test (χ²) or Fisher's exact test was used for categorical variables. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

In total, 84 MLWHIV were included from May 2014 to August 2015, all of them were on ART for at least two years. Median age was 47 (40-52) years. The time of HIV diagnosis was 12 (8-17) years, and the duration of ART was 10 (6-15.5) years. Considering the class of antiretrovirals: 98.7% were using nucleoside analogue reverse transcriptase inhibitors (NRTI), 65% were using non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), 49.3% were using protease inhibitors, and a few (7.5%) were on integrase inhibitors. All of them had an undetectable viral load. The CD4 count was 582 (411-769) cells/mm³ and the CD4 nadir was 113.5 (37.8-249.3) cells/mm³ (1).

The median TT levels were 396.5 (314.8-490.2) ng/dL, SHBG 45.4 (35.0-60.2) nmol/L, and cFT 6.6 (5.3- 7.4) ng/dL. Considering only the TT value, the TD frequency was 19 (22.6%), and when calculating the FT, the DT frequency increased to 37 (44%).

The majority (54.8%) of participants were eutrophic, and 10 (12%) had increased WC. DM occurred in 4 participants (4.8%), MS in 12 (14.3%), and hypovitaminosis D in 66 participants (79.5%).

A total of 72 participants were evaluated by DXA, and changes in Bone Mineral density (BM) occurred in 33 participants: 9.7% had osteoporosis, 30.5% had osteopenia, and 5.5% had low bone mineral density for

their age. The frequency of low LM was 27.7% using the Baumgartner criterion and 5% using the FNIH criterion. Lipodystrophy was observed in 45 participants (53.6%).

The frequency of increased FMI was 38.6%, and the frequency of increased A/G was 81.4% (Table 2).

Table 1. General characteristics of the population and comparison of groups with and without Testosterone Deficiency (TD) by cFT criterion.

-	All (84)	With TD (37)	Without TD (47)	p value
Age (years) (Median IQ:25-75)	47.0 (40.0-52.0)	50 (46.0-57.0)	45 (38.0-50.0)	0.005
Smoking (%)	21 (25.0)	10 (27.03)	11 (23.4)	0.890
Alcoholism (%)	4 (5.0)	1 (2.7)	3 (6.5)	0.620
HIV data (Median IQ:25-75)	-	-	-	-
Time of ART (years)	10 (6.0-15.5)	11 (8.0-16.0)	9.5 (6.0-15.0)	0.532
Time of HIV diagnosis (years)	12 (8.0-17)	11 (10.0-17.0)	12.5 (8.0-16.0)	0.840
Viral load copies (copies/mm ³)	0 (0-0)	0 (0-0)	0 (0-0)	0.519
CD4 count (cells/mm ³)	582 (411.0-769.0)	645.5(437.5-777.8)	508 (390.0-749.0)	0.245
CD4 nadir	113.5 (37.8-249.3)	105 (43.0-229.0)	116 (31.0-259.0)	0.930
Antiretroviral therapy (ART) %	-	-	-	-
Protease inhibitor	39 (49.3)	16 (43.2)	23 (54.0)	0.490
Nucleoside analogue reverse transcriptase inhibitors	78 (98.7)	37 (100.0)	41 (95.0)	0.490
Integrase inhibitor	6 (7.5)	2 (5.4)	4 (9.4)	0.689
Non-nucleoside analogue reverse transcriptase inhibitors.	51 (65.0)	25 (70.3)	26 (60.5)	0.674
Anthropometric data	-	-	-	-
Weight (kg) (Median IQ:25-75)	72.9 (64.4-82.0)	75.40 (66.0-86.3)	71.8 (64.3-80.9)	0.297
Body mass index (kg/m ²) (Median IQ:25-75)	24.3 (22.4-26.2)	24.9 (21.9-28.3)	23.91 (22.5-26.4)	0.488
Waist circumference (cm) (Median IQ:25-75)	90.8 (84.0-97.5)	92 (84.0-102.0)	88.5 (84.3-94.8)	0.070
Neck circumference (cm) (Median IQ:25-75)	38 (36.3-40.0)	38 (37.0-40.0)	38 (36.1-40.0)	0.199
Increased WC (%)	10 (12.0)	8 (21.6)	2 (4.3)	0.016
Increased WHtR	60 (71.4)	28 (76.0)	32 (70.0)	0.710
Nutritional status (%)	-	-	-	-
Eutrophic	46 (54.8)	19 (51.3)	27 (57.5)	0.730
Overweight	32 (38.1)	14 (37.8)	18 (38.3)	1.000
Obesity	6 (7.1)	4 (11.0)	2 (4.2)	0.390
Comorbidities (%)	-	-	-	-
Diabetes Mellitus	4 (4.8)	2 (5.4)	2 (4.3)	1.000
Metabolic syndrome	12 (14.3)	10 (27.0)	2 (4.3)	0.004
Vitamin D status (%)	-	-	-	-
<30 (ng/dL)	66 (79.5)	32 (86.5)	34 (74.0)	0.182
<20 (ng/dL)	37 (44.6)	21 (56.8)	16 (24.8)	0.075
Increased SHBG (%)	27 (31.2)	16 (43.2)	11 (23.4)	0.054
Laboratory tests (Median IQ:25-75)	-	-	-	-
Total testosterone (ng/dL)	396.5 (314.8-490.2)	327.0 (267.0-402.0)	444.0 (390.0-511.0)	< 0.001
SHBG (nmol/L)	45.4 (35.1-60.2)	50.2 (32.7-65.8)	44.4 (35.7-55.1)	0.169
Calculated free testosterone (ng/dL)	6.6 (5.3-7.4)	5.0 (4.5-5.9)	7.3 (6.8-9.4)	<0.001

Note: Data presented as n (%); Median (IQ: 25-75).

Abbreviations: TD: testosterone deficiency; HIV: human immunodeficiency virus; ART: antiretroviral therapy;

BMI: body mass index; WC: waist circumference WHtR: waist-to-height ratio; IDF: International Diabetes Association; NCEP: National Cholesterol Education Program; PTH: parathyroid hormone; 25(OH)D3: 25 OH vitamin D; SHBG: sex hormone binding globulin

Table 2. DXA data: Comparison between groups with and without Testosterone Deficiency (TD) using the cFT criterion.

-	All (72)	With TD (32)	Without TD (40)	p value
Bone mass (Median IQ:25-75)	-	-	-	-
BMD L1-L4 (g/cm ²)	1.1 (1.0 - 1.2)	1.1 (1.0 - 1.2)	1.1 (1.0 ; 1.2)	0.567
T-score L1-L4	-1.2 (-1.5 ; -0.3)	- 1.2 (-1.6 ; -0.3)	-1.2 (-1.5 ; -0.4)	0.878
Z-score L1-L4	-1.1 (-1.4 ; 0.1)	-1.1 (-1.5 ; 0.1)	-1.0 (-1.4 ; -0.3)	0.489
BMD femoral neck (g/cm ²)	1.0 (0.9 - 1.1)	1.0 (0.9 ; 1.1)	1.0 (0.9 ; 1.1)	0.316
T-score femoral neck	-0.8 (-1.5 ; -0.1)	-0.6 (-1.5 ; -0.2)	-0.9 (-1.4 ; -0.1)	0.748
Z-score femoral neck	-0.1 (-0.7;0.3)	-0.2 (-0.7 ; 0.3)	-0.1 (-0.7 ; 0.4)	0.682
BMD total femur (g/cm ²)	1.0 (0.9 - 1.1)	1.0 (0.9 - 1.1)	1.0 (0.9 ; 1.1)	0.895
T-score total femur	-0.6 (-1.2 ; 0.0)	-0.6 (-1.3 ; 0.0)	-0.7 (-1.2 ; -0.1)	0.847
Z-score total femur	0.9 (0.9 - 1.0)	-0.4 (-0.8 ; 0.1)	-0.3 (-0.7 ; 0.1)	0.574
BMD distal radius third (g/cm ²)	0.9 (0.9 - 1.0)	0.9 (0.9 - 1.0)	0.9 (0.9 ; 1.0)	0.469
T-score distal radius third	-0.7 (-1.3 ; -0.1)	-0.8 (-1.4 ; 0.0)	-0.5 (-1.1 ; -0.1)	0.557
BMD ultradistal radius (g/cm ²)	0.5 (0.4 - 0.5)	0.5 (0.4 - 0.5)	0.5 (0.4 ; 0.6)	0.074
T-score ultradistal radius	-0.8 (-1.6 ; 0.4)	-1.1 (-1.8 ; -0.2)	-0.6 (-1.5 ; 0.9)	0.065
Bone mass classification (%)	-	-	-	-
Normal BM	39 (54.2)	12 (37.5)	27 (67.5)	0.021
Low BM for age	4 (5.5)	0	4 (10.0)	0.120
osteopenia	22 (30.5)	16 (50)	6 (15.0)	0.003
osteoporosis	7 (9.7)	4 (12.5)	3 (7.5)	0.690
Lipodystrophy (%)	-	-	-	-
Lipohypertrophy	33 (39.8)	17 (45.9)	16 (34.8)	0.307
Lipoatrophy	17 (23.6)	6 (18.8)	11 (27.5)	0.392
Total (LH and/or LA)	45 (53.6)	21 (56.8)	24 (51.1)	0.609
Lean mass (Median IQ:25-75)	-	-	-	-
Appendicular lean mass (kg)	23.6 (21.1 - 26.1)	23.4 (20.9 - 26.0)	24.2 (21.2 - 26.1)	0.961
Baumgartner (kg/m ²)	8.1 (7.2 - 9.0)	7.8 (7.1 - 9.2)	8.2 (7.4 - 8.9)	0.590
FNIH	1.0 (0.9 - 1.1)	0.9 (0.9 - 1.1)	1.0 (0.9 - 1.1)	0.316
Lean mass classification (%)	-	-	-	-
Baumgartner (kg/m ²)	20 (27.7)	11 (33.0)	9 (23.0)	0.480
FNIH	4 (5.5)	2 (6.3)	2 (5.0)	1.000
Fat mass (Median IQ:25-75)	-	-	-	-
Trunk fat percentage	14.8 (11.7 - 18.2)	15.6 (12.2 - 19.2)	14.5 (10.0 - 17.6)	0.210
Leg fat percentage	18.8 (14.8 - 23.7)	21.4 (15.8 - 25.9)	18.1 (13.9 - 22.0)	0.109
FMR	1.6 (1.2 - 3.3)	1.5 (1.2 - 2.1)	1.5 (1.3 - 1.8)	0.711
FMI (kg/m ²)	5.3 (4.0 - 7.2)	5.8 (4.3 - 8.4)	5.2 (3.9 - 6.7)	0.056
A/G	1.4 (1.1 - 1.7)	1.3 (1.1 - 1.6)	1.5 (1.3 - 1.8)	0.162
Fat mass classification (%)	-	-	-	-
Increased FMI	27 (38.6)	15 (48.4)	12 (30.8)	0.136
Increased A/G	57 (81.4)	25 (80.6)	32 (82.1)	0.881

Note: Data presented as n (%); Median (IQ: 25-75).

Abbreviations: TD: testosterone deficiency; BMD: bone mineral density; BM: bone mass; FNIH: Foundation for the National Institutes of Health; FMR: fat mass ratio; FMI: fat mass index; A/G: android gynoid ratio (A/G).

Using the cFT criterion, and comparing groups with and without TD, those with TD were older (50 vs 45 years, $p<0.01$), had a higher frequency of MS (27% vs 4.3%,

$p<0.01$), a higher frequency of increased WC (21.6% vs 4.3%, $p<0.05$), lower frequency of normal BM (37.5% vs 67.5%, $p<0.05$), and higher frequency of osteopenia (50%

vs 15%, $p < 0.05$). There was no difference between groups in relation to CD4 count, duration, or type of ART, frequency of low lean mass, lipodystrophy, or fat mass.

When evaluating the correlation between cFT levels and the analyzed variables, a positive correlation was observed with the T-score of the ultradistal radius ($R = 0.25$, $p = 0.031$) and with the BMD of the ultradistal radius ($R = 0.23$, $p = 0.047$). Negative correlations were found with Waist Circumference (WC) ($R = -0.25$, $p = 0.021$) and age ($R = -0.30$, $p = 0.005$).

4. DISCUSSION

In this observational cross-sectional study, the frequency of TD in MLWHIV was evaluated using two criteria, the levels of TT and cFT. We also verified metabolic dysfunctions and body composition, as assessed by DXA, in groups with and without TD. Most of the included men were middle-aged and had been using ART for more than 2 years.

Comparing the cFT and TT, a higher frequency of TD diagnosis was observed when using the first criterion, 44% vs 22.6% ($p < 0.001$) (Fig. 1). Monroe *et al.* [25] observed that, in MLWHIV, the use of TT alone would lead to a loss of TD diagnosis in 30% of the sample. Pezzaioli *et al.* [26] also compared the two criteria and found a frequency of 20.2% versus 10.6% when using the cFT and TT criteria, respectively. Using cFT, twice as many participants were diagnosed with TD. Most studies in the post-ART era have assessed the frequency of TD using mixed criteria, including TT and/or cFT values. TT levels to determine TD were variable, from 280 to 346 ng/dL. Regarding cFT, most authors used values < 6.5 ng/dL. The non-

standardization of criteria implies a large variability in the prevalence of TD in MLWHIV. Using mixed criteria, we observed a variation from 8.7% to 34.5% [8, 9, 25-31]. Aggarwal *et al.* [27] measured cFT using the Enzyme-linked Immunosorbent Assay (ELISA) technique and found a frequency of 66% TD in MLWHIV. Data from these studies are compiled in Table 3.

Previous studies have demonstrated a direct relationship between CD4 count and testosterone levels [9, 27, 29, 32]. Lachâtre *et al.* [8] reported an inverse correlation between CD4 nadir and testosterone deficiency, with values above 200 cells/mm³ acting as a protective factor. However, in the present study, neither CD4 count nor CD4 nadir was associated with cFT levels. One possible explanation is that all participants had undetectable viral loads and satisfactory CD4 counts, resulting in a relatively homogeneous sample in terms of viral suppression.

We did not observe an association between the time of HIV diagnosis, the duration of ART, the type of ART, and TD. Previous studies have also not found any association between these parameters [28, 29]. However, in the study by Lachâtre *et al.* [8], greater exposure to ART, regardless of the class used, was associated with TD.

Regarding age, the present study corroborated that increasing age is associated with an increase in the prevalence of TD, which also occurs in the non-HIV-infected population. Slama *et al.* [33] looked at cFT levels in 499 men (182 HIV-infected and 267 HIV-uninfected) over a 10-year period and observed a 1.2% per year decline in these levels in both groups.

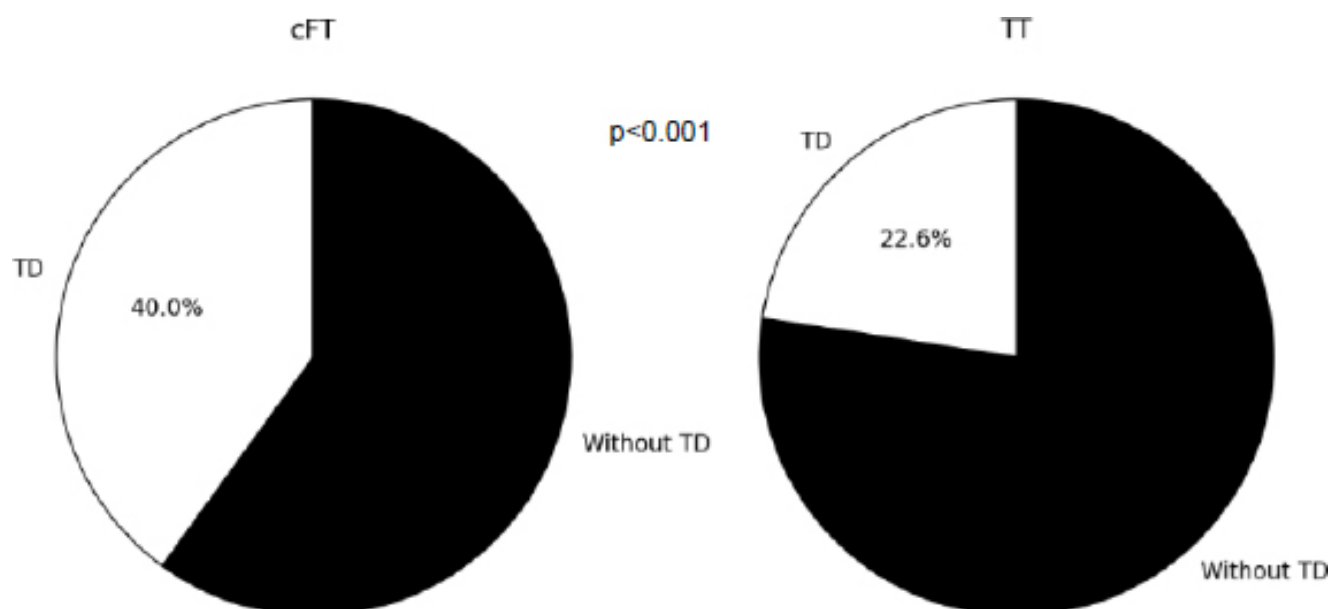


Fig. (1). Frequency of testosterone deficiency (TD) based on total testosterone (TT) vs free calculated testosterone (cFT) criteria.

Table 3. Prevalence of testosterone deficiency (TD) in HIV-infected men in previous studies.

Author's name	Year of Publication	Number of Participants	Prevalence of TD	Diagnostic Criteria
Monroe <i>et al.</i> [25]	2014	364	9.3%	TT<300 ng/dL or cFT <5 ng/dL
Gomes <i>et al.</i> [28]	2016	245	29.4%	TT <280 ng/dL and/or cFT <6.5 ng/dL
Bajaj <i>et al.</i> [9]	2017	81	25.9%	TT <300 ng/dL
Aggarwal <i>et al.</i> [27]	2018	100	66%	TL <0.384 ng/dL
Pongener <i>et al.</i> [29]	2019	120	23.3%	TT<300 ng/dL
Postel <i>et al.</i> [30]	2021	87	34.5%	FT < 6.5 ng/dL
Pezzaioli <i>et al.</i> [26]	2021	94	10.6% pela TT 20.2% pela TLc	TT <346 ngdL or cFT<6.5 ng/dL
Quiros-Roldan <i>et al.</i> [31]	2021	107	30.8%	TT ≤346 ng/dL or cFT ≤6.5 ngldL
Lachâtre <i>et al.</i> [8]	2022	231	8.7%	cFT<7.0 ng/dL

Our data demonstrate a 27% frequency of metabolic syndrome (MS) in the TD group, and we also observed an association between these conditions. However, these findings are conflicting in the literature. Gomes *et al.* [28] found a frequency of MS of 45.8% in 72 HIV-positive individuals with TD; however, they did not find differences in the frequency of MS comparing groups with and without TD. Lachâtre *et al.* [8] found a frequency of MS of 10% in 20 HIV-positive individuals with TD and found no difference in the frequency of MS between the groups with and without TD. Nevertheless, low testosterone levels in men are associated with an increased risk of developing metabolic syndrome regardless of BMI or insulin resistance [34]. The mechanism is still uncertain, but it is suggested that it is bidirectional; hypogonadism increases the risk of metabolic syndrome and *vice versa* [35].

Lipodystrophy is an adverse event associated with the continuous use of ART; its frequency in people living with HIV varies from a small percentage to 80% [36]. This variability occurs due to the use of different methodologies to characterize lipodystrophy. In this study, we employed direct methods, including DXA and abdominal adiposity measurements, to assess lipodystrophy and observed a frequency of 56.8% in men with TD; however, we did not find an association between TD and lipodystrophy. Fat mass ratio has also been proposed in the HIV population as a criterion for lipodystrophy [23]; nonetheless, there is no defined cut-off for diagnosis. In this study, we did not observe an association between FMR and TD. Gomes *et al.* [28] also found no association between testosterone deficiency and lipodystrophy when comparing 72 MLWHIV and TD with 173 MLWHIV without TD; however, WC values > 102 cm were more frequent in the TD group. The current study also demonstrated an association between TD and WC > 102cm, in addition to an inverse correlation between WC and cFT levels, which suggests that this criterion may be a predictor of TD in MLWHIV.

The TD group showed a lower frequency of normal bone mass and a higher frequency of osteopenia. No differences were observed in relation to other factors that influence of bone mass, such as levels of 25-hydrovitamin-D, PTH, renal function, or smoking. Goh *et al.* [37] carried out a systematic review to evaluate the risk factors associated with reduced bone mass in people living with

HIV, and an association was demonstrated between low testosterone levels and reduced BMD. According to a study by Abreu *et al.*, it was demonstrated that MLWHIV with hypogonadism have a 5.9 times greater risk of low bone mass than those with normal cFT levels [38].

In this study, both BMD and ultradistal radius T-score showed a weak positive correlation with cFT levels. Studies carried out in patients with hypogonadism secondary to the use of GnRH analogues due to prostate cancer showed a loss of bone mass mainly at the site of the ultradistal radius, where there is a predominance of trabecular bone in relation to cortical bone [39, 40].

People living with HIV have a higher prevalence of low lean mass than controls without HIV, which has been estimated at 28.8% [41]. Our data did not show an association between TD and low lean mass in MLWHIV. A recent meta-analysis [42] selected studies that investigated factors associated with low lean mass, as analyzed by DXA; however, TD was not among the predictors evaluated in these studies. In addition to our study, we are unaware of any other publication that has studied the association between low lean mass, as assessed by DXA, and low cFT levels.

Increased fat mass was associated with hypogonadism [6]. However, we found no association between TD and increased fat mass quantified by FMI or A/G ratio. Lachâtre *et al.* [8], who studied MLWHIV, also did not find any difference in the percentage of body fat assessed by DXA when comparing groups with and without TD. However, they found a correlation between a fat percentage >19% and hypogonadism, which suggests that this parameter can be used to identify MLWHIV at risk of hypogonadism [8].

5. LIMITATIONS OF THE STUDY

There were limitations to our study. First, external validity is a concern, because this was a single-center, hospital-based sample with well-controlled HIV infection, and it may have differed from the typical MLWHIV in the community. Second, the cross-sectional design limited us to describing associations and not to elaborating causal relationships.

We observed many controversies in the literature

regarding the changes associated with TD in MLWHIV, especially in middle-aged individuals. More prospective studies are needed to evaluate metabolic dysfunctions and changes in body composition in MLWHIV and TD.

CONCLUSION

The frequency of TD in MLWHIV was 44% when using the cFT criterion. The cFT criterion identified twice as many participants with TD as with TT. Its diagnosis was associated with harmful conditions such as metabolic syndrome, changes in bone mass, and greater abdominal circumference, which suggests the importance of screening for TD and the use of cFT for its diagnosis; however, further studies are needed to support the use of this method as a diagnostic criterion.

LIST OF ABBREVIATIONS

AIDS	= Acquired Immunodeficiency Syndrome
A/G	= Android Gynoid Ratio
ALM	= Appendicular Lean Mass Index
ART	= Antiretroviral therapy
BM	= Bone Mass
BMD	= Bone Mineral Density
BMI	= Body Mass Index
cFT	= calculated Free Testosterone
DXA	= Dual-energy X-ray absorptiometry
DM	= Diabetes Mellitus
FM	= Fat Mass
FMI	= Fat Mass Index
FMR	= Fat Mass Ratio
FN	= Femoral Neck
IDSA	= Infectious Diseases Society of America
HIV	= Human Immunodeficiency Virus
LA	= Lipotrophy
LM	= Lean Mass
LH	= Lipohypertrophy
MLWHIV	= Men Living With HIV
MS	= Metabolic Syndrome
NC	= Neck Circumference (NC)
NCEP ATPIII	= National Cholesterol Education Program Adult Treatment Panel III)
SHBG	= Sex Hormone Binding Globulin
TD	= Testosterone Deficiency
TF	= Total Femur
TT	= Total Testosterone
UD	= Ultradistal Radius
WC	= Waist Circumference

WHtR = Waist-to-Height Ratio

25 (OH)D3 = 25-OH vitamin D TOTAL

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Research Ethics Committee of the University Hospital Antonio Pedro CAAE 17322613.9.0000.5243.

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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