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Hypogonadism: a neglected comorbidity in young and middle-aged HIV-positive men on effective combination antiretroviral therapy

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Objective: Male hypogonadism is poorly characterized in young-to-middle-aged people with HIV (PWH). We used a reliable free testosterone assay to assess the prevalence and predictive factors for male hypogonadism in PWH on effective combined antiretroviral therapy (cART).

Design: A French cross-sectional study from January 2013 to June 2016.

Methods: We included HIV-1-infected men aged between 18 and 50 years with HIV loads of 50 RNA copies/ml or less, on effective cART for at least 6 months. Hypogonadism was defined, according to guidelines, as a mean calculated serum free testosterone concentration less than 70pg/ml (Vermeulen equation). Sociodemographic, anthropometric, bone-densitometry, hormonal, immunovirological, metabolic, and therapeutic parameters were collected. The IIEF-5, HAM-D, and AMS scales, respectively, assessed erectile function, depression, and quality of life.

Results: Overall, 240 patients were enrolled, 231 were analyzed. Low free testosterone concentrations (<70pg/ml) were recorded in 20 patients (8.7%), and were exclusively of secondary origin. In multivariable analysis, the risk factors predictive of male hypogonadism were age more than 43 years [adjusted *odds ratio* (aOR) 3.17, 95% confidence interval (95% CI) 1.02–9.86; $P=0.04$], total fat percentage more than 19% (aOR 3.5, 95% CI 1.18–10.37; $P=0.02$), and treatment including efavirenz (aOR 3.77, 95% CI 1.29–10.98; $P=0.02$). A nadir CD4+ T-cell count more than 200 cells/ μ l (aOR 0.22, 95% CI 0.07–0.65; $P<0.01$) were protective.

Conclusion: Male hypogonadism remains common in young-to-middle-aged PWH with stably suppressed viral replication. Treatment including efavirenz, being over 43 years old, and having a total body fat percentage greater than 19% could be used as criteria for identifying PWH at risk. Early screening for male hypogonadism might improve care by identifying patients requiring testosterone replacement.

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Introduction

Male hypogonadism is common in people with HIV (PWH) despite the widespread use of combined antiretroviral therapy (cART). Before the widespread use of cART, male hypogonadism was the most common endocrine abnormality detected in PWH [1]. Male hypogonadism was often associated with advanced-stage of HIV-infection and especially with low CD4⁺ cell count, weight loss, and AIDS wasting [2–5]. Male hypogonadism is also correlated with aging and a number of comorbid conditions (chronic hepatitis C virus infection, use of psychotropic and intravenous drugs) [6–8]. It is mostly caused by impairment of the hypothalamic–pituitary axis (HPA) [9]. It may affect overall quality of life and can lead to osteopenia/osteoporosis, erectile dysfunction/low libido, metabolic syndrome, a decrease in lean body mass/muscle strength and depression; its diagnosis is therefore important [10–13]. Recent studies have estimated its prevalence at 9.3–70% in PWH [4,14–18].

Total testosterone levels are affected by changes in sex-hormone-binding globulin (SHBG) levels in PWH, in whom free testosterone assays are recommended for the diagnosis of male hypogonadism [10,12,13,16]. These assays should be performed according to a well defined method using a reliable technique [Vermeulen equation or equilibrium dialysis (available in only a few specialized laboratories)] [10,12,13,19]. Only limited clinical data obtained with a reliable free testosterone assay are available for analyses of the prevalence of male hypogonadism and factors associated with this condition in PWH [15,16]. Virological suppression is now generally achieved due to the widespread use of cART in PWH in industrialized countries [20], but none of the published studies was conducted in a population of AIDS history-free PWH on effective cART.

Otherwise, osteopenia/osteoporosis [21–23], erectile dysfunction/low libido [24], metabolic syndrome [25], decrease in lean body mass/muscle strength, and depression [26] are widely described in PWH. These disorders may affect the quality of life of patients, which remains today one of the major issues in the overall care of patients. They are classically multifactorial in PWH (e.g. osteoporosis associated with length of time on HIV infection, weight loss, aging, and some cART [27], or erectile dysfunction usually associated with aging, depression, and length of time on cART [28]).

We therefore used a reliable free testosterone assay to determine the prevalence of male hypogonadism (and its origin), and to investigate the predictive factors potentially associated with male hypogonadism, including

osteoporosis, erectile dysfunction, metabolic syndrome and body composition, in young-to-middle-aged, AIDS history-free, HIV-infected men on effective cART.

Materials and methods

Study design and participants

We conducted a cross-sectional study in PWH attending consultations at two French university hospitals (Tourcoing Hospital and Bicetre Hospital/AP-HP). The study was approved by the Nord-Pas-De-Calais Ethic Committee, in accordance with the 2008 Declaration of Helsinki. We identified potential participants with Nadis computer software. Recruitment began in January 2013, for a planned period of 42 months. The study design is shown in Fig. 1.

HIV-1-infected men aged between 18 and 50 years were eligible for the study if they displayed a stable suppression of HIV replication (HIV-RNA \leq 50 copies/ml) on cART for at least 6 months at the time of screening. Key exclusion criteria included HIV-2 infection, hepatitis B and C, cirrhosis, a glomerular filtration rate estimated by the Cockcroft-Gault method of less than 30 ml/min, past or ongoing opportunistic infection, current cancer, treatment with testosterone or other anabolic agents, antiandrogens, a GnRH (gonadotropin-releasing hormone) analog, estrogens, glucocorticoids, growth hormones or IGF-1 (insulin-like growth factor-1) in the previous three months, and a pituitary, testicular, or adrenal disease with or without treatment. Full inclusion and exclusion criteria are provided in Appendix 1, <http://links.lww.com/QAD/C448>. All participants gave written informed consent before the study began.

Outcomes

The main outcome variable was biochemical hypogonadism, defined as a mean serum free testosterone concentration less than 70 pg/ml, in accordance with guidelines [11,29]. Sociodemographic, anthropometric, bone-densitometry, hormonal, immunological, virological, metabolic, and therapeutic parameters were recorded. The International Index of Erectile Function 5 (IIEF-5) score, the Hamilton Depression Rating scale (HAM-D) and the Aging Male Symptoms (AMS) scale were used to evaluate erectile function, depression, and quality of life, respectively [30,31].

Procedures

The main parameters, IIEF-5 score, HAM-D scale, AMS scale, and the first venous blood sample were collected at screening. A second venous blood sample

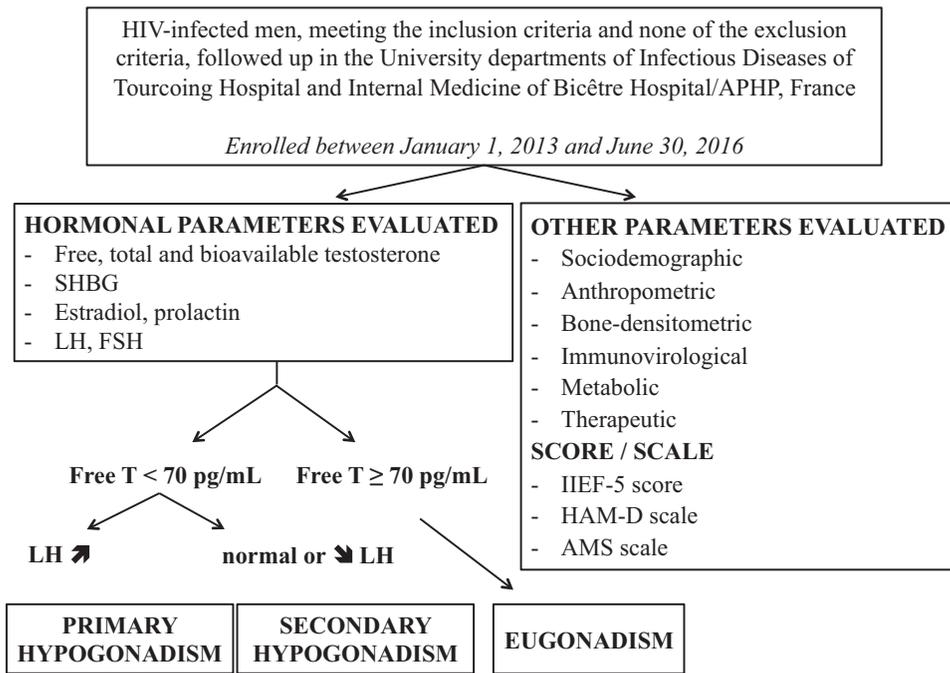


Fig. 1. Study design. APHP, Assistance Publique - Hôpitaux de Paris, Paris Public Academic Hospital Network; FSH, follicle-stimulating hormone; HAM-D scale, Hamilton rating scale for depression; IIEF-5, International index of erectile function-5; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; T, testosterone.

was obtained on day 8, for the determination of mean serum free testosterone concentration and for the total testosterone assay. Venous blood samples were collected in the morning, between 0700 and 0900 h, fasting, as recommended [12]. The reference thresholds used for most biochemical parameters were those of the corresponding laboratories. However, the thresholds used for total testosterone and free testosterone were determined in accordance with European guidelines [11], based on the results of the study by Bhasin *et al.* [29] published in 2011, which was performed on a large cohort of young men (19–40 years of age) with a reliable method. Dual-energy X-ray absorptiometry (DXA) was carried out before week 2, locally, at each site, together with determinations of HIV-RNA, CD4⁺ and CD8⁺ T-cell counts, and vitamin D. HIV-DNA, hormonal, and metabolic parameter determinations were performed centrally, in specialized laboratories at Lille Hospital (France).

Free testosterone concentration was calculated according to the Vermeulen equation, from total testosterone, SHBG, and albumin concentrations [19]. Serum total testosterone, SHBG, estradiol, prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels were determined. Total testosterone concentration was determined by two different methods: a radioimmunoassay (RIA) (with the ‘Coat-A-Count Total Testosterone’ RIA kit; Siemens Healthcare Diagnostics Inc., Los Angeles, California, USA) with an interassay precision of less than 11%; and a chemiluminescent microparticle immunoassay (CMIA) on

an Architect i2000 immunoassay analyser (‘ARCHITECT 2nd Generation Testosterone assay’; Abbott Diagnostics, Abbott Park, Illinois, USA) with an interassay precision of less than 10%. We switched from the RIA to the CMIA assay due to Siemens’ decision to stop producing the radioimmunoassay kits in April 2015. The correlation between the two testosterone assays was evaluated on a sample of 34 serum samples, by Fleiss intraclass correlation evaluation. The intraclass correlation coefficient (ICC) was 0.94, with a 95% confidence interval of [0.88;0.97]. Estradiol was assayed by RIA, and LH, FSH, prolactin, and SHBG were determined by chemiluminescence immunoassays.

Duration of HIV infection, HIV-DNA load, CD4⁺ and CD8⁺ T-cell counts, CD4⁺ T-cell nadir, and CD4⁺/CD8⁺ T-cell ratio were determined. HIV-RNA load was analyzed on site with an ultrasensitive real-time PCR method. HIV-DNA load was also determined with an ultrasensitive real-time PCR method (Generic HIV-DNA assay; Biocentric, France). CD4⁺/CD8⁺ T-cell count ratios were determined by flow cytometry. The duration of exposure to ART and the current ART regimen were recorded. Drugs were classified into the following ART classes: nucleoside reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors, and integrase inhibitors.

Age, lifestyle, BMI, waist/hip circumference ratio, and serum 25-OH vitamin D concentration were noted. Lumbar spine (L1–L4) and hip (left total femur) bone

mineral densitometry (BMD) Z-score, and total body composition, including total fat content expressed as a percentage of total mass, appendicular lean mass (kg), and appendicular lean mass index (kg/m^2) were evaluated by DEXA (dual-energy X-ray absorptiometry [32]). Sarcopenia was defined as follows: appendicular lean mass < 20 kgs or appendicular lean mass index less than $7 \text{ kg}/\text{m}^2$ [33]. For patients attending of Tourcoing Hospital, DEXA was performed in the Department of Nuclear Medicine, Lille Hospital (France), with a Hologic Discovery A device (Hologic, USA). For patients attending Bicêtre Hospital/AP-HP, DEXA was performed in the Department of Nuclear Medicine, Bicêtre Hospital/AP-HP (France), with a Prodigy Advance GE Lunar device (GE Healthcare, UK). Given the differences in calibration between these two machines, conversion formulas were obtained from GE Healthcare, UK, to harmonize the measurements. Patients were considered to have a normal BMD, osteopenia, or osteoporosis if the lumbar or femoral Z-score was at least -1 , between -1 and -2 , or -2 or less, respectively [32]. 25-OH vitamin D levels were determined by an electrochemiluminescence assay (ECLIA).

Metabolic syndrome was defined as the combination of at least three of the following five criteria: waist circumference more than 102 cm, plasma triglyceride concentration at least 1.5 g/l, serum high-density lipoprotein (HDL)-cholesterol concentration less than 0.4 g/l, blood pressure at least 130/85 mmHg, and fasting blood glucose concentration at least 1.1 g/l [34]. HOMA-IR, used to evaluate insulin resistance, was defined as follows: fasting insulin (mIU/l) \times fasting blood glucose concentration (mmol/l)/22.5 [35]. Total cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides, glucose, and insulin were determined by colorimetry.

International Index of Erectile Function (IIEF)-5 score was classified as follows: uninterpretable (1–4), erectile dysfunction (5–20), normal (21–25) [30]. Hamilton Rating Scale for Depression (HAM-D) scores were classified as follows: depression (≥ 8), normal (0–7) [31]. Aging Male Symptoms scale (AMS scale) scores were classified as follows: deterioration in quality of life (> 27), no deterioration in quality of life (≤ 26).

Statistical analysis

We first described the baseline characteristics of patients enrolled in the study. We described quantitative variables using medians and interquartile ranges (IQRs), and compared the results from the two study centers in a nonparametric Wilcoxon rank-sum test. We summarized qualitative variables using percentages and compared the results of the two centers in a chi-squared test.

Factors associated with male hypogonadism were then identified with univariable and multivariable logistic regression models. The ‘log-linear’ hypothesis was

verified for each quantitative variable. Variables for which the ‘log-linear’ hypothesis was rejected were introduced as class in the univariable and multivariable models. Variables were added to the multivariable model if found to be associated with male hypogonadism in univariable analysis (P -value < 0.25). We developed the multivariable model by backward stepwise regression analysis. In the multivariable analysis, P values less than 0.05 were considered to be significant. The adequacy of the model was assessed with the Hosmer–Lemeshow test.

SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina, USA) was used for all analysis.

This trial is registered with ClinicalTrials.gov, under number NCT02665559.

Results

As shown in the study flow chart (Fig. 2), 2388 PWH, including 1758 men, followed up in the University department of Infectious Diseases of Tourcoing Hospital and 2184 PWH, including 1384 men, followed up in the University department of Internal Medicine of Bicêtre Hospital/APHP were screened between January 1, 2013, and June 30, 2016. Of these patients, 421 men infected with HIV were meeting the inclusion/noninclusion criteria. Finally, 240 patients were enrolled and 231 patients were analyzed. Testosterone data (D0 or D8) were missing for the other nine patients.

Most patients [187 (77.9%)] were MSM, and their median age at baseline (Table 1) was 43 years (IQR: 36–47 years). The patients with free testosterone deficiency were older than the eugonadal patients (45.5 versus 43 years; $P < 0.01$). Most patients had CD4^+ T-cell counts above 500 cells/ μl , with a median CD4^+ T-cell count of 632 cells/ μl (IQR: 500–766 cells/ml) and a median duration of undetectable viral load of almost 3 years [33.8 months (IQR: 15.6–66.6 months)]. HIV infection was diagnosed a median of 8 years before the study (IQR: 4–13 years). Hypogonadal patients had a longer duration of viral load suppression (58.8 versus 33.5 months; $P = 0.02$) and a lower CD4^+ T-cell nadir (256 versus 302 cells/ μl ; $P < 0.01$) than eugonadal patients. No differences in CD4^+ T-cell counts or time since the diagnosis of HIV infection were observed between these two groups. The median duration of exposure to cART was 47.5 months (IQR: 20.3–100 months) and 200 (95%), 113 (47.1%), 92 (38.3%), and 52 (21.7%) patients were treated with combinations containing an NRTI, NNRTI, protease inhibitor, or integrase inhibitor, respectively. The patients with free testosterone deficiency had been receiving global cART (78.2 versus 46.2 months; $P = 0.04$), NRTI (76 versus 45 months; $P = 0.04$), protease inhibitor (99.7 versus

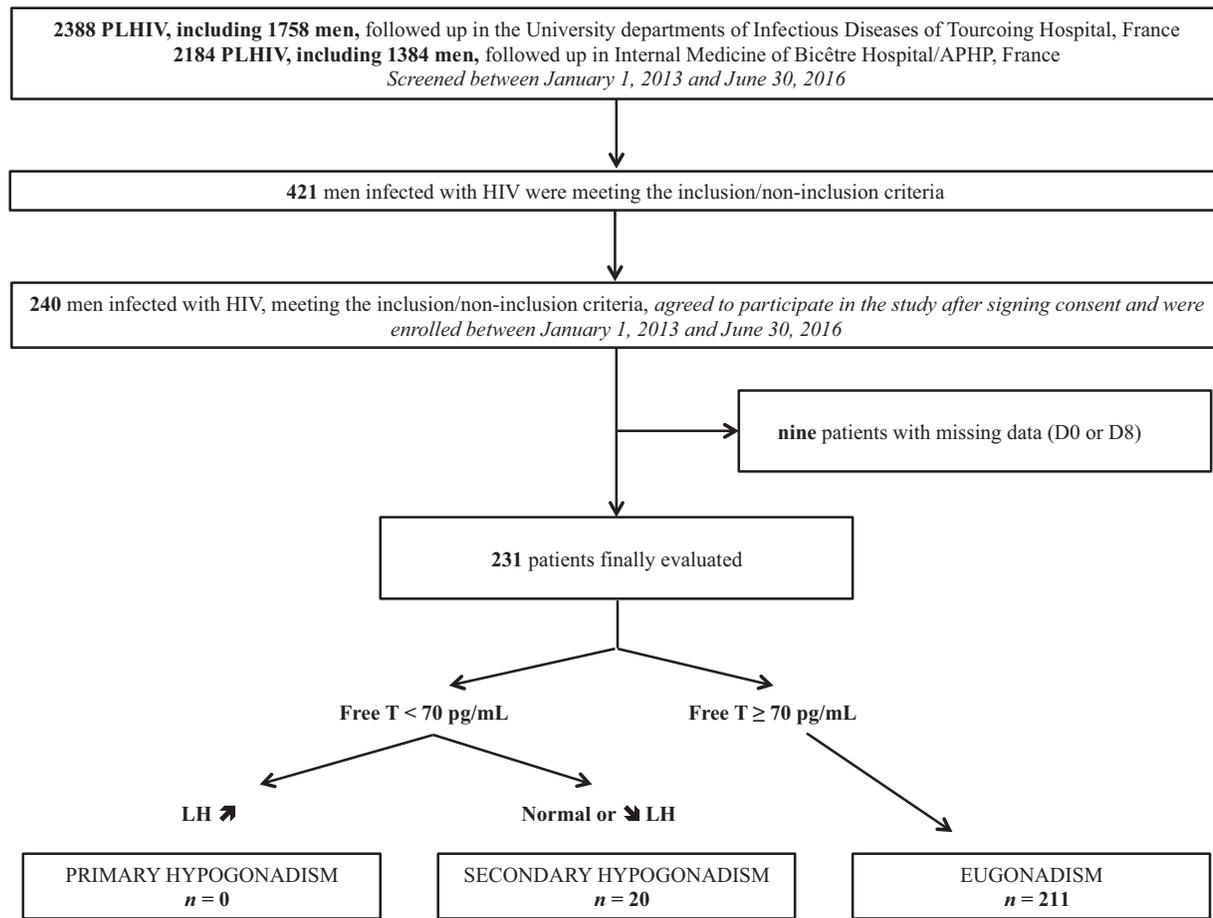


Fig. 2. Flow chart. APHP, Assistance Publique - Hôpitaux de Paris, Paris Public Academic Hospital Network; D, day; LH, luteinizing hormone; n, number of patients; PWH, people living with HIV; T, testosterone

24.3; $P = 0.01$), and II (55.9 versus 17.9 months; $P = 0.01$) for longer than the eugonadal patients. High SHBG levels were detected in 112 patients (47%), and were more frequent in the hypogonadal group [15 patients (75%) versus 91 patients (43.5%); $P < 0.01$]. Median LH, FSH, prolactin, and estradiol levels were normal with no significant difference between groups for the first three. Analyzing the worst BMD Z-scores at any two sites, 75 patients (32.6%) met the definition of osteopenia and 36 (15.7%) met the definition of osteoporosis. Most patients were neither overweight nor obese, with a median BMI of 23 (IQR: 21–25) and only 22 patients (9.2%) had metabolic syndrome. Appendicular lean mass and appendicular lean mass index were normal in most patients, with median levels of 25.9 kg (IQR: 23.9–28.1) and 8.2 kg/m² (IQR: 7.6–8.8), respectively. More than half the patients reported having erectile dysfunction and deterioration in quality of life (133 patients (55.4%) in both cases), 80 patients (33.3%) had depressive symptoms.

Mean serum free testosterone concentration was low (< 70 pg/ml) in 20 patients (8.7%), and mean serum total testosterone concentration was low (< 348 ng/dl) in nine patients (3.9%). Male hypogonadism was exclusively of

secondary origin, as indicated by the normal or low levels of LH.

In multivariable analysis (Table 2), the parameters independently associated with male hypogonadism were age more than 43 years [adjusted odds ratio (aOR) 3.17, 95% CI 1.02–9.86; $P = 0.04$], total fat percentage more than 19% (aOR 3.5, 95% CI 1.18–10.37; $P = 0.02$), and a treatment regimen including efavirenz (aOR 3.77, 95% CI 1.29–10.98; $P = 0.02$), all of which were identified as risk factors. A CD4⁺ cell count nadir more than 200 cells/ μ l (aOR 0.22, 95% CI 0.07–0.65; $P < 0.01$) was found to be protective. Like IIEF-5 score, none of the infectious or metabolic parameters were associated with male hypogonadism.

Discussion

Male hypogonadism, which is widely associated with advanced stages of HIV infection, used to affect up to 50% of men with AIDS [3,5]. Despite the widespread use of cART, it remains common among HIV-infected men,

Table 1. Baseline characteristics of the entire cohort and according to the threshold testosterone concentration.

	Normal range	Entire cohort Patients (n = 240)	Hypogonadism FT < 70 pg/ml Patients (n = 20)	Eugonadism FT > 70 pg/ml Patients (n = 211)	P
Sociodemographic parameters (n = 231)					
Age (years)	18–50	43 [36–47]	45.5 [43.5–50]	43 [36–47]	<0.01
Mode of contamination/HIV					
MSM	–	187 (77.9)	–	–	–
Lifestyle (n = 231)					
Active smoking	–	98 (40.8)	9 (45)	85 (40)	0.81
Alcohol > 20g/day	–	21 (8.8)	1 (5)	20 (9)	0.82
Psychoactive drugs	–	36 (15)	2 (10)	34 (16)	0.75
Infectious parameters (n = 231)					
Duration of HIV infection (years)	–	8 [4–13]	9 [6–17]	7 [3–13]	0.14
Duration of HIV load undetectability (months)	–	33.8 [15.6–66.6]	58.8 [41.4–80.6]	33.5 [15.5–66.1]	0.02
Immunological parameters (n = 231)					
CD4 ⁺ (cells/ μ l)	700–1100	632 [500–766]	580 [553–696]	633 [508–769]	0.28
CD4 ⁺ /CD8 ⁺ ratio	> 1	0.9 [0.7–1.2]	0.9 [0.7–1.1]	1 [0.7–1.2]	0.68
CD4+ nadir (cells/ μ l)	–	298 [218–404]	256 [152–299]	302 [221–414]	<0.01
Therapeutic parameters					
Duration of exposure to cART (months) (n = 231)	–	47.5 [20.3–100]	78.2 [51.3–135]	46.2 [19.3–101]	0.04
Duration of exposure to NRTI (months) (n = 226)	–	45.9 [18.9–90.8]	76 [51.3–91.6]	45 [17.9–97.1]	0.04
Duration of exposure to NNRTI (months) (n = 113)	–	43.5 [19–76.2]	69.8 [46.3–80.4]	42.5 [18.7–74.3]	0.06
Duration of exposure to PI (months) (n = 92)	–	29.7 [12.9–85.2]	99.7 [28.2–152.4]	24.3 [12.8–74.6]	0.01
Duration of exposure to II (months) (n = 52)	–	20.2 [9–49.8]	55.9 [55.3–68.6]	17.9 [8.2–36.9]	0.01
Ongoing cART (n = 231)					
NRTI	–	200 (95)	17 (85)	199 (95)	0.1
NNRTI	–	113 (47.1)	10 (50)	96 (45)	0.81
PI	–	92 (38.3)	10 (50)	80 (38)	0.34
II	–	52 (21.7)	5 (25)	47 (22.3)	0.78
Hormonal parameters (n = 231)					
Free testosterone (pg/ml)	\geq 70	103.9 [89.2–126.9]	–	–	–
Total testosterone (ng/dl)	\geq 348	585 [482–693.5]	–	–	–
SHBG > 42.2nmol/l ^a	–	112 (47)	15 (75)	91 (43.5)	<0.01
LH (U/l)	0.6–12	3.7 [2.8–4.9]	3.9 [1.9–5.5]	3.7 [2.8–4.9]	0.6
FSH (U/l)	0.9–12	4.1 [2.9–5.1]	3.9 [2.7–7.1]	4.1 [2.9–5.8]	0.8
Prolactin (ng/ml)	3.5–19.4	7 [5–10]	6 [5–7.5]	7 [5–10]	0.4
Estradiol (pg/ml)	9–62	20 [16–26]	–	–	–
Anthropometric/bone-densitometry parameters BMI (kg/m ²)	18.5–24.9	23 [21–25]	24 [22–26]	23 [21–25]	0.41
Bone mineral density (BMD) (n = 230)					
Worst BMD Z-score					0.18
Normal	\geq - 1	119 (51.7)	13 (65)	104 (50)	
Osteopenia	- 1 > et > - 2	75 (32.6)	3 (15)	72 (35)	
Osteoporosis	\leq - 2	36 (15.7)	4 (20)	29 (14)	
Body composition (n = 230) % Fat mass (total mass)					
Trunk (%)	–	18 [14–26]	21 [15–25]	18 [14–26]	0.4
Total (%)	–	18.9 [15.1–23.2]	21 [17–25]	18 [15–23]	0.2
Appendicular lean mass (kg)	> 20	25.9 [23.9–28.1]	25 [23.8–28.1]	25.9 [23.9–28.1]	0.61
Appendicular lean mass index (kg/m ²)	> 7	8.2 [7.6–8.8]	7.9 [7.7–8.6]	8.2 [7.6–8.9]	0.42
Metabolic parameters (n = 231)					
Metabolic syndrome	–	22 (9.2)	2 (10)	19 (9)	0.7

Table 1 (continued)

	Normal range	Entire cohort Patients (n = 240)	Hypogonadism FT < 70 pg/ml Patients (n = 20)	Eugonadism FT > 70 pg/ml Patients (n = 211)	P
IIEF-5 score (n = 231) Pathological	(5–20)	133 (55.4)	13 (65)	115 (55)	0.48
HAM-D scale Pathological	(≥ 8)	80 (33.3)	3 (15)	74 (35)	0.05
AMS-scale Pathological	0–27	133 (55.4)	12 (60)	113 (53.5)	0.78

The data shown are medians [IQR] and numbers (%). IQR, interquartile range; n, number of patients. BMD, bone mineral density; cART, combined antiretroviral therapy; FT, free testosterone; II, integrate inhibitor; IIEF-5, international index of erectile function-5; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SHBG, sex hormone-binding globulin.
^aThreshold between normal and high.

but its prevalence is unclear, with a wide range of estimates, from 9.3 to 70%, reported in recent studies [4,14–18,36]. The male hypogonadism prevalence of 8.7% reported here is twice that for the general population of the same age [37]. The prevalence of male hypogonadism in the general population is well established, and can therefore be compared indirectly with that of our cohort, despite being based on total testosterone levels. The use of a reliable free testosterone assay in young-to-middle-aged AIDS-free men in whom HIV replication is stably suppressed may account for the lower, but more accurate prevalence rate reported here than in previous studies [4,14–18]. Recent studies and guidelines recommend the use of free testosterone assays for male hypogonadism diagnosis in some physiological or pathological situations, including HIV infection, due to changes in SHBG levels [10,12,13,16]. This is particularly relevant in our study, in which half the patients had high SHBG levels and more than half the patients with male hypogonadism would have not been diagnosed if only total testosterone assays had been used. Recent studies have shown that low free testosterone concentration is associated with androgen deficiency-related symptoms, even in the presence of normal total testosterone concentrations [38]. Moreover, the prevalence reported here is similar to the values reported for the general population of older men [37].

Male hypogonadism is rare in young-to-middle-aged individuals in the general population, in which it is mostly attributed to a congenital pituitary or gonadal dysfunction [10,11]. Male hypogonadism may be of testicular origin, but is mostly of hypothalamic-pituitary origin in PWH [9]. Our data are consistent with published studies identifying hypothalamic-pituitary axis impairment as the exclusive cause of male hypogonadism. Compared with other systemic diseases [39], HIV infection is itself a specific cause of hypogonadism [40,41]. One of the first reasons for this is the occurrence of significant immune disorders (inappropriate secretion of cytokines) [42]. Several studies have also demonstrated a direct cytopathic effect of the virus, which may cause gonadal dysfunction [43]. Also, testosterone deficiency is strongly associated with the decline of CD4⁺ T-cell counts [5]. Despite the widespread use of cART, CD4⁺ T-cell counts remain associated with male hypogonadism [4,5,14,36]. Consistent with published findings, the CD4⁺ T-cell count nadir was found to be associated with male hypogonadism in our study, with values greater than 200 cells/μl considered protective. Moreover, we report for the first time a correlation between male hypogonadism and any class of antiretroviral drugs. Lipodystrophy in PWH may manifest as breast lipohypertrophy also known as gynecomastia, and may be promoted by cART regimens including efavirenz [44,45]. The aromatization of testosterone to estradiol in patients with gynecomastia could explain the association between male hypogonadism and efavirenz found in this study, this especially as gynecomastia has been reported to be

Table 2. Factors associated with male hypogonadism.

	Univariable analysis			Multivariable analysis		
	OR	Patients (<i>n</i> = 231) 95% CI	<i>P</i>	aOR	Patients (<i>n</i> = 215) 95% CI	<i>P</i>
Sociodemographic parameters						
Age (≥ 43 years)	3.66	1.29–10.44	0.01	3.17	1.02–9.86	0.04
Lifestyle						
Active smoking	1.21	0.48–3.05	0.68	–	–	–
Alcohol > 20g/day	0.86	0.21–3.48	0.83	–	–	–
Psychoactive drugs	0.57	0.12–2.60	0.47	–	–	–
Infectious parameters						
Duration of HIV infection (years) (> 10)	0.88	0.34–2.30	0.79	–	–	–
Duration of HIV nondetectability (months) (> 33)	4.36	1.41–13.48	0.01	–	–	–
Immunological parameters						
CD4 ⁺ (cells/ μ l) (> 500)	0.59	0.22–1.56	0.29	–	–	–
CD4 ⁺ /CD8 ⁺ ratio (> 1)	0.48	0.18–1.29	0.14	–	–	–
CD4 ⁺ nadir (cells/ μ l) (> 200)	0.25	0.09–0.66	0.01	0.22	0.07–0.65	<0.01
Therapeutic parameters						
Duration of exposure to cART (months) (> 52)	3.39	1.19–9.67	0.02	–	–	–
Duration of exposure to NRTI (months) (> 48)	3.29	1.19–9.76	0.02	–	–	–
Duration of exposure to NNRTI (months) (> 48)	2.32	0.91–5.90	0.08	–	–	–
Duration of exposure to PI (months) (> 33)	1.29	0.49–3.40	0.60	–	–	–
Duration of exposure to Ii (months) (> 20)	2.37	0.80–7.07	0.12	–	–	–
Ongoing cart						
NRTI	0.31	0.09–1.22	0.09	–	–	–
NNRTI	1.19	0.48–3.00	0.69	–	–	–
Efavirenz	2.68	1.03–6.98	0.04	3.77	1.29–10.98	0.02
Protease inhibitors	1.64	0.65–4.10	0.29	–	–	–
Integrase inhibitors	1.16	0.4–3.37	0.78	–	–	–
Anthropometric and bone-densitometry parameters						
BMI (kg/m ²) (≥ 25)	1.67	0.61–4.61	0.32	–	–	–
Bone mineral density (BMD) Worst BMD Z-score (versus normal)						
Osteopenia	0.33	0.09–1.21	0.09	–	–	–
Osteoporosis	1.10	0.33–3.64	0.87	–	–	–
Body composition % Fat mass (total mass) (> 19) Total (%)	2.60	0.96–7.02	0.06	3.5	1.18–10.37	0.02
Metabolic parameters						
Metabolic syndrome	1.12	0.24–5.21	0.88	–	–	–
IIEF-5 score (pathological versus normal)	1.55	0.60–4.04	0.37	–	–	–

Univariable analysis: data are shown as *odds ratios* (ORs) with 95% confidence intervals (95% CI). Multivariable analysis: data are shown as adjusted *odds ratios* (aORs) with 95% confidence intervals (95% CI). BMD, bone mineral density; cART, combined antiretroviral therapy; FT, free testosterone; Ii, integrase inhibitor; IIEF-5, international index of erectile function-5; *n*, number of patients; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SHBG, sex hormone-binding globulin.

associated with male hypogonadism [46]. However, the association between male hypogonadism and efavirenz does not disappear when estradiol is added to the multivariable model. To our knowledge, there is no other mechanism to date to explain this correlation. Moreover, several publications now report the risk of weight gain on effective cART including integrase inhibitors [47,48]. By analogy and taking into account the current widespread prescription of integrase inhibitors, it seems necessary to remain vigilant on the possible occurrence of male hypogonadism secondary to this weight gain in PWH treated with integrase inhibitors. On the contrary, as SHBG levels increase with age [10], HIV infection seems to lead to an early decline in circulating testosterone levels in PWH [17], even in AIDS history-free HIV-infected men on effective cART, as indicated in our study. As reported for other comorbid conditions observed during HIV infection [49], the early onset of male hypogonadism may reflect the premature aging of PWH [17].

Not surprisingly, age was identified as a risk factor for male hypogonadism in our study, and the patients with testosterone deficiency were older than the eugonadal patients. The correlation between age and male hypogonadism is well established [6,14,15,17,36], but our findings (based on a reliable free testosterone assay) show for the first time that this correlation is independent of viral control and of total body fat percentage. Indeed, male hypogonadism was also associated with total body fat content, as reported for obese patients with or without HIV infection in whom excess adipose tissue can provoke male hypogonadism by promoting the aromatization of testosterone to estradiol [15,17,50]. In a recent publication, low free testosterone and visceral fat were reported as independently associated to poor health status and frailty, being possible hallmarks of unhealthy conditions in young-to-middle-aged HIV-infected men. The authors concluded to an association between multimorbidity, frailty and body fat mass to each other and to sex steroids

(among which free testosterone), concurring together to functional male hypogonadism in HIV [51]. This information is of clinical relevance suggesting that testosterone deficiency in PWH with visceral adiposity may potentially be reversed through weight loss and visceral fat reduction.

No association was found between male hypogonadism and osteopenia/osteoporosis neither erectile dysfunction/ low libido, nor metabolic syndrome, nor decrease in lean body mass/muscle strength, nor depression, nor deterioration in quality of life. The young age of patients [median age of 43 years (IQR: 36–47 years)], their short duration of HIV infection [median of 8 years (IQR: 4–13 years)], and short duration of exposure to cART [median exposure time of 47.5 months (IQR: 20.3–100 months)] would all account for our results (Table 1). The relatively small size of the hypogonadal group could also account for our findings and represents one of the limits of this work. However, more than half the patients (entire cohort) reported having erectile dysfunction and deterioration in quality of life and third the patients had depressive symptoms. These results are in line with the data in the literature specifying the multifactorial origin of depressive disorders, erectile disorders, and impairment of quality of life in PWH [24,52,53]. A larger sample of the population may allow us to conclude.

In this study, male hypogonadism was defined biochemically. Each patient diagnosed with male hypogonadism had at least one clinical sign of male hypogonadism and was referred to a specialist and this consultation provided an opportunity to discuss the possibility of introducing testosterone supplementation. Current Endocrine Society clinical guidelines recommend adjuvant treatment with testosterone at least in the short term, in HIV-infected men with weight loss and low testosterone levels, to promote gains in muscle strength and lean body mass [12,13]. Today, the major issue in the overall care of PWH is not to ignore a disorder that could affect their quality of life. Knowing how to recognize male hypogonadism therefore seems essential. Determining the factors associated with male hypogonadism could help identify patients at risk and discuss the indication for testosterone supplementation.

Conclusion

The prevalence of male hypogonadism was not negligible in our population of young and middle-aged, AIDS history-free, HIV-infected men on effective cART. The early onset of hypogonadism may reflect the premature aging of HIV-infected patients. Our findings suggest that cART regimens including efavirenz, age over 43 years, and total body fat content exceeding 19% could be used as

criteria for the identification of PWH at high risk of hypogonadism. Viral replication is stably suppressed in most patients in industrialized countries. Screening for this endocrine disorder, from venous blood samples collected early in the morning, and with a reliable free testosterone assay, is thus a key element of the overall management of HIV-infected patients.

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A C and A P were the principal investigators A C, A P, M.L. designed the trial and developed the protocol. B.S. was responsible for the biochemical/hormonal investigations. L.B. was responsible for the virological investigations. P.A. was responsible for the statistical analysis. G.L. and E.D. were responsible for the investigations with Dexa. A.P., F.A., Y.Q., E.S., C.G., and A.C. enrolled patients. P.C., M.M. coordinated data collection and regulatory requirements. C.A., P.A., L. M., and F.B. interpreted the data. A.P., M.L., C.A. generated the tables and figures. M.L., A.C., and A.P. wrote the manuscript, and all authors reviewed, revised, and approved the final manuscript.

Appendix 1: Full inclusion and exclusion criteria of the study.

Full inclusion and exclusion criteria of the study are provided in the Appendix 1.

Conflicts of interest

A.C. reports grants from Viiv, Gilead, and Janssen.

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