

# Hypogonadotropic hypogonadism in human immunodeficiency virus-infected men: uncommonly low testosterone levels

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## Summary

Hypogonadotropic hypogonadism (HH) is common and occurs prematurely in HIV-infected men. However, HH with very low testosterone has not been described. Three men with normal pubertal development and HIV1 diagnosis at the ages of 22, 34 and 35 years. All complained of decreased libido, anejaculation and erectile dysfunction thirteen years, six months and one year after HIV diagnosis, respectively. Two had depressive syndrome and two were treated with antiretroviral therapy. Laboratory tests revealed isolated HH in all. Sellar and head CT scans were normal and all had normal CD4 count. They started testosterone replacement therapy, with symptoms improvement. Causes of HH in HIV-infected men include undernutrition, severe illness, drugs, pituitary dysfunction and comorbidities. Despite having none of these conditions (except two that were treated with low-dose psychotropics), our patients had HH with uncommonly low testosterone. This suggests that a different mechanism contributes to severe HH in HIV-infected men.

## Learning points:

- The pathogenesis of hypogonadotropic hypogonadism in HIV-infected men is multifactorial and androgen deficiency is more often a consequence of secondary hypogonadism than primary hypogonadism.
- Causes of hypogonadotropic hypogonadism in HIV-infected men include undernutrition, severe illness, drugs (psychotropics, opiates, megestrol acetate or steroids), pituitary dysfunction (tumor, hyperprolactinemia), an AIDS-related lesion (very rarely) and comorbid conditions, such as antibody to hepatitis C virus seropositivity and injection drug use.
- Highly active antiretroviral therapy (HAART), particularly protease inhibitor therapy has been associated with sexual dysfunction in men, but the causal nature of this relation has not been clearly established.
- Hypogonadotropic hypogonadism with uncommonly low testosterone levels are not usually associated with the conditions referred and this suggests that a different mechanism could contribute to severe hypogonadotropic hypogonadism in HIV-infected men.
- Screening for hypogonadism in all HIV-infected men might help to understand its etiology.



## Background

Hypogonadism was commonly reported in the era prior to the onset of highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV)-infected men, particularly in those with more advanced degrees of immunosuppression ( $CD4 < 100$  cells/mm<sup>3</sup>) (1). In fact, initial estimates demonstrated that hypogonadism occurred in 30–50 percent of men with acquired immune deficiency syndrome (AIDS)-related wasting (2, 3). Since HIV therapy is now initiated at earlier stages of HIV infection than in the past, the prevalence of hypogonadism is lower, being present in about 20% of men who receive HAART (4, 5). Hypogonadism in HIV-infected men presents similarly to androgen deficiency in the general population and is characterized by loss of facial and body hair, decreased muscle mass and strength, high percentage of body fat, low libido, erectile dysfunction, testicular atrophy, infertility and sometimes gynecomastia (2, 3, 6, 7, 8, 9, 10). Depression, fatigue, low energy, poor concentration, mild anemia and low bone mineral density with osteoporotic fractures may also occur (2, 3, 6, 7, 8, 9, 10).

There are no guidelines approved for the diagnosis of hypogonadism in HIV-infected men. However, the cut-off used for the general population is commonly used in HIV-infected men: a clinical suspicion of hypogonadism is confirmed with a low serum total testosterone level (generally  $< 300$  ng/mL) in two different samples in the morning (8:00 h) (1, 2, 3, 4, 5, 6, 7). As sexual hormone-binding globulin (SHBG) is more frequently increased in HIV-infected men, levels of free testosterone should be measured because total testosterone levels may be normal in an HIV-infected male, but free testosterone levels may be low (2, 3, 6).

Normal or low levels of gonadotropins (LH and FSH) in the setting of a low testosterone level are consistent with hypogonadotropic hypogonadism and such patients should be evaluated for possible reversible etiologies of gonadotropin deficiency, like hyperprolactinemia (1, 2, 3, 5, 6). The other hormones that reflect the anterior pituitary function (adrenocorticotrophic hormone (ACTH), cortisol, growth hormone (GH), insulin growth factor-1 (IGF-1), thyroid-stimulating hormone (TSH) and free T<sub>4</sub> (FT<sub>4</sub>)) should also be measured (2, 3). Besides, a pituitary magnetic resonance imaging (MRI) must be carried out in patients with confirmed hypogonadotropic hypogonadism, to rule out a pituitary or hypothalamic lesion (2, 3).

Treatment of hypogonadal HIV-infected men has been shown to increase muscle mass, strength and quality of life and to improve depression indices and bone mass (2, 3, 5). Patients with low libido and/or other hypogonadal symptoms, low bone mineral density and low body mass or weight loss despite viral suppression on HAART, have indication for testosterone replacement therapy (2, 3, 5). Although it is usually well tolerated, testosterone-related side effects include acne, oiliness of skin and, with chronic administration, erythrocytosis and testicular atrophy (2, 3, 5). As the long-term effects of the hypothalamic–pituitary–gonadal axis suppression and the possibility of promoting or unmasking malignancy of the prostate remain unanswered, testosterone should not be initiated in a patient with a history of prostate cancer, a palpable prostate nodule or an elevated prostate-specific antigen (2, 3, 5).

Although hypogonadism is common and occurs prematurely in HIV-infected men and despite the degree of testosterone serum levels impairment varies according to several conditions such as the patients' age, hypogonadotropic hypogonadism with very low testosterone has not been described.

We present three HIV-infected men with severe hypogonadotropic hypogonadism and normal pubertal development.

## Case presentation

### Patient 1

Forty-year-old man, with HIV and dyslipidemia, referred to the endocrinology outpatient department at the age of 32 years. The diagnosis of HIV was made when he was aged 22 years, and at the age of 25 years, he started HAART: indinavir 400 mg (protease inhibitor), lamivudine 300 mg (reverse-transcriptase inhibitor) and stavudine 40 mg (reverse-transcriptase inhibitor). Seven years later, the patient complained of decreased libido, anejaculation and erectile dysfunction. CD4 count (1321.9 cells/ $\mu$ L; reference value  $\geq 500$ ) was normal.

### Patient 2

Thirty-four-year-old man with HIV diagnosed at the age of 34 years and depressive syndrome treated with escitalopram. He was referred to the endocrinology



outpatient department at the age of 34 years, due to decreased libido, anejaculation and erectile dysfunction that started six months after HIV diagnosis. The patient was not treated with HAART and had normal CD4 count (562.9 cells/ $\mu$ L).

### Patient 3

Forty-one-year-old man, with HIV and depressive syndrome treated with mirtazapine. The HIV diagnosis was made when he was aged 35 years and HAART with emtricitabine and etravirine (reverse-transcriptase inhibitors) was started immediately. One year after the diagnosis, the patient complained of decreased libido, anejaculation and erectile dysfunction but he was only referred to the endocrinology outpatient department five years later. At that time, he had normal CD4 count (718.3 cells/ $\mu$ L).

### Investigation

Serum total testosterone and estradiol were assayed by chemiluminescence immunoassay and free testosterone by radioimmunoassay.

Laboratory tests revealed isolated hypogonadotropic hypogonadism in all patients (Table 1).

The results from sellar and head computed tomography were normal in all of them, namely the pituitary gland had normal size and density and the pituitary stalk was centered and had normal thickness.

### Outcome and follow-up

They started testosterone replacement therapy (patient 1: first with testosterone gel 50mg every 48h and nowadays with intramuscular testosterone undecanoate 1000mg every 12 weeks; patient 2: intramuscular

testosterone enanthate 250mg every three weeks and patient 3: intramuscular testosterone undecanoate 1000mg every 12 weeks), with plasma testosterone levels normalization and symptoms improvement.

### Discussion

The pathogenesis of hypogonadotropic hypogonadism in HIV-infected men is multifactorial and androgen deficiency is more often a consequence of secondary hypogonadism than primary hypogonadism (2, 3, 4, 5, 7, 8); causes of hypogonadotropic hypogonadism in HIV-infected men include undernutrition, severe illness, drugs (psychotropics, opiates, megestrol acetate or steroids), pituitary dysfunction (tumor, hyperprolactinemia), an AIDS-related lesion (very rarely), the HIV virus replication and co-morbid conditions, such as antibody to hepatitis C virus seropositivity and injection drug use (2, 3, 4, 5). Also, HAART, particularly protease inhibitor therapy has been associated with sexual dysfunction in men, but the causal nature of this relation has not been clearly established as many of these patients have normal testosterone levels and some studies have demonstrated that initiation of HAART, including protease inhibitor, can restore testosterone levels to normal (2, 3, 6).

Two of the patients (patient 2 and patient 3) had depressive syndrome and were treated with low-dose psychotropics (one with escitalopram and the other with mirtazapine) and one patient (patient 1) was treated with a protease inhibitor. However, the symptoms suggestive of hypogonadism were not temporally associated with the start of the psychotropic drugs in patients 2 and 3 or with the start of the protease inhibitor in patient 1 (the complaints only appeared seven years after the beginning of the protease inhibitor). Moreover, our patients had hypogonadotropic hypogonadism with uncommonly

**Table 1** Laboratory tests on admission to the endocrinology consultation.

Variable	Values			Reference values
	Patient 1	Patient 2	Patient 3	
FSH (U/L)	1.48	0.7	1.30	23.0–116.3
LH (U/L)	0.46	<0.12	<0.07	15.9–54.0
Total testosterone (ng/dL)	24.2	<10	37	240–830
Free testosterone (pg/mL)	0.66	0.46	0.43	8.8–27
Estradiol (pg/mL)	<10	29	24	<40
Prolactin (ng/mL)	5.1	6.1	4.1	1.8–20.0
TSH ( $\mu$ g/mL)	2.22	1.46	0.829	0.55–4.78
FT <sub>4</sub> (ng/dL)	1.13	1.14	0.95	0.80–1.76
ACTH (pg/mL)	35.3	21.9	8.77	0–46.0
Cortisol ( $\mu$ g/dL)	11.7	17.8	11.55	4.3–23.0
IGF-1 (ng/mL)	170	219	214	87.0–238.0



low testosterone levels, not usually associated with the conditions referred. This suggests that a different mechanism could contribute to severe hypogonadotropic hypogonadism in HIV-infected men. We hypothesize that the HIV infection, by unknown mechanisms, induces changes in the hypothalamic–pituitary system that may cause this severe hypogonadotropic hypogonadism.

Screening for hypogonadism in HIV-infected men is recommended only in those with clinical suspicion of hypogonadism and in those with comorbidities such as hepatitis C and injection drug use (4). Our case reports suggest that maybe screening for hypogonadism in all HIV-infected men might help to understand its etiology.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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#### Patient consent

Written informed consent has been obtained from the patients for publication of the submitted article.

#### Author contribution statement

A C G researched data, contributed to the discussion and wrote the manuscript. J M A contributed to the discussion and reviewed/edited the manuscript. S G contributed to the discussion, and reviewed/edited the manuscript. J F contributed to the discussion and reviewed/edited the manuscript. M R M reviewed/edited the manuscript.

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