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Review Article

Hypogonadism in Human Immunodeficiency Virus-Positive Men

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In recent years, the life expectancy for those living with human immunodeficiency virus (HIV) with access to combined antiretroviral therapy (cART) has increased. As men live longer, the role testosterone plays in sexual function as well as in general well-being is becoming increasingly important. Here we discuss the available literature concerning androgens and HIV disease. A review was undertaken by using a PubMed search with the umbrella terms *HIV* or *AIDS* and *testosterone* or *androgens* spanning 1985 to 2011. Significant articles found in references in the primary search were also included. The reported prevalence of androgen deficiency appears to be greater in HIV-infected males than in the general population. Androgen deficiency is usually associated with low luteinizing hormone and follicle-stimulating hormone and is sensitive to the type of measurement of testosterone used. Rates of hypogonadism may be falling since the advent of cART. Causes of low testosterone levels have been attributed to chronic illness, HIV replication, cART, opportunistic infections, comorbidities and co-infections, wasting, and normal age-related declines. Studies of testosterone treatment in HIV-positive men are lacking in standardization and outcome measures.

Keywords: *Androgens; HIV; Hypogonadism; Testosterone*

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INTRODUCTION

In recent years, the rate of growth of the human immunodeficiency virus (HIV) epidemic has slowed with a reduction in the annual number of new HIV infections and a dramatic reduction in HIV-associated mortality [1-3]. Life expectancy for those living with HIV with access to combined antiretroviral therapy (cART) is increasing. Thus, globally, the total number of individuals living with HIV remains high and was estimated to be around 33 million at the end of 2009 [1]. With this increased life expectancy, complications related to both HIV infection and to cART are increasingly common and important. As men live longer and are generally healthier than they were before the introduction of cART, the role testosterone plays in sexual function as well as in general well-being is becoming increasingly important. In this review, we discuss the available literature concerning androgens and HIV disease.

METHODS

A review was undertaken by using a PubMed search with the umbrella terms *HIV* or *AIDS* and *testosterone* or *androgens* spanning 1985 to 2011. Significant papers found in references in the primary search were also included. The present article first reviews the clinical aspects of naturally occurring androgens in HIV disease and then considers androgen therapy.

PREVALENCE OF HYPOGONADISM IN HIV-POSITIVE MALES

1. Prior to the advent of combined antiretroviral therapy

Early on in the HIV epidemic, before the introduction of cART, high rates of hypogonadism were reported anecdotally in a number of publications. In an early paper by Dobs et al. [4] in 1988, the authors reported that 20 or 40 males with acquired immune deficiency syndrome (AIDS)-related weight loss had total testosterone (TT) levels within the

hypogonadal range.

In 1991 low rates of hypogonadism were observed by Raffi et al. [5], with 10 of 67 men with HIV (15%) having a TT level < 300 ng/dL. Among those with an AIDS diagnosis, the prevalence of hypogonadism was statistically significantly higher (29%) than in asymptomatic patients and those with other early-stage HIV disease. Low testosterone levels were mainly seen in association with normal or low pituitary hormone levels. Testosterone responses to gonadotropin-releasing hormone were investigated and found to be normal, which is suggestive of a functional deficit in the hypothalamic-pituitary axis.

2. Sex hormone-binding globulin

In 1995 Laudat et al. [6] measured androgen levels along with sex hormone-binding globulin (SHBG) levels in 58 asymptomatic HIV-positive men compared with 11 HIV-negative men as controls. SHBG levels were found to be significantly higher, and non-SHBG-bound testosterone was lower, in cases than in controls, even in men with early asymptomatic HIV infection. The finding of high levels of SHBG was borne out in several subsequent studies and consequently it has been observed that the high concentration of SHBG in this population may frequently result in an increase in TT values, alongside a reduction in free testosterone (FT) or bioavailable testosterone [7].

In a more recent study by Moreno-Perez et al. [7], SHBG, albumin, TT, and FT were measured and bioavailable testosterone was calculated by using the equation described by Vermeulen et al. [8]. Ninety HIV-positive men were included in this arm of the study, and 72% had a suppressed HIV viral load on cART. Using the calculated bioavailable testosterone level as a measure, hypogonadism was observed in just 13% of the population studied, and TT and FT were found to have a sensitivity of just 25% and 33%, respectively, in predicting hypogonadism in this population. These results suggest that because albumin and SHBG levels are frequently abnormal in HIV-positive individuals, the measurement and calculation of bioavailable testosterone is especially important in HIV-positive men to accurately assess testosterone status, particularly in those with borderline low FT or TT levels.

3. Hypogonadism in the era of cART

The effect of cART therapy on testosterone levels in this population is unclear and studies show conflicting results. A study performed in 2007 by Crum-Cianflone et al. [9] aimed to establish the prevalence and risk factors for hypogonadism among a modern cohort of HIV-infected men. Three hundred HIV-positive men were enrolled in this study; 60% were taking cART with good immune response. Seventeen percent (50/296) of the men had a morning TT level below 300 ng/dL and a further 16% had a borderline testosterone level (300–400 ng/dL). No association was observed between low levels of testosterone and current, past, or cumulative use of HIV medications.

Wunder et al. [10] studied the affect of cART therapy on androgen levels over time. Data were derived from the stored serum samples of 97 participants, and luteinizing hormone (LH), follicle-stimulating hormone (FSH), and FT were measured at baseline and after 2 years of successful cART. At baseline, 68 of 97 patients (70%) had subnormal FT levels for the age-adjusted normal range, and LH levels were low in 44%, normal in 47%, and high in 9%. No significant changes in FT, LH, or FSH were observed after 2 years of successful ARV therapy. More than 60% remained hypogonadal after 2 years of cART, with 24% of those originally hypogonadal returning to normal levels and 32% of those originally within normal levels becoming hypogonadal after 2 years of therapy. The authors acknowledged that the use of stored serum samples was a limiting factor in the interpretation of these findings.

Effective treatment with antiretroviral therapy has been shown to increase lean body mass, particularly in individuals with low CD4 counts at the initiation of treatment [11]. Dube et al. [12] noted an increase in FT after the initiation of antiretroviral therapy, along with an increase in fat-free mass, which appeared to be more marked with certain types and classes of cART.

Rates of hypogonadism among HIV-negative men in the Massachusetts Male Aging Study were reported as between 6% and 12% among 40- to 69-year-old American males [13]. Whereas studies in HIV-positive men have shown high levels of biochemical hypogonadism, in clinical practice, a diagnosis of testosterone deficiency is usually made in conjunction with consistent clinical symptoms and signs [14]. Testosterone deficiency may cause nonspecific symptoms such as fatigue, depressed mood, weakness, and sexual dysfunction. These nonspecific symptoms are also frequently independently associated with chronic illness, depression, HIV seropositivity, opportunistic infections, and taking cART therapy. Careful history, examination, and appropriate investigation are therefore essential when trying to ascertain whether biochemical hypogonadism is clinically relevant in an individual.

HIV WASTING AND TESTOSTERONE

The U.S. Centers for Disease Control and Prevention classification system for HIV disease staging and classification defines HIV wasting syndrome as an involuntary weight loss of more than 10% of baseline body weight in association with either chronic diarrhea or chronic weakness [15]. In well-resourced settings, wasting among HIV-positive persons taking cART is now much less common and is frequently rapidly reversed with nutritional supplementation and appropriate treatment to control HIV viral replication. However, even in the era of cART, HIV-associated weight loss remains prevalent. A large, retrospective observational study of a contemporary managed care population in the United States observed that even among a modern cohort of HIV-positive persons, almost 1 in 10 had evidence of HIV-associated weight loss [16].

A study presented in 2000 by Desyatnik et al. [17] inves-

tigated the association between clinical wasting and hypogonadism by conducting a retrospective review of 88 HIV-positive male patients on cART for at least 6 months. Hypogonadism was observed in 20% of the participants and wasting (weight loss >5% of ideal body weight) in 42% of the participants, with no correlation observed between wasting and hypogonadism.

The same year, a paper was published by Rietschel et al. [18] that looked at androgen levels in a group of HIV-positive men with wasting, of whom 70% were receiving cART. The authors found that 21% of patients receiving cART had hypogonadism compared with 15% of those not receiving cART. Comparison was also made with a control group of HIV-positive men without wasting, and total and FT levels were not significantly different for subjects with and without wasting.

The contributions of catabolic cytokines to HIV-associated wasting and weight loss in a group of HIV-positive men were investigated by Roubenoff et al. [19]. Those authors studied a group of 172 HIV-positive men and found that both tumor necrosis factor (TNF)-alpha and interleukin-1-beta production by peripheral blood mononuclear cells predicted loss of lean body mass, and that serum FT was inversely associated with TNF-alpha production. After adjustment for cytokine production, serum FT alone was not an independent predictor of lean body mass.

Among HIV-positive persons living in resource-poor settings, wasting syndromes are more commonly encountered and may be due to lack of nutritional intake as well as lack of appropriate cART and concomitant infections. In this instance, appropriate remedy of any exacerbating underlying cause of wasting is indicated before consideration of androgen replacement.

METABOLIC SYNDROME

The metabolic syndrome (MS) is a term used to describe the clustering of risk factors for cardiovascular disease, including abnormal lipids, hypertension, insulin resistance, and intra-abdominal liposity. In HIV-negative cohorts, MS has been associated with low levels of testosterone [20,21]. In HIV-positive cohorts, the prevalence of MS varies and has been reported to be between 7% and 45% (compared with between 7% and 31% in HIV-negative populations), and this may contribute to the high rates of androgen deficiency observed in HIV-positive cohorts [22-25].

LIPODYSTROPHY

Lipodystrophy syndrome has been reported in as many as 41% of people with HIV and comprises changes in body fat distribution including both fat loss (lipoatrophy) and fat accumulation (lipohypertrophy) [26]. Combined ART can cause mitochondrial toxicity and dysfunction and may be a cause of adverse metabolic effects such as lipodystrophy and insulin resistance. Changes in sex hormones including testosterone may play a role in the altered fat distribution and insulin sensitivity of male patients with HIV-lipodystrophy.

ABNORMAL TESTOSTERONE METABOLISM AND RAISED ESTRADIOL

There is evidence that men on ART develop low sexual desire that can be associated with raised estradiol levels. Richardson et al. [27] postulated that the abnormal androgen metabolism seen in HIV-positive men results in increased aromatization of testosterone to estradiol, perhaps occurring within the increased central adipose tissue seen in lipodystrophy and MS.

ANDROGENS, SEXUAL FUNCTION, AND HIV

High rates of sexual dysfunction have been well described among men with HIV. In particular, erectile dysfunction (ED) is prevalent and has been reported to be present in between 9% and 74% of HIV-positive men [28]. In that study, Guaraldi et al. [28] studied 133 HIV-positive men and found prevalence rates of ED of 55% and 65% of men aged less than or more than 50 years old, respectively. Comparison of TT and FT was made in those with and those without ED and no significant differences were observed.

In the large study by Crum-Cianflone et al. [9], ED was reported in 175 of 285 men (61%) and rates of hypogonadism were not significantly different between those with and those without ED. No association was observed between ED and use of HIV medications. Similarly, in a cross-sectional study by Lallemand et al. [29], 111 of 156 HIV-positive men (71%) on cART reported sexual dysfunction and no association was found between sexual dysfunction and type of cART used.

The study by Moreno-Perez et al. [7] revealed that 100% of patients (12/12) with hypogonadism as measured by calculated free testosterone (CFT) had ED, but only one quarter of the patients with ED were hypogonadal. CFT or bioavailable testosterone level is an accurate way of identifying ED related to low testosterone levels, but the causes of ED in HIV-positive men are diverse and frequently multifactorial.

AGE

Hypogonadism is associated with increasing age, and TT has been shown to decrease year on year in HIV-negative populations as they move through their fourth and fifth decades of life [13,30]. Within developed countries, we are now caring for an aging cohort of HIV-positive individuals and it is predicted that as prognosis continues to improve for individuals living with HIV, there will be increasing numbers of older people living with HIV [31,32]. We may reasonably expect that the numbers of HIV-positive men with late-onset hypogonadism are set to increase in the future.

In a study in 2005, Klein et al. [33] set out to examine the

prevalence and association of hypogonadism in males aged over 50 years and at risk of or living with HIV. In a sample of over 500 men aged >49 years, of whom 275 were HIV-positive, the authors noted that raised TT was associated with HIV positivity but the free androgen index was not associated with HIV status.

Among HIV-positive women, early loss of ovarian function and early menopause have been described in some study populations [34-36]. Unexpectedly high numbers of HIV-positive women reaching menopause very early have also been reported [34,37]. It may be that men living with HIV infection are more prone to a syndrome of late-onset androgen deficiency or an "early andropause," heralded by dysregulation of the hypothalamic-pituitary axis [38].

BONE MINERAL DENSITY AND TESTOSTERONE

High rates of osteopenia and osteoporosis have been reported in HIV-infected cohorts and prevalence rates range between 22%–71% and 3%–33%, respectively [39]. Loss of bone mineral density (BMD) in the context of HIV may be exacerbated by cART, vitamin D deficiency, alcohol and drug use, smoking, low body mass index, and HIV infection itself. Hypogonadism may be an additive risk factor for low BMD and should be managed appropriately as part of osteoporosis management, including measures to improve calcium and vitamin D nutrition and increase weight-bearing exercise as well as specific pharmacologic therapy, including in some cases testosterone replacement [40].

RECREATIONAL DRUG USE

Injection drug use is a risk factor for HIV acquisition and is not uncommon among some HIV-infected cohorts. Marijuana, opiates, anabolic steroids, and alcohol can all inhibit gonadal function [41], and a study by Wisniewski of androgen levels showed that FT concentrations were lower in men who used cocaine or opiates irrespective of HIV status [42].

TREATMENT OF HYPOGONADISM AND WASTING IN HIV-POSITIVE MEN

The literature regarding treatments for hypogonadism in HIV-positive men is wide-ranging and includes a multitude of therapy options. ART in this population has been extensively studied and includes different forms of synthetic testosterone in addition to metabolic steroids.

1. Types of therapy

1) Testosterone

The use of different types of testosterone replacement therapy in HIV-positive men has been well studied; however, many of the studies had small patient populations and the outcome measures were not uniform across the studies. In a meta-analysis of testosterone therapy (given in different forms, i.e., intramuscular or transdermal) in HIV wasting syndrome, eight trials met the inclusion criteria for a total of 417 patients. A difference in lean body mass was seen in the testosterone group compared with the placebo group and the difference was greater in trials that utilized intramuscular testosterone [43]. Two studies by Bhasin et al. [44] and Grinspoon et al. [45] examined the effect of combining resistance training with or without testosterone treatment and found that body weight and maximum strength in various exercises was noted to increase significantly in both the testosterone group and the exercise group. Testosterone and exercise combined did not produce greater results than testosterone alone [44].

2) Intramuscular testosterone

The majority of studies have shown not only increases in weight, but also overall changes in body composition with intramuscular testosterone treatment. In a double-blind placebo-controlled trial of 51 HIV-positive men with evidence of wasting and hypogonadism, patients were randomly assigned to receive testosterone enanthate 300 mg every 3 weeks or placebo. Gains in fat-free mass, lean body mass, and muscle mass were seen in the treatment group versus placebo at 6 months. Testosterone was tolerated well and significant benefits were also perceived in terms of improved quality of life, improved appearance, and feeling better [46].

Other studies have looked at testosterone replacement with the use of testosterone cypionate 200 mg initially and 400 mg biweekly in HIV-positive men with sexual dysfunction (with or without hypogonadism) [47,48]. Improved mood, energy, and libido; weight gain; and increase in muscle mass were observed. Men who had low-normal levels of testosterone were just as likely to respond as were hypogonadal men [48] and the increase in muscle mass was greater for men with wasting at presentation [47].

Testosterone enanthate and testosterone cypionate are both short-acting testosterone formulations and are of relatively low cost. They are typically administered every 10 to 14 days. Supraphysiologic levels may be seen after 24 hours, with levels gradually declining to baseline hypogonadal levels in 2 weeks. Individuals may experience an initial “high” followed by feeling low as the euphoria wears off [49,50].

Testosterone undecanoate is the first long-acting injectable testosterone formulation that has been shown to maintain stable testosterone levels in hypogonadal men [51]. This formulation was not available in the United States at the time of this writing. A review of the database at the National Library of Medicine did not show any publications on the effects of long-acting intramuscular testosterone formulations in HIV-related hypogonadism.

3) Testosterone gel

One advantage of testosterone gel is its ease of use, and there is some evidence that there are fewer fluctuations in daily serum testosterone levels with gel administration

than with injectable formulations [52]. In 2007, Bhasin et al. [53] studied the effect of 10 g testosterone gel daily versus placebo in HIV-positive hypogonadal men with abdominal obesity. Visceral fat did not differ significantly between the groups, but decreases in total and subcutaneous fat mass in testosterone-treated men compared with placebo were observed, along with increases in lean body mass.

4) Transscrotal testosterone

Only one study to date has looked at the effects of a transscrotal delivery system of testosterone in HIV-positive men with hypogonadism and wasting. In that study, 133 men were randomized to receive 6 mg of testosterone daily or placebo patches. Increases in morning serum testosterone and FT were noted in the treatment arm, but no changes in body cell mass or total weight were seen between the groups and no changes were reported in quality of life [54].

5) Anabolic steroids

There is evidence that anabolic steroids promote greater increases in muscle and lean body mass than does testosterone [55]; however, the most important and widely observed adverse effect of anabolic steroids with high anabolic potential is liver toxicity. Oxymetholone is an anabolic steroid that has high anabolic potency compared with its androgenic effects. In a study of 89 HIV-positive men and women with wasting, patients were assigned to oxymetholone or placebo [56]. Increases were observed in total body weight, lean body mass, and body cellular mass in the oxymetholone groups. Quality of life parameters including appetite and food intake, improved well-being, and decreased weakness and fatigue were significantly improved in the treatment groups only. Toxicities included grades III and IV liver toxicities.

The metabolic steroid nandrolone has shown promise as a treatment in men with HIV wasting. In a study of HIV-positive men with wasting who failed to gain weight despite nutritional intervention, body composition was performed after open label treatment with nandrolone decanoate. After 16 weeks, significant gains in total weight and lean body mass and changes in quality of life parameters were observed [57].

DEPRESSION

Many studies report quality of life parameters such as mood, sexual dysfunction, libido, fatigue, weakness, and appetite as part of the overall benefit of androgen replacement therapy; however, not all studies have found positive effects [58,59]. One of the major difficulties in studying quality of life parameters is the lack of standardization across studies, which results in difficulty performing meta-analysis [52].

The relationship between testosterone levels and depression was evaluated in a randomized placebo-controlled study by Grinspoon et al. [60]. Depression scores were compared between eugonadal and hypogonadal men by use of the Beck Depression Inventory. The authors found that testosterone levels were significantly inversely associated with Beck score. Subjects were then randomized in a placebo-controlled trial of testosterone enanthate 300 mg intramuscularly every 3 weeks [43]. A significant decrease in the Beck score was shown in the testosterone treatment arm but not in the placebo treatment arm.

Another study compared fluoxetine and testosterone in HIV-positive men with major depression, subthreshold major depression, or dysthymia [61]. Men were randomized to receive 400 mg intramuscular testosterone cypionate biweekly, fluoxetine 60 mg/d, or double placebo. Among the subjects, mood response rates were not significantly different between the groups; however, improvement in fatigue in the testosterone group was significant.

BONE MINERAL DENSITY

The relationship between testosterone and BMD is well established, and testosterone treatment has been used in men with evidence of osteopenia [62]. Although increases in BMD have been shown in HIV-negative hypogonadal men [63], testosterone treatment among HIV-positive hypogonadal men with osteopenia is less well studied. In a study looking at testosterone replacement in eugonadal HIV-positive men with wasting syndrome [64], men were assigned to either testosterone enanthate 200 mg/wk or placebo with or without progressive resistance training. The authors found that subjects had lower baseline lumbar spine and hip BMD and that testosterone replacement significantly increased lumbar spine BMD over 3 months, whereas resistance training had no effect. No increases in BMD were seen in the hip or femoral neck region.

CONCLUSIONS

- The reported prevalence of hypogonadism among HIV-positive men varies widely and depends on the type of measurement of testosterone used.
- Androgen deficiency appears to be more common in HIV-infected males than in the general population.
- Hypogonadism is commonly secondary to hypothalamic-pituitary axis dysfunction and associated low LH and FSH levels and not to primary testicular failure.
- Since the advent of cART, rates of hypogonadism may be falling compared with early in the HIV epidemic but men with HIV infection remain at risk owing to complications of HIV infection, comorbidities, and toxicities associated with HAART and the aging cohort.
- Causes of low testosterone levels are complex and have been attributed to factors including chronic illness, HIV virus, medications used to treat HIV, opportunistic infections, comorbidities and coinfections, and normal age-related declines.
- Low levels of testosterone have been variably associated with low CD4 cell count, high HIV viral load, increasing age, increasing length of time diagnosed with HIV, disease

progression, lean body mass, MS, wasting, lipodystrophy, and recreational drug use.

・Symptoms and signs of androgen deficiency in HIV-positive males are similar to those in HIV-negative males and overlap with symptoms commonly seen in HIV infection, regardless of androgen status. Symptoms include sexual dysfunction, fatigue, weakness, depression, and accelerated loss of BMD.

・Studies show that intramuscular injection of testosterone is effective in changing body composition in hypogonadal and eugonadal men with wasting. Studies are lacking in standardization and outcome measures making meta-analysis difficult, especially when evaluating changes in quality of life parameters, mood, and sexual function.

・Anabolic steroids show promise in treating both hypogonadal and eugonadal men who show evidence of HIV-associated wasting; however, whether treatment with these medications is more effective than testosterone replacement remains to be seen and toxicities may preclude them as standard treatment.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. UNAIDS. AIDS epidemic update [Internet]. Geneva: UNAIDS; c2009 [cited 2012 Jan 14]. http://www.unaids.org/en/media/unaids/contentassets/dataimport/pub/report/2009/jc1700_epi_update_2009_en.pdf.
2. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338:853-60.
3. Detels R, Munoz A, McFarlane G, Kingsley LA, Margolick JB, Giorgi J, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. JAMA 1998;280:1497-503.
4. Dobs AS, Dempsey MA, Ladenson PW, Polk BF. Endocrine disorders in men infected with human immunodeficiency virus. Am J Med 1988;84(3 Pt 2):611-6.
5. Raffi F, Brisseau JM, Planchon B, Remi JP, Barrier JH, Grolleau JY. Endocrine function in 98 HIV-infected patients: a prospective study. AIDS 1991;5:729-33.
6. Laudat A, Blum L, Guechot J, Picard O, Cabane J, Imbert JC, et al. Changes in systemic gonadal and adrenal steroids in asymptomatic human immunodeficiency virus-infected men: relationship with the CD4 cell counts. Eur J Endocrinol 1995;133:418-24.
7. Moreno-Perez O, Escoin C, Serna-Candel C, Portilla J, Boix V, Alfayate R, et al. The determination of total testosterone and free testosterone (RIA) are not applicable to the evaluation of gonadal function in HIV-infected males. J Sex Med 2010;7:2873-83.
8. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666-72.
9. Crum-Cianflone NF, Bavaro M, Hale B, Amling C, Truett A, Brandt C, et al. Erectile dysfunction and hypogonadism among men with HIV. AIDS Patient Care STDS 2007;21:9-19.
10. Wunder DM, Bersinger NA, Fux CA, Mueller NJ, Hirschel B, Cavassini M, et al. Hypogonadism in HIV-1-infected men is common and does not resolve during antiretroviral therapy. Antivir Ther 2007;12:261-5.
11. Shikuma CM, Zackin R, Sattler F, Mildvan D, Nyangweso P, Alston B, et al. Changes in weight and lean body mass during highly active antiretroviral therapy. Clin Infect Dis 2004;39:1223-30.
12. Dube MP, Parker RA, Mulligan K, Tebas P, Robbins GK, Roubenoff R, et al. Effects of potent antiretroviral therapy on free testosterone levels and fat-free mass in men in a prospective, randomized trial: A5005s, a substudy of AIDS Clinical Trials Group Study 384. Clin Infect Dis 2007;45:120-6.
13. Araujo AB, O'Donnell AB, Brambilla DJ, Simpson WB, Longcope C, Matsumoto AM, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2004;89:5920-6.
14. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995-2010.
15. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;41(RR-17):1-19.
16. Siddiqui J, Phillips AL, Freedland ES, Sklar AR, Darkow T, Harley CR. Prevalence and cost of HIV-associated weight loss in a managed care population. Curr Med Res Opin 2009;25:1307-17.
17. Desyatnik M, Baaj A, Fisher A. The prevalence of hypogonadism in HIV-infected patients receiving HAART (TuPeB3180). Poster session presented at: 13th International AIDS Conference; 2000 Jul 9-14; Durban, South Africa.
18. Rietschel P, Corcoran C, Stanley T, Basgoz N, Klibanski A, Grinspoon S. Prevalence of hypogonadism among men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy. Clin Infect Dis 2000;31:1240-4.
19. Roubenoff R, Grinspoon S, Skolnik PR, Tchetgen E, Abad L, Spiegelman D, et al. Role of cytokines and testosterone in regulating lean body mass and resting energy expenditure in HIV-infected men. Am J Physiol Endocrinol Metab 2002;283:E138-45.
20. Selvin E, Feinleib M, Zhang L, Rohrmann S, Rifai N, Nelson WG, et al. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care 2007;30:234-8.
21. Rodriguez A, Muller DC, Metter EJ, Maggio M, Harman SM, Blackman MR, et al. Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. J Clin Endocrinol Metab 2007;92:3568-72.
22. Cubero JM, Domingo P, Sambeat M, Ordonez-Llanos J, Rodriguez-Espinosa J, Snchez-Quesada JL, et al. Prevalence of metabolic syndrome among human immunodeficiency virus-infected subjects is widely influenced by the diagnostic criteria. Metab Syndr Relat Disord 2011;9:345-51.
23. Fernández-Berges D, Cabrera de Leon A, Sanz H, Elosua R, Guembe MJ, Alzamora M, et al. Metabolic syndrome in Spain: prevalence and coronary risk associated with harmonized definition and WHO proposal. DARIOS study. Rev Esp Cardiol (Engl Ed) 2012;65:241-8.
24. Jordan HT, Tabaei BP, Nash D, Angell SY, Chamany S, Kerker B. Metabolic syndrome among adults in New York City, 2004 New York City Health and Nutrition Examination Survey. Prev

Chronic Dis 2012;9:E04.
25. Lao XQ, Zhang YH, Wong MC, Xu YJ, Xu HF, Nie SP, et al. The prevalence of metabolic syndrome and cardiovascular risk factors in adults in southern China. BMC Public Health 2012;12:64.
26. Calza L, Masetti G, Piergentili B, Trapani F, Cascavilla A, Manfredi R, et al. Prevalence of diabetes mellitus, hyperinsulinaemia and metabolic syndrome among 755 adult patients with HIV-1 infection. Int J STD AIDS 2011;22:43-5.
27. Richardson D, Goldmeier D, Frize G, Lamba H, De Souza C, Kocsis A, et al. Letrozole versus testosterone. a single-center pilot study of HIV-infected men who have sex with men on highly active anti-retroviral therapy (HAART) with hypoactive sexual desire disorder and raised estradiol levels. J Sex Med 2007;4:502-8.
28. Guaraldi G, Beggi M, Zona S, Luzi K, Orlando G, Carli F, et al. Erectile dysfunction is not a mirror of endothelial dysfunction in HIV-infected patients. J Sex Med 2012;9:1114-21.
29. Lallemand F, Salhi Y, Linard F, Giami A, Rozenbaum W. Sexual dysfunction in 156 ambulatory HIV-infected men receiving highly active antiretroviral therapy combinations with and without protease inhibitors. J Acquir Immune Defic Syndr 2002;30: 187-90.
30. McLachlan RI, Allan CA. Defining the prevalence and incidence of androgen deficiency in aging men: where are the goal posts? J Clin Endocrinol Metab 2004;89:5916-9.
31. Health Protection Agency. HIV in the United Kingdom: 2010 Report. Health Prot Rep 2010:4(47).
32. Kirk JB, Goetz MB. Human immunodeficiency virus in an aging population, a complication of success. J Am Geriatr Soc 2009;57: 2129-38.
33. Klein RS, Lo Y, Santoro N, Dobs AS. Androgen levels in older men who have or who are at risk of acquiring HIV infection. Clin Infect Dis 2005;41:1794-803.
34. Cejtin HE, Kalinowski A, Bacchetti P, Taylor RN, Watts DH, Kim S, et al. Effects of human immunodeficiency virus on protracted amenorrhea and ovarian dysfunction. Obstet Gynecol 2006;108: 1423-31.
35. Schoenbaum EE, Hartel D, Lo Y, Howard AA, Floris-Moore M, Arnsten JH, et al. HIV infection, drug use, and onset of natural menopause. Clin Infect Dis 2005;41:1517-24.
36. Clark RA, Mulligan K, Stamenovic E, Chang B, Watts H, Andersen J, et al. Frequency of anovulation and early menopause among women enrolled in selected adult AIDS clinical trials group studies. J Infect Dis 2001;184:1325-7.
37. Fantry LE, Zhan M, Taylor GH, Sill AM, Flaws JA. Age of menopause and menopausal symptoms in HIV-infected women. AIDS Patient Care STDS 2005;19:703-11.
38. Cohan GR. HIV-associated hypogonadism. AIDS Read 2006;16: 341-5, 348, 352-4.
39. Cotter AG, Powderly WG. Endocrine complications of human immunodeficiency virus infection: hypogonadism, bone disease and tenofovir-related toxicity. Best Pract Res Clin Endocrinol Metab 2011;25:501-15.
40. Ebeling PR. Androgens and osteoporosis. Curr Opin Endocrinol Diabetes Obes 2010;17:284-92.
41. Cooper OB, Brown TT, Dobs AS. Opiate drug use: a potential contributor to the endocrine and metabolic complications in human immunodeficiency virus disease. Clin Infect Dis 2003;37 Suppl 2:S132-6.
42. Wisniewski AB, Brown TT, John M, Frankowicz JK, Cofranceso J Jr, Golub ET, et al. Hypothalamic-pituitary-gonadal function in men and women using heroin and cocaine, stratified by HIV status. Gend Med 2007;4:35-44.
43. Kong A, Edmonds P. Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis. Lancet Infect Dis 2002;2:692-9.
44. Bhasin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA 2000;283:763-70.
45. Grinspoon S, Corcoran C, Parlman K, Costello M, Rosenthal D, Anderson E, et al. Effects of testosterone and progressive resistance training in eugonadal men with AIDS wasting. A randomized, controlled trial. Ann Intern Med 2000;133:348-55.
46. Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, et al. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998;129:18-26.
47. Rabkin JG, Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. Arch Gen Psychiatry 2000;57:141-7.
48. Rabkin JG, Wagner GJ, Rabkin R. Testosterone therapy for human immunodeficiency virus-positive men with and without hypogonadism. J Clin Psychopharmacol 1999;19:19-27.
49. Corona G, Rastrelli G, Forti G, Maggi M. Update in testosterone therapy for men. J Sex Med 2011;8:639-54.
50. Edelstein D, Basaria S. Testosterone undecanoate in the treatment of male hypogonadism. Expert Opin Pharmacother 2010;11:2095-106.
51. Dobs AS, Cofrancesco J, Nolten WE, Danoff A, Anderson R, Hamilton CD, et al. The use of a transscrotal testosterone delivery system in the treatment of patients with weight loss related to human immunodeficiency virus infection. Am J Med 1999;107: 126-32.
52. Scott JD, Wolfe PR, Anderson P, Cohan GR, Scarsella A. Prospective study of topical testosterone gel (AndroGel) versus intramuscular testosterone in testosterone-deficient HIV-infected men. HIV Clin Trials 2007;8:412-20.
53. Bhasin S, Parker RA, Sattler F, Haubrich R, Alston B, Umbleja T, et al. Effects of testosterone supplementation on whole body and regional fat mass and distribution in human immunodeficiency virus-infected men with abdominal obesity. J Clin Endocrinol Metab 2007;92:1049-57.
54. Snyder PJ, Lawrence DA. Treatment of male hypogonadism with testosterone enanthate. J Clin Endocrinol Metab 1980;51:1335-9.
55. Dudgeon WD, Phillips KD, Carson JA, Brewer RB, Durstine JL, Hand GA. Counteracting muscle wasting in HIV-infected individuals. HIV Med 2006;7:299-310.
56. Hengge UR, Stocks K, Wiehler H, Faulkner S, Esser S, Lorenz C, et al. Double-blind, randomized, placebo-controlled phase III trial of oxymetholone for the treatment of HIV wasting. AIDS 2003;17:699-710.
57. Gold J, High HA, Li Y, Michelmore H, Bodsworth NJ, Finlayson R, et al. Safety and efficacy of nandrolone decanoate for treatment of wasting in patients with HIV infection. AIDS 1996;10:745-52.
58. Berger JR, Pall L, Hall CD, Simpson DM, Berry PS, Dudley R. Oxandrolone in AIDS-wasting myopathy. AIDS 1996;10: 1657-62.
59. Coodley GO, Coodley MK. A trial of testosterone therapy for HIV-associated weight loss. AIDS 1997;11:1347-52.
60. Grinspoon S, Corcoran C, Stanley T, Baaj A, Basgoz N, Klibanski A. Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. J Clin Endocrinol Metab 2000;85:60-5.
61. Rabkin JG, Wagner GJ, McElhiney MC, Rabkin R, Lin SH.

Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial. J Clin Psychopharmacol 2004;24:379-85.
62. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536-59.
63. Clay PG, Lam AI. Testosterone replacement therapy for bone loss prevention in HIV-infected males. Ann Pharmacother 2003;37: 582-5.
64. Fairfield WP, Finkelstein JS, Klibanski A, Grinspoon SK. Osteopenia in eugonadal men with acquired immune deficiency syndrome wasting syndrome. J Clin Endocrinol Metab 2001;86: 2020-6.