Special Article

Human Immunodeficiency Virus Infection and Male Hypogonadism: A Review

Noppadol Kietsiriroje MD*

** Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand*

Hypogonadism is a common complication among HIV infected patients. The prevalence of hypogonadism is 30 to 50% in HIV infected men with wasting syndrome and 20 to 25% in those without wasting syndrome. HIV infection affects the entire hypothalamus-pituitary-gonadal axis via both direct and indirect effects, which are defined in four categories, 1) direct effect of HIV particles, 2) opportunistic infections, 3) HIV-related malignancy and its treatment, and 4) medications that are used for HIV infection or its opportunistic infection. The association between HIV infection, hypogonadism, and cardiovascular diseases has yet to be determined; however, there are data that HIV infection and its treatment, particularly protease inhibitors, worsened the metabolic profiles, which were surrogate markers of cardiovascular diseases. Considerably more attention should be paid to the diagnosis of hypogonadism in this group particularly because HIV infection increases both sex hormone-binding globulin and total testosterone level. Testosterone replacement shows benefits on mood, body composition, and seems to benefit the metabolic profile in HIV infected men with low body mass index.

Keywords: HIV, Male, Hypogonadism, Testosterone, Deficiency

J Med Assoc Thai 2015; 98 (10): 1045-55
Full text. e-Journal: *http://www.jmatonline.com*

Hypogonadism is a clinical condition characterized by low serum testosterone levels occurring in association with any of the signs and symptoms including sexual dysfunction, weight and muscle mass loss, fatigue, depressed mood, and anemia[1,2]. General symptoms of hypogonadism are briefly listed in Table 1.

Among HIV infected patients, hypogonadism is also associated with low lean muscle mass, sexual dysfunction, and depression[4-7]. Hypogonadism seems to be common among HIV infected men; however, the prevalence of hypogonadism in this patient group has not been determined. It is quite difficult to diagnose hypogonadism in men because the symptoms are non-specific and the classical clinical signs of hypogonadism (testicular atrophy, abnormal patterns of hair growth, and gynecomastia) may be absent[8]. Some questionnaires (ADAM, AMS, and MMAS) have been developed to detect hypogonadism in men, but there are no questionnaires that have good specificity in the diagnosis of this condition[9]. Moreover, the total testosterone level that is used for the diagnosis of hypogonadism has many limitations and lacks standardization particularly among HIV infected patients. Testosterone deficiency has some associations with cardiovascular diseases as a marker of chronic illness[3]. Testosterone replacement in testosterone deficient men shows benefit mostly on the body composition and some metabolic profiles. A recent retrospective study showed its benefit on survival[10]. However, there is lack of data of its benefit on the metabolic profile or survival of HIV men.

This article reviewed the prevalence, pathogenesis, association to cardiovascular disease, diagnosis, and benefits of testosterone replacement of hypogonadism in HIV infected men.

Correspondence to:
Kietsiriroje N, Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Kanjanavanish Road, Korhong, Hat Yai, Songkhla 90110, Thailand.
Phone: +66-74-451463, Fax: +66-74-455855
E-mail: Knoppado@medicine.psu.ac.th

Prevalence

Before the highly active antiretroviral therapy (HAART) era, the prevalence of hypogonadism ranged from 30% to 50% in men who had HIV and the wasting syndrome[11,12]. After the initiation of HAART, there has been a marked decrease in advanced AIDS and the wasting syndrome. However, the prevalence of hypogonadism in post-HAART era is still as high as 20% to 25% in HIV infected men being treated for wasting syndrome[13]. The prevalence of hypogonadism in HIV infected patients is higher in all age-groups particularly in younger ages compared to the general

Table 1. Clinical manifestations of testosterone deficiency*

Physical	Psychological	Sexual
• Decreased BMD	• Depressed mood	• Diminished libido
• Decreased muscle mass and strength	• Diminished energy, sense of vitality, or well-being	• Erectile dysfunction
• Increased body fat or BMI	• Impaired cognition and memory	• Difficulty achieving orgasm
• Gynecomastia		• Decreased morning erection
• Anemia		• Decreased performance
• Frailty		
• Fatigue		

BMD = bone mineral density; BMI = body mass index
* Adopted from reference[3]

population[14] and the prevalence of hypogonadism in the HIV infected patients increased with older age[15]. However, the true prevalence of hypogonadism in HIV infected patients is not yet well-defined because of differences of cut-off values of serum testosterone and in different age ranges. Moreover, there were many limitations in the previous studies on testosterone deficiency in HIV infected men including a lack of information on gonadotropins, the small number of enrolled subjects, a possibility of inappropriate blood sampling, a possibility of inaccurate measurement of free testosterone alone by inaccurate assays and the retrospective design of the studies.

The prevalence of hypogonadism in HIV infected patients in the pre- and post-HAART eras was illustrated in Fig. 1.

Pathogenesis of hypogonadism in HIV infected patients

There were many studies from animal models and human studies that tried to find relationships between an HIV infection and the low testosterone stage in HIV infected patients. Many mechanisms possibly affected are the testicular function and hypothalamus-pituitary-gonadal axis (HPG). An overview of the pathogenesis of hypogonadism in HIV infected patients was illustrated in Fig. 2.

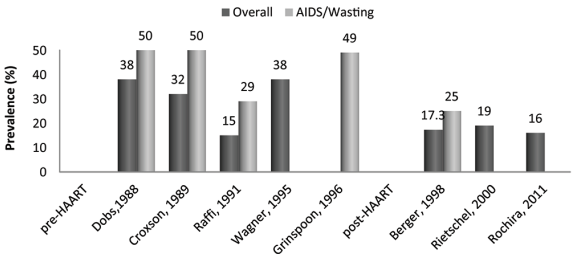

Fig. 1 Prevalence of hypogonadism in HIV infected patients in the pre- and post-HAART era[5,12-14,16-19].

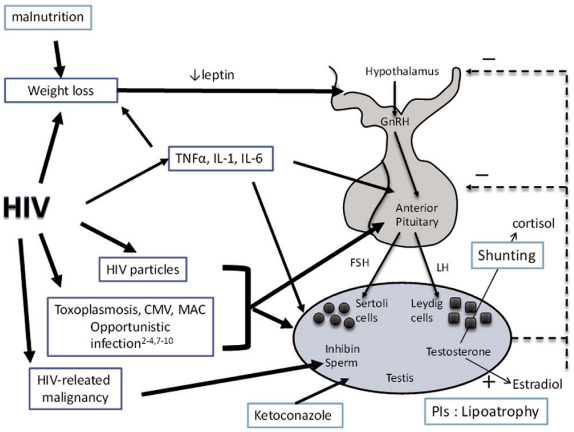

Fig. 2 Pathogenesis of hypogonadism in HIV infected patients. An HIV infection with opportunistic infections including toxoplasmosis, cytomegalovirus, *Mycobacterium avium* complex, and HIV-related malignancy affects both testes and the anterior pituitary gland and leads to dysfunction of both organs. The inflammatory process and cytokines suppress anterior pituitary function. Malnutrition and weight loss suppress hypothalamus function. Ketoconazole has an inhibitory effect on steroidogenesis by inhibiting the cytochrome P450 system. Protease inhibitors increase aromatizing of testosterone to estradiol which in turn has negative feedback to both the anterior pituitary and hypothalamus. In the HIV-infection, there is a shunting effect to produce cortisol rather than sex hormone. HIV: human immunodeficiency virus, CMV: cytomegalovirus, MAC: *Mycobacterium avium* complex, TNF: tumor necrotic factor, IL-: interleukin, FSH: follicle stimulating hormone, LH: lutenizing hormone, GnRH: gonadotropin releasing hormone, PIs: protease inhibitors.

HIV and testicular dysfunction

The causes of testicular dysfunction in HIV infected patients are divided into four categories: 1) a direct effect of HIV particles, 2) infections, usually with mixed opportunistic pathogens, 3) HIV-related malignancy and its treatment, and 4) medications that are used for HIV infection or its opportunistic infection.

The testis is a reservoir for the HIV virus because its protective mechanism protects the virus from antiretroviral agents[20]. The affected cells susceptible to HIV infection are testicular T lymphocytes, macrophages[20-23], and the testicular germ cells[24]. Although spermatozoa have no CD4 receptor for HIV, there are many alternative receptors for a virus that have been described in a review elsewhere[25]. The transient increase in testosterone level without any significant modifications of the luteinizing hormone (LH) was reported in the early phase of infection from both animal models and observational human studies[21,26-28]. The testosterone level will decrease at the late phase of the infection[12,17,29]. Some studies reported the low serum testosterone levels in men with AIDS, in some cases associated with high serum LH and follicle stimulating hormone (FSH) levels which implied that there was primary testicular failure[16,30]. From the autopsy studies revealed histological changes in the testes, which were common in patients who died from AIDS. Common findings at autopsy include hypospermatogenesis with Sertoli cells predominantly line the tubules[31,32], maturation arrest of spermatogenesis, thickened basement membrane, tubular hyalinization, and decreased number of Leydig cells and interstitial infiltrate[27,29,31,33-36]. All of these findings may contribute to the low testosterone level in HIV infected patients.

Much evidence has demonstrated HIV particles in the male genital organs. Da Silva et al reported on the histological sections of the testes and prostate that were stained with an anti-HIV P17 monoclonal antibody[37]. HIV protein expression was demonstrated in the lymphocytes of the seminiferous tubules and interstitium of the testes in nine of 23 patients studied by Pudney and Anderson[38]. Additionally, a study using PCR in situ hybridization, showed HIV DNA selectively infecting the spermatogonia in the testes of 11 of 12 HIV infected men[39]. In addition to the HIV particle itself, in AIDS, the testicular damage may be occurred by opportunistic infections, which included cytomegalovirus, toxoplasmosis, and the *Mycobacterium avium* complex[19,31,40]. In the pre-HAART era, the testicular dysfunction in AIDS patients was also affected by HIV-related malignancies, which most frequently were Kaposi's sarcoma, lymphoma, and its treatment.

Medications that are used for HIV infection or opportunistic infections also affect testicular function. Ketoconazole is an inhibitor of the cytochrome P450 system at various levels and results in a decrease of testicular steroidogenesis[41]. HIV infected patients who took antiretroviral drugs had higher level of estradiol, which in turn had negative feedback on the HPG axis and higher prevalence of the lack of sexual desire[42].

Hypothalamus and pituitary dysfunction in the HIV infected patients

Early studies on hypogonadism among HIV infected patients during the 1980s, autopsies revealed a direct infection of HIV virus particles in the anterior pituitary tissue[33]. Moreover, other opportunistic infections including cytomegalovirus, Pneumocystis carinii, and toxoplasmosis were also reported from autopsy studies[11,27,33,43,44].

Acute and chronic illnesses are well-known as causes of secondary hypogonadism. In HIV infected patients, some factors affect the HPG axis include weight loss and catabolic cytokines[45]. In response to starvation, the leptin level falls rapidly and this response suppresses luteinizing hormone pulsation and decreases the testosterone level[46]. Interleukin-1β (IL-1β) at high levels inhibits the binding of LH to Leydig cells and blocks testicular steroidogenesis. Tumor necrotic factor-α (TNF-α) affects the central process and at the level of the gonads which results in low serum testosterone[27].

The interplay among HIV infection, testosterone deficiency, and cardiovascular diseases

It is well-known that metabolic syndrome (MetS) is associated with a significant cardiovascular risk[47]. In addition, an association between the androgen deficiency and metabolic disorders including hypertension, dyslipidemia, diabetes, obesity, and asthma/COPD has been observed[48]. Many small population-based prospective cohorts have reported a lower total testosterone and lower sex hormone-binding globulin (SHBG) associated with the development of MetS[49-51] and diabetes mellitus[51,52] in middle-aged to elderly men. A systematic review reported that men who had higher testosterone levels (RR 0.58, 0.39 to 0.87) or SHBG level (RR 0.48, 0.34 to 0.69) compared to lower testosterone or SHBG levels had a lower risk

in development of type 2 diabetes[53]. Two meta-analytic studies on endogenous testosterone level mortality have reported the same conclusion that the lower testosterone levels were associated with increased risk of all causes and cardiovascular disease (CVD) mortality but not CVD incidence[54,55]. However, there is significant heterogeneity across studies limiting the validity of these data. One plausible conclusion may be that low testosterone is simply a marker of poor general health status.

An HIV infection is associated with a lower testosterone level as mentioned early. Moreover, an HIV infection itself is one of the CVD risk factors other than traditional risk factors. After initiation of anti-retroviral therapy, survival from the HIV infection has dramatically improved, and because of this longer life expectancy, cardiovascular mortality among HIV infected patients can be observed. Moreover, premature atherosclerosis involving coronary, peripheral, and cerebral arteries has been observed in young HIV infected adults and children without traditional coronary risk factors[56]. One retrospective analysis suggested that the risk of cardiovascular disease may be greater in younger (18-34 years old) HIV infected patients and exposure to antiretroviral therapy may contribute to the incidence of the coronary heart diseases (CHD) among younger individuals with HIV when certain comorbidities have been adjusted[57]. There was also an epidemiological study that reported an increased incidence of ischemic stroke in patients with HIV infection[58,59].

From the largest prospective study, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) that enrolled 23,468 participants, most subjects were thin middle-aged male patients with low cardiovascular risk factors. The median duration of HIV-1 infection was 3.5 years and the median cumulative exposure to combination antiretroviral therapy was 1.9 years. The primary endpoint was the incidence of myocardial infarction. Of the 23,468 participants, 126 (0.5%) had the first myocardial infarction during follow-up (incidence = 3.5 events per 1,000 persons per year) and the incidence of myocardial infarction increased with increasing exposure to HAART with the demographic risk adjusted relative rate equal to 1.26 (95% CI 1.12 to 1.41) per additional year of exposure to HAART[60]. To collect adequate myocardial infarction event rates to determine an effect of the class of antiretroviral drugs on the incidence of myocardial infarction, a follow-up study was conducted with a median follow-up of 4.5 years per patient and 345 events (incidence = 3.65 per 1,000 person-years). The author concluded that exposure to protease inhibitors (RR 1.16, 95% CI 1.10 to 1.23) was associated with an increased risk of myocardial infarction which was partly explained by dyslipidemia but not to the exposure to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) (RR 1.05, 95% CI 0.98 to 1.13)[61].

The mechanisms of vascular diseases in HIV infected patients are unknown but may relate to inflammatory cytokines and other adhesive molecules, endothelial dysfunction induced by the HIV infection and protease inhibitors, metabolic disturbances from HAART and other traditional cardiovascular risk factors[62]. HAART causes some metabolic disorders including lipodystrophy, dyslipidemia, insulin resistance, and hyperglycemia, which contribute to other cardiovascular risks[63].

The association between testosterone and cardiovascular disease does not yet demonstrate cause and effect, but testosterone deficiency would be a rather poor marker for cardiovascular disease because they share the same common factors (dyslipidemia, hyperglycemia, and insulin resistance). Therefore, testosterone deficiency may be a predictor for poor patient status which leads to a poor cardiovascular outcome. Furthermore, an HIV infection will deteriorate the testosterone level and metabolic profile, which will increase the risk for cardiovascular disease.

The interplay among HIV infection, testosterone deficiency, and cardiovascular diseases was illustrated in Fig. 3.

Diagnosis

The diagnosis of hypogonadism is based on symptoms, signs, and biochemical evidence. However there are no persistent criteria for a diagnosis that are dependent on a clinical guideline.

The diagnosis of testosterone deficiency among HIV infected patients is based on the same recommendation as the general population. In the present review, the author used the criteria for diagnosis based on the 2006 Endocrine Society Clinical Practice Guideline, which is summarized below[64].

1. The patients should have consistent symptoms and signs.

2. Use morning total testosterone level by a reliable assay at least two times apart.

3. If the total testosterone level was equivocal or there were alterations of SHBG, use the free or bioavailable testosterone level.

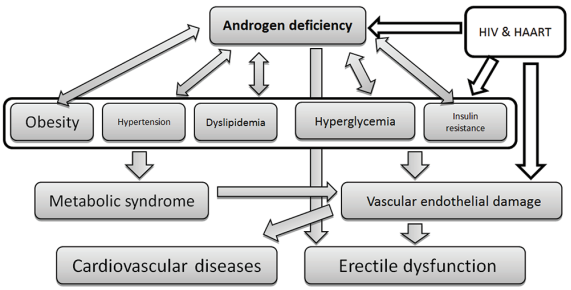

Fig. 3 Interplay among HIV infection, testosterone deficiency and cardiovascular diseases. The cardiovascular diseases are considered to be caused by vascular endothelial dysfunction. Many metabolic disorders including obesity, hypertension, dyslipidemia, and diabetes mellitus are well-known risk factors of cardiovascular diseases and are associated with the androgen deficiency. The androgen deficiency may worsen metabolic disorders which may increase risk of the cardiovascular diseases. HIV infection may be a risk factor of the cardiovascular diseases through 3 mechanisms, 1) decreasing the testosterone level, 2) worsening insulin resistance which is a side-effect from ARVs, and 3) HIV particles directly damage endothelial cells.

4. For the cut-off level of testosterone, use the lower limit of the normal testosterone range established in our reference laboratory. In area that has no normal reference range for total testosterone and free testosterone, the recommended lower limit of total testosterone and free testosterone are 280-300 ng/dl and 50-90 pg/ml, respectively.

5. The evaluation of androgen deficiency should not be made during an acute or subacute illness.

To apply this guideline to diagnose androgen insufficiency among HIV infected patients, some limitations should be noted.

1. HIV infected patients may manifest some less specific symptoms and signs of testosterone deficiency by the disease itself.

2. The HIV disease increases the SHBG level[65] that affects the total testosterone level. However, an equilibrium dialysis for free testosterone level measurement is usually available only in large laboratory centers.

3. The HIV infected patient may have some comorbidities and drug interference.

One study that reported the use of total testosterone by radioimmunoassay presented a sensitivity of less than 30% in the diagnosis of hypogonadism among 90 HIV infected males[66] whilst another study reported that using criteria of total testosterone lower than 300 ng/dl and free testosterone lower than 50 pg/ml diagnosed hypogonadism in HIV infected men only 24% and 19%, respectively and threshold for diagnosing hypogonadism using free testosterone lower than 100 pg/ml and the presence of one or more hypogonadal symptom increased yield for diagnosis to 64%[67].

Therefore, the diagnosis of testosterone deficiency among HIV infected patients is challenging and one should interpret with care. In case of suspected hypogonadotropic hypogonadism, more information including a neurological examination, other pituitary hormone assays or imaging studies may be considered to exclude hypothalamic-pituitary lesion.

Benefits of testosterone replacement therapy (TRT)

In the non-HIV infected population

The benefits of TRT in men with a low testosterone level are usually involved with body composition including increase fat-free mass, decrease fat mass, increased muscle strength, and increase bone mineral density. Moreover, TRT also has positive effects on the mood and senses of sexual well-being (but not erectile function)[1,68]. Data on the effects of testosterone therapy on lipid profiles are inconsistent but there is a tendency to reduce the total cholesterol, HDL, and LDL levels in low-normal or normal testosterone level patients[68,69].

The effect of TRT on insulin resistance has been studied in a 12-month, prospective randomized-controlled trial that enrolled 220 hypogonadal men with type 2 diabetes and/or MetS[70]. From this study, TRT reduced HOMA-IR by 15.2% (95% CI 3 to 26, $p = 0.018$) compared with placebo at six months. There were no significant differences between treatments in HbA1c, fasting plasma glucose (FPG), fasting serum insulin, or HOMA-B. Some explanations of why there were no significant differences in HbA1c, FPG, and fasting serum insulin might be concomitant medications including oral antidiabetic drugs were allowed, which might have overshadowed the effect of TRT. Further, the size of the population may have inadequate power to detect the differences and the 6-month duration may have been too short. TRT basically increases fat-free masses which in turn improves insulin resistance (HOMA-IR) but not insulin secretion (HOMA-B).

Up until now, the benefit of testosterone therapy on cardiovascular outcome is still inconclusive. A result from a meta-analysis[69] which studied the effect of testosterone therapy on cardiovascular

outcome in patients with a low or low-normal testosterone level concluded that the odds ratio between testosterone therapy and any cardiovascular event, cardiovascular death, fatal and nonfatal myocardial infarction and other cardiovascular events (e.g., angina, arrhythmia, revascularization procedures, stroke) pooled across trials was 1.82 (95% CI 0.78 to 4.23). However, it should be noted that there were many limitations in interpreting the data.

1. There was heterogeneity of population across each trial.

2. The low testosterone level cut-offs in each trial were different.

3. The routes of administration in each trial were different.

4. Four out of six studies used short-term testosterone therapy (3-26 weeks). Only two out of six studies reported a median time used for testosterone therapy of three years.

Another meta-analysis, including six randomized clinical studies which enrolled 258 patients with coronary heart diseases with a mean follow-up of 23 weeks reported that TRT significantly increased the treadmill test duration and time to decrease the ST-segment depression by 1 mm which reflected an increased exercise capacity of the patients, (difference in mean = 57.40 seconds, 9.90-104.90)[54].

The effect of TRT on mortality rate has been reported in an observational study that enrolled 1,031 male veterans with low testosterone level with a mean age of approximately 60 years old and a 40.5-month average follow-up time. The study reported improved survival from TRT (hazard ratio 0.47, 95% CI 0.29 to 0.76)[10]. Because it was an observational study, the residual confounding may still be a source of bias, so large randomized clinical trials are needed to confirm the effect of TRT on the mortality rate.

In conclusion, TRT has benefits on body composition, muscle strength, bone mass density, and sexual well-being and it may have benefits on insulin resistance, cardiovascular outcome, and survival.

In HIV infected population

Data of TRT among HIV infected patients are scarce and limited. Most of the studies using TRT in HIV participants involved 1) HIV infected patients with weight loss (>5%), 2) short-term treatment duration (12-24 weeks), 3) small sample sizes in each study, 4) lean-body mass, total body weight and death that were usually the primary outcomes, and 5) significant heterogeneities across the trials. The effect of TRT on body composition showed small improvements in lean-body mass and total body weight. The average change in lean body mass was 1.3 kg (95% CI, 0.6 to 2.0), while the average change in total body weight was 1.1 kg (95% CI, 0.3 to 2.0). There was particular improvement of lean body mass and body weight in male participants with borderline gonadal status when TRT was used with supraphysiological doses and intramuscular route of administration. There were no differences on the adverse or death outcomes. These results suggest that TRT may be useful to improve lean body mass and body weight in the treatment of HIV infected patients with weight loss, however, because of the limitations, treatment recommendations cannot be established[71].

The effect of TRT on depressive mood in HIV infected patients regardless of gonadal status in a meta-analysis that compared the effect of short-term TRT and placebo on 248 participants with HIV/AIDS, better depression score was observed in the treatment group (OR 0.41, 95% CI 0.24 to 0.69)[72]. The TRT may also improve sexual function, sexual desire, and energy among HIV infected men with low or borderline testosterone level[73,74].

The effects of TRT on insulin resistance, lipid profile, or cardiovascular outcome in HIV infected men are still unknown. There was only one study tried to demonstrate the effects of testosterone gel 10 g daily on whole body and visceral fat mass, insulin resistance, and lipid profile in HIV infected men with abdominal obesity and low testosterone level. The author concluded that using testosterone gel 10 g/day for 24 weeks was associated with greater decrease in whole body, total, and subcutaneous abdominal fat mass and a greater increase in lean mass compared to placebo, but the effect on visceral fat mass was not different between groups. There were no differences of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and HOMA-IR index between groups[75].

In conclusion, TRT has small positive effect on body composition in HIV infected patient with weight loss and low or borderline testosterone level. TRT also improves depressive mood in HIV infected patient. There is lack of evidence of TRT on cardiovascular outcome or surrogate markers of cardiovascular diseases. To use TRT in HIV-infected men with low testosterone at our center, we consider TRT in HIV infected patients who have low testosterone level, low BMI and in particular multiple cardiovascular risk factors to improve body composition, quality of

life, and possibly improve metabolic profiles of the patients.

Conclusion

Hypogonadism is more common and occurs earlier in HIV infected patients than in the general population; however, the definite criteria for diagnosis are not yet determined. The pathogenesis of hypogonadism from HIV infection involves the entire HPG axis. A low testosterone level is associated with many metabolic disorders and increased mortality, which has been determined as a marker for health status. HIV infection and its treatment contribute risks for hypogonadism and cardiovascular diseases. Data on the benefits of TRT among HIV infected patients are scarce. However, if the data on TRT from the general population is presumed to be applicable, TRT should have benefits for the HIV infected patients as well.

What is already known on this topic?

The prevalence of hypogonadism among HIV infected patients is higher than general population. Testosterone deficiency associates with development of metabolic syndrome and diabetes mellitus, which are cardiovascular risk factors. HIV infection and HAART are also direct cardiovascular risk factors. TRT can improve body composition, muscle strength, bone density, mood, and senses of sexual well-being. It may improve insulin resistance and glycemic but the improvement on cardiovascular outcome is still inconclusive.

What this review adds?

• The pathogenesis of hypogonadism in HIV infected patients involves entire hypothalamus-pituitary-gonadal axis.

• The challenge on diagnosis of testosterone deficiency among HIV infected patients.

• Interrelationship among HIV infection, testosterone deficiency, and cardiovascular risk factors.

• Benefits of TRT in treatment of HIV-infected men with low or borderline testosterone.

Potential conflicts of interest

None.

References

1. 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.
2. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004; 350: 482-92.
3. Traish AM, Miner MM, Morgentaler A, Zitzmann M. Testosterone deficiency. Am J Med 2011; 124: 578-87.
4. Bhasin S, Javanbakht M. Can androgen therapy replete lean body mass and improve muscle function in wasting associated with human immunodeficiency virus infection? JPEN J Parenter Enteral Nutr 1999; 23 (6 Suppl): S195-201.
5. Grinspoon S, Corcoran C, Lee K, Burrows B, Hubbard J, Katznelson L, et al. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. J Clin Endocrinol Metab 1996; 81: 4051-8.
6. 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.
7. Salmimies P, Kockott G, Pirke KM, Vogt HJ, Schill WB. Effects of testosterone replacement on sexual behavior in hypogonadal men. Arch Sex Behav 1982; 11: 345-53.
8. 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.
9. Travison TG, Araujo AB, Wruck LM, Kupelian V, O'Donnell AB, McKinlay JB. Assessment of screening evaluations is not straightforward Comment on: "Comparison of screening questionnaires for the diagnosis of hypogonadism" [J.E. Morley, H.M. Perry III, R.T. Kevorkian, P. Patrick, Maturitas 53 (2006) 424-429]. Maturitas 2006; 54: 305-6.
10. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012; 97: 2050-8.
11. Aron DC. Endocrine complications of the acquired immunodeficiency syndrome. Arch Intern Med 1989; 149: 330-3.
12. Dobs AS, Dempsey MA, Ladenson PW, Polk BF.

Endocrine disorders in men infected with human immunodeficiency virus. Am J Med 1988; 84: 611-6.
13. Crum NF, Furtek KJ, Olson PE, Amling CL, Wallace MR. A review of hypogonadism and erectile dysfunction among HIV-infected men during the pre- and post-HAART eras: diagnosis, pathogenesis, and management. AIDS Patient Care STDS 2005; 19: 655-71.
14. Rochira V, Zirilli L, Orlando G, Santi D, Brigante G, Diazzi C, et al. Premature decline of serum total testosterone in HIV-infected men in the HAART-era. PLoS One 2011; 6: e28512.
15. 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.
16. Croxson TS, Chapman WE, Miller LK, Levit CD, Senie R, Zumoff B. Changes in the hypothalamic-pituitary-gonadal axis in human immunodeficiency virus-infected homosexual men. J Clin Endocrinol Metab 1989; 68: 317-21.
17. 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.
18. Wagner G, Rabkin JG, Rabkin R. Illness stage, concurrent medications, and other correlates of low testosterone in men with HIV illness. J Acquir Immune Defic Syndr Hum Retrovirol 1995; 8: 204-7.
19. 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.
20. Roulet V, Satie AP, Ruffault A, Le Tortorec A, Denis H, Guist'hau O, et al. Susceptibility of human testis to human immunodeficiency virus-1 infection in situ and in vitro. Am J Pathol 2006; 169: 2094-103.
21. Le Tortorec A, Le Grand R, Denis H, Satie AP, Mannioui K, Roques P, et al. Infection of semen-producing organs by SIV during the acute and chronic stages of the disease. PLoS One 2008; 3: e1792.
22. Paranjpe S, Craigo J, Patterson B, Ding M, Barroso P, Harrison L, et al. Subcompartmentalization of HIV-1 quasispecies between seminal cells and seminal plasma indicates their origin in distinct genital tissues. AIDS Res Hum Retroviruses 2002; 18: 1271-80.
23. Shehu-Xhilaga M, Kent S, Batten J, Ellis S, Van der Meulen J, O'Bryan M, et al. The testis and epididymis are productively infected by SIV and SHIV in juvenile macaques during the post-acute stage of infection. Retrovirology 2007; 4: 7.
24. Muciaccia B, Filippini A, Ziparo E, Colelli F, Baroni CD, Stefanini M. Testicular germ cells of HIV-seropositive asymptomatic men are infected by the virus. J Reprod Immunol 1998; 41: 81-93.
25. Le Tortorec A, Dejucq-Rainsford N. HIV infection of the male genital tract--consequences for sexual transmission and reproduction. Int J Androl 2010; 33: e98-108.
26. Christeff N, Gharakhanian S, Thobie N, Rozenbaum W, Nunez EA. Evidence for changes in adrenal and testicular steroids during HIV infection. J Acquir Immune Defic Syndr 1992; 5: 841-6.
27. Sellmeyer DE, Grunfeld C. Endocrine and metabolic disturbances in human immunodeficiency virus infection and the acquired immune deficiency syndrome. Endocr Rev 1996; 17: 518-32.
28. Merenich JA, McDermott MT, Asp AA, Harrison SM, Kidd GS. Evidence of endocrine involvement early in the course of human immunodeficiency virus infection. J Clin Endocrinol Metab 1990; 70: 566-71.
29. Dejucq N, Jegou B. Viruses in the mammalian male genital tract and their effects on the reproductive system. Microbiol Mol Biol Rev 2001; 65: 208-31.
30. 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.
31. Chabon AB, Stenger RJ, Grabstald H. Histopathology of testis in acquired immune deficiency syndrome. Urology 1987; 29: 658-63.
32. Yoshikawa Y, Truong LD, Fraire AE, Kim HS. The spectrum of histopathology of the testis in acquired immunodeficiency syndrome. Mod Pathol 1989; 2: 233-8.
33. Poretsky L, Can S, Zumoff B. Testicular dysfunction in human immunodeficiency virus-infected men. Metabolism 1995; 44: 946-53.

34. Dalton AD, Harcourt-Webster JN. The histopathology of the testis and epididymis in AIDS--a post-mortem study. J Pathol 1991; 163: 47-52.
35. De Paepe ME, Waxman M. Testicular atrophy in AIDS: a study of 57 autopsy cases. Hum Pathol 1989; 20: 210-4.
36. Salehian B, Jacobson D, Swerdloff RS, Grafe MR, Sinha-Hikim I, McCutchan JA. Testicular pathologic changes and the pituitary-testicular axis during human immunodeficiency virus infection. Endocr Pract 1999; 5: 1-9.
37. da Silva M, Shevchuk MM, Cronin WJ, Armenakas NA, Tannenbaum M, Fracchia JA, et al. Detection of HIV-related protein in testes and prostates of patients with AIDS. Am J Clin Pathol 1990; 93: 196-201.
38. Pudney J, Anderson D. Orchitis and human immunodeficiency virus type 1 infected cells in reproductive tissues from men with the acquired immune deficiency syndrome. Am J Pathol 1991; 139: 149-60.
39. Nuovo GJ, Becker J, Simsir A, Margiotta M, Khalife G, Shevchuk M. HIV-1 nucleic acids localize to the spermatogonia and their progeny. A study by polymerase chain reaction in situ hybridization. Am J Pathol 1994; 144: 1142-8.
40. Nistal M, Santana A, Paniaqua R, Palacios J. Testicular toxoplasmosis in two men with the acquired immunodeficiency syndrome (AIDS). Arch Pathol Lab Med 1986; 110: 744-6.
41. Pont A, Graybill JR, Craven PC, Galgiani JN, Dismukes WE, Reitz RE, et al. High-dose ketoconazole therapy and adrenal and testicular function in humans. Arch Intern Med 1984; 144: 2150-3.
42. Lamba H, Goldmeier D, Mackie NE, Scullard G. Antiretroviral therapy is associated with sexual dysfunction and with increased serum oestradiol levels in men. Int J STD AIDS 2004; 15: 234-7.
43. Milligan SA, Katz MS, Craven PC, Strandberg DA, Russell IJ, Becker RA. Toxoplasmosis presenting as panhypopituitarism in a patient with the acquired immune deficiency syndrome. Am J Med 1984; 77: 760-4.
44. Sano T, Kovacs K, Scheithauer BW, Rosenblum MK, Petito CK, Greco CM. Pituitary pathology in acquired immunodeficiency syndrome. Arch Pathol Lab Med 1989; 113: 1066-70.
45. Kalyani RR, Gavini S, Dobs AS. Male hypogonadism in systemic disease. Endocrinol Metab Clin North Am 2007; 36: 333-48.
46. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med 2010; 152: 93-100.
47. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program - Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care 2007; 30: 8-13.
48. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract 2006; 60: 762-9.
49. Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab 2005; 90: 2618-23.
50. Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. J Clin Endocrinol Metab 2006; 91: 843-50.
51. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004; 27: 1036-41.
52. Vikan T, Schirmer H, Njolstad I, Svartberg J. Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men. Eur J Endocrinol 2010; 162: 747-54.
53. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2006; 295: 1288-99.
54. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol 2011; 165: 687-701.
55. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol

Metab 2011; 96: 3007-19.
56. Mu H, Chai H, Lin PH, Yao Q, Chen C. Current update on HIV-associated vascular disease and endothelial dysfunction. World J Surg 2007; 31: 632-43.
57. Currier JS, Taylor A, Boyd F, Dezii CM, Kawabata H, Burtcel B, et al. Coronary heart disease in HIV-infected individuals. J Acquir Immune Defic Syndr 2003; 33: 506-12.
58. Ovbiagele B, Nath A. Increasing incidence of ischemic stroke in patients with HIV infection. Neurology 2011; 76: 444-50.
59. Voelker R. Stroke increase reported in HIV patients. JAMA 2011; 305: 552.
60. Friis-Moller N, Sabin CA, Weber R, d'Arminio MA, El Sadr WM, Reiss P, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 2003; 349: 1993-2003.
61. Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El Sadr W, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007; 356: 1723-35.
62. Sudano I, Spieker LE, Noll G, Corti R, Weber R, Luscher TF. Cardiovascular disease in HIV infection. Am Heart J 2006; 151: 1147-55.
63. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med 2005; 352: 48-62.
64. 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.
65. Martin ME, Benassayag C, Amiel C, Canton P, Nunez EA. Alterations in the concentrations and binding properties of sex steroid binding protein and corticosteroid-binding globulin in HIV+patients. J Endocrinol Invest 1992; 15: 597-603.
66. 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.
67. Blick G. Optimal diagnostic measures and thresholds for hypogonadism in men with HIV/AIDS: comparison between 2 transdermal testosterone replacement therapy gels. Postgrad Med 2013; 125: 30-9.
68. Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf) 2005; 63: 280-93.
69. Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Bolona ER, Sideras K, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007; 82: 29-39.
70. Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care 2011; 34: 828-37.
71. Johns K, Beddall MJ, Corrin RC. Anabolic steroids for the treatment of weight loss in HIV-infected individuals. Cochrane Database Syst Rev 2005; (4): CD005483.
72. Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: systematic review and meta-analysis. J Psychiatr Pract 2009; 15: 289-305.
73. Rabkin JG, Rabkin R, Wagner G. Testosterone replacement therapy in HIV illness. Gen Hosp Psychiatry 1995; 17: 37-42.
74. 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.
75. 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.

ภาวะพร่องฮอร์โมนเพศชายในผู้ติดเชื้อเอชไอวี

นพดล เกียรติศิริโรจน์

ภาวะพร่องฮอร์โมนเพศชายสามารถพบได้ถึง 30-50% ในผู้ที่ติดเชื้อเอชไอวีที่มีน้ำหนักลดลงอย่างมาก และ 20-25% ในผู้ติดเชื้อเอชไอวีที่ไม่มีอาการน้ำหนักลด การติดเชื้อเอชไอวีทำให้การเกิดภาวะพร่องฮอร์โมนเพศชายโดยรบกวน hypothalamus-pituitary-gonadal axis ทั้งทางตรงและทางอ้อม ซึ่งสามารถจำแนกกลไกการเกิดได้จาก 4 กลุ่ม คือ 1) เชื้อไวรัสเอชไอวี 2) เชื้อฉวยโอกาส 3) มะเร็งและการรักษามะเร็งอันเกิดจากเชื้อเอชไอวี และ 4) ยาต้านไวรัสและยาที่ใช้รักษาโรคติดเชื้อฉวยโอกาสอื่น ๆ ความสัมพันธ์ระหว่างการติดเชื้อเอชไอวี ภาวะพร่องฮอร์โมนเพศชาย และโรคหัวใจหลอดเลือดยังต้องรอการพิสูจน์ อย่างไรก็ตามมีข้อมูลที่พิสูจน์ให้เห็นว่า การติดเชื้อเอชไอวีและการได้ยาต้านไวรัสมีความเกี่ยวข้องกับความเสี่ยงการเกิดโรคหัวใจหลอดเลือด การวินิจฉัยภาวะพร่องฮอร์โมนเพศชายในกลุ่มผู้ติดเชื้อเอชไอวีมีความท้าทายเนื่องจากการติดเชื้อเอชไอวีจะเพิ่มระดับ total testosterone เนื่องจากการเพิ่มขึ้นของ sex hormone-binding globulin การใช้ฮอร์โมน testosterone สามารถเพิ่มสัดส่วนกล้ามเนื้อและน้ำหนักตัว สามารถช่วยลดอาการซึมเศร้า และอาจมีผลดีต่อการลดปัจจัยเสี่ยงทางเมตาบอลิสมของโรคหัวใจหลอดเลือดในผู้ติดเชื้อเอชไอวีที่มีดัชนีมวลกายน้อยได้