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HIV/AIDS (C YOON, SECTION EDITOR)

Title: Updates on Testosterone Deficiency in Men Living With HIV and the Cardiovascular Implications

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Abstract

Purpose of Review This review evaluates recent literature (2020–2025) on testosterone deficiency (TD) and its cardiovascular implications in men living with HIV (MLH), focusing on prevalence, underlying mechanisms, diagnostic challenges, and management strategies, including cardiovascular risks linked to testosterone replacement therapy (TRT).

Recent Findings TD remains highly prevalent in MLH, often manifesting earlier than in the general population due to chronic inflammation and immune dysregulation. While TRT's cardiovascular risks have been debated, recent studies indicate no significant increase in major cardiovascular events among TRT users compared to placebo, though some adverse effects remain a concern.

Summary With HIV now a chronic condition due to antiretroviral therapy (ART), the focus has shifted to managing non-infectious comorbidities like TD. MLH experience TD at younger ages and require personalized care to address this condition and its associated risks effectively.

Keywords HIV · Testosterone · cardiovascular risk · hypogonadism

Introduction

What is Currently Known About Testosterone Deficiency in Men Living with HIV?

Since the advent of highly active antiretroviral therapy (ART), the treatment of HIV has transitioned to a chronic disease. This shift has brought about a change in the complications that men living with HIV (MLH) face, moving from opportunistic infectious to chronic non-infectious comorbidities [1]. These comorbidities, including liver, renal, cardiovascular diseases, osteoporosis, metabolic disorders, and cancers, present unique challenges for MLH. Testosterone deficiency (TD), also known as male hypogonadism, is a clinical syndrome that commonly occurs in MLH. It is characterized by consistently low levels of serum testosterone accompanied by symptoms that align with TD. In MLH, the presence of low testosterone in conjunction with low or inappropriately normal gonadotropin levels is considered secondary hypogonadism and is thought to be from HIV-associated dysfunction of the hypothalamic-pituitary–gonadal (HPG) axis [1].

The prevalence of TD in MLH is estimated to be 34.5% [2]. In men without HIV, the prevalence of biochemical male hypogonadism also increases with age, affecting approximately 12% of men aged 50 to 59 and rising to 49% in those aged 80 and older [3]. In MLH, the prevalence of TD increases with age; however, this population is affected earlier on in life [4]. Hypogonadism is seen in MLH in their 20-40 s, whereas in men without HIV, hypogonadism is a rare disease before the age of 40 [5]. However, the prevalence of hypogonadism among MLH varies considerably across studies, reflecting the heterogeneity in diagnostic criteria and patient populations studied [6]. The variability in hypogonadism prevalence

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among studies is mainly due to differing definitions and variabilities in the type of testosterone levels reported, thresholds, and reference ranges used [7]. These differences may significantly impact the reported prevalence and the understanding of hypogonadism in MLH [6, 7].

Why does Testosterone Deficiency Affect Men Living with HIV?

Chronic Inflammation has been linked to TD. Pro-inflammatory cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) for example, have been implicated in the suppression of the HPG axis, leading to reduced secretion of gonadotropin-releasing hormone (GnRH) and subsequent downstream effects on luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [5]. Chronic illness, weight loss, and malnutrition are additional factors contributing to the disruption of the HPG axis in people living with HIV. The catabolic state induced by HIV-related wasting syndrome, as well as possible opportunistic infections and malignancies that may necessitate chemotherapy or radiation, exacerbates the suppression of the HPG axis [8]. This can result in a more intricate interaction between secondary and primary hypogonadism. In such cases, direct damage to the gonads caused by HIV or its treatments can lead to primary hypogonadism, which is typically marked by elevated levels of gonadotropins. The initiation of antiretroviral therapy (ART) has also been associated with varying effects on testosterone levels. While some studies report an increase in testosterone following ART initiation, suggesting a partial restoration of HPG function or a direct impact of ART on gonadal function, the underlying mechanisms remain incompletely understood [9].

Methods

This review was conducted using advanced searches on PubMed from the National Library of Medicine. The review aims to provide an updated analysis of the literature on testosterone deficiency and cardiovascular disease in MLH from 2020 to 2025. We utilized targeted keywords, including "cardiovascular disease," "testosterone deficiency," "hypogonadism," "testosterone replacement therapy," and "HIV." Our review focused on research studies that have been influential in shaping the fields of endocrinology and cardiology.

A Reminder of the Role of Testosterone in the Body

Testosterone is crucial in regulating secondary male characteristics and contributes to masculine traits. These include male hair distribution, changes in the voice by deepening the vocal tone. It also promotes anabolic effects, such as growth spurts during puberty via stimulating tissue growth at the epiphyseal plate and later closure, and the development of skeletal muscle through increased protein synthesis. Additionally, testosterone enhances erythropoiesis, leading to a higher hematocrit in males compared to females. As testosterone levels decline with age, men may consequently experience reduced testicular size, decreased libido, lower bone density, muscle mass loss, increased fat accumulation, and reduced erythropoiesis, which can result in anemia [10]. In circulation, testosterone is mainly bound to sex hormone binding globulin (SHBG), which modulates the delivery of testosterone to tissues. The abundance of SHBG and testosterone are highly related and can affect the ability to measure testosterone levels in the body [11]. In MLH, SHBG are elevated when compared to men without HIV and therefore highlights the importance of measuring SHBG together with a complete hormonal profile to properly diagnose and classify hypogonadism in MLH complaining about sexual symptoms [12, 13].

What is the Relation of Testosterone and Cardiovascular Disease Risk?

Testosterone influences cardiovascular disease (CVD) risk and all-cause mortality in men. Lower levels of testosterone are associated with an increased risk of both all-cause mortality and cardiovascular mortality. Men with baseline testosterone concentrations below 7.4 nmol/L (213 ng/dL) demonstrated a higher risk of all-cause mortality, and those with levels below 5.3 nmol/L (153 ng/dL) have been shown to be at increased risk of CVD mortality [14]. Additionally, when accounting for confounding variables, men with TD have been shown to have an increased risk of stroke, and venous thromboembolism at 1 and 5 years [15]. Testosterone deficiency is hypothesized to contribute as a risk factor for CVD in men, partly due to its contribution to increased large artery stiffness [16]. This arterial stiffness is believed to arise from elevated oxidative stress, which leads to reduced production of nitric oxide, degradation of elastin, and an increase in collagen deposition [16, 17]. Additionally, TD is reported to increase levels of low-density lipoprotein and total cholesterol and decrease high-density lipoprotein, all well-established risk factors for atherosclerosis [18, 19]. See Fig. 1.

What is Known About Testosterone Replacement Therapy and Cardiovascular Risk?

The controversy surrounding testosterone replacement therapy (TRT) and its cardiovascular safety has been debated for many years. Early randomized controlled

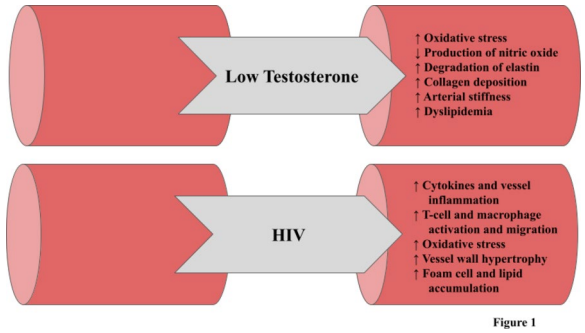

Fig. 1 Proposed mechanism of testosterone and HIV on the systemic vasculature. This figure exemplifies the similarities of both TD and HIV on the vascular system and therefore the potential to enhance CVD risk. Both conditions lead to vessel injury and endothelial dysfunction, which increase the CVD risk in this population and emphasize the importance of early treatment for people with these comorbidities

trials of TRT yielded conflicting results and had limitations that hindered the generalizability of their findings. For instance, studies such as the Copenhagen Study and the Testosterone in Older Men with Mobility Limitations (TOM) trial suggested an increased risk of mortality or cardiovascular events with TRT [20, 21]. In contrast, the Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) trial found no significant differences in the progression of subclinical atherosclerosis markers, like carotid intima-media thickness and coronary artery calcium scores, or in cardiovascular events over three years between the TRT and placebo groups [21]. Similarly, the cardiovascular arm of the Testosterone Trials noted greater increases in non-calcified and total plaque volumes over 12 months in the TRT group compared to placebo, though there were no differences in CAC scores or cardiovascular events [22]. The clinical significance of these plaque changes remains unclear, but they highlight the complexity of TRT's effects and the potential implications for cardiovascular risk.

Building on previous meta-analyses of RCTs, which did not find a link between TRT and major adverse cardiovascular events, a more recent comprehensive meta-analysis conducted by Jaiswal et al. provides crucial insights into the cardiovascular implications of TRT. By analyzing data from 30 RCTs, including 11,502 patients, they report no significant differences in the rates of myocardial infarction, stroke, or cardiovascular mortality between the TRT and placebo groups [23]. Additionally, The Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial, demonstrated that in men with hypogonadism and pre-existing or a high risk of cardiovascular disease, TRT was noninferior to placebo with respect to the incidence of major adverse cardiac events. However, patients on TRT did have a higher incidence of atrial fibrillation, acute kidney injury, and pulmonary embolism [20].

HIV-Associated Cardiovascular Disease is Currently an Established Risk for People Living with HIV

People living with HIV have an increased relative risk of 1.4 to 2.1 for myocardial infarction [23]. HIV infection has been established to create a pro-inflammatory state in the systemic vessels. The inflammatory state and immune system activation contribute to altered vessel biology, accelerated atherogenesis, plaque formation, and plaque instability. Despite antiretroviral therapy (ART), persistent activation of CD8 + T cells may be fueled in people living with HIV by ongoing anti-HIV responses and stimulation from poorly controlled opportunistic pathogens, such as cytomegalovirus. The clinical significance of these persistent T-cell abnormalities is underscored by their association with increased ischemic heart disease risk, characterized by low CD4 + T cell counts, elevated CD8 + T cell counts, and a low CD4 ratio. These findings highlight the importance of early HIV diagnosis and prompt ART initiation to optimize recovery of T-cell homeostasis. HIV-associated CVD has also been attributed to the metabolic effects of ARTs. Although newer ART regimens, including integrase strand transfer inhibitors, exhibit a more favorable lipid profile and potentially lower CVD risk, they are also associated with increased weight gain, leaving the overall impact on cardiometabolic risk uncertain [24, 25]. Consequently, contemporary studies continue to demonstrate an excess CVD risk in people living with HIV, attributable in part to persistent inflammation despite viral suppression.

How to Diagnose Testosterone Deficiency?

To diagnose TD it is necessary to recognized the clinical signs and symptoms prior to proceeding to laboratory testing. MLH with hypogonadism exhibit signs and symptoms of androgen deficiency that are similar to those seen in the general population. Symptoms can vary from specific, suggestive, and non-specific symptoms of TD. Specific symptoms of TD include incomplete or delayed sexual development, loss of body hair (axillary and pubic hair), and very small testes (< 6 mL). Suggestive symptoms include reduced sexual desire (libido) and activity, decreased spontaneous erections, erectile dysfunction, breast discomfort, gynecomastia, inability to father children, low sperm count, height loss, low trauma fracture, low bone mineral density, hot flushes, and sweats. Non-specific symptoms are difficult to attest to TD but include decreased energy, motivation,

initiative, and self-confidence, as well as feeling sad or blue, depressed mood, persistent low-grade depressive disorder, poor concentration and memory, sleep disturbance, increased sleepiness, mild unexplained anemia, reduced muscle bulk and strength, increased body fat, and body mass index [3, 4].

Laboratory evaluation for TD in MLH requires caution and an understanding of the effects of HIV virus in the body. In addition to total and free testosterone levels, sex hormone binding globulin (SHBG), luteinizing hormone (LH) and follicular stimulating hormone (FSH) may need to be assessed (see Table 1). In MLH, the levels of SHBG have been demonstrated to be elevated, and therefore are necessary information to diagnose TD beyond testosterone levels. In MLH, it is recommended that morning fasting total testosterone and free testosterone be measured as initial diagnostic tests. To meet the diagnostic criteria for low testosterone, both the American Urological Association (AUA) and the Endocrine Society (ES) require that testosterone levels be low on two separate occasions [26]. However, the cutoffs for defining low testosterone differ between the guidelines: the AUA sets the threshold at less than 300 ng/dL, while the ES recommends using the standard established by the CDC, which is 264 ng/dL. While the presentation of testosterone deficiency may appear similar regardless of HIV status, interpreting testosterone levels demands careful consideration of the clinical context particularly in the context of HIV.

What is the Current Management for Testosterone Deficiency in MLH?

The Endocrine Society Guidelines recommends against routine screening for TD in MLH. However, it does emphasize the importance of recognizing that MLH are of higher risk. It has been seen that 26% of MLH have low total testosterone concentrations and up to 40% when considering solely free testosterone levels [27]. Hypogonadism has also been seen as a suggestive indicator of frailty and poor health status in MLH [6]. Similarly, the guidelines from the Infectious Diseases Society of America recommend testing morning serum testosterone levels in adult cisgender men who present with symptoms such as decreased libido, erectile dysfunction, reduced bone mass or low-trauma fractures, hot flashes, or night sweats [28].

TRT is also frequently utilized in MLH experiencing weight loss or HIV-associated wasting. Short-term TRT has been shown to improve body weight and increase lean body mass in this population, provided that other causes of weight loss have been ruled out [29]. However, when TRT is used over time, it has been shown to have an inverse relationship with testosterone and weight loss. This is attributed to the stimulatory effects on lipolysis, decreased lipogenesis, and an increase in lean body mass [30]. Current guidelines recommend a course of testosterone therapy lasting between 3 to 6 months, with studies indicating that intramuscular testosterone esters are the most effective form of TRT for achieving weight gain in these individuals [31]. However, there remains a lack of clear long-term recommendations for MLH, who continue to experience weight loss as a result of the chronic infection. The decision to continue therapy beyond the initial recommended period is typically made on a case-by-case basis at the discretion of the patient and their physician. This individualized approach considers the patient's ongoing symptoms, overall health status, and response to therapy. With that in consideration, there is a risk of long-term TRT side effects, including testicular atrophy, permanent inability to produce natural hormones, and testosterone withdrawal when TRT is stopped [26].

What are Current Testosterone Replacement Therapy Options?

There are many treatment options available for TRT for men with TD, each with its unique benefits and considerations. While there have been some observed benefits between formulations, treatment is decided by patient preference, cost, and availability. Testosterone gels and solutions are commonly used and applied directly to the skin [32]. These products provide a steady release of testosterone into the bloodstream, maintaining normal levels throughout the day. While

Table 1 Summary of the indications for TRT in MLH. MLH have two potential indications for TRT. It is important to recognize the necessity to measure free testosterone in MLH because their total testosterone may appear normal due to elevated SHBG

Testosterone Replacement Therapy for MLH			
Indications	Diagnostics	Results	Treatment
Weight loss of unexplained origin Symptoms of low testosterone	• Measure morning fasting total testosterone, free testosterone, SHBG • If low, order LH and FSH to consider causes of hypogonadism	Confirmatory of TD • Low total testosterone • Normal or low total testosterone and low free testosterone	TRT for 3 to 6 months, further treatment at patient/provider discretion TRT to maintain testosterone in 500 to 600 ng/dL range and correct symptoms of low testosterone

generally well-tolerated, some users may experience mild skin irritation. Transdermal patches offer another option by delivering a controlled dose of testosterone over 24 hours; however, skin irritation is a common issue that may necessitate discontinuation in some cases [33].

Injectable forms of testosterone, including testosterone enanthate and testosterone cypionate, are long-acting options administered intramuscularly, with dosing intervals typically ranging from one to three weeks. These injections are effective in restoring normal testosterone levels but can cause fluctuations in energy, mood, and libido due to varying testosterone levels between doses. An extra-long-acting injectable option, testosterone undecanoate, requires less frequent administration (every 10 to 14 weeks) but is associated with potential adverse reactions, necessitating its use in a controlled medical setting [34].

Oral testosterone options, such as methyltestosterone and oral testosterone undecanoate, are available but are generally not recommended due to concerns about liver toxicity and potential cardiovascular risks. Methyltestosterone, in particular, is associated with significant liver side effects and less effective virilization, while oral testosterone undecanoate bypasses the liver but carries warnings about cardiovascular events. The choice of TRT should be tailored to the individual's needs, preferences, and medical conditions, with careful monitoring to manage potential side effects effectively [34].

How is Testosterone Replacement Therapy Monitored?

Once beginning TRT, it is suggested for patients to be evaluated in 3–12 months and then annually to assess TD symptoms and screen for adverse effects [34]. Laboratory work should be performed 3–6 months after starting TRT and should aim to increase testosterone levels to the mid-normal range. The timing of testosterone measurement varies significantly depending on the formulation of TRT selected by the patient and must be carefully taken into consideration. Physicians must also screen the patient's hematocrit within 3–6 months after starting treatment. Indications to stop include a hematocrit greater than 54%. In this case, it is recommended to stop TRT until hematocrit decreases to a safe level and evaluate the patient for hypoxia and sleep apnea before reinitiating TRT with a reduced dose. Additionally, for patients aged 55–69 years and men aged 40–69 years who are at an increased risk for prostate cancer and opt for prostate monitoring, it is recommended to recheck prostate specific antigen and perform digital rectal exam within 3–12 months of initiating TRT [34].

Future Directions

MLH represent an at-risk population with a distinct set of physiological and clinical considerations that complicate the diagnosis and management of testosterone deficiency. Despite the progress in ART and the improved life expectancy of MLH, this population continues to experience higher rates of hypogonadism at an earlier age compared to the general population. Furthermore, the interplay between HIV-related chronic inflammation, immune activation, and endocrine dysfunctions such as testosterone deficiency remains poorly understood, warranting more in-depth exploration specially to provide guidance for replenishment.

Future research is needed to understand the long-term cardiovascular effects of testosterone replacement therapy in MLH, especially considering the persistent inflammation and altered lipid metabolism in these patients. Studies that evaluate the safety and efficacy of different TRT formulations in MLH are essential, particularly in the context of their potential to exacerbate or mitigate cardiovascular risks. Future research is also necessary to identify biomarkers that can more accurately predict the risk of cardiovascular events in MLH, allowing for more personalized and effective treatment plans. In addition, future studies are needed to examine CVD risk in cisgender women with HIV that use testosterone as therapy or as part of a gender affirming hormone regimen.

Conclusions

Testosterone deficiency in men MLH is a prevalent condition that significantly impacts their quality of life and long-term health outcomes, particularly in relation to cardiovascular disease. MLH present with unique clinical challenges, including higher rates of testosterone deficiency at a younger age and a complex interplay between chronic inflammation, immune activation, and endocrine dysfunction.

The management of testosterone deficiency in this population requires a nuanced approach that considers the distinct pathophysiological mechanisms at play. While MLH have their unique CVD risks, the cardiovascular safety of TRT has been established with recent clinical trials and refutes several previous concerns regarding TRT. Additionally, the risk of hypogonadism and HIV presents a potentially compounding risk for CVD. In MLH, the need for early and accurate diagnosis, personalized treatment strategies, and careful monitoring cannot be overstated.

Further research is necessary to advance the understanding of the implications of TRT in MLH, develop more effective treatment protocols, and ultimately

improve the long-term health outcomes for this and other vulnerable populations. As we continue to enhance our understanding of the intersection between HIV, hypogonadism, and cardiovascular health, it is essential that we prioritize the needs of MLH in future studies and clinical guidelines. By doing so, we can ensure that this at-risk group receives the comprehensive and tailored care they require to manage their health effectively in the long term.

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  - This study is significant as it evaluates the cardiovascular safety of testosterone-replacement therapy in men with hypogonadism who are at high cardiovascular risk. Through a large, randomized, placebo-controlled trial, it found that testosterone therapy was noninferior to placebo regarding major adverse cardiac events, providing crucial information for clinicians treating hypogonadism in patients with cardiovascular concerns. However, the study also noted higher incidences of atrial fibrillation, acute kidney injury, and pulmonary embolism in the testosterone group, highlighting the need for careful monitoring.
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  - This meta-analysis provides a comprehensive evaluation of the cardiovascular safety of TRT in men with hypogonadism. By analyzing 30 randomized controlled trials with over 11,000 patients, it concludes that TRT does not increase the risk of cardiovascular events, stroke, myocardial infarction, or all-cause mortality compared to placebo. These findings offer reassurance regarding the cardiovascular safety of TRT for clinicians treating hypogonadal men.
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  - This study investigates the cardiovascular safety of integrase strand transfer inhibitors (INSTIs) in treatment-naïve people with HIV, a topic of concern in the field of HIV management. Using a target trial framework to reduce confounding, the study found no increased risk of cardiovascular events associated with INSTI-based antiretroviral therapy compared to other ART regimens. These findings provide reassurance regarding the use of INSTIs in HIV treatment, highlighting their safety in relation to cardiovascular outcomes over both short- and long-term follow-up.

Author Contribution M.G. wrote the abstract, introduction, methods, A Reminder of the Role of Testosterone in the Body, What is the Relation of Testosterone and Cardiovascular Disease Risk, What is known about Testosterone Replacement Therapy and Cardiovascular Risk?, HIV-associated Cardiovascular Disease is Currently an Established Risk for People Living with HIV, What is the Current Management for Testosterone Deficiency in MLH?, V. L. wrote How to Diagnose Testosterone Deficiency?, What are Current Testosterone Replacement Therapy Options?, How is Testosterone Replacement Therapy Monitored? , Future directions, Conclusions, Fig. 1, and Table 1. C.M. reviewed the paper and edited the paper as needed.

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Declaration

Conflict of Interest Michael Garcia, Valeria Londono, and Claudia Martinez declare they have no financial interests.

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