

Testosterone, HIV, and cardiovascular disease risk

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There has been a recent increase in the use of testosterone supplementation among young adults in the United States, despite the controversy of testosterone replacement therapy (TRT) and cardiovascular safety. The lower testosterone levels and earlier age of TRT use in persons living with HIV (PLHIV) is of particular relevance for this population because cardiovascular disease (CVD) comorbidities are known to be increased among PLHIV. There is very limited data on TRT in PLHIV, as such, in this article, we sought to compile current evidence regarding the diagnosis and management of testosterone deficiency

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Introduction

There has been a recent increase in the use of testosterone supplementation among young adults in the United States, despite of the controversy of testosterone replacement therapy (TRT) and cardiovascular safety [1]. A challenging population in whom to approach TRT are persons living with HIV (PLHIV); not only has HIV infection been associated with the presence of lower testosterone levels but also PLHIV are provided TRT at a younger age compared to their seronegative counterparts [2]. The lower testosterone levels and earlier age of TRT use in PLHIV is of particular relevance for this population because cardiovascular disease (CVD) comorbidities are known to be increased among PLHIV. Therefore, in this article, we sought to compile current evidence regarding the diagnosis and management of testosterone deficiency and its link to CVD risk including among PLHIV.

Testosterone

Endogenous testosterone is an androgen steroid that plays a role in the growth of male reproductive tissues and other secondary sexual characteristics [3]. Testosterone levels generally range from 300 to 1000 ng/dl, with 95% of healthy men between the age 40- and 79-years-old, expected to have total testosterone levels in the range 156–914 ng/dl (2.5–97.5th percentile) [4]. Compared to the sudden decrease of estrogen with menopause in women, the level of testosterone declines gradually with age in men. With increased life expectancy of men worldwide and the availability of testosterone supplementation, there has been an increase in the use of exogenous testosterone

[5]. Currently available preparations of testosterone supplementation are oral, buccal, transdermal, subcutaneous, and intramuscular injection, which differ in formulations, route of administration, dose and interval to be used (pharmacokinetics), and safety profiles (see Table 1).

Testosterone deficiency

Testosterone deficiency is clinically relevant when patients have low total testosterone levels combined with signs and/or symptoms of testosterone deficiency [6]. The most common signs of testosterone deficiency include anemia, osteopenia and osteoporosis, abdominal obesity, and development of the metabolic syndrome. Symptoms of testosterone deficiency may be categorized as sexual or nonsexual. Sexual symptoms include erectile dysfunction, diminished frequency of morning erections, and decrease in sexual thoughts (low libido), as well as difficulty in achieving orgasm and the reduced intensity of them. Nonsexual symptoms include fatigue, impotence, impaired concentration, depression, and decreased sense of vitality and/or well-being [7]. The Endocrine Society Guidelines recommend measuring serum testosterone in situations in which the prevalence of hypogonadism is high, among these are as follows: diseases of the sellar region (such as prolactinomas or opportunistic infections of the pituitary or hypothalamus), medications that affect testosterone production, such as high-dose glucocorticoids for a prolonged period and sustained-release opioids, weight loss associated with HIV, end-stage renal disease and maintenance hemodialysis, moderate to severe chronic obstructive lung disease, infertility, osteoporosis or low-trauma fracture, especially in young men, and type 2 diabetes mellitus [6].

Testosterone in blood is mainly bound to serum proteins with only 2% of the hormone circulating as free testosterone. Sex hormone binding globulin (SHBG) accounts for

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Table 1 Different testosterone supplementation forms, preparations and disadvantages

Testosterone formulation type	Preparation (trade name in the USA)	Disadvantages and toxicity
Long-acting injections (intramuscular)	Testosterone enanthate (Delatestryl) and Testosterone cypionate (Depo-Testosterone)	Fluctuating serum testosterone levels, 21-gauge needles needed for long-acting esters
Extra-long-acting injections (intramuscular)	Testosterone undecanoate (Aveed)	Injection-associated pulmonary oil micro-embolism (POME), restricted access in the USA, trochar needed for extra-long acting esters
Transdermal patches	Testosterone transdermal 24-hour patch (Androderm)	Skin rash, poor adherence
Transdermal gels/pumps/solutions	Three testosterone gels (AndroGel, Testim, and Fortesta) and one solution (Axiron) are available	Normal serum testosterone levels not achieved in all hypogonadal males, potential for skin transfer
Oral testosterone	Testosterone undecanoate (Andriol, Restandol, Jatenzo)	Gastrointestinal side effects
Testosterone subcutaneous implants (pellets)	Testosterone implant pellets (Testopel)	Incision required for insertion, pellet extrusion, infection, fibrosis, no information available on optimal dosing
Buccal testosterone	Buccal testosterone system (Striant)	Poor adherence, gum irritation

60% of testosterone binding, and 40% of the total testosterone is bound by albumin or other proteins. Biochemical parameters commonly used to assess androgen deficiency include total testosterone, free testosterone, calculated free testosterone, bioavailable testosterone, and the free androgen index. Bioavailable or free testosterone is considered the most accurate one to be measured. Liquid chromatography-tandem mass spectrometry is the gold standard for measuring total testosterone, while equilibrium dialysis is the gold standard for measuring free testosterone levels [8]. Clinically, morning total testosterone, free testosterone, calculated free testosterone, and free androgen is the most widely accepted substitute parameter; however, results may be misleading, when the SHBG is elevated [9]. The diagnosis of low testosterone is made only after two low total testosterone measurements have been taken on separate occasions between 8 and 11 am, due to the circadian rhythm of testosterone production by the testes [7]. Free testosterone measurement is recommended in cases where abnormal SHBG levels are suspected. The two most common scenarios, where these levels may be abnormal, are aging, which increases SHBG, and obesity, which decreases SHBG. The Endocrine Society and the AUA recommend using a total testosterone level below 300 ng/dl, with repeated measurements of morning total testosterone as a reasonable cutoff in support of the diagnosis of low testosterone [10,11].

Testosterone levels and cardiovascular disease risk

Low testosterone levels have been associated with an increased incidence of major adverse cardiac events, such as myocardial infarction, stroke, and possible cardiovascular-related mortality [12–14]. In longitudinal studies, the baseline testosterone level was lower in those men with an increased cardiovascular mortality [15]. Additionally, a cross-sectional study of 1545 males suggested that a low total testosterone level is likely to be a marker for risk factors associated with heart failure and angina. Lower serum testosterone levels were associated with a BMI > 35 kg/m², elevated HDL levels, diabetes and a metabolic equivalent score (METs) < 12 kcal/kg/h [3]. Recently, another

study compared 13 467 individuals with normal testosterone levels to 4771 individuals with low testosterone levels. Persons with a low testosterone level were older and had a substantially higher prevalence of comorbidities (diabetes mellitus, hypertension, cerebrovascular disease, and coronary artery disease). Despite the higher prevalence of comorbidities in the low testosterone group, there was a higher absolute risk of death and a higher absolute risk of cardiovascular outcomes, even when adjusting for confounding variables such as age, diabetes mellitus, hypertension, cerebrovascular disease, and coronary artery disease [16]. This body of evidence demonstrates the association of increased CVD risk with low testosterone levels; however, the role of testosterone replacement therapy in CVD risk remains controversial.

Recommendations for testosterone replacement therapy

As previously described, the clinical decision to recommend TRT is based on low serum testosterone levels in combination with related clinical symptoms. The goal of TRT is to restore blood testosterone to standard physiologic levels. According to the currently recommended guidelines, it is suggested that the concentration of total testosterone is restored to the mid-normal range (per the International Society for Sexual Medicine), or to the middle tercile of the normal reference range (per the American Urological Association).

Side effects of testosterone replacement therapy

Well-documented adverse effects of testosterone replacement therapy include the following:

- Elevation in the levels of prostate-specific antigen (PSA): Studies have shown that prostate volumes and PSA levels increase in response to TRT [6]. Theoretically, prostate cancer is a testosterone-dependent phenomenon, and experts have hypothesized that there may be an increased risk of prostate cancer in patients taking exogenous testosterone [17]. However, there is currently no definitive evidence that administration of exogenous testosterone increases the incidence of prostate cancer [17].

- b) Erythrocytosis: This is a common side effect of TRT, mostly seen in testosterone ester use. Testosterone has a stimulating effect on erythropoiesis, and the elevation of hemoglobin (Hgb)/hematocrit (Hct) is the most frequent adverse event related to TRT. During TRT, levels of Hgb/Hct generally rise over the first 6 months, then tend to plateau [18–20]. To address this, it is recommended that prior to commencing TRT, all patients undergo a baseline measurement of Hgb/Hct. If the Hct exceeds 50%, clinicians should consider withholding TRT until the etiology of the high Hct is explained [6]. Venous thromboembolism due to erythrocytosis has been reported in patients on TRT. However, to date, there is no definitive evidence linking testosterone therapy to a higher incidence of venous thromboembolic events [21].

Cardiovascular disease risk and testosterone replacement therapy

As previously mentioned, low testosterone levels have been associated with increased CVD risk. However, studies that describe cardiovascular benefits or harm in men on TRT have yielded inconsistent and controversial results [22,23]. In late 2016, the FDA approved class-wide labeling changes for all prescription testosterone products, highlighting serious adverse outcomes associated with TRT, including myocardial infarctions, heart failure, and cerebrovascular events. We have compiled below the available evidence on the association of TRT and CVD risk.

Several studies have suggested the increase cardiovascular disease risk of testosterone replacement therapy

In 2010, the effects of testosterone therapy on muscle performance and physical function in older men with mobility limitations were studied in the TOM trial, this was a placebo-controlled randomized study, which enrolled 209 men to assess the effects of administering exogenous testosterone gel vs. placebo in men 65 years and older, who had baseline-limited mobility and low total testosterone levels demonstrated potential harmful cardiovascular effects of TRT [22]. The authors reported that the risk of cardiovascular-related adverse events remained significantly greater [odds ratio 5.8; 95% confidence interval (CI): 1.2–28.4, $P = 0.03$] among men in the testosterone group, after adjustment for age group, body-mass index, smoking status, high-density lipoprotein cholesterol level, the presence or absence of diabetes, hyperlipidemia, and hypertension [22]. Indeed, this study was discontinued early due to higher rates of cardiovascular events especially myocardial infarction in the TRT group (23 vs. 5 patients) [24].

Subsequently, a retrospective study of men (mean age: 60 ± 3 -years-old) with low testosterone levels (<300 ng/dl), who underwent coronary angiograms in the Veterans Affairs system, investigated the relationship between

TRT and all-cause mortality, myocardial infarction and stroke. At 3 years, the primary outcome occurred more frequently in the TRT group (25.7%), when compared to that of the non-TRT group (19.9%), hazard ratio, 1.29; 95% CI: 1.04–1.58 [25]. More recently, one of the seven coordinated trials of the Testosterone Trials (TTrials) that focused on cardiovascular outcomes suggested that treatment with testosterone gel for 1 year was associated with a significantly greater increase in coronary artery noncalcified plaque volume, measured by coronary computed tomographic angiography in older men with symptomatic hypogonadism [26].

On the contrary, other studies have also suggested a protective or null association between TRT and CVD

Several meta-analyses published between 2005 and 2010 illustrated that TRT had no significant effects on the occurrence of major adverse cardiovascular events [18,19,27]. A large observational study of 1031 male veterans, older than 40 years of age, who had low total testosterone levels, showed the risk of all-cause mortality was lower in men who were receiving TRT [28]. In addition, a second study, which investigated the risk of myocardial infarction (MI) in a cohort of men 65 years of age and older receiving TRT, using a national sample from the Medicare beneficiary database, reported that there was no increased risk of MI associated with TRT use [29].

A few other clinical trials have analyzed the effects of TRT on cardiovascular risk. The Testosterone's Effect on Atherosclerosis Progression in Aging Men (TEAAM) Trial, published in 2015, concluded that among older men with low or low-normal testosterone levels, TRT administration for 3 years vs. a placebo did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium, nor did this improve overall sexual function or health-related quality of life. This trial was only powered to evaluate atherosclerosis progression, and these findings could not be translated to establishing cardiovascular safety of testosterone use in older men [30].

Hence, at present, the data supporting the cardiovascular safety of TRT remain controversial. Limitations of most of these studies included the relatively small number of participants, differences in the inclusion and exclusion criteria, heterogeneity in the measurement and diagnosis of hypogonadism, and underpowered studies to evaluate cardiovascular events. The linkage between TRT and CVD risk remains unclear; however, data does exist to suggest an association between the two.

Testosterone levels in persons living with HIV

According to the Center for Disease Control (CDC), there were 1 122 900 PLHIV in the US at the end of 2015. Several previous studies have confirmed that not only has the prevalence of testosterone deficiency increased in PLHIV (13–40%), but also there is a much younger age of

onset, when compared to the general population [31–38]. In the years preceding the use of antiretroviral therapy (ART), hypergonadotropic hypogonadism (also referred to as primary testosterone deficiency) was the main pattern of testosterone deficiency [39]. It is hypothesized that the virus has a direct toxic/inflammatory effect on Leydig cells in the testes, leading to a decrease in Leydig cell number. Since the advent of ART, there has been a shift in the pattern of testosterone deficiency, with hypogonadotropic hypogonadism – also referred to as secondary testosterone deficiency – being more prevalent [40]. The study involving the greatest number of HIV-infected patients found secondary hypogonadism in 183 of the 212 hypogonadal patients with total serum testosterone levels less than 300 ng/dl (86%) [41]. Although the exact mechanism of how HIV leads to testosterone deficiency in the ART era is unclear, multiple theories exist:

- The virus per se may influence pituitary function because HIV has been found in pituitary cells in a small percentage of cases (12%), and may account for hypothalamus and pituitary damage [42].
- ART may directly interfere with several biochemical pathways involved in the control of pituitary hormonal secretion [43].
- HIV infection and ART are indirectly responsible for body composition changes that occur in the context of HIV-related lipodystrophy. Adiposity, mainly visceral fat, can inhibit gonadotropin secretion through increased aromatization of androgens, and ultimately through the inhibitory effect of estrogens at both the hypothalamic and pituitary levels [44].
- A poor health status may induce the hypogonadal state. Critical illness leads to hypogonadotropic hypogonadism and testosterone deficiency is common in men suffering from systemic disorders [45,46].
- Other factors such as the use of opiates may also contribute to hypogonadotropic hypogonadism, especially given the recent opioid abuse epidemic. Opiates can suppress the hypothalamic-pituitary axis, and this mechanism may operate in HIV-infected men with a history of use of injection drugs or methadone therapy [47]

How to diagnose testosterone deficiency in persons living with HIV?

As for the general population, the diagnosis of testosterone deficiency in PLHIV is made when patients have low total testosterone levels, combined with symptoms and/or signs, of testosterone deficiency as previously outlined. However, symptoms of testosterone deficiency are common in PLHIV, independent of their gonadal status. In clinical practice, this becomes a challenge as most of the signs and symptoms of hypogonadism overlap with those of HIV infection [41]:

- Osteoporosis is common among men with HIV [48].
- Body image changes and the stigma of the disease negatively affect self-esteem, sexuality, and mood [49].

- The fear of HIV transmission compromises sexuality, which may mimic sexual symptoms such as low libido [49].
- The coexistence of several comorbidities, together with the related poor health status, influences negatively both mood and sexuality [50].

With this view, the presence of sleep-related erections, adequate testes and sperm volume, and hot flashes or sweats all remain reliable indicators of testosterone status, as they do not depend on psychological correlates [51,52].

Specific to PLHIV, SHBG measurement is essential to prevent false negatives in diagnosing testosterone deficiency. SHBG levels often increase in PLHIV due to a high prevalence of visceral obesity, related to lipodystrophy-associated-fat redistribution, especially in patients with severe liver dysfunction [53–55]. The Endocrine Society recommends obtaining an initial free testosterone concentration using either equilibrium dialysis or estimating this value, using recommended formulae (including total testosterone, SHBG, and albumin levels), see Fig. 1 [56]. This is distinct from the general population, in whom measurement of serum total testosterone concentration (free plus protein bound fractions) is usually the initial test of choice. Determining the etiology of testosterone deficiency in PLHIV remains important. For secondary hypogonadism, a pituitary/hypothalamic MRI scan in PLHIV with advanced immunodeficiency (CD4 cell count < 200/μl) is recommended to evaluate for opportunistic infections (e.g., *Cryptococcus neoformans*, *Toxoplasma gondii*) affecting the pituitary gland or hypothalamus [57], whereas for primary hypogonadism, a scrotal ultrasound should be performed in untreated PLHIV and advanced immunodeficiency (CD4 cell count <200/μl) who have testicular pain, fever, or constitutional symptoms to evaluate for opportunistic infections affecting the testes. Testicular opportunistic infections rarely occur in the setting of viral suppression [58].

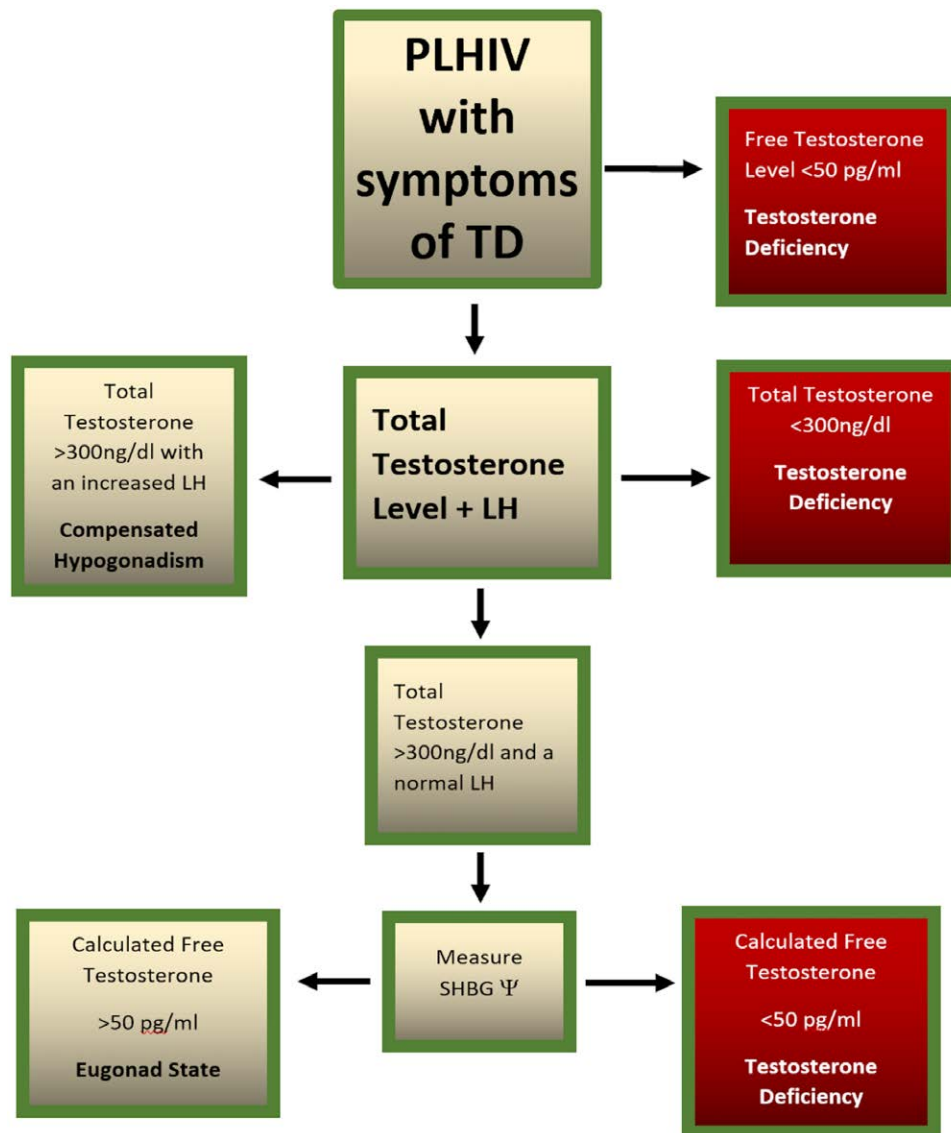
When to replace testosterone in persons living with HIV?

Currently, the HIV Medicine Association of the Infectious Diseases Society of America recommends TRT in PLHIV with a low serum testosterone level (confirmed on at least two occasions in the morning without concurrent acute illness), and with any of the following [59]:

- Symptoms of androgen deficiency (e.g., fatigue, hot flashes/sweats, decreased libido, erectile dysfunction)
- Unexplained weight loss
- Low bone mineral density

PLHIV with testosterone deficiency, who are yet to begin ART, may benefit from a period of observation and monitoring as initiating ART may lead to increased testosterone levels. It is advised to recheck for low testosterone levels after these patients have achieved normal immune status and weight [60] TRT has particularly been useful

Fig. 1



Demonstrating the algorithm for TD work-up in PLHIV. LH, luteinizing hormone; TD, testosterone deficiency, PLHIV, persons living with HIV; SBHG, sex hormone binding globulin.

in promoting weight gain and increased lean body mass and bone density in patients with AIDS wasting syndrome [61,62].

As discussed earlier, testosterone deficiency is more prevalent in PLHIV. With the advent of ART and increasing life expectancies, testosterone deficiency prevalence is predicted to increase and with it, the use of TRT among PLHIV [63]. A study that investigated the pattern of TRT use in PLHIV found a significant association with an age of at least 35 years, white race, diagnosis of AIDS wasting syndrome, hepatitis C co-infection, protease inhibitor-based ART, and nadir CD4 cell count of 200 cells/ μl or less [64]. The younger age of PLHIV using TRT, combined with the already increased risk of CVD

in this population adds to the conundrum around the cardiovascular safety of TRT, not only in the general population, but more so in PLHIV. As in the general population, drug selection for TRT in PLHIV depends primarily on patient preference; however, one of the transdermal approaches is advised (e.g. patch, gel, or solution) as first-line treatment because of their ease of administration, lack of wide fluctuations in testosterone levels, and fewer adverse effects compared with periodic injections. There are no important interactions with any ART. TRT use is continued as long as there is clinical benefit and no significant adverse effects. We propose monitoring clinical effectiveness, testosterone levels, and adverse drug effects at 3–6 months, 12 months, and annually thereafter

with the target goal being attainment of morning serum testosterone levels in the mid-normal range.

Testosterone and cardiovascular disease risk in persons living with HIV

The increased risk and growing burden of CVD in an aging population of PLHIV pose important challenges for physicians. A recent large meta-analysis evaluating nearly 800 000 PLHIV suggested that PLHIV may be twice as likely (RR 2.16) to develop cardiovascular disease as their seronegative counterparts [65]. In addition, PLHIV who have had a prior myocardial infarction, cardiomyopathy, heart failure, or arrhythmia have been shown to have a 4.5-fold increased risk for sudden cardiac death [66–71]. However, there is a paucity of data pertaining to testosterone levels and the risk of CVD in PLHIV. A cross-sectional analysis of 534 PLHIV and 322 seronegative counterparts sought to investigate the impact of testosterone on subclinical CVD. The investigators found that though PLHIV had lower free testosterone levels (88.7 ng/dl vs. 101.7 ng/dl, $P = 0.0004$), free testosterone levels were not associated with the presence of coronary artery calcium or log carotid intima-media thickness. However, free testosterone was associated with carotid lesion presence (adjusted odds ratio 1.69; 95% CI: 1.06–2.71) in PLHIV [72]. Another study sought to determine the prevalence of erectile dysfunction, testosterone deficiency, and risk of coronary artery disease (CAD) in a cohort of young to middle-aged men with HIV in Belgium. They analyzed 244 PLHIV in the outpatient setting and found that 61.9% self-reported symptoms of erectile dysfunction, and of this number 36.7% were diagnosed with testosterone deficiency on laboratory analysis. The 10-year risk of CAD in the cohort was 4.3% (interquartile range: 3.6–5.7) and was significantly higher in men with erectile dysfunction, 5.1% (interquartile range 4.4–6.6) compared with men without it 3.1% (interquartile range 2.5–4.2). In this study, testosterone deficiency and erectile dysfunction (ED) was highly prevalent amongst middle-aged PLHIV and the presence of ED in this group was associated with increased risk of CAD [40]. Furthermore, data from the Multicenter AIDS Cohort Study (MACS), which evaluated 1286 PLHIV compared to seronegative controls, showed that TRT use was higher among PLHIV of all age strata, with an age-adjusted prevalence of 17% vs. 5% among the seronegative group, respectively (adjusted prevalence ratio = 3.7, $P < 0.001$). Interestingly, they reported that TRT use was higher among men in the highest compared to the lowest CVD risk score category (based on the American Heart Association/American College of Cardiology 10-year CVD risk score) in a multivariable model (13.4% vs. 5.2%, adjusted prevalence ratio 2.21, CI: 1.15–4.28). In summary, there is still little data regarding testosterone levels/use and CVD risk in PLHIV; however, the theoretical enhanced CVD risk in this population and potential

drug interactions with ART calls for further studies to help clarify this clinical dilemma.

Conclusion and future perspectives

Despite the long-standing controversies regarding the potential role of testosterone in cardiovascular health, questions persist, especially in an era when TRT use has become a common practice among the general public. The knowledge regarding the role of TRT, especially in populations already at risk for CVD such as in the context of HIV, is timely and further research is needed to address this clinical gap. There is very limited data on TRT in PLHIV. In an era when global testosterone sales have increased exponentially, the known increased cardiovascular risk of PLHIV and potentially TRT emphasizes the crucial need for further research in this arena.

Key points

1. Testosterone deficiency is associated with an increased incidence of major adverse cardiac events, such as myocardial infarction, stroke, and possible cardiovascular-related mortality.
2. Persons living with HIV are also at an increased risk of cardiovascular disease and with a higher prevalence of testosterone deficiency.
3. Despite class-wide labeling changes by the FDA for all prescription testosterone products highlighting the risk of major adverse cardiac events, a varying body of evidence exists both for and against the risk of cardiovascular disease. Elucidating this interplay of testosterone levels and cardiovascular disease in persons living with HIV remains essential.

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Conflicts of interest

There are no conflicts of interest.

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