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2

Testosterone and other treatments for transgender males and non-binary trans masculine individuals

A. Dimakopoulou (Endocrinologist)[a], L.J. Seal (Endocrinologist)[a,b,*]

[a] Department of Endocrinology, Gender Identity Clinic, Tavistock & Portman NHS Foundation Trust, London, UK
[b] St George's University of London Medical School, UK

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Testosterone therapy is the main hormonal treatment offered in transmen to alleviate somatic gender dysphoria. Testosterone can be administered via topical or injectable preparations to achieve physical changes resulting in masculinisation and improve quality of life for the treated individuals. The aim of our paper is to outline methods for testosterone replacement, their impact on main body systems of transmen, potential associated health risks and long term follow up. Androgen use in transgender medicine is safe with appropriate endocrine guidance and monitoring. Studies with longer follow-up period, including those who may prefer low dose testosterone, interested in pregnancy or older people may further improve the management of female-to-male transgender persons.

Introduction

The incidence of gender incongruence has increased over the last few decades. With time there has been a shift in the epidemiology of this condition. Previously it was more common for people birth assigned male to present to gender services in the UK. More recent studies have suggested that amongst adolescents being referred to gender identity clinics those assigned female at birth and transitioning to a male gender role are greater in proportion compared to those assigned male at birth and transitioning to

* Correspondence to: Gender Identity Clinic, Tavistock and Portman NHS Foundation Trust, Lief House, NW1 5HR, UK.
E-mail address: lseal@sgul.ac.uk (L.J. Seal).

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Table 1
Physical effects seen with testosterone therapy, and typical expected timings [28].

Effect	Onset (months)	Maximum (years)
Skin oiliness / acne	1-6	1-2
Body fat redistribution	1-6	2-5
Cessation of menses	2-6	-
Clitoral enlargement	3-6	1-2
Vaginal atrophy (if it occurs)	3-6	1-2
Deepening of voice	3-12	1-2
Increased muscle mass / strength	6-12	2-5
Facial / body hair growth	6-12	4-5
Scalp hair loss (varies)	6-12	-

a female gender role [1] As a result, the incidence of gender dysphoria for transgendered men is estimated to be between 1:31,153 to 1:10,000 [2], whilst a more recent meta-analysis estimated the prevalence to have risen to 2.6/100 000 [3]. In addition, more people who have a non-binary gender identity rather than a binary masculine gender identity are presenting to gender services for treatment. Although the prevalence rates remain largely unknown, a recent study suggested that approximately 10 % of people attending a large single centre gender clinical have a non-binary gender identity [4].

The cornerstone of endocrine therapy for gender incongruent people is testosterone replacement, as it results in the development of the secondary sexual characteristics of the desired gender. Testosterone treatment is effective in suppressing ovarian function, lowering voice frequency, increasing facial hair-growth, and achieving more masculine body appearances. This review article presents the physical changes on testosterone treatment, options for such treatment depending on the gender identity, menstrual suppression, fertility preservation, potential risks, and side effect monitoring in the long term.

The expected changes resulting from testosterone treatment and the timescale for these to occur

Ovarian function and other genital changes

The first physical change noticed by a transgender man on testosterone treatment is an increase in the size of the clitoris, which starts by 3 to 4 months and is complete by one year (Table 1) [5]. The final clitoral length can range from 4 to 5 cm and does not allow penetrative intercourse. Periods usually stop within 2 to 3 cycles from the start of testosterone therapy, the high level of testosterone in the blood providing negative feedback to the pituitary gland, causing inhibition of gonadotrophin secretion, with subsequent ovarian and menstrual suppression [6]. Hence, amenorrhoea can be successfully achieved in 93 % of premenopausal transgender men, within six months of commencing testosterone treatment [7,8]. The suppression of menstruation is one of the most desired physical changes from those seeking masculinising hormonal therapy. It is interesting that ovarian morphology changes, with multiple ovarian cysts developing within 6 months of treatment and ovarian appearances similar to polycystic ovaries, have been reported [8]. More research is required to establish whether these changes affect subsequent ovarian function and fertility.

Facial and Body Hair

Testosterone treatment in transgender men stimulates facial and body hair growth in a male-pattern distribution. Hair growth typically increases on the face, chest, abdomen, lower back and inner thighs [5,10]. It is reported that the mean Ferriman-Gallwey score increases in transgender men from 0 to 13 points, after at least six months of testosterone therapy [11]. The onset of facial hair development is typically 6 to 9 months and is complete by 48 to 56 months (Table 1) [12,13].

Testosterone not only increases hair growth, but also promotes the development of sebaceous glands and is accompanied by a coarsening of the facial skin texture. Although, severe acne is unlikely to occur with testosterone treatment, skin becomes oily in texture and prone to acneiform lesions [14].

Nonetheless, a third of transgender men taking testosterone on a dose-response basis did not develop acne, as lower testosterone doses may not have effects on skin texture [15].

Scalp hair loss is a known effect of testosterone replacement in transgender men. It is important that the possibility of alopecia is discussed with them at the start of therapy. The incidence of alopecia increases with age of transgender men [14]. For some people this may be a desirable male feature, but for others this is an unwanted effect. Topical minoxidil can be used, to mitigate the scalp hair loss. If alopecia is associated with nail pitting or scalp itch, a dermatology opinion should be sought to excluded dermatological disorders associated with scalp hair loss, such as eczema or psoriasis [16].

Body shape

Testosterone therapy in transgender men induces body changes that are similar to the changes induced in hypogonadal cisgender men treated with testosterone [17,18]. Masculine body shape development has been observed, with a decrease in hip to waist ratio, more muscle definition and increased upper body strength [5,10]. Significant increases in lean body mass have also been observed in transgender men receiving injectable testosterone treatment for five years, compared to their lean body mass at the start of testosterone treatment [19]. A multicentre prospective observational study showed that total body fat decreased over a 5-year period, while the amount of visceral adipose tissue, lipid profile and HOMA-IR did not change in transgendered men treated with testosterone [20].

The rate of obesity in transgender men increases on testosterone treatment. Studies suggest that the incidence of obesity increases from 39% before treatment with testosterone, to 47% after treatment with testosterone [21], but a reduced hip to waist ratio, and no change in insulin dynamics, may mean that the increase in body weight has less of an impact on cardiovascular risk.

Mood and cognition

Studies suggest that testosterone replacement has a positive effect on mood. Testosterone therapy led to significant improvement in the depression Minnesota Multiphasic Personality Inventory (MMPI) clinical score after five months, when given in combination with psychotherapy, in transgender men [22]. Also, transgender men reported high energy, aggression, and increased libido, in a similar way to hypogonadal cisgender men receiving testosterone treatment [23]. Moreover, they felt “more settled” as the physical changes in their body confirmed their experienced gender role. Studies show that transgender men on testosterone also have better visuo-spatial ability [24].

Voice

Testosterone causes growth of the larynx and thickening of the vocal cords, which leads to a reduction in the fundamental frequency of the larynx and deepens the voice to a masculine sound [25]. The voice breaks after about 9 to 12 months of testosterone treatment but can take up to two years to complete (Table 1) [12]. Interestingly, adolescents on GnRH treatment, followed by testosterone therapy over a two-year study period, can achieve deepening of the voice within 3 months [26]. A minimum of nine months of testosterone treatment has been required for transgender persons to significantly lower their voice frequency [27]. A lower voice pitch can improve vocal dysphoria. However, voice and communication therapy are also required for voice masculinisation, as deepened pitch alone may not achieve the desired voice characteristics.

Transgender men undergoing a binary physical transition

For transgender men seeking a masculine body, testosterone is the mainstay of treatment. The physical changes that follow testosterone administration in a transgender man resemble a cis gender male puberty pattern and take 2 to 5 years to complete [6]. Testosterone treatment given in adult doses blocks ovarian function and can be effective as a single agent treatment for transmen and non-binary transmasculine individuals. The adult testosterone doses used are the same as those used for cisgender hypogonadal men (Table 2).

Table 2
A list of the testosterone preparations commonly used at the largest UK transgender health clinic and how they are monitored [6].

Preparation	Dose	Frequency	Monitoring	Testosterone target range
Testosterone esters or Testosterone enanthate IM injection	250 mg of 1 ml Dose titration: from 150 mg (0.6 ml) to 250 mg (1 ml) vial	7-35 days	• Trough level on day of injection, prior to injection • Peak level 7 days later	• Trough level: 8-12 nmol/L • Peak level: 25-30 nmol/L
Testosterone undecanoate IM injection	500 mg-1000 mg of 4 ml vial	6-15 weekly following a loading dose	Trough level on day of injection, prior to injection	15-20 nmol/L
Testosterone topical	Dose titration from 20 mg to 80 mg	Daily	Ensure no gel on arms and 4 – 6 h after gel application	15-20 nmol/L

The first line of treatment are the short acting testosterone ester injections, or gel therapy [6]. These are chosen as they have a shorter duration of action and are more easily reversible if complications occur. In the longer term, the longer acting injection testosterone undecanoate is also effective and more convenient, as injections are administered less frequently.

Testosterone treatment for non-binary trans masculine people wishing partial masculinisation

When deciding what hormonal interventions are appropriate for a non-binary trans masculine person it is important that the degree of fluidity of the person's current gender expression is assessed; a clear formulation of the mix of male, female, and neutral physical features is made. This is often based on the context of a multidisciplinary team so that the social psychological and physical implications of hormone therapy can be adequately explored.

It is also important to advise the individual that the hormonal regimens used in this field have not been examined by randomised controlled clinical trials. Therefore, the current therapeutic options offered are based on extrapolating information from pubertal induction in cis children and the treatment of trans men undergoing a binary transition, to the non-binary situation [29].

The clinical approach for non-binary people that request partial masculinisation is to either use an adult male dose of testosterone for a time limited period to produce partial pubertal development or to use lower than usual doses of testosterone to achieve a partial physical development [30].

Knowledge of the physical changes that occur in cisgender puberty and pubertal induction in binary trans men does give us information on the likely effects of testosterone in non-binary trans masculine people. Considering cisgender male puberty, genital growth and therefore clitoral enlargement is an inevitable consequence of testosterone treatment [5,10] Libido is also extremely likely to increase, as we know from literature in the treatment of low libido in cisgender females that raising the testosterone to the upper part of the female normal range results in an increase in sexual drive [31].

Testosterone increases the growth of the larynx, and this occurs at a stage of puberty where the testosterone level is still moderate [32]. If the individual desires masculinisation, but to not affect laryngeal growth then very low doses of testosterone therapy will be needed, certainly below a plasma testosterone value of 7nmol/l. In binary trans men the voice usually breaks after 6–12 months of testosterone therapy [12]. Therefore, another approach to keep laryngeal growth unaffected is to limit the duration of testosterone treatment rather than reducing the testosterone dose.

Hormone treatment will not significantly affect the size of the breast or alter the body contour of the chest and consequently surgical intervention is required to achieve this if required.

When considering development of a masculine body fat distribution, muscle development and physique, we know that these changes occur early in puberty but will take the full 5 years of pubertal development to complete [12]. The changes in lean body mass and strength are also dose dependent [17] and therefore if these physical changes are desired by an individual other changes, such as increase in facial hair and body hair, increased genital size, and the risk of scalp hair loss must be accepted by the non-binary person.

Testosterone has been shown to affect mood with increased sexual drive, more effective social gender role change and a tendency towards aggression [18]. In the studies using low dose testosterone therapy for sexual dysfunction in cisgender females, summarized by Davis et al. [31], there have been no reports of aggression or impulsivity in cisgender women treated with androgens. Neither has there been a significant rate of behavioural side effects of androgen treatment reported in trans men treated with full testosterone replacement doses [33]. It is therefore difficult to advise non-binary masculine people on the likely effects of lower testosterone doses on their mood.

While lower than usual doses of testosterone are typically used in non-binary people, it is unlikely that menstruation will be suppressed. Hence, if menstrual suppression is required additional agents, such as progestins or gonadotrophin releasing hormone (GnRH) analogues, will need to be used..

The options to stop menstruation if not achieved by testosterone alone

An observational retrospective study in Maine, USA showed that testosterone treatment, without previous GnRH or progestin therapy, in adult transmen optimised testosterone levels and induced

Table 3
Typical preparations used for masculinisation in non-binary trans masculine people.

Preparation	Dose	Frequency	Monitoring	Testosterone target range
Testosterone esters or Testosterone enantate IM injection	50-250 mg of 1 ml Dose titration: from 150 mg (0.6 ml) to 250 mg (1 ml) vial	7-35 days	• Trough level on day of injection, prior to injection • Peak level 7 days later	• Individualised to person's desired physical changes
Testosterone undecanoate IM injection	1000 mg of 4 ml vial	6-15 weekly following a loading face	Trough level on day of injection, prior to injection	Individualised to person's desired physical changes
Testosterone topical	Dose titration from 20 mg to 80 mg	Daily	Ensure no gel on arms and 4 – 6 h after gel application	Individualised to person's desired physical changes

amenorrhoea in 90.8% of patients [34]. However, testosterone therapy alone does not suppress menstruation in 1 out of 10 transmasculine people. If this is the case progestins, such as medroxyprogesterone acetate 10 mg three times daily or norethisterone 2.5–15 mg/day, can be used to stop the periods [35]. Norethisterone is generally avoided, because it can be aromatised to ethinylestradiol and therefore, produce feminisation [36]. Medroxyprogesterone acetate can be given orally daily or intramuscularly via depot-medroxyprogesterone acetate when non-daily intervention is desired [37]. The parenteral preparations, however, have been associated with significant irregular bleeding when they are initiated. Irregular genital bleeding may be difficult for trans men as bleeding can have a strong negative impact psychologically.

More recently, GnRH analogues have also been used to suppress menstruation in transmasculine individuals, after completion of gonadal puberty, while using testosterone therapy. It is important to try and optimise the testosterone values to prevent a reduction in bone mineral density [38].

In non-binary people where target testosterone values may be below the adult male range it is important to consider that bone health may be compromised, and cardiovascular risk may be increased by alterations in lipid profiles. It is recommended in this situation that bone density monitoring by DEXA scanning every 3–5 years, as well as regular monitoring of the lipid profile, is undertaken [39].

The implications of testosterone hormone treatment for fertility

Transgender men should have their fertility plans discussed early and, if necessary, should be given the option for preserving fertility before they commence testosterone treatment. According to a case-series (n = 85), 40% of transgender persons undergoing oophorectomy after at least 3 years of androgen therapy had normal ovarian size, 50% had simple follicular cysts, 6% polycystic ovaries (PCO) and 4% had ovarian atrophy [40]. It appears that the prevalence of PCO amongst transmen treated with long term testosterone is not different compared to the general population, as proven by ultrasound evaluation in another case-control study (n = 136). [41,42]. However, the implication of this morphology on reproductive function in trans masculine people is unknown. Similarly, anti-Mullerian hormone (AMH) levels representing ovarian reserve, were observed to remain unchanged in transgender men taking testosterone for at least one year, compared to pre-testosterone treatment AMH levels [43,44]. Interestingly, a matched retrospective study of 26 transmasculine patients showed the same number of retrieved oocytes, compared with 130 cis-gender women, attending a single IVF clinic. All 7 fresh or frozen transfers resulted in live births [44].

Transgender adolescents that may decide to suppress puberty at an early age should have fertility options discussed with them promptly. The discussion should include the implications of early pubertal blockade on subsequent fertility, because fertility may be compromised after pubertal suppression [38].

In adults, current evidence suggests that ovarian reserve remains largely unchanged on testosterone treatment alone, because fertility outcomes via assisted reproduction therapies in young transgender men seeking fertility are comparable to the general cis-female population. Nonetheless, definitive advice regarding fertility outcomes after long term testosterone treatment requires further research.

The risks associated with testosterone treatment

Cholesterol and lipids

There is a significant gender difference in cholesterol levels with cisgender males having higher total cholesterol, low density lipoprotein (LDL) cholesterol and triglyceride (TG), with lower plasma HDL cholesterol compared to cis-gender women [4]. Therefore, cisgender males are more likely to have cardiovascular disease than cisgender females. A previous study showed no change in total cholesterol or LDL cholesterol in transgender men taking testosterone replacement. There was only a minor increase triglyceride and a decrease in serum HDL levels [45]. A more recent meta-analysis showed that the changes in lipid parameters were progressive, so that by 24 months of testosterone therapy TG levels were higher (+0.24 mmol/l; 95% CI: 0–0.48 mmol/l) compared to baseline. This analysis found minimal reports of myocardial infarction, stroke, VTE, and death events [46]. Larger scale follow up studies have shown that the myocardial infarction rate in transgender men is either below or the same as the

cisgender male population. The rate of myocardial infarction in transgender men has been reported to be one third the expected rate in the general cisgender male population [33] over 17 years. In another European study the myocardial infarction rate was the same as the cisgender male population (SIR 1[0.53–1.74]), but higher than the cisgender female (3.69 [1.94–6.42]) [47]. In a further large American study, the hazard ratio for myocardial infarction in transgender men was 0.7 [0.3–1.8] compared to cisgender men and 1.3 [0.7–2.5] compared to cisgender females [48]. In conlusion, there appears to be an adverse effect on lipid parameters from testosterone therapy, but this does not translate into an increased risk of cardiovascular disease in transgender men compared to the general cis-male population.

Polycythaemia

Testosterone increases the production of red blood cells by increasing the levels of erythropoietin in the blood [49]. Subsequently, the number of red blood cells can increase and lead to high haematocrit (polycythaemia), which then causes increased viscosity. Haematocrit above 48% has been related to an increased risk of stroke as red blood cell volume increases and plasma volume decreases [50]. In essence, the incidence of stroke in transgender men was reported as 23.4/1000, which is significantly higher than control cis-men (9.4/1000; $p = 0.03$), but not significantly different when compared to control cis-females (14.9/1000) [51]. The development of polycythaemia is more common with injectable forms of testosterone and if polycythaemia develops on testosterone treatment changing to a topical form of testosterone, would be recommended [52]. Actions including maintaining good hydration and addressing other course of polycythaemia such as obstructive sleep apnoea, smoking, obesity should be implemented and if these measures fail to correct polycythaemia then therapeutic venesection can be used to manage polycythaemia induced by testosterone treatment.

Venous thromboembolism

There have been reports of a possible link between the use of testosterone replacement therapy and increased VTE risk in cis-men [53]. However, these studies were criticised for including data on events such as avascular necrosis of the femoral head which are not classically viewed as VTE events. Larger epidemiological studies have demonstrated that there is no link between testosterone therapy and thromboembolism risk, and these data were summarised in a recent meta-analysis (OR 1.41 (95% CI: 0.96–2.27) [54].

Liver Function

Historically, anabolic steroids were used for hormonal replacement in transgender men and abnormal liver function had been observed in 32% of people using these regimens [55]. However, current treatment protocols no longer recommend anabolic steroids. In modern protocols mild changes in liver function are seen in about 4–7% of transgender men [33], but these are usually mild, transient and treatment can remain unaffected. Observational studies investigating liver function in transmen treated with testosterone, over a mean follow-up period of thirty months, showed no significant impairment of liver function tests, between baseline and end of follow-up period [13]. Routine monitoring of liver function in patients on testosterone replacement is recommended [6,12,56].

Cancer risk

In transgender men, where testosterone may be aromatised to oestrogen and the normal menstrual cycle does not occur, there may be an excess of oestrogen without progesterone production. In theory this could lead to endometrial hyperplasia, which would be a risk for developing endometrial cancer in the long term. There have only been 5 cases of endometrial cancer reported in a transgender man on testosterone therapy, suggesting this risk is low [57]. Moreover, studies looking at the uterus of transgender men, removed via hysterectomy, show the endometrium becomes thin and underdeveloped on testosterone replacement [9]. There was however one study that suggested that the endometrium could thicken in 15% of transgender men [58]. There is no consensus on the requirement for endometrial

monitoring. In some large UK centres alternate year ultrasound monitoring is undertaken to look for endometrial hyperplasia, whilst in other centres the approach can vary from annual ultrasound scan to only scanning if the person is symptomatic [59]. There is currently no consensus on the required frequency of screening. Ovarian cancer risk appears to be very low; there have been only three cases reported following testosterone therapy for a prolonged period.

Breast cancer risk appears to be very low in transgender men, a recent meta-analysis suggesting that the risk of breast cancer is 0.2 [0.1–0.5] compared to cisgender females but this rate is significantly higher than that seen in cisgender males [60]. As male chest reconstruction is not a total mastectomy, transgender men should check the breast tissue left behind regularly by self-examination. In conclusion, for breast cancer transgender men should be counselled that breast tissue remains on their chest wall and they should perform regular breast self-examination [6].

Osteoporosis

Observational studies in transgender men show that testosterone therapy appears to maintain bone mineralisation [61]. More recently standard dose testosterone therapy has been shown to increase cortical bone thickness [62] and a meta-analysis found no significant impact of testosterone therapy on bone mineral density, at any site of the skeleton of transgender men [63].

There has been one study suggesting a decrease in bone mineral density of transgender men, who were on low testosterone doses after oophorectomy. An inverse relationship was shown between gonadotropin concentration and bone mass suggesting that low sex steroid concentrations may result in low bone mineralisation in transmen taking low dose testosterone [64].

This finding has implications for non-binary trans masculine people, who wish to use testosterone doses below the standard adult male range. Non-binary people should be counselled that there is a risk of reduction in bone mineral concentrations and therefore it would be prudent to monitor bone mineralisation with DEXA scanning every three to five years. If bone mass cannot be maintained by the levels of sex steroid used to assist the gender presentation of the individual, further measures, such as bisphosphonate therapy or anabolic agents to maintain bone health, may be required. Individuals should be advised about the possible need for these agents before commencing therapy. It is advisable in this situation for non-binary trans masculine individuals to take calcium and vitamin D supplements for bone protection.

Atrophic vaginitis

It has been observed that 65% of transgender men experience genital pain or discomfort during sexual activity, after at least 7 months of testosterone use [65]. Sexual function remained unaffected in this observational study. The pain or discomfort in transmen was attributed to vaginal atrophy associated with increased testosterone, decreased oestrogen and subsequently less lubrication in the vagina [66] Topical oestrogen cream is recommended for treatment of such symptoms, as it is not systemically absorbed and does not exacerbate gender dysphoria. Recent study suggests that the vaginal microbiota, which is exposed to testosterone, offers a possible explanation for the development of atrophic vaginitis [67] and possibly a target for future treatments.

The long-term follow-up for transgender individuals on masculinising hormone treatment

There have been several studies looking at the long-term safety of hormone treatment in transgender people. These studies suggest that long-term treatment with testosterone in transgender men results in a life expectancy that is not different from the general cisgender population [33,47,48,68]. Regular monitoring of testosterone levels, liver function, lipid profile and haematocrit is recommended in the first 2 years following the initiation of hormone therapy, but thereafter these should be monitored annually once established on testosterone therapy [69] to prevent hyperlipidaemia, polycythaemia, and liver dysfunction. An additional long-term follow up requirement for non-binary individuals on low dose testosterone is bone density monitoring with DEXA bone scan every 2–3 years.

Conclusion

Testosterone replacement in masculine binary and non-binary gender incongruent people is a long-established and safe treatment. It is best provided in a multi-disciplinary setting so that the psychosocial implications for testosterone therapy can be considered. Treatment goals and expected time frame for physical changes on testosterone treatment are best discussed at the initial assessment, along with the potential metabolic risk and side effects. Fertility preservation should be discussed early, ideally before initiating testosterone treatment. Testosterone replacement to achieve adult male testosterone level is recommended, so that bone mineralisation is preserved. However, when lower testosterone doses are required, usually by non-binary people, monitoring of bone health by DEXA should be considered. In discussing testosterone replacement of people with non-binary gender identity, we must explain the benefits, as well as the limitations to allow their expectations of therapy to match what is physically possible and avoid regrets.

Reasearch agenda

- More research is required into testosterone treatment for non-binary individuals to ensure evidence-based knowledge on benefits and risks of lower dose testosterone replacement.
- Fertility outcomes after long term testosterone hormone therapy require further investigation.
- The role of testosterone therapy in the development of endometrial hyperplasia needs to be further elucidated, along with best management strategies.
- Atrophic vaginitis is an area of concern for transmen and further research is required to identify the most effective therapies.

Practice points

- Testosterone treatment is fundamental to the treatment of transgender male people as it induces the secondary sexual characteristics of the person's experienced gender.
- Testosterone replacement can cause side effects, such as high haematocrit, high triglycerides, and atrophic vaginitis, which should be discussed promptly during the individual's transition journey.
- Fertility preservation is best discussed before testosterone initiation, although can be achieved at any point with appropriate guidance.
- Testosterone replacement appears to be safe in the longer term, with no difference in cardiovascular events between transmen and the general cis-men population.

Consent for publication

Not applicable.

Declaration of Competing Interest

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