Transgender Athletes

Prohibited Substances: Testosterone, Spironolactone

1. Introduction

With continuously evolving social, legal, cultural, ethical and clinical practice models globally, participation of transgender athletes is becoming increasingly common in sports at all levels. Gender identities that are not stereotypically associated with a person's recorded sex at birth should not be considered pathologic, even when requiring medical interventions.

For transgender and gender diverse people, multiple terms have been/are used. For the purpose of this document, the terms transgender male and transgender female athletes are used. Individuals who were recorded female sex at birth who masculinize their bodies are typically referenced as transgender males. Vice versa, individuals recorded male at birth who feminize their bodies are typically referenced as transgender females. Other individuals may have identities outside the binary gender system, but for the purposes of this document, the term transgender will be used.

The exclusive purpose of this medical information is to define the criteria for granting a Therapeutic Use Exemption (TUE) for the treatment with substances on the Prohibited List to transgender athletes. It is not the purpose of this medical information to define the criteria for the eligibility of these athletes to participate in competitive sport, which is entirely left to the different sporting federations and organizations.

The individual sporting federations and organizations need to decide on the eligibility of transgender athletes in their sport, and a TUE can only be considered for eligible athletes. In both transgender male and transgender female athletes, therapy is principally aimed at achieving testosterone levels within the normal range associated with the gender identity.

Since testosterone is the critical factor influencing performance in sports, it is important that the criteria for the granting of a TUE ensure that both transgender male and transgender female athletes have physiological androgen exposure within the ranges of the non-transgender male and non-transgender female athletes with whom they compete. Some sports organizations may define upper limits or threshold values of testosterone for athletes who want to participate in the female category in their sport.

Levels of circulating testosterone and their influence on muscle mass and strength generally exhibit considerable inter-individual variability in males and females. In transgender athletes, physical outcomes are further influenced by the duration and the type of treatment (hormones and/or surgical).

2. Diagnosis

a. Medical history

Transgender/gender diverse individuals are those with a gender identity other than their sex designated at birth (that is usually based on the external genitalia). TUECs need to recognize that there is no typical presentation but a broad range of presentations. Previously used diagnostic terms aimed at defining pathologies are infrequently used nowadays and unrelated to treatment recommendations. Some transgender/gender diverse individuals may require medical and/or surgical interventions to align their bodies more closely with their gender identity.

Medical history will elaborate on the diagnostic workup and consequent treatment. Many individuals require both hormone therapy and surgery, while others need only one of these treatment options, and some need neither to resolve the symptoms they experience. For transgender male athletes, the most common surgery is masculinizing chest reconstruction. Other masculinizing surgeries include hysterectomy and/or oophorectomy along with genital reconstruction surgeries. For transgender female athletes, the classic gender affirming surgeries include facial feminization surgeries, breast augmentation, genital reconstruction surgery, and orchidectomy.

b. Diagnostic criteria

The ICD-11 distinguishes “Conditions related to sexual health” and introduces the term gender incongruence as the new term (HA6Z).

In transgender athletes who are eligible for competition based on the rules of their respective sport, the process that will have taken place relating to gender affirming medical care may vary considerably depending on the medical community and the law in the respective country.

c. Relevant medical information

Transgender athletes may be granted a TUE only once their eligibility has been established with their sport federation. The respective criteria and characteristics of eligibility defined by their sport need to be documented in the TUE application.

A TUE application needs to include a report by a health professional providing care for transgender persons and detail the medical history including any previous partially or fully reversible physical treatment. This report should be complemented by a report from a medical provider (often an endocrinologist) on initiation of hormone therapy and a surgical report, where applicable. Prior to treatment, a full general medical assessment needs to be completed to assess the individual risk associated with the different therapeutic options.

3. Treatment

Hormone therapy will be an essential intervention for most transgender athletes who seek medical treatment.

a. Name of prohibited substances

The gender-affirming hormone administered to transgender male athletes is testosterone which is prohibited. Testosterone, various testosterone esters, including long acting or oral testosterone undecanoate, testosterone cypionate, testosterone enanthate, or mixed testosterone esters might be used depending on the medical indication as well as local and individual logistics. Note: Dihydrotestosterone and compounded testosterone are not accepted treatments.

The gender-affirming hormone administered to transgender female athletes is estrogen, which is not prohibited. The only prohibited substance administered to transgender female athletes for therapeutic purposes is the antiandrogen and diuretic spironolactone. Spironolactone binds to the androgen receptor and competes with DHT, the active metabolite of testosterone, blocking its action. Although the mechanism is unknown, spironolactone may also reduce overall testosterone levels. Spironolactone allows reduction in the estrogen doses required to optimize the hormone regime.

Notes:

- Athletes who apply for a TUE for spironolactone, which is in Class S5 of the Prohibited List, Diuretics and Masking Agents, will also need to apply for TUE for any threshold substances they might take simultaneously (e.g., salbutamol, formoterol, cathine, pseudoephedrine, methylephedrine, ephedrine).

- Gonadotropin-Releasing Hormone (GnRH) analogues are used in adjunct with estrogens as long-term therapy in transgender female athletes and lower testosterone levels more effectively than other estrogen-anti-androgen combinations. They are currently prohibited in male athletes due to their initial stimulation effect on testosterone. Transgender athletes who are eligible to participate as females in their sport do not require a TUE for GnRH analogues. If a transgender athlete is feminizing the body while still participating as a male in their sport and is therefore subject to anti-doping regulations for male athletes, then a TUE should be requested.

- Currently, there is no known lower limit of normal testosterone levels in non-transgender females. However, individual sporting federations and organizations may define upper limits or threshold values of testosterone for athletes who want to participate in the female category in their sport. As mentioned in the introduction, this is an eligibility issue.

b. Route of administration

i. Transgender male athletes:

1. Intramuscular or subcutaneous: testosterone undecanoate, cypionate, enanthate or mixed esters. The treatment must be recorded by a health professional and kept available for review at any time.
2. Testosterone pellets might be inserted subcutaneously and provide constant testosterone levels avoiding peaks and troughs.
3. Testosterone patches, gels and creams slowly diffuse testosterone through the skin and have a daily dosing regimen avoiding peaks. There is a risk with skin contact causing inadvertent exposure to other athletes, and therefore the site of application must be covered in contact sports. Axillary and nasal application forms have been introduced. A buccal testosterone tablet is also available.
4. Oral administration of testosterone undecanoate has been less frequently used previously because the first-pass metabolism of testosterone created very low and unsatisfactory oral bioavailability. Oral testosterone undecanoate was only absorbed via gut lymphatics when taken together with a fatty meal. Novel formulation(s) of oral testosterone undecanoate that overcome this problem, may become more available in the future.

   Alkylated androgens such as 17α-methyl testosterone are hepatotoxic and should not be used.

ii. Transgender female athletes:

Spironolactone is administered orally.

c. Dosage and frequency

i. **Transgender male athletes**:

Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism. The exact dosage and frequency are to be determined by the prescribing endocrinologist utilizing standard dosage regimens.

Intramuscular administration of testosterone cypionate, enanthate or mixed testosterone esters every one to four weeks may result in fluctuating blood testosterone levels with peaks and troughs. The recommended standard doses are a maximum dose of 100–125 mg weekly, or 200–250 mg every two to three weeks. More stable and physiological levels are achieved with shorter intervals between doses (e.g., weekly versus every two weeks). Even more stable levels may be achieved with long-acting testosterone undecanoate, which may be well suited for transgender male athletes competing at the elite level. The standard dosing regimen requires a loading dose (1000 mg) during initiation of treatment and then four 1000 mg doses per year. Optimal clinical results may require individual dose titration around the 12-week dose interval, ranging between 10–14 weeks, according to clinical effects and trough serum levels.

For injectable testosterone, peak testosterone (24–48 hours after injection) levels can transiently exceed the normal reference upper limit. Therefore, the dosage should be monitored with mid-interval (midway between two successive injections) or trough (at the time of next scheduled injection) serum testosterone levels. The testosterone product, dosage and timing of the previous treatment with injectable testosterone products, as well as the testosterone levels, must be recorded and submitted to the ADO for annual review or for dosage changes.

Testosterone gel can be monitored by serum testosterone levels at any time. Any change in product, dosage or treatment schedule of testosterone should be approved by the ADO.

Oral testosterone undecanoate administration is usually twice or thrice daily with meals.

ii. Transgender female athletes:

Spironolactone 100–200 mg taken daily. Higher doses up to 400 mg might be required to achieve low level testosterone thresholds defined by the sport.

d. Recommended duration of treatment

Testosterone therapy is life-long in transgender male athletes unless contraindications occur (for TUE validity see 7).

Spironolactone in combination with estrogen in transgender female athletes is also life-long unless there is removal of the gonads, or where therapy is changed to use another testosterone-lowering agent (e.g., GnRH analogues if available and/or indicated).

4. Other non-prohibited alternative treatments

Transgender male athletes require hormonal treatment with testosterone, for which there is no non-prohibited alternative.

In transgender female athletes, GnRH analogues (not prohibited in females) or progestin cyproterone acetate (in general not prohibited) may be used and in fact achieve lower testosterone levels than estrogen/spironolactone combinations. In addition, the anti-androgens flutamide and bicalutamide may be used. Although flutamide and bicalutamide have associations with liver injury and cyproterone acetate has a number of concerning associations, safety and comparative effectiveness data are not sufficiently robust to mandate one approach versus another. Furthermore, cost and availability in some countries might prevent athletes from gaining access to some therapies.

5. Consequences to health if treatment is withheld

In transgender athletes, hormones help to optimize a gender role experience congruent with gender identity, improve quality of life, and reduce mental health problems. It has been shown that the incidence of mental health problems is higher prior to hormonal treatment in transgender persons requiring medical management.

In transgender male and female athletes, there is an increased risk of bone density loss after gonadectomy if gender affirming hormone therapy is interrupted or insufficient.

6. Treatment monitoring

To control for the secondary effects of receiving long-term hormone therapy, any transgender athlete needs permanent thorough medical monitoring by a health professional providing care for transgender persons or experienced clinicians as applicable. Providers should be knowledgeable of the most up-to-date hormone guidelines by the World Professional Association for Transgender Health (WPATH) and/or The Endocrine Society (see references).

It is the transgender male athlete's responsibility to provide the TUEC with a complete record of testosterone prescriptions of oral, gel or buccal testosterone products and date, dosage and name of medical personnel administering injections of testosterone. Furthermore, regular serum testing as ordered by the athletes prescribing physician, at least once or twice a year, and its relation to the dosing schedule should be clearly noted and sent to the ADO.

Unannounced urine testing (at least 1–2 times per year) should be conducted by the ADO. Furthermore, regular serum testing as ordered by the athlete's health professional providing care (at least 1–2 times per year) is required and the relation to injection timing or gel application should be clearly noted.

Furthermore, the hematocrit should be monitored regularly (initially every three, later every six months) since testosterone therapy may cause erythrocytosis (hematocrit > 54%), which may result in performance enhancement but also represents a health risk.

In transgender female athletes, the therapeutic goal of spironolactone combination therapy will have to consider the eligibility criteria of the sport that may define testosterone threshold values. The sport will also define the exact method and how often values are to be monitored.

7. TUE validity and recommended review process

As mentioned above, hormone replacement is usually continued lifelong, unless medical contraindications arise. TUE validity should be for ten (10) years in transgender male athletes with a mandatory requirement for annual follow-up reports including testosterone dosing regimens and testosterone levels to be submitted to the TUEC as above.

TUE validity should also be for ten (10) years in transgender female athletes with a requirement for annual follow-ups (the sport's eligibility criteria might define further review needs). In transgender female athletes who undergo orchidectomy, spironolactone will no longer be necessary after the intervention.

8. Any appropriate precautionary matters

Absolute contraindications to testosterone therapy include pregnancy (not applicable in case of transgender male after hysterectomy) and untreated polycythemia with a hematocrit of 55% or higher.

Baseline laboratory values including hematocrit are important to both assess initial risk and evaluate possible future adverse events. All transgender male athletes need to be carefully monitored for cardiovascular and diabetes risk factors. Even though testosterone has not been shown to increase risk in healthy patients, it might do so in those with risk factors. Lipid profiles might be affected and may be regularly assessed.

Spironolactone is typically contraindicated in patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, hyperkalemia, Addison's disease, and with concomitant use of eplerenone (anti-mineralocorticoid used in chronic heart failure), all conditions rather unlikely to be seen in active athletes.

Being given a potassium-sparing diuretic, transgender female athletes receiving spironolactone should be monitored for their blood pressure reactions and hyperkalemia.

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