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Caring for Gender-Diverse Patients

Gender-Affirming Hormone Therapy

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INTRODUCTION

People who are transgender, gender diverse, or gender non-conforming have a gender identity that differs from their sex assigned at their birth. A recent study done by the Pew Research Center shows that 1.6% of American adults identify as transgender or nonbinary, and among young adults 18-29 years of age, it is even more common, at 5.1%.[1]

Gender-diverse people have high rates of health disparities, including higher rates of human immunodeficiency virus (HIV), substance use, mental health disorders, and victimization, much of which is attributable to minority stress; as opposed to stress that is experienced by everyone, minority stress has its roots in stigma and prejudice.[2] Suicide risk is high in gender-diverse populations: between 22% and 43% of transgender people have attempted suicide in their lifetime.[3] Importantly, good social support mitigates some of this risk — in one study of trans youth 16-24 years of age, the risk of suicide attempt in individuals with strongly supportive parents was 4% compared to 57% in those with somewhat supportive to not-at-all supportive parents.[4]

In addition, gender-diverse individuals face significant discrimination in medical settings. According to a study performed in 2022 by the Center for American Progress, 16% of transgender respondents reported that their provider used harsh/abusive language and 10% reported providers refusing to see them. There are challenges outside of discrimination, as well — a lack of training in gender-affirming care means that 30% of transgender respondents reported having to teach their provider about their gender so they receive appropriate medical (not even necessarily gender-affirming) care.[5]

Ample evidence shows that gender-affirming hormone therapy (GAHT) improves mental health outcomes for appropriate patients.[6,7]

How does a provider assess whether an adult patient is a good candidate for GAHT?

According to the World Professional Association for Transgender Health (WPATH) Standards of Care, the following are needed to begin gender-affirming hormone therapy in adults 18 years of age and older:

1. Patients should have marked and sustained gender incongruence — typically defined as being at least six months in duration.
2. Patients should have the ability to consent to starting hormone therapy and understand the potential impact on reproductive options.
3. Patients should have appropriate co-management of mental health conditions and physical health conditions that could negatively impact the outcome of treatments.[8-10]

In addition, a comprehensive medical, behavioral, social, gender, and sexual history should be obtained (see Table 1). Relevant physical exam steps should be completed; a genital exam is generally not necessary prior to initiating treatment.

In this article, we will review two fictionalized patient cases to introduce providers to prescribing

gender-affirming hormone therapy for adults. Both patients meet WPATH criteria for initiating GAHT. Prescription of GAHT for adolescents is beyond the scope of this article. These cases in no way encompass the wide variety of experiences and identities lived by gender-diverse persons but seek to teach some basic principles. Every patient may have different goals. It is worth noting that for some persons who may not want a drastic change in their physical appearance, hormone therapy should be started at a low dose and titrated slowly.

CASE 1: AH

AH is a 28-year-old patient who presents as a new patient to a primary care office to discuss gender-affirming hormone therapy. AH identifies as a transgender (or "trans") woman and uses she/her pronouns. She had a male sex assigned at birth.

AH has known since early childhood that something was different about how she felt in her body. As a young child, she had more traditionally "feminine" interests and got along better with other young girls. She would frequently ask her parents if she could become a girl, but stopped when it was clear this was upsetting her parents.

During puberty, she experienced extreme distress at her pubertal changes. She started to experience severe depression in her adolescent years, culminating in a suicide attempt and psychiatric hospitalization at age 16 years.

She first identified as trans at age 18 years, after learning about the trans community and realizing that the concept of being transgender finally explained how she had been feeling. She started identifying as a woman at that time to supportive friends but was not "out" to her family due to concerns about her safety while living at home. In her mid-20s, with the help of a supportive gender-affirming therapist, she started living independently and had improvement in her depression. She started identifying as a woman to those around her, growing out her scalp hair, doing laser removal of her facial and body hair, and experimenting with more "feminine" clothes.

She has developed a strong support system with friends, a long-term partner, and a few supportive family members. She presents at this time to discuss gender-affirming hormone therapy. She strongly desires the development of breasts, a more "feminine" body shape, a more "feminine" voice, and the reduction of facial and body hair. She does not want biological children.

What medications would you use for gender-affirming hormone therapy for AH?

The most common medications used would be estradiol and an antiandrogen. A common starting dosage would be estradiol oral 2 mg daily and spironolactone oral 50 mg daily.[9,10]

The goals of these medications are to further develop "feminine" secondary sex characteristics and suppress or minimize "masculine" secondary sex characteristics.[9,10] The expected effects and timeline of secondary sex characteristic development are listed in Tables 2 and 3 on page 76. Patients should be informed that it may take months to start seeing the effects of GAHT and that maximal effect can take three to five years. Providers should review the expected effects of the medication, timeline to effect, and potential adverse effects with patients before initiating therapy. Of note: most of the potential side effects from estrogen and antiandrogen therapies are

Table 1. Recommended History and Physical Exam for Gender-Affirming Hormone Therapy Assessment[9,10]

Gender Identity History
• History of experienced gender awareness and the development, exploration, and persistence of that gender
• Desire for future fertility
Medical History
• Personal history of arterial or cerebrovascular disease, arterial or venous thromboembolism, hypertension, hormone-sensitive cancer, polycythemia, pituitary adenoma, liver disease, HIV infection, and other sexually transmitted infections
• Prior use of prescribed or unprescribed hormone therapy or surgical procedures
Behavioral Health History
• History of mental health diagnoses and treatment, psychiatric hospitalizations, past or present suicidality
Family History
• Family history of any cancer, cardiovascular disease, diabetes, or blood clotting disorders
Social History
• Family, chosen family, history of rejection and acceptance
• Living situation and safety
• Sexual history, sexual orientation
Physical Exam
• Genital exam at first visit usually not necessary
• Anatomic inventory of organs present to guide organ-appropriate screenings (pap smear for persons with a cervix, mammogram for persons with breasts, discussion of prostate screening for persons with prostates)

similar to the potential health risks seen in cisgender women — that is, a woman whose gender matches their sex assigned at birth.

Providers should ensure special attention is paid to discussing fertility effects — gender-affirming hormone therapy may cause potentially permanent infertility. Anyone desiring future fertility should be referred to a fertility specialist prior to starting GAHT.

Oral estradiol is the most commonly used formulation of estradiol due to cost and ease of use (see Table 4). The preferred estrogen formulation is 17-beta estradiol rather than ethinyl estradiol (commonly used in oral contraceptives) or conjugated estrogens (often used to treat menopausal symptoms); the latter two would impose a higher thrombotic risk. Providers should consider use of transdermal estradiol for patients who have risk factors for atherosclerotic cardiovascular disease or venous thromboembolism as it confers a lower thrombotic risk than oral or injectable formulations.

Spironolactone is the most commonly used antiandrogen as it has a stronger antiandrogenic effect than the 5-alpha reductase inhibitors. 5-alpha reductase inhibitors may be more effective for patients with significant alopecia or patients who cannot tolerate spironolactone. The 5-alpha reductase inhibitors block the conversion of testosterone to its more potent form, dihydrotestosterone (DHT).

GAHT is not an effective contraceptive on its own. Patients who are sexually active with someone who can get pregnant should ensure contraception is used.

What lab testing should be done prior to starting GAHT?

A comprehensive metabolic panel should be completed prior to starting spironolactone.

Table 2. Effects of Estrogen/Antiandrogen Therapy[9,10]

Expected Effects	Adverse Effects
Potentially Permanent • Breast growth • Decreased size of testicles ***Typically Reversible*** • Loss of muscle mass • Fat redistribution from abdomen to buttocks, hips, and thighs • Softening of skin • Decreased facial and body hair growth • Slowed androgenic hair loss • Reduced sex drive and decreased strength of erections	***Estradiol*** • Nausea (most common) • Increased risk of VTE, although overall risk remains low; transdermal estradiol safer for those at higher risk • Potentially permanent infertility — time to infertility and permanence varies greatly person-to-person • Possible increased risk of cardiovascular disease • Possible increased risk of hypertension, gallbladder disease, worsening of existing liver disease, migraines, and prolactinoma • Somewhat increased risk of breast cancer compared to cisgender men (although still significantly decreased compared to cisgender women) ***Any Antiandrogenic Medication*** • Erectile dysfunction and decreased sex drive (sildenafil and tadalafil may be used if needed) ***Spironolactone*** • Polydipsia, polyuria, and orthostasis • Rarely hyperkalemia and renal dysfunction — caution in those with preexisting renal disease or use of ACE inhibitor, ARB, or loop diuretic

VTE = venous thromboembolism, ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker

Table 3. Timeline of Changes After Estrogen/Antiandrogen Therapy Initiation (earliest onset to maximal effect)[9,10]

	1mo	3mo	6mo	1yr	2yr	3yr	4yr	5yr
Decreased spontaneous erections	■	■	■	■				
Decreased libido	■	■	■	■				
Decreased testicular volume		■	■	■	■	■		
Breast growth		■	■	■	■	■		
Decreased sperm production		approx.	■	■	■	■	■	■
Decreased muscle mass		■	■	■	■			
Fat redistribution		■	■	■	■	■		
Decreased hair growth			■	■	■	■	■	■

What lab testing should be done to monitor efficacy of GAHT in this patient?

Typically, total testosterone, estradiol, and a basic metabolic panel should be checked every three months while titrating therapy and then yearly thereafter. A pregnancy test is not necessary.

Goal estradiol levels for patients seeking full feminizing effect are typically in the natal female range of 100-200 pg/ml. Goal testosterone levels are typically less than 55 ng/dl. If patients are on injectable therapy, levels should be checked mid-cycle.[9,10]

CASE 2: PW

PW is a 22-year-old patient seeking gender-affirming hormone therapy. He identifies as transmasculine and uses he/they pronouns. He had a female sex assigned at birth.

PW states that they never felt "right" in their body ever since early childhood. He was always quite sporty, called a "tomboy," but never felt like that label fit correctly. His parents remember that he was extremely distressed when he had to wear dresses growing up and when people described him and his sisters as "the girls of the family." Starting in early adolescence, he was able to identify that he did not feel like a girl inside.

He started puberty at an early age and started menstruating at age 11. He felt severe dysphoria related to breast growth and menstruation. He had significant depression in early adolescence and was later diagnosed with bipolar 2 disorder at age 16. He was started on lamotrigine, and his mood has been stable on this medication since then.

He has a generally supportive family and came out as gender fluid at age 14 to friends and family, meaning he had a gender identity that was not fixed. As he then explored his gender identity further, he came out as transmasculine around age 18, meaning he identified as masculine, although not necessarily male. He tends to dress in more androgynous clothes and binds his breasts daily.

He has been doing voice training online to try to develop a more "masculine" voice. He is interested in gender-affirming hormone therapy, with the goal of developing a more "masculine" body shape, stopping menstruation/monthly bleeding, and developing body/facial hair growth. He thinks he is interested in top surgery in the future. He does not think he wants biological children but would like to talk to a fertility specialist to discuss options before deciding, and he is referred to a fertility specialist before initiation of GAHT.

What medication would you start for gender-affirming hormone therapy for this patient?

The most commonly used medication in this setting is testosterone, which is most often administered via injection. A typical starting dose may be testosterone cypionate 50 mg subcutaneous once weekly.[9,10]

The goal of androgenizing therapies is to develop more "masculine" secondary sex characteristics and to suppress or minimize "feminine" secondary sex characteristics. The expected effects and timeline of

Table 4. Dosage Chart for Commonly Used Medications[9,10]

Formulation	Name	Dose Frequency	Low Dose	Common Dose	Max Dose	Med Notes
Oral	Estradiol tablet	Daily to twice daily	1-2 mg	4-6 mg	8 mg	Cheap and easy to administer.
Transdermal estradiol patches	Climara	Weekly	0.05 mg	0.1-0.2 mg	0.4 mg	Lowest thromboembolic and cardiovascular risk; difficult to get more than two patches to be covered by insurance at a time.
	Vivelle-Dot	Twice weekly				
Injectables *Intramuscular*	Estradiol valerate	Every 2 weeks	5 mg	10-15 mg	30 mg	Can also be given weekly — cut dose in half if dosing weekly. May have wider fluctuations in hormonal levels than other formulations. Learning to inject hormones is an additional skill patients must learn.
	Estradiol cypionate	Every 2 weeks	1.5 mg	3-6 mg	10 mg	
Antiandrogens						
Spironolactone	Spironolactone	Once to twice daily	25 mg BID	50-100 mg QD-BID	200 mg BID	
5-alpha-reductase inhibitors	Finasteride	Daily	1 mg	1-5 mg	10 mg	
	Dutasteride	Daily	–	0.5 mg	0.5 mg	

development on secondary sex characteristics are listed in Tables 5 and 6.

Patients should be informed that it may take months to start seeing the effects of GAHT and that maximal effect can take three to five years to develop. Providers should review the expected effects of the medication, timeline to effect, and potential adverse effects with patients before initiating therapy. Of note: most of the potential side effects from testosterone are similar to potential health risks seen in cisgender men. Providers should discuss the potentially permanent fertility effects of these medications.

Several formulations are available and effective (see Table 7). The most commonly used formulation for testosterone administration is injectable testosterone, which has a low cost and increases testosterone quickly and efficiently. Transdermal testosterone is also commonly used and may produce a steadier state of hormone levels but a slightly more gradual physical change.

Androgenizing therapy is not reliable contraception for individuals capable of pregnancy; therefore, pregnancy testing should always be a consideration as needed, and counseling regarding pregnancy and contraception is essential. No forms of birth control are absolutely contraindicated; however, combined estrogen-progesterone forms of birth control might interfere with androgenizing therapy.

What testing should be done at baseline for PW?

Baseline testing should include hematocrit and pregnancy testing if pregnancy is possible.

What follow-up testing should be done for this patient?

Typically, total testosterone and hematocrit should be assessed every three months while titrating therapy and then yearly. Pregnancy status should be checked as indicated. Goal total testosterone levels for patients seeking full masculinizing effect are typically in the upper end of the normal cisgender male range, 650-1,000 ng/dl. If patients are on injectable therapy, the level should be checked mid-cycle.[9,10]

At follow-up visits for patients on GAHT, providers should assess adherence, barriers to getting medications, and side effects. Providers should discuss physical changes and satisfaction to goals, as well as mental health, sexual health, relationships and intimate part-

Table 5. Effects of Androgenizing Therapy[9,10]

Expected Effects	Potential Adverse Effects
Potentially Permanent • Lower pitch of voice • Enlargement of clitoris • Increased facial and body hair growth • Possible hair loss on scalp ***Typically Reversible*** • Increase in lean muscle mass • Redistribution of fat from hips and buttocks to the abdomen • Cessation of menses • Skin changes, including worsened acne • Increased sex drive • Changes in mood or thinking	• Polycythemia • Potentially irreversible infertility • Pelvic pain and atrophy of vaginal walls, which can increase susceptibility to sexually transmitted infections and pain during penetrative intercourse • Possible increased risk of hyperlipidemia and atherosclerotic cardiovascular disease compared to cisgender women, but likely comparable risk to cisgender men • Increased appetite, weight gain, sweating, increased risk of sleep apnea • Possible increase in irritability/aggression • Teratogen if patient becomes pregnant (birth control recommended if sexually active with partner capable of causing pregnancy)

Table 6. Timeline of Changes After Testosterone Initiation (earliest onset to maximal effect)[9,10]

	1mo	3mo	6mo	1yr	2yr	3yr	4yr	5yr
Oily skin/acne	■	■	■	■	■			
Fat redistribution	■	■	■	■	■	■	■	■
Vaginal atrophy	■	■	■	■	■			
Clitoral enlargement	■	■	■	■	■			
Cessation of menses		■	■					
Facial/body hair growth			■	■	■	■	■	■
Increased muscle mass			■	■	■	■	■	■
Deepening of voice			■	■	■			

Table 7. Testosterone Formulations[9,10]

Formulation/ Administration	Med Name	Dose Frequency	Low Dose	Common Dose	Max Dose	Med Notes
Short-acting injectable *Subcutaneous (typically preferred) or intramuscular*	Testosterone cypionate or enanthate	1-2 weeks (double listed doses if administering biweekly)	25-50 mg	80-100 mg	125 mg	Less frequent dosing leads to higher testosterone level fluctuation. Learning to inject hormones is an additional skill patients must learn.
Transdermal *For all transdermal, avoid skin-skin contact in area of application until completely absorbed.*	Testosterone gel 1% (AndroGel 1%, Testim)	Daily	12.5-25 mg	50 mg	100 mg	1 pump = 12.5 mg Apply to shoulders and upper arms.
Long-acting	TESTOPEL (subcutaneous implantation)	Every 3 months	2 pellets	2-6 pellets	6 pellets	75 mg/pellet: dose range 150-450 mg

ner violence, and pregnancy prevention. Providers should also inquire about the patient's social transition and plans for medical or non-medical gender-affirming treatments.

CONCLUSION

Gender-diverse people experience high levels of discrimination and health disparities, and special attention should be paid to ensuring that clinical environments are affirming for these populations. GAHT can help achieve significant improvement in mental health for gender-diverse patients and is within the purview of primary care providers.

HELPFUL SMARTPHRASES IN EPIC

.ebtransintakemasculinizing
Intake form for patients seeking masculinizing therapy

.ebtransintakefeminizing
Intake form for patients seeking feminizing therapy

.ebconsentfort
Consent form for masculinizing therapy

.ebconsentfore
Consent form for feminizing therapy

.tgncgoalsform
Form for patient to complete with goals for transition

Scan QR code at right for information regarding therapies beyond hormone therapy for gender-diverse persons, as well as definitions for key terms in this article. ➔

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