Invited Review Providing Gender-Affirming Care to Transgender and Gender-Diverse Individuals With and at Risk for HIV

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Transgender and gender-diverse populations have unique medical and psychosocial needs. It is important that clinicians address these needs with a gender-affirming approach in all aspects of health care for these populations. Given the significant burden of HIV experienced by transgender people, such approaches in providing HIV care and prevention are essential both to engage this population in care and to work toward ending the HIV epidemic. This review presents a framework for practitioners caring for transgender and gender-diverse individuals to deliver affirming, respectful health care in HIV treatment and prevention settings.

Keywords: transgender health, HIV, HIV prevention, gender-affirming care

Introduction

Gender and sex are complex constructs that have garnered considerable attention recently across multiple spheres including health care.¹ In the United States, more than 1.6 million people older than 13 years identify as transgender or gender nonconforming, representing approximately 0.5% of adults and 1.4% of youth.² This population experiences enormous health disparities, particularly related to sexual health. Transgender women in the

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Send correspondence to Olivia T. Van Gerwen, MD, MPH; University of Alabama at Birmingham, 703 19th Street South, ZRB 218A, Birmingham, AL, 35294; oliviavangerwen@uabmc.edu. United States have an estimated HIV prevalence of 42%³ as well as prevalence rates for bacterial sexually transmitted infections (STIs) that are higher than those for other populations.⁴ These disparities are worsened by suboptimal engagement in health care by transgender people, which itself is driven by stigma, discrimination, and limited access to affirming practitioners.⁵ The aim of this review is to equip clinicians with tools to provide culturally sensitive, gender-affirming health care for transgender and gender-diverse populations, specifically in the setting of HIV treatment and prevention.

Gender and Sexual Identity Terminology

Although transgender and gender-diverse people have always existed, the current shifting cultural and political landscape toward recognition and

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support for these individuals underscores the importance of health care practitioners having better

Table 1. Common Gender Identity Terms and Their Characteristics^a

Gender identity term	Characteristics	
Cisgender female or woman	Person assigned female sex at birth whose gender identity is female or woman	
Cisgender male or man	Person assigned male sex at birth whose gender identity is male or man	
Genderqueer	Person who does not follow gender identity or expression for their sex assigned at birth; they may identify as neither, both, or a combination of binary genders	
Nonbinary	Person who does not identify with binary ex- pectations of being strictly a man or a woman	
Transgender	Person whose gender identity and sex as- signed at birth do not correspond	
	 Transgender female or transgender woman or male-to-female (MTF)^b 	
	 Transgender male or transgender man or female-to-male (FTM)^b 	

^aThe terms included are the most common, but dozens more are used, and terminology continually evolves.

^bMedical model terms (not recommended for use unless an individual prefers them).

understanding for the needs of these people. Basic needs include the correct use of common gender identity terms and an appreciation that each gender identity has several components.

Sex refers to the physiologic and genetic characteristics of an individual, such as genitalia, reproductive anatomy, and composition of X and Y chromosomes; it is assigned at birth.⁶ Examples of sex include male, female, or intersex.⁷ Gender, by contrast, is a social construct defined by the behavioral or cultural norms of either men or women.⁶ Every person, regardless of the sex assigned at birth, has a gender identity, which is the individual's internal subjective sense of being a boy or girl, a man or woman, or another gender identity.7 Gen*der expression* is the manner in which individuals express their gender identity to society in terms of physical appearance and clothing.⁷ Sexual identities such as sexual and romantic attractions are distinct from *gender* but similar to *gender identity*; each individual has a personal sexual identity. Notably, these concepts exist on a spectrum, and assumptions about any of them for an individual should be avoided.

Transgender individuals are those whose sex assigned at birth does not align with their gender identity, whereas *cisgender* individuals experience congruence between their sex assigned at birth and gender identity. Many individuals do not feel that the binary genders of "male" and "female" describe their identity, so they may identify as another gender such as *gender nonconforming*, or *nonbinary*. Table 1 lists common gender identities and their characteristics.

Gender-Affirming Health Care

Gender affirmation refers to the process of recognizing, accepting, and expressing one's gender identity; as applied to health care practitioners, it refers to supporting patients in these areas.⁸ Gender affirmation is often conceptualized in 4 domains: medical, social, psychologic, and legal.⁹ Although this review focuses largely on the medical domain, the other 3 domains are important for clinicians who care for gender-diverse people to be familiar with so that they can provide comprehensive, genderaffirming care.

Methods for socially affirming gender identities can include asking about and using the person's chosen name and pronouns during all clinic encounters. For psychologic and legal gender affirmation, clinicians may provide support and refer individuals to appropriate resources such as gender-affirming mental health clinicians and legal professionals who may be able to help with gender-marker (ie, the designated gender on an individual's identifying documents such as driver licenses) and namechange processes, respectively.

An essential component of providing genderaffirming medical care is appropriate documentation of all encounters to ensure that costs are covered by insurance. At this time, we recommend that clinicians document each patient's experience of *gender dysphoria*, which refers to the distress related to having incongruence between gender identity and sex assigned at birth and has a specific ICD-10 code. Importantly, not all patients seeking or receiving gender-affirming therapies experience dysphoria related to their gender. However, billing these visits using a gender dysphoria code is the easiest way to ensure insurance coverage.

Medication class	Route	Suggested starting dose range	Suggested maximum dose
Feminizing hor	mone therapy		
Estrogens			
	Oral or sublingual estradiol	2.0 mg daily	8.0 mg daily
	Transdermal estradiol patch	0.1 mg daily	0.4 mg daily
	Parenteral estradiol valerate (IM/SQ)	20 mg every 2 weeks	40 mg every 2 weeks
	Parenteral estradiol cypionate (IM/SQ)	2 mg every 2 weeks	5 mg every 2 weeks
Antiandrogens			
	Oral spironolactone	100 mg daily	200 mg twice daily
	Oral cyproterone acetate ^b	10 mg daily	same as starting dose
	Parenteral GnRH agonists (IM/SQ)	3.75–7.50 mg monthly	same as starting dose
	Parenteral GnRH agonist depot formulation (IM/SQ)	11.25 mg every 3 months or 22.5 mg every 6 months	same as starting dose
Progesterone			
	Oral micronized progesterone	100 mg daily	200 mg daily
Masculinizing l	normone therapy		
	Parenteral testosterone enanthate/cypionate (IM/SQ)	50–100 mg weekly or 100–200 mg every 2 weeks	same as starting dose
	Parenteral testosterone undecanoate (IM)	1000 mg every 12 weeks or 750 mg every 10 weeks	same as starting dose
	Transdermal testosterone patches	2.0 mg daily	8.0 mg daily
	Testosterone topical gel 1%	50 mg daily ^c	100 mg daily

Table 2. Common Gender-Affirming Hormone Therapy Regimens^a

 $\label{eq:stability} Abbreviations: IM, intramuscular; GnRH, gonadotropin-releasing hormone; SQ, subcutaneous.$

^a Adapted from Coleman¹¹ and Deutch.¹²

^b Not available in the United States.

^c 30 mg = 1 pump.

Several sets of clinical guidelines are useful for practitioners caring for transgender and genderdiverse people; these include guidelines from the Endocrine Society, the World Professional Association of Transgender Health, and the University of California San Francisco.^{10–12} All discuss approaches to the 2 main components of gender-affirming medical care: gender-affirming hormone therapy (GAHT) and surgical care.

Gender-Affirming Hormone Therapy

Despite nuanced differences in approach among the various guidelines, all share the same basic tenets of GAHT, which are described in Table 2. In general, masculinizing hormone therapy consists of administering exogenous testosterone via either long-acting injectable routes (eq, subcutaneous, intramuscular) or shorter-acting topical routes (eq, gels, patches). Feminizing hormone therapy involves the administration of exogenous estrogen as well as adjunctive therapies aimed at blocking testosterone. Estradiol can be administered orally, transdermally via patches, or injected intramuscularly or subcutaneously. The choice of route for these medications is best determined on an individual basis. accounting for insurance coverage, safety, patient preference, and cost. Testosterone-blocking adjunctive therapies for feminizing hormone regimens include spi-

ronolactone, gonadotropin-releasing hormone (GnRH) agonists, and finasteride.

Monitoring of people receiving GAHT requires laboratory testing every 3 months for the first year of therapy. The 3 guideline documents differ slightly in this aspect but in general agree that practitioners should consider testing for testosterone and estradiol levels, electrolyte levels, hematocrit values (for people receiving testosterone), lipid levels, and liver function. It is also important for clinicians to ask patients at these intervals about their perceived progress since starting hormone therapy, including positive and negative effects of medications on their body or mood. Counseling to set appropriate expectations for the changes they may experience from GAHT is essential. The majority of people experience the most dramatic results within the first 6 months, but treatment can take up to 3 years for some individuals to reach desired results.

Gender-Affirming Procedures and Surgery

Although many individuals desire gender-affirming procedures and surgeries, it is important to understand that not all wish to pursue such treatments. Early in the patient-clinician relationship, practitioners should assess the individual's goals for desired procedures as well as any previous procedures the person may have undergone, whether under the supervision of licensed health care practitioners or otherwise. In general, data on outcomes for various procedures are limited because genderaffirming surgery is a growing field; however, available studies suggest promising outcomes for patient satisfaction and quality of life for transgender individuals who have undergone these procedures.^{13,14} Colloquially, gender-affirming surgeries are grouped as "top" surgery (ie, involving the chest or breasts), "bottom" surgery (ie, involving the genitourinary or reproductive organs), or cosmetic surgery.

Among transgender women, approximately 4% to 25% undergo gender-affirming surgical procedures.¹⁵ These procedures include breast augmentation, orchiectomy, chondrolaryngoplasty, facial feminization surgery, vaginoplasty, labioplasty, and vulvoplasty.¹¹ In recent years, increasing numbers of transgender women are undergoing genital surgeries,¹⁶ likely aided by increases in the number of health care practitioners gaining this expertise and offering such procedures as well as by changes in insurance coverage that make these procedures more financially feasible.¹⁶ Despite this increased utilization, cost remains a substantial barrier preventing many transgender people from pursuing desired surgical procedures.^{17,18}

Cosmetic procedures are also utilized by this population, including fillers, which are used by an estimated 10% to 17% of transgender women. Most commonly, loose fillers are injected into the breasts, face, hips, and buttocks to achieve a more feminine-appearing silhouette. Whereas licensed clinicians safely inject substances such as silicone and other fillers in many patients, people desiring such treatments may seek unlicensed individuals to overcome barriers of cost and availability.¹⁹ Thus, counseling should be given on the potential risks of accessing such procedures outside of the health care system; risks include potential for acquisition of bloodborne pathogens (eg, HIV, viral hepatitis), filler migration, inflammation, emboli, disfigurement, and death.

For transgender men, an estimated 25% to 50% undergo gender-affirming top surgery, which often involves breast reduction or chest reconstruction.¹⁵ Hysterectomy and bilateral salpingectomy-oophorectomy (estimated prevalence, 14%)²⁰ not only offer gender-affirmation via removal of reproductive organs, but also may provide dysphoria relief by eliminating menstruation or the risk of becoming pregnant. Bottom genital surgeries are also available, although less common (prevalence, 2%–5%), including metoidioplasty, phalloplasty, urethroplasty, and scrotoplasty.¹⁵ However, these genital procedures can be complex and require extensive surgical expertise and close follow-up.

HIV in Transgender Populations

In the general US population, the estimated prevalence of HIV is 0.39%, which is significantly lower than estimates among transgender women and transgender men (42.0% and 3.2%, respectively).^{5,21} Transgender people of color experience the most significant HIV burden, with 51% of transgender women and 58% of transgender men with HIV identifying as Black or African American.²²

Significant data demonstrate that transgender women with HIV have poorer outcomes across the entire HIV care cascade, including lower rates of retention in care, use of, as well as adherence to, antiretroviral therapy (ART), and viral suppression.^{23–27} Data from the Ryan White HIV/AIDS Program in 2020 showed that viral suppression rates among transgender women were significantly lower than those of other populations. For example, 89.5% of cisgender individuals were virally suppressed compared with 84.2% of transgender women.²⁸ Within this group of transgender women, rates of viral suppression were even lower for those who were African American (81%), aged 20 years to 24 years (73.9%), aged 25 years to 29 years (79%), experiencing unstable housing (71.6%), and particularly those who were Black and experiencing unstable housing (66.9%).²⁸

Several factors have been associated with viral non-suppression among transgender women, including prioritization of transition-related medical care over HIV care, concerns about drug–drug interactions between ART and GAHT, negative experiences with health care professionals and systems, fear of discrimination, HIV stigma, and mental health and substance use comorbidities.^{29,30}

Drug–Drug Interactions

Although drug–drug interactions between ART and GAHT medications are cited as major concerns

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among transgender women with HIV, there are relatively few such interactions. According to the 2022 US Department of Health and Human Services HIV/AIDS Treatment Guidelines, ART regimens with the least potential to interact with GAHT are those that are most commonly prescribed as part of first-line therapy: all nucleoside reverse transcriptase inhibitors (nRTIs), unboosted integrase strand transfer inhibitors (InSTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs), particularly rilpivirine and doravirine.³¹

Some medication classes have the potential to increase or decrease levels of GAHT components, so monitoring patients on these medications and adjusting GAHT drug dosages based on the desired clinical effects, adverse effects, and serum hormone concentrations are essential. Medications that may decrease estradiol levels include protease inhibitors boosted with ritonavir, efavirenz, etravirine, and nevirapine, with the latter 3 also having the potential to decrease testosterone and finasteride levels. Medications that may increase testosterone, finasteride, or dutasteride levels include boosted elvitegravir as well as protease inhibitors boosted by either cobicistat or ritonavir. The effects of boosted elvitegravir and protease inhibitors boosted with cobicistat on estradiol levels are unclear.

Medical Comorbidities

People with HIV who are receiving ART are at risk of long-term medical comorbidities, including weight gain, cardiovascular disease, low bone mineral density, and renal dysfunction. For transgender individuals on GAHT, these comorbidities have the potential to be augmented and can yield similar sequelae.

Weight Gain. Certain components of ART regimens, particularly InSTIs and tenofovir alafenamide (TAF), have been associated with weight gain.^{32,33} This phenomenon is multifactorial for most individuals, with lifestyle factors such as diet and exercise likely having roles. Further, especially for people with advanced, long-standing HIV infection, weight gain may represent a reversal of HIV-related wasting and a return to a healthy weight. However, there are situations for which initiation of ART can contribute to weight gain and associated metabolic sequelae such as diabetes and hyperlipidemia. For persons on GAHT, weight-related changes are also commonly observed, including changes in fat distribution and muscle mass. For transgender individuals taking estrogen as part of a feminizing GAHT regimen, loss of muscle mass and weight gain are frequently observed. Increased muscle mass is expected for individuals taking testosterone as a part of masculinizing GAHT, but the weight gain is variable. In addition to the stress associated with transition, weight gain in people initiating GAHT can thus be multifactorial.³⁴

For transgender individuals with HIV who are on ART as well as GAHT, weight gain may be compounded; thus, shared decision making on how to approach such changes is imperative. For many, changes in fat distribution, weight gain, and muscle mass are desired as part of their transition, so monitoring other metabolic parameters (eg, levels for hemoglobin A1c and lipids) is reasonable. Currently, switching ART components is not recommended for most people experiencing weight gain, and lifestyle modifications should be prioritized. As an alternative, if an ART switch is deemed appropriate using a patient-centered approach, an NNRTI-based regimen could be considered.³¹ If individuals taking estrogen are experiencing significant weight gain with which they are not happy, reducing their estrogen dose could be discussed if the person is amenable.

Cardiovascular Risk. Inflammation, associated with HIV infection, increases the risk of cardiovascular disease, especially in aging populations.³⁵ Compounding that risk is the potential for certain components of ART regimens, namely protease inhibitors and abacavir, to potentially increase cardiovascular risk as well.^{36,37} More recently, associations between TAF and dyslipidemia have also been proposed.³⁸

GAHT regimens with estrogen are associated with increased venous thromboembolic risk³⁹ as well as potential increased risk of hypertension, dyslipidemia, and stroke.⁴⁰ Notably, these associations are extrapolated from data in cisgender women being treated with estrogens for menopause-related

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symptoms. Discussions of these potential adverse events are important to have with people who are with HIV and taking estrogens as part of a feminizing GAHT regimen. With ART, avoiding regimens containing protease inhibitors, abacavir, and TAF may be considered to decrease cardiovascular risk. Estrogen injectables and patches should also be considered for people older than 40 years, given their lower potential for adverse cardiovascular events versus oral treatment.⁴¹ These considerations are particularly important in older populations, as cardiovascular risk increases with age.

Overlying these medication factors are the roles of lifestyle and equity components as well as stress in cardiovascular risk. Transgender people experience poorer cardiovascular outcomes than their cisgender counterparts for multifactorial reasons, including the likely major drivers of psychosocial and minority stress factors (eg, discrimination, lack of affordable housing, and limited access to health care).⁴² The provision of comprehensive medical and social services to populations such as transgender people with HIV has the potential to reduce some of this stress and possibly improve cardiovascular outcomes.

Another major lifestyle factor to be considered is tobacco use. Counseling patients on smoking cessation at initiation of GAHT with estrogens is very important. However, withholding estrogens altogether is not recommended for people who continue to smoke. Harm reduction strategies can be applied in a shared decision-making process to help people identify ways to reduce and eventually quit smoking entirely.

Bone Health and Renal Impairment. Although limited, some data suggest that transgender women may be at risk of osteoporosis, especially with underutilization of hormones after gonadectomy or the use of androgen blockers with insufficient estrogen.^{12,43,44} Long-term use of ART regimens containing tenofovir disoproxil fumarate (TDF) have also been associated with decreases in bone mineral density.⁴⁵ For transgender women with HIV, balancing the need for estrogen and androgen blocker is essential, especially after gonadectomy. Avoiding ART regimens containing TDF in favor of those containing TAF, which has less impact on bone mineral density, can also help promote bone health. Health modifications such as addition of regular, lightweight-bearing exercise are also beneficial.

In addition to its impact on bone mineral density, TDF also adversely affects renal function. Therefore, TAF-containing regimens are preferred for people with underlying renal disease.⁴⁶ In monitoring renal parameters for transgender people, clinicians need to recognize that changes in body composition and lean body mass associated with GAHT can affect creatinine levels. Therefore, after a person has taken GAHT longer than 6 months, monitoring creatinine clearance and calculations of ideal body weight should be based on gender identity rather than on sex assigned at birth.⁴⁷

HIV Prevention and Transgender Populations

Within the past decade, several biomedical options for HIV prevention have become available, including 2 oral antiviral combinations of tenofovir and emtricitabine, TDF/FTC and TAF/FTC, and 1 long-acting injectable antiretroviral, cabotegravir (CAB-LA).⁴⁸ Despite the demonstrated efficacy and safety of HIV pre-exposure prophylaxis (PrEP) in transgender populations, the uptake, adherence, and persistence of PrEP among transgender men and transgender women have been suboptimal.^{49–52} Reasons include concerns about drug–drug interactions with GAHT, competing health care priorities, and limited access to gender-affirming care practitioners.^{52–54}

Some regions in the United States have had improvement in PrEP uptake in recent years, however. In San Francisco in 2013, for example, among a cohort of transgender women (n = 233), only 14% had heard of PrEP and 1% were willing to take it.55 When the same survey was repeated there in 2019–2020, 94% of the cohort of 201 transgender women had heard of PrEP and 45% had taken PrEP in the previous 12 months.⁵⁶ Despite such improvements in PrEP awareness and uptake, PrEP persistence is still challenging among transgender populations. Another San Francisco study reported that the median days to PrEP discontinuation among transgender women who have sex with men was 120 days. As for reasons for low PrEP uptake, the explanations for low persistence are complex and require further study.57

The first step toward effective individual HIV prevention is identifying the person's risk of acquiring HIV infection. The 2021 CDC HIV PrEP guidelines provide useful risk assessment tools for sexually active persons, such as asking about HIV serostatus of partners and recent history of bacterial STIs.⁴⁸ It is important that clinicians assess transgender people for HIV risk factors as for patients of any gender identity. One qualitative study among transgender women in the southeastern United States found that when clinicians conflated HIV risk with gender identity and made assumptions about sexual behaviors based on gender identity, transgender women felt alienated and stigmatized.⁵³

Practitioners should discuss the various options available with transgender people desiring to start HIV PrEP, taking into consideration each person's gender identity, sex assigned at birth, medical comorbidities, and sexual behaviors. Use of CAB-LA has been studied and deemed safe and effective in people of all genders; however, the medication cannot be used in individuals who have silicone injection or fillers involving the buttocks because the CAB-LA injection is administered there.⁵⁸ Oral options for transgender women include daily FTC/ TDF and daily FTC/TAF; however, no studies have yet assessed efficacy of FTC/TAF in individuals participating in receptive neovaginal sex.48 Given that people assigned female at birth were not included in the landmark clinical trial assessing efficacy of daily FTC/TAF, this option is not currently recommended for transgender men or nonbinary people assigned female at birth.59

For nondaily oral PrEP, also known as the "2-1-1" regimen or event-driven dosing of FTC/TDF, current CDC guidelines include this regimen as an option for cisgender men who have sex with men based on efficacy data from 2 trials that included this population.^{48,60,61} However, the 2022 IAS–USA guidelines offer a CIII recommendation rating for prescribing event-driven PrEP for transgender individuals, extrapolating from pharmacokinetic data from the Ipergay trial.^{62,63} Given no direct data on the efficacy of this dosing regimen in any transgender population engaging in any kind of sexual behaviors, we recommend shared decision making

between patient and clinician in the choice of dosing regimen.

Drug-drug interactions between GAHT and PrEP medications are a major concern of transgender individuals.53 As such, the interplay between these 2 medication groups has been an area of active research in transgender health in recent years, and no evidence of bidirectional effects between PrEP and GAHT has been established. The iBrEATHe trial (Truvada for HIV Pre-exposure Prophylaxis Using Daily Directly Observed Therapy to Look at Potential Interactions Between Truvada and Hormone Therapy) demonstrated that among transgender women on estrogen therapy as well as transgender men on testosterone, serum hormone concentrations were not impacted after 4 weeks of therapy with FTC/ TDF. In addition, dried blood spots had comparable serum FTC/TDF levels after 4 weeks of therapy regardless of gender identity and GAHT regimen.^{64,65} Results of the DISCOVER trial (Emtricitabine and Tenofovir Alafenamide vs Emtricitabine and Tenofovir Disoproxil Fumarate for HIV Pre-exposure Prophylaxis) found comparable TFV-DP concentrations between transgender women on GAHT and cisgender men who have sex with men for those taking FTC/TAF. Finally, initial findings in a subset of patients (n = 53) from the HPTN (HIV Prevention Trials Network) 083 study suggest that GAHT does not impact CAB-LA concentrations.66

Improving HIV Prevention and Care Engagement in Transgender Communities

Creating care environments that facilitate gender affirmation is key to improving engagement in HIV prevention and care among transgender populations. Transgender people with HIV who have health care practitioners that affirm their gender by using their chosen name and pronouns are more likely to be virally suppressed.⁶⁷ Integration of gender health with HIV care is also associated with higher rates of viral suppression, fewer clinician visits, and facilitation of open discussions related to an individual's concerns about HIV and gender-related health care.⁶⁸

Transgender representation in health care environments is also essential to creating safe spaces for people who have traditionally experienced blatant discrimination in these settings. Use of peer navigation services and hiring of transgender staff can ease the discomforts of engaging in care and promote advancement along the HIV care continuum.⁶⁹ Displays of allyship such as including transgender images throughout clinic spaces and providing gender-neutral restrooms are also impactful. Given the various forms of violence, stigma, and discrimination experienced by transgender people,²⁰ applying a trauma-informed lens to HIV care is another important consideration.⁷⁰

The ways in which clinics collect gender-related data are key to creating an affirming environment for the transgender and nonbinary community. This process begins with clinic and health-system intake forms, including how these data are entered into electronic medical records by staff. Collecting such data has been deemed acceptable not only by transgender and gender-diverse populations, but also by cisgender, heteronormative populations.⁷¹ Either via direct questions on intake forms or when conversing with individuals, clinic staff should ask each person for their preferred name and pronouns. In addition, we recommend using the 2-step method that allows clinicians to reconcile both current gender identity and sex assigned at birth.¹² Other best practices include obtaining and maintaining organ inventories for patients that account for any prior gender-affirming procedures, as well as the use of neutral, nongendered language in general.¹²

Conclusion

Transgender patients are highly impacted by the HIV epidemic as well as many other health care disparities. Creating gender-affirming care environments and providing evidence-based, high-quality care for those with and at risk for HIV are essential components of ending the HIV epidemic.

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