Background

Defining Sexual and Gender Minority Populations

Sexual identity and gender identity are highly personal to each individual and may change over time. It is important to understand that sexual orientation and gender identity are distinct concepts: sexual orientation describes who a person feels romantic or sexual attraction toward whereas gender identity is a person’s innermost sense of gender of self, which does not necessarily correspond with a person's assigned sex at birth. The term “sexual minorities” typically refers to individuals who identify as lesbian, gay, bisexual, or any other non-heterosexual identity, whereas the term “gender minorities” refers to individuals who have gender identities that are not associated with their birth sex. Increasingly, there is recognition that self-identification of gender can be non-binary, with some individuals experiencing a gender identity that is outside the categories of man or woman. Sexual and gender minorities may include lesbian, gay, bisexual, transgender queer, intersex, and asexual (LGBTQIA) individuals, as well as others. Most available epidemiologic and medical literature has focused on lesbian, gay, bisexual, and transgender (LGBT) persons. This review on sexual and gender minority persons will focus on issues related to living with HIV, risk for acquiring HIV, and general health.

LGBT Populations in the United States

In the United States, a 2016 Gallup Poll reported that approximately 10 million persons self-identified as LGBT and this number steadily increased from 2012-2016 (Figure 1).[1] In this same poll, the authors estimated that about 4.1% of persons age 18 and older in the United States self-identified as LGBT, up from 3.5% in 2012 (Figure 2).[1] Persons born in 1980-1998 (so called "millennials") have the highest percentage identifying as LGBT and this number has increased from 5.8% to 7.3% during 2012-2016 (Figure 3).[1] The percentage of persons self-reporting as LGBT varies significantly based on race/ethnicity (Figure 4).[1] Sexual and gender minority populations in the United States experience significant health disparities and poorer health outcomes compared with heterosexual and cisgender peers.[2,3,4] Many sexual and gender minorities have higher rates of HIV infection and comprise a significant group that requires HIV medical care and HIV prevention.[5,6,7,8]
Terminology

Terms used to describe sexual orientation and gender identity are evolving, expanding; whether terms are considered negative or not varies between individuals and cultural communities. Whenever possible, it is best to use the terminology that the person in the clinic or hospital prefers to use to describe themselves. The following glossary is adapted based on terminology used in a number of excellent resources, including The Gay and Lesbian Alliance Against Defamation (GLAAD), the Fenway Institute, and the UC Davis LGBTQIA Resource Center.[9,10,11] The following terms are particularly relevant to this review and are listed in alphabetical order:

- **Asexual**: Someone who generally does not feel sexual attraction or a desire for partnered sexuality; some asexual have sexual activity.
- **Bisexual**: Someone who has sexual and/or emotional attraction to both men and women.
- **Bottom Surgery**: Describes gender affirming genital surgery. This is distinct from top surgery, which refers to gender affirming chest surgery.
- **Cisgender**: A person who identifies as the same sex they were assigned at birth.
- **Gay**: Someone who has sexual and/or emotional attraction to people of their same gender. The term “gay” is used more often to describe men than women, while “lesbian” is the more commonly used term to refer to women with same-gender attraction. The term “homosexual” is not recommended for use as it is considered offensive and derogatory by many people.
- **Gender**: The identity and/or expression as a man or a woman, or as an individual who falls between or outside the male-female binary categorization.
- **Gender Affirming Care**: A multidimensional process of aligning one’s social, medical, and legal status with one’s current gender identity.
- **Gender Affirming Surgeries**: A variety of surgical interventions that may be undertaken to align a person’s physical appearance with their gender identity, including but not limited to genital reconstruction.
- **Gender Dysphoria**: Describes discomfort or distress that may arise from a discrepancy between a person’s gender identify and that person’s sex as assigned at birth; this term should not be used interchangeably with gender nonconforming since only some individuals who are gender nonconforming experience gender dysphoria.
- **Gender Expression**: External manifestation of one’s gender, expressed through characteristics such as name, pronouns, clothing, haircut, and behavior.
- **Gender Fluid**: Describes a person who does not identify as having a fixed gender. Individuals may identify as male, female, or both. They may also identify as outside of the male-female binary construction.
- **Gender Identity**: A person’s gender identity describes a deep, internal sense of their gender.
- **Gender Nonconforming**: A term used to describe individuals whose gender expression is different from conventional expectations of masculinity or femininity. This term should not be used interchangeably with gender dysphoria since only some individuals who are gender nonconforming experience gender dysphoria.
- **Genderqueer**: A person who experiences their gender identity and/or expression as falling outside of the categories of man and woman. This term is not synonymous with transgender but rather is an example of a non-binary gender identity. Genderqueer individuals may identify as both male and female, neither male nor female, or a combination of male and female.
- **Gender Transition**: Describes the process when a person alters their body to affirm their desired gender. A transition may include a name change, a different pronoun preference, changes in legal documents, and gender-affirming medical treatments and/or surgeries. The term “gender affirmation” is often used interchangeably with gender transition.
- **GLBT**: Refers to gay, lesbian, bisexual, and transgender persons; often used interchangeably with LGBT (lesbian, gay, bisexual, and transgender).
- **Intersex**: This term is used to describe persons who without medical intervention have
variations in primary or secondary sex characteristics that do not fit neatly into society’s definitions of male or female.

- **Lesbian**: A woman whose sexual and emotional attraction is to other women. Some women may prefer to use the term lesbian while others may prefer to identify as gay or otherwise.
- **LGBT**: Refers to lesbian, gay, bisexual, and transgender; often used interchangeably with GLBT—for gay, lesbian, bisexual, and transgender.
- **LGBTQ**: Refers to lesbian, gay, bisexual, transgender, and queer; the Q at the end of LGBTQ may also refer to questioning.
- **LGBTQIA**: Refers to lesbian, gay, bisexual, transgender, queer (or questioning), intersex, and asexual.
- **MSM**: Refers to men who have sex with men. This usually refers to cisgender men and may include men who have sex only with men (gay men) and men who have sex with both men and women (bisexual men).
- **Non-binary**: refers to a transgender or nonconforming person who does not identify as either female or male.
- **Pansexual**: someone who has physical, romantic, and/or emotional attraction to persons of any sex or gender.
- **Queer**: Someone whose sexual identity is not heterosexual, and who may not identify as LGBT. The term genderqueer is often used to describe sexual identity.
- **Sexual Orientation**: Describes physical and/or emotional attraction to another person, which is distinct from gender identity. Sexual orientation is often considered to have three distinct dimensions: identity, behavior, and attraction. Use of the term sexual preference is not recommended.
- **Same Gender Loving**: A term used primarily in the African-American community to describe someone whose sexual and/or emotional attractions are to persons of the same gender.
- **Sex**: The sex (male or female) a person is assigned at birth.
- **They/Them/Their**: These are pronouns that are considered neutral and often used by persons who have a gender identity that is nonconforming or nonbinary.
- **Top Surgery**: Describes gender-affirming chest surgery. This is distinct from bottom surgery, which refers to gender-affirming genital surgery.
- **Transgender**: An umbrella term used to describe someone whose gender identity and/or gender expression differs from what is typically associated with the sex they were assigned at birth. Some now use the term person of trans experience instead of transgender.
- **Transgender Man**: A person who is assigned female at birth but identifies and lives as a man. A transgender man is sometimes referred to as transman, transmasculine, or female-to-male (FTM).
- **Transgender Woman**: A person who is assigned male at birth and identifies and lives as a woman. A transgender woman is sometimes referred to as transwoman, transfeminine, or male-to-female (MTF).
- **Transition**: Usually refers to the process of a transgender person altering their body to affirm their gender identity. A transition may include a name change, a different pronoun, changes in legal documents, and gender-affirming medical treatments and/or surgeries. This process is typically complicated and occurs over a prolonged period of time.
- **Transsexual**: Describes a person who has a gender identity that is opposite their gender assigned at birth. The use of the term transsexual is controversial and considered outdated by some. Most experts recommend that clinicians now use the term transgender instead of transsexual.
Medical Care for LGBT Persons

Challenges in Obtaining Health Insurance Coverage

Sexual and gender minority persons traditionally have faced significant barriers to health care, resulting in decreased access and utilization of services, particularly preventative care services.[12,13] Lack of health insurance has historically been a major barrier for LGBT persons, but the enactment of the Affordable Care Act and the expansion of marriage rights have served to expand health care insurance coverage and many now qualify for coverage through employers, Medicaid, Medicare, or Veterans Affairs.[14] Despite these recent advances, LGBT individuals continue to report more cost-related barriers to care and more unmet needs than non-LGBT peers.[13,15] Transgender individuals may have specific challenges to accessing appropriate care. Some states and programs specifically exclude coverage for care related to gender transition. State Medicaid programs generally fall into one of three categories related to gender transition medical services: (1) explicit coverage, (2) no explicit policy regarding gender affirmation therapies, and (3) explicit exclusion. Some states prohibit private health insurance plans sold in the state from excluding coverage for transition-related care.

Establishing an Informed and Welcoming Clinic Environment

Beyond insurance obstacles, sexual and gender minorities often struggle with finding medical providers who have training and experience working with LGBT populations and often face discrimination from health care providers.[13,16,17] In addition, gender identity is increasingly understood to exist along a spectrum, with some individuals not identifying exclusively as male or female, and the lack of data about non-binary gender minorities presents another obstacle to evidence-based care.[9] Creating an inclusive, culturally responsive, and welcoming clinical environment is an important first step in providing optimal clinical care services for LGBT persons and for reducing HIV acquisition and transmission risk within sexual and gender minority communities. This process can involve training in cultural awareness and diversity, along with educating clinical staff about the unique health needs of sexual and gender minority populations. For LGBT persons living with HIV, the most effective interventions to improve the HIV care cascade will differ based on the specific population.

LGBT Resources for Medical Providers

The lack of medical care data for LGBT and non-binary gender minorities presents an obstacle for optimal evidence-based care recommendations. Nevertheless, several organizations have generated excellent resources for the medical care of LGBT persons based on the best available evidence. These resources include general LGBT healthcare and those specific to LGBT persons living with HIV.

- **National LGBT Health Education Center:** The National LGBT Health Education Center—A Program of the Fenway Institute, “provides educational programs, resources, and consultation to health care organizations with the goal of optimizing quality, cost-effective health care for LGBT people.” Many educational resources and webinars are available on the website.

- **The Center of Excellence for Transgender Health:** The University of California at San Francisco’s Center of Excellence for Transgender Health website has access to a learning center that includes the extensive Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People.

- **Health Professionals Advancing LGBT Equality:** The organization Health Professionals Advancing LGBT Equality (formerly known as Gay & Lesbian Medical Association) includes information for patients and medical providers, a provider directory for medical providers for LGBT persons.
Cisgender Men who have Sex with Men (MSM)

HIV Epidemiology in MSM

In this epidemiology section, the term MSM will be used to describe men who have sex with men, regardless of whether they identify as gay, bisexual, or other men who have sex with men who do not identify with those terms. In the United States 2015 HIV prevalence estimates, MSM was reported as the HIV risk factor for an estimated 56% (632,300 of 1,122,000) of persons 13 years and older living with HIV, with an additional 5% reporting MSM and injection drug use as their risk factor for HIV (Figure 5).

In the United States, for the HIV incidence estimates in 2015, MSM was the identified HIV risk factor in 68% (26,200 of 38,500) of new HIV infections (Figure 6).

Comparing new diagnoses of HIV in MSM in 2016 among different racial ethnic groups shows the most number of cases, by far, in blacks/African Americans (Figure 7). Once diagnosed, black MSM also experience significantly lower rates of retention in care than non-black MSM, and this strongly correlates with increased mortality. In 2006, among the 26,570 MSM newly diagnosed with HIV, 11,678 (44%) were 20-29 years of age (Figure 8).

Transgender MSM also have a high risk of acquiring HIV; this is discussed in more detail in the Transgender Women and Transgender Men sections in this review.

Knowledge of HIV Status in MSM

In the United States, from 2010-2015, the percentage of MSM living with HIV who had undiagnosed HIV steadily declined, from 19.8% in 2010 to a low of 16.7% in 2015 (Figure 9). A limited number of states (Hawaii and New York) and cities/county (San Francisco and Seattle-King County) have met the federal benchmark goal of less than 10% of MSM living with HIV remaining undiagnosed.

Knowledge of their HIV status is important so that MSM with HIV have the opportunity to engage in care and attain health benefits from antiretroviral therapy, and MSM without HIV can take measures to prevent infection. For MSM with HIV, knowledge of their infection and treatment with antiretroviral therapy can dramatically reduce the risk of HIV transmission to sex partners.

Risk Factors for Acquiring HIV in MSM

A combination of individual-level and socio-structural factors underlie the elevated risk for HIV transmission and acquisition among MSM. Individual factors associated with HIV acquisition include number of sex partners, use of drugs or alcohol during sex, and condomless anal intercourse. In recent years, the selection of partners online has emerged as another individual-level risk factor, with data showing that MSM who initiate sexual encounters online have higher rates of condomless anal intercourse.

Structural risk factors that contribute to HIV risk are layered, with poverty, unemployment, incarceration, and racism converging to increase risk in vulnerable communities, most notably in African American MSM. Ethnographic research has shown that sexual orientation-based discrimination in home or social neighborhoods also increases HIV acquisition risk behavior.

Retention in Care in MSM

Recent data indicate that persons diagnosed with HIV infection but not retained in care are responsible for the highest percentage of HIV transmissions; in 2009, an estimated 54% of new HIV cases among MSM resulted from transmission of HIV from men who were aware of their HIV status but not retained in medical care, while 34% of transmissions were from MSM who were unaware of their HIV infection. These data highlight the important role engagement in care plays in preventing new HIV infections and are concerning given some studies show fewer than 50% of MSM with diagnosed HIV infection are retained in medical care.
Primary Medical Care for MSM

Primary medical care for MSM should incorporate the same elements of history taking, physical examination, and preventative health interventions as for other male patients while also focusing on health issues that disproportionately impact MSM—such as sexually transmitted infections, mental health problems, and problematic recreational drug and alcohol use.[35,36,37] Medical providers caring for MSM should have awareness that issues may surface due to past experiences of stigma, rejection, and physical and psychological abuse.[35,36] Developing a trusting relationship that encourages disclosure of relevant sexual and drug activity and mental health concerns is crucial to providing competent care that can meaningfully improve health outcomes.[35]

Mental Health in MSM

Men who have sex with men have approximately twice the rate of depression compared with heterosexual men.[35,36,38] Similarly, MSM who have HIV infection have a greater risk of major depressive disorder than MSM who do not have HIV infection, with one meta-analysis reporting that 10.4% of MSM living with HIV infection met criteria for depression compared with 5.7% of MSM without HIV infection.[39] Some studies suggest that HIV appears to amplify suicide risk, including MSM living with HIV, even for those receiving effective antiretroviral therapy.[40,41,42,43] It is important to note that estimates of depressive disorders in the overall population of individuals living with HIV have varied widely, based on the particular study subjects and the presence of factors such as stage of HIV disease and concurrent drug use.[39,44] Available data also show that MSM have increased prevalence of generalized anxiety disorder and panic disorder compared to heterosexual men.[35,38] Depression and anxiety among MSM living with HIV predict increased sexual risk behaviors, decreased medication adherence, and development of eating disorders.[45,46] Medical providers should be aware of the high rates of mood and anxiety disorders in MSM patients, perform appropriate screening and be prepared to offer or refer for appropriate behavioral counseling and pharmacologic treatment.

Smoking in MSM

Estimates of smoking rates among MSM are higher than in heterosexual men, with estimates in MSM ranging from 23 to 66% based on the particular study population and when the study was performed.[35,47,48,49] In a 2014 National Health Interview, 23.1% of gay or bisexual men reported smoking versus 18.7% of heterosexual men.[50] In the Multicenter AIDS Cohort Study (MACS), a study that enrolled more than 7,000 gay and bisexual men (with and without HIV infection) during the period 1984 to 2012, the prevalence of smoking was slightly higher among MSM living with HIV (44.1%) compared with MSM not living with HIV (37.9%).[51] Evidenced-based smoking cessation treatment options should be offered to MSM who smoke, regardless of HIV status.

Substance Use in MSM

Substance use is common among MSM, including a high rate of alcohol and illicit drug use (methamphetamine, cocaine, poppers, other club drugs) in the context of sex.[28,35,52,53,54] In a convenience sample of MSM living in 6 United States cities, one-third of the respondents reported alcohol use in the past week and 30% reported use of cocaine, poppers, or marijuana.[55,56,57] One study showed a correlation between heavy alcohol use in MSM with HIV and condomless anal intercourse with HIV-seronegative or HIV-seropositive partners.[53] One study found that recent use of methamphetamine was associated with increased levels of rectal mucosa inflammatory cytokines, regardless of HIV serostatus, a finding that may at least partially explain the increased risk of HIV acquisition and transmission in MSM who use methamphetamine.[58] Screening for substance use and referral for treatment (if indicated) is important for providers caring for MSM, though most interventions and treatment programs have not yet been tailored to the MSM population.[35]
Screening for Sexually Transmitted Infections in MSM

Compared with heterosexual men and women, MSM have higher rates of infection with HIV; syphilis; human papillomavirus (HPV) infection; herpes simplex virus 2 (HSV-2); hepatitis A, B, and C viruses; and fluoroquinolone-resistant gonorrhea.[35,37] Among MSM with HIV infection, rates of sexually transmitted infections are high, but are significantly decreased by risk reduction counseling and at least biannual screening.[59] Medical providers caring for MSM should have competence in taking a detailed sexual history, delivering patient-centered safer sex counseling, and offering appropriate sexually transmitted infection screening. According to the CDC 2015 STD Treatment Guidelines, the following screening schedule is recommended for sexually-active MSM living with HIV.[60,61]

- **Chlamydia**: Testing for chlamydia should be performed at the initial HIV visit and at least annually thereafter; testing is recommended every 3 to 6 months for MSM who have multiple partners or their sex partners have multiple partners. The testing for chlamydia should occur regardless of history of condom use. The preferred testing method is a *Chlamydia trachomatis* nucleic acid amplification test (NAAT). The testing sites should include all anatomic sites of exposure during sexual activity within the prior year, including urethral and/or rectal tests if the person has had potential exposures at those sites. A urine sample should be obtained to screen for urethral infection and a swab from the rectum is used as the screening method for rectal infection. Routine testing for oropharyngeal chlamydia infection is not recommended.

- **Gonorrhea**: Testing for gonorrhea should be performed at the initial HIV visit and at least annually thereafter; testing is recommended every 3 to 6 months for MSM who are sexually active and at risk, or have sex partners with multiple partners. The testing for gonorrhea should occur regardless of history of condom use. The preferred testing method for *Neisseria gonorrhoeae* is a NAAT. The testing sites should include all anatomic sites involved in sexual activity within the prior year, including urethral (urine), rectal (swab), and/or pharynx (swab).

- **Syphilis**: Testing for syphilis should be performed at the initial visit and at least annually thereafter; testing is recommended every 3 to 6 months if sexually active and at risk, or if sex partners have multiple partners. For sexually active MSM, testing for syphilis should occur regardless of the history of condom use. In the United States, rates of primary and second syphilis have increased significantly among MSM in recent years. All men newly diagnosed with HIV should save screening for syphilis. The preferred screening method is serologic testing, which requires a blood draw.

- **Hepatitis B Virus (HBV)**: Screening should consist of hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc total), and hepatitis B surface antibody (anti-HBs).[62] MSM who are nonimmune to hepatitis B should be vaccinated.

- **Hepatitis C Virus (HCV)**: Since 2000, HCV infection has emerged as an important sexually transmitted infection among MSM with HIV in the United States, Europe, Asia, and Australia.[63,64,65,66,67] Researchers have identified several risk factors associated with the sexual acquisition of HCV, including noninjection recreational drug use, condomless receptive anal intercourse, use of sex toys, and concurrent sexually transmitted diseases.[68] The CDC 2015 STD Guidelines and the HHS Guidelines for the Prevention and Treatment of Opportunistic Infections recommend annual HCV testing in sexually active MSM with HIV.[61,69] Screening for HCV infection is generally done with an antibody-based blood test, with all positive antibody tests followed by an HCV RNA NAAT to determine if the individual has resolved or chronic HCV infection.

Screening for Anal Cancer in MSM

The incidence of anal cancer in the general population is 2 to 3 per 100,000 person-years but among MSM the incidence is higher; for HIV-negative MSM, the rate is 5 per 100,000 person-years and for MSM living with HIV, the rate jumps to 77.8 per 100,000 person-years.[70] Anal Pap smear testing is an option to screen for HPV-induced anal dysplasia. Using atypical squamous cells of undetermined significance as the cutoff for abnormal, this test has an estimated sensitivity for
dysplasia of 81 to 87% and specificity of 39 to 41%.\[70\] However, long term clinical outcomes data for anal dysplasia screening in MSM are lacking. Existing national guidelines do not currently recommend routine screening for anal cancer in MSM, regardless of HIV status, but some state guidelines recommend routine anal pap testing among high risk populations such as MSM living with HIV.\[71,72\]

**Immunizations in MSM**

Men who have sex with men should receive routine, age-appropriate vaccinations according to the Advisory Committee for Immunization Practices (ACIP) immunization schedule.\[73,74\] The ACIP schedule also identifies MSM as a special health category for whom hepatitis A and hepatitis B vaccinations are indicated.\[74\] All MSM who are 26 years of age and younger, including those with HIV infection, should also receive the HPV vaccine series, if they have not already received it; note the HPV vaccine recommendation for MSM (give through age 26 years) is different than the recommendation to immunize heterosexual men (through age 21 years).\[73,74,75\]

**Nonoccupational Postexposure Prophylaxis (nPEP) in MSM**

In the United States, most persons receiving non-occupational postexposure prophylaxis (nPEP) or preexposure prophylaxis (PrEP) are MSM.\[76\] Accordingly, medical providers who care for MSM should develop competence to provide both nPEP and PrEP for appropriate MSM patients in order to prevent them from becoming infected with HIV. The use of nPEP involves a strategy whereby antiretroviral therapy is administered to an individual when potential high-risk exposure to HIV has occurred within the past 72 hours; in 2016 the Centers for Disease Control and Prevention (CDC) issued updated nPEP recommendations.\[77\] The topic of nPEP is addressed in detail in the review on Nonoccupational Postexposure Prophylaxis in Module 5 (Prevention of HIV).

**Preexposure Prophylaxis (PrEP) in MSM**

Similar to nPEP, most of the persons in the United States who are eligible for and are receiving preexposure prophylaxis (PrEP) are MSM. The administration of PrEP involves giving a daily dose of tenofovir DF-emtricitabine to persons not infected with HIV, but who have substantial risk for acquiring HIV infection. Several large clinical trials (iPrEx, IPERGAY, and PROUD) involving MSM with ongoing exposure to HIV have demonstrated a substantial reduction in the rate of HIV acquisition with the use of PrEP.\[78,79,80\] In 2012, the U.S. Food and Drug Administration (FDA) approved tenofovir DF-emtricitabine for PrEP, and in May 2014 the U.S. Public Health Service and the CDC issued a clinical practice guideline for the use of PrEP.\[81\] Sexually active MSM with risk factors for acquiring HIV, such as having an HIV-positive sex partner, recent bacterial sexually transmitted infection, high number of sex partners, history of inconsistent or no condom use, and/or commercial sex work, should be considered for PrEP, according to the U.S Public Health Service clinical practice guideline. In general, all sexually active MSM should be evaluated for the potential use of PrEP. The topic of PrEP is addressed in detail in the review on Preexposure Prophylaxis in Module 5 (Prevention of HIV).
Cisgender Women who have Sex with Women (WSW)

HIV Epidemiology in WSW

Based on available data, cisgender women who have sex only with other cisgender women appear to have a very low risk of acquiring HIV infection,[82,83] with only rare reported cases of HIV transmission.[84,85,86,87,88] There are no data on true incidence and prevalence of HIV infection among women who have sex only with women.

Knowledge of HIV Status in WSW

Data from the National HIV Surveillance System, which is used to estimate the percentage of persons infected with HIV who are aware and unaware of their infection status, does not include information specific to women who have sex with women (WSW). Early in the HIV epidemic, the possibility that HIV can be transmitted from female-to-female was questioned. Since then it has been recognized to rarely occur, but there are no yearly CDC surveillance data about HIV status among WSW, whether their sexual activity occurs exclusively with women or not.[87,89]

Risk Factors for Acquiring HIV in WSW

For many women, sexual identity categories do not necessarily align with sexual behavior.[90] For example, the National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 reported that among sexually-experienced women 19-59 years of age in the United States, 7.1% reported ever having sex with a woman and for these women 53% reported their sexual orientation as heterosexual, 28% reported as bisexual, and 19% as lesbian.[90] In one survey of 6,935 women who self-identified as lesbian, 77% reported they had at least one lifetime male partner.[91] In addition, in a separate survey, 96.6% of women who had ever had sex with women reported they had also previously had sex with a male partner.[90] Thus, when ascertaining HIV acquisition and transmission risks among WSW, it is important to clarify past and recent sexual history since women may have acquired HIV from a male partner.[90,92] In addition, WSW can acquire HIV from injection drug use.

Sexually Transmitted Infections in WSW

Relatively limited data exist regarding risk of sexually transmitted diseases, including HIV, among cisgender women who have sex with other cisgender women.[93,94] The following summarizes risk of STDs among WSW, based on available data, and as outlined in the 2015 STD Treatment Guidelines: (1) transmission of HPV can occur between female sex partners and infection is common, (2) transmission of HSV is inefficient, but can occur, (3) transmission of syphilis can occur but reports are rare, (4) transmission of Chlamydia trachomatis occurs more frequently than previously thought, (5) bacterial vaginosis is common.[60,95,96,97,98,99] Women who have sex with women often do not use barrier protection, both because of the perceived low risk of sexually transmitted infections and also because there is no risk of pregnancy with cisgender female partners.[100,101]

Primary Medical Care for WSW

In general, WSW should receive primary medical and preventative health care services similar to those provided to women who have only male partners.[36,102] When compared with heterosexual women, cisgender WSW were 30% less likely than heterosexual women to have an annual routine medical examination and bisexual women were more than twice as likely to not seek medical care.[103] It is important to create a nonjudgmental, welcoming, candid, and inclusive clinical environment. Given the very limited data on HIV in WSW, most of the content in the sections that follow will focus on general issues of health in WSW.
Mental Health in WSW

Several studies have suggested that WSW have higher rates of depression, anxiety, and suicidal ideation and/or suicide attempt as compared to other women.\[103,104,105,106] In the 2013 and 2014 National Health Interview Survey, lesbian women reported a 1.34-fold increased risk of moderate psychological stress and a 1.45-fold increased risk of severe psychological stress when compared with heterosexual women.\[107] As with other sexual minority groups, stress from discrimination and rejection has been proposed as one reason for the higher prevalence of mental health disorders. In short, sexual minorities, including WSW, are subject to institutionalized prejudice, social stress, and social exclusion that may translate to internal shame and expectations of rejection.\[7,36,105] Primary care providers should be aware of the increased prevalence of mood disorders in WSW and be prepared to offer or refer for appropriate behavioral counseling and pharmacologic treatment.

Smoking in WSW

Data from the Women’s Health Initiative, the 2013 and 2014 National Health Interview Survey, and other studies show that tobacco use is more common in lesbian and bisexual women compared to heterosexual women.\[102,103,108] Lesbian and bisexual women also have higher rates of e-cigarette use compared with heterosexual women.\[109] Evidence-based smoking cessation treatment options should be offered to WSW who smoke.

Substance Use in WSW

A large systematic review found that WSW are at significantly higher risk of alcohol dependence, drug dependence, and any substance use disorder compared with heterosexual women.\[105] A subsequent population-based survey confirmed that WSW have higher rates of binge drinking than other women.\[103] In the 2013 and 2014 National Health Interview Survey, lesbian women reported a 2.6-fold higher rate of heavy current alcohol consumption.\[107] Screening for substance use disorders should be offered to WSW, with referral to appropriate behavioral and pharmacologic treatment programs if needed.

Obesity in WSW

A recent systematic literature review of 37 studies found that, following adolescence, sexual minority women (lesbian or bisexual) had a higher body mass index than heterosexual women.\[110] Other studies also support this finding.\[111] The higher body mass index among lesbian and bisexual women does not necessarily correlate with higher prevalence of cardiovascular disease, hypertension, or diabetes.\[110,112] The reasons for greater prevalence of obesity among WSW have not been fully elucidated, but it does not appear to be associated with less healthy dietary patterns.\[113] Because higher body mass index has not translated to increased cardiovascular disease risk among WSW, it is unclear what interventions, if any, should be adopted for WSW who have elevated body mass index. Women who have sex with women who are unhappy with their body image should be linked to medical and community resources that are culturally responsive to WSW.

Screening for Breast, Cervical, and Anal Cancer in WSW

There is theoretical concern that WSW are at increased risk of breast cancer due to higher rates of nulliparity, smoking, obesity, and alcohol use.\[108] It is unclear, however, whether these behavioral factors, which are known to increase the risk of breast and gynecologic cancers, actually translate into significantly higher cancer rates in WSW; this uncertainty stems from the lack of data on sexual orientation in national databases and registries that collect information on cancer incidence and mortality.\[114] Because HPV infection is common in WSW, the 2015 STD Treatment Guidelines recommend offering cervical cancer screening to all women, regardless of sexual orientation or
sexual practices. [60] There are no recommendations to routinely perform screening for anal cancer in WSW (or in cisgender women who have sex with men). Since there are no unique guidelines for breast cancer screening in WSW, screening should follow general breast cancer screening guidelines for all women.[115,116]
Transgender Women

Epidemiology

In the United States, approximately 0.4 to 0.6% of adults self-identify as transgender, with recent surveys estimating 1.0 to 1.4 million transgender persons living in the United States.[117,118,119] Transgender women (male-to-female and also referred to as trans women) in the United States have an HIV prevalence of greater than 20%, which is markedly higher than in other adults of reproductive age.[120,121,122] In the United States, the HIV prevalence rates among transgender women differs significantly based on race, with an HIV prevalence of 56.3% among African American transgender women, 16.7% among white transgender women, and 16.1% among Hispanic transgender women.[120] The National HIV Surveillance System identified 1,974 transgender women newly diagnosed with HIV during 2009-2014.[123] Among the transgender women newly diagnosed with HIV, more than 60% were 20 to 34 years of age (Figure 10).[123] There were marked racial disparities among transgender women newly diagnosed with HIV, with blacks comprising 51% of these new diagnoses and Hispanics 29% (Figure 11).[123] Based on residence in the United States, the highest number of transgender persons diagnosed with HIV during 2009-2014 resided in the South (Figure 12).[123]

Knowledge of HIV Status

Transgender women are more likely to be unaware of their HIV status compared with other groups. As a result of a major emphasis on increased HIV screening and diagnosis, the overall proportion of persons living with HIV in the United States who are unaware of their HIV diagnosis has decreased from 25% in 2003 to 14% in 2011.[34,124] Among transgender women, however, lack of awareness of HIV status remains a significant problem.[120,125,126]

Risk Factors for Acquiring HIV

Multiple intersecting structural, interpersonal, and individual vulnerabilities place transgender women at disproportionate risk for acquiring HIV infection.[127,128] An early study conducted in San Francisco identified four risk factors independently associated with HIV seropositivity in transgender women: African American race, a history of injection drug use, low education level, and multiple sex partners.[122] Other studies have revealed that sexual activities that increase risk of HIV acquisition, including condomless anal intercourse, drug use during sex, and exchange of sex for money, are more common among transgender women than among other groups.[120,129,130] Several studies have shown that transgender women engaging in sex work are much more likely to have HIV infection compared with non-transgender female sex workers.[128,131,132] Although rates of injection drug use appear to be low among transgender women, needle sharing for the purpose of injecting hormones (or silicone) may serve as a potential route for HIV and HCV acquisition.[120,127] High rates of homelessness, incarceration, and unemployment further elevate HIV risk among transgender women. Compounding this considerable risk profile, transgender women can be hard to reach for prevention efforts because the population is not well defined, data collection methods generally do not distinguish between assigned sex and gender identity, and transgender persons with HIV are often marginalized by multiple layers of stigma.[133]

Medical Care for Transgender Women

The following information is intended to provide an introduction to and brief overview of medical care for transgender women and for non-binary individuals who desire feminization. Excellent comprehensive documents that provide guidance for gender-affirming care are available through the Center of Excellence for Transgender Health, Fenway Health, the Endocrine Society, and the World Professional Association for Transgender Health (WPATH).[9,134,135,136] We recommend reviewing and using these documents when providing gender-affirming clinical care. The Center of Excellence
for Transgender Health and Fenway Health also provide formal training in transgender medicine: WPATH Gender Education Initiative (GEI) and The National LGBT Health Education Center.[9, 137]

Approach to Gender-Affirming Care for Transgender Women

The approach to gender-affirming therapy for transgender women and gender non-binary persons desiring feminization is generally the same regardless of HIV status, except that drug interactions between hormonal therapies and antiretroviral agents need to be considered in persons with HIV.[138] For individuals desiring feminization, options include medical interventions (hormonal therapy), surgery (e.g. bilateral orchiectomy, feminizing vaginoplasty, breast augmentation, facial feminization procedures, tracheal cartilage shave, and voice surgery), and cosmetic procedures (e.g. electrolysis).[9, 134, 139] The decision to take gender-affirming hormones or to have gender-affirming surgery is a significant one, and a medical provider-client discussion regarding the risks and benefits of gender-affirming treatment is essential.[140, 141] Psychotherapy is generally recommended, but not required, for the receipt of gender-affirming treatment.[134]

Principles of Feminizing Hormone Therapy

The most common approach to feminizing hormone therapy is to use estrogen to promote female secondary sexual characteristics in conjunction with an antiandrogen to suppress male secondary sexual characteristics.[141] To date, no randomized controlled trials comparing various hormonal-affirming protocols have been conducted and management remains largely based on expert opinion.[9, 134, 136, 141] Prior to initiating hormonal therapy, WPATH recommends all of the following criteria should be met: (1) persistent, well-documented gender dysphoria, (2) capacity to make a fully informed decision about treatment, (3) adult (or legally able to give informed consent), and (4) reasonably controlled medical or mental health conditions, if present.[134] Note that additional criteria are required for the use of feminizing hormone therapy in children and adolescents. Since gender-affirming hormonal therapy is off-label and may be associated with serious complications, many experts recommend having the client sign an informed consent document prior to starting hormonal treatments; other experts recommend simply documenting the informed consent process in the medical chart.[9, 134, 141] A sample consent form is available in the Fenway Health document—The Medical Care of Transgender Persons.[9]

Goals of Feminizing Hormone Therapy

Specific feminizing goals may include breast development, redistribution of body subcutaneous fat, reduction in body hair, softening of the skin, diminution in muscle mass, atrophy of the testicles, and slowing of scalp hair loss.[141] Transition is a gradual process, with the onset of most feminizing effects occurring within several months (Figure 13); maximal feminizing effects usually require at least 2 to 3 years (Figure 14).[142] Transgender women naturally have varying levels of and tissue responses to estrogen and testosterone.[141] Most experts recommend monitoring serum estradiol and serum testosterone levels approximately every 3 months during the first year of feminizing hormone therapy (or until a stable level is reached) and then at least twice yearly thereafter, with a goal of obtaining levels equivalent to normal levels for premenopausal females—100-200 pg/mL for estradiol and less than 50 ng/dL for testosterone.[136] Doses of the estrogen and antiandrogen should be adjusted to maintain these levels. Some gender non-binary and other individuals may desire feminization but not full gender transition and therefore estradiol goals may be lower.

Estrogen Feminizing Hormone Therapy

The mainstay of all feminization protocols is estrogen therapy.[141] The estrogen dose required for adequate feminization is highly individual based on a person's goals. All transgender women and gender non-binary individuals initiating estrogen feminization therapy should start on a low dose and titrate upward as needed, depending on the clinical response. The doses required to achieve the desired effects are generally at least two to three times higher than doses typically used for
hormone replacement therapy in postmenopausal cisgender women.[9,141,143,144] Some individuals take doses far in excess of the recommended doses in an effort to achieve more rapid and greater responses, but this is not recommended due to potential adverse effects. Many types of estrogen products are available including various oral, transdermal, and injectable formulations; these different estrogen medications have activity at the same receptors and will generate similar effects if used at equipotent doses.[145] Some centers recommend obtaining informed consent prior to starting feminizing hormonal therapy; a sample consent form is available in the Fenway Health document—The Medical Care of Transgender Persons.[9] The following summarizes the major estrogen preparations used for feminizing hormone therapy.[9,134,136,141]

- **Oral Estrogen:** Use of oral or sublingual estradiol is relatively inexpensive and is easily titrated. Multiple brands of oral and sublingual estradiol (17 beta-estradiol) are available; the sublingual preparations are more commonly used than oral. The starting dose for estradiol is usually 2 mg once daily orally and increased to 4 mg once daily after 4 to 12 weeks; most dissolve the tablet under the tongue. The dose should be titrated and adjusted based on clinical response and serum estradiol levels; the maximum recommended dose of estradiol is 6 mg/day. Oral or sublingual estrogen use may cause a higher risk of venous thromboembolism than injectable or transdermal forms of estrogen. Ethinyl estradiol, which is a synthetic estrogen used in oral contraceptive preparations, or conjugated equine estrogen tablets are not recommended for feminizing hormonal therapy because of an increased risk of venous thromboembolism and/or cardiovascular disease.

- **Transdermal Estrogen:** The use of transdermal estradiol is preferred by many experts for feminizing hormone therapy because the transdermal preparation provides a steady level of estrogen and overall lower estrogen exposure. The lower exposure to estrogen is particularly important for individuals who have higher baseline risk of thromboembolism (e.g. smokers, those age 40 or older, or those with a history of venous thromboembolism). The estrogen patches are more expensive than most oral estrogens and may not be covered by insurance. In addition, transdermal estrogen avoids first-pass liver metabolism and thus may have an advantage over oral agents in the setting of liver disease. There are many brands of estradiol transdermal; the usual starting dose is 0.025 mg or 0.05 mg applied once or twice weekly and increased over 4 to 12 weeks to a dose of 0.1 mg twice weekly.

- **Parenteral Estrogen:** Parenteral formulations of estrogen are used less frequently but may be a good option for some individuals, especially if the oral or transdermal preparations fail to achieve target estradiol levels. The recommended starting dose for estradiol valerate is 5 to 10 mg intramuscular (IM) every 2 weeks, increasing to a usual maintenance dose of 10 to 20 mg IM every 2 weeks. The estradiol cypionate recommended dose is 2 to 10 mg IM every week.

### Antiandrogen Feminizing Treatments

Antiandrogens are used to lower testosterone levels (or block tissue effects of testosterone) and thereby reduce the doses of estrogens required for feminization.[141,142,143,146] The most common antiandrogen strategies used for this purpose consist a combination of one or more of the following: androgen blockers (e.g. spironolactone), 5-alpha reductase inhibitors (e.g. finasteride and dutasteride), and bilateral orchiectomy surgery.[9,136,141] Most experts recommend use of spironolactone as the first-line antiandrogen approach with gender non-binary persons desiring feminization. If a person has a bilateral orchiectomy, they will no longer require antiandrogen therapy.

- **Spironolactone:** Most experts in the United States recommend spironolactone as the antiandrogen agent of choice for transgender women or gender non-binary individuals who desire feminization. This medication works by directly inhibiting testosterone secretion and by inhibiting androgen binding to androgen receptors. The dose of spironolactone ranges from 25 to 400 mg per day. The usual starting dose is 25 to 50 mg once daily, increasing every 2 to 4 weeks to a typical dose of 200 mg once daily (or 100 mg twice daily). The
maximum dose is 200 mg twice daily.

- **5-Alpha Reductase Inhibitors**: The 5-alpha reductase inhibitors work as antiandrogens by partially blocking the conversion of testosterone to the more potent androgen dihydrotestosterone. These agents have relatively weak activity in persons with low testosterone levels (low substrate). Two 5-alpha reductase inhibitors—finasteride and dutasteride—have been used as a component of feminizing therapy. Finasteride is usually started at a dose of 1 mg once per day and titrated to desired effect, up to a usual dose of 2.5-5 mg once daily. Dutasteride is given at a dose of 0.5 mg once daily. The 5-alpha reductase inhibitors are often used in transgender women or gender non-binary persons who have male pattern baldness.

- **Progestins**: The use of progestins, such as medroxyprogesterone acetate or micronized progesterone can suppress testosterone secretion, but the use of progestins for trans feminine individuals is controversial. Many experts do not advise routine use of progestins as part of feminization therapy because of increased risk of cardiovascular disease and breast cancer, particularly in older persons who are also taking conjugated estrogen.

- **Gonadotropin Releasing Hormone (GnRH) Agonists**: The GnRH agonists are synthetic analogs of GnRH chronic use causes down-regulation of GnRH receptors, which results in decreased secretion of sex hormones (androgen and estradiol). These agents are also referred to as luteinizing releasing hormone agonists (LHRH). Specific agents occasionally used as part of feminization therapy include leuprolide, goserelin, and nafarelin. These GnRH agonists are very expensive and typically reserved for delaying puberty in transgender youth. The use of GnRH agonists is not part of routine feminization therapy for transgender adult women. When these agents are used, the typical doses are leuprolide 3.75 mg to 7.5 mg IM once monthly and goserelin 3.6 mg subcutaneous implant monthly.

- **Orchiectomy**: Bilateral orchiectomy may be considered for select transgender women who are intolerant of antiandrogen therapy; if the scrotum is removed with the orchiectomy, it will reduce the amount of skin available for labiaplasty, should labiaplasty be desired in the future.

**Potential Adverse Effects of Feminizing Hormonal Therapy**

Estrogen therapy may cause a wide range of adverse effects, including venous thromboembolism, cardiovascular disease, depression, hypertension, hyperthyroidism, glucose abnormalities, sexual dysfunction, and prolactinoma. The use of estrogens is contraindicated in anyone with known estrogen-responsive cancer and should be used cautiously in patients with a history of thromboembolism, severe thrombophlebitis, diabetes, liver disease, renal disease, cardiac disease, hyperlipidemia, preexisting biliary disease, or a strong family history of estrogen-responsive malignancy. Smokers should be counseled to quit prior to starting estrogen therapy. The risks and benefits must be reviewed with patients prior to starting estrogen therapy. Side effects associated with spironolactone therapy include hypotension and hyperkalemia, and the drug is contraindicated in those with renal insufficiency or baseline serum potassium of greater than 5.5 mEq/L.

**Monitoring on Feminizing Hormone Therapy**

Regardless of the regimen chosen, all persons receiving gender-affirming hormonal treatment require close follow-up to evaluate effectiveness of the therapy and to monitor for adverse effects. The following summarizes recommendations for routine baseline laboratory studies and laboratory monitoring:

- **Baseline Laboratory Studies**: The recommended routine baseline studies for individuals initiating hormonal feminizing therapy should include a basic metabolic panel (including blood urea nitrogen, creatinine, and potassium), aminotransferase levels, lipid profile, and a fasting glucose or hemoglobin A1c level. A baseline prolactin level is indicated only if the patient has a history of hyperprolactinemia or pituitary adenoma, or is also taking medications that increase prolactin levels, such as antipsychotics.
Monitoring Serum Estradiol and Testosterone Levels: Most experts recommend monitoring serum estradiol and serum testosterone approximately every 3 months during the first year of transition (or until a stable level is reached) and then at least twice yearly thereafter, with a goal for levels equivalent to normal levels for premenopausal females—100 to 200 pg/mL for estradiol and less than 50 ng/dL for testosterone. The doses of estrogens and antiandrogens should be adjusted to maintain these levels. The Center of Excellence for Transgender Health protocols also specify appropriate intervals for measurement of various hormone levels.

Monitoring for Toxicity: For persons receiving spironolactone, a serum potassium, blood urea nitrogen, and creatinine should be checked 2 to 4 weeks after starting or changing the dose of spironolactone. Routine twice yearly monitoring should include a basic metabolic panel (including blood glucose, potassium, blood urea nitrogen, and creatinine) and lipid panel. A serum prolactin level should be performed yearly as a screen for prolactinoma, which can develop in transgender women or gender non-binary individuals taking estrogen therapy; some experts only recommend obtaining prolactin levels for 2 to 3 years, assuming the levels remain normal and the person has no symptoms that would suggest a prolactinoma.

Drug Interactions between Hormonal and Antiretroviral Treatments

Hormonal therapies, like other medications, can interact with other pharmacologic treatments. Although drug interactions can occur between hormonal therapies and certain antiretroviral medications, there are no known life-threatening interactions, and taking antiretroviral medications for HIV infection is not a contraindication to starting hormonal treatment. Some protease inhibitors and nonnucleoside reverse transcriptase inhibitors may interact with estrogens, since they all undergo metabolism through the cytochrome P450 system. No studies have specifically examined these interactions in the context of gender-affirming care, but pharmacokinetic data are available for the interactions of antiretroviral agents with estrogens and progestins in cisgender women. In general, boosted protease inhibitors and the nonnucleoside reverse transcriptase inhibitors efavirenz, etravirine, and nevirapine (but not rilpivirine) may decrease blood levels of estrogens. Thus, clinicians should monitor the effects of hormonal therapies and adjust doses of estrogens or antiandrogens if indicated. There are no known drug interactions between ethinyl estradiol and nucleoside reverse transcriptase inhibitors, integrase inhibitors, or CCR5 antagonists. There are no known significant drug interactions between the most commonly used anti-androgen, spironolactone, and antiretroviral medications.

Gender-Affirming Surgery

Many different surgical treatments are available for transgender women and gender non-binary individuals, depending on their needs and goals. Options include breast and/or chest surgery (“top surgery”), genital surgery (“bottom surgery”), and other interventions, such as facial feminization surgery, vocal cord surgery, and thyroid cartilage reduction. A full discussion of surgical options and outcomes is beyond the scope of this Topic Review but it is important to note that many studies show that surgical intervention can improve subjective well-being and sexual function.

Health Care Maintenance

Cardiovascular Disease

Data on the effects of estrogen on cardiovascular disease risk in transgender women are mixed. Some older studies suggested transgender women have an increased risk of developing cardiovascular disease, but these studies were confounded by the use of ethinyl estradiol, a formulation of estrogen that is not recommended for transgender women. There are no cardiovascular disease screening guidelines that are specific to transgender women or gender non-
binary individuals taking estrogen. Because many experts now consider HIV as an independent cardiovascular risk factor, clinicians caring for transgender women with HIV infection should screen for and consider aggressive management of cardiovascular risk factors.

**Bone Health**

It remains unclear whether assessment of bone mineral density in transgender women should be based on sex assigned at birth or assigned gender. In addition, there is no consensus for obtaining bone mineral density testing in transgender women. The Center of Excellence for Transgender Health recommends (1) obtaining bone density evaluation in all transgender persons beginning at age 65 and (2) considering bone density evaluation in transgender women aged 50 to 64 years who have osteoporosis risk factors or who, at any age, had orchiectomy surgery and have not taken estrogen therapy for at least 5 years. Because HIV infection and some antiretroviral medications can increase the risk of osteoporosis, transgender women with HIV may have an even higher risk of developing osteoporosis. The HIV Primary Care Guidelines recommend bone density screening for all men living with HIV older than age 50, postmenopausal women living with HIV, and those individuals with other osteoporosis risk factors; no specific recommendations exist for transgender women with HIV.

**Cancer Screening**

No standardized cancer screening recommendations exist for the transgender or gender non-binary populations. In general, the recommendation for cancer screening should be based on whether the body part meets criteria for screening. For example, transgender women without known elevated breast cancer risk should follow standard breast screening guidelines. For transgender women, most experts recommend prostate cancer screening in accordance with guidelines for the general population. Note that for transgender women on estrogen therapy, the prostate volume is reduced and prostate specific antigen (PSA) will be lowered; some experts have recommended adjusting the upper limit of normal to 1.0 ng/mL in transgender women receiving hormonal therapy.

**Mental Health in Transgender Women**

Transgender and gender non-binary individuals are at risk for mental health disorders and psychological distress due to multiple overlapping risk factors, including gender dysphoria, high rates of psychological and physical abuse, social exclusion, stigma, and victimization. Although data are lacking on exact prevalence rates, several diagnoses have been found at higher frequency among transgender individuals compared to the general population, including depression, anxiety, posttraumatic stress disorder, and substance use disorders. In a prospective study of 230 transgender women of color aged 19 to 59 years in the New York City area, the 12-month prevalence of major depression was more than 5 times higher than corresponding rates in the general population. A retrospective study at an urban community health center found that transgender youth aged 12 to 29 years had a 2-fold to 3-fold increased risk of depression, anxiety disorder, and both inpatient and outpatient mental health treatment. For transgender women living with HIV, the burden of mental health disorders is likely even higher than in transgender women without HIV infection. The burden of mental health disorders is reflected in the high rate of suicide attempts among transgender individuals; across Canada, Europe, and the United States, the lifetime risk of a suicide attempt for a transgender person is estimated at 22 to 43%. Transgender women living with HIV infection likely have even higher suicide risk. Unfortunately, transgender individuals with mental health disorders often face health care discrimination and have difficulty finding appropriate medical and psychiatric providers, as well as difficulty accessing emergency care.

**Substance Use in Transgender Women**
Transgender women have a higher prevalence of substance use disorders compared with the general population. The prevalence of substance use disorders is particularly high among transgender female youth.\cite{168,169} Transgender women are at particularly high risk of discrimination and victimization, and research has shown that as many as 35% of transgender people who experience discrimination use drugs and alcohol as a coping mechanism.\cite{168} Another study demonstrated that transgender women who experience physical or psychological abuse due to gender expression or identity have 3- to 4-fold higher odds of alcohol, marijuana, or cocaine use, as well as 8-fold higher odds of any drug use.\cite{162} Several demographic, social, and structural risk factors also are associated with substance use among the transgender population, including older age, intimate partner violence, depression, posttraumatic stress disorder, unstable housing, housing discrimination, and engagement in sex work.\cite{168} There is limited research into substance use among transgender women living with HIV, but given high rates of substance abuse among both persons living with HIV and the transgender population, it is likely that transgender women with HIV infection are at high risk for substance use.\cite{170,171} Substance use is likely one factor that contributes to high HIV prevalence rates among transgender women.\cite{169}
Transgender Men

Epidemiology

In the United States, there are an estimated 1.0 to 1.4 million adults who self-identify as transgender. Among transgender men living in the United States an estimated 5 to 10% are living with HIV. The National HIV Surveillance System identified 361 transgender men newly diagnosed with HIV during 2009-2014 and 30% of these new HIV diagnoses occurred in persons 25-34 years of age. There were marked racial disparities among transgender women diagnosed with HIV, with blacks accounting for 58% of these new diagnoses. Based on residence where the individual was diagnosed with HIV, the most, by far, occurred in the South.

Knowledge of HIV Status

Little is known about awareness of HIV status in transgender men. Additional research and reporting are needed to better estimate the undiagnosed HIV fraction in transgender men in the United States.

Risk Factors for Acquiring HIV

Transgender men appear to face similar discrimination, stigma, victimization, and rates of depression and suicide as transgender women, yet risk of acquiring HIV risk is generally lower than in transgender women. Some experts, however, have argued that the risk of acquiring HIV in transgender men has been underestimated. A study of transgender men in San Francisco identified several HIV risk factors, including housing insecurity, injection drug use, and a high number of sex partners. Transgender men who have sex with cisgender men or transgender women represent a subpopulation of transgender men that may be at elevated HIV risk. More research is needed to better estimate HIV risk and to guide HIV prevention efforts among the transgender men.

Medical Care for Transgender Men

The following information is intended to provide an introduction to and brief overview of medical care for transgender men and gender non-binary persons desiring masculinizing therapy. Excellent comprehensive documents that provide guidance for gender-affirming care are available through the Center of Excellence for Transgender Health, Fenway Health, the Endocrine Society, and the World Professional Association for Transgender Health (WPATH). We recommend reviewing and using these documents if providing gender-affirming clinical care for transgender men or gender non-binary persons. The Center of Excellence for Transgender Health and Fenway Health also provide formal training in transgender medicine: WPATH Gender Education Initiative (GEI) and The National LGBT Health Education Center.

Approach to Gender-Affirming Care for Transgender Men

The approach to gender-affirming therapy for transgender men and for gender non-binary persons is usually the same regardless of HIV infection status. For individuals desiring female-to-male transition or masculinizing therapy, options include medical interventions (hormonal therapy), surgery (e.g. breast reduction, phalloplasty, scrotoplasty, and hysterectomy). The decision to take gender-affirming hormones or to have gender-affirming surgery is a significant one, and a medical provider-client discussion regarding the risks and benefits of gender-affirming treatment is essential. Psychotherapy is generally recommended, but not required, for the receipt of gender-affirming treatment.

Principles of Masculinizing Hormone Therapy
The same general principles of hormone therapy apply to transgender men (and non-binary persons desiring masculinizing therapy) as with transgender women, including the requirement for a thorough baseline evaluation to ensure that patients have well-documented, persistent gender dysphoria, capacity and age of majority to make fully-informed decisions, and reasonably controlled physical and mental health conditions.[134]

**Goals of Masculinizing Hormone Therapy**

Testosterone therapy is the mainstay of masculinizing therapy for transgender men, and it can be delivered through the intramuscular or topical route. Specific masculinizing goals often include an increase in facial and body hair, increase in muscle mass, decrease in breast mass, deepening of the voice, and reduction or cessation of menses. Some of these effects, such as changes in voice pitch, muscle mass, and hair growth, usually start to occur within months (Figure 18), but masculinization is a gradual process and it generally takes years to experience maximal masculinization effects (Figure 19).[134,136,176] For transgender men on long-term testosterone therapy, most experts recommend maintaining serum total testosterone levels in the male physiologic male range of 300 to 800 ng/dL and serum estradiol levels less than 50 pg/mL; ideal levels may be different for gender non-binary persons and depend on an individual person’s goals.

**Testosterone Masculinizing Hormone Therapy**

In general, daily administration of transdermal testosterone (gel or patches) approximates physiologic testosterone levels better than parenteral testosterone, which is typically given every 1 to 2 weeks. The doses listed below for testosterone masculinizing therapy are suggested initial and maintenance doses.[9,136,176] The long-acting injectable testosterone undecanoate is not available in the United States. The maintenance doses may need to be adjusted based on testosterone levels, desired masculinizing effects, and adverse effects. Some individuals who desire a more androgenous appearance may prefer lower-dose testosterone therapy. Common physiologic effects in transgender men and gender non-binary persons receiving testosterone include increased muscle mass and strength, decreased fat mass, acne, increased facial and body hair, scalp hair loss, deepening of the voice, vaginal atrophy, clitoromegaly, cessation of menses, and increased libido.[136]

- **Parenteral Testosterone**: The usual starting dose of testosterone enanthate (or testosterone cypionate) is 40 to 80 mg IM weekly and increased by 20 to 40 mg every 2 to 4 weeks to reach a maintenance dose of 100 to 200 mg IM every 2 weeks (or 50 to 100 mg IM every week).
- **Long-Acting Parenteral Testosterone**: The usual starting dose for long-acting injectable testosterone undecanoate is a 750 mg IM initial dose, 750 mg IM repeated 4 weeks later, with a maintenance dose of 1,000 mg IM every 10 weeks. As an alternative to IM testosterone, subcutaneous testosterone is considered safe and acceptable, typically with less pain and local side effects compared with IM injections.
- **Transdermal Testosterone Gel**: There are several testosterone gel preparations. The most common is testosterone 1.6% gel. The usual starting dose for testosterone gel (1.6%) is 12.5 mg daily, with an increase by 12.5 to 25 mg per day every 2 to 4 weeks, until a maintenance dose of 50 to 100 mg per day is reached.
- **Transdermal Testosterone Patch**: The initial dose for the transdermal testosterone patch is a 2.0 to 2.5 mg patch applied daily and replaced every 24 hours; after 2 to 4 weeks the dose can be increased to 4.0 to 5.0 mg per day. For the testosterone transdermal patch, the usual maintenance dose is 6.0 to 7.5 mg per day.

**Medications for Cessation of Menses**

For transgender men and gender non-binary persons who retain their uterus, testosterone therapy alone may cause cessation of menses within 1 to 6 months.[136] For individuals who continue to have uterine bleeding after several months of testosterone, options include use of a gestational
agent, such as medroxyprogesterone acetate at a dose of 5 to 10 mg daily, or endometrial ablation. Transgender men taking testosterone still have the potential to become pregnant and birth control should always be recommended. Receiving testosterone while pregnant could cause serious toxicity to the fetus; thus, any person receiving testosterone who becomes pregnant should stop the testosterone immediately.

**Potential Adverse Effects of Testosterone Therapy**

Common adverse effects of testosterone therapy include erythrocytosis (hematocrit greater than 50%), hepatotoxicity, coronary artery disease, decreased HDL cholesterol, increased triglycerides, hypertension, weight gain, vaginal atrophy, acne, and male pattern baldness.\[9,136,176\] In addition, masculinizing hormone therapy may cause emotional effects, such as irritability and anger.

**Monitoring of Persons on Masculinizing Hormone Therapy**

All patients receiving gender-affirming hormonal treatment require close follow-up to evaluate effectiveness of the therapy and to monitor for adverse effects. The following summarizes recommendations for routine baseline laboratory studies and laboratory monitoring:\[9,136,176\]

- **Baseline Laboratory Studies:** The recommended baseline studies for individuals initiating hormonal masculinizing therapy with testosterone include a complete blood count, lipid panel, basic metabolic panel (including, blood urea nitrogen, creatinine, and potassium), aminotransferase levels, and a fasting glucose or hemoglobin A1c level.

- **Monitoring Testosterone Levels:** Most experts recommend monitoring serum testosterone levels approximately every 3 months during the first year of transition. Subsequently, it reasonable to follow testosterone levels every 6 to 12 months, assuming they remain in the goal range. The serum total testosterone level should fall into the male physiologic male range of 400 to 800 ng/dL. The timing of when to check a testosterone level varies based on the testosterone preparation. For testosterone enanthate or testosterone cypionate, it is recommended to check midway between injections; for transdermal testosterone, it is optimal to check at least 2 hours after application (and persons must have been using the topical testosterone for at least 1 week). Maintaining levels higher than 800 ng/dL ("supraphysiologic" levels) significantly increases the risk of testosterone-related adverse effects and is not recommended.\[136\] There may be some instances in which calculation of bioavailable free testosterone may help in clinical decision making and there may be instances in which checking an estradiol is indicated, though it is not done routinely; more detail on this is available in guidelines from the Center of Excellence for Transgender Health.\[176\]

- **Monitoring for Toxicity:** For persons receiving testosterone, the hemoglobin (or hematocrit) should be followed every 3 months for the first year, then every 6 to 12 months thereafter, assuming it remains in the normal male range (the normal male range should be used, although labs may report normal ranges for women for a patient with female sex assigned at birth). Lipid panel and aminotransferase levels should be followed every 6 to 12 months.

**Gender Affirming Surgery**

Masculinizing surgical options include chest reconstruction ("top surgery") and genital surgery ("bottom surgery"), genital gender-affirming surgeries include hysterectomy, oophorectomy, vaginectomy, scrotoplasty, phalloplasty, and/or metoidioplasty.\[134,153,154\] Of these surgeries, phalloplasty carries the highest complication rate, but case series have demonstrated high levels of patient satisfaction following the procedure.\[177,178\] A full discussion of surgical options and outcomes is beyond the scope of this Topic Review, but is addressed in other more comprehensive resources.\[134,153,154\]
Health Care Maintenance

Compared with the available literature on transgender women, less research and guidance exist on the health needs of transgender men.\[175,179,180\]

- **Cardiovascular Disease**: There are no cardiovascular screening guidelines that are specific to transgender men with or without HIV infection. Available data suggest that transgender men have cardiovascular risk comparable to non-transgender men. Transgender men have a relatively high rate of smoking (approximately 25%) and all smokers should be encouraged to stop smoking.
- **Bone Health**: Both testosterone and estrogen are protective against osteoporosis. The Center of Excellence for Transgender Health recommends the same osteoporosis screening for transgender men as for transgender women; bone density evaluation should be performed in all transgender men beginning at age 65, in transgender men aged 50 to 64 years with osteoporosis risk factors, and in transgender men of any age who have had oophorectomy and who do not use hormone replacement for at least 5 years.\[176\]
- **Cancer Screening**: Transgender men and gender non-binary persons who retain a cervix and uterus should undergo the same screening for cervical cancer as for cisgender women; they should also receive education about signs and symptoms of endometrial cancer.\[136,159\] Mammography is not indicated following gender-affirming bilateral mastectomy; transgender men who have undergone mastectomy surgery should have an annual breast examination, with follow-up mammogram if abnormalities are found in clinical practice.\[136\] Transgender men who do not have mastectomy surgery should have routine mammogram screening performed based on recommendations for cisgender women. Transgender men receiving testosterone do not develop a prostate and therefore there is no risk of developing prostate cancer.

Mental Health

There are high rates of depression and suicide in transgender persons, including trans men, which reflects the elevated burden of mental health issues. One early study found that more than half of transgender men had depression and almost one-third had attempted suicide.\[122\] Unfortunately, many studies related to mental health in transgender persons either do not differentiate between transgender men and women, or had very low numbers of transgender men. Thus, the burden of mental health disorders and suicide among transgender men is not well characterized. Suicide risk has been linked to victimization, discrimination, and harassment based on transgender status.\[181\] Recent evidence suggests that access to gender-affirming testosterone therapy improves mental health for many transgender men.\[182\]

Drug Interactions Between Hormonal and Antiretroviral Treatments

There are limited data on drug interactions between testosterone and antiretroviral therapy; based on available data, there are no known significant drug interactions between testosterone and any antiretroviral medication.\[150\]
Summary Points

- Sexual and gender minority populations in the United States experience significant barriers to health care, resulting in lower utilization of services, wide health disparities, and poorer health outcomes compared with heterosexual and cisgender peers.
- Terminology to describe sexual and gender minority populations is dynamic and ever-changing. Whenever possible, it is best to ask and use the terminology the individual uses.
- Knowledge of HIV status has improved to approximately 87% among men who have sex with men (MSM) but remains below the target of 90% among transgender women.
- In 2015, cisgender men who have sex with men accounted for 56% of all persons living with HIV in the United States.
- Although HIV prevalence is low among cisgender women who have sex with women, they may be at risk for sexually transmitted infections and they generally access healthcare less frequently than heterosexual women.
- Transgender women have 35 times the risk of acquiring HIV infection than other adults of reproductive age, and HIV prevalence is twice as high among African American transgender women compared with transgender women of other racial and ethnic groups.
- Transgender men have an HIV prevalence of approximately 5 to 10% and most transgender men newly diagnosed with HIV are 25 to 34 years of age.
- Primary care for sexual and gender minorities should incorporate routine preventative care and focus on issues that disproportionately affect these populations, particularly mental health disorders, substance use disorders, and sexually transmitted infections.
- Gender affirmation is a multidimensional process of aligning one’s social, medical, and legal status with one’s current gender identity.
- Treatment with hormonal therapy or surgery (or both) may alleviate distress due to gender dysphoria and is a key part of gender-affirming treatment for many individuals; goals of this therapy depend on an individual’s desired effects.
- Medical providers should be aware of potential benefits and risks of gender-affirming hormone therapies and follow available evidence-informed protocols.
Citations


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[PubMed Abstract]


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Figures

Figure 1 Number of Adults Identifying as LGBT —United States, 2012-2016

Figure 2 Percentage of Adults Identifying as LGBT —United States, 2012-2016

Figure 3 Percentage of Adults Identifying as LGBT, by Age Group: United States, 2012-2016

Figure 4 Percentage of Adults Identifying as LGBT, by Race/Ethnicity: United States, 2016

Figure 5 Estimated Number of Persons Living with HIV in United States, by Transmission Category, 2015


Total = 1,122,900

Male-to-Male Sex 56%
Male-to-Male Sex & Injection Drug Use 5%
Female Heterosexual 18%
Male Heterosexual 9%
Female Injection Drug Use 5%
Male Injection Drug Use 7%
+Other <1%

*Other = hemophilia, blood transfusion, and risk factor not reported or identified.

*Estimate for persons ≥13 years of age living with diagnosed or undiagnosed HIV infection
**Figure 6 Estimates of New HIV Infections in the United States, by Transmission Category, 2015**


<table>
<thead>
<tr>
<th>Transmission Category</th>
<th>Estimated Number of New HIV Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-to-Male Sexual Contact</td>
<td>26,200</td>
</tr>
<tr>
<td>Male Injection Drug Use</td>
<td>1,300</td>
</tr>
<tr>
<td>Female Injection Drug Use</td>
<td>930</td>
</tr>
<tr>
<td>Male-male sexual and Injection Drug Use</td>
<td>1,200</td>
</tr>
<tr>
<td>Males with Heterosexual Contact</td>
<td>2,800</td>
</tr>
<tr>
<td>Females with Heterosexual Contact</td>
<td>6,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38,500</strong></td>
</tr>
</tbody>
</table>
Figure 7 Diagnosis of HIV Infection in MSM in United States by Race/Ethnicity, 2016

Figure 8 New Diagnosis of HIV Infection in MSM in United States, by Age Group, 2016

Figure 9 Percentage of MSM with Undiagnosed HIV in United States, 2010-2015

Figure 10 Transgender Women (Male to Female) Diagnosed with HIV by Age Group, United States, 2009-2014

Figure 11 Transgender Women (Male to Female) Diagnosed with HIV by Race/Ethnicity, United States, 2009-2014


<table>
<thead>
<tr>
<th>Racial/Ethnic Group</th>
<th>New HIV Diagnosis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>13</td>
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<tr>
<td>Asian</td>
<td>37</td>
</tr>
<tr>
<td>Black/African American</td>
<td>1,002</td>
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<tr>
<td>Hispanic/Latino</td>
<td>578</td>
</tr>
<tr>
<td>Multiple Race</td>
<td>121</td>
</tr>
<tr>
<td>Native Hawaiian/Other Pacific Islander</td>
<td>11</td>
</tr>
<tr>
<td>White</td>
<td>212</td>
</tr>
</tbody>
</table>
Figure 12 Transgender Women (Male to Female) Diagnosed with HIV by Region, United States, 2009-2014

**Figure 13 Onset of Feminizing Effects with Gender-Affirming Hormone Therapy in Transgender Women**

This figure shows approximate time for onset of certain effects with gender-affirming hormone therapy in transgender women. Note the onset of male sexual dysfunction and scalp hair changes is highly variable. Gender-affirming hormone therapy in transgender women has little impact on voice changes.

Figure 14 Time to Maximum Feminizing Effects with Gender-Affirming Hormone Therapy in Transgender Women

This figure shows approximate time for maximal effects with gender-affirming hormone therapy in transgender women. Note the time to maximal effect of male sexual dysfunction and scalp hair changes is highly variable. The time for maximal effect on softening of skin is not known. The time to maximal effect for decreased sperm production and for decreased hair growth is greater than 3 years.

Figure 15 Transgender Men (Female to Male) Diagnosed with HIV by Age Group, United States, 2009-2014

Figure 16 Transgender Men (Female to Male) Diagnosed with HIV by Race/Ethnicity, United States, 2009-2014


<table>
<thead>
<tr>
<th>Racial/Ethnic Group</th>
<th>New HIV Diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>3</td>
<td>0.8</td>
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<tr>
<td>Asian</td>
<td>5</td>
<td>1.4</td>
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<tr>
<td>Black/African American</td>
<td>211</td>
<td>58.4</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>55</td>
<td>15.2</td>
</tr>
<tr>
<td>Multiple Races</td>
<td>31</td>
<td>8.6</td>
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<tr>
<td>Native Hawaiian/Other Pacific Islander</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>White</td>
<td>56</td>
<td>15.5</td>
</tr>
</tbody>
</table>
Figure 17 Transgender Men (Female to Male) Diagnosed with HIV by Region, United States, 2009-2014

Figure 18 Onset of Masculinizing Effects with Gender-Affirming Hormone Therapy in Transgender Men

This figure shows approximate time for onset of certain masculinizing features associated with onset of use of testosterone in transgender men.

Figure 19 Time to Reach Maximal Masculinizing Effects with Gender-Affirming Hormone Therapy in Transgender Men

This figure shows approximate time to reach maximal effect with certain masculinizing features associated with onset of use of testosterone in transgender men.