

CLINICAL PRACTICE

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Primary Care for Men Who Have Sex with Men

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

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A 43-year-old gay man presents to a physician's office for primary care. He has one long-term partner who is not infected with the human immunodeficiency virus (HIV) and with whom he has anal sex without condoms. He reports having had occasional anal sex with two other men during the past 6 months, with inconsistent use of condoms. He reports no tobacco or drug use and has one alcoholic drink daily. The patient has received vaccinations against infection with hepatitis A virus (HAV) and hepatitis B virus (HBV). A test for HIV infection is negative. What additional tests would be appropriate, and what would you advise the patient to help him reduce his risk of HIV infection?

THE CLINICAL PROBLEM

MEN WHO HAVE SEX WITH MEN, MANY OF WHOM IDENTIFY THEMSELVES as gay, are a distinct population that is at increased risk for certain health conditions.^{1,2} Some, but not all, of these conditions are directly related to sexual behavior. HIV infection continues to be the major health problem affecting men who have sex with men. In this population, the HIV infection rate increased by 12% between 2009 and 2013, with nearly 31,000 new infections annually.³

One goal of the Healthy People 2020 campaign, sponsored by the Department of Health and Human Services, is to “improve the health, safety, and well-being of lesbian, gay, bisexual, and transgender individuals.”⁴ As is the case for other populations, the population of men who have sex with men have health issues that are influenced by age, race and ethnic group, educational level and socioeconomic status, and geographic location. These factors can influence the experience of “coming out,” societal acceptance, and the likelihood of discrimination, all of which modulate a patient's physical and mental health.⁵ Such psychosocial factors have been proposed as drivers of the overlapping health problems of HIV and other sexually transmitted infections and the mental health issues in men who have sex with men.⁶ This review discusses the unique set of health considerations in the primary care setting for men who have sex with men.

STRATEGIES AND EVIDENCE

SEXUAL HISTORY

It is not possible to provide health care that is appropriate for men who have sex with men without eliciting a history of same-sex activity or same-sex attraction. This discussion should include questions about a patient's sexual identity


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KEY CLINICAL POINTS

PRIMARY CARE FOR MEN WHO HAVE SEX WITH MEN

- Providers should identify men who have sex with men so that appropriate medical care can be administered.
- The vaccinations provided for men who have sex with men should include those against the hepatitis A virus, hepatitis B virus, human papillomavirus (in men ≤ 26 years of age), and in certain regions, *Neisseria meningitidis*.
- A detailed discussion of sexual activity is essential to guide strategies for the prevention of infection with the human immunodeficiency virus (HIV) and for the administration of tests for sexually transmitted infections.
- Men who are at increased risk for HIV infection, especially those who have anal sex with multiple partners without the use of condoms, should be offered preexposure prophylaxis to reduce the risk of HIV acquisition.
- Testing for sexually transmitted infections should occur once or twice a year, depending on the patient's ongoing sexual activity.

— whether the patient describes himself as gay, bisexual, heterosexual, transgender, or gender nonconforming — and his sexual behavior (including the sex of partners).⁵ Some men who have sex with men do not identify themselves as gay. The Institute of Medicine recommends that health care providers collect and store data on sexual orientation and gender identity in electronic health records.⁵ Patients should be questioned directly about sexual activity with other men; in one study involving men who had sex with men, the proportion who reported having discussed their sexual behavior with their provider was 40% among black men, 52% among Hispanic men, 53% among Asian men, and 81% among non-Hispanic white men.⁷ (A list of resources that include suggested guidelines on obtaining such a history in a culturally appropriate manner can be found in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

In order to counsel patients about the risk of acquiring HIV and other sexually transmitted infections, providers should first inquire about types of sexual activity (e.g., oral sex, anal sex, and oral–anal sex) and the use or nonuse of condoms during various sexual activities. The risk of acquiring HIV infection is greatest among those who practice receptive anal intercourse (estimated at 1.43% per sex act with an HIV-infected partner); the risk is almost 10 times as high among these men as it is among men who have insertive anal sex (estimated at 0.16% per sex act with an HIV-infected partner),⁸ and the estimated risk is considerably lower among men who have oral sex, although this rate is difficult to quan-

tify.⁹ The consistent use of condoms during anal sex has been associated with a risk of HIV acquisition that is 70% lower than the risk without the consistent use of condoms.¹⁰ Men who report having sex without condoms should be asked whether they are with a single partner who is known to be HIV-uninfected or with casual partners and whether the use of drugs or alcohol is involved.

SEXUALLY TRANSMITTED INFECTIONS

Providers should ask about symptoms and signs of sexually transmitted infections in the rectum, pharynx, and urethra and order appropriate diagnostic tests as needed (Table 1). In assessing a patient for possible rectal infection, it is important to ask the patient about anal pain and discharge (which are consistent with proctitis). The presence of these symptoms should prompt testing for syphilis and for infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis*; testing for these infections requires a rectal swab for use in nucleic acid amplification testing. Detection of *C. trachomatis* in a patient with proctitis should prompt treatment for lymphogranuloma venereum (L1, L2, and L3 serotypes of *C. trachomatis*), which is a well-described cause of proctitis.¹¹ The presence of palpable nodules detected on digital rectal examination or of anal bleeding should be evaluated by means of anoscopy, during which the clinician should look for anal condyloma, anal fissures or fistulae, hemorrhoids, and anal cancer (which is rare).

Even in the absence of symptoms, screening for sexually transmitted infections — including serologic testing for HIV and syphilis and oral,

Table 1. Recommendations for Primary Care in Men Who Have Sex with Men.*

Recommendation	Comments
General	
Ask questions about sexual behavior and identity	For sexual behavior, ask questions such as “Are you having sex?” and “Do you have sex with men, women, or both?”; for sexual identity, ask “Do you consider yourself to be straight, gay, or bisexual?”
Conduct an ongoing assessment of sexual activity	Ask about numbers of partners, types of sexual activity (receptive and insertive anal sex, oral sex, oral–anal sex), and use of condoms. Examples of questions include “Have you had receptive anal sex, meaning ‘a penis in your anus or rectum’?” If the answer is yes, ask “How often do you use condoms for this purpose? Never, sometimes, or always?”
Reduction of risk of HIV	
Ask the patient about HIV status Recommend consistent use of condoms Inform the patient about the availability of postexposure prophylaxis Ask the patient to consider HIV preexposure prophylaxis	Discuss a plan that will help the patient reduce his risk of HIV infection. All patients should be encouraged to disclose their HIV status and to discuss the status of their sexual partners. Patients who use condoms consistently should be encouraged to continue this behavior. For patients who report having unprotected sex, especially unprotected receptive anal sex, determine the context in which the unprotected sex occurs (e.g., condoms were not available; drugs or alcohol were involved) and encourage consistent use of condoms. For patients who occasionally engage in sexual behavior that puts them at risk for infection, determine the frequency (e.g., one episode every 3–6 mo) and develop a plan the patient can follow to obtain access to postexposure prophylaxis. Patients who engage in high-risk sexual behaviors more frequently should be encouraged to consider preexposure prophylaxis.
Screening for sexually transmitted infections	
Obtain urinary, rectal, and pharyngeal specimens to conduct nucleic acid amplification tests for <i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i> Conduct tests for syphilis and infection with HIV and HCV	Test asymptomatic, sexually active men who have sex with men for these infections annually, and test those who engage in high-risk sexual behavior at least twice yearly. Syphilis and rectal infections with <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> are often not accompanied by symptoms. Patients who do have symptoms consistent with a sexually transmitted infection should undergo appropriate testing.
Vaccination	
Recommend vaccination against infection with HAV, HBV, HPV, and meningococcus	For patients who do not have a history of vaccination against infection with HAV or HBV, consider serologic testing before vaccination. Offer HPV vaccination to all men who have sex with men through 26 yr of age. The 9-valent HPV vaccine offers the broadest protection. Meningococcal vaccination should be considered in patients who are sexually active men; several outbreaks of meningococcal meningitis have been reported in this group.
Other screening	
Inquire about depression and about the use of tobacco, drugs, and alcohol Consider screening for anal pre-cancer or cancer	Consider the possibility of tobacco, drug, and alcohol use and depression, each of which is more common among men who have sex with men than in the rest of the population. Strategies used to treat these conditions in the general population should be applied to gay men. Screening for anal cancer can be considered starting at 30 yr of age, although its benefits have not yet been proved.

* HAV denotes hepatitis A virus, HBV hepatitis B virus, HCV hepatitis C virus, HIV human immunodeficiency virus, and HPV human papillomavirus.

rectal, and urinary testing for *N. gonorrhoeae* and *C. trachomatis* — is recommended for sexually active men who have sex with men and should be performed once a year or, for patients at higher risk, twice a year.¹¹ Unlike urethral infections, rectal gonorrhea and chlamydial infections are often asymptomatic.¹²

DISEASES PREVENTED BY VACCINES

Men who have sex with men are at increased risk for several vaccine-preventable infections (Table 1). HBV virus is spread through contaminated blood and sexual contact and during childbirth. The Centers for Disease Control and Prevention (CDC) recommends vaccination of

previously unvaccinated adults who are at increased risk for infection, including men who have sex with men.¹¹ Despite this recommendation, many have not been vaccinated against HBV and remain susceptible to infection.¹³ Unvaccinated men who have sex with men should be tested for HBV infection, and vaccination should be offered if tests for HBV surface antigen and surface antibody are negative.¹¹ The CDC recommends administration of the first dose of vaccine at the time of serologic testing and states that postvaccination serologic testing is not necessary, except in immunosuppressed patients.¹¹

HAV is transmitted through fecal–oral contact.¹¹ Men who have sex with men are at increased risk for the acquisition of HAV infection if they engage in sexual practices such as oral–anal sex; outbreaks of HAV infections in this population have been reported.¹³ Vaccination should be offered to men who have sex with men if they do not have a documented history of HAV vaccination and are not immune according to the results of serologic testing.¹¹ The CDC recommends administration of the first dose of vaccine at the time of serologic testing and states that postvaccination serologic testing is not necessary.¹¹

Outbreaks of meningococcal meningitis have been reported among men who have sex with men.^{14,15} This population is reported to have an increased prevalence of oropharyngeal colonization with *N. meningitidis* as compared with the general population,¹⁶ but population-level data are lacking to confirm whether they are at increased risk for meningococcal disease. Current guidelines from the Advisory Committee on Immunization Practices (ACIP) do not include men who have sex with men as a group that is at high risk for meningococcal disease and do not recommend routine vaccination.¹⁷ However, vaccination of men who have sex with men is recommended by many local health departments¹⁸ and is prudent for men in this population who are living in or traveling to areas with reported outbreaks.

Anal infection with high-risk types of human papillomavirus (HPV) can lead to anal cancer, which has a pathogenesis that is similar to that of cervical cancer.¹⁹ The risk of anal cancer is 30 times as high among men who have sex with

men as it is among heterosexual men.²⁰ In one placebo-controlled, randomized trial involving young gay men who were not infected with HIV, the quadrivalent HPV vaccine reduced the risk of persistent anal infection with HPV and associated intraepithelial neoplasia, which is a precursor to anal cancer.²¹ In another study, the vaccine was shown to be cost-effective when administered to young men who have sex with men, regardless of whether they had HIV infection.²² The ACIP recommends routine vaccination of men who have sex with men through 26 years of age.²³ A 9-valent version of this vaccine was recently approved by the Food and Drug Administration and is preferred over the quadrivalent vaccine, since it offers broader protection than the quadrivalent vaccine.²⁴ Data are lacking on the efficacy of vaccination in men older than 26 years of age who have sex with men, but the safety and immunogenicity of vaccination in this age group have been established.²⁵ Although vaccination may be beneficial in this older group, decisions regarding its use must address costs and take into account the fact that with increasing age the likelihood that a man has already been exposed to high-risk HPV types also increases.

HIV PREVENTION

Men who have sex with men should be offered routine HIV testing once or twice a year (Table 1).¹¹ Early diagnosis is critical to ensure that antiretroviral therapy is initiated for the personal health benefit of the patient and to decrease the risk of transmission to sexual partners.¹¹ As part of a comprehensive risk-reduction strategy, preexposure prophylaxis and postexposure prophylaxis should be considered for men who have sex with men if they are at high risk for HIV infection. Preexposure prophylaxis involves the ongoing use of antiretroviral medications in HIV-uninfected men to prevent the acquisition of HIV. The CDC recommends preexposure prophylaxis for men who have an HIV-infected sexual partner, who have recently had syphilis or infection with *N. gonorrhoeae* or *C. trachomatis*, or who have had a high number of sexual partners, a history of anal sex without the use of condoms, or a history of commercial sex work.^{26,27} Those who report having had anal sex with multiple partners without the use of condoms, especially receptive anal sex, are at the highest risk for acquiring

HIV infection.⁸ An HIV-infected partner who is receiving antiretroviral therapy and who has suppressed plasma HIV RNA is unlikely to transmit HIV.²⁸

In 2012, the Food and Drug Administration approved fixed-dose tenofovir disoproxil fumarate–emtricitabine for use as preexposure prophylaxis. In a randomized, placebo-controlled trial, daily administration of this regimen reduced the incidence of HIV-1 infection among men who had sex with men by 42%, despite inconsistent adherence, as measured by drug concentrations.²⁹ Observed efficacy in clinical trials of preexposure prophylaxis is strongly related to adherence to therapy, with little or no efficacy noted in clinical trials with the lowest adherence rates.^{30–32} The CDC and others have provided guidance to help clinicians support adherence to preexposure prophylaxis.^{27,33}

Two subsequent placebo-controlled, randomized trials of tenofovir disoproxil fumarate–emtricitabine in men who have sex with men showed reductions of 86% in the incidence of infection with HIV type 1 with the use of daily dosing³⁴ or an on-demand strategy.³⁵ With the on-demand strategy, participants took 2 tablets 2 to 24 hours before having sex, followed by 1 tablet a day for 2 days; participants received a median of 14 tablets per month. In both trials, investigators enrolled men who had a recent history of anal sex without the use of condoms and observed very high HIV infection rates in the control groups (8.9 and 6.6 infections per 100 patient-years). Cost-effectiveness analyses have supported the use of preexposure prophylaxis in higher-risk populations (those with expected HIV incidence of $\geq 2\%$ per year) among whom there is an efficacy of at least 50%. Both criteria were met in these two trials.³⁶

Table 2 reviews the selection of appropriate candidates for preexposure prophylaxis and recommended follow-up procedures. Discussions regarding the potential use of preexposure prophylaxis should include attention to the risks associated with the medications (e.g., renal insufficiency and loss of bone density) and the risks of HIV transmission in various circumstances.

An alternative approach to the prevention of infection with HIV is postexposure prophylaxis. This strategy involves the use of antiretroviral medications (e.g., tenofovir disoproxil fumarate–emtricitabine and raltegravir) soon after an isolat-

ed incident of high-risk exposure (within 72 hours, and preferably within 24 hours) in conjunction with HIV testing; treatment is continued for 28 days.³⁷ No efficacy data from randomized clinical trials are available. There is general agreement in international guidelines that postexposure prophylaxis should be offered to men who report having unprotected anal intercourse with a known HIV-infected partner or a partner whose serostatus is unknown.³⁸ A plan for accessing postexposure prophylaxis in a timely manner should be discussed, since efficacy diminishes as the time between exposure and initiation of antiretroviral medications increases.³⁷ This strategy should be considered for patients who report isolated incidents of high-risk exposure, whereas preexposure prophylaxis should be considered in patients with ongoing or repeated exposures.

SCREENING FOR ALCOHOL, DRUG, AND TOBACCO USE

According to a meta-analysis that included 25 studies of lesbian, gay, and bisexual people, these groups were at a significantly higher risk for depression, anxiety, and alcohol dependence than heterosexual people.³⁹ A proposed explanation is that chronic stress resulting from stigma and disadvantaged status in society may increase the risk of these conditions.⁴⁰ Men who have sex with men should be screened periodically for alcohol and drug use (Table 1). They are also more likely than heterosexual men to use tobacco⁴¹ and should be asked about tobacco use periodically and, when relevant, offered strategies for cessation that have been proved useful in broader populations.

TRANSMISSION OF HEPATITIS C VIRUS

Although most transmissions of hepatitis C virus (HCV) occur through contaminated blood during the use of injection drugs, HCV transmission may also occur in men who have sex with men, particularly those who have unprotected anal intercourse with multiple partners.^{42–44} Most cases of HCV infection among men who have sex with men occur in men who are infected with HIV.⁴⁴ The CDC recommends regular screening for HCV infection among HIV-infected men who have sex with men and recommends one-time HCV testing before the initiation of preexposure HIV prophylaxis and for all persons born between 1945 and 1965.^{11,26} Guidelines from the American

Table 2. Recommendations for Preexposure Prophylaxis in Men Who Have Sex with Men.

Steps	Recommendation	Comments
Check clinical indications	Indications for men who have sex with men include having an HIV-infected partner; a recent diagnosis of syphilis, gonorrhea, or chlamydia; a report of inconsistent use or no use of condoms; and a report of commercial sex work.	Patients with a recent history of unprotected anal sex with HIV-infected partners or partners whose serostatus is unknown have the greatest need for preexposure prophylaxis.
Screen before administering preexposure prophylaxis	Test results for HIV and HBV should be negative, renal function should be normal, patient should not be taking any contraindicated medications.	An HIV antigen–antibody combination test is preferred because it will identify recent HIV infection. Patients with symptoms of acute HIV infection (e.g., fever, rash, or sore throat) should be tested for acute HIV infection with an HIV nucleic acid amplification test or plasma HIV RNA test before preexposure prophylaxis is initiated. Patients should have a calculated creatinine clearance of >60 ml/min. Patients with chronic HBV infection are eligible for preexposure prophylaxis, which is also effective against chronic HBV infection; consultation with a provider experienced in treating HBV is recommended. Cessation of tenofovir disoproxil fumarate–emtricitabine may lead to flares in HBV infection.
Prescribe medications	A daily, fixed-dose combination tablet of 300 mg of tenofovir disoproxil fumarate with 200 mg of emtricitabine should be prescribed.	Only a 90-day supply should be dispensed. A negative result on HIV testing should be confirmed before a refill is prescribed.
Conduct follow-up testing	Testing for HIV status and assessment of side effects and ongoing sexual activities associated with the risk of HIV should be performed every 3 mo. At 3 mo and every 6 mo thereafter, renal function should be assessed. Testing for sexually transmitted infections should be performed every 6 mo.	In addition to HIV testing, patients should be informed about the symptoms of acute HIV infection. Appropriate testing for acute HIV infection should be ordered if symptoms develop.
Provide support for adherence	Patient adherence to regimen should be checked at each follow-up visit; support should be provided with the use of adherence strategies.	Ongoing assessment of adherence should be performed. The provider should start by asking the patient about adherence and discussing any challenges to adherence. This discussion should be followed by specific questions about the frequency of missed doses. If needed, an adherence plan should be developed that focuses on the scheduling of pill taking, the use of reminder devices (e.g., pillboxes or alarms), organizational skills (e.g., location of pills and plans for taking pills when away from home), and a discussion of social support (e.g., are household members and friends aware that patient is pursuing preexposure prophylaxis and if so, are they supportive?). Barriers to adherence, such as substance use or depression, should be identified and managed if possible.

Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and International Antiviral Society—USA state that periodic testing should be offered to persons with ongoing risk factors for exposure to HCV.⁴⁵

AREAS OF UNCERTAINTY

The best use of preexposure prophylaxis for HIV infection remains controversial. According to an analysis of U.S. retail pharmacy data, the number of new prescriptions for preexposure prophylaxis appears to have increased sharply during 2014.⁴⁶ Included among the barriers to widespread use are the reluctance of some providers to prescribe preexposure prophylaxis and the general lack or limited nature of insurance coverage. One concern is that preexposure prophylaxis may lead to more frequent high-risk sexual activity, which could potentially negate the benefits.⁴⁷ Although the data available to inform this view are limited, one randomized, open-label trial of preexposure prophylaxis did not show higher rates of sexually transmitted bacterial infections or self-reported high-risk behaviors in the active-treatment group.³⁴ Rare cases of antiviral drug resistance have been reported in persons who acquired HIV infection while undergoing preexposure prophylaxis.²⁶ Research on alternative agents for preexposure prophylaxis is ongoing and includes investigation of agents that are not associated with kidney or bone toxic effects and long-acting, injectable formulations that would obviate the need for daily adherence.

It is unclear whether screening for anal cancer is warranted in men who have sex with men; the incidence in this population is estimated to be 35 cases per 100,000 patient-years,²⁰ and the incidence is twice as high among those who are infected with HIV.⁴⁸ These rates are similar to or higher than the rate of cervical cancer before the introduction of routine screening for cervical cancer. The strategy for prevention is similar to that for the prevention of cervical cancer and includes cytologic analysis and high-resolution anoscopy-guided biopsy, techniques that can be used to identify precancerous lesions of the anus, for which treatment may reduce the risk of anal cancer.⁴⁹ Screening should be considered for men who have sex with men if trained providers are available to perform these procedures,

but patients should understand that diagnostic procedures and precancer treatments for anal cancer have associated risks, including the risk of anal pain and bleeding, and that high-quality data showing that screening reduces the risk of anal cancer are not available. A randomized clinical trial of such screening is under way (ClinicalTrials.gov number, NCT02135419).

GUIDELINES

The CDC provides guidelines for the screening of men who have sex with men for sexually transmitted infections.¹¹ The CDC has also issued recommendations for the use of preexposure prophylaxis for HIV infection.^{26,27} The ACIP has issued vaccine recommendations for men who have sex with men, including recommendations for routine HPV vaccination in those who are 26 years of age or younger and routine vaccination against HAV and HBV.^{11,13,23} The recommendations in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has a long-term partner who is HIV-negative, but he has had recent anal sex with partners whose HIV serostatus is unknown and reports inconsistent condom use. In order to advise men who have sex with men on strategies intended to reduce the risk of HIV infection, it is critical to obtain a detailed sexual history (including the types of sexual activity they have and whether, or how frequently, they use condoms). These patients should also receive counseling on the risks and benefits of preexposure prophylaxis. For patients who decide to start preexposure prophylaxis with tenofovir disoproxil fumarate–emtricitabine, the importance of sustained adherence should be emphasized. The patient in the vignette should return for clinical evaluation and HIV testing within 1 month and undergo quarterly evaluation thereafter. Renal function should be monitored. The patient should be tested for sexually transmitted infections at least twice yearly. At each follow-up visit, his sexual activity should be reassessed and risk-reduction counseling, including the consistent use of condoms, should be

emphasized. I would also discuss with the patient the possibility of vaccinations against HPV infection and meningococcal disease in addition to screening for anal cancer. However, I would explain that data are currently lacking to support these interventions.

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