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STDs Update: Prevention, Special Populations, HIV and Syphilis

Sexually Transmitted Diseases Treatment Guidelines, 2015

These guidelines for the treatment of persons who have or are at risk for sexually transmitted diseases (STDs) were updated by CDC after consultation with a group of professionals knowledgeable in the field of STDs who met in Atlanta on April 30–May 2, 2013. The information in this report updates the Sexually Transmitted Diseases Treatment Guidelines, 2010 (MMWR Recomm Rep 2010;59 [No. RR–12]). *These updated guidelines discuss 1) alternative treatment regimens for* Neisseria gonorrhoeae; *2) the use of nucleic acid amplification tests for the diagnosis of trichomoniasis; 3) alternative treatment options for genital warts; 4) the role of* Mycoplasma genitalium *in urethritis/cervicitis and treatment-related implications; 5) updated HPV vaccine recommendations and counseling messages; 6) the management of persons who are transgender; 7) annual testing for hepatitis C in persons with HIV infection; 8) updated recommendations for diagnostic evaluation of urethritis; and 9) retesting to detect repeat infection. Physicians and other health-care providers can use these guidelines to assist in the prevention and treatment of STDs.*

Introduction

The term sexually transmitted diseases (STDs) refers to a variety of clinical syndromes and infections caused by pathogens that can be acquired and transmitted through sexual activity. Physicians and other health-care providers play a critical role in preventing and treating STDs. These guidelines for the treatment of STDs are intended to assist with that effort. Although these guidelines emphasize treatment, prevention strategies and diagnostic recommendations also are discussed.

This document updates CDC's *Sexually Transmitted Diseases Treatment Guidelines, 2010* (*1*). These recommendations should be regarded as a source of clinical guidance rather than prescriptive standards; health-care providers should always consider the clinical circumstances of each person in the context of local disease prevalence. These guidelines are applicable to any patient-care setting that serves persons at risk for STDs, including family-planning clinics, HIV-care clinics, correctional health-care settings, private physicians' offices, Federally Qualified Health Centers (FQHCs), and other primary-care facilities. These guidelines focus on treatment and counseling and do not address other community services and interventions that are essential to STD/HIV prevention efforts.

Methods

These guidelines were developed by CDC staff and an independent workgroup for which members were selected on the basis of their expertise in the clinical management of STDs. Members of the multidisciplinary workgroup included representatives from federal, state, and local health departments; public- and private-sector clinical providers; clinical and basic science researchers; and numerous professional organizations. All workgroup members disclosed potential conflicts of interest; several members of the workgroup acknowledged receiving financial support for clinical research from commercial companies. All potential conflicts of interest are listed at the end of the workgroup member section.

In 2012, CDC staff and workgroup members were charged with identifying key questions regarding treatment and clinical management that were not addressed in the 2010 STD Treatment Guidelines (*1*). To answer these questions and synthesize new information available since publication of the 2010 Guidelines, workgroup members collaborated with CDC staff to conduct a systematic literature review using an extensive MEDLINE database evidence-based approach (e.g., using published abstracts and peer-reviewed journal articles). These reviews also focused on four principal outcomes of STD therapy for each individual disease or infection: 1) treatment of infection based on microbiologic eradication; 2) alleviation of signs and symptoms; 3) prevention of sequelae; 4) prevention of transmission, including advantages such as cost-effectiveness and other advantages (e.g., single-dose formulations and directly observed therapy) and disadvantages (e.g., side effects) of specific regimens. The outcome of the literature review informed development of background materials, including tables of evidence from peer-reviewed publications summarizing the type of study (e.g., randomized controlled trial or case series), study population and setting,

treatments or other interventions, outcome measures assessed, reported findings, and weaknesses and biases in study design and analysis.

In April 2013, the workgroup's research was presented at an in-person meeting of the multidisciplinary workgroup members. Each key question was discussed, and pertinent publications were reviewed in terms of strengths, weaknesses, and relevance. The workgroup evaluated the quality of evidence, provided answers to the key questions, and rated the recommendations based on the United Services Preventive Services Task Forces (USPSTF) modified rating system (http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm). The discussion culminated in a proposal of recommendations to be adopted for consideration by CDC. (More detailed description of the key questions, search terms, and systematic search and review process is available at http://www.cdc.gov/std/tg2015/evidence.htm). Following the April meeting, the literature was searched periodically by CDC staff to identify subsequently published articles warranting consideration by the workgroup either through e-mail or conference calls.

CDC developed draft recommendations based on the workgroup's proposal. To ensure development of evidence-based recommendations, a second independent panel of public health and clinical experts reviewed the draft recommendations. The recommendations for STD screening during pregnancy, cervical cancer screening, and HPV vaccination were developed after CDC staff reviewed the published recommendations from other professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), USPSTF, American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and the Advisory Committee on Immunization Practices (ACIP) as part of the initial review process. The sections on hepatitis B virus (HBV) and hepatitis A virus (HAV) infections are based on previously published recommendations (2–4).

Throughout this report, the evidence used as the basis for specific recommendations is discussed briefly. More comprehensive, annotated discussions of such evidence will appear in background papers that will be available in a supplement issue of the journal *Clinical Infectious Diseases* after publication of these treatment guidelines. When more than one therapeutic regimen is recommended, the recommendations are listed alphabetically unless prioritized based on efficacy, tolerance, or costs. For infections with more than one recommended regimen, listed regimens have similar efficacy and similar rates of intolerance or toxicity unless otherwise specified. Recommended regimens should be used primarily; alternative regimens can be considered in instances of notable drug allergy or other medical contraindications to the recommended regimens.

Clinical Prevention Guidance

The prevention and control of STDs are based on the following five major strategies (5):

- accurate risk assessment and education and counseling of persons at risk on ways to avoid STDs through changes in sexual behaviors and use of recommended prevention services;
- pre-exposure vaccination of persons at risk for vaccine-preventable STDs;
- identification of asymptomatically infected persons and persons with symptoms associated with STDs;
- effective diagnosis, treatment, counseling, and follow up of infected persons; and
- evaluation, treatment, and counseling of sex partners of persons who are infected with an STD.

STD/HIV Risk Assessment

Primary prevention of STDs includes performing an assessment of behavioral risk (i.e., assessing the sexual behaviors that may place persons at risk for infection) as well as biologic risk (i.e., testing for risk markers for HIV acquisition or transmission). As part of the clinical encounter, health-care providers should routinely obtain sexual histories from their patients and address risk reduction as indicated in this report. Guidance for obtaining a sexual history is available on the CDC Division of STD Prevention resource page (http://www.cdc.gov/std/treatment/resources.htm) and in the curriculum provided by CDC's STD/HIV Prevention Training Centers (http://nnptc.org/clinical-ptcs). Effective interviewing and counseling skills characterized by respect, compassion, and a nonjudgmental attitude toward all patients are essential to obtaining a thorough sexual history and delivering effective prevention messages. Effective techniques for facilitating rapport with patients include the use of 1) open-ended questions (e.g., "Tell me about any new sex partners you've had since your last visit," and "What has your experience with using condoms been like?"); 2) understandable, nonjudgmental language ("Are your sex partners men, women, or both?""Have you ever had a sore or scab on your penis?"); and 3) normalizing language ("Some of my patients have difficulty using a condom with every sex act. How is it for you?"). The "Five P's" approach to obtaining a sexual history is one strategy for eliciting information concerning five key areas of interest (Box 1). For additional information about gaining cultural competency when working with certain populations (e.g., gay, bisexual, or other men who have sex with men [MSM], women who have sex with women [WSW], or transgender men and women) see MSM, WSW, and Transgender Men and Women.

BOX 1. The Five P's: Partners, Practices, Prevention of Pregnancy, Protection from STDs, and Past History of STDs

1. Partners
   - "Do you have sex with men, women, or both?"
   - "In the past 2 months, how many partners have you had sex with?"
   - "In the past 12 months, how many partners have you had sex with?"
   - "Is it possible that any of your sex partners in the past 12 months had sex with someone else while they were still in a sexual relationship with you?"
2. Practices
   - "To understand your risks for STDs, I need to understand the kind of sex you have had recently."
   - "Have you had vaginal sex, meaning 'penis in vagina sex'?" If yes, "Do you use condoms: never, sometimes, or always?"
   - "Have you had anal sex, meaning 'penis in rectum/anus sex'?" If yes, "Do you use condoms: never, sometimes, or always?"
   - "Have you had oral sex, meaning 'mouth on penis/vagina'?"
   - For condom answers:
   - If "never": "Why don't you use condoms?"
   - If "sometimes": "In what situations (or with whom) do you use condoms?"
3. Prevention of pregnancy
   - "What are you doing to prevent pregnancy?"
4. Protection from STDs
   - "What do you do to protect yourself from STDs and HIV?"
5. Past history of STDs
   - "Have you ever had an STD?"
   - "Have any of your partners had an STD?"

   Additional questions to identify HIV and viral hepatitis risk include:
   - "Have you or any of your partners ever injected drugs?"
   - "Have your or any of your partners exchanged money or drugs for sex?"
   - "Is there anything else about your sexual practices that I need to know about?"

In addition to obtaining a behavioral risk assessment, a comprehensive STD/HIV risk assessment should include STD screening, because STDs are biologic markers of risk, particularly for HIV acquisition and transmission among some MSM. STD screening is an essential and underutilized component of an STD/HIV risk assessment in most clinical settings. Persons seeking treatment or evaluation for a particular STD should be screened for HIV and other STDs as indicated by community prevalence and individual risk factors (see prevention section and sections on chlamydia, gonorrhea, and syphilis). Persons should be informed about all the STDs for which they are being tested and notified about tests for common STDs (e.g., genital herpes and human papillomavirus [HPV]) that are available but not being performed. Efforts should be made to ensure that all persons receive care regardless of individual circumstances (e.g., ability to pay, citizenship or immigration status, language spoken, or specific sex practices).

STD/HIV Prevention Counseling

After obtaining a sexual history from their patients, all providers should encourage risk reduction by providing prevention counseling. Prevention counseling is most effective if provided in a nonjudgmental and empathetic manner appropriate to the patient's culture, language, gender, sexual orientation, age, and developmental level. Prevention counseling for STD/HIV should be offered to all sexually active adolescents and to all adults who have received an STD diagnosis, have had an STD in the past year, or have multiple sexual partners.

USPSTF recommends high-intensity behavioral counseling for all sexually active adolescents and for adults at increased risk for STDs and HIV (*6,7*). Such interactive counseling, which can be resource intensive, is directed at a person's risk, the situations in which risk occurs, and the use of personalized goal-setting strategies. One such approach, known as client-centered STD/HIV prevention counseling, involves tailoring a discussion of risk reduction to the individual situation. While one large study in STD clinics (Project RESPECT) demonstrated that this approach was associated with lower acquisition of curable STDs (e.g., trichomoniasis, chlamydia, gonorrhea, and syphilis) (*8*), another study conducted 10 years later in the same settings but different contexts (Project AWARE) did not replicate this result (*9*). Briefer provider-delivered prevention messages have been shown to be feasible and to decrease subsequent STDs in HIV primary-care settings (*10*). Other approaches use motivational interviewing to move clients toward achievable risk-reduction goals. Client-centered counseling and motivational interviewing can be used effectively by clinicians and staff trained in these approaches. CDC provides additional information on these and other effective behavioral interventions at http://effectiveinterventions.org. Training in client-centered counseling is available through the CDC STD/HIV National Network of Prevention Training Centers (http://nnptc.org).

In addition to one-on-one STD/HIV prevention counseling, videos and large-group presentations can provide explicit information concerning STDs and reducing disease transmission (e.g., how to use condoms correctly and the importance of routine screening). Group-based strategies have been effective in reducing the occurrence of STDs among persons at risk, including those attending STD clinics (*11*).

Because the incidence of some STDs, notably syphilis, is higher in persons with HIV infection, the use of client-centered STD counseling for persons with HIV infection continues to be strongly encouraged by public health agencies and other health organizations. A recent federal guideline recommends that clinical and nonclinical providers assess an individual's behavioral and biologic risks for acquiring or transmitting STD and HIV, including having sex without condoms, recent STDs, and partners recently treated for STDs. This guideline also recommends that clinical and nonclinical providers offer or make referral for 1) regular screening for several STDs, 2) onsite STD treatment when indicated, and 3) risk-reduction interventions tailored to the individual's risks (*12*). Brief risk-reduction counseling delivered by medical providers during HIV primary-care visits coupled with routine STD screening has been shown to reduce STD incidence in persons with HIV infection (*10*). Several other specific methods have been designed for the HIV care setting (http://effectiveinterventions.org) (*13–15*).

Prevention Methods

Pre-exposure Vaccination

Pre-exposure vaccination is one of the most effective methods for preventing transmission of human papillomavirus (HPV), HAV, and HBV. HPV vaccination is recommended routinely for boys and girls aged 11 or 12 years and can be administered beginning at 9 years of age. Either bivalent, quadrivalent, or 9-valent HPV vaccine is recommended for females, whereas quadrivalent vaccine or 9-valent vaccine is recommended for males (*16*) http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html. Vaccination is recommended through age 26 years for all females and through age 21 years for all males that have not received any or all of the vaccine doses. For persons with HIV infection and for MSM, vaccination is recommended through age 26 years (*16*). Further details regarding HPV vaccination are available in another section of this document (see HPV Vaccine), at http://www.cdc.gov/std/hpv, and at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html.

Hepatitis B vaccination is recommended for all unvaccinated, uninfected persons being evaluated or treated for an STD (*3,4*).

In addition, hepatitis A and B vaccines are recommended for MSM, injection-drug users (IDUs), persons with chronic liver disease (CLD), and persons with HIV infection who have not yet been infected with one or both types of hepatitis virus (*3,4,17*). Details regarding hepatitis A and B vaccination are available at http://www.cdc.gov/hepatitis.

Abstinence and Reduction of Number of Sex Partners

The most reliable way to avoid transmission of STDs is to abstain from oral, vaginal, and anal sex or to be in a long-term, mutually monogamous relationship with a partner known to be uninfected. For persons who are being treated for an STD other than HIV (or whose partners are undergoing treatment), counseling that encourages abstinence from sexual intercourse until completion of the entire course of medication is crucial. A recent trial conducted among women on the effectiveness of counseling messages demonstrated that women whose sexual partners have used condoms may benefit from a hierarchical message that includes condoms, whereas women without such experience might benefit more from an abstinence-only message (*18*). A more comprehensive discussion of abstinence and other sexual practices than can help persons reduce their risk for STDs is available in *Contraceptive Technology, 20th Edition (19)*.

Male Condoms

When used consistently and correctly, male latex condoms are highly effective in preventing the sexual transmission of HIV infection. In heterosexual HIV serodiscordant relationships (i.e., those involving one infected and one uninfected partner) in which condoms were consistently used, HIV-negative partners were 80% less likely to become infected with HIV compared with persons in similar relationships in which condoms were not used (*20,21*). Moreover, studies demonstrate that consistent condom use reduces the risk for other STDs, including chlamydia, gonorrhea, and trichomoniasis (*22–24*). By limiting lower genital tract infections, condoms also might reduce the risk of developing pelvic inflammatory disease (PID) in women (*25*). In addition, consistent and correct use of latex condoms reduces the risk for HPV infection and HPV-associated diseases, genital herpes, hepatitis B, syphilis, and chancroid when the infected area or site of potential exposure is covered (*26–32*).

Condoms are regulated as medical devices and are subject to random sampling and testing by the U.S. Food and Drug Administration (FDA). Each latex condom manufactured in the United States is tested electronically for holes before packaging. Rate of condom breakage during sexual intercourse and withdrawal is approximately two broken condoms per

100 condoms used in the United States. Rates of breakage and slippage may be slightly higher during anal intercourse (*33,34*). The failure of condoms to protect against STD or unintended pregnancy usually results from inconsistent or incorrect use rather than condom breakage (*35*). Users should check the expiration or manufacture date on the box or individual package. Latex condoms should not be used beyond their expiration date or more than 5 years after the manufacturing date. Male condoms made of materials other than latex are available in the United States and can be classified in two general categories: 1) polyurethane and other synthetic and 2) natural membrane.

Polyurethane male condoms provide comparable protection against STDs/HIV and pregnancy to that of latex condoms (*19,24*). These can be substituted for latex condoms by persons with latex allergy, are generally more resistant to deterioration, and are compatible with use of both oil-based and water-based lubricants. The effectiveness of other synthetic male condoms to prevent sexually transmitted infections has not been extensively studied, and FDA-labeling restricts their recommended use to latex-sensitive or allergic persons. Natural membrane condoms (frequently called "natural skin" condoms or [incorrectly] "lambskin" condoms) are made from lamb cecum and can have pores up to 1,500 nm in diameter. Although these pores do not allow the passage of sperm, they are more than 10 times the diameter of HIV and more than 25 times that of HBV. Moreover, laboratory studies demonstrate that sexual transmission of viruses, including hepatitis B, herpes simplex, and HIV, can occur with natural membrane condoms (*19*). While natural membrane condoms are recommended for pregnancy prevention, they are not recommended for prevention of STDs and HIV.

Providers should advise that condoms must be used consistently and correctly to be effective in preventing STDs and HIV infection; providing instructions about the correct use of condoms can be useful. Communicating the following recommendations can help ensure that patients use male condoms correctly:

- Use a new condom with each sex act (i.e., oral, vaginal, and anal).
- Carefully handle the condom to avoid damaging it with fingernails, teeth, or other sharp objects.
- Put the condom on after the penis is erect and before any genital, oral, or anal contact with the partner.
- Use only water-based lubricants (e.g., K-Y Jelly, Astroglide, AquaLube, and glycerin) with latex condoms. Oil-based lubricants (e.g., petroleum jelly, shortening, mineral oil, massage oils, body lotions, and cooking oil) can weaken latex and should not be used; however, oil-based lubricants can generally be used with synthetic condoms.

- Ensure adequate lubrication during vaginal and anal sex, which might require the use of exogenous water-based lubricants.
- To prevent the condom from slipping off, hold the condom firmly against the base of the penis during withdrawal, and withdraw while the penis is still erect.

Additional information about male condoms is available at http://www.cdc.gov/condomeffectiveness/index.html.

Female Condoms

Several condoms for females are globally available, including the FC2 Female Condom, Reddy condom, Cupid female condom, and Woman's condom (*36*). Use of female condoms can provide protection from acquisition and transmission of STDs, although data are limited (*36*). Although female condoms are more costly compared with male condoms, they offer the advantage of being a female-controlled STD/HIV prevention method, and the newer versions may be acceptable to both men and women. Although the female condom also has been used during receptive anal intercourse, efficacy associated with this practice remains unknown (*37*). Additional information about the female condom is available at http://www.ashasexualhealth.org/sexual-health/all-about-condoms/female-condoms.

Cervical Diaphragms

In observational studies, diaphragm use has been demonstrated to protect against cervical gonorrhea, chlamydia, and trichomoniasis (*38*). However, a trial examining the effect of a diaphragm plus lubricant on HIV acquisition among women in Africa showed no additional protective effect when compared with the use of male condoms alone. Likewise, no difference by study arm in the rate of acquisition of chlamydia, gonorrhea, or herpes occurred (*39,40*). Diaphragms should not be relied on as the sole source of protection against HIV or other STDs.

Topical Microbicides and Spermicides

Nonspecific topical microbicides are ineffective for preventing HIV (*41–45*). Spermicides containing N-9 might disrupt genital or rectal epithelium and have been associated with an increased risk for HIV infection. Condoms with N-9 are no more effective than condoms without N-9; therefore, N-9 alone or in a condom is not recommended for STD or HIV prevention (*41*). N-9 use has also been associated with an increased risk for bacterial urinary tract infections in women (*46,47*). No proven topical antiretroviral agents exist for the prevention of HIV, though trials are underway to evaluate several candidates for vaginal and rectal microbicides using tenofovir and other antiretroviral drugs.

Nonbarrier Contraception, Surgical Sterilization, and Hysterectomy

Contraceptive methods that are not mechanical barriers offer no protection against HIV or other STDs. Sexually active women who use hormonal contraception (i.e., oral contraceptives, patch, ring, implants, injectables, or intrauterine hormonal methods), have nonhormonal intrauterine devices (IUDs), have been surgically sterilized, or have had hysterectomies should be counseled to use condoms to reduce the risk for STDs, including HIV infection. Women who take oral contraceptives and are prescribed certain antimicrobials should be counseled about potential interactions (*19*).

Whether hormonal contraception raises a woman's risk for acquiring HIV or another STD is unclear. A systematic review of epidemiologic evidence found that most studies showed no association between use of oral contraceptives and HIV acquisition among women. Studies examining the association between progestin-only injectables and HIV acquisition have had mixed results; some studies show a higher risk of acquisition among women using depo-medroxyprogesterone acetate (DMPA), while other studies do not (*48*). The World Health Organization (WHO) and CDC reviewed the evidence on hormonal contraception and HIV acquisition and concluded that data are insufficient to recommend that women modify their hormonal contraceptive practices, but that women using progestin-only injectables should be strongly advised to also use condoms as an HIV prevention strategy (*49,50*).

Male Circumcision

Male circumcision reduces the risk for HIV and some STDs in heterosexual men. Three randomized, controlled trials performed in regions of sub-Saharan Africa where generalized HIV epidemics involving predominantly heterosexual transmission were occurring demonstrated that male circumcision reduced the risk for HIV acquisition among men by 50%–60% (*51–53*). In these trials, circumcision was also protective against other STDs, including high-risk genital HPV infection and genital herpes (*54–56*). Follow up studies have demonstrated sustained benefit of circumcision for HIV prevention (*57*) and that the effect is not mediated solely through a reduction in herpes simplex virus type 2 (HSV-2) infection or genital ulcer disease (*58*).

WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have recommended that male circumcision efforts be scaled up as an effective intervention for the prevention of heterosexually acquired HIV infection (*59*). These organizations also recommend that countries with hyperendemic and generalized HIV epidemics and low prevalence of male circumcision expand access to safe male circumcision services within the context of ensuring universal access to comprehensive HIV prevention, treatment, care, and support. In the United States, the American Academy of Pediatrics (AAP) recommends that newborn male circumcision be available to families that desire it, as the benefits of the procedure, including prevention of penile cancers, urinary tract infections, genital ulcer disease, and HIV outweigh the risks (*60*). ACOG has also endorsed the AAP's policy statement (*60*). In light of these benefits, the American Urological Association states that male circumcision should be considered an option for risk reduction, among other strategies (*61*).

No definitive data exist to determine whether male circumcision reduces HIV acquisition in MSM, although one randomized trial is ongoing in China (*62*). A review found a modest protective effect among men who were the insertive partner for anal intercourse, but the evidence was rated as poor. Further higher quality studies are needed to confirm any potential benefit of male circumcision for this population (*62*).

Emergency Contraception

Unprotected intercourse exposes women to risks for STDs and unplanned pregnancy. Providers managing such women should offer counseling about the option of emergency contraception (EC) if pregnancy is not desired. The options for EC in the United States include the copper IUD and emergency contraceptive pills (ECPs) (*63*). ECPs are available in the following formulations: ulipristal acetate in a single dose (30 mg), levonorgestrel in a single dose (1.5 mg) or as a split dose (0.75 mg each taken 12 hours apart), or combined estrogen and progestin (Yuzpe regimen). Some ECPs can be obtained over the counter; ECPs can also be provided through advance prescription or supply from providers (*64,65*). Emergency insertion of a copper IUD up to 5 days after sex can reduce pregnancy risk by more than 99% (*66*). ECPs are most efficacious when initiated as soon as possible after unprotected sex but have some efficacy up to 5 days later. ECPs are ineffective (but not harmful) if the woman is already pregnant (*67*). A 2012 Cochrane review summarized the efficacy, safety, and convenience of various methods of emergency contraception (*67*). More information about EC is available in the 20th edition of *Contraceptive Technology (19)* or http://www.arhp.org/topics/emergency-contraception.

Postexposure Prophylaxis for HIV and STD

Guidelines for the use of postexposure prophylaxis (PEP) aimed at preventing HIV infection and other STDs as a result of sexual exposure are discussed in another section of this report (see Sexual Assault and STDs). Genital hygiene methods (e.g., vaginal washing and douching) after sexual exposure are ineffective in protecting against HIV and STDs

and might increase the risk for bacterial vaginosis (BV), some STDs, and HIV infection (*68*).

Antiretroviral Treatment of Persons with HIV Infection to Prevent HIV Infection in Partners

The randomized controlled trial HPTN 052 demonstrated that in HIV serodiscordant, heterosexual couples, HIV antiretroviral therapy in the infected partner decreases the risk for transmission to the uninfected partner by 96% (*69*). Therefore, antiretroviral therapy not only is beneficial to the health of persons with HIV infection, but also reduces the risk for continued transmission. For these reasons, treatment should be offered to all persons with HIV infection. Detailed guidance for prescribing antiretroviral regimens can be found in the U.S. Department of Health and Human Services' HIV treatment guidelines at http://aidsinfo.nih.gov/guidelines (*70*).

HSV Treatment of Persons with HIV and HSV Infections to Prevent HIV Infection in Uninfected Partners

Providing HSV treatment to persons co-infected with HIV and HSV has not been demonstrated to be beneficial in reducing HIV acquisition in uninfected partners. A large randomized, controlled trial evaluated 3,408 serodiscordant heterosexual couples enrolled at 14 Africa sites in which the partner with HIV infection was also seropositive for HSV-2. The co-infected partner was randomized to receive either placebo or acyclovir 400-mg twice per day, and the primary outcome was HIV transmission to the uninfected partner. Use of acyclovir had no effect on HIV transmission (*71*). These findings are consistent with those from a previous trial that found no benefit of acyclovir in preventing HIV-1 acquisition in persons who were seropositive for HSV-2 (*72*).

Preexposure Prophylaxis for HIV

Certain large, randomized, placebo-controlled trials examining daily oral antiretroviral preexposure prophylaxis (PrEP) with a fixed-dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) have demonstrated safety (*73*) and a substantial reduction in the rate of HIV acquisition for MSM (*74*), HIV-discordant heterosexual couples (*75*), and heterosexual men and women recruited as individuals (*76*). In addition, one clinical trial involving IDUs (*77*) and one involving heterosexual HIV-discordant couples (*75*) demonstrated substantial efficacy and safety of daily oral PrEP with TDF alone when combined with repeated condom provision, sexual risk-reduction counseling, and the diagnosis and treatment of STDs. High adherence to oral PrEP with TDF alone or in a fixed-dose combination with FTC was strongly associated with protection from infection.

Data suggest that when administered orally, levels of TDF are lower in vaginal tissue than rectal tissue, potentially explaining why high levels of adherence were needed to yield benefits among women in these trials (*78*). Despite initial concerns about PrEP fostering antiretroviral resistance among persons who become infected, standard tests employed in these studies detected emergence of resistance only in persons inadvertently started on PrEP during acute HIV infection, not in persons who were initially uninfected but later became infected while taking PrEP medication (*79*).

The U.S. Public Health Service (USPHS) has issued recommendations on the basis of these trial results and the FDA approval of an indication for the use of TDF/FTC for PrEP. USPHS recommends that clinicians evaluate HIV-negative men and women who are sexually active or injecting illicit drugs and consider PrEP as a prevention option for persons whose sexual or injection behaviors and epidemiologic context place them at substantial risk for acquiring HIV infection. Comprehensive guidance for the use of daily PrEP to reduce the risk for acquiring HIV infection can be found at http://www.cdc.gov/hiv/prevention/research/prep/index.html.

HIV Seroadaptation Strategies

Seroadaptive strategies for HIV prevention have largely originated within communities of MSM. They are predicated on knowledge of self and partner HIV-infection status. One specific seroadaptive practice is serosorting, which includes limiting anal sex without a condom to partners with the same HIV status as their own, or choosing to selectively use condoms only with HIV serodiscordant partners. Another practice among serodiscordant couples is seropositioning, in which the person with HIV infection is the receptive partner for anal intercourse. Observational studies have consistently found that serosorting confers greater risk of HIV infection than consistent condom use, but is lower risk compared with anal intercourse without a condom and without serosorting (*80–82*). Serosorting practices have been associated with increased risk of STDs including chlamydia and gonorrhea (*83,84*).

Serosorting is not recommended for the following reasons: 1) too many MSM who have HIV do not know they are infected because they have not been tested for HIV recently, 2) men's assumptions about the HIV status of their partners might be wrong, and 3) some men with HIV infection might not disclose or may misrepresent their HIV status. All of these factors increase the risk that serosorting could lead to HIV infection. Additional information is available at http://www.cdc.gov/msmhealth/serosorting.htm or http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en.

Retesting After Treatment to Detect Repeat Infections

Retesting several months after diagnosis of chlamydia, gonorrhea, or trichomoniasis can detect repeat infection and potentially can be used to enhance population-based prevention *(85,86)*. Any person who tests positive for chlamydia or gonorrhea, along with women who test positive for trichomonas, should be rescreened 3 months after treatment. Any person who receives a syphilis diagnosis should undergo follow-up serologic syphilis testing per current recommendations (see Syphilis). Further details on retesting can be found in the specific sections on chlamydia, gonorrhea, syphilis, and trichomonas within this report.

Partner Services

The term "partner services" refers to a continuum of clinical evaluation, counseling, diagnostic testing, and treatment designed to increase the number of infected persons brought to treatment and to disrupt transmission networks. This continuum includes efforts undertaken by health departments, medical providers, and patients themselves. The term "public health partner services" refers to efforts by public health departments to identify the sex- and needle-sharing partners of infected persons to assure their medical evaluation and treatment.

Clinicians can provide partner services by counseling infected persons and providing them with written information and medication to give to their partners (if recommended and allowable by state law), directly evaluating and treating sex partners, and cooperating with state and local health departments. Clinicians' efforts to ensure the treatment of a patient's sex partners can reduce the risk for reinfection and potentially diminish transmission of STDs *(87)*. Therefore, clinicians should encourage all persons with STDs to notify their sex partners and urge them to seek medical evaluation and treatment. Timespent counseling patients on the importance of notifying partners is associated with improved notification outcomes *(88)*. When possible, clinicians should advise persons to bring their primary sex partner along with them when returning for treatment and should concurrently treat both persons. Although this approach can be effective for a main partner *(89,90)*, it might not be feasible approach for additional sex partners. Some evidence suggests that providing patients with written information to share with sex partners can increase rates of partner treatment *(87)*.

The types and comprehensiveness of public health partner services and the specific STDs for which they are offered vary by public health agency and the geographic burden of STDs. In most areas of the United States, health departments routinely attempt to provide partner services to all persons with early syphilis (primary, secondary, and early latent syphilis) and persons with a new diagnosis of HIV infection. It is also recommended that health departments provide partner services for persons who might have cephalosporin-resistant gonorrhea. In contrast, relatively few U.S. health departments routinely provide partner services to persons with gonorrhea, chlamydial infection, trichomonas, or other STDs *(91)*. Clinicians should familiarize themselves with public health practices in their area, but in most instances, providers should understand that responsibility for ensuring the treatment of partners of persons with STDs other than syphilis and HIV rests with the diagnosing provider and the patient.

Many health departments now use the internet to notify the sex partners of persons with STDs *(92)*, especially MSM and in cases where no other identifying information is available (http://www.ncsddc.org/Internet_Guidelines). Clinical providers are unlikely to participate directly in internet partner notification. Internet sites allowing patients to send anonymous e-mail or text messages advising partners of their exposure to an STD are operational in some areas; anonymous notification via the internet is considered better than no notification at all and might be an option in some instances. However, because the extent to which these sites affect partner notification and treatment is uncertain, patients should be encouraged either to notify their partners in person or by telephone, personal e-mail, or text message; alternatively, patients can authorize a medical provider or public health professional to do so.

Expedited Partner Therapy

Expedited Partner Therapy (EPT), also termed patient-delivered partner therapy (PDPT), is the clinical practice of treating the sex partners of persons who receive chlamydia or gonorrhea diagnoses by providing medications or prescriptions to the patient. Patients then provide partners with these therapies without the health-care provider having examined the partner (see http://www.cdc.gov/std/ept). Unless prohibited by law or other regulations, medical providers should routinely offer EPT to heterosexual patients with chlamydia or gonorrhea infection when the provider cannot confidently ensure that all of a patient's sex partners from the prior 60 days will be treated. If the patient has not had sex in the 60 days before diagnosis, providers should attempt to treat a patient's most recent sex partner. EPT is legal in most states. However, providers should visit http://www.cdc.gov/std/ept to obtain updated information for their state. Providing patients with appropriately packaged medication is the preferred approach to PDPT because data on the efficacy of PDPT using prescriptions is limited and many persons do not fill the prescriptions given to them by a sex partner. Medication or prescriptions provided for PDPT

should be accompanied by treatment instructions, appropriate warnings about taking medications (if the partner is pregnant or has an allergy to the medication), general health counseling, and a statement advising that partners seek medical evaluation for any symptoms of STD, particularly PID.

The evidence supporting PDPT is based on three U.S. clinical trials involving heterosexual men and women with chlamydia or gonorrhea *(93–95)*. All three trials reported that more partners were treated when patients were offered PDPT: two reported statistically significant declines in the rate of reinfection and one observed a lower risk of persistent or recurrent infection that was statistically nonsignificant. A fourth trial in the United Kingdom did not demonstrate a difference in the risk of reinfection or in the numbers of partners treated between persons offered PDPT and those advised to notify their sex partners *(96)*.

U.S. trials and a meta-analysis of PDPT revealed that the magnitude of reduction in reinfection of index case-patients compared with patient referral differed according to the STD and the sex of the index case-patient *(87,93–95)*. However, across trials, reductions in chlamydia prevalence at follow-up were approximately 20%; reductions in gonorrhea at follow-up were approximately 50%. Existing data suggest that PDPT also might have a role in partner management for trichomoniasis; however, no single partner management intervention has been shown to be more effective than any other in reducing trichomoniasis reinfection rates *(97,98)*. No data support use of PDPT in the routine management of patients with syphilis. Data on the use of PDPT for gonorrhea or chlamydial infection among MSM are limited *(99,100)*. Published studies suggest that >5% of MSM without a previous HIV diagnosis have a new diagnosis of HIV infection when evaluated as partners of patients with gonorrhea or chlamydial infection *(101,102)*. As a result, PDPT should not be used routinely in MSM. All persons who receive bacterial STD diagnoses and their sex partners, particularly MSM, should be tested for HIV infection.

Reporting and Confidentiality

The accurate and timely reporting of STDs is integral to public health efforts to assess morbidity trends, allocate limited resources, and assist local health authorities in partner notification and treatment. STD/HIV and acquired immunodeficiency syndrome (AIDS) cases should be reported in accordance with state and local statutory requirements. Syphilis (including congenital syphilis), gonorrhea, chlamydia, chancroid, HIV infection, and AIDS are reportable diseases in every state. Because the requirements for reporting other STDs differ by state, clinicians should be familiar with the reporting requirements applicable within their jurisdictions.

Reporting can be provider- or laboratory-based or both. Clinicians who are unsure of state and local reporting requirements should seek advice from state or local health department STD programs. STDs and HIV reports are kept strictly confidential. In most jurisdictions, such reports are protected by statute or regulation. Before conducting a follow-up of a positive STD-test result, public health professionals should consult the patient's health-care provider if possible to verify the diagnosis and determine the treatments being received.

Special Populations

Pregnant Women

Intrauterine or perinatally transmitted STDs can have severely debilitating effects on pregnant women, their partners, and their fetuses. All pregnant women and their sex partners should be asked about STDs, counseled about the possibility of perinatal infections, and provided access to screening and treatment, if needed.

Recommendations to screen pregnant women for STDs are based on disease severity and sequelae, prevalence in the population, costs, medico-legal considerations (e.g., state laws), and other factors. The screening recommendations in this report are generally broader (i.e., more pregnant women will be screened for more STDs than would by following other screening recommendations) and are consistent with other CDC guidelines.

Recommended Screening Tests

- All pregnant women in the United States should be screened for HIV infection at the first prenatal visit, even if they have been previously tested *(103,104)*. Screening should be conducted after the woman is notified of the need to be screened for HIV as part of the routine panel of prenatal tests, unless she declines (i.e., opt-out screening). For women who decline HIV testing, providers should address their objections, and when appropriate, continue to encourage testing. Women who decline testing because they have had a previous negative HIV test should be informed of the importance of retesting during each pregnancy. Testing pregnant women and treating those who are infected are vital not only to maintain the health of the woman, but to reduce perinatal transmission of HIV through available antiretroviral and obstetrical interventions. Retesting in the third trimester (preferably before 36 weeks' gestation) is recommended for women

at high risk for acquiring HIV infection (e.g., women who use illicit drugs, have STDs during pregnancy, have multiple sex partners during pregnancy, live in areas with high HIV prevalence, or have partners with HIV infection). Rapid HIV screening should be performed on any woman in labor who has not been screened for HIV during pregnancy unless she declines. If a rapid HIV test result is positive in these women, antiretroviral prophylaxis should be administered without waiting for the results of the confirmatory test (*105*).

- A serologic test for syphilis should be performed for all pregnant women at the first prenatal visit (*106*). When access to prenatal care is not optimal, rapid plasma reagin (RPR) card test screening (and treatment, if that test is reactive) should be performed at the time that a pregnancy is confirmed. Women who are at high risk for syphilis or live in areas of high syphilis morbidity should be screened again early in the third trimester (at approximately 28 weeks' gestation) and at delivery. Some states require all women to be screened at delivery. Neonates should not be discharged from the hospital unless the syphilis serologic status of the mother has been determined at least one time during pregnancy and preferably again at delivery if at risk. Any woman who delivers a stillborn infant should be tested for syphilis.

- All pregnant women should be routinely tested for hepatitis B surface antigen (HBsAg) at the first prenatal visit even if they have been previously vaccinated or tested (*107*). Women who were not screened prenatally, those who engage in behaviors that put them at high risk for infection (e.g., having had more than one sex partner in the previous 6 months, evaluation or treatment for an STD, recent or current injection-drug use, and an HBsAg-positive sex partner) and those with clinical hepatitis should be retested at the time of admission to the hospital for delivery. Pregnant women at risk for HBV infection also should be vaccinated. To avoid misinterpreting a transient positive HBsAg result during the 21 days after vaccination, HBsAg testing should be performed before vaccine administration. All laboratories that conduct HBsAg tests should test initially reactive specimens with a licensed neutralizing confirmatory test. When pregnant women are tested for HBsAg at the time of admission for delivery, shortened testing protocols can be used, and initially reactive results should prompt expedited administration of immunoprophylaxis to neonates (*107*). Pregnant women who are HBsAg positive should be reported to the local or state health department to ensure that they are entered into a case-management system and that timely and appropriate prophylaxis is provided to their infants. Information concerning the pregnant woman's HBsAg status should be provided to the hospital in which delivery is planned and to the health-care provider who will care for the newborn. In addition, household and sex contacts of women who are HBsAg positive should be vaccinated. Women who are HBsAg positive should be provided with, or referred for, appropriate counseling and medical management.

- All pregnant women aged <25 years and older women at increased risk for infection (e.g., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection) should be routinely screened for *Chlamydia trachomatis* at the first prenatal visit (*108*). Women aged <25 years and those at increased risk for chlamydia also should be retested during the third trimester to prevent maternal postnatal complications and chlamydial infection in the neonate. Pregnant women found to have chlamydial infection should have a test-of-cure to document chlamydial eradication (preferably by nucleic acid amplification testing [NAAT]) 3–4 weeks after treatment and then retested within 3 months. Screening during the first trimester might prevent the adverse effects of chlamydia during pregnancy, but evidence for such screening is lacking.

- All pregnant women aged <25 years and older women at increased risk for gonorrhea (e.g., those with a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection) should be screened for *N. gonorrhoeae* at the first prenatal visit (*108*). Additional risk factors for gonorrhea include inconsistent condom use among persons not in mutually monogamous relationships, previous or coexisting sexually transmitted infection, and exchanging sex for money or drugs. Clinicians should consider the communities they serve and might choose to consult local public health authorities for guidance on identifying groups that are at increased risk. Gonococcal infection, in particular, is concentrated in specific geographic locations and communities. Women found to have gonococcal infection should be treated immediately and retested within 3 months. Pregnant women who remain at high risk for gonococcal infection also should be retested during the third trimester to prevent maternal postnatal complications and gonococcal infection in the neonate.

- All pregnant women at risk for HCV infection should be screened for hepatitis C antibodies at the first prenatal visit. The most important risk factor for HCV infection is past or current injection drug use (*109*). Additional

risk factors include having had a blood transfusion before July 1992, receipt of an unregulated tattoo, having been on long-term hemodialysis, intranasal drug use, and other percutaneous exposures. No established treatment regimen exists for pregnant women infected with HCV. However, all women with HCV infection should receive appropriate counseling and supportive care as needed (see Hepatitis C, Prevention). No vaccine is available to prevent HCV transmission.

- Pregnant women should undergo a Papanicolau (Pap) test at the same frequency as nonpregnant women, although recommendations for management of abnormal Pap tests in pregnancy differ (*110*).

Other Tests

- Evidence does not support routine screening for BV in asymptomatic pregnant women at high risk for preterm delivery (*111*). Symptomatic women should be evaluated and treated (see Bacterial Vaginosis).
- Evidence does not support routine screening for *Trichomonas vaginalis* in asymptomatic pregnant women. Women who report symptoms should be evaluated and treated appropriately (see Trichomonas).
- Evidence does not support routine HSV-2 serologic screening among asymptomatic pregnant women. However, type-specific serologic tests might be useful for identifying pregnant women at risk for HSV infection and guiding counseling regarding the risk for acquiring genital herpes during pregnancy. In the absence of lesions during the third trimester, routine serial cultures for HSV are not indicated for women in the third trimester who have a history of recurrent genital herpes.

For a more detailed discussion of STD screening and treatment among pregnant women, refer to the following references: *Screening for HIV in Pregnant Women: Systematic Review to Update the* 2005 *U.S. Preventive Services Task Force Recommendation (103); Screening for HIV: U.S. Preventive Services Task Force Recommendation Statement (104); ACOG/AAP Guidelines for Perinatal Care (112); Rapid HIV Antibody Testing During Labor and Delivery for Women of Unknown HIV Status: A Practical Guide and Model Protocol (113); Viral Hepatitis in Pregnancy (114); Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States — Recommendations of the Immunization Practices Advisory Committee (ACIP) (4); Screening for Chlamydia and Gonorrhea: U.S. Preventive Services Task Force Recommendation Statement (108); Canadian guidelines on sexually transmitted infections (115); USPSTF recommendations for STI screening (116); and Screening for Bacterial Vaginosis in Pregnancy to*

Prevent Preterm Delivery: U.S. Preventive Services Task Force Recommendation Statement (111).

Adolescents

In the United States, prevalence rates of many sexually acquired infections are highest among adolescents and young adults (*117,118*). For example, the reported rates of chlamydia and gonorrhea are highest among females during their adolescent and young adult years, and many persons acquire HPV infection at this time.

Persons who initiate sex early in adolescence are at higher risk for STDs, along with adolescents residing in detention facilities, those who use injection drugs, adolescents attending STD clinics, and young men who have sex with men (YMSM). Factors contributing to this increased risk during adolescence include having multiple sexual partners concurrently, having sequential sexual partnerships of limited duration, failing to use barrier protection consistently and correctly, having increased biologic susceptibility to infection, and facing multiple obstacles to accessing health care (*118*).

All 50 states and the District of Columbia explicitly allow minors to consent for their own health services for STDs. No state requires parental consent for STD care, although some states restrict a minor's ability to provide consent on the basis of age or type of service (i.e., prevention, diagnosis, or treatment only). No state requires that providers notify parents that an adolescent minor has received STD services, except in limited or unusual circumstances. However, many states authorize parental notification of a minor's receipt of STD services, even where the minor can legally provide his or her own consent to the service (http://www.guttmacher.org/statecenter/spibs/spib_OMCL.pdf; http://www.cahl.org/state-minor-consent-laws-a-summary-third-edition). Protecting confidentiality for such care, particularly for adolescents enrolled in private health insurance plans, presents multiple problems. After a claim has been reported, many states mandate that health plans provide a written statement to the beneficiary indicating the service performed, the charges covered, what the insurer allows, and the amount for which the patient is responsible (i.e., explanation of benefit [EOB]) (*119*). In addition, federal laws obligate notices to beneficiaries when claims are denied, including alerting beneficiaries who need to pay for care until the allowable deductible is reached. For STD detection- and treatment-related care, an EOB or medical bill that is received by a parent might disclose services provided and list STD laboratory tests performed or treatment given.

Despite the high rates of infections documented in the adolescent population, providers frequently fail to inquire about sexual behaviors, assess STD risks, provide risk-reduction

counseling, and ultimately, screen for asymptomatic infections during clinical encounters. Discussions concerning sexual behavior should be appropriate for the patient's developmental level and should be aimed at identifying risk behaviors (e.g., multiple partners; unprotected oral, anal, or vaginal sex; and drug-use behaviors). Careful, nonjudgmental, and thorough counseling is particularly vital for adolescents who might not feel comfortable acknowledging their engagement in behaviors that place them at high risk for STDs.

Screening Recommendations

Routine laboratory screening for common STDs is indicated for sexually active adolescents. The following screening recommendations summarize published federal agency and medical professional organizations' clinical guidelines for sexually active adolescents.

- Routine screening for *C. trachomatis* on an annual basis is recommended for all sexually active females aged <25 years (*108*). Evidence is insufficient to recommend routine screening for *C. trachomatis* in sexually active young men based on efficacy and cost-effectiveness. However, screening of sexually active young males should be considered in clinical settings serving populations of young males with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and STD clinics) and should be offered to YMSM (see Special Populations, MSM) (*120,121*).
- Routine screening for *N. gonorrhoeae* on an annual basis is recommended for all sexually active females <25 years of age (*108*). Gonococcal infection is concentrated in specific geographic locations and communities. Clinicians should consider the communities they serve and might choose to consult local public health authorities for guidance on identifying groups that are at increased risk. Screening should be offered to YMSM (see MSM section).
- HIV screening should be discussed and offered to all adolescents. Frequency of repeat screenings of those who are at risk for HIV infection should be based on level of risk (*122,123*). Persons who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.
- The routine screening of adolescents who are asymptomatic for certain STDs (e.g., syphilis, trichomoniasis, BV, HSV, HPV, HAV, and HBV) is not generally recommended. However, YMSM and pregnant adolescent females should be screened for syphilis.
- Guidelines from USPSTF, ACOG, and ACS recommend that cervical cancer screening begin at age 21 years (*124–126*). This recommendation is based on the low

incidence of cervical cancer and limited utility of screening for cervical cancer in adolescents (*127*).

Primary Prevention Recommendations

Primary prevention and anticipatory guidance to recognize symptoms and behaviors associated with STDs are strategies that can be incorporated into any or all types of health-care visits for adolescents and young adults. The following recommendations for primary prevention of STDs (i.e., vaccination and counseling) are based on published federal agency and medical professional organizations' clinical guidelines for sexually active adolescents and young adults.

- The HPV vaccine, bivalent, quadrivalent, or 9-valent, is recommended routinely for females aged 11 and 12 years and can be administered beginning at 9 years of age (*16*) http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html. Vaccination is also recommended for females aged 13–26 years who have not yet received all doses or completed the vaccine series. The quadrivalent or 9-valent HPV vaccine is recommended routinely for males aged 11 and 12 years and also can be administered beginning at 9 years of age (*16*). Vaccination with quadrivalent or the 9-valent HPV vaccine is recommended for males aged 13–21 years who have not yet received all doses or completed the vaccine series, although males aged 22–26 years also can be vaccinated (*16*). For persons with HIV infection and for MSM, vaccination is recommended through age 26. HPV vaccination has not been associated with a change in perceptions about risks posed by sexual behavior (*128*).
- The HBV vaccination series is recommended for all adolescents and young adults who have not previously received the hepatitis B vaccine (*3,4*).
- The HAV vaccination series should be offered to adolescents and young adults who have not previously received the HAV vaccine series.
- Information regarding HIV infection, testing, transmission, and implications of infection should be regarded as an essential component of the anticipatory guidance provided to all adolescents and young adults as part of health care (*122*).
- Health-care providers who care for adolescents and young adults should integrate sexuality education into clinical practice. Providers should counsel adolescents about the sexual behaviors that are associated with risk for acquiring STDs and educate patients regarding evidence-based prevention strategies, all of which include a discussion about abstinence and other risk-reduction behaviors (e.g., consistent and correct condom use and reduction in the number of sex partners). Interactive counseling approaches,

such as high-intensity behavioral counseling (HIBC) and motivational interviewing, are effective STD/HIV prevention strategies. USPSTF recommends high-intensity behavioral counseling for all sexually active adolescents (7) to prevent sexually transmitted infections.* Educational materials (e.g., handouts, pamphlets, and videos) can reinforce office-based educational efforts.

Children

Management of children who have STDs requires close cooperation between clinicians, laboratorians, and child-protection authorities. Official investigations, when indicated, should be initiated promptly. Certain diseases (e.g., gonorrhea, syphilis, and chlamydia), if acquired after the neonatal period, strongly suggest sexual contact. For other diseases (e.g., HPV infections and vaginitis), the association with sexual contact is not as clear (see Sexual Assault and STDs).

Persons in Correctional Facilities

Multiple studies have demonstrated that persons entering correctional facilities have high rates of STDs (including HIV) and viral hepatitis (http://www.cdc.gov/hepatitis/Settings/corrections.htm), especially those aged ≤35 years (118). Incarcerated persons are more likely to have low socioeconomic status, live in urban areas, and be ethnic and racial minorities. Risk behaviors for contracting STDs (e.g., having unprotected sex; having multiple sexual partners; using drugs and alcohol; and engaging in commercial, survival, or coerced sex) are common among incarcerated populations. Before incarceration, many have had limited access to medical care.

Although no comprehensive national guidelines regarding STD care and management have been developed for correctional populations, growing evidence demonstrates the utility of expanded STD screening and treatment services in correctional settings. For example, in jurisdictions with comprehensive, targeted jail screening, more chlamydial infections among females (and males if screened) are detected and subsequently treated in the correctional setting than any other single reporting source (118,129) and might represent the majority of reported cases in certain jurisdictions (130).

Both men and women ≤35 years of age in juvenile and adult detention facilities have been reported to have higher rates of chlamydia (131) and gonorrhea (118) than their nonincarcerated counterparts in the community, and across many studies, rates have been consistently higher among women than men. Syphilis seroprevalence rates, which can

indicate previous or current infection, are considerably higher among adult men and women than in adolescents, consistent with the overall national syphilis trends (132). Detection and treatment of early syphilis in correctional facilities might impact rates of transmission (133).

In short-term facilities, including jails and juvenile detention facilities that commonly house entrants for <1 year, up to half of entrants are released back in the community within 48 hours. As a result, treatment completion rates for those screened for STDs and who receive STD diagnoses in short-term facilities might not be optimal. However, because of the mobility of incarcerated populations in and out of the community, the impact of screening in correctional facilities on the prevalence of infections among detainees and subsequent transmission in the community after release might be considerable (134). Moreover, treatment completion rates of ≥95% can be achieved by offering screening at or shortly after intake, facilitating earlier receipt of test results; follow-up of untreated persons can be conducted through public health outreach (130).

Universal screening for chlamydia and gonorrhea in women ≤35 years entering juvenile and adult correctional facilities has been a long-standing recommendation. However, no such recommendation existed for men until 2006, when CDC convened a consultation on male chlamydia screening (121) that resulted in recommendations to screen men <30 years for chlamydia at intake into jails.

Whereas several studies have shown a high prevalence of trichomonas among incarcerated persons, none have demonstrated the impact of trichomonas screening in correctional facilities (135–137). Women who report vaginal discharge should be evaluated and treated appropriately.

Chlamydia and Gonorrhea Screening

Women ≤35 and men <30 years in correctional facilities should be screened for chlamydia and gonorrhea. Chlamydia and gonorrhea screening should be conducted at intake.

Syphilis Screening

Universal screening should be conducted on the basis of the local area and institutional prevalence of early (primary, secondary, and early latent) infectious syphilis. Correctional facilities should stay apprised of syphilis prevalence as it changes over time.

Men Who Have Sex with Men

The term "men who have sex with men" (MSM) describes a heterogeneous group of men who have varied behaviors, identities, and health-care needs (138). Some MSM are at high risk for HIV infection and other viral and bacterial STDs

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* STI is the term used by USPSTF to describe the syndromes caused by various pathogens that can be acquired and transmitted through sexual activity.

because MSM may practice anal sex, and the rectal mucosa is uniquely susceptible to certain STD pathogens. In addition, multiple sex partners, substance use, and sexual network dynamics of MSM increase risk for HIV and STDs in this population. The frequency of unsafe sexual practices and the reported rates of bacterial STDs and incident HIV infection declined substantially in MSM from the 1980s through the mid-1990s. However, since that time, increased rates of early syphilis (primary, secondary, or early latent), gonorrhea, and chlamydial infection and higher rates of sexual risk behaviors have been documented among MSM in the United States and virtually all industrialized countries.

Approximately two thirds of the cases of primary and secondary syphilis diagnoses in the United States are in MSM, particularly those in ethnic minority groups (*118,139,140*). Increased syphilis screening in MSM demonstrated a doubling of early syphilis detection; however, 71% of the syphilis diagnoses occurred when the patient sought care for symptoms (*141*). Acute HIV infection has been associated with a recent or concurrent STD, including syphilis, among men at a municipal STD clinic (*142*) and in the multisite iPrex study (*143*), and several studies have demonstrated that early syphilis is associated with HIV infection among MSM (*144,145*). Factors associated with increases in syphilis among MSM have included substance abuse (e.g., methamphetamine), having multiple anonymous partners, and seeking sex partners through the internet (*146,147*). One study found that 5.9% of MSM had repeat primary or secondary syphilis infection within 2 years of an initial infection; factors associated with repeat syphilis infection were HIV infection, black race, and having ≥10 recent sexual partners *(148)*. Because of this risk for repeat infection, these data suggest that prevention efforts should include follow up serologic testing.

Gonococcal infection in MSM has been associated with similar risk factors, including having multiple anonymous partners and abuse of substances, particularly crystal methamphetamine (*149*). Rectal gonococcal rates are increasing among MSM with HIV infection, underscoring the importance of obtaining an accurate, current sexual history and asking about correlates of increased risk (e.g., anonymous sex and substance use) (*150*). Insertive oral sex has been associated with urethral gonorrhea acquisition (*151,152*); the prevalence of pharyngeal gonorrhea and pharyngeal chlamydia has been demonstrated to be 7.3% and 2.3%, respectively (*153*). In a multicity study, rectal gonorrhea and rectal chlamydia prevalence rates among MSM were 5.4% and 8.9%, respectively (*154*). Rectal gonorrhea and chlamydia infections, especially those that are recurrent, have been associated with increased risk for HIV seroconversion among MSM (*155,156*). MSM with new HIV infection diagnoses are more likely than

HIV-uninfected MSM to receive a diagnosis of asymptomatic gonorrhea (25.9% versus 10.9%, p<0.001) and chlamydia (18.5% vs 7.8%, p<0.001) (*157*). Thus, rectal gonorrhea and chlamydia screening in MSM might be a cost-effective intervention in certain urban settings (*158*).

MSM remain at disproportionate risk for HIV acquisition and transmission in the United States, particularly those who are black or Hispanic. Factors that increase the risk for HIV infection in MSM include either receptive or insertive anal sex without a condom, having another STD, having sex with anonymous partners without a condom, and using methamphetamines or drugs that enhance sexual performance (*159*).

Substantial numbers of MSM remain unaware of their serostatus (up to 44% in one recent survey of young men in minority populations) (*160*). Unfortunately, many men are not asked about STD-related risks, including the gender of sex partners. Even if gender of sex partners is ascertained, many MSM, including those with HIV infection, are neither asked about risky sexual behaviors nor provided with routine STD testing (especially at anatomic sites of exposure for gonorrhea or chlamydia), often because of the discomfort associated with these discussions (*161–163*). Clinicians should routinely ask sexually active MSM about symptoms consistent with common STDs, including urethral discharge, dysuria, genital and perianal ulcers, regional lymphadenopathy, skin rash, and anorectal symptoms consistent with proctitis (e.g., discharge and pain on defecation or during anal intercourse) and then perform appropriate diagnostic testing. In addition, providers should offer evidence-based counseling on safer sex using interventions that have been demonstrated to decrease STD incidence in clinical-care settings (*10*).

Clinicians should be familiar with local resources available to assist MSM with syphilis and HIV partner services as well as HIV linkage and retention in care. In addition, interventions promoting behavior change also might be appropriate. In recent years, medical educational materials have been developed in print (*164*) and through electronic media (http://www.lgbthealtheducation.org) to increase primary-care provider knowledge and cultural competency regarding the diagnosis and management of STDs and other clinical conditions in the lesbian, gay, bisexual, and transgender populations. Electronic media is also an important tool for disseminating and collecting information to and from MSM. Because many MSM meet partners online and seek health information from websites, increased use of the internet for STD prevention might be warranted. MSM are amenable to receiving HIV and STD risk-reduction messages online (*165*) and willing to respond to requests for partner identification from public health authorities through the internet (*166*).

The following screening tests should be performed at least annually for sexually active MSM, including those with HIV infection.

- HIV serology, if HIV status is unknown or negative and the patient himself or his sex partner(s) has had more than one sex partner since most recent HIV test.
- Syphilis serology to establish whether persons with reactive tests have untreated syphilis, have partially treated syphilis, are manifesting a slow serologic response to appropriate prior therapy, or are serofast.
- A test for urethral infection[†] with *N. gonorrhoeae* and *C. trachomatis* in men who have had insertive intercourse[§] during the preceding year (testing of the urine using NAAT[†] is the preferred approach).
- A test for rectal infection[†] with *N. gonorrhoeae* and *C. trachomatis* in men who have had receptive anal intercourse[§] during the preceding year (NAAT of a rectal specimen is the preferred approach).
- A test for pharyngeal infection[†] with *N. gonorrhoeae* in men who have had receptive oral intercourse[§] during the preceding year (NAAT of a pharyngeal specimen is the preferred approach). Testing for *C. trachomatis* pharyngeal infection is not recommended.

MSM with HIV infection are also at risk for STDs. Data from a study of 557 adults with HIV infection receiving primary care in four U.S. cities demonstrate that 13% had STD at study enrollment, and 7% had incident STD at 6 months; among MSM with HIV infection, STD incidence was 20% (*10*). Excluding trichomoniasis, 94% of incident STDs were diagnosed in MSM. All MSM with HIV infection entering care should be screened for gonorrhea and chlamydia at appropriate anatomic sites of exposure, as well as for syphilis (*17*). The frequency of follow-up testing might be dictated by subsequent behavior; screening is recommended annually, at a minimum, to include syphilis serologic testing and chlamydia and gonorrhea screening at exposed anatomic sites (*138*). STD screening rates in HIV clinics have been suboptimal. In one study involving eight U.S. cities, although syphilis testing was provided to most MSM with HIV infection, <10% were screened for extra-genitourinary gonorrhea or chlamydia, and <20% provided the urine or urethral specimens needed for testing (*162*). More frequent STD screening (i.e., for syphilis, gonorrhea, and chlamydia) at 3–6-month intervals is indicated for MSM, including those with HIV infection if risk behaviors

persist or if they or their sexual partners have multiple partners. Evaluation for HSV-2 infection with type-specific serologic tests also can be considered if infection status is unknown in persons with previously undiagnosed genital tract infection.

HPV infection and HPV-associated conditions (e.g., anogenital warts and anal squamous intraepithelial lesions) are highly prevalent among MSM. The quadrivalent vaccine is recommended routinely for MSM through age 26 years (*16,167,168*); the efficacy of this vaccine in preventing HPV associated diseases in men aged >26 years is unknown.

Data are insufficient to recommend routine anal-cancer screening with anal cytology in persons with HIV infection or HIV-negative MSM. More evidence is needed concerning the natural history of anal intraepithelial neoplasia, the best screening methods and target populations, safety of and response to treatments, and other programmatic considerations before screening can be routinely recommended. However, some clinical centers perform anal cytology to screen for anal cancer among high-risk populations (e.g., persons with HIV infection and MSM), followed by high-resolution anoscopy for those with abnormal cytologic results (e.g., ASC-US).

All MSM should be tested for HBsAg to detect chronic HBV infection. Prompt identification of chronic infection with HBV is essential to ensure necessary care and services to prevent transmission to others (*169*). Screening among past or current drug users should include HCV and HBV testing. Vaccination against hepatitis A and B is recommended for all MSM in whom previous infection or vaccination cannot be documented (*2,3*). Preimmunization serologic testing might be considered to reduce the cost of vaccinating MSM who are already immune to these infections, but this testing should not delay vaccination. Vaccinating persons who are immune to HAV or HBV infection because of previous infection or vaccination does not increase the risk for vaccine-related adverse events (see Hepatitis A and Hepatitis B).

Sexual transmission of HCV can occur, especially among MSM with HIV infection (see Emerging Issues, Hepatitis C). Serologic screening for HCV is recommended at initial evaluation of persons with newly diagnosed HIV infection. Because of accumulating evidence of acute HCV infection acquisition among persons with HIV infection (especially MSM with HIV infection [*170–175*]) and because regular screening for HCV infection is cost effective (*176,177*), MSM with HIV infection should be regularly screened for HCV. Screening should be performed at least yearly and more frequently depending on specific circumstances (e.g., local HCV prevalence and incidence, high-risk sexual behavior, and concomitant ulcerative STDs or STD-related proctitis). Screening should be performed using HCV antibody assays

[†] Regardless of condom use during exposure.

[§] Commerically available NAATs have not been cleared by FDA for these indications, but they can be used by laboratories that have met all regulatory requirements for an off-label procedure. Source: CDC. Recommendations for the laboratory-based detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* — 2014. MMWR Recomm Rep 2014;63(No RR-2):1-19.

followed by HCV RNA testing for those with a positive antibody result (*178*).

Women Who Have Sex with Women

Women who have sex with women (WSW) are a diverse group with variations in sexual identity, sexual behaviors, sexual practices, and risk behaviors. Recent studies indicate that some WSW, particularly adolescents and young women as well as women with both male and female partners, might be at increased risk for STDs and HIV based on reported risk behaviors (*179–183*). Certain studies have highlighted the wide diversity of sexual practices and examined use of protective/risk reduction strategies among populations of WSW (*184–186*). Use of barrier protection with female partners (gloves during digital-genital sex, condoms with sex toys, and latex or plastic barriers [also known as dental dams for oral-genital sex]) was infrequent in all studies. Despite this, few comprehensive and reliable resources of sexual health information for WSW are available (*187*).

Few data are available on the risk for STDs conferred by sex between women, but transmission risk probably varies by the specific STD and sexual practice (e.g., oral-genital sex; vaginal or anal sex using hands, fingers, or penetrative sex items; and oral-anal sex) (*188,189*). Practices involving digital-vaginal or digital-anal contact, particularly with shared penetrative sex items, present a possible means for transmission of infected cervicovaginal or anal secretions. This possibility is most directly supported by reports of shared trichomonas infections (*190,191*) and by concordant drug resistance genotype testing and phylogenetic linkage analysis identifying HIV transmitted sexually between women (*192,193*). Most self-identified WSW (53%–97%) have had sex with men in the past and might continue this practice, with 5%–28% of WSW reporting male partners within the past year (*189,194–196*).

HPV, which can be transmitted through skin-to-skin contact, is common among WSW, and sexual transmission of HPV likely occurs between female sex partners (*197–199*). HPV DNA has been detected through polymerase chain reaction (PCR)-based methods from the cervix, vagina, and vulva in 13%–30% of WSW (*197,198*). Among WSW who reported never having had a male sexual partner, 26% had antibodies to HPV-16, and 42% had antibodies to HPV-6 (*197*). High- and low-grade squamous intraepithelial lesions (SIL) have been detected on Pap tests in WSW who reported no previous sex with men *(197,198,200,201)*. WSW are at risk for acquiring HPV from both their female partners and from current or prior male partners, and thus are at risk for cervical cancer. Therefore, routine cervical cancer screening should be offered to all women, regardless of sexual orientation or sexual practices, and women should be offered HPV vaccine as per current guidelines (*16*).

Genital transmission of HSV-2 between female sex partners is inefficient, but can occur. A U.S. population-based survey among women aged 18–59 years demonstrated an HSV-2 seroprevalence of 30% among women reporting same-sex partners in the past year, 36% among women reporting same-sex partners in their lifetime, and 24% among women reporting no lifetime same-sex behavior (*195*). HSV-2 seroprevalence among women self-identifying as "homosexual or lesbian" was 8%, similar to a prior clinic-based study of WSW (*195,196*). The relatively frequent practice of orogenital sex among WSW might place them at higher risk for genital infection with HSV-1, a hypothesis supported by the recognized association between HSV-1 seropositivity and previous number of female partners among WSW. Thus, sexual transmission of HSV-1 and HSV-2 can occur between female sex partners. This information should be communicated to women as part of a larger sexual health counseling and evaluation effort.

Less is known regarding transmission of bacterial STDs between female partners. Transmission of syphilis between female sex partners, probably through oral sex, has been reported. Although the rate of transmission of *C. trachomatis* between women is unknown, infection also might be acquired from past or current male partners. More recent data suggests that *C. trachomatis* infection among WSW might be more common than previously believed (*179,202*). Reports of same-sex behavior in women should not deter providers from offering and providing screening for STDs, including chlamydia, according to current guidelines.

BV is common among women in general and even more so among women with female partners (*203,204*). Sexual behaviors that facilitate the transfer of vaginal fluid and bacteria between partners may be involved in the pathogenesis of BV. A study including monogamous couples demonstrated that female sex partners frequently share identical genital *Lactobacillus* strains (*205*). Within a community-based cohort of WSW, extravaginal (i.e., oral and rectal) reservoirs of BV-associated bacteria were a risk factor for incident BV (*206*). Several new studies have examined the impact of specific sexual practices on the vaginal microflora (*207–209*) and on recurrent (*210*) or incident (*211,212*) BV among WSW and non-WSW. These studies have continued to support, though have not proven, the hypothesis that sexual behaviors, specific BV-associated bacteria, and possibly exchange of vaginal or extravaginal microbiota (e.g., oral bacterial communities) between partners might be involved in the pathogenesis of BV in WSW.

Although BV is common in WSW, routine screening for BV is not recommended. Results of a randomized trial using a

behavioral intervention to reduce persistent BV among WSW through reduced sharing of vaginal fluid on hands or sex toys has been published (*213*). Although women randomized to the intervention were 50% less likely to report receptive digital-vaginal contact without gloves than controls and reported sharing sex toys infrequently, these women had no reduction in persistent BV at 1 month post-treatment and no reduction in incident episodes of recurrent BV. To date, no reported trials have examined the potential benefits of treating female partners of women with BV; thus, no recommendation can be made regarding partner therapy in WSW. Increasing awareness of signs and symptoms of BV in women and encouraging healthy sexual practices (e.g., avoiding shared sex toys, cleaning shared sex toys, and barrier use) might benefit women and their partners. WSW are at risk for acquiring bacterial, viral, and protozoal STDs from current and prior partners, both male and female. WSW should not be presumed to be at low or no risk for STDs based on sexual orientation. Report of same sex behavior in women should not deter providers from considering and performing screening for STDs and cervical cancer according to current guidelines. Effective screening requires that care providers and their female patients engage in a comprehensive and open discussion of sexual and behavioral risks that extends beyond sexual identity.

Transgender Men and Women

Persons who are transgender identify with a sex that differs from that they were assigned at birth. Transgender women ("trans-women" or "transgender male to female") identify as women but were born with male anatomy. Similarly, transgender men (also referred to as "trans-men" or "transgender female to male") identify as men but were born with female anatomy. However, transgender persons might use different and often fluid terminology to refer to themselves through their life course. Gender identity is independent from sexual orientation. Persons who are transgender might have sex with men, women, or both and consider themselves to be heterosexual, gay, lesbian, or bisexual. Prevalence studies of transgender persons in the overall population have been limited and often based on small convenience samples.

Transgender Women

A systematic review of studies of HIV among transgender women suggests that the prevalence of HIV in the United States is 27.7% among all transgender women and 56.3% among black transgender women (*214*). Data also suggests high rates of HIV among transgender women globally (*215*). Bacterial STD prevalence varies among transgender women, but is based largely on convenience samples. Providers caring for

transgender women should have knowledge of their patients' current anatomy and patterns of sexual behavior before counseling them about STD and HIV prevention (*216*). Most transgender women have not undergone genital affirmation surgery and may retain a functional penis *(217–219)*; in this instance, they might engage in insertive oral, vaginal, or anal sex with men and women.

Transgender Men

The few studies of HIV prevalence and incidence in transgender men suggest that although some transgender men engage in risky behaviors, they have a lower prevalence of HIV than transgender women (*220*). Providers should consider the anatomic diversity among transgender men, because many still have a vagina and cervix and are at risk for bacterial STDs, cervical HPV, and cervical cancer (*221*).

Recommendations

Clinicians should assess STD- and HIV-related risks for their transgender patients based on current anatomy and sexual behaviors. Because of the diversity of transgender persons regarding surgical affirming procedures, hormone use, and their patterns of sexual behavior, providers must remain aware of symptoms consistent with common STDs and screen for asymptomatic STDs on the basis of behavioral history and sexual practices.

Emerging Issues
Hepatitis C

HCV infection is the most common chronic bloodborne infection in the United States, with an estimated 2.7 million persons living with chronic infection (*222*). HCV is not efficiently transmitted through sex (*170,223*). Studies of HCV transmission between heterosexual or homosexual couples have yielded mixed results, but generally have found either no or very minimally increased rates of HCV infection in partners of persons with HCV infection compared with those whose partners are not HCV-infected (*223–230*). However, data indicate that sexual transmission of HCV can occur, especially among persons with HIV infection. Increasing incidence of acute HCV infection among MSM with HIV infection has been reported in New York City (*231,232*) and Boston (*175,177*), along with multiple European cities *(233–235)*. These men usually engage in high-risk and traumatic sexual practices and might have concurrent genital ulcerative disease or STD-related proctitis (*233,235*). Other common practices associated with new cases of HCV infection include group sex and use of cocaine and other nonintravenous drugs during sex.

Certain studies have revealed that risk increases commensurate with increasing numbers of sex partners among heterosexual persons with HIV infection (*225,226,236–238*) and MSM (*239–242*), especially if their partners are also coinfected with HIV (*234,235,239–243*).

Persons newly infected with HCV typically are either asymptomatic or have a mild clinical illness. HCV RNA can be detected in blood within 1–3 weeks after exposure. The average time from exposure to antibody to HCV (anti-HCV) seroconversion is 8–9 weeks, and anti-HCV can be detected in >97% of persons by 6 months after exposure. Chronic HCV infection develops in 70%–85% of HCV-infected persons; 60%–70% of chronically infected persons develop evidence of active liver disease. Most infected persons remain unaware of their infection because they are not clinically ill. However, infected persons serve as a source of transmission to others and are at risk for CLD and other HCV-related chronic diseases decades after infection.

HCV is primarily transmitted parenterally, usually through shared drug-injection needles and paraphernalia. HCV also can be transmitted through exposures in health-care settings as a consequence of inadequate infection-control practices (*244*). Transmission following receipt of blood, tissues, and organs from donors with HCV infection has occurred only rarely since 1992, when routine screening of these donated products was mandated in the United States. Tattoos applied in regulated settings have not been associated with HCV transmission, although those obtained in unregulated settings have been linked to such transmission (*224*). Occupational and perinatal exposures also can result in transmission of HCV, but such transmission is uncommon.

Acute hepatitis C is a reportable condition in 49 states, and matching viral hepatitis and HIV surveillance registries can facilitate early detection of social networks of HCV transmission among MSM with HIV infection. Suspected clusters of acute HCV infection should be reported to the appropriate public health authorities.

HCV screening is recommended by CDC and USPSTF for all persons born during 1945–1965 and others based on their risk for infection or on a recognized exposure, including past or current injection drug use, receiving a blood transfusion before 1992, long-term hemodialysis, being born to a mother with HCV infection, intranasal drug use, receipt of an unregulated tattoo, and other percutaneous exposures (*109,224,245*).

Diagnosis

Testing for HCV infection should include use of an FDA-cleared test for antibody to HCV (i.e., immunoassay, EIA, or enhanced chemiluminescence immunoassay and, if recommended, a supplemental antibody test) followed by NAAT to detect HCV RNA for those with a positive antibody result (*178*). Persons with HIV infection with low CD4-positive cell count might require further testing by NAAT because of the potential for a false-negative antibody assay.

Persons determined to be anti-HCV positive should be evaluated (by referral or consultation, if appropriate) for the presence of acute infection; presence, severity, or development of CLD; and eligibility for treatment. Nucleic acid testing, including reverse transcriptase polymerase chain reaction (RT-PCR) to detect HCV RNA, is necessary to confirm the diagnosis of current HCV infection, and testing of liver function (alanine aminotransferase level) provides biochemical evidence of CLD.

Treatment

Providers should consult with specialists knowledgeable about management of hepatitis C infection. Further, they can consult existing guidelines to learn about the latest advances in the management of hepatitis C (http://www.hcvguidelines.org).

Management of Sex Partners

Because incident HCV has not been demonstrated to occur in heterosexual couples followed over time (*223,227–229*), condom use might not be necessary in such circumstances. Persons with HCV infection with one long-term, steady sex partner do not need to change their sexual practices. However, they should discuss the low but present risk for transmission with their partner and discuss the need for testing (*170,245*). Heterosexuals and MSM with HCV infection and more than one partner, especially those with concurrent HIV infection, should protect their partners against HCV and HIV acquisition by using male latex condoms (*231,234,235*). Partners of persons with HCV and HIV infection should be tested for HCV and HIV, if not known to be infected.

Other Management Considerations

All persons with HCV for whom HIV and HBV infection status is unknown should be tested for these infections. Those who have HIV or HBV should be referred for or provided with appropriate care and treatment.

Prevention

Reducing the burden of HCV infection and disease in the United States requires implementation of both primary and secondary prevention activities. Primary prevention reduces or eliminates HCV transmission, whereas secondary prevention activities are aimed at reducing CLD and other chronic diseases in persons with HCV infection by first identifying them and then providing medical management and antiviral therapy, if appropriate. No vaccine for hepatitis C is available, and

prophylaxis with immune globulin is not effective in preventing HCV infection after exposure.

Persons with HCV infection should be provided information regarding how to protect their liver from further harm (i.e., hepatotoxic agents); for instance, persons with HCV infection should be advised to avoid drinking alcohol and taking any new medicines (including over-the-counter and herbal medications) without checking with their clinician. In addition, a determination for the need of hepatitis A and B vaccination should be made; persons who are not immune should be vaccinated.

To reduce the risk for transmission to others, persons with HCV infection should be advised 1) not to donate blood, body organs, other tissue, or semen; 2) not to share any personal items that might have blood on them (e.g., toothbrushes and razors); and 3) to cover cuts and sores on the skin to keep the virus from spreading by blood or secretions. Women with HCV infection do not need to avoid pregnancy or breastfeeding.

Persons who use or inject drugs should be counseled about the importance of stopping drug-use behaviors and provided with assistance to enter and complete substance-abuse treatment (including relapse prevention). Persons who continue to inject drugs despite counseling should be encouraged to take the following additional steps to reduce personal and public health risks:

- never reuse or share syringes, water, or drug preparation equipment;
- only use syringes obtained from a reliable source (e.g., pharmacies);
- use a new, sterile syringe to prepare and inject drugs;
- if possible, use sterile water to prepare drugs; otherwise, use clean water from a reliable source (e.g., fresh tap water);
- use a new or disinfected container (i.e., cooker) and a new filter (i.e., cotton) to prepare drugs;
- clean the injection site before injection with a new alcohol swab; and
- safely dispose of syringes after one use.

Postexposure Follow-Up

No postexposure prophylaxis has been demonstrated to be effective against HCV. HCV testing is recommended for health-care workers after percutaneous or permucosal exposures to HCV-positive blood. Children born to women with HCV infection also should be tested for HCV. Prompt identification of acute infection is important, because outcomes are improved when treatment is initiated early in the course of illness.

Special Considerations

Pregnancy

Routine screening for HCV infection is not recommended for all pregnant women. Pregnant women with a known risk factor for HCV infection should be offered screening. Although the rate for transmission is highly variable, up to six of every 100 infants born to HCV-infected women become infected; this infection occurs predominantly during or near delivery, and no treatment or delivery method—such as caesarian section—has been demonstrated to decrease this risk (*246*). However, the risk is increased by the presence of maternal HCV viremia at delivery and is two- to threefold greater if the woman is coinfected with HIV. HCV has not been shown to be transmitted through breast milk, although mothers with HCV infection should consider abstaining from breastfeeding if their nipples are cracked or bleeding. Infants born to mothers with HCV infection should be tested for HCV infection; because maternal antibody is present for the first 18 months of life and before the infant mounts an immunologic response, nucleic acid testing is recommended (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6218a5.htm?s_cid=mm6218a5_w).

HIV Infection

All persons with HIV infection should undergo serologic screening for HCV at initial evaluation (*17,247*). Providers should be aware of the likelihood that MSM with HIV infection will acquire HCV after initial screening. Because of accumulating evidence of acute HCV infection acquisition in persons with HIV infection, especially MSM, and cost-effectiveness of regular screening (*176,177*), periodic HCV screening should be considered (*170–175*). For persons with HIV infection, HCV screening with HCV antibody assays can be considered at least yearly in those at high risk for infection and more frequently depending on specific circumstances (e.g., community HCV prevalence and incidence, high-risk sexual behavior, and concomitant ulcerative STDs and STD-related proctitis). Indirect testing (e.g., ALT) is not recommended for detecting incident HCV infections because such testing, especially if performed once a year, can miss many persons who have reverted after acute HCV infection to a normal ALT level at the time of testing (*175,177*). Conversely, ALT can be elevated by antiretroviral and other medications, alcohol, and toxins. If ALT levels are being monitored, persons with HIV infection who experience new and unexplained increases in ALT should be tested for acute HCV infection and evaluated for possible medication toxicity or excessive alcohol use.

Continued unprotected sexual contact between partners with HIV infection can facilitate spread of HCV, as the virus can be recovered from the semen of men with HIV (*248*).

Specific prevention practices (e.g., barrier precautions that limit contact with body fluids during sexual contact with other MSM) should be discussed.

Because a minimal percentage of persons with HIV infection fail to develop HCV antibodies, HCV RNA testing should be performed in persons with unexplained liver disease who are anti-HCV negative. The course of liver disease is more rapid in HIV/HCV coinfected persons, and the risk for cirrhosis is nearly twice that of persons with HCV infection alone. Coinfected persons receiving HIV antiviral regimens are now being treated for HCV after their CD4+ cell counts increase, optimizing their immune response.

Mycoplasma genitalium

M. genitalium was first identified in the early 1980s (249) and has become recognized as a cause of male urethritis, responsible for approximately 15%–20% of nongonococcal urethritis (NGU) cases, 20%–25% of nonchlamydial NGU, and approximately 30% of persistent or recurrent urethritis (250). In most settings, it is more common than *N. gonorrhoeae* but less common than *C. trachomatis*. While *M. genitalium* is often the sole pathogen detected, coinfection with *C. trachomatis* is not uncommon in selected areas (251–253).

Although strong and consistent evidence has linked *M. genitalium* to urethritis in men, it remains unknown whether this infection can cause male infertility or other male anogenital tract disease syndromes. The organism has been detected in men with epididymitis in a limited number of cases, but this has not been extensively investigated. Similarly, *M. genitalium* has been found in the rectum, but detection is infrequently accompanied by rectal symptoms, and its presence does not appear to cause a syndrome of clinical proctitis.

The pathogenic role of *M. genitalium* is less definitive in women than it is in men. *M. genitalium* can be found in the vagina, cervix, and endometrium and, like chlamydial and gonococcal infections, *M. genitalium* infections in women are commonly asymptomatic. *M. genitalium* can be detected in 10%–30% of women with clinical cervicitis, and most (253–259) studies have found that this organism is more common among women with cervicitis than those without this syndrome (251,260,261).

M. genitalium is found in the cervix and/or endometrium of women with PID more often than in women without PID (262–271), and endosalpingitis develops in nonhuman primates after inoculation with *M. genitalium,* suggesting that this organism can cause PID. *M. genitalium* has been detected in 2%–22% of PID cases (median: 10%) depending on the setting, but the frequency with which *M. genitalium*-infected women experience PID has been under studied. Although one study in Sweden reported a substantial increase in risk for postabortal PID among women with *M. genitalium* (262), the proportion of *M. genitalium*-positive women who subsequently experienced PID in two other studies was relatively low (<5%) (272,273), and evidence from serologic studies assessing the association of PID with antibody to *M. genitalium* is inconsistent. Overall, evidence suggests that *M. genitalium* can cause PID, but that this occurs less frequently than it does with *C. trachomatis* (271,273).

A few seroepidemologic studies have found that women with tubal factor infertility are more likely to have antibodies to *M. genitalium* than fertile women, suggesting that this organism might cause female infertility. However, more research is needed. On the basis of certain reports, *M. genitalium* was uncommonly identified in women who experience adverse pregnancy outcomes, but was associated with increased risk for preterm delivery in one U.S. and another Peruvian study (274,275). Data are scarce regarding *M. genitalium* and ectopic pregnancy.

Diagnostic Considerations

M. genitalium is a slow-growing organism. Culture can take up to 6 months, and only a few laboratories in the world are able to recover clinical isolates. Therefore, NAAT is the preferred method for *M. genitalium* detection. In research settings, *M. genitalium* is diagnosed by NAAT testing of urine, urethral, vaginal, and cervical swabs and through endometrial biopsies, typically using in-house PCR or assays intended for research use only. NAAT tests (polymerase chain reaction or transcription mediated amplification) for *M. genitalium* are available in some large medical centers and commercial laboratories, but there is no diagnostic test for *M. genitalium* that is cleared by the FDA for use in the United States. In the absence of validated tests, *M. genitalium* should be suspected in cases of persistent or recurrent urethritis and may be considered in persistent or recurrent cases of cervicitis and PID.

Treatment

M. genitalium lacks a cell wall, and thus antibiotics targeting cell-wall biosynthesis (e.g., beta-lactams including penicillins and cephalosporins) are ineffective against this organism. Given the diagnostic challenges, treatment of most *M. genitalium* infections will occur in the context of syndromic management for urethritis, cervicitis, and PID.

Urethritis and Cervicitis

The 7-day doxycycline regimen recommended for treatment of urethritis is largely ineffective against *M. genitalium* with a median cure rate of approximately 31% (276–278). The 1-g single dose of azithromycin was significantly more effective

against *M. genitalium* than doxycycline in two randomized urethritis treatment trials (*276,277*) and is preferred over doxycycline. However, resistance to azithromycin appears to be rapidly emerging. The median cure rate for both men and women is approximately 85%, but was only 40% in the most recent trial (*278*). Persons with treatment failures after the 1-g azithromycin regimen frequently have macrolide-resistant strains, suggesting that single-dose azithromycin therapy might select for resistance. A longer course of azithromycin (an initial 500-mg dose followed by 250 mg daily for 4 days) might be marginally superior to the single dose regimen (*279–281*). However, in some settings, approximately 50% of all *M. genitalium* infections are caused by organisms that are already resistant to azithromycin (*282*), and persons who do not respond to the 1-g azithromycin regimen generally do not benefit from retreatment with the extended dose regimen.

Moxifloxacin (400 mg daily x 7, 10 or 14 days) has been successfully used to treat *M. genitalium* in men and women with previous treatment failures, with cure rates of 100% in initial reports (*280,283*). However, moxifloxacin has been used in only a few cases, and the drug has not been tested in clinical trials. Although generally considered effective, studies in Japan, Australia, and the United States have reported moxifloxacin treatment failures after the 7 day regimen (*284–287*).

PID

Recommended PID treatment regimens are based on antibiotics that are not effective against *M. genitalium*. Therefore, clinicians might consider *M. genitalium* in cases that do not respond to therapy within 7–10 days. Where validated *M. genitalium* testing is available, clinicians might test women with PID for *M. genitalium.* When *M. genitalium* is detected, a regimen of moxifloxacin 400 mg/day for 14 days has been effective in eradicating the organism (*288*). Nevertheless, no data have been published that assess the benefits of testing women with PID for *M. genitalium,* and the importance of directing treatment against this organism is currently unknown.

Follow-up

In settings where validated *M. genitalium* testing is available, persons with persistent urethritis, cervicitis, or PID accompanied by persistent detection of *M. genitalium* might be treated with moxifloxacin. However, routine tests-of-cure in asymptomatic persons are not recommended.

Management of Sex Partners

Sex partners should be managed according to guidelines for patients with nongonococcal urethritis (NGU), cervicitis, and PID. In settings with access to validated *M. genitalium* tests,

partner testing and treatment of identified infections might be considered.

Special Considerations

HIV Infection

Persons who have an *M. genitalium* infection and HIV infection should receive the same treatment regimen as those who are HIV negative. Treatment of most *M. genitalium* infections will occur in the context of syndromic management for urethritis, cervicitis, and PID (See *Mycoplasma genitalium*, Treatment).

HIV Infection: Detection, Counseling, and Referral

HIV infection typically begins with a brief acute retroviral syndrome, transitions to a multi-year chronic illness that progressively depletes CD4 T-lymphocytes critical for maintenance of effective immune function, and ends with symptomatic, life-threatening immunodeficiency. This late stage of infection, known as acquired immunodeficiency syndrome (AIDS), develops over months to years with an estimated median time of approximately 11 years (*289*). In the absence of treatment, virtually all persons with AIDS will die from AIDS-related causes; however with antiretroviral therapy, persons provided early effective treatment can expect to live a near normal lifespan (*290–292*). Early diagnosis of HIV infection and linkage to care are essential not only for the patients' own health but also to reduce the risk for transmitting HIV to others. As of March 2012, U.S. guidelines recommend all persons with HIV infection diagnoses be offered effective antiretroviral therapy (*70*).

As of 2011, approximately 16% of the estimated 1.2 million persons with HIV infection in the United States are unaware of their infection (http://www.cdc.gov/hiv/pdf/2011_Monitoring_HIV_Indicators_HSSR_FINAL.pdf). Knowledge of HIV-infection status has important clinical implications, because HIV infection alters the immune system and thereby affects the diagnosis, evaluation, treatment, and follow-up of some other STDs. Diagnosing HIV infection during the acute phase of disease is particularly important (see Acute HIV Infection). Persons with acute HIV infection are highly infectious, because HIV concentrations are extremely high in plasma and genital secretions following initial infection (*293–296*). However, tests for HIV antibodies are often negative during this phase of infection, causing persons to mistakenly believe they are uninfected and unknowingly continue to engage in behaviors associated with HIV transmission. Of persons with acute HIV infection, 50%–90% are symptomatic, many of whom seek medical care

(*297,298*). Because persons with no HIV-associated symptoms might present for assessment or treatment of a concomitantly acquired STD, providers serving persons at risk for STDs are in a position to diagnose HIV infection in persons during the acute phase of infection.

Despite the availability of effective antiretroviral therapy, many cases of HIV infection continue to be diagnosed at advanced stages, as evidenced by low CD4 cell counts. Nationally, the proportion of patients who receive AIDS diagnoses at or within 12 months of their HIV diagnosis in 2010 was 32% (*299*). Since 2006, CDC has recommended efforts to increase HIV testing by streamlining the consent process and expanding opt-out testing to all health-care settings, including those serving persons at risk for STDs (*122*). HIV testing facilitates early diagnosis, which reduces the spread of disease, extends life expectancy, and reduces costs of care. However, rates of testing remain low: CDC estimates that in 2008, only 45% of adults aged 18–64 years had ever been tested (*300*), and that during 2006–2009 approximately 41% of persons with newly diagnosed HIV infection had never been previously tested (*301*).

Comprehensive HIV treatment services are usually not available in facilities focusing primarily on STD treatment (e.g., STD clinics). In such settings, patients with a new diagnosis of HIV infection or those with an existing diagnosis of HIV infection who are not engaged in regular on-going care should be linked promptly to a health-care provider or facility experienced in caring for HIV-infected patients (*70*). Providers working in STD clinics should be knowledgeable about the treatment options available in their communities, educate HIV-infected persons about their illness, and link these patients to HIV-related care and support services. Provision of care also should include behavioral and psychosocial services, especially for alcohol and drug addiction and for mental health problems.

A detailed discussion of the complex issues required for the management of HIV infection is beyond the scope of this report; however this information is available elsewhere (*17,70,247*). These HIV care and management resources are updated frequently, and the most current versions are available online (see URLs accompanying each reference). These resources provide additional information about the diagnosis, medical management, and counseling of persons with HIV infection, referral for support services, and management of sex and injection-drug partners in STD-treatment facilities. In addition, subsequent sections of this report briefly discuss HIV infection during pregnancy and among infants and children.

Detection of HIV Infection: Screening

All persons who seek evaluation and treatment for STDs should be screened for HIV infection. Screening should be routine, regardless of whether the patient reports any specific behavioral risks for HIV infection. Persons at high risk for HIV infection with early syphilis, gonorrhea, or chlamydia should be screened at the time of the STD diagnosis, even if an HIV test was recently performed. Some STDs, especially rectal gonorrhea and syphilis, are a risk marker for HIV acquisition (*142,145,156*).

CDC recommends HIV screening for patients aged 13–64 years in all health-care settings (*122*). Persons should be notified that testing will be performed, but retain the option to decline or defer testing (an opt-out approach) (*302*). Consent for HIV screening should be incorporated into the general informed consent for medical care in the same manner as other screening or diagnostic tests. A separate consent form for HIV testing is not recommended.

Providing prevention counseling in conjunction with HIV diagnostic testing or as part of HIV screening programs should not be required in health-care settings. However, some persons might be more likely to think about HIV and consider their risk-related behavior when undergoing an HIV test. HIV testing presents providers with an opportunity to conduct HIV/STD prevention counseling and communicate risk-reduction messages.

Diagnosing HIV Infection

HIV infection can be diagnosed by serologic tests that detect antibodies against HIV-1 and HIV-2 and by virologic tests that detect HIV antigens or ribonucleic acid (RNA). Testing begins with a sensitive screening test, usually an antigen/antibody combination or antibody immunoassay (IA). Available serologic tests are both highly sensitive and specific and can detect all known subtypes of HIV-1. Most can also detect HIV-2 and uncommon variants of HIV-1 (e.g., group O and group N). Rapid HIV tests enable clinicians to make a preliminary diagnosis of HIV infection within 30 minutes. However, most rapid antibody assays become reactive later than conventional laboratory-based antibody or combination antigen/antibody serologic assays, and thus can produce negative results in recently infected persons.

The recommended diagnostic algorithm for HIV infection consists of a laboratory-based immunoassay, which if repeatedly reactive is followed by a supplemental test (e.g., an HIV-1/HIV-2 antibody differentiation assay, Western blot, or indirect immunofluorescence assay). However, available HIV laboratory antigen/antibody immunoassays detect HIV infection earlier than these supplemental tests. Therefore, during very early

stages of HIV infection, discordant HIV test results (reactive immunoassay results with negative supplemental test results) have been erroneously interpreted as negative (*303*). This problem is minimized by use of a combination HIV-1/HIV-2 antigen-antibody (Ag/Ab) immunoassay, which if reactive is followed by an HIV-1/HIV-2 antibody differentiation assay (*304*). This algorithm confers an additional advantage, as it can detect HIV-2 antibodies after the initial immunoassay. Although HIV-2 is uncommon in the United States, accurate identification is important because monitoring and therapy for HIV-2 differs from that for HIV-1 (*305*). RNA testing is performed on all specimens with reactive immunoassay but negative supplemental antibody test results to determine whether the discordance represents acute HIV infection.

The following are specific recommendations that apply to testing for HIV infection.

- HIV screening is recommended for all persons who seek evaluation or treatment for STDs. This testing should be performed at the time of STD diagnosis (e.g., early syphilis, gonorrhea, and chlamydia) in populations at high risk for HIV infection.
- HIV testing must be voluntary and free from coercion. Patients must not be tested without their knowledge.
- Opt-out HIV screening (notifying the patient that an HIV test will be performed, unless the patient declines) is recommended in all health-care settings.
- Specific signed consent for HIV testing should not be required. General informed consent for medical care is considered sufficient to encompass informed consent for HIV testing.
- Use of Ag/Ab combination tests is encouraged unless persons are unlikely to receive their HIV test results.
- Preliminary positive screening tests for HIV infection must be followed by additional testing to definitively establish the diagnosis.
- Providers should be alert to the possibility of acute HIV infection and perform an antigen/antibody immunoassay or HIV RNA in conjunction with an antibody test. Persons suspected of recently acquired HIV infection should be referred immediately to an HIV clinical-care provider.

Acute HIV Infection

Health-care providers should be knowledgeable about the symptoms and signs of acute retroviral syndrome, which develops in 50%–90% of persons within the first few weeks after they become infected with HIV (*298*). Acute retroviral syndrome is characterized by nonspecific symptoms, including fever, malaise, lymphadenopathy, and skin rash. Suspicion of acute retroviral syndrome should prompt urgent assessment with an antigen/antibody immunoassay or HIV RNA in

conjunction with an antibody test. If the immunoassay is negative or indeterminate, then testing for HIV RNA should follow. Clinicians should not assume that a laboratory report of a negative HIV antibody test result indicates that the necessary RNA screening for acute HIV infection has been conducted. Further, HIV home-testing kits only detect HIV antibodies and therefore will not detect acute HIV infection.

Persons with acute HIV infection are highly infectious because the concentration of virus in plasma and genital secretions is extremely elevated during this stage of infection (*294,306*). Antiretroviral therapy during acute HIV infection is recommended, because it substantially reduces infectiousness to others, improves laboratory markers of disease, may decrease severity of acute disease, lowers viral set-point, reduces the size of the viral reservoir, decreases rate of viral mutation by suppressing replication, and preserves immune function (*70*). Persons who receive an acute HIV infection diagnosis should be referred immediately to an HIV clinical-care provider, provided prevention counseling (e.g., advised to reduce number of partners and to use condoms correctly and consistently), and screened for STDs. Information should be provided on the availability of postexposure prophylaxis for sexual and needle-sharing partners not known to have HIV infection if the most recent contact was within the 72 hours preceding HIV diagnosis (http://www.cdc.gov/hiv).

After Establishing a New HIV Diagnosis

Persons with newly diagnosed HIV infection should be informed about 1) the importance of promptly initiating medical care for their own health and to reduce further transmission of HIV, 2) the effectiveness of HIV treatments, and 3) what to expect as they enter medical care for HIV infection (*70*). They should be linked promptly to a health-care provider or facility experienced in caring for patients with HIV. Persons with symptoms or signs that suggest advanced HIV infection (e.g., fever, weight loss, diarrhea, cough, shortness of breath, and oral candidiasis) should be immediately evaluated or referred for evaluation. Persons experiencing psychologic distress should be referred accordingly (see Counseling for Persons with HIV Infection and Referral to Support Services). Detailed and regularly updated recommendation for the initial management of persons with HIV infection can be found elsewhere (*17,70,247*).

Counseling for Persons with HIV Infection and Referral to Support Services

Providers should expect persons with HIV infection to be distressed when first informed of a positive test result. Such persons face multiple major adaptive challenges, including

coping with the reactions of others to a stigmatizing illness, developing and adopting strategies for maintaining physical and emotional health, initiating changes in behavior to prevent HIV transmission to others, and reducing the risk for acquiring additional STDs. Many persons will require assistance with making reproductive choices, gaining access to health services, and coping with changes in personal relationships. Therefore, behavioral and psychosocial services are an integral part of health care for persons with HIV infection.

Persons testing positive for HIV infection have unique needs. Some require referral for specific behavioral interventions (e.g., a substance abuse program), mental health disorders (e.g., depression), and emotional distress, while others require assistance with securing and maintaining employment and housing. Women should be counseled or appropriately referred regarding reproductive choices and contraceptive options, and persons with multiple psychosocial problems might be candidates for comprehensive risk-reduction counseling and other support services.

The following are specific recommendations for HIV counseling and linkage to services that should be offered to patients before they leave the testing site.

- Persons who test positive for HIV should be counseled, either on-site or through referral, concerning the behavioral, psychosocial, and medical implications of HIV infection.
- Health-care providers should assess the need for immediate medical care and psychosocial support.
- Providers should link persons with newly diagnosed HIV infection to services provided by health-care personnel experienced in the management of HIV infection. Additional services that might be needed include substance abuse counseling and treatment, treatment for mental health disorders or emotional distress, reproductive counseling, risk-reduction counseling, and case management. Providers should follow up to ensure that patients have received services for any identified needs.
- Persons with HIV infection should be educated about the importance of ongoing medical care and what to expect from these services.

Several successful, innovative interventions to assist persons with HIV infection reduce the possibility of transmission to others have been developed for diverse at-risk populations, and these can be locally replicated or adapted (*12,15,307–310*). Involvement of nongovernment and community-based organizations might complement such efforts in the clinical setting.

Management of Sex Partners and Injection-Drug Partners

Clinicians providing services to persons with HIV infection should determine whether any partners should be notified concerning possible exposure to HIV (*122,311*). In the context of HIV management, "partner" includes sex partners and persons with whom syringes or other injection equipment is shared. Partner notification is an important component of disease management, because early diagnosis and treatment of HIV infection reduces risk for HIV transmission, decreases individual morbidity and mortality risk, and provides the opportunity to modify risk behaviors. Partner notification for HIV infection should be confidential. Specific guidance regarding spousal notification varies by jurisdiction. Detailed recommendations concerning identification, notification, diagnosis, and treatment of exposed partners are available in CDC's *Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infections* (See Partner Services) (*311*).

The following are specific recommendations for implementing partner-notification procedures:

- Health-care providers should inform persons with HIV infection about partner services including processes, benefits, and risks.
- Persons with HIV infection should be encouraged to notify their partners and to refer them for counseling and testing.
- Health-care providers should assist in the partner-notification process, either directly or by referral to health department partner-notification programs, which might attempt to contact them.
- If persons with HIV infection are unwilling to notify their partners or cannot ensure their partners will seek counseling, HIV care staff or health department personnel should use confidential partner notification procedures. Health department staff are trained to employ public health investigation strategies to confidentially locate persons who are hard to reach, whereas most clinical providers do not have the time or expertise to conduct this type of partner notification.
- Partners who have been reached and are not known to have HIV infection should be offered postexposure prophylaxis with combination antiretrovirals if they were exposed to genital secretions or blood of a partner with HIV infection though sex or injection-drug use within the preceding 72 hours (*312*).

STD Testing During HIV Care

At the initial HIV care visit, providers should test all sexually active persons with HIV infection for curable STDs (e.g., syphilis, gonorrhea, and chlamydia) and perform testing at least annually during the course of HIV care (*12*). Specific testing includes syphilis serology and NAAT for *N. gonorrhoeae* and *C. trachomatis* at the anatomic site of exposure, as the preferred approach. Women with HIV infection should also be screened for trichomonas at the initial visit and annually thereafter. Women should be screened for cervical cancer precursor lesions by cervical Pap tests per existing guidelines (*247*).

More frequent screening for curable STDs might be appropriate depending on individual risk behaviors and the local epidemiology of STDs. Many STDs are asymptomatic, and their diagnosis might indicate risk behavior that should prompt referral for partner services and prevention counseling (*10*). Pathogen-specific sections of this document provide more detailed information on screening, testing, and treatment.

Special Considerations

Pregnancy

All pregnant women should be tested for HIV infection during the first prenatal visit. A second test during the third trimester, preferably at <36 weeks' gestation, should be considered for all pregnant women and is recommended for those known to be at high risk for acquiring HIV, those who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women, and women seen in clinical settings in which prenatal screening identifies at least one pregnant women with HIV infection per 1,000 women screened (*122*). Diagnostic algorithms for HIV infection in pregnant women are not different than those for nonpregnant women (See Diagnosis, HIV Infection). Pregnant women should be informed about being tested for HIV as part of the panel of prenatal tests (*103,122*); for women who decline, providers should address concerns that pose obstacles to testing and encourage testing at subsequent prenatal visits. Women who decline testing because they have had a previous negative HIV test result should be informed about the importance of retesting during each pregnancy. Women with no prenatal care should be tested for HIV at the time of delivery.

Testing pregnant women is important not only because knowledge of infection status can help maintain the health of the woman, but because it enables receipt of interventions (i.e., antiretroviral and obstetrical) that can substantially reduce the risk for perinatal transmission of HIV. After a pregnant woman has been identified as having HIV infection, she should be educated about the benefits of antiretroviral treatment for her health and for reducing the risk for transmission to her infant. In the absence of antiretroviral treatment, a mother's risk of transmitting HIV to her neonate is approximately 30% but can be reduced to <2% through antiretroviral treatment, obstetrical interventions (i.e., elective cesarean section at 38 weeks of pregnancy), and breastfeeding avoidance (*105*). Pregnant women who have HIV infection should be linked to an HIV care provider and given appropriate antenatal and postpartum treatment and advice. Detailed and regularly updated recommendations for the initial management of persons with HIV infection and pregnancy are available in existing guidance at http://aidsinfo.nih.gov/guidelines.

HIV Infection Among Neonates, Infants, and Children

Diagnosis of HIV infection in a pregnant woman indicates the need to evaluate and manage the HIV-exposed neonate and consider whether the woman's other children might be infected. Detailed recommendations regarding diagnosis and management of HIV in neonates and children of mothers with HIV infection are beyond the scope of this report and can be found at http://aidsinfo.nih.gov/guidelines. Exposed neonates and children with HIV infection should be referred to physicians with such expertise.

Diseases Characterized by Genital, Anal, or Perianal Ulcers

In the United States, most young, sexually active patients who have genital, anal, or perianal ulcers have either genital herpes or syphilis. The frequency of each condition differs by geographic area and population; however, genital herpes is the most prevalent of these diseases. More than one etiologic agent (e.g., herpes and syphilis) can be present in a genital, anal, or perianal ulcer. Less common infectious causes of genital, anal, or perianal ulcers include chancroid and donovanosis. Genital herpes, syphilis, and chancroid have been associated with an increased risk for HIV acquisition and transmission. Genital, anal, or perianal lesions can also be associated with infectious as well as noninfectious conditions that are not sexually transmitted (e.g., yeast, trauma, carcinoma, aphthae, fixed drug eruption, and psoriasis).

A diagnosis based only on medical history and physical examination frequently is inaccurate. Therefore, all persons who have genital, anal, or perianal ulcers should be evaluated; in settings where chancroid is prevalent, a test for *Haemophilus ducreyi* also should be performed. Specific evaluation of genital, anal, or perianal ulcers includes 1) syphilis serology, darkfield examination, or PCR testing if available; 2) culture or PCR

testing for genital herpes; and 3) serologic testing for type-specific HSV antibody.

No FDA-cleared PCR test to diagnose syphilis is available in the United States, but two FDA-cleared PCR tests are available for the diagnosis of HSV-1 and HSV-2 in genital specimens. Some clinical laboratories have developed their own syphilis and HSV PCR tests and have conducted Clinical Laboratory Improvement Amendment (CLIA) verification studies in genital specimens. Type-specific serology for HSV-2 might be helpful in identifying persons with genital herpes (see Genital Herpes, Type-Specific Serologic Tests). In addition, biopsy of ulcers can help identify the cause of ulcers that are unusual or that do not respond to initial therapy. HIV testing should be performed on all persons with genital, anal, or perianal ulcers not known to have HIV infection (see Diagnostic Considerations, sections on Syphilis, Chancroid, and Genital Herpes Simplex Virus).

Because early treatment decreases the possibility of transmission, public health standards require health-care providers to presumptively treat any patient with a suspected case of infectious syphilis at the initial visit, even before test results are available. Presumptive treatment of a patient with a suspected first episode of genital herpes also is recommended, because successful treatment depends on prompt initiation of therapy. The clinician should choose the presumptive treatment on the basis of clinical presentation (i.e., HSV lesions begin as vesicles and primary syphilis as a papule) and epidemiologic circumstances (e.g., high incidence of disease among populations and communities and travel history). For example, syphilis is so common in MSM that any man who has sex with men presenting with a genital ulcer should be presumptively treated for syphilis at the initial visit after syphilis and HSV tests are performed. After a complete diagnostic evaluation, at least 25% of patients who have genital ulcers have no laboratory-confirmed diagnosis (313).

Chancroid

The prevalence of chancroid has declined in the United States (118). When infection does occur, it is usually associated with sporadic outbreaks. Worldwide, chancroid appears to have declined as well, although infection might still occur in some regions of Africa and the Caribbean. Like genital herpes and syphilis, chancroid is a risk factor in the transmission and acquisition of HIV infection (314).

Diagnostic Considerations

A definitive diagnosis of chancroid requires the identification of *H. ducreyi* on special culture media that is not widely available from commercial sources; even when these media are used, sensitivity is <80% (315). No FDA-cleared PCR test for *H. ducreyi* is available in the United States, but such testing can be performed by clinical laboratories that have developed their own PCR test and have conducted CLIA verification studies in genital specimens.

The combination of a painful genital ulcer and tender suppurative inguinal adenopathy suggests the diagnosis of chancroid (316). For both clinical and surveillance purposes, a probable diagnosis of chancroid can be made if all of the following criteria are met: 1) the patient has one or more painful genital ulcers; 2) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid; 3) the patient has no evidence of *T. pallidum* infection by darkfield examination of ulcer exudate or by a serologic test for syphilis performed at least 7 days after onset of ulcers; and 4) an HSV PCR test or HSV culture performed on the ulcer exudate is negative.

Treatment

Successful treatment for chancroid cures the infection, resolves the clinical symptoms, and prevents transmission to others. In advanced cases, scarring can result despite successful therapy.

Recommended Regimens
Azithromycin 1 g orally in a single dose
OR
Ceftriaxone 250 mg IM in a single dose
OR
Ciprofloxacin 500 mg orally twice a day for 3 days
OR
Erythromycin base 500 mg orally three times a day for 7 days

Azithromycin and ceftriaxone offer the advantage of single-dose therapy. Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported. However, because cultures are not routinely performed, data are limited regarding the current prevalence of antimicrobial resistance.

Other Management Considerations

Men who are uncircumcised and patients with HIV infection do not respond as well to treatment as persons who are circumcised or HIV-negative. Patients should be tested for HIV infection at the time chancroid is diagnosed. If the initial test results were negative, a serologic test for syphilis and HIV infection should be performed 3 months after the diagnosis of chancroid.

Follow-Up

Patients should be re-examined 3–7 days after initiation of therapy. If treatment is successful, ulcers usually improve symptomatically within 3 days and objectively within 7 days after therapy. If no clinical improvement is evident, the clinician must consider whether 1) the diagnosis is correct, 2) the patient is coinfected with another STD, 3) the patient is infected with HIV, 4) the treatment was not used as instructed, or 5) the *H. ducreyi* strain causing the infection is resistant to the prescribed antimicrobial. The time required for complete healing depends on the size of the ulcer; large ulcers might require >2 weeks. In addition, healing is slower for some uncircumcised men who have ulcers under the foreskin. Clinical resolution of fluctuant lymphadenopathy is slower than that of ulcers and might require needle aspiration or incision and drainage, despite otherwise successful therapy. Although needle aspiration of buboes is a simpler procedure, incision and drainage might be preferred because of reduced need for subsequent drainage procedures.

Management of Sex Partners

Regardless of whether symptoms of the disease are present, sex partners of patients who have chancroid should be examined and treated if they had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms.

Special Considerations

Pregnancy

Data suggest ciprofloxacin presents a low risk to the fetus during pregnancy, with a potential for toxicity during breastfeeding (*317*). Alternate drugs should be used during pregnancy and lactation. No adverse effects of chancroid on pregnancy outcome have been reported.

HIV Infection

Persons with HIV infection who have chancroid should be monitored closely because they are more likely to experience treatment failure and to have ulcers that heal slowly. Persons with HIV infection might require repeated or longer courses of therapy, and treatment failures can occur with any regimen. Data are limited concerning the therapeutic efficacy of the recommended single-dose azithromycin and ceftriaxone regimens in persons with HIV infection.

Genital HSV Infections

Genital herpes is a chronic, life-long viral infection. Two types of HSV can cause genital herpes: HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2, and approximately 50 million persons in the United States are infected with this type of genital herpes (*318*). However, an increasing proportion of anogenital herpetic infections have been attributed to HSV-1 infection, which is especially prominent among young women and MSM (*319–321*).

Most persons infected with HSV-2 have not had the condition diagnosed. Many such persons have mild or unrecognized infections but shed virus intermittently in the anogenital area. As a result, most genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs. Management of genital HSV should address the chronic nature of the disease rather than focusing solely on treatment of acute episodes of genital lesions.

Diagnostic Considerations

The clinical diagnosis of genital herpes can be difficult, because the painful multiple vesicular or ulcerative lesions typically associated with HSV are absent in many infected persons. Recurrences and subclinical shedding are much more frequent for genital HSV-2 infection than for genital HSV-1 infection (*322,323*). A patient's prognosis and the type of counseling needed depend on the type of genital herpes (HSV-1 or HSV-2) causing the infection; therefore, the clinical diagnosis of genital herpes should be confirmed by type-specific laboratory testing (*321,324*). Both type-specific virologic and type-specific serologic tests for HSV should be available in clinical settings that provide care to persons with or at risk for STDs. Persons with genital herpes should be tested for HIV infection.

Virologic Tests

Cell culture and PCR are the preferred HSV tests for persons who seek medical treatment for genital ulcers or other mucocutaneous lesions. The sensitivity of viral culture is low, especially for recurrent lesions, and declines rapidly as lesions begin to heal. Nucleic acid amplification methods, including PCR assays for HSV DNA, are more sensitive and are increasingly available (*325–327*). PCR is the test of choice for diagnosing HSV infections affecting the central nervous system and systemic infections (e.g., meningitis, encephalitis, and neonatal herpes). Viral culture isolates and PCR amplicons should be typed to determine which type of HSV is causing the infection. Failure to detect HSV by culture or PCR, especially in the absence of active lesions, does not indicate an absence of HSV infection because viral shedding is intermittent. Cytologic detection of cellular changes associated with HSV infection is an insensitive and nonspecific method of diagnosing genital lesions (i.e., Tzanck preparation) and therefore should not be relied on. Although a direct immunofluorescence (IF) assay using fluorescein-labeled monoclonal antibodies is also

available to detect HSV antigen from genital specimens, this assay lacks sensitivity (*328*).

Type-Specific Serologic Tests

Both type-specific and type-common antibodies to HSV develop during the first several weeks after infection and persist indefinitely. Accurate type-specific HSV serologic assays are based on the HSV-specific glycoprotein G2 (HSV-2) and glycoprotein G1 (HSV-1). Providers should only request type-specific glycoprotein G (gG)-based serologic assays when serology is performed for their patients (*329–331*).

Both laboratory-based assays and point-of-care tests that provide results for HSV-2 antibodies from capillary blood or serum during a clinic visit are available. The sensitivities of these glycoprotein G type-specific tests for the detection of HSV-2 antibody vary from 80%–98%; false-negative results might be more frequent at early stages of infection (*330,332,333*). The most commonly used test, HerpeSelect HSV-2 Elisa might be falsely positive at low index values (1.1–3.5) (*334–336*). Such low values should be confirmed with another test, such as Biokit or the Western blot (*337*). The HerpeSelect HSV-2 Immunoblot should not be used for confirmation, because it uses the same antigen as the HSV-2 Elisa. Repeat testing is indicated if recent acquisition of genital herpes is suspected. The HerpeSelect HSV-1 Elisa is insensitive for detection of HSV-1 antibody. IgM testing for HSV 1 or HSV-2 is not useful, because IgM tests are not type-specific and might be positive during recurrent genital or oral episodes of herpes (*337*).

Because nearly all HSV-2 infections are sexually acquired, the presence of type-specific HSV-2 antibody implies anogenital infection. In this instance, education and counseling appropriate for persons with genital HSV infections should be provided. The presence of HSV-1 antibody alone is more difficult to interpret. Many persons with HSV-1 antibody have oral HSV infection acquired during childhood, which might be asymptomatic. However, acquisition of genital HSV-1 is increasing, and genital HSV-1 also can be asymptomatic (*318–321,338*). Lack of symptoms in a person who is HSV-1 seropositive does not distinguish anogenital from orolabial or cutaneous infection, and regardless of site of infection, these persons remain at risk for acquiring HSV-2.

Type-specific HSV serologic assays might be useful in the following scenarios: 1) recurrent genital symptoms or atypical symptoms with negative HSV PCR or culture; 2) clinical diagnosis of genital herpes without laboratory confirmation; and 3) a patient whose partner has genital herpes. HSV serologic testing should be considered for persons presenting for an STD evaluation (especially for those persons with multiple sex partners), persons with HIV infection, and MSM at increased risk for HIV acquisition. Screening for HSV-1 and HSV-2 in the general population is not indicated.

Management of Genital Herpes

Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. Counseling regarding the natural history of genital herpes, sexual and perinatal transmission, and methods to reduce transmission is integral to clinical management.

Systemic antiviral drugs can partially control the signs and symptoms of genital herpes when used to treat first clinical and recurrent episodes or when used as daily suppressive therapy. However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. Randomized trials have indicated that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir (*339–347*). Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. Topical therapy with antiviral drugs offers minimal clinical benefit and is discouraged.

First Clinical Episode of Genital Herpes

Newly acquired genital herpes can cause a prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even persons with first-episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy.

Recommended Regimens*
Acyclovir 400 mg orally three times a day for 7–10 days
OR
Acyclovir 200 mg orally five times a day for 7–10 days
OR
Valacyclovir 1 g orally twice a day for 7–10 days
OR
Famciclovir 250 mg orally three times a day for 7–10 days
* Treatment can be extended if healing is incomplete after 10 days of therapy.

Established HSV-2 Infection

Almost all persons with symptomatic first-episode genital HSV-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. Intermittent asymptomatic shedding occurs in persons with genital HSV-2 infection, even in those with longstanding or clinically silent infection. Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or

episodically to ameliorate or shorten the duration of lesions. Some persons, including those with mild or infrequent recurrent outbreaks, benefit from antiviral therapy; therefore, options for treatment should be discussed. Many persons prefer suppressive therapy, which has the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners (*348,349*).

Suppressive Therapy for Recurrent Genital Herpes

Suppressive therapy reduces the frequency of genital herpes recurrences by 70%–80% in patients who have frequent recurrences (*345–348*); many persons receiving such therapy report having experienced no symptomatic outbreaks. Treatment also is effective in patients with less frequent recurrences. Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for as long as 6 years and with valacyclovir or famciclovir for 1 year (*350,351*). Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment (*352*).

The frequency of genital herpes recurrences diminishes over time in many persons, potentially resulting in psychological adjustment to the disease. Therefore, periodically during suppressive treatment (e.g., once a year), providers should discuss the need to continue therapy. However, neither treatment discontinuation nor laboratory monitoring in a healthy person is necessary.

Treatment with valacyclovir 500 mg daily decreases the rate of HSV-2 transmission in discordant, heterosexual couples in which the source partner has a history of genital HSV-2 infection (*349*). Such couples should be encouraged to consider suppressive antiviral therapy as part of a strategy to prevent transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy also is likely to reduce transmission when used by persons who have multiple partners (including MSM) and by those who are HSV-2 seropositive without a history of genital herpes.

Recommended Regimens
Acyclovir 400 mg orally twice a day
OR
Valacyclovir 500 mg orally once a day*
OR
Valacyclovir 1 g orally once a day
OR
Famciclovir 250 mg orally twice a day
* Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in persons who have very frequent recurrences (i.e., ≥10 episodes per year).

Acyclovir, famciclovir, and valacyclovir appear equally effective for episodic treatment of genital herpes (*342–346*), but famciclovir appears somewhat less effective for suppression of viral shedding (*353*). Ease of administration and cost also are important considerations for prolonged treatment.

Episodic Therapy for Recurrent Genital Herpes

Effective episodic treatment of recurrent herpes requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin.

Recommended Regimens
Acyclovir 400 mg orally three times a day for 5 days
OR
Acyclovir 800 mg orally twice a day for 5 days
OR
Acyclovir 800 mg orally three times a day for 2 days
OR
Valacyclovir 500 mg orally twice a day for 3 days
OR
Valacyclovir 1 g orally once a day for 5 days
OR
Famciclovir 125 mg orally twice daily for 5 days
OR
Famciclovir 1 gram orally twice daily for 1 day
OR
Famciclovir 500 mg once, followed by 250 mg twice daily for 2 days

Severe Disease

Intravenous (IV) acyclovir therapy should be provided for patients who have severe HSV disease or complications that necessitate hospitalization (e.g., disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g., meningoencephalitis). The recommended regimen is acyclovir 5–10 mg/kg IV every 8 hours for 2–7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy. HSV encephalitis requires 21 days of intravenous therapy. Impaired renal function warrants an adjustment in acyclovir dosage.

Counseling

Counseling of infected persons and their sex partners is critical to the management of genital herpes. The goals of counseling include helping patients cope with the infection and preventing sexual and perinatal transmission. Although initial counseling can be provided at the first visit, many patients benefit from learning about the chronic aspects of the disease after the acute illness subsides. Multiple resources, including websites (http://www.ashasexualhealth.org) and

printed materials, are available to assist patients, their partners, and clinicians who become involved in counseling (*354,355*).

Although the psychological effect of a serologic diagnosis of HSV-2 infection in a person with asymptomatic or unrecognized genital herpes appears minimal and transient (*356,357*), some HSV-infected persons might express anxiety concerning genital herpes that does not reflect the actual clinical severity of their disease; the psychological effect of HSV infection can be substantial. Common concerns regarding genital herpes include the severity of initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners, and ability to bear healthy children. The misconception that HSV causes cancer should be dispelled.

The following topics should be discussed when counseling persons with genital HSV infection:

- the natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and the attendant risks of sexual transmission;
- the effectiveness of suppressive therapy for persons experiencing a first episode of genital herpes in preventing symptomatic recurrent episodes;
- use of episodic therapy to shorten the duration of recurrent episodes;
- importance of informing current sex partners about genital herpes and informing future partners before initiating a sexual relationship;
- potential for sexual transmission of HSV to occur during asymptomatic periods (asymptomatic viral shedding is more frequent in genital HSV-2 infection than genital HSV-1 infection and is most frequent during the first 12 months after acquiring HSV-2);
- importance of abstaining from sexual activity with uninfected partners when lesions or prodromal symptoms are present;
- effectiveness of daily use of valacyclovir in reducing risk for transmission of HSV-2, and the lack of effectiveness of episodic or suppressive therapy in persons with HIV and HSV infection in reducing risk for transmission to partners who might be at risk for HSV-2 acquisition;
- effectiveness of male latex condoms, which when used consistently and correctly can reduce (but not eliminate) the risk for genital herpes transmission (*27,358,359*);
- HSV infection in the absence of symptoms (type-specific serologic testing of the asymptomatic partners of persons with genital herpes is recommended to determine whether such partners are already HSV seropositive or whether risk for acquiring HSV exists);
- risk for neonatal HSV infection; and

- increased risk for HIV acquisition among HSV-2 seropositive persons who are exposed to HIV (suppressive antiviral therapy does not reduce the increased risk for HIV acquisition associated with HSV-2 infection) (*75,347*).

Asymptomatic persons who receive a diagnosis of HSV-2 infection by type-specific serologic testing should receive the same counseling messages as persons with symptomatic infection. In addition, such persons should be educated about the clinical manifestations of genital herpes.

Pregnant women and women of childbearing age who have genital herpes should inform the providers who care for them during pregnancy and those who will care for their newborn infant about their infection. More detailed counseling messages are described in Special Considerations, Genital Herpes in Pregnancy.

Management of Sex Partners

The sex partners of persons who have genital herpes can benefit from evaluation and counseling. Symptomatic sex partners should be evaluated and treated in the same manner as patients who have genital herpes. Asymptomatic sex partners of patients who have genital herpes should be questioned concerning histories of genital lesions and offered type-specific serologic testing for HSV infection.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Allergic and other adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described (*360*).

HIV Infection

Immunocompromised patients can have prolonged or severe episodes of genital, perianal, or oral herpes. Lesions caused by HSV are common among persons with HIV infection and might be severe, painful, and atypical. HSV shedding is increased in persons with HIV infection. Whereas antiretroviral therapy reduces the severity and frequency of symptomatic genital herpes, frequent subclinical shedding still occurs (*361,362*). Clinical manifestations of genital herpes might worsen during immune reconstitution early after initiation of antiretroviral therapy.

Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV among persons with HIV infection (*363–365*). HSV type-specific serologic testing can be offered to persons with HIV infection during their initial evaluation if infection status is unknown, and suppressive antiviral therapy can be considered in those who have HSV-2 infection. Suppressive anti-HSV

therapy in persons with HIV infection does not reduce the risk for either HIV transmission or HSV-2 transmission to susceptible sex partners (*71,366*).

<table>
<tr><td>Recommended Regimens for Daily Suppressive Therapy in Persons with HIV</td></tr>
<tr><td>Acyclovir 400–800 mg orally twice to three times a day
    OR
Valacyclovir 500 mg orally twice a day
    OR
Famciclovir 500 mg orally twice a day</td></tr>
</table>

<table>
<tr><td>Recommended Regimens for Episodic Infection in Persons with HIV</td></tr>
<tr><td>Acyclovir 400 mg orally three times a day for 5–10 days
    OR
Valacyclovir 1 g orally twice a day for 5–10 days
    OR
Famciclovir 500 mg orally twice a day for 5–10 days</td></tr>
</table>

For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg IV every 8 hours might be necessary.

Antiviral-resistant HSV

If lesions persist or recur in a patient receiving antiviral treatment, HSV resistance should be suspected and a viral isolate obtained for sensitivity testing (*367*). Such persons should be managed in consultation with an infectious-disease specialist, and alternate therapy should be administered. All acyclovir-resistant strains are also resistant to valacyclovir, and most are resistant to famciclovir. Foscarnet (40–80 mg/kg IV every 8 hours until clinical resolution is attained) is often effective for treatment of acyclovir-resistant genital herpes (*368,369*). Intravenous cidofovir 5 mg/kg once weekly might also be effective. Imiquimod is a topical alternative (*370*), as is topical cidofovir gel 1%; however, cidofovir must be compounded at a pharmacy (*371*). These topical preparations should be applied to the lesions once daily for 5 consecutive days.

Clinical management of antiviral resistance remains challenging among persons with HIV infection, necessitating other preventative approaches. However, experience with another group of immunocompromised persons (hematopoietic stem-cell recipients) demonstrated that persons receiving daily suppressive antiviral therapy were less likely to develop acyclovir-resistant HSV compared with those who received episodic therapy for outbreaks (*372*).

Genital Herpes in Pregnancy

Most mothers of newborns who acquire neonatal herpes lack histories of clinically evident genital herpes (*373,374*). The risk for transmission to the neonate from an infected mother is high (30%–50%) among women who acquire genital herpes near the time of delivery and low (<1%) among women with prenatal histories of recurrent herpes or who acquire genital HSV during the first half of pregnancy (*375,376*).

Prevention of neonatal herpes depends both on preventing acquisition of genital HSV infection during late pregnancy and avoiding exposure of the neonate to herpetic lesions and viral shedding during delivery. Because the risk for herpes is highest in newborn infants of women who acquire genital HSV during late pregnancy, these women should be managed in consultation with maternal-fetal medicine and infectious-disease specialists.

Women without known genital herpes should be counseled to abstain from vaginal intercourse during the third trimester with partners known or suspected of having genital herpes. In addition, pregnant women without known orolabial herpes should be advised to abstain from receptive oral sex during the third trimester with partners known or suspected to have orolabial herpes. Type-specific serologic tests may be useful for identifying pregnant women at risk for HSV infection and guiding counseling regarding the risk for acquiring genital herpes during pregnancy. For example, such testing could be offered to women with no history of genital herpes whose sex partner has HSV infection. However, the effectiveness of antiviral therapy to decrease the risk for HSV transmission to pregnant women by infected partners has not been studied. Routine HSV-2 serologic screening of pregnant women is not recommended.

All pregnant women should be asked whether they have a history of genital herpes. At the onset of labor, all women should be questioned carefully about symptoms of genital herpes, including prodromal symptoms, and all women should be examined carefully for herpetic lesions. Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally. Although cesarean delivery does not completely eliminate the risk for HSV transmission to the neonate, women with recurrent genital herpetic lesions at the onset of labor should deliver by cesarean delivery to reduce the risk for neonatal HSV infection.

Many infants are exposed to acyclovir each year, and no adverse effects in the fetus or newborn attributable to the use of this drug during pregnancy have been reported. Acyclovir can be safely used to treat women in all stages of pregnancy, along with those who are breastfeeding (*317,377*). Although data regarding prenatal exposure to valacyclovir and famciclovir are limited, data from animal trials suggest these drugs also pose a low risk in pregnant women. Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant

women with severe HSV infection. Suppressive acyclovir treatment late in pregnancy reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term (*378–380*). However, such treatment may not protect against transmission to neonates in all cases (*381*). No data support use of antiviral therapy among HSV-seropositive women without a history of genital herpes.

Recommended regimen for suppressive therapy of pregnant women with recurrent genital herpes *
Acyclovir 400 mg orally three times a day   OR   **Valacyclovir** 500 mg orally twice a day
* Treatment recommended starting at 36 weeks of gestation. (**Source:** American College of Obstetricians and Gynecologists. Clinical management guidelines for obstetrician-gynecologists. Management of herpes in pregnancy. ACOG Practice Bulletin No. 82. Obstet Gynecol 2007;109:1489–98.)

Neonatal Herpes

Newborn infants exposed to HSV during birth, as documented by maternal virologic testing of maternal lesions at delivery or presumed by observation of maternal lesions, should be followed carefully in consultation with a pediatric infectious-disease specialist. Guidance is available on management of neonates who are delivered vaginally in the presence of maternal genital HSV lesions (*382*).

Surveillance cultures or PCR of mucosal surfaces of the neonate to detect HSV infection might be considered before the development of clinical signs of neonatal herpes to guide initiation of treatment. In addition, administration of acyclovir might be considered for neonates born to women who acquired HSV near term because the risk for neonatal herpes is high for these infants. All infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and that involving the central nervous system.

Granuloma Inguinale (Donovanosis)

Granuloma inguinale is a genital ulcerative disease caused by the intracellular gram-negative bacterium *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*). The disease occurs rarely in the United States, although it is endemic in some tropical and developing areas, including India; Papua, New Guinea; the Caribbean; central Australia; and southern Africa (*383–385*). Clinically, the disease

is commonly characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy; subcutaneous granulomas (pseudobuboes) also might occur. The lesions are highly vascular (i.e., beefy red appearance) and bleed. Extragenital infection can occur with extension of infection to the pelvis, or it can disseminate to intra-abdominal organs, bones, or the mouth. The lesions also can develop secondary bacterial infection and can coexist with other sexually transmitted pathogens.

Diagnostic Considerations

The causative organism of granuloma inguinale is difficult to culture, and diagnosis requires visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy. No FDA-cleared molecular tests for the detection of *K. granulomatis* DNA exist, but such an assay might be useful when undertaken by laboratories that have conducted a CLIA verification study.

Treatment

Several antimicrobial regimens have been effective, but only a limited number of controlled trials have been published (*383*). Treatment has been shown to halt progression of lesions, and healing typically proceeds inward from the ulcer margins; prolonged therapy is usually required to permit granulation and re-epithelialization of the ulcers. Relapse can occur 6–18 months after apparently effective therapy.

Recommended Regimen
Azithromycin 1 g orally once per week or 500 mg daily for at least 3 weeks and until all lesions have completely healed

Alternative Regimens
Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed   OR   **Ciprofloxacin** 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed   OR   **Erythromycin** base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed   OR   **Trimethoprim-sulfamethoxazole** one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed

The addition of another antibiotic to these regimens can be considered if improvement is not evident within the first few days of therapy. Addition of an aminoglycoside to these regimens is an option (gentamicin 1 mg/kg IV every 8 hours).

Other Management Considerations

Persons should be followed clinically until signs and symptoms have resolved. All persons who receive a diagnosis of granuloma inguinale should be tested for HIV.

Follow-up

Patients should be followed clinically until signs and symptoms resolve.

Management of Sex Partners

Persons who have had sexual contact with a patient who has granuloma inguinale within the 60 days before onset of the patient's symptoms should be examined and offered therapy. However, the value of empiric therapy in the absence of clinical signs and symptoms has not been established.

Special Considerations

Pregnancy

Doxycycline should be avoided in the second and third trimester of pregnancy because of the risk for discoloration of teeth and bones, but is compatible with breastfeeding (*317*). Data suggest that ciprofloxacin presents a low risk to the fetus during pregnancy (*317*). Sulfonamides are associated with rare but serious kernicterus in those with G6PD deficiency and should be avoided in third trimester and during breastfeeding (*317*). For these reasons, pregnant and lactating women should be treated with a macrolide regimen (erythromycin or azithromycin). The addition of an aminoglycoside (gentamicin 1 mg/kg IV every 8 hours) can be considered if improvement is not evident within the first few days of therapy.

HIV Infection

Persons with both granuloma inguinale and HIV infection should receive the same regimens as those who do not have HIV infection. The addition of an aminoglycoside (gentamicin 1 mg/kg IV every 8 hours) can be considered if improvement is not evident within the first few days of therapy.

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is caused by *C. trachomatis* serovars L1, L2, or L3 (*386,387*). The most common clinical manifestation of LGV among heterosexuals is tender inguinal and/or femoral lymphadenopathy that is typically unilateral. A self-limited genital ulcer or papule sometimes occurs at the site of inoculation. However, by the time patients seek care, the lesions have often disappeared. Rectal exposure in women or MSM can result in proctocolitis mimicking inflammatory bowel disease, and clinical findings may include mucoid and/or hemorrhagic rectal discharge,

anal pain, constipation, fever, and/or tenesmus (*388,389*). Outbreaks of LGV protocolitis have been reported among MSM (*390–392*). LGV can be an invasive, systemic infection, and if it is not treated early, LGV proctocolitis can lead to chronic colorectal fistulas and strictures; reactive arthropathy has also been reported. However, reports indicate that rectal LGV can be asymptomatic (*393*). Persons with genital and colorectal LGV lesions can also develop secondary bacterial infection or can be coinfected with other sexually and nonsexually transmitted pathogens.

Diagnostic Considerations

Diagnosis is based on clinical suspicion, epidemiologic information, and the exclusion of other etiologies for proctocolitis, inguinal lymphadenopathy, or genital or rectal ulcers. Genital lesions, rectal specimens, and lymph node specimens (i.e., lesion swab or bubo aspirate) can be tested for *C. trachomatis* by culture, direct immunofluorescence, or nucleic acid detection (*394*). NAATs for *C. trachomatis* perform well on rectal specimens, but are not FDA-cleared for this purpose. Many laboratories have performed the CLIA validation studies needed to provide results from rectal specimens for clinical management. MSM presenting with protocolitis should be tested for chlamydia; NAAT performed on rectal specimens is the preferred approach to testing.

Additional molecular procedures (e.g., PCR-based genotyping) can be used to differentiate LGV from non-LGV *C. trachomatis* in rectal specimens. However, they are not widely available, and results are not available in a timeframe that would influence clinical management.

Chlamydia serology (complement fixation titers ≥1:64 or microimmunofluorescence titers >1:256) might support the diagnosis of LGV in the appropriate clinical context. Comparative data between types of serologic tests are lacking, and the diagnostic utility of these older serologic methods has not been established. Serologic test interpretation for LGV is not standardized, tests have not been validated for clinical proctitis presentations, and *C. trachomatis* serovar-specific serologic tests are not widely available.

Treatment

At the time of the initial visit (before diagnostic tests for chlamydia are available), persons with a clinical syndrome consistent with LGV, including proctocolitis or genital ulcer disease with lymphadenopathy, should be presumptively treated for LGV. As required by state law, these cases should be reported to the health department.

Treatment cures infection and prevents ongoing tissue damage, although tissue reaction to the infection can result in scarring. Buboes might require aspiration through intact skin

or incision and drainage to prevent the formation of inguinal/femoral ulcerations.

Recommended Regimen
Doxycycline 100 mg orally twice a day for 21 days

Alternative Regimen
Erythromycin base 500 mg orally four times a day for 21 days

Although clinical data are lacking, azithromycin 1 g orally once weekly for 3 weeks is probably effective based on its chlamydial antimicrobial activity. Fluoroquinolone-based treatments also might be effective, but the optimal duration of treatment has not been evaluated.

Other Management Considerations

Patients should be followed clinically until signs and symptoms have resolved. Persons who receive an LGV diagnosis should be tested for other STDs, especially HIV, gonorrhea, and syphilis. Those who test positive for another infection should be referred for or provided with appropriate care and treatment.

Follow-up

Patients should be followed clinically until signs and symptoms resolve.

Management of Sex Partners

Persons who have had sexual contact with a patient who has LGV within the 60 days before onset of the patient's symptoms should be examined and tested for urethral, cervical, or rectal chlamydial infection depending on anatomic site of exposure. They should be presumptively treated with a chlamydia regimen (azithromycin 1 g orally single dose or doxycycline 100 mg orally twice a day for 7 days).

Special Considerations

Pregnancy

Pregnant and lactating women should be treated with erythromycin. Doxycycline should be avoided in the second and third trimester of pregnancy because of risk for discoloration of teeth and bones, but is compatible with breastfeeding (*317*). Azithromycin might prove useful for treatment of LGV in pregnancy, but no published data are available regarding an effective dose and duration of treatment.

HIV Infection

Persons with both LGV and HIV infection should receive the same regimens as those who are HIV negative. Prolonged therapy might be required, and delay in resolution of symptoms might occur.

Syphilis

Syphilis is a systemic disease caused by *Treponema pallidum*. The disease has been divided into stages based on clinical findings, helping to guide treatment and follow-up. Persons who have syphilis might seek treatment for signs or symptoms of primary syphilis infection (i.e., ulcers or chancre at the infection site), secondary syphilis (i.e., manifestations that include, but are not limited to, skin rash, mucocutaneous lesions, and lymphadenopathy), or tertiary syphilis (i.e., cardiac, gummatous lesions, tabes dorsalis, and general paresis). Latent infections (i.e., those lacking clinical manifestations) are detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are late latent syphilis or syphilis of unknown duration. *T. pallidum* can infect the central nervous system and result in neurosyphilis, which can occur at any stage of syphilis. Early neurologic clinical manifestations (i.e., cranial nerve dysfunction, meningitis, stroke, acute altered mental status, and auditory or ophthalmic abnormalities) are usually present within the first few months or years of infection. Late neurologic manifestations (i.e., tabes dorsalis and general paresis) occur 10–30 years after infection.

Diagnostic Considerations

Darkfield examinations and tests to detect *T. pallidum* directly from lesion exudate or tissue are the definitive methods for diagnosing early syphilis (*395*). Although no *T. pallidum* detection tests are commercially available, some laboratories provide locally developed and validated PCR tests for the detection of *T. pallidum* DNA. A presumptive diagnosis of syphilis requires use of two tests: a nontreponemal test (i.e., Venereal Disease Research Laboratory [VDRL] or Rapid Plasma Reagin [RPR]) and a treponemal test (i.e., fluorescent treponemal antibody absorbed [FTA-ABS] tests, the *T. pallidum* passive particle agglutination [TP-PA] assay, various enzyme immunoassays [EIAs], chemiluminescence immunoassays, immunoblots, or rapid treponemal assays). Although many treponemal-based tests are commercially available, only a few are approved for use in the United States. Use of only one type of serologic test is insufficient for diagnosis and can result in false-negative results in persons tested during primary syphilis and false-positive results in persons without syphilis.

False-positive nontreponemal test results can be associated with various medical conditions and factors unrelated to syphilis, including other infections (e.g., HIV), autoimmune conditions, immunizations, pregnancy, injection-drug use, and older age (*395,396*). Therefore, persons with a reactive nontreponemal test should always receive a treponemal test to confirm the diagnosis of syphilis.

Nontreponemal test antibody titers might correlate with disease activity and are used to follow treatment response. Results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results obtained using the same serologic test. Sequential serologic tests in individual patients should be performed using the same testing method (VDRL or RPR), preferably by the same laboratory. The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titers frequently are slightly higher than VDRL titers. Nontreponemal test titers usually decline after treatment and might become nonreactive with time; however, in some persons, nontreponemal antibodies can persist for a long period of time, a response referred to as the "serofast reaction." Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. However, 15%–25% of patients treated during the primary stage revert to being serologically nonreactive after 2–3 years (*397*). Treponemal antibody titers do not predict treatment response and therefore should not be used for this purpose.

Some clinical laboratories are screening samples using treponemal tests, typically by EIA or chemiluminescence immunoassays (*398,399*). This reverse screening algorithm for syphilis testing can identify persons previously treated for syphilis, those with untreated or incompletely treated syphilis, and persons with false-positive results that can occur with a low likelihood of infection. Persons with a positive treponemal screening test should have a standard nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions. If the nontreponemal test is negative, the laboratory should perform a different treponemal test (preferably one based on different antigens than the original test) to confirm the results of the initial test. If a second treponemal test is positive, persons with a history of previous treatment will require no further management unless sexual history suggests likelihood of re-exposure. In this instance, a repeat nontreponemal test in 2–4 weeks is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent infection, previously untreated persons should be treated for late latent syphilis. If the second treponemal test is negative and the epidemiologic risk and clinical probability for syphilis are low, further evaluation or treatment is not indicated. Two studies demonstrate that high quantitative index values from treponemal EIA/CIA tests correlate with TPPA positivity; however, the range of optical density values varies among different treponemal immunoassays, and the clinical significance of these findings warrant further investigation (*400,401*).

For most persons with HIV infection, serologic tests are accurate and reliable for diagnosing syphilis and following a patient's response to treatment. However, atypical nontreponemal serologic test results (i.e., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV-infection status. When serologic tests do not correspond with clinical findings suggestive of early syphilis, presumptive treatment is recommended for persons with risk factors for syphilis, and use of other tests (e.g., biopsy and PCR) should be considered.

Further testing is warranted for persons with clinical signs of neurosyphilis (e.g., cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense). Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. The diagnosis of neurosyphilis depends on a combination of cerebrospinal fluid (CSF) tests (CSF cell count or protein and a reactive CSF-VDRL) in the presence of reactive serologic test results and neurologic signs and symptoms. CSF laboratory abnormalities are common in persons with early syphilis and are of unknown significance in the absence of neurologic signs or symptoms (*402*). CSF-VDRL is highly specific but insensitive. In a person with neurologic signs or symptoms, a reactive CSF-VDRL (in the absence of blood contamination) is considered diagnostic of neurosyphilis. When CSF-VDRL is negative despite the presence of clinical signs of neurosyphilis, reactive serologic test results, and abnormal CSF cell count and/or protein, neurosyphilis should be considered. In this instance, additional evaluation using FTA-ABS testing on CSF may be warranted. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Neurosyphilis is highly unlikely with a negative CSF FTA-ABS test, especially among persons with nonspecific neurologic signs and symptoms (*403*).

Among persons with HIV infection, CSF leukocyte count usually is elevated (>5 white blood cell count [WBC]/mm^3). Using a higher cutoff (>20 WBC/mm^3) might improve the specificity of neurosyphilis diagnosis (*404*).

Treatment

Penicillin G, administered parenterally, is the preferred drug for treating persons in all stages of syphilis. The preparation used (i.e., benzathine, aqueous procaine, or aqueous crystalline), dosage, and length of treatment depend on the stage and clinical manifestations of the disease. Treatment for late latent syphilis and tertiary syphilis require a longer duration of therapy, because organisms theoretically might be dividing more slowly (the validity of this rationale has not been assessed). Longer treatment duration is required for persons with latent syphilis of unknown duration to ensure that those who did not acquire syphilis within the preceding year are adequately treated.

Selection of the appropriate penicillin preparation is important, because *T. pallidum* can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by some forms of penicillin. Combinations of benzathine penicillin, procaine penicillin, and oral penicillin preparations are not considered appropriate for the treatment of syphilis. Reports have indicated that practitioners have inadvertently prescribed combination benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin product (Bicillin L-A) widely used in the United States. Practitioners, pharmacists, and purchasing agents should be aware of the similar names of these two products to avoid using the inappropriate combination therapy agent for treating syphilis (*405*).

The effectiveness of penicillin for the treatment of syphilis was well established through clinical experience even before the value of randomized controlled clinical trials was recognized. Therefore, nearly all recommendations for the treatment of syphilis are based not only on clinical trials and observational studies, but many decades of clinical experience.

Special Considerations

Pregnancy

Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin (see Management of Persons Who Have a History of Penicillin Allergy).

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, fever, and other symptoms that can occur within the first 24 hours after the initiation of any therapy for syphilis. Patients should be informed about this possible adverse reaction and how to manage it if it occurs. The Jarisch-Herxheimer reaction occurs most frequently among persons who have early syphilis, presumably because bacterial burdens are higher during these stages. Antipyretics can be used to manage symptoms, but they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction might induce early labor or cause fetal distress in pregnant women, but this should not prevent or delay therapy (see Syphilis During Pregnancy).

Management of Sex Partners

Sexual transmission of *T. pallidum* is thought to occur only when mucocutaneous syphilitic lesions are present. Such manifestations are uncommon after the first year of infection. Persons exposed sexually to a person who has primary, secondary, or early latent syphilis should be evaluated clinically and serologically and treated according to the following recommendations:

- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis within 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative.
- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis >90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain. If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis.
- In some areas or populations with high rates of syphilis, health departments recommend notification and presumptive treatment of sex partners of persons with late latent syphilis who have high nontreponemal serologic test titers (i.e., >1:32), because high titers might be indicative of early syphilis. These partners should be managed as if the index case had early syphilis.
- Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings.
- The following sex partners of persons with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation: partners who have had sexual contact within 1) 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis, 2) 6 months plus duration of symptoms for those with secondary syphilis, and 3) 1 year for persons with early latent syphilis.

Primary and Secondary Syphilis

Treatment

Parenteral penicillin G has been used effectively to achieve clinical resolution (i.e., the healing of lesions and prevention of sexual transmission) and to prevent late sequelae. However, no comparative trials have been conducted to guide the selection of an optimal penicillin regimen. Substantially fewer data are available for nonpenicillin regimens.

Recommended Regimen for Adults*
Benzathine penicillin G 2.4 million units IM in a single dose
* Recommendations for treating syphilis in persons with HIV infection and pregnant women are discussed elsewhere in this report (see Syphilis among Persons with HIV infection and Syphilis during Pregnancy).

Available data demonstrate that use of additional doses of benzathine penicillin G, amoxicillin, or other antibiotics do not enhance efficacy when used to treat primary and secondary syphilis, regardless of HIV status (*406,407*).

Recommended Regimen for Infants and Children
Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose

Infants and children aged ≥1 month who receive a diagnosis of syphilis should have birth and maternal medical records reviewed to assess whether they have congenital or acquired syphilis (see Congenital Syphilis). Infants and children aged ≥1 month with primary and secondary syphilis should be managed by a pediatric infectious-disease specialist and evaluated for sexual abuse (e.g., through consultation with child-protection services) (see Sexual Assault or Abuse of Children).

Other Management Considerations

All persons who have primary and secondary syphilis should be tested for HIV infection. In geographic areas in which the prevalence of HIV is high, persons who have primary or secondary syphilis should be retested for acute HIV in 3 months if the first HIV test result was negative.

Persons who have syphilis and symptoms or signs suggesting neurologic disease (e.g., cranial nerve dysfunction, meningitis, stroke, and hearing loss) or ophthalmic disease (e.g., uveitis, iritis, neuroretinitis, and optic neuritis) should have an evaluation that includes CSF analysis, ocular slit-lamp ophthalmologic examination, and otologic examination. Treatment should be guided by the results of this evaluation.

Invasion of CSF by *T. pallidum* accompanied by CSF laboratory abnormalities is common among adults who have primary or secondary syphilis (*402*). In the absence of clinical neurologic findings, no evidence supports variation from the recommended treatment regimen for primary and secondary syphilis. Symptomatic neurosyphilis develops in only a limited number of persons after treatment with the penicillin regimens recommended for primary and secondary syphilis. Therefore, unless clinical signs or symptoms of neurologic or ophthalmic involvement are present, routine CSF analysis is not recommended for persons who have primary or secondary syphilis.

Follow-Up

Clinical and serologic evaluation should be performed at 6 and 12 months after treatment; more frequent evaluation might be prudent if follow-up is uncertain or if repeat infection is a concern. Serologic response (i.e., titer) should be compared with the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, and definitive criteria for cure or failure have not been well established. In addition, nontreponemal test titers might decline more slowly for persons previously treated for syphilis (*408,409*).

Persons who have signs or symptoms that persist or recur and those with at least a fourfold increase in nontreponemal test titer persisting for >2 weeks likely experienced treatment failure or were re-infected. These persons should be retreated and reevaluated for HIV infection. Because treatment failure usually cannot be reliably distinguished from reinfection with *T. pallidum*, a CSF analysis also should be performed; treatment should be guided by CSF findings.

Failure of nontreponemal test titers to decline fourfold within 6–12 months after therapy for primary or secondary syphilis might be indicative of treatment failure. However, clinical trial data have demonstrated that 15%–20% of persons with primary and secondary syphilis treated with the recommended therapy will not achieve the fourfold decline in nontreponemal titer used to define response at 1 year after treatment (*406,409*). Serologic response to treatment appears to be associated with several factors, including the person's stage of syphilis (earlier stages are more likely to decline fourfold and become negative) and initial nontreponemal antibody titers (lower titers are less likely to decline fourfold than higher titers) (*409*). Optimal management of persons who have less than a fourfold decline in titers after treatment of syphilis is unclear. At a minimum, these persons should receive additional clinical and serologic follow-up and be evaluated for HIV infection. If additional follow-up cannot be ensured, retreatment is recommended. Because treatment failure might be the result of unrecognized CNS infection, CSF examination can be considered in such situations.

For retreatment, weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended, unless

CSF examination indicates that neurosyphilis is present (see Neurosyphilis). Serologic titers might not decline despite a negative CSF examination and a repeated course of therapy (*410*). In these circumstances, although the need for additional therapy or repeated CSF examinations is unclear, it is not generally recommended.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Data to support use of alternatives to penicillin in the treatment of primary and secondary syphilis are limited. However, several therapies might be effective in nonpregnant, penicillin-allergic persons who have primary or secondary syphilis. Regimens of doxycycline 100 mg orally twice daily for 14 days (*411,412*) and tetracycline (500 mg four times daily for 14 days) have been used for many years. Compliance is likely to be better with doxycycline than tetracycline, because tetracycline can cause gastrointestinal side effects and requires more frequent dosing. Although limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone (1–2 g daily either IM or IV for 10–14 days) is effective for treating primary and secondary syphilis, the optimal dose and duration of ceftriaxone therapy have not been defined (*413*). Azithromycin as a single 2 g oral dose has been effective for treating primary and secondary syphilis in some populations (*414–416*). However, *T. pallidum* chromosomal mutations associated with azithromycin and other macrolide resistance and treatment failures have been documented in multiple geographical areas in the United States (*417–419*). Accordingly, azithromycin should not be used as first-line treatment for syphilis and should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used in MSM, persons with HIV, or pregnant women. Careful clinical and serologic follow-up of persons receiving any alternative therapies is essential.

Persons with a penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin. Skin testing for penicillin allergy might be useful in some circumstances in which the reagents and expertise are available to perform the test adequately (see Management of Persons Who Have a History of Penicillin Allergy).

Pregnancy

Pregnant women with primary or secondary syphilis who are allergic to penicillin should be desensitized and treated with penicillin. For more information, see Management of Persons Who Have a History of Penicillin Allergy and Syphilis During Pregnancy.

HIV Infection

Persons with HIV infection who have primary or secondary syphilis should be treated as those without HIV infection. For more information on treatment and management, see Syphilis in Persons with HIV infection.

Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of primary, secondary, or tertiary disease. Persons who have latent syphilis and who acquired syphilis during the preceding year are classified as having early latent syphilis, a subset of latent syphilis. Persons can receive a diagnosis of early latent syphilis if, during the year preceding the diagnosis, they had 1) a documented seroconversion or a sustained (>2 week) fourfold or greater increase in nontreponemal test titers; 2) unequivocal symptoms of primary or secondary syphilis; or 3) a sex partner documented to have primary, secondary, or early latent syphilis. In addition, for persons with reactive nontreponemal and treponemal tests whose only possible exposure occurred during the previous 12 months, early latent syphilis can be assumed. In the absence of these conditions, an asymptomatic person should be considered to have latent syphilis. Nontreponemal serologic titers usually are higher early in the course of syphilis infection. However, early latent syphilis cannot be reliably diagnosed solely on the basis of nontreponemal titers. All persons with latent syphilis should have careful examination of all accessible mucosal surfaces (i.e., the oral cavity, perianal area, perineum and vagina in women, and underneath the foreskin in uncircumcised men) to evaluate for mucosal lesions.

Treatment

Because latent syphilis is not transmitted sexually, the objective of treating persons in this stage of disease is to prevent complications and transmission from a pregnant woman to her fetus. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available to guide choice of specific regimens or duration. Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early latent syphilis do not enhance efficacy, regardless of HIV infection (*406,407*).

Recommended Regimens for Adults*
Early Latent Syphilis Benzathine penicillin G 2.4 million units IM in a single dose
Late Latent Syphilis or Latent Syphilis of Unknown Duration Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
* Recommendations for treating syphilis in persons with HIV infection and pregnant women are discussed elsewhere in this report (see Syphilis in Persons with HIV infection and Syphilis during Pregnancy).

Recommended Regimens for Infants and Children
Early Latent Syphilis Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose
Late Latent Syphilis Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as 3 doses at 1-week intervals (total 150,000 units/kg up to the adult total dose of 7.2 million units)

Infants and children aged ≥1 month diagnosed with latent syphilis should be managed by a pediatric infectious-disease specialist and receive a CSF examination. In addition, birth and maternal medical records should be reviewed to assess whether these infants and children have congenital or acquired syphilis. For those with congenital syphilis, treatment should be undertaken as described in the congenital syphilis section in this document. Those with acquired latent syphilis should be evaluated for sexual abuse (e.g., through consultation with child protection services) (see Sexual Assault or Abuse of Children). These regimens are for penicillin nonallergic children who have acquired syphilis and who have normal CSF examination results.

Other Management Considerations

All persons who have latent syphilis should be tested for HIV infection. Persons who receive a diagnosis of latent syphilis and have neurologic signs and symptoms (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis or stroke) should be evaluated for neurosyphilis (see Neurosyphilis).

If a person misses a dose of penicillin in a course of weekly therapy for latent syphilis, the appropriate course of action is unclear. Clinical experience suggests that an interval of 10–14 days between doses of benzathine penicillin for latent syphilis might be acceptable before restarting the sequence of injections (i.e., if dose 1 is given on day 0, dose 2 is administered between days 10 and 14). Pharmacologic considerations suggest that an interval of 7–9 days between doses, if feasible, might be more optimal (*420–422*). Missed doses are not acceptable for pregnant women receiving therapy for latent syphilis (*423*).

Pregnant women who miss any dose of therapy must repeat the full course of therapy.

Follow-Up

Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. A CSF examination should be performed if 1) a sustained (>2 weeks) fourfold increase or greater in titer is observed, 2) an initially high titer (≥1:32) fails to decline at least fourfold within 12–24 months of therapy, or 3) signs or symptoms attributable to syphilis develop. In such circumstances, patients with CSF abnormalities should be treated for neurosyphilis. If the CSF examination is negative, retreatment for latent syphilis should be administered. Serologic titers might fail to decline despite a negative CSF examination and a repeated course of therapy, especially if the initial nontreponemal titer is low (<1:8); in these circumstances, the need for additional therapy or repeated CSF examinations is unclear but is generally not recommended. Serologic and clinical monitoring should be offered along with a reevaluation for HIV infection.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

The effectiveness of alternatives to penicillin in the treatment of latent syphilis has not been well documented. Nonpregnant patients allergic to penicillin who have clearly defined early latent syphilis should respond to antibiotics recommended as alternatives to penicillin for the treatment of primary and secondary syphilis (see Primary and Secondary Syphilis, Treatment). The only acceptable alternatives for the treatment of latent syphilis are doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily), each for 28 days. The efficacy of these alternative regimens in persons with HIV infection has not been well studied. These therapies should be used only in conjunction with close serologic and clinical follow-up, especially in persons with HIV infection. On the basis of biologic plausibility and pharmacologic properties, ceftriaxone might be effective for treating latent syphilis. However, the optimal dose and duration of ceftriaxone therapy have not been defined; treatment decisions should be discussed in consultation with a specialist. Persons with a penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin. Skin testing for penicillin allergy might be useful in some circumstances in which the reagents and expertise are available to perform the test adequately (see Management of Persons Who Have a History of Penicillin Allergy).

Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin. For more information, see Management of Persons Who Have a History of Penicillin Allergy and Syphilis during Pregnancy.

HIV Infection

Persons with HIV infection with latent syphilis should be treated as persons who do not have HIV infection. For more information on treatment and management of latent syphilis, see Syphilis in Persons with HIV Infection.

Tertiary Syphilis

Tertiary syphilis refers to gummas and cardiovascular syphilis but not to neurosyphilis. Guidelines for all forms of neurosyphilis (e.g., early or late neurosyphilis) are discussed elsewhere in these recommendations (see Neurosyphilis). Persons who are not allergic to penicillin and have no evidence of neurosyphilis should be treated with the following regimen.

Recommended Regimen
Tertiary Syphilis with Normal CSF Examination **Benzathine penicillin G** 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

Other Management Considerations

All persons who have tertiary syphilis should be tested for HIV infection and should receive a CSF examination before therapy is initiated. Persons with CSF abnormalities should be treated with a neurosyphilis regimen. Some providers treat all persons who have cardiovascular syphilis with a neurosyphilis regimen. These persons should be managed in consultation with an infectious-disease specialist. Limited information is available concerning clinical response and follow-up of persons who have tertiary syphilis.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Providers should ask patients about known allergies to penicillin. Any person allergic to penicillin should be treated in consultation with an infectious-disease specialist.

Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin. For more information,

see Management of Persons Who Have a History of Penicillin Allergy and Syphilis during Pregnancy.

HIV Infection

Persons with HIV infection who have tertiary syphilis should be treated as described for persons without HIV infection. For more information on the management of tertiary syphilis in persons with HIV infection, see Syphilis in Persons with HIV Infection.

Neurosyphilis

Treatment

CNS involvement can occur during any stage of syphilis, and CSF laboratory abnormalities are common in persons with early syphilis, even in the absence of clinical neurologic findings. No evidence exists to support variation from recommended treatment for syphilis at any stage for persons without clinical neurologic findings, with the exception of tertiary syphilis. If clinical evidence of neurologic involvement is observed (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis or stroke), a CSF examination should be performed.

Syphilitic uveitis or other ocular manifestations (e.g., neuroretinitis and optic neuritis) can be associated with neurosyphilis. A CSF examination should be performed in all instances of ocular syphilis, even in the absence of clinical neurologic findings. Ocular syphilis should be managed in collaboration with an ophthalmologist and according to the treatment and other recommendations for neurosyphilis, even if a CSF examination is normal. In instances of ocular syphilis and abnormal CSF test results, follow-up CSF examinations should be performed to assess treatment response.

Recommended Regimen
Neurosyphilis and Ocular Syphilis **Aqueous crystalline penicillin G** 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days

If compliance with therapy can be ensured, the following alternative regimen might be considered.

Alternative Regimen
Procaine penicillin G 2.4 million units IM once daily   PLUS **Probenecid** 500 mg orally four times a day, both for 10–14 days

The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen

used for latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Other Management Considerations

The following are other considerations in the management of persons who have neurosyphilis:

- All persons who have neurosyphilis should be tested for HIV.
- Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such drugs have not been proven to be beneficial.

Follow-Up

If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the cell count is normal. Follow-up CSF examinations also can be used to evaluate changes in the CSF-VDRL or CSF protein after therapy; however, changes in these two parameters occur more slowly than cell counts, and persistent abnormalities might be less important (*424,425*). Leukocyte count is a sensitive measure of the effectiveness of therapy. If the cell count has not decreased after 6 months, or if the CSF cell count or protein is not normal after 2 years, retreatment should be considered. Limited data suggest that in immunocompetent persons and persons with HIV infection on highly active antiretroviral therapy, normalization of the serum RPR titer predicts normalization of CSF parameters following neurosyphilis treatment (*425*).

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Limited data suggest that ceftriaxone 2 g daily either IM or IV for 10–14 days can be used as an alternative treatment for persons with neurosyphilis (*426,427*). Cross-sensitivity between ceftriaxone and penicillin can occur, but the risk for penicillin cross-reactivity between third-generation cephalosporins is negligible (*428–431*) (see Management of Persons Who Have a History of Penicillin Allergy). If concern exists regarding the safety of ceftriaxone for a patient with neurosyphilis, skin testing should be performed (if available) to confirm penicillin allergy and, if necessary, penicillin desensitization in consultation with a specialist is recommended. Other regimens have not been adequately evaluated for treatment of neurosyphilis.

Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin. For more information, see Syphilis during Pregnancy.

HIV Infection

Persons with HIV infection who have neurosyphilis should be treated as described for persons without HIV infection. For more information on neurosyphilis, see Syphilis in Persons with HIV infection.

Persons with HIV Infection

Diagnostic Considerations

Interpretation of treponemal and nontreponemal serologic tests for persons with HIV infection is the same as for the HIV-uninfected patient. Although rare, unusual serologic responses have been observed among persons with HIV infection who have syphilis; although most reports have involved post-treatment serologic titers that were higher than expected (high serofast) or fluctuated, false-negative serologic test results and delayed appearance of seroreactivity have also been reported (*432*).

When clinical findings are suggestive of syphilis but serologic tests are nonreactive or their interpretation is unclear, alternative tests (e.g., biopsy of a lesion, darkfield examination, and PCR of lesion material) might be useful for diagnosis. Neurosyphilis should be considered in the differential diagnosis of neurologic signs and symptoms in persons with HIV infection.

Treatment

Persons with HIV infection who have early syphilis might be at increased risk for neurologic complications (*433*) and might have higher rates of serologic treatment failure with recommended regimens. The magnitude of these risks is not defined precisely, but is likely small. Although long-term (>1 year) comparative data are lacking, no treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in persons with HIV infection than the syphilis regimens recommended for persons without HIV infection (*406*). Careful follow-up after therapy is essential. The use of antiretroviral therapy as per current guidelines might improve clinical outcomes in persons with HIV infection and syphilis (*425,434,435*).

Primary and Secondary Syphilis among Persons with HIV Infection

Recommended Regimen
Benzathine penicillin G, 2.4 million units IM in a single dose

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis do not result in enhanced efficacy (*406,407*).

Other Management Considerations

Most persons with HIV infection respond appropriately to the recommended benzathine penicillin treatment regimen for primary and secondary syphilis. CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in persons with HIV infection, even in those without syphilis. The clinical and prognostic significance of such CSF laboratory abnormalities in persons with primary and secondary syphilis who lack neurologic symptoms is unknown. Certain studies have demonstrated that among persons with HIV infection and syphilis, CSF abnormalities are associated with a CD4 count of ≤350 cells/mL and/or an RPR titer of ≥1:32 (*404,436,437*); however, CSF examination has not been associated with improved clinical outcomes in the absence of neurologic signs and symptoms. All persons with HIV infection and syphilis should have a careful neurologic exam (*425,434,435*).

Follow-Up

Persons with HIV infection and primary or secondary syphilis should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy; those who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or persons who have a sustained [>2 weeks] fourfold increase or greater in titer) should be managed in the same manner as HIV-negative patients (i.e., a CSF examination and retreatment guided by CSF findings). In addition, CSF examination and retreatment can be considered for persons whose nontreponemal test titers do not decrease fourfold within 12–24 months of therapy. If CSF examination is normal, treatment with benzathine penicillin G administered as 2.4 million units IM each at weekly intervals for 3 weeks is recommended. Serologic titers might not decline despite a negative CSF examination and a repeated course of therapy (*410*). In these circumstances, the need for additional therapy or repeated CSF examinations is unclear, but is not generally recommended. Serologic and clinical monitoring should be provided.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Persons with HIV infection who are penicillin-allergic and have primary or secondary syphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative persons. Persons with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see Management of Persons Who Have a History of Penicillin Allergy). The use of alternatives to penicillin has not been well studied in persons with HIV infection; azithromycin is not recommended in persons with HIV infection and primary and secondary syphilis. Alternative therapies should be used only in conjunction with close serologic and clinical follow-up.

Latent Syphilis among Persons with HIV Infection

Recommended Regimen for Early Latent Syphilis
Benzathine penicillin G, 2.4 million units IM in a single dose

Recommended Regimen for Late Latent Syphilis
Benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks

Other Management Considerations

All persons with HIV infection and syphilis should undergo a careful neurologic examination; those with neurologic symptoms or signs should undergo immediate CSF examination. In the absence of neurologic symptoms, CSF examination has not been associated with improved clinical outcomes and therefore is not recommended.

Follow-Up

Patients should be evaluated clinically and serologically at 6, 12, 18, and 24 months after therapy. If, at any time, clinical symptoms develop or a sustained (>2 weeks) fourfold or greater rise in nontreponemal titers occurs, a CSF examination should be performed and treatment administered accordingly. If the nontreponemal titer does not decline fourfold after 24 months, CSF examination can be considered and treatment administered accordingly, although initial low titers (<1:8) might not decline. Even after retreatment, serologic titers might fail to decline. In these circumstances, the need for repeated CSF examination or additional therapy is unclear but is generally not recommended. Serologic and clinical monitoring should be provided.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

The efficacy of alternative nonpenicillin regimens in persons with HIV infection has not been well studied, and these therapies should be used only in conjunction with close serologic and clinical follow-up. Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (See Management of Persons Who Have a History of Penicillin Allergy).

Neurosyphilis Among Persons with HIV Infection

All persons with HIV infection and syphilis should receive a careful neurologic examination. Persons with HIV infection and neurosyphilis should be treated according to the recommendations for HIV-negative persons with neurosyphilis (See Neurosyphilis).

Follow Up

Persons with HIV infection and neurosyphilis should be managed according to the recommendations for HIV-negative persons with neurosyphilis (see Neurosyphilis). Limited data suggest that changes in CSF parameters might occur more slowly in persons with HIV infection, especially those with more advanced immunosuppression (424,434).

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Persons with HIV infection who are penicillin-allergic and have neurosyphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative patients with neurosyphilis (See Neurosyphilis). Several small observational studies conducted in persons with HIV infection with neurosyphilis suggest that ceftriaxone 1–2 g IV daily for 10–14 days might be effective as an alternate agent (438–440). The possibility of cross-sensitivity between ceftriaxone and penicillin exists, but the risk of penicillin cross-reactivity between third- generation cephalosporins is negligible (428–431) (see Management of Persons Who Have a History of Penicillin Allergy). If concern exists regarding the safety of ceftriaxone for a person with HIV infection and neurosyphilis, skin testing should be performed (if available) to confirm penicillin allergy and, if necessary, penicillin desensitization

in consultation with a specialist is recommended. Other regimens have not been adequately evaluated for treatment of neurosyphilis.

Syphilis During Pregnancy

All women should be screened serologically for syphilis early in pregnancy (106). Most states mandate screening at the first prenatal visit for all women (441). In populations in which receipt of prenatal care is not optimal, RPR test screening and treatment (if the RPR test is reactive) should be performed at the time pregnancy is confirmed (442). Antepartum screening by nontreponemal antibody testing is typical, but treponemal antibody testing is being used in some settings. Pregnant women with reactive treponemal screening tests should have additional quantitative nontreponemal testing, because titers are essential for monitoring treatment response. For communities and populations in which the prevalence of syphilis is high and for women at high risk for infection, serologic testing should also be performed twice during the third trimester: once at 28–32 weeks' gestation and again at delivery. Any woman who has a fetal death after 20 weeks' gestation should be tested for syphilis. No mother or neonate should leave the hospital without maternal serologic status having been documented at least once during pregnancy, and if the mother is considered high risk, documented at delivery.

Diagnostic Considerations

Seropositive pregnant women should be considered infected unless an adequate treatment history is documented clearly in the medical records and sequential serologic antibody titers have declined appropriately for the stage of syphilis. In general, the risk for antepartum fetal infection or congenital syphilis at delivery is related to the stage of syphilis during pregnancy, with the highest risk occurring with the primary and secondary stage. Quantitative maternal nontreponemal titer, especially if >1:8, might be a marker of early infection and bacteremia. However, risk for fetal infection is still significant in pregnant women with late latent syphilis and low titers. Pregnant women with stable, serofast low antibody titers who have previously been treated for syphilis might not require additional treatment; however, rising or persistently high antibody titers might indicate reinfection or treatment failure, and treatment should be considered.

If a treponemal test (e.g., EIA or CIA) is used for antepartum syphilis screening, all positive EIA/CIA tests should be reflexed to a quantitative nontreponemal test (RPR or VDRL). If the nontreponemal test is negative, then the results are considered discrepant and a second treponemal test (TP-PA preferred) should be performed, preferably on the same specimen. If the second treponemal test is positive, current or past syphilis

infection can be confirmed. For women with a history of adequately treated syphilis who do not have ongoing risk, no further treatment is necessary. Women without a history of treatment should be staged and treated accordingly with a recommended penicillin regimen. If the second treponemal test is negative, the positive EIA/CIA is more likely to represent a false-positive test result in low-risk women with no history of treated syphilis (*400*). If the woman is at low risk for syphilis, lacks signs or symptoms of primary syphilis, has a partner with no clinical or serologic evidence of syphilis, and is likely to follow up, repeat serologic testing within 4 weeks can be considered to determine whether the EIA/CIA remains positive or if the RPR/VDRL or the TP-PA becomes positive. If both the RPR and TP-PA remain negative, no further treatment is necessary. If follow-up is not possible, women without a history of treated syphilis should be treated according to the stage of syphilis.

Treatment

Penicillin G is the only known effective antimicrobial for preventing maternal transmission to the fetus and treating fetal infection (*443*). Evidence is insufficient to determine optimal, recommended penicillin regimens (*444*).

Recommended Regimen
Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.

Other Management Considerations

- Some evidence suggests that additional therapy is beneficial for pregnant women. For women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin 2.4 million units IM can be administered 1 week after the initial dose (*445–447*).
- When syphilis is diagnosed during the second half of pregnancy, management should include a sonographic fetal evaluation for congenital syphilis. However, this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (i.e., hepatomegaly, ascites, hydrops, fetal anemia, or a thickened placenta) indicate a greater risk for fetal treatment failure (*448*); cases accompanied by these signs should be managed in consultation with obstetric specialists. Evidence is insufficient to recommend specific regimens for these situations.
- Women treated for syphilis during the second half of pregnancy are at risk for premature labor and/or fetal distress if the treatment precipitates the Jarisch-Herxheimer reaction (*449*). These women should be advised to seek

obstetric attention after treatment if they notice any fever, contractions, or decrease in fetal movements. Stillbirth is a rare complication of treatment, but concern for this complication should not delay necessary treatment. No data are available to suggest that corticosteroid treatment alters the risk for treatment-related complications in pregnancy.
- Missed doses are not acceptable for pregnant women receiving therapy for late latent syphilis (*423*). Pregnant women who miss any dose of therapy must repeat the full course of therapy.
- All women who have syphilis should be offered testing for HIV infection.

Follow-Up

Coordinated prenatal care and treatment are vital. At a minimum, serologic titers should be repeated at 28–32 weeks' gestation and at delivery. Serologic titers can be checked monthly in women at high risk for reinfection or in geographic areas in which the prevalence of syphilis is high. Providers should ensure that the clinical and antibody responses are appropriate for the patient's stage of disease, although most women will deliver before their serologic response to treatment can be assessed definitively. Inadequate maternal treatment is likely if delivery occurs within 30 days of therapy, clinical signs of infection are present at delivery, or the maternal antibody titer at delivery is fourfold higher than the pretreatment titer.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

No proven alternatives to penicillin are available for treatment of syphilis during pregnancy. Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions (see Management of Persons Who Have a History of Penicillin Allergy).

Tetracycline and doxycycline are contraindicated in the second and third trimester of pregnancy (*317*). Erythromycin and azithromycin should not be used, because neither reliably cures maternal infection or treats an infected fetus (*444*). Data are insufficient to recommend ceftriaxone for treatment of maternal infection and prevention of congenital syphilis.

HIV Infection

Placental inflammation from congenital infection might increase the risk for perinatal transmission of HIV. All women

with HIV infection should be evaluated for syphilis and receive a penicillin regimen appropriate for the stage of infection. Data are insufficient to recommend any alternative regimens for pregnant women with HIV infection (see Syphilis Among Persons with HIV infection).

Congenital Syphilis

Effective prevention and detection of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit. Additional testing at 28 weeks' gestation and again at delivery is warranted for women who are at increased risk or live in communities with increased prevalence of syphilis infection (*442,450*). Moreover, as part of the management of pregnant women who have syphilis, information concerning ongoing risk behaviors and treatment of sex partners should be obtained to assess the risk for reinfection. Routine screening of newborn sera or umbilical cord blood is not recommended, as diagnosis at this time does not prevent symptomatic congenital syphilis in some newborns. No mother or newborn infant should leave the hospital without maternal serologic status having been documented at least once during pregnancy, and preferably again at delivery if at risk.

Evaluation and Treatment of Neonates (Infants Aged <30 Days)

The diagnosis of congenital syphilis can be difficult, as maternal nontreponemal and treponemal IgG antibodies can be transferred through the placenta to the fetus, complicating the interpretation of reactive serologic tests for syphilis in neonates. Therefore, treatment decisions frequently must be made on the basis of 1) identification of syphilis in the mother; 2) adequacy of maternal treatment; 3) presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate; and 4) comparison of maternal (at delivery) and neonatal nontreponemal serologic titers using the same test, preferably conducted by the same laboratory. Any neonate at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

All neonates born to mothers who have reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal serologic test (RPR or VDRL) performed on the neonate's serum, because umbilical cord blood can become contaminated with maternal blood and yield a false-positive result, and Wharton's jelly within the umbilical cord can yield a false-negative result. Conducting a treponemal test (i.e., TP-PA, FTA-ABS, EIA, or CIA) on neonatal serum is not recommended because it is difficult to interpret. No commercially available immunoglobulin (IgM) test can be recommended.

All neonates born to women who have reactive serologic tests for syphilis should be examined thoroughly for evidence of congenital syphilis (e.g., nonimmune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash, and pseudoparalysis of an extremity). Pathologic examination of the placenta or umbilical cord using specific staining (e.g., silver) or a *T. pallidum* PCR test using a CLIA-validated test should be considered; DFA-TP reagents are not available. Darkfield microscopic examination or PCR testing of suspicious lesions or body fluids (e.g., bullous rash and nasal discharge) also should be performed. In addition to these tests, for stillborn infants, skeletal survey demonstrating typical osseous lesions might aid in the diagnosis of congenital syphilis.

The following scenarios describe the congenital syphilis evaluation and treatment of neonates born to women who have reactive serologic tests for syphilis during pregnancy. Maternal history of infection with *T. pallidum* and treatment for syphilis must be considered when evaluating and treating the neonate for congenital syphilis in most scenarios, except when congenital syphilis is proven or highly probable (See Scenario 1).

Scenario 1: Proven or highly probable congenital syphilis

Any neonate with:
1. an abnormal physical examination that is consistent with congenital syphilis;
   OR
2. a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer;[¶]
   OR
3. a positive darkfield test or PCR of lesions or body fluid(s).

Recommended Evaluation

- CSF analysis for VDRL, cell count, and protein[**]
- Complete blood count (CBC) and differential and platelet count
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver-function tests, neuroimaging, ophthalmologic examination, and auditory brain stem response).

[¶] The absence of a fourfold or greater titer for a neonate does not exclude congenital syphilis.

[**] CSF test results obtained during the neonatal period can be difficult to interpret; normal values differ by gestational age and are higher in preterm infants. Values as high as 25 white blood cells (WBCs)/mm^3 and/or protein of 150 mg/dL might occur among normal neonates; lower values (i.e., 5 WBCs/mm^3 and protein of 40 mg/dL) might be considered the upper limits of normal. Other causes of elevated values should be considered when an infant is being evaluated for congenital syphilis.

Recommended Regimens
Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days   OR **Procaine penicillin G** 50,000 units/kg/dose IM in a single daily dose for 10 days

If more than 1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding the use of other antimicrobial agents (e.g., ampicillin). When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis. The use of agents other than penicillin requires close serologic follow-up to assess adequacy of therapy.

Scenario 2: Possible Congenital Syphilis

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer and one of the following:

1. mother was not treated, inadequately treated, or has no documentation of having received treatment;
    OR
2. mother was treated with erythromycin or a regimen other than those recommended in these guidelines (i.e., a nonpenicillin G regimen);[††]
    OR
3. mother received recommended treatment <4 weeks before delivery.

Recommended Evaluation

- CSF analysis for VDRL, cell count, and protein**
- CBC, differential, and platelet count
- Long-bone radiographs

A complete evaluation is not necessary if 10 days of parenteral therapy is administered, although such evaluations might be useful. For instance, a lumbar puncture might document CSF abnormalities that would prompt close follow-up. Other tests (e.g., CBC, platelet count, and bone radiographs) can be performed to further support a diagnosis of congenital syphilis.

[††] A women treated with a regimen other than recommended in these guidelines should be considered untreated.

Recommended Regimens

Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
    OR
Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days
    OR
Benzathine penicillin G 50,000 units/kg/dose IM in a single dose

Before using the single-dose benzathine penicillin G regimen, the complete evaluation (i.e., CSF examination, long-bone radiographs, and CBC with platelets) must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed, if the CSF analysis is uninterpretable because of contamination with blood, or if follow-up is uncertain, a 10-day course of penicillin G is required. If the neonate's nontreponemal test is nonreactive and the provider determines that the mother's risk of untreated syphilis is low, treatment of the neonate with a single IM dose of benzathine penicillin G 50,000 units/kg for possible incubating syphilis can be considered without an evaluation.

Neonates born to mothers with untreated early syphilis at the time of delivery are at increased risk for congenital syphilis, and the 10-day course of penicillin G may be considered even if the complete evaluation is normal and follow-up is certain.

Scenario 3: Congenital Syphilis less likely

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer and both of the following are true:

1. mother was treated during pregnancy, treatment was appropriate for the stage of infection, and treatment was administered >4 weeks before delivery and
2. mother has no evidence of reinfection or relapse.

Recommended Evaluation

No evaluation is recommended.

Recommended Regimen
Benzathine penicillin G 50,000 units/kg/dose IM in a single dose*
* Another approach involves not treating the infant, but rather providing close serologic follow-up every 2–3 months for 6 months for infants whose mother's nontreponemal titers decreased at least fourfold after appropriate therapy for early syphilis or remained stable for low-titer, latent syphilis (e.g., VDRL <1:2; RPR <1:4).

Scenario 4: Congenital Syphilis unlikely

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer and both of the following are true:

1. mother's treatment was adequate before pregnancy and
2. mother's nontreponemal serologic titer remained low and stable (i.e., serofast) before and during pregnancy and at delivery (VDRL <1:2; RPR <1:4).

Recommended Evaluation

No evaluation is recommended.

> **Recommended Regimen**
>
> No treatment is required, but infants with reactive nontreponemal tests should be followed serologically to ensure the nontreponemal test returns to negative (see Follow-Up). Benzathine penicillin G 50,000 units/kg as a single IM injection might be considered, particularly if follow-up is uncertain and the neonate has a reactive nontreponemal test.

Follow-Up

All neonates with reactive nontreponemal tests should receive careful follow-up examinations and serologic testing (i.e., a nontreponemal test) every 2–3 months until the test becomes nonreactive. In the neonate who was not treated because congenital syphilis was considered less likely or unlikely, nontreponemal antibody titers should decline by age 3 months and be nonreactive by age 6 months, indicating that the reactive test result was caused by passive transfer of maternal IgG antibody. At 6 months, if the nontreponemal test is nonreactive, no further evaluation or treatment is needed; if the nontreponemal test is still reactive, the infant is likely to be infected and should be treated. Treated neonates that exhibit persistent nontreponemal test titers by 6–12 months should be re-evaluated through CSF examination and managed in consultation with an expert. Retreatment with a 10-day course of a penicillin G regimen may be indicated. Neonates with a negative nontreponemal test at birth and whose mothers were seroreactive at delivery should be retested at 3 months to rule out serologically negative incubating congenital syphilis at the time of birth. Treponemal tests should not be used to evaluate treatment response because the results are qualitative and passive transfer of maternal IgG treponemal antibody might persist for at least 15 months.

Neonates whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. A reactive CSF Venereal Disease Research Laboratory (VDRL) test or abnormal CSF indices that persist and cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis and should be managed in consultation with an expert.

Special Considerations

Penicillin Allergy

Infants and children who require treatment for congenital syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should be desensitized and then treated with penicillin (see Management of Persons with a History of Penicillin Allergy). Skin testing remains unavailable for infants and children because the procedure has not been standardized for this age group. Data are insufficient regarding the use of other antimicrobial agents (e.g., ceftriaxone) for congenital syphilis in infants and children. If a nonpenicillin G agent is used, close clinical, serologic, and CSF follow-up is required in consultation with an expert.

Penicillin Shortage

During periods when the availability of aqueous crystalline penicillin G is compromised, the following is recommended (see http://www.cdc.gov/std/treatment/drugnotices/penicilling.htm).

1. For neonates with clinical evidence of congenital syphilis (Scenario 1), check local sources for aqueous crystalline penicillin G (potassium or sodium). If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 U/kg/dose IM a day in a single daily dose for 10 days).

If aqueous or procaine penicillin G is not available, ceftriaxone (in doses appropriate for birthweight) can be considered with careful clinical and serologic follow-up and in consultation with an expert, as evidence is insufficient to support the use of ceftriaxone for the treatment of congenital syphilis. Management might include a repeat CSF examination at age 6 months if the initial examination was abnormal. Ceftriaxone must be used with caution in infants with jaundice.

2. For neonates without any clinical evidence of congenital syphilis (Scenario 2 and Scenario 3), use
   a. procaine penicillin G, 50,000 U/kg/dose IM a day in a single dose for 10 days
   OR
   b. benzathine penicillin G, 50,000 U/kg IM as a single dose.

If any part of the evaluation for congenital syphilis is abnormal or was not performed, CSF examination is not interpretable, or follow-up is uncertain, procaine penicillin G is recommended. A single dose of ceftriaxone is inadequate therapy.

3. For premature infants who have no clinical evidence of congenital syphilis (Scenario 2 and Scenario 3) and might not tolerate IM injections because of decreased muscle mass, IV ceftriaxone can be considered with careful clinical and serologic follow-up and in consultation with an expert. Ceftriaxone dosing must be adjusted according to birthweight.

HIV Infection

Evidence is insufficient to determine whether neonates who have congenital syphilis and HIV or whose mothers have HIV infection require different therapy or clinical management than is recommended for all neonates. All neonates with congenital syphilis and HIV infection should be managed similarly as neonates with congenital syphilis who do not have HIV infection.

Evaluation and Treatment of Infants and Children with Congenital Syphilis

Infants and children aged ≥1 month who are identified as having reactive serologic tests for syphilis should be examined thoroughly and have maternal serology and records reviewed to assess whether they have congenital or acquired syphilis (see Primary and Secondary Syphilis and Latent Syphilis, Sexual Assault or Abuse of Children). Any infant or child at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

Recommended Evaluation

- CSF analysis for VDRL, cell count, and protein
- CBC, differential, and platelet count
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver function tests, abdominal ultrasound, ophthalmologic examination, neuroimaging, and auditory brain-stem response)

Recommended Regimen

Aqueous crystalline penicillin G 200,000–300,000 units/kg/day IV, administered as 50,000 units/kg every 4–6 hours for 10 days

If the infant or child has no clinical manifestations of congenital syphilis and the evaluation (including the CSF examination) is normal, treatment with up to 3 weekly doses of benzathine penicillin G, 50,000 U/kg IM can be considered. A single dose of benzathine penicillin G 50,000 units/kg IM up to the adult dose of 2.4 million units in a single dose can be considered after the 10-day course of IV aqueous penicillin to provide more comparable duration of treatment in those who have no clinical manifestations and normal CSF. All of the above treatment regimens also would be adequate for children who might have other treponemal infections.

Follow-Up

Careful follow-up examinations and serologic testing (i.e., a nontreponemal test) of infants and children treated for congenital syphilis after the neonatal period (30 days of age) should be performed every 3 months until the test becomes nonreactive or the titer has decreased fourfold. The serologic response after therapy might be slower for infants and children than neonates. If these titers increase at any point for more than 2 weeks or do not decrease fourfold after 12–18 months, the infant or child should be evaluated (e.g., through CSF examination), treated with a 10-day course of parenteral penicillin G, and managed in consultation with an expert. Treponemal tests should not be used to evaluate treatment response, because the results are qualitative and persist after treatment; further, passive transfer of maternal IgG treponemal antibody might persist for at least 15 months after delivery.

Infants or children whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. After 2 years of follow-up, a reactive CSF VDRL test or abnormal CSF indices that persists and cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis and should be managed in consultation with an expert.

Special Considerations

Penicillin Allergy

Infants and children who require treatment for congenital syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should be desensitized and treated with penicillin (see Management of Persons with a History of Penicillin Allergy). Skin testing remains unavailable for infants and children because the procedure has not been standardized for this age group. Data are insufficient regarding the use of other antimicrobial agents (e.g., ceftriaxone) for congenital syphilis in infants and children. If a nonpenicillin G agent is used, close clinical, serologic, and CSF follow-up is required in consultation with an expert.

Penicillin Shortage

During periods when the availability of penicillin G is compromised, management options are similar to
   options for the neonate (see Evaluation and treatment of infants during the first month of life).

1. For infants and children with clinical evidence of congenital syphilis, procaine penicillin G (50,000 U/kg/dose IM up to the adult dose of 2.4 million units a day in a single daily dose for 10 days) is recommended. A single dose of benzathine penicillin G 50,000 units/kg

IM up to the adult dose of 2.4 million units in a single dose can be considered after the 10-day course of procaine penicillin. If procaine or benzathine penicillin G is not available, ceftriaxone (in doses appropriate for age and weight) can be considered with careful clinical and serologic follow-up. Infants and children receiving ceftriaxone should be managed in consultation with an expert, as evidence is insufficient to support the use of ceftriaxone for the treatment of congenital syphilis in infants or children. For infants aged ≥30 days, use 75 mg/kg IV/IM of ceftriaxone a day in a single daily dose for 10–14 days (dose adjustment might be necessary based on current weight). For children, the dose should be 100 mg/kg of ceftriaxone a day in a single daily dose.

2. For infants and children without any clinical evidence of infection (see Scenario 2 and Scenario 3), use
   a. procaine penicillin G, 50,000 U/kg/dose IM a day in a single dose for 10 days or
   b. benzathine penicillin G, 50,000 U/kg IM as a single dose.

If any part of the evaluation for congenital syphilis is abnormal or not performed, CSF examination is not interpretable, or follow-up is uncertain, procaine penicillin G is recommended.

HIV Infection

Evidence is insufficient to determine whether infants and children who have congenital syphilis and HIV or whose mothers have HIV infection require different therapy or clinical management than is recommended for all infants and children. All infants and children with congenital syphilis and HIV infection should be managed like infants and children without HIV infection.

Management of Persons Who Have a History of Penicillin Allergy

No proven alternatives to penicillin are available for treating neurosyphilis, congenital syphilis, or syphilis in pregnant women. Penicillin also is recommended, whenever possible, for persons with HIV infection. The prevalence of reported penicillin allergy in the United States is about 8%–10% (451–453) and might be higher in hospitalized persons (454). The prevalence of reported penicillin allergy in developing countries is unknown; however, limited data suggest that penicillin is one of the most frequently reported allergies in some developing countries (455,456). Of persons reporting penicillin allergy, 10%–15% have a positive skin test suggestive of a penicillin allergy; these persons are at risk for an immunoglobulin E (IgE)-mediated allergic response to penicillin such as urticaria, angioedema, or anaphylaxis (i.e., upper airway obstruction, bronchospasm, or hypotension) (428–430,457,458). Re-administration of penicillin to patients with a history of IgE-mediated hypersensitivity reactions can cause severe, immediate reactions. Because anaphylactic reactions to penicillin can be fatal, every effort should be made to avoid administering penicillin to penicillin-allergic persons, unless they undergo induction of drug tolerance (also referred to as "desensitization") to temporarily eliminate IgE-mediated hypersensitivity. However, many persons with a reported history of penicillin allergy likely have had other types of adverse drug reactions or have lost their sensitivity to penicillin over time and can safely be treated with penicillin.

Penicillin skin testing with the major and minor determinants of penicillin can reliably identify persons at high risk for IgE-mediated reactions to penicillin (458,459). Although the testing reagents are easily generated, only the major determinant (benzylpenicilloyl poly-L-lysine [Pre-Pen]) and penicillin G have been available commercially. These two tests identify an estimated 90%–99% of the allergic patients. However, because skin testing without the minor determinants would still fail to identify 1%–10% of allergic persons and because serious or fatal reactions can occur among these minor-determinant–positive persons, caution should be exercised when the full battery of skin-test reagents is not available (Box 2) (457–460). Manufacturers are working on a minor determinant mixture, but at the time of publication, no such product has been cleared by FDA for use in the United States. Penicillin skin testing has been used in a variety of settings to improve antibiotic use (453,461–463).

Some studies have reported cross-reactivity rates as high as 10% among persons with a history of penicillin allergy who take cephalosporins. However, more recent studies indicate a lower rate (<2.5%) of cross reactivity between these drugs (428–431,464). Risk is highest with first-generation cephalosporins and cephalosporins that have similar R-group side chains to specific penicillins (465,466). The risk for penicillin cross-reactivity between most second-generation (cefoxitin) and all third generation cephalosporins (cefixime and ceftriaxone) is negligible (428–431); cefoxitin, cefixime, and ceftriaxone do not have an R group side chain similar to penicillin G.

Recommendations

Persons with a history of severe non-IgE-mediated reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, and hemolytic anemia) are not candidates

BOX 2. Skin-test reagents for identifying persons at risk for adverse reactions to penicillin

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Major Determinant
- Benzylpenicilloyl poly-L-lysine (PrePen) (AllerQuest, Plainville Connecticut) (6 x 10–5M)

Minor Determinant Precursors*
- Benzylpenicillin G (10–2M, 3.3 mg/mL, 10,000 units/mL)
- Benzylpenicilloate (10–2M, 3.3 mg/mL)
- Benzylpenicilloate (or penicilloyl propylamine) (10–2M, 3.3 mg/mL)

Positive Control
- Commercial histamine for intradermal skin testing (1.0 mg/mL)

Negative Control
- Diluent (usually saline) or allergen diluent

Source: Adapted from Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med 1987;107:204–15.

* Aged penicillin is not an adequate source of minor determinants. Penicillin G should either be freshly prepared or come from a fresh-frozen source.

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for skin testing or challenge and should avoid penicillins indefinitely. If the full battery of skin-test reagents is available, including both major and minor determinants (see Penicillin Allergy Skin Testing), persons who report a history of penicillin reaction and who are skin-test negative can receive conventional penicillin therapy. Persons with positive skin test results should be desensitized before initiating treatment.

If the full battery of skin-test reagents, including the minor determinants, is not available, skin testing should be conducted using the major determinant (Pre-Pen) and penicillin G. Those persons who have positive test results should be desensitized. For persons with negative skin tests, a subsequent observed challenge to the penicillin of choice is recommended. In addition, for persons with a history of severe or recent suspected IgE-mediated reactions to penicillin with negative skin testing, the penicillin of choice should be given by graded challenge. If the major determinant is not available for skin testing, all persons with a history suggesting IgE-mediated reactions to penicillin (e.g., anaphylaxis, angioedema, bronchospasm, or urticaria) should be desensitized in a hospital setting. In persons with reactions not likely to be IgE-mediated, outpatient-monitored graded challenges can be considered.

Penicillin Allergy Skin Testing

Persons at high risk for anaphylaxis, including those who 1) have a history of penicillin-related anaphylaxis or other IgE-mediated reactions, asthma, or other diseases that would make anaphylaxis more dangerous or 2) are being treated with beta-adrenergic blocking agents should be tested with 100-fold dilutions of the full-strength skin-test reagents before being tested with full-strength reagents. In these situations, testing should be performed in a monitored setting in which treatment for an anaphylactic reaction is available. If possible, antihistamines (e.g., chlorpheniramine maleate, fexofenadine, diphenhydramine HCL, and hydroxyzine) should not have been taken within the 5 days before skin testing.

Procedures

Dilute the antigens in saline either 100-fold for preliminary testing (if the patient has had a IgE-mediated reaction to penicillin) or 10-fold (if the patient has had another type of immediate, generalized reaction to penicillin within the preceding year). Pre-Pen is provided full-strength (6 x 10–5 meq penicilloyl) in a single dose ampoule. Penicillin G is diluted to 10,000 IU/ml in saline and aliquoted in sterile vials that remain stable for at least 6 months if frozen.

Epicutaneous (Prick) Tests

Duplicate drops of skin-test reagent are placed on the volar surface of the forearm. The underlying epidermis is pierced with a 26-gauge needle without drawing blood. An epicutaneous test is positive if the average wheal diameter after 15 minutes is ≥4 mm larger than that of negative controls; otherwise, the test is negative. The histamine controls should be positive to ensure that results are not falsely negative because of the effect of antihistaminic drugs.

Intradermal Test

If epicutaneous tests are negative, duplicate 0.02-mL intradermal injections of negative control and antigen solutions are made into the volar surface of the forearm by using a 26- or 27-gauge needle on a syringe. The margins of the wheals induced by the injections should be marked with a ball point pen. An intradermal test is positive if the average wheal diameter 15 minutes after injection is >2 mm larger than the initial wheal size and also is >2 mm larger than the negative histamine controls. Otherwise, the tests are negative. If the duplicates are discordant, a second set of duplicate tests can be used to resolve the ambiguity.

Desensitization

Persons who have a positive skin test to one of the penicillin determinants can be desensitized (Table 1). This is a

straightforward, relatively safe procedure that can be performed orally or intravenously. Modified protocols might be considered based on an individual's symptoms, drug of choice, and route of administration (467–469). Although the two approaches have not been compared, oral desensitization is regarded as safer and easier to perform. Desensitization should occur in a hospital setting because serious IgE-mediated allergic reactions can occur; the procedure can usually be completed in approximately 4–12 hours, after which time the first dose of penicillin is administered. After desensitization, penicillin should be maintained continuously for the duration of the course of therapy. Once the course is completed, if penicillin is required in the future, the desensitization procedure should be repeated.

Diseases Characterized by Urethritis and Cervicitis

Urethritis

Urethritis, as characterized by urethral inflammation, can result from infectious and noninfectious conditions. Symptoms, if present, include dysuria; urethral pruritis; and mucoid, mucopurulent, or purulent discharge. Signs of urethral discharge on examination can also be present in persons without symptoms. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *Mycoplasma genitalium* has also been associated with urethritis and, less commonly, prostatitis (470–474). If point-of-care diagnostic tools (e.g., Gram, methylene blue [MB] or gentian violet [GV] stain microscopy, first void urine with microscopy, and leukocyte esterase) are not available, drug regimens effective against both gonorrhea and chlamydia should be administered. Further testing to determine the specific etiology is recommended to prevent complications, re-infection, and transmission because a specific diagnosis might improve treatment compliance, delivery of risk reduction interventions, and partner notification. Both chlamydia and gonorrhea are reportable to health departments. NAATs are preferred for the detection of *C. trachomatis* and *N. gonorrhoeae,* and urine is the preferred specimen in males (394). NAAT-based tests for the diagnosis of *T. vaginalis* in men have not been cleared by FDA; however, some laboratories have performed the CLIA-compliant validation studies (475) needed to provide such testing.

Etiology

Several organisms can cause infectious urethritis. The presence of Gram-negative intracellular diplococci (GNID)

TABLE 1. Oral desensitization protocol for persons with a positive skin test*

Penicillin V suspension dose[†]	Amount[§] (units/mL)	mL	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

Source: Wendel GO, Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. N Engl J Med 1985;312:1229–32.

* Observation period was 30 minutes before parenteral administration of penicillin.
[†] Interval between doses, 15–30 minutes; elapsed time, 4–8 hours; cumulative dose, 1.3 million units.
[§] The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

or MB/GV purple intracellular diplococci on urethral smear is indicative of presumed gonorrhea infection, which is frequently accompanied by chlamydial infection. NGU, which is diagnosed when microscopy of urethral secretions indicates inflammation without GNID or MB/GV purple intracellular diplococci, is caused by *C. trachomatis* in 15%–40% of cases; however, prevalence varies by age group, with a lower burden of disease occurring among older men (476). Documentation of chlamydial infection as the etiology of NGU is essential because of the need for partner referral for evaluation and treatment to prevent complications of chlamydia, especially in female partners. Complications of *C. trachomatis*-associated NGU among males include epididymitis, prostatitis, and reactive arthritis.

M. genitalium, which can be sexually transmitted, is associated with symptoms of urethritis as well as urethral inflammation and accounts for 15%–25% of NGU cases in the United States (470–473). However, FDA-cleared diagnostic tests for *M. genitalium* are not available.

T. vaginalis can cause NGU in heterosexual men, but the prevalence varies substantially by region of the United States and within specific subpopulations. In some instances, NGU can be acquired by fellatio (i.e., oral penile contact), sometimes because of specific pathogens such as HSV, Epstein Barr Virus, and adenovirus (476); data supporting other *Mycoplasma* species and *Ureaplasma* as etiologic agents are inconsistent. Diagnostic

"This course was developed from the public domain document: Sexually Transmitted Disease Treatment Guidelines, 2015 – U.S Department of Health and Human Services, Centers for Disease Control and Prevention (CDC)."