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Sexually Transmitted Diseases Treatment Guidelines, 2010

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CONTENTS

Sexually Transmitted Diseases Treatment Guidelines, 2010

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Summary

*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 18–30, 2009. The information in this report updates the 2006 Guidelines for Treatment of Sexually Transmitted Diseases (*MMWR *2006;55[No. RR–11]). Included in these updated guidelines is new information regarding 1) the expanded diagnostic evaluation for cervicitis and trichomoniasis; 2) new treatment recommendations for bacterial vaginosis and genital warts; 3) the clinical efficacy of azithromycin for chlamydial infections in pregnancy; 4) the role of* Mycoplasma genitalium *and trichomoniasis in urethritis/cervicitis and treatment-related implications; 5) lymphogranuloma venereum proctocolitis among men who have sex with men; 6) the criteria for spinal fluid examination to evaluate for neurosyphilis; 7) the emergence of azithromycin-resistant* Treponema pallidum*; 8) the increasing prevalence of antimicrobial-resistant* Neisseria gonorrhoeae*; 9) the sexual transmission of hepatitis C; 10) diagnostic evaluation after sexual assault; and 11) STD prevention approaches.*

Introduction

The term sexually transmitted diseases (STDs) is used to refer to a variety of clinical syndromes 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.

These recommendations should be regarded as a source of clinical guidance and not prescriptive standards; health-care providers should always consider the clinical circumstances of each person in the context of local disease prevalence. They are applicable to various patient-care settings, including family-planning clinics, private physicians' offices, managed care organizations, and other primary-care facilities. These guidelines focus on the treatment and counseling of individual patients and do not address other community services and interventions that are essential to STD/human immunodeficiency virus (HIV) prevention efforts.

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Methods

These guidelines were developed using a multistage process. Beginning in 2008, CDC staff members and public and private sector experts knowledgeable in the field of STDs systematically reviewed literature using an evidence-based approach (e.g., published abstracts and peer-reviewed journal articles), focusing on the common STDs and information that had become available since publication of the *2006 Guidelines for Treatment of Sexually Transmitted Diseases* (*1*). CDC staff members and STD experts developed background papers and tables of evidence that summarized 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. CDC staff then developed a draft document on the basis of this evidence-based review. In April 2009, this information was presented at a meeting of invited consultants (including public- and private-sector professionals knowledgeable in the treatment of patients with STDs), where all evidence from the literature reviews pertaining to STD management was discussed.

Specifically, participants identified key questions regarding STD treatment that emerged from the literature reviews and discussed the information available to answer those questions. Discussion focused on four principal outcomes of STD therapy for each individual disease: 1) treatment of infection based on microbiologic eradication; 2) alleviation of signs and symptoms; 3) prevention of sequelae; and 4) prevention

of transmission. Cost-effectiveness and other advantages (e.g., single-dose formulations and directly observed therapy [DOT]) of specific regimens also were discussed. The consultants then assessed whether the questions identified were relevant, ranked them in order of priority, and answered the questions using the available evidence. In addition, the consultants evaluated the quality of evidence supporting the answers on the basis of the number, type, and quality of the studies.

The sections on hepatitis B virus (HBV) and hepatitis A virus (HAV) infections are based on previously published recommendations of the Advisory Committee on Immunization Practices (ACIP) (*2–4*). The recommendations for STD screening during pregnancy and cervical cancer screening were developed after CDC staff reviewed the published recommendations from other professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), United States Preventive Services Task Force (USPSTF), and ACIP.

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 published in a supplement issue of the journal *Clinical Infectious Diseases*. When more than one therapeutic regimen is recommended, the sequence is alphabetized unless the choices for therapy are prioritized based on efficacy, convenience, or cost. For those infections with more than one recommended regimen, almost all 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 significant drug allergy or other contraindications to the recommended regimens.

Clinical Prevention Guidance

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

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

Primary prevention of STDs begins with changing the sexual behaviors that place persons at risk for infection. Health-care providers have a unique opportunity to provide education and counseling to their patients (*5,6*). As part of the clinical interview, health-care providers should routinely and regularly obtain sexual histories from their patients and address management of risk reduction as indicated in this report. Guidance in obtaining a sexual history is available in *Contraceptive Technology, 19th edition* (*7*) and in the curriculum provided by CDC's STD/HIV Prevention Training Centers (http://www.stdhivpreventiontraining.org). 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 to delivering prevention messages effectively. Key techniques that can be effective in 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's your experience with using condoms been like?"); 2) understandable language ("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 an example of an effective strategy for eliciting information concerning five key areas of interest (Box 1).

Efforts should be made to ensure that all patients are treated regardless of individual circumstances (e.g., ability to pay, citizenship or immigration status, language spoken, or specific sex practices). Patients seeking treatment or screening for a particular STD should be evaluated for all common STDs. All patients should be informed about all the STDs for which they are being tested and notified about tests for common STDs (e.g., genital herpes) that are available but not being performed.

STD/HIV Prevention Counseling

USPSTF recommends high-intensity behavioral counseling for all sexually active adolescents and for adults at increased risk for STDs and HIV (*5,6*). All providers should routinely obtain a sexual history from their patients and encourage risk-reduction using various strategies; effective delivery of prevention messages requires that providers communicate general risk-reduction messages relevant to the client and that providers educate the client about specific actions that can reduce the risk for STD/HIV transmission (e.g., abstinence, condom use, limiting the number of sex partners, modifying sexual practices, and vaccination), each of which is discussed separately in this report (see Prevention Methods). Prevention counseling is most effective if provided in a nonjudgmental and empathetic manner appropriate to the patient's culture, language, sex, sexual orientation, age, and developmental level.

Box 1. The Five P's: Partners, Prevention of Pregnancy, Protection from STDs, Practices, 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. Prevention of pregnancy
   - "What are you doing to prevent pregnancy?"
3. Protection from STDs
   - "What do you do to protect yourself from STDs and HIV?"
4. 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 not use condoms?"

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 any of your partners exchanged money or drugs for sex?"
   - "Is there anything else about your sexual practices that I need to know about?"

Interactive counseling approaches directed at a patient's personal risk, the situations in which risk occurs, and the use of personalized goal-setting strategies are effective in STD/HIV prevention (*5,6*). One such approach, known as client-centered STD/HIV prevention counseling, involves tailoring a discussion of risk reduction to the patient's individual situation. Client-centered counseling can increase the likelihood that the patient undertakes or enhances current risk-reduction practices, especially among persons seeking STD care. One such approach, known as Project RESPECT, demonstrated that a brief counseling intervention led to a reduced frequency of STD/HIV risk-related behaviors and resulted in lowered acquisition rates for curable STDs, including trichomoniasis, chlamydia, gonorrhea, and syphilis (*8,9*). Practice models based on Project RESPECT have been successfully implemented in clinic-based settings. Other approaches use motivational interviewing to move clients toward achievable risk reduction goals. CDC provides additional information on these and other effective behavioral interventions at http://effectiveinterventions.org.

Interactive counseling can be used effectively by all health-care providers, counselors, and other clinical staff trained in counseling approaches. Extensive training is not a prerequisite for effective risk reduction counseling; however, the quality of counseling is improved when providers receive training in prevention counseling methods and skill-building approaches, providers are periodically observed when providing counseling and given immediate feedback by persons with expertise in the counseling approach, counselors are periodically evaluated and patients asked to evaluate their level of satisfaction, and providers have access to expert assistance or referral for challenging situations. Training in client-centered counseling is available through the CDC STD/HIV Prevention Training Centers (http://www.stdhivpreventiontraining.org).

In addition to individual prevention counseling, videos and large group presentations can provide explicit information concerning STDs and instruction to reduce disease transmission (e.g., how to use condoms correctly). Group-based strategies have been effective in reducing the occurrence of additional STDs among persons at high risk, including those attending STD clinics (*10*).

Because the incidence of some STDs, notably syphilis, is higher in HIV-infected persons, the use of client-centered STD counseling for HIV-infected persons has been strongly encouraged by public health agencies and other health organizations. Consensus guidelines issued by CDC, the Health Resources and Services Administration, the HIV Medicine Association of the Infectious Diseases Society of America, and the National Institutes of Health emphasize that STD/HIV risk assessment,

STD screening, and client-centered risk reduction counseling should be provided routinely to HIV-infected persons (*11*). Several specific methods have been designed for the HIV care setting (*12–14*), and additional information regarding these approaches is available at http://effectiveinterventions.org.

Prevention Methods

Abstinence and Reduction of Number of Sex Partners

A 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 an uninfected partner. For persons who are being treated for an STD (or whose partners are undergoing treatment), counseling that encourages abstinence from sexual intercourse until completion of the entire course of medication is crucial. A more comprehensive discussion of abstinence and other sexual practices than can help persons reduce their risk for STDs is available in *Contraceptive Technology, 19th Edition* (7). For persons embarking on a mutually monogamous relationship, screening for common STDs before initiating sex might reduce the risk for future disease transmission.

Pre-exposure Vaccination

Pre-exposure vaccination is one of the most effective methods for preventing transmission of some STDs. Two human papillomavirus (HPV) vaccines are available for females aged 9–26 years to prevent cervical precancer and cancer (*15,16*): the quadrivalent HPV vaccine (Gardasil) and the bivalent HPV vaccine (Cervarix). Gardasil also prevents genital warts. Routine vaccination of females aged 11 or 12 years is recommended with either vaccine, as is catch-up vaccination for females aged 13–26 years. Gardasil can be administered to males aged 9–26 years to prevent genital warts (*17*). Details regarding HPV vaccination are available at www.cdc.gov/std/hpv.

Hepatitis B vaccination is recommended for all unvaccinated, uninfected persons being evaluated for an STD (*3,4*). In addition, hepatitis A and B vaccines are recommended for men who have sex with men (MSM) and injection-drug users (IDUs) (*2–4*); each of these vaccines should also be administered to HIV-infected persons who have not yet been infected with one or both types of hepatitis virus. Details regarding hepatitis A and B vaccination are available at http://www.cdc.gov/hepatitis.

Male Condoms

When used consistently and correctly, male latex condoms are highly effective in preventing the sexual transmission of HIV infection. In heterosexual 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 HIV-infected compared with persons in similar relationships in which condoms were not used (*18*).

Moreover, studies show condoms can reduce the risk for other STDs, including chlamydia, gonorrhea, and trichomoniasis; by limiting lower genital tract infections, condoms also might reduce the risk for women developing pelvic inflammatory disease (PID) (*19,20*). In addition, consistent and correct use of latex condoms also reduces the risk for genital herpes, syphilis, and chancroid when the infected area or site of potential exposure is covered, although data for this effect are more limited (*21–24*). Additional information is available at www.cdc.gov/condomeffectiveness/latex.htm.

Cohort studies have demonstrated that condoms protect against the acquisition of genital HPV infection. A prospective study among newly sexually active women who were attending college demonstrated that consistent and correct condom use was associated with a 70% reduction in risk for HPV transmission (*25*). Use of condoms also appears to reduce the risk for HPV-associated diseases (e.g., genital warts and cervical cancer) and mitigate the adverse consequences of infection with HPV. Condom use has been associated with higher rates of regression of cervical intraepithelial neoplasia (CIN) and clearance of HPV infection in women (*26*) and with regression of HPV-associated penile lesions in men (*27*).

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. Rates of condom breakage during sexual intercourse and withdrawal are approximately two broken condoms per 100 condoms used in the United States. The failure of condoms to protect against STD transmission or unintended pregnancy usually results from inconsistent or incorrect use rather than condom breakage (*28*).

Male condoms made of materials other than latex are available in the United States. Two general categories of nonlatex condoms exist. The first type is made of polyurethane or other synthetic material and provides protection against STDs/HIV and pregnancy equal to that of latex condoms (*29*). These can be substituted for latex condoms by persons with latex allergy. Although they have had higher breakage and slippage rates when compared with latex condoms and are usually more costly, the pregnancy rates among women whose partners use these condoms are similar to those asociated with use of latex condoms (*30*).

The second type is natural membrane condoms (frequently called "natural" condoms or, incorrectly, "lambskin" condoms).

These condoms are usually 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 (*29*). Moreover, laboratory studies demonstrate that viral STD transmission can occur with natural membrane condoms (*29*). Use of natural membrane condoms for prevention of STDs is not recommended.

Providers should advise their patients that condoms must be used consistently and correctly to be effective in preventing STDs; 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.
- 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.

Female Condoms

Laboratory studies indicate that the female condom (Reality) is an effective mechanical barrier to viruses, including HIV, and to semen. The first female condom approved for use in the United States consisted of a lubricated polyurethane sheath with a ring on each end that is inserted into the vagina. A newer version made from nitrile is now available in the United States.

A limited number of clinical studies have evaluated the efficacy of female condoms in providing protection from STDs, including HIV (*31,32*). Although female condoms are costly compared with male condoms, sex partners should consider using a female condom when a male condom cannot be used properly. The female condom also has been used for STDs/HIV protection during receptive anal intercourse (*33*); although it might provide some protection in this setting, its efficacy remains unknown.

Cervical Diaphragms

In observational studies, diaphragm use has been demonstrated to protect against cervical gonorrhea, chlamydia, and trichomoniasis (*34*). A recent trial examined the effect of use of a diaphragm plus polycarbophil (Replens) lubricant on HIV acquisition in women in Africa relative to male condom use alone. The study revealed that neither the diaphragm nor the lubricant gel provided additional protective effect when compared with the use of condoms alone (*35*). Likewise, no difference by study arm in the rate of acquisition of chlamydia or gonorrhea occurred; however, data from participants who reported following the protocol for the use of these products suggested that consistent use of the diaphragm plus gel might reduce acquisition of gonorrhea (*36*). Diaphragms should not be relied on as the sole source of protection against HIV infection. Diaphragm and nonoxynol-9 (N-9) spermicide use have been associated with an increased risk for bacterial urinary-tract infections in women (*37*).

Topical Microbicides and Spermicides

Studies examining nonspecific topical microbicides for the prevention of HIV and STD have demonstrated that these products are ineffective (*38,39*). Studies of spermicides containing N-9 have demonstrated that they should not be recommended for STDs/HIV prevention (*40*), and more recent randomized controlled trials have failed to show a protective effect against HIV acquisition for BufferGel (a vaginal buffering agent), Carraguard (a carrageenan derivative) (*41*), cellulose sulfate (an HIV entry inhibitor), (*42*) and SAVVY (1.0% C31G, a surfactant) (*43,44*).

Initial results from a study in which participants used 0.5% PRO2000 vaginal gel (a synthetic polyanion polymer that blocks cellular entry of HIV) on a daily basis appeared promising, reducing the rate of HIV acquisition by 30% relative to no gel (*45*). However, a recent randomized trial of approximately 9,000 women failed to show any protective effect (*46*).

Topical antiretroviral agents for the prevention of HIV appear more promising. Use of tenofovir gel during sexual intercourse significantly reduced the rate of HIV acquisition (i.e., by 39%) in a study of South African women (*47*). Additional studies are being undertaken to elucidate the optimal dosing regimens for this drug.

Other products remain under study, including VivaGel, a topical vaginal microbicide. A list of products under development is maintained by the Alliance for Microbicide Development at www.microbicide.org.

Condoms and N-9 Vaginal Spermicides

Condoms lubricated with spermicides are no more effective than other lubricated condoms in protecting against the

transmission of HIV and other STDs (www.cdc.gov/condomeffectiveness/latex.htm). Furthermore, frequent use of spermicides containing N-9 has been associated with disruption of the genital epithelium, which might be associated with an increased risk for HIV transmission (*40*). Therefore, use of condoms lubricated with N-9 is not recommended for STD/HIV prevention; in addition, spermicide-coated condoms cost more, have a shorter shelf-life than other lubricated condoms, and have been associated with urinary-tract infection in young women (*37*).

Rectal Use of N-9 Spermicides

N-9 can damage the cells lining the rectum, which might provide a portal of entry for HIV and other sexually transmissible agents. Therefore, it should not used as a microbicide or lubricant during anal intercourse by MSM or by women.

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, Norplant, and Depo-Provera), have intrauterine devices (IUDs), have been surgically sterilized, or have had hysterectomies should be counseled regarding the use of condoms and the risk for STDs, including HIV infection, because these women might incorrectly perceive that they are not at risk for these diseases. Women who take oral contraceptives and are prescribed certain antibiotics should be counseled about potential interactions (*7*).

Male Circumcision

Although male circumcision should not be substituted for other HIV risk-reduction strategies, it has been shown to reduce 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% (*48–50*). In these trials, circumcision was also protective against other STDs, including high-risk genital HPV infection and genital herpes (*51–54*). Despite these data, male circumcision has not been demonstrated to reduce the risk for HIV or other STDs among MSM (*55*). The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have recommended that male circumcision be scaled up as an effective intervention for the prevention of heterosexually acquired HIV infection (*56*). 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. Similar recommendations have not been made in the United States, although evidence regarding the role of male circumcision in the prevention of HIV/AIDS is under review (*57*).

Emergency Contraception (EC)

Women who might have been exposed to STDs during a recent act of unprotected intercourse also are at risk for pregnancy. Providers managing such women should offer counseling about the option of EC if pregnancy is not desired. In the United States, EC products are available over-the-counter to women aged ≥17 years and by prescription to younger women. If these EC pill products are not readily accessible, many commonly available brands of oral contraceptive pills can effectively provide EC, but women must be instructed to take an appropriate and specified number of tablets at one time. All oral EC regimens are efficacious when initiated as soon as possible after unprotected sex, but have some efficacy as long as 5 days later. EC is ineffective (but is also not harmful) if the woman is already pregnant (*58*). More information about EC is available in the 19th edition of *Contraceptive Technology* (*7*) or http://ec.princeton.edu/emergency-contraception.html.

Insertion of an IUD up to 7 days after unprotected sex can reduce pregnancy risk by more than 99% (*7*). However, this method is not advisable for a woman who may have untreated cervical gonorrhea or chlamydia, who is already pregnant, or who has other contraindications to IUD use.

Postexposure Prophylaxis (PEP) for HIV and STD

Guidelines for the use of PEP aimed at preventing HIV infection as a result of sexual exposure are available and are discussed in 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 STD and might increase the risk for bacterial vaginosis, some STDs, and HIV (59).

Pre-exposure Prophylaxis (PrEP) for HIV and STD

Antiretroviral therapy (ART) has the potential to impact transmission and acquisition of HIV. In HIV-infected persons, ART reduces viral load and presumably reduces infectiousness (*60*). In HIV-uninfected persons, ART might reduce susceptibility to infection, a concept supported both by animal studies and by a study of safety and acceptability involving West African women (*61,62*). A randomized, placebo-controlled

trial involving South African women recently demonstrated that use of tenofovir gel associated with sexual intercourse significantly reduced the rate of HIV and herpes simplex virus type 2 (HSV-2) acquisition by 39% and 51%, respectively (*47,63*).

Several large randomized controlled trials of PrEP are either underway or planned. These involve the oral use of non-nucleoside reverse transcriptase inhibitors (tenofovir or tenofovir-emtricitabine) or vaginal use of 1% tenofovir gel.

Retesting to Detect Repeat Infections

Retesting several months after a diagnosis of chlamydia or gonorrhea can detect repeat infection and potentially can be used to enhance population-based prevention (*64*). Further details on retesting can be found in the specific sections on chlamydia and gonorrhea within this report.

Partner Management

Partner management refers to a continuum of activities designed to increase the number of infected persons brought to treatment and disrupt transmission networks. Part of this continuum is partner notification — the process by which providers or public health authorities learn about the sex- and needle-sharing partners of infected patients and help to arrange for partner evaluation and treatment. Clinical-care providers can obtain this information and help to arrange for evaluation and treatment of sex partners directly or by cooperating with state and local health departments. The types and comprehensiveness of existing partner services and the specific STDs for which they are offered vary by provider, public health agency, and geographic area. Ideally, persons referred to such services should also receive health counseling and should be referred for other health services as appropriate.

Data are limited regarding whether partner notification effectively decreases exposure to STDs and whether it reduces the incidence and prevalence of these infections in a community. Nevertheless, evaluations of partner notification interventions have documented the important contribution this approach can make to case-finding in clinical and community contexts (*65*). When partners are treated, index patients have reduced risk for reinfection. Therefore, providers should encourage persons with STDs to notify their sex partners and urge them to seek medical evaluation and treatment. Further, providers can ask patients to bring partners with them when returning for treatment. Time spent with index patients to counsel them on the importance of notifying partners is associated with improved notification outcomes (*66*).

When patients diagnosed with chlamydia or gonorrhea indicate that their partners are unlikely to seek evaluation and treatment, providers can offer patient-delivered partner therapy (PDPT), a form of expedited partner therapy (EPT) in which partners of infected persons are treated without previous medical evaluation or prevention counseling. Because EPT might be prohibited in some states and is the topic of ongoing legislation in others (*67*), providers should visit www.cdc.gov/std/ept to obtain updated information for their individual jurisdiction. Any medication or prescription 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 personal medical evaluation, particularly women with symptoms of STDs or PID.

The evidence supporting PDPT is based on three clinical trials that included heterosexual men and women with chlamydia or gonorrhea. The trials and meta-analyses 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 (*68–71*). However, across trials, reductions in chlamydia prevalence at follow-up were approximately 20%; reductions in gonorrhea at follow-up were approximately 50%. Rates of notification increased in some trials and were equivalent to patient referral without PDPT in others. 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 reinfection rates (*72,73*). No data support the use of PDPT in the routine management of patients with syphilis. No studies have been published involving PDPT for gonorrhea or chlamydia among MSM.

Public health program involvement with partner notification services varies by locale and by STD. Some programs have considered partner notification in a broader context, developing interventions to address sexual and social networks in which persons are exposed to STDs. Prospective evaluations incorporating the assessment of venues, community structure, and social and sexual contacts in conjunction with partner notification efforts have improved case-finding and illustrated transmission networks (*74,75*). While such efforts are beyond the scope of individual clinicians, support of and collaboration with STD programs by clinicians are critical to the success of social network-based interventions.

Certain evidence supports the use of the internet to facilitate partner notification (*76*), especially among MSM and in cases where no other identifying information is available, and many health departments now conduct formal internet partner notification (IPN) (http://www.ncsddc.org/upload/wysiwyg/documents/NGuidelinesforInternet.htm). Clinical providers are unlikely to participate directly in IPN. However, when discussing partner notification approaches with patients,

they should be aware of the value of the internet in this type of communication and should know where to refer patients who are interested in using the internet to notify partners about their diagnosis.

Reporting and Confidentiality

The accurate and timely reporting of STDs is integral to 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, 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. Clinicians who are unsure of state and local reporting requirements should seek advice from state or local health departments or STD programs. STDs and HIV reports are kept strictly confidential. In most jurisdictions, such reports are protected by statute from subpoena. Before conducting a follow-up of a positive STD-test result, public health professionals should consult the patient's health-care provider to verify the diagnosis and to 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 treatment, if needed.

Recommended Screening Tests

- All pregnant women in the United States should be screened for HIV infection as early in pregnancy as possible (77). Screening should be conducted after the woman is notified that she will 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 strongly. 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 patient, 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 HIV-infected partners). Rapid HIV screening should be performed on any woman in labor who has an undocumented HIV status 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 (*78*).
- A serologic test for syphilis should be performed on all pregnant women at the first prenatal visit (*79*). In populations in which the amount of prenatal care delivered 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, live in areas of high syphilis morbidity, or are previously untested 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. Infants 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. 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) during an early prenatal visit (i.e., a visit during the first trimester), even if they have been previously vaccinated or tested (*80*). 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 use an FDA-cleared HBsAg test and perform testing according to the manufacturer's labeling, including testing of 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 infants (*80*).

- All pregnant women should be routinely screened for *Chlamydia trachomatis* (see Chlamydia Infections, Diagnostic Considerations) during the first prenatal visit (*81*). Women aged ≤25 years and those at increased risk for chlamydia (e.g., women who have a new or more than one sex partner) also should be retested during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant. Women found to have chlamydial infection during the first trimester should be retested within approximately 3–6 months, preferably in the third trimester. Screening during the first trimester might prevent the adverse effects of chlamydia during pregnancy, but supportive evidence for such screening is lacking.
- All pregnant women at risk for gonorrhea or living in an area in which the prevalence of *Neisseria gonorrhoeae* is high should be screened at the first prenatal visit for *N. gonorrhoeae* (*82*). Women aged <25 years are at highest risk for gonorrhea infection. Other risk factors for gonorrhea include a previous gonorrhea infection, other STDs, new or multiple sex partners, inconsistent condom use, commercial sex work, and drug use. Pregnant women found to have gonococcal infection during the first trimester should be retested within approximately 3–6 months, preferably in the third trimester. Uninfected pregnant women who remain at high risk for gonococcal infection also should be retested during the third trimester.
- All pregnant women at high risk for hepatitis C infection should be screened for hepatitis C antibodies (see Hepatitis C, Diagnostic Considerations) at the first prenatal visit. Women at high risk include those with a history of injection-drug use and those with a history of blood transfusion or organ transplantion before 1992.
- Pregnant women should undergo a Papanicolau (Pap) test at the same frequency as nonpregnant women, although recommendations for their management differ (*83,84*).

Other Tests

- Evidence does not support routine testing for bacterial vaginosis (BV) in pregnancy. For asymptomatic pregnant women at high risk for preterm delivery, evidence is insufficient to assess the balance of benefits and harms of screening for BV (*85*). 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 previously undiagnosed women during pregnancy.

Other Concerns

- 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 for 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. Pregnant women who are HBsAg positive should receive information regarding hepatitis B that addresses:
  - modes of transmission;
  - perinatal concerns (e.g., breastfeeding is not contraindicated);
  - prevention of HBV transmission, including the importance of postexposure prophylaxis for the newborn infant and hepatitis B vaccination for household contacts and sex partners; and
  - evaluation for and treatment of chronic HBV infection.
- No treatment is available for pregnant women infected with hepatitis C virus (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.
- In the absence of lesions during the third trimester, routine serial cultures for herpes simplex virus (HSV) are not indicated for women who have a history of recurrent genital herpes. Prophylactic cesarean delivery is not indicated for women who do not have active genital lesions at the time of delivery.
- The presence of genital warts is not an indication for cesarean delivery.

For a more detailed discussion of STD testing and treatment among pregnant women, refer to the following references: *Prenatal screening for HIV: A Review of the evidence for the U.S. Preventive Services Task Force* (*86*); *Revised*

Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Setting (*77*); *Guidelines for Perinatal Care* (*87*); *Rapid HIV Antibody Testing During Labor and Delivery for Women of Unknown HIV Status*: *A Practical Guide and Model Protocol* (*88*); *Viral Hepatitis in Pregnancy* (*89*); *Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States — Recommendations of the Immunization Practices Advisory Committee (ACIP)* (*4*); *Screening for Chlamydial Infection: U.S. Preventive Services Task Force Recommendation Statement* (*81*); *Canadian guidelines on sexually transmitted infections* (*90*); *USPSTF recommendations for STI screening (91);* and *Screening for Bacterial Vaginosis in Pregnancy to Prevent Preterm Delivery: U.S. Preventive Services Task Force Recommendation Statement* (*85*).

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

Adolescents

In the United States, prevalence rates of many sexually acquired infections are highest among adolescents (*92,93*). For example, the reported rates of chlamydia and gonorrhea are highest among females aged 15–19 years, and many persons acquire HPV infection during their adolescent years.

Persons who initiate sex early in adolescence are at higher risk for STDs, along with persons residing in detention facilities, attending STD clinics, young men having sex with men (YMSM), and youth who use injection drugs. 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 experiencing multiple obstacles to accessing health care (*92*).

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 or requires that providers notify parents that an adolescent minor has received STD services, except in limited or unusual circumstances.

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 a beneficiary indicating the benefits and charges covered or not covered by the health plan (i.e., explanation of benefit [EOB]). In addition, federal laws obligate notices to beneficiaries when claims are denied, including alerting consumers who need to pay for care until the allowable deductable 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 any laboratory tests performed. This type of mandated notification breeches confidentiality, and at a minimum, could prompt parents and guardians to question the costs and reasons for service provision.

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, fail to screen for asymptomatic infections during clinical encounters. Sexual health discussions should be appropriate for the patient's developmental level and should be aimed at identifying risk behaviors (e.g., 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* of all sexually active females aged ≤25 years is recommended annually (*81*). Evidence is insufficient to recommend routine screening for *C. trachomatis* in sexually active young men based on feasibility, efficacy, and cost-effectiveness. However, screening of sexually active young men should be considered in clinical settings associated with high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and STD clinics) (*81,94*).
- Routine screening for *N. gonorrhoeae* in all sexually active women at risk for infection is recommended annually (*82*). Women aged <25 years are at highest risk for gonorrhea infection. Other risk factors that place women at increased risk include a previous gonorrhea infection, the presence of other STDs, new or multiple sex partners, inconsistent condom use, commercial sex work, and drug use.
- HIV screening should be discussed with all adolescents and encouraged for those who are sexually active and those who use injection drugs (*77,95*).

- The routine screening of adolescents who are asymptomatic for certain STDs (e.g., syphilis, trichomoniasis, BV, HSV, HPV, HAV, and HBV) is not recommended. However, YMSM and pregnant adolescent females might require more thorough evaluation.
- Guidelines from USPSTF and ACOG recommend that cervical cancer screening begin at age 21 years (*96,97*), a recommendation based on the low incidence of cervical cancer and limited utility of screening for younger adolescents (*98*). However, the American Cancer Society (ACS) recommends that women start cervical screening with Pap tests 3 years after initiating sexual activity, but by no later than age 21 years (*99*).

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. 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:

- The HPV vaccine, either Cervarix or Gardasil, is recommended for 11 and 12 year-old females. The vaccine series can be started at 9 years of age. Catch-up vaccination is recommended for females aged 13–26 years who have not yet received or completed the vaccine series (*16*). The quadrivalent (Gardasil) HPV vaccine can also be used in males and females aged 9–26 years to prevent genital warts (*17*).
- The HBV vaccination series is recommended for all adolescents. Adolescents who have not previously received hepatitis B vaccine should be vaccinated routinely at any age with an appropriate dose and schedule (*3,4*).
- The HAV vaccination series for children and adolescents aged 2–18 years should be offered in areas with existing hepatitis A vaccination programs. In areas without existing hepatitis A vaccination programs, catch-up vaccination of unvaccinated children aged 2–18 years can be considered (*2*).
- 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 as part of health care (*77*).
- Health-care providers who care for children and adolescents should integrate sexuality education into clinical practice. Providers should counsel adolescents about the sexual behaviors that are associated with risk for acquiring STDs and should educate patients using evidence-based prevention strategies, all of which include a discussion about abstinence and other risk-reduction behaviors (e.g., consistent and correct condom use). USPSTF recommends high-intensity behavioral counseling to prevent STIs* for all sexually active adolescents (*6*).

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, are virtually 100% indicative of 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, especially those aged ≤35 years (*93*). 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 [prostitution to earn money for food, shelter, or drugs], or coerced sex) are common among incarcerated populations. Before incarceration, many have had limited access to medical care, especially to community-based clinical prevention services.

Although no comprehensive national guidelines regarding STD care and management have been developed for correctional populations, the utility of expanded STD services in correctional settings has been reported (*100*). Capacity to provide STD care also varies by type of correctional facility. For example, local juvenile detention facilities and jails are short-term facilities (often housing entrants for ≤1 year) where up to half of all entrants are released back to the community within 48 hours of arrest, thereby complicating efforts to provide comprehensive STD services. These services are likely more conducive to prisons and state juvenile confinement facilities, which are long-term, secure facilities where entrants are held for a longer period of time.

Most institutions, especially those for adults, do not routinely screen for STDs. Diagnostic testing of inmates with symptoms indicative of an STD is the more common practice in juvenile detention and jail facilities. However, screening for asymptomatic infections facilitates the identification and

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

treatment of persons with otherwise undetected infections, which not only eliminates complications for the individual, but reduces the prevalence of infection among detainees who are released back into the local community.

Females in juvenile detention facilities and young women ≤35 years of age have been reported to have high rates of chlamydia (*101*) and gonorrhea (*93*). Syphilis seroprevalence rates, which can indicate previous infection, are considerably higher among adult men and women than in adolescents, consistent with the overall national syphilis trends (*102*).

Chlamydia and Gonorrhea Screening

Universal screening of adolescent females for chlamydia and gonorrhea should be conducted at intake in juvenile detention or jail facilities. Universal screening of adult females should be conducted at intake among adult females up to 35 years of age (or on the basis of local institutional prevalence data).

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.

MSM

Subgroups of MSM are at high risk for HIV infection and other viral and bacterial STDs. 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 unsafe sexual behaviors have been documented among MSM in the United States and virtually all industrialized countries (*103,104*). The effect of these behavioral changes on HIV transmission has not been ascertained, but preliminary data suggest that the incidence of HIV infection is increasing among MSM in some urban centers, particularly among MSM from racial and ethnic minority groups (*105*) and among those who use nonprescription drugs during sex, particularly methamphetamine and volatile nitrites (also known as "poppers"). These adverse trends likely reflect the 1) changing attitudes concerning HIV infection that have accompanied advances in HIV therapy, resulting in improved quality of life and survival for HIV-infected persons; 2) changing patterns of substance abuse; 3) demographic shifts in MSM populations; and 4) changes in sex partner networks resulting from new venues for partner acquisition (e.g., the internet). Increases in bacterial STDs are not necessarily accompanied by increases in HIV incidence; for example, oral sex may permit efficient spread of bacterial STDs but not HIV, as does serosorting (preferential selection of sex partners of the same serostatus) among HIV-infected MSM (*106,107*).

Clinicians should assess the STD-related risks for all male patients, including a routine inquiry about the sex of sex partners. MSM, including those with HIV infection, should routinely undergo nonjudgmental STD/HIV risk assessment and client-centered prevention counseling to reduce the likelihood of acquiring or transmitting HIV or other STDs. Clinicians should be familiar with the local community resources available to assist MSM at high risk in facilitating behavioral change and to enable the conduct of partner notification activities. Clinicians also 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, including discharge and pain on defecation or during anal intercourse. Clinicians should perform appropriate diagnostic testing on all symptomatic patients.

Routine laboratory screening for common STDs is indicated for all sexually active MSM. The following screening tests should be performed at least annually for sexually active MSM:

- HIV serology, if HIV negative or not tested within the previous year;
- syphilis serology, with a confirmatory testing to establish whether persons with reactive serologies have incident untreated syphilis, have partially treated syphilis, or are manifesting a slow serologic response to appropriate prior therapy;
- 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 nucleic acid amplification testing (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 swab is the preferred approach); and
- a test for pharyngeal infection[§] with *N. gonorrhoeae* in men who have had receptive oral intercourse[†] during the preceding year (NAAT is the preferred approach). Testing for *C. trachomatis* pharyngeal infection is not recommended.

Evaluation for HSV-2 infection with type-specific serologic tests also can be considered if infection status is unknown; knowledge of HSV-2 serostatus might be helpful in identifying persons with previously undiagnosed genital tract infection.

[†] Regardless of history of condom use during exposure.

[§] Commercially available NAATS are not FDA cleared for these indications, but they can be used by laboratories that have met all regulatory requirements for an off-label procedure.

Because of the increased incidence of anal cancer in HIV-infected MSM, screening for anal cytologic abnormalities can be considered; however, evidence is limited concerning the natural history of anal intraepithelial neoplasias, the reliability of screening methods, the safety and response to treatments, and the programmatic support needed for such a screening activity.

More frequent STD screening (i.e., at 3–6-month intervals) is indicated for MSM who have multiple or anonymous partners. In addition, MSM who have sex in conjunction with illicit drug use (particularly methamphetamine use) or whose sex partners participate in these activities should be screened more frequently.

All MSM should be tested for HBsAg to detect HBV infection. Prompt identification of chronic infection with HBV is essential to ensure necessary care and services to prevent transmission to others (*108*). HBsAg testing should be made available in STD treatment settings. In addition, 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 B, Prevaccination Antibody Screening). Sexual transmission of hepatitis C virus infection can occur, especially among HIV-infected MSM. Serologic screening for hepatitis C infection is recommended at initial evaluation of newly diagnosed HIV-infected persons. HIV-infected MSM can also acquire HCV after initial screening; therefore, men with new and unexplained increases in alanine aminotransferase (ALT) should be tested for acute HCV infection. To detect acute HCV infection among HIV-infected MSM with high-risk sexual behaviors or concomitant ulcerative STDs, routine HCV testing of HIV-infected MSM should be considered.

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, young women, and women with both male and female partners, might be at increased risk for STDs and HIV as a result of certain reported risk behaviors (*109–112*). WSW are at risk for acquiring bacterial, viral, and protozoal infections 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. Effective screening requires that providers and their female clients engage in a comprehensive and open discussion not only about sexual identify, but sexual and behavioral risks.

Few data are available on the risk for STDs transmitted by sex between women, but 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 [*113,114*]). Practices involving digital-vaginal or digital-anal contact, particularly with shared penetrative sex items, present a possible means for transmission of infected cervicovaginal secretions. This possibility is most directly supported by reports of metronidazole-resistant trichomoniasis (*115*) and genotype-concordant HIV transmitted sexually between women who reported these behaviors (*116*) and by the high prevalence of BV among monogamous WSW (*117*).

Transmission of HPV can occur with skin-to-skin or skin-to-mucosa contact, which can occur during sex between women. HPV DNA has been detected through polymerase chain reaction (PCR)-based methods from the cervix, vagina, and vulva in 13%–30% of WSW, and high- and low-grade squamous intraepithelial lesions (SIL) have been detected on Pap tests in WSW who reported no previous sex with men (*118*). However, most self-identified WSW (53%–99%) report having had sex with men and indicate that they might continue this practice in the future (*119*). Therefore, routine cervical cancer screening should be offered to all women, regardless of sexual preference or sexual practices, and women should be offered HPV vaccine in accordance with current guidelines.

Limited data demonstrate that HSV-2 genital transmission between female sex partners is probably inefficient but can occur. The relatively frequent practice of orogenital sex among WSW might place them at higher risk for genital infection with herpes simplex virus type 1 (HSV-1), a hypothesis supported by the recognized association between HSV-1 seropositivity and number of female partners among WSW (*120*).

Although the rate of transmission of *C. trachomatis* between women remains largely unknown, infection also can be acquired from past or current male partners. Recent data suggest that *C. trachomatis* infection among WSW might be more common than previously thought (*121*); transmission of syphilis between female sex partners (likely through oral sex) also has been reported. Therefore, report of same-sex behavior in women should not deter providers from screening these women for STDs, including chlamydia and syphilis, as recommended.

BV is common among women in general and even more so among women with female partners. Sexual behaviors that

facilitate the transfer of vaginal fluid and/or bacteria between partners might be involved in the pathogenesis of BV. A recent study demonstrated that female sex partners frequently share identical genital *Lactobacillus* strains (*122*). Although BV is common in WSW, routine screening for BV is not recommended, nor is the treatment of partners of women with BV. Encouraging awareness of signs and symptoms of BV in women and encouraging healthy sexual practices (e.g., cleaning shared sex toys between uses) might be helpful.

HIV Infection: Detection, Counseling, and Referral

HIV infection represents a spectrum of disease that can begin with a brief acute retroviral syndrome that typically transitions to a multiyear chronic and clinically latent illness. Without treatment, this illness eventually progresses to a symptomatic, life-threatening immunodeficiency disease known as AIDS. In untreated patients, the time between HIV infection and the development of AIDS varies, ranging from a few months to many years with an estimated median time of approximately 11 years (*123*). HIV replication is present during all stages of the infection and progressively depletes CD4 lymphocytes, which are critical for maintenance of effective immune function. When the CD4 cell count falls below 200 cells/μL, patients are at high risk for life-threatening AIDS-defining opportunistic infections (e.g., *Pneumocystis pneumonia*, *Toxoplasma gondii* encephalitis, disseminated *Mycobacterium avium* complex disease, tuberculosis, and bacterial pneumonia). In the absence of treatment, virtually all HIV-infected persons will die of AIDS.

Early diagnosis of HIV infection is essential to ensuring that patients are referred promptly for evaluation, provided treatment (if indicated), and linked into counseling and related support services to help them reduce their risk for transmitting HIV to others. Diagnosing persons during acute infection is particularly important. It is during this phase that HIV-infected persons are most infectious (*124–126*), but test negative for HIV antibodies and therefore unknowingly continue to engage in those high-risk behaviors associated with HIV transmission. Providers are in a particularly good position to diagnose persons during acute HIV infection because such persons might present for assessment and treatment of a concomitantly acquired STD during this phase of the disease. Knowing that a patient is infected with HIV has important clinical implications because HIV infection alters the immune system and thereby affects the diagnosis, evaluation, treatment, and follow-up of other STDs.

Even in the era of highly effective antiretroviral therapy (HAART), HIV infection is often diagnosed in persons with advanced infection (i.e., persons with low CD4 cell counts). Nationally, the proportion of patients diagnosed with AIDS at or within 12 months of their HIV diagnosis in 2007 was 32% (*127*). Since 2006, CDC has endorsed efforts to increase HIV testing by streamlining the consent process and expanding opt-out testing to all health-care settings, especially STD clinics (*77*). However, rates of testing remain unacceptably low: in 2006, only 40% of surveyed adults had ever been tested, and <25% of high-risk adults had been tested during the preceding 12 months (*128*).

Proper management of HIV infection requires medical therapy, which for many patients should be coupled with behavioral and psychosocial services. Comprehensive HIV treatment services are usually not available in facilities focusing primarily on STD treatment (e.g., STD clinics); therefore, patients diagnosed in these settings ideally should be referred to a health-care provider or facility experienced in caring for HIV-infected patients. Nonetheless, providers working in STD-treatment facilities should be knowledgeable about the treatment options available in their communities, educate persons who test positive for HIV about the illness, and know where to refer their patients for support services and HIV care.

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 in other published resources (*129–131*). In subsequent sections of this report, additional types of HIV-related information about the diagnosis of HIV infection, counseling of HIV-infected patients, referral of patients for support services (including medical care), and management of sex and injection-drug partners in STD-treatment facilities is provided. In addition, this report discusses HIV infection during pregnancy and among infants and children.

Detection of HIV Infection: Screening and Establishing a Diagnosis

All persons who seek evaluation and treatment for STDs should be screened for HIV infection. Screening should be routine, regardless of whether the patient is known or suspected to have specific behavioral risks for HIV infection.

Consent and Pretest Information

CDC recommends HIV screening for patients aged 13–64 years in all health-care settings (*77*). Patients should be notified that testing will be performed, but given the option to decline or defer testing (i.e., provided with opt-out testing)

(*128*). Assent is inferred unless the patient verbally declines testing. Separate written consent for HIV testing should not be required; in most facilities, general consent for medical care is considered sufficient to encompass consent for HIV testing. Providing prevention counseling along with HIV diagnostic testing or as part of HIV screening programs is not a requirement within health-care settings. In addition, routine opt-out testing (instead of traditional written informed consent with pre-and post-test counseling) might be precluded in some jurisdictions by local laws and regulations, although many state and local authorities have updated laws and regulations to facilitate adoption of routine opt-out testing. Information about regulations in specific jurisdictions is available through the National Clinicians Consultation Center at www.nccc.ucsf.edu.

Prevention Counseling

Prevention counseling should be offered and encouraged in all health-care facilities that serve patients at high risk (e.g., STD clinics), because these facilities routinely elicit information about the behaviors that place persons at high risk for HIV. Prevention counseling need not be explicitly linked to HIV testing. However, some patients might be more likely to think about HIV and consider their risk-related behavior when undergoing an HIV test. HIV testing presents an excellent opportunity to provide or arrange for prevention counseling to assist with behavior changes that can reduce risk for acquiring HIV infection.

Establishing the Diagnosis of HIV Infection

HIV infection can be diagnosed by serologic tests that detect antibodies against HIV-1 and HIV-2 and by virologic tests that can detect HIV antigens or ribonucleic acid (RNA). Antibody testing begins with a sensitive screening test (e.g., the conventional or rapid enzyme immunoassay [EIA]). Currently 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). The advent of HIV rapid serologic testing has enabled clinicians to make an accurate presumptive diagnosis of HIV infection within half an hour, which could potentially facilitate the identification of the approximately 250,000 persons estimated to be living with undiagnosed HIV in the United States (*127*).

Reactive screening tests must be confirmed by a supplemental antibody test (i.e., Western blot [WB] and indirect immunofluorescence assay [IFA]) or virologic test (i.e., the HIV-1 RNA assay) (*132*). A confirmed positive antibody test result indicates that a person is infected with HIV and capable of transmitting the virus to others. HIV antibody is detectable in at least 95% of patients within 3 months after infection. Although a negative antibody test result usually indicates that a person is not infected, antibody tests cannot exclude recent infection. Virologic tests for HIV-1 RNA can also be used to identify acute infection in persons who are negative for HIV antibodies.

The majority of HIV infections in the United States are caused by HIV-1. However, HIV-2 infection should be suspected in persons who have epidemiologic risk factors or an unusual clinical presentation. Epidemiologic factors associated with HIV-2 infection include having lived in or having a sex partner from an HIV-2 endemic area (e.g., West Africa and some European countries such as Portugal, where HIV-2 prevalence is increasing), having a sex partner known to be infected with HIV-2, or having received a blood transfusion or nonsterile injection in an HIV-2-endemic area. Specific testing for HIV-2 is also indicated when clinical evidence of HIV infection exists but tests for HIV-1 antibodies or HIV-1 viral load are negative, or when HIV-1 WB results exhibit the unusual indeterminate pattern of gag (p55, p24, p17) plus pol (p66, p51, p31) bands in the absence of env (gp160, gp120, gp41) bands.

Health-care providers should be knowledgeable about acute HIV infection and the symptoms and signs of acute retroviral syndrome, which develops in 50%–80% of acutely infected patients. Acute retroviral syndrome is characterized by nonspecific symptoms, including fever, malaise, lymphadenopathy, and skin rash. It frequently occurs in the first few weeks after HIV infection, before antibody test results become positive. Suspicion of acute retroviral syndrome should result in prompt nucleic acid testing (HIV plasma RNA) in addition to an HIV antibody test to detect the presence of HIV. A positive HIV nucleic acid test should be confirmed by subsequent antibody testing to document seroconversion. Acutely infected patients are highly contagious during this stage of infection because the concentration of virus in plasma and genital secretions is extremely elevated (*125,133*). Antiretroviral therapy might benefit the health of persons with recently acquired HIV infection and reduce their infectiousness to others, but evidence to support this recommendation is still inconclusive and awaits the outcomes of several clinical trials currently underway (*129*). Notwithstanding, patients with acute HIV infection should be referred immediately to an HIV clinical-care provider. Diagnosis of HIV infection should prompt efforts to reduce behaviors that could transmit HIV to others (*134*).

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

- HIV screening is recommended for all persons who seek evaluation and treatment for STDs.

- HIV testing must be voluntary and free from coercion. Patients must not be tested without their knowledge.
- HIV screening after 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. In most settings, general informed consent for medical care is considered sufficient to encompass informed consent for HIV testing.
- Use of rapid HIV tests should be considered, especially in clinics where a high proportion of patients do not return for HIV test results.
- Positive screening tests for HIV antibody must be confirmed by a supplemental test before the diagnosis of HIV infection can be established.
- Providers should be alert to the possibility of acute HIV infection and perform a nucleic acid test in addition to an antibody test for HIV, if indicated. Persons suspected of recently acquired HIV infection should be referred for immediate consultation with an infectious disease specialist.

Persons with newly diagnosed HIV infection who receive care in the STD treatment setting should be informed of the importance of promptly initiating medical care, the effectiveness of HIV treatments, and about what to expect as they enter medical care for HIV infection (131). In nonemergent situations, the initial evaluation of HIV-positive patients usually includes the following:

- Detailed medical history, including sexual and substance abuse history; vaccination history; previous STDs; travel history; and assessment for specific HIV-related symptoms or diagnoses;
- physical examination, including a gynecologic examination for women;
- testing for *N. gonorrhoeae* and *C. trachomatis* (in women perform Pap test and wet mount examination or culture of vaginal secretions for *Trichomonas vaginalis*);
- complete blood and platelet counts, blood chemistry profile, and lipid profile;
- toxoplasma antibody test;
- testing for antibodies to hepatitis C virus;
- testing for previous or present infections with HAV or HBV infection (recommended if determined to be cost-effective before considering vaccination) (see Hepatitis A and Hepatitis B);
- syphilis serology;
- CD4 T-lymphocyte analysis and determination of HIV plasma viral load;
- HIV genotypic resistance testing;
- tuberculin skin test (sometimes referred to as a purified protein derivative);
- urinalysis; and
- chest radiograph.

Type-specific testing for HSV-2 infection can be considered if herpes infection status is unknown. A first dose of hepatitis A and hepatitis B vaccine should be administered at this first visit for previously unvaccinated persons for whom vaccine is recommended (see Hepatitis A and Hepatitis B). In subsequent visits, when the results of laboratory tests are available, antiretroviral therapy can be offered based on existing guidance (*129*). Recommendations for the prophylaxis of opportunistic infections and vaccinations in HIV-infected adults and adolescents are available (*130,131*).

Providers should be alert to the possibility of new or recurrent STDs and should treat such conditions aggressively. Diagnosis of an STD in an HIV-infected person indicates on-going or recurrent high-risk behavior and should prompt referral for counseling. Because many STDs are asymptomatic, routine screening for curable STDs (e.g., syphilis, gonorrhea, and chlamydia) should be performed at least annually for all sexually active, HIV-positive persons. Women should be screened annually for cervical cancer precursor lesions by cervical Pap tests. More frequent STD screening might be appropriate depending on individual risk behaviors, the local epidemiology of STDs, and whether incident STDs are detected by screening or by the presence of symptoms.

Recently identified HIV infection might not have been recently acquired; persons newly diagnosed with HIV might be at any stage of infection. Therefore, health-care providers should be alert for symptoms or signs that suggest advanced HIV infection (e.g., fever, weight loss, diarrhea, cough, shortness of breath, and oral candidiasis). The presence of any of these symptoms should prompt urgent referral to an infectious diseases provider. Similarly, providers should be alert for signs of psychological distress and be prepared to refer patients accordingly (see Counseling for Patients with HIV Infection and Referral to Support Services).

Counseling for Patients with HIV Infection and Referral to Support Services

Those persons who test positive for HIV should receive prevention counseling before leaving the testing site. Such persons should receive or be referred for a medical evaluation and, if indicated, be provided with behavioral and psychological services as determined by a thorough psychosocial evaluation, which can also be used to identify high-risk behaviors.

Providers who refer their HIV-positive patients to other professionals should establish means to ensure that these patients are linked successfully to such services, especially to on-going medical care.

Providers should expect persons to be distressed when first informed of a positive HIV 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 HIV-infected persons.

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

The following are specific recommendations for HIV counseling and referral:

- Persons who test positive for HIV antibody should be counseled, either on site or through referral, concerning the behavioral, psychosocial, and medical implications of HIV infection.
- Health-care providers should be alert for medical or psychosocial conditions that require immediate attention.
- Providers should assess the needs of newly diagnosed persons for immediate medical care or support and should link them to services provided by health-care personnel experienced in providing care for HIV-infected persons. Such persons might need medical care or services for substance abuse, mental health disorders, emotional distress, reproductive counseling, risk-reduction counseling, and case management. Providers should follow up to ensure that patients have received the needed services.
- Patients should be educated about the importance of follow-up medical care as well as what to expect.

Several successful, innovative interventions for HIV prevention have been developed for diverse at-risk populations, and these can be locally replicated or adapted (*11–14,135,136*). Involvement of nongovernment organizations and community-based organizations might complement such efforts in the clinical setting.

Management of Sex Partners and Injection-Drug Partners

Clinicians evaluating HIV-infected persons should determine whether any partners should be notified concerning possible exposure to HIV (*77,137*). In the context of HIV management, the term "partner" includes not only sex partners, but persons who share syringes or other injection equipment. Partner notification is an important component of disease management, because early diagnosis and treatment of HIV infection might reduce morbidity and provide the opportunity to encourage risk-reduction 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 *Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infections* (*137*).

Two complementary notification processes, patient referral and provider referral, can be used to identify partners. With patient referral, patients directly inform their partners of their exposure to HIV infection, whereas with provider referral, trained health department personnel locate partners on the basis of information provided by the patient. During the provider referral notification process, the confidentiality of patients is protected; their names are not revealed to partners who are notified. Many state and local health departments provide these services.

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

- HIV-infected patients should be encouraged to notify their partners and to refer them for counseling and testing. If requested by the patient, health-care providers should assist in this process, either directly or by referral to health department partner-notification programs.
- If patients are unwilling to notify their partners or if they cannot ensure that their partners will seek counseling, physicians or health department personnel should use confidential partner notification procedures.
- Partners who have been reached and were exposed to genital secretions and/or blood of an HIV-infected partner though sex or injection-drug use within the preceding 72 hours should be offered postexposure prophylaxis with combination antiretrovirals (*78*).

Special Considerations

Pregnancy

All pregnant women in the United States should be tested for HIV infection as early during pregnancy as possible. A second test during the third trimester, preferably at <36 weeks' gestation, should be considered for all pregnant women and is recommended for women 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 living in facilities in which prenatal screening identifies at least one HIV-infected pregnant women per 1,000 women screened (*77*). An RNA test should be used in conjunction with an HIV antibody test for women who have signs or symptoms consistent with acute HIV infection. The patient should first be informed that she will be tested for HIV as part of the panel of prenatal tests, unless she declines, or opts-out, of screening (*77,86*). For women who decline, providers should continue to strongly encourage testing and address concerns that pose obstacles to testing. Women who decline testing because they have had a previous negative HIV test should be informed about the importance of retesting during each pregnancy. Testing pregnant women is particularly important not only to maintain the health of the patient, but because interventions (i.e., antiretroviral and obstetrical) can reduce the risk for perinatal transmission of HIV.

After a pregnant woman has been identified as being HIV-infected, she should be educated about the risk for perinatal infection. Evidence indicates that, in the absence of antiretroviral and other interventions, 15%–25% of infants born to HIV-infected mothers will become infected with HIV; such evidence also indicates that an additional 12%–14% of infants born to infected mothers who breastfeed into the second year of life will become infected (*138,139*).

The risk for perinatal HIV transmission can be reduced to <2% through the use of antiretroviral regimens and obstetrical interventions (i.e., zidovudine or nevirapine and elective cesarean section at 38 weeks of pregnancy) and by avoiding breastfeeding (*138,140*). Pregnant women who are HIV-infected should be counseled concerning their options (either on-site or by referral), given appropriate antenatal treatment, and advised not to breastfeed their infants.

HIV Infection Among Infants and Children

Diagnosis of HIV infection in a pregnant woman indicates the need to consider whether the woman's other children might be infected. Infants and young children with HIV infection differ from adults and adolescents with respect to the diagnosis, clinical presentation, and management of HIV disease. For example, because maternal HIV antibody passes through the placenta, antibody tests for HIV are expected to be positive in the sera of both infected and uninfected infants born to seropositive mothers. A definitive determination of HIV infection for an infant aged <18 months is usually based on HIV nucleic acid testing (141). Management of infants, children, and adolescents who are known or suspected to be infected with HIV requires referral to physicians familiar with the manifestations and treatment of pediatric HIV infection (*142,143*).

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. HSV, syphilis, and chancroid have been associated with an increased risk for HIV transmission, and genital, anal, or perianal lesions might be associated with conditions that are not sexually transmitted (e.g., yeast, trauma, carcinoma, aphthae, fixed drug eruption, and psoriasis).

A diagnosis based only on the patient's medical history and physical examination frequently is inaccurate. Therefore, all patients who have genital, anal, or perianal ulcers should be evaluated with a serologic test for syphilis and a diagnostic evaluation for genital herpes; in settings where chancroid is prevalent, a test for *Haemophilus ducreyi* should also be performed. Specific tests for evaluation of genital, anal, or perianal ulcers include 1) syphilis serology and darkfield examination; 2) culture for HSV or PCR testing for HSV; and 3) serologic testing for type-specific HSV antibody.

No FDA-cleared PCR test to diagnose either herpes or syphilis is available in the United States; however, such testing can be performed by clinical laboratories that have developed their own tests and have conducted a Clinical Laboratory Improvement Amendment (CLIA) verification study. 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 genital, anal, or perianal 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

who are not known to have HIV infection (see Diagnostic Considerations, sections on Syphilis, Chancroid, and Genital Herpes Simplex Virus).

Health-care providers frequently must treat patients before test results are available, because early treatment decreases the possibility of ongoing transmission and because successful treatment of genital herpes depends on prompt initiation of therapy. The clinician should empirically treat for the diagnosis considered most likely on the basis of clinical presentation and epidemiologic circumstances (including travel history); even after complete diagnostic evaluation, at least 25% of patients who have genital ulcers have no laboratory-confirmed diagnosis.

Chancroid

The prevalence of chancroid has declined in the United States (*93*). 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. Chancroid, as well as genital herpes and syphilis, is a risk factor in the transmission of HIV infection (*144*).

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% (*145*). 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 a CLIA verification study.

The combination of a painful genital ulcer and tender suppurative inguinal adenopathy suggests the diagnosis of chancroid (*146*). A probable diagnosis of chancroid, for both clinical and surveillance purposes, can be made if all of the following criteria are met: 1) the patient has one or more painful genital ulcers; 2) 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; 3) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid; and 4) a test for HSV 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 intramuscularly (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

* Ciprofloxacin is contraindicated for pregnant and lactating women.

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

Ciprofloxacin is contraindicated during pregnancy and lactation. No adverse effects of chancroid on pregnancy outcome have been reported.

HIV Infection

HIV-infected patients who have chancroid should be monitored closely because, as a group, they are more likely to experience treatment failure and to have ulcers that heal more slowly. HIV-infected patients might require repeated or longer courses of therapy than those recommended for HIV-negative patients, and treatment failures can occur with any regimen. Because data are limited concerning the therapeutic efficacy of the recommended ceftriaxone and azithromycin regimens in HIV-infected patients, these regimens should be used for such patients only if follow-up can be ensured.

Genital HSV Infections

Genital herpes is a chronic, life-long viral infection. Two types of HSV have been identified as causing genital herpes: HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2, and at least 50 million persons in the United States are infected with this type of genital herpes (*147*). However, an increasing proportion of anogenital herpetic infections in some populations has been attributed to HSV-1 infection.

Most persons infected with HSV-2 have not been diagnosed with genital herpes. Many such persons have mild or unrecognized infections but shed virus intermittently in the genital tract. As a result, the majority of 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 and go beyond the treatment of acute episodes of genital ulcers.

Diagnosis of HSV Infection

The clinical diagnosis of genital herpes is both nonsensitive and nonspecific. The classical painful multiple vesicular or ulcerative lesions are absent in many infected persons. HSV-1 is causing an increasing proportion of first episodes of anogenital herpes in some populations (e.g., young women and MSM) and might now account for most of these infections (*148,149*). Recurrences and subclinical shedding are much less frequent for genital HSV-1 infection than for genital HSV-2 infection (*150,151*). A patient's prognosis and the type of counseling needed depends 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 laboratory testing (*152*). Both virologic and type-specific serologic tests for HSV should be available in clinical settings that provide care for persons diagnosed with or at risk for STDs.

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. PCR assays for HSV DNA are more sensitive and are increasingly used in many settings (153,154). PCR is the test of choice for detecting HSV in spinal fluid for diagnosis of HSV infection of the central nervous system (CNS). Viral culture isolates should be typed to determine which type of HSV is causing the infection. Failure to detect HSV by culture or PCR does not indicate an absence of HSV infection, because viral shedding is intermittent. The use of cytologic detection of cellular changes of HSV infection is an insensitive and nonspecific method of diagnosis, both for genital lesions (i.e., Tzanck preparation) and for cervical Pap smears and therefore should not be relied upon.

Type-Specific Serologic Tests

Both type-specific and nontype-specific 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). Such assays first became commercially available in 1999, but older assays that do not accurately distinguish HSV-1 from HSV-2 antibody (despite claims to the contrary) remain on the market (*155*); providers should specifically request serologic type-specific glycoprotein G (gG)-based assays when serology is performed for their patients (*156–158*).

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%, and false-negative results might be more frequent at early stages of infection. The specificities of these assays are ≥96%. False-positive results can occur, especially in patients with a low likelihood of HSV infection. Repeat or confirmatory testing might be indicated in some settings, especially if recent acquisition of genital herpes is suspected. IgM testing for HSV is not useful, because the

IgM tests are not type-specific and might be positive during recurrent episodes of herpes (*159*).

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 herpes should be provided. The presence of HSV-1 antibody alone is more difficult to interpret. Most persons with HSV-1 antibody have oral HSV infection acquired during childhood, which might be asymptomatic. However, acquisition of genital HSV-1 appears to be increasing, and genital HSV-1 also can be asymptomatic (*147–149*). Lack of symptoms in an HSV-1 seropositive person 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 cultures; 2) a clinical diagnosis of genital herpes without laboratory confirmation; or 3) a partner with 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 herpes episodes 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 (160–168). 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 its use 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

Famciclovir 250 mg orally three times a day for 7–10 days

OR

Valacyclovir 1 g orally twice 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 might prefer suppressive therapy, which has the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners (*169,170*).

Suppressive Therapy for Recurrent Genital Herpes

Suppressive therapy reduces the frequency of genital herpes recurrences by 70%–80% in patients who have frequent recurrences (*166–169*); 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 (*171,172*). Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment.

The frequency of recurrent genital herpes outbreaks diminishes over time in many patients, and the patient's psychological adjustment to the disease might change. Therefore, periodically during suppressive treatment (e.g., once a year), providers should discuss the need to continue therapy with the patient.

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 (*170*). 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
Famciclovir 250 mg orally twice a day
OR
Valacyclovir 500 mg orally once a day*
OR
Valacyclovir 1 g orally once a day

* Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥10 episodes per year).

Acyclovir, famciclovir, and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding (*163–167,173*). 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
Famciclovir 125 mg orally twice daily for 5 days
OR
Famciclovir 1000 mg orally twice daily for 1 day
OR
Famciclovir 500 mg once, followed by 250 mg twice daily 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

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. Acyclovir dose adjustment is recommended for impaired renal function.

Counseling

Counseling of infected persons and their sex partners is critical to the management of genital herpes. The goals of counseling include 1) helping patients cope with the infection and 2) preventing sexual and perinatal transmission (*174,175*). 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.ashastd.org) and printed materials, are available to assist patients, their partners, and clinicians who become involved in counseling.

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 (*176*), 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 frequently is 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 recommendations apply to counseling of persons with genital HSV infection:

- Persons who have genital herpes should be educated concerning the natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and the attendant risks of sexual transmission.
- Persons experiencing a first episode of genital herpes should be advised that suppressive therapy is available and effective in preventing symptomatic recurrent episodes

and that episodic therapy often is useful in shortening the duration of recurrent episodes.

- All persons with genital HSV infection should be encouraged to inform their current sex partners that they have genital herpes and to inform future partners before initiating a sexual relationship.
- Sexual transmission of HSV can 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.
- All persons with genital herpes should remain abstinent from sexual activity with uninfected partners when lesions or prodromal symptoms are present.
- The risk for HSV-2 sexual transmission can be decreased by the daily use of valacyclovir by the infected person. Episodic therapy does not reduce the risk for transmission and its use should be discouraged for this purpose among persons whose partners might be at risk for HSV-2 acquisition.
- Infected persons should be informed that male latex condoms, when used consistently and correctly, might reduce the risk for genital herpes transmission (*21–23*).
- Sex partners of infected persons should be advised that they might be infected even if they have no 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.
- The risk for neonatal HSV infection should be explained to all persons, including men. Pregnant women and women of childbearing age who have genital herpes should inform their providers who care for them during pregnancy and those who will care for their newborn infant about their infection. Pregnant women who are not known to be infected with HSV-2 should be advised to abstain from intercourse with men who have genital herpes during the third trimester of pregnancy. Similarly, pregnant women who are not known to be infected with HSV-1 should be counseled to avoid genital exposure to HSV-1 during the third trimester (e.g., oral sex with a partner with oral herpes and vaginal intercourse with a partner with genital HSV-1 infection).
- Asymptomatic persons diagnosed with 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.
- When exposed to HIV, HSV-2 seropositive persons are at increased risk for HIV acquisition. Patients should be informed that suppressive antiviral therapy does not reduce the increased risk for HIV acquisition associated with HSV-2 infection (*177,178*).

Management of Sex Partners

The sex partners of patients 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 lesions. 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 acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described (*179*).

HIV Infection

Immunocompromised patients can have prolonged or severe episodes of genital, perianal, or oral herpes. Lesions caused by HSV are common among HIV-infected patients and might be severe, painful, and atypical. HSV shedding is increased in HIV-infected persons. Whereas antiretroviral therapy reduces the severity and frequency of symptomatic genital herpes, frequent subclinical shedding still occurs (180). Clinical manifestations of genital herpes might worsen during immune reconstitution after initiation of antiretroviral therapy.

Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV among HIV-positive persons (*181–183*). The extent to which suppressive antiviral therapy will decrease HSV transmission from this population is unknown. HSV type-specific serologies can be offered to HIV-positive persons during their initial evaluation if infection status is unknown, and suppressive antiviral therapy can be considered in those who have HSV-2 infection.

Recommended Regimens for Daily Suppressive Therapy in Persons with HIV

Acyclovir 400–800 mg orally twice to three times a day

OR

Famciclovir 500 mg orally twice a day

OR

Valacyclovir 500 mg orally twice a day

Recommended Regimens for Episodic Infection in Persons with HIV

Acyclovir 400 mg orally three times a day for 5–10 days

OR

Famciclovir 500 mg orally twice a day for 5–10 days

OR

Valacyclovir 1 g orally twice a day for 5–10 days

Acyclovir, valacyclovir, and famciclovir are safe for use in immunocompromised patients in the doses recommended for treatment of genital herpes. For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg IV every 8 hours might be necessary.

If lesions persist or recur in a patient receiving antiviral treatment, HSV resistance should be suspected and a viral isolate should be obtained for sensitivity testing (*184*). Such persons should be managed in consultation with an HIV specialist, and alternate therapy should be administered. All acyclovir-resistant strains are resistant to valacyclovir, and the majority are resistant to famciclovir. Foscarnet, 40 mg/kg IV every 8 hours until clinical resolution is attained, is frequently effective for treatment of acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg once weekly might also be effective. Imiquimod is a topical alternative, as is topical cidofovir gel 1%, which is not commercially available and must be compounded at a pharmacy. These topical preparations should be applied to the lesions once daily for 5 consecutive days.

Clinical management of antiviral resistance remains challenging among HIV-infected patients, and other preventative approaches might be necessary. 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 with outbreaks (*185*).

Genital Herpes in Pregnancy

Most mothers of infants who acquire neonatal herpes lack histories of clinically evident genital herpes (*186*). 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 histories of recurrent herpes at term or who acquire genital HSV during the first half of pregnancy (*187*). However, because recurrent genital herpes is much more common than initial HSV infection during pregnancy, the proportion of neonatal HSV infections acquired from mothers with recurrent herpes is substantial. Prevention of neonatal herpes depends both on preventing acquisition of genital HSV infection during late pregnancy and avoiding exposure of the infant to herpetic lesions during delivery. Because the risk for herpes is high in infants of women who acquire genital HSV during late pregnancy, these women should be managed in consultation with an infectious disease specialist.

Women without known genital herpes should be counseled to abstain from 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. Some specialists believe that type-specific serologic tests are useful to identify pregnant women at risk for HSV infection and to guide counseling regarding the risk for acquiring genital herpes during pregnancy and that such testing should be offered to uninfected women 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.

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 section does not completely eliminate the risk for HSV transmission to the infant, women with recurrent genital herpetic lesions at the onset of labor should deliver by cesarean section to prevent neonatal HSV infection.

The safety of systemic acyclovir, valacyclovir, and famciclovir therapy in pregnant women has not been definitively established. Available data do not indicate an increased risk for major birth defects compared with the general population in women treated with acyclovir during the first trimester (*188*) — findings that provide assurance to women who have had prenatal exposure to acyclovir. However, data regarding prenatal exposure to valacyclovir and famciclovir are too limited to provide useful information on pregnancy outcomes. Acyclovir can be administered orally to pregnant women with first episode genital herpes or severe recurrent herpes and should be administered IV to pregnant women with severe HSV infection. Acyclovir treatment late in pregnancy reduces the frequency of cesarean sections among women who have recurrent genital herpes by diminishing the frequency of recurrences at term (*189–191*); the effect of antiviral therapy late in pregnancy on the incidence of neonatal herpes is not known. No data support the use of antiviral therapy among HSV seropositive women without a history of genital herpes.

Neonatal Herpes

Infants exposed to HSV during birth, as documented by maternal virologic testing or presumed by observation of maternal lesions, should be followed carefully in consultation with a pediatric infectious disease specialist. Surveillance cultures of mucosal surfaces to detect HSV infection might be considered before the development of clinical signs of neonatal herpes. In addition, administration of acyclovir might be considered for infants 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 21 days for disseminated and CNS disease or for 14 days for disease limited to the skin and mucous membranes.

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 (*192,193*). Clinically, the disease is commonly characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy; subcutaneous granulomas (pseudoboboes) might also occur. The lesions are highly vascular (i.e., beefy red appearance) and bleed easily on contact. The clinical presentation also can include hypertrophic, necrotic, or sclerotic variants. Extragenital infection can occur with extension of infection to the pelvis, or it can disseminate to intraabdominal organs, bones, or the mouth. The lesions also can develop secondary bacterial infection and can coexist with other sexually transmitted pathogens.

The causative organism 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 (*192*). 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 reepithelialization of the ulcers. Relapse can occur 6–18 months after apparently effective therapy.

Recommended Regimen

Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed

Alternative Regimens

Azithromycin 1 g orally once per week 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 an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens can be considered if improvement is not evident within the first few days of therapy.

Follow-Up

Patients should be followed clinically until signs and symptoms have resolved.

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

Pregnancy is a relative contraindication to the use of sulfonamides. Pregnant and lactating women should be treated with the erythromycin regimen, and consideration should be given to the addition of a parenteral aminoglycoside (e.g., gentamicin). Azithromycin might prove useful for treating granuloma inguinale during pregnancy, but published data are lacking. Doxycycline and ciprofloxacin are contraindicated in pregnant women.

HIV Infection

Persons with both granuloma inguinale and HIV infection should receive the same regimens as those who are HIV

negative; however, the addition of a parenteral aminoglycoside (e.g., gentamicin) can also be considered.

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is caused by *C. trachomatis* serovars L1, L2, or L3 (194). 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, including mucoid and/or hemorrhagic rectal discharge, anal pain, constipation, fever, and/or tenesmus (*195,196*). LGV is an invasive, systemic infection, and if it is not treated early, LGV proctocolitis can lead to chronic, colorectal fistulas and strictures. Genital and colorectal LGV lesions can also develop secondary bacterial infection or can be coinfected with other sexually and nonsexually transmitted pathogens.

Diagnosis is based on clinical suspicion, epidemiologic information, and the exclusion of other etiologies for proctocolitis, inguinal lymphadenopathy, or genital or rectal ulcers. *C. trachomatis* testing also should be conducted, if available.

Genital 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. NAATs for *C. trachomatis* are not FDA-cleared for testing rectal specimens, although some laboratories have performed the CLIA validation studies that are needed to provide results for clinical management. Additional molecular procedures (e.g., PCR-based genotyping) can be used to differentiate LGV from non-LGV *C. trachomatis*, but these are not widely available.

Chlamydia serology (complement fixation titers >1:64) can support the diagnosis of LGV in the appropriate clinical context. Comparative data between types of serologic tests are lacking, and the diagnostic utility of serologic methods other than complement fixation and some microimmunofluorescence procedures 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.

In the absence of specific LGV diagnostic testing, patients with a clinical syndrome consistent with LGV, including proctocolitis or genital ulcer disease with lymphadenopathy, should be treated for LGV as described in this report.

Treatment

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. Doxycycline is the preferred treatment.

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 might also be effective, but extended treatment intervals are likely required.

Follow-Up

Patients should be followed clinically until signs and symptoms have resolved.

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, tested for urethral or cervical chlamydial infection, and treated with a chlamydia regimen (azithromycin 1 gm 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. Azithromycin might prove useful for treatment of LGV in pregnancy, but no published data are available regarding its safety and efficacy. Doxycycline is contraindicated in pregnant women.

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*. On the basis of clinical findings, the disease has been divided into a series of overlapping stages, which are used to help guide treatment and follow-up. Persons who have syphilis might seek treatment for signs or symptoms of primary infection (i.e., ulcer

or chancre at the infection site), secondary infection (i.e., manifestations that include, but are not limited to, skin rash, mucocutaneous lesions, and lymphadenopathy), neurologic infection (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities, which might occur through the natural history of untreated infection), or tertiary infection (i.e., cardiac or gummatous lesions). 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 either late latent syphilis or latent syphilis of unknown duration. Treatment for both late latent syphilis and tertiary syphilis might require a longer duration of therapy because organisms might be dividing more slowly; however, the validity of this concept has not been assessed.

Diagnostic Considerations

Darkfield examinations and tests to detect *T. pallidum* in lesion exudate or tissue are the definitive methods for diagnosing early syphilis (*197*). Although no *T. pallidum* detection tests are commercially available, some laboratories provide locally developed PCR tests for the detection of *T. pallidum*. A presumptive diagnosis of syphilis is possible with the use of two types of serologic tests: 1) nontreponemal tests (e.g., Venereal Disease Research Laboratory [VDRL] and RPR) and 2) treponemal tests (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] tests, the *T. pallidum* passive particle agglutination [TP-PA] assay, various EIAs, and chemiluminescence immunoassays). The use of only one type of serologic test is insufficient for diagnosis, because each type of test has limitations, including the possibility of false-positive test results in persons without syphilis. False-positive nontreponemal test results can be associated with various medical conditions unrelated to syphilis, including autoimmune conditions, older age, and injection-drug use (*198,199*); therefore, persons with a reactive nontreponemal test should receive a treponemal test to confirm the diagnosis of syphilis.

Nontreponemal test antibody titers may correlate with disease activity, and 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 that were obtained using the same serologic test. Sequential serologic tests in individual patients should be performed using the same testing method (e.g., 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 (*200*). Treponemal test antibody titers should not be used to assess treatment response.

Some clinical laboratories and blood banks have begun to screen samples using treponemal tests, typically by EIA or chemiluminescence immunoassays (*201,202*). This strategy will identify both persons with previous treatment for syphilis and persons with untreated or incompletely treated syphilis. The positive predictive value for syphilis associated with a treponemal screening test result might be lower among populations with a low prevalence of syphilis.

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, then 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. 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, further evaluation or treatment is not indicated.

For most HIV-infected persons, serologic tests are accurate and reliable for the diagnosis of syphilis and for following a patient's response to treatment. However, atypical syphilis serologic test results (i.e., unusually high, unusually low, or fluctuating titers) can occur in HIV-infected persons. When serologic tests do not correspond with clinical findings suggestive of early syphilis, use of other tests (e.g., biopsy and darkfield microscopy) should be considered.

Clinical signs of neurosyphilis (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities) warrant further investigation and treatment for neurosyphilis. Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. Cerebrospinal fluid (CSF) laboratory abnormalities are common in persons with early syphilis. The VDRL in cerebrospinal fluid (CSF-VDRL),

which is highly specific but insensitive, is the standard serologic test for CSF. When reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis; however in early syphilis, it can be of unknown prognostic significance (*203*). Most other tests are both insensitive and nonspecific and must be interpreted in relation to other test results and the clinical assessment. Therefore, the laboratory diagnosis of neurosyphilis usually depends on various combinations of reactive serologic test results, CSF cell count or protein, and a reactive CSF-VDRL with or without clinical manifestations. Among persons with HIV infection, the 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 (*204*). The CSF-VDRL might be nonreactive even when neurosyphilis is present; therefore, additional evaluation using FTA-ABS testing on CSF can be considered. 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 (*205*).

Treatment

Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis. The preparation used (i.e., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of the disease. 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 (*206*).

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 the recommendations for the treatment of syphilis are based not only on clinical trials and observational studies, but approximately 50 years of clinical experience.

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 Patients Who Have a History of Penicillin Allergy).

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, fever, and other symptoms that usually occur within the first 24 hours after the initiation of any therapy for syphilis. Patients should be informed about this possible adverse reaction. The Jarisch-Herxheimer reaction occurs most frequently among patients 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. Although such manifestations are uncommon after the first year of infection, persons exposed sexually to a patient who has syphilis in any stage should be evaluated clinically and serologically and treated with a recommended regimen, according to the following recommendations:

- Persons who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be treated presumptively.
- Persons who were exposed >90 days before the diagnosis of primary, secondary, or early latent syphilis in a sex partner should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.
- For purposes of partner notification and presumptive treatment of exposed sex partners, patients with syphilis of unknown duration who have high nontreponemal serologic test titers (i.e., >1:32) can be assumed to have early syphilis. For the purpose of determining a treatment regimen, however, serologic titers should not be used to differentiate early from late latent syphilis (see Latent Syphilis, Treatment).
- Long-term sex partners of patients who have latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation findings.

Sexual partners of infected patients should be considered at risk and provided treatment if they have had sexual contact with the patient within 3 months plus the duration of symptoms for patients diagnosed with primary syphilis, 6 months

plus duration of symptoms for those with secondary syphilis, and 1 year for patients with early latent syphilis.

Primary and Secondary Syphilis

Treatment

Parenteral penicillin G has been used effectively for more than 50 years 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 adequately conducted to guide the selection of an optimal penicillin regimen (i.e., the dose, duration, and preparation). 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 HIV-infected persons and pregnant women are discussed later in this report (see Syphilis among HIV–Infected Persons and Syphilis in Pregnancy).

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early syphilis (primary, secondary, and early latent) do not enhance efficacy, regardless of HIV status.

Recommended Regimen for Infants and Children

Infants and children aged ≥1 month diagnosed with syphilis should have a CSF examination to detect asymptomatic neurosyphilis, and birth and maternal medical records should be reviewed to assess whether such children have congenital or acquired syphilis (see Congenital Syphilis). Children with acquired primary or secondary syphilis should be evaluated (e.g., through consultation with child-protection services) (see Sexual Assault or Abuse of Children) and treated by using the following pediatric regimen.

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

Other Management Considerations

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

Patients who have syphilis and symptoms or signs suggesting neurologic disease (e.g., meningitis 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 (*203*). Therefore, in the absence of clinical neurologic findings, no evidence exists to support variation from the recommended treatment regimen for early 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 or treatment failure is documented, routine CSF analysis is not recommended for persons who have primary or secondary syphilis.

Follow-Up

Treatment failure can occur with any regimen. However, assessing response to treatment frequently is difficult, and definitive criteria for cure or failure have not been established. In addition, nontreponemal test titers might decline more slowly for persons who previously have had syphilis (*207*). Clinical and serologic evaluation should be performed 6 months and 12 months after treatment; more frequent evaluation might be prudent if follow-up is uncertain.

Patients who have signs or symptoms that persist or recur or who have a sustained fourfold increase in nontreponemal test titer (i.e., compared with the maximum or baseline titer at the time of treatment) probably failed treatment or were reinfected. These patients 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.

Although 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, clinical trial data have demonstrated that >15% of patients with early syphilis treated with the recommended therapy will not achieve the two dilution decline in nontreponemal titer used to define response at 1 year after treatment (*208*). Persons whose titers do not decline should be reevaluated for HIV infection. Optimal management of such patients is unclear. At a minimum, these patients should receive additional clinical and serologic follow-up. 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). In rare instances, serologic titers do not decline despite a negative CSF examination and a repeated course of therapy. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear, but is not generally recommended.

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Data to support the use of alternatives to penicillin in the treatment of early syphilis are limited. However, several therapies might be effective in nonpregnant, penicillin-allergic patients who have primary or secondary syphilis. Doxycycline 100 mg orally twice daily for 14 days (*209,210*) and tetracycline (500 mg four times daily for 14 days) are regimens that have been used for many years. Compliance is likely to be better with doxycycline than tetracycline, because tetracycline can cause gastrointestinal side effects. Although limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone (1 g daily either IM or IV for 10–14 days) is effective for treating early syphilis, the optimal dose and duration of ceftriaxone therapy have not been defined (*211*). Azithromycin as a single 2-g oral dose is effective for treating early syphilis (*212–214*). However, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been documented in several geographical areas in the United States (*215–217*). As such, the use of azithromycin should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used in MSM or pregnant women. Close 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 Patients Who Have a History of Penicillin Allergy).

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

See Syphilis Among HIV-Infected Persons.

Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of disease. Patients who have latent syphilis and who acquired syphilis during the preceding year are classified as having early latent syphilis. Patients' conditions can be diagnosed as early latent syphilis if, during the year preceding the evaluation, they had 1) a documented seroconversion or fourfold or greater increase in titer of a nontreponemal test; 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 whose only possible exposure occurred during the previous 12 months, reactive nontreponemal and treponemal tests are indicative of early latent syphilis. In the absence of these conditions, an asymptomatic person should be considered to have late latent syphilis or syphilis of unknown duration. Nontreponemal serologic titers usually are higher during early latent syphilis than late latent syphilis. However, early latent syphilis cannot be reliably distinguished from late latent syphilis solely on the basis of nontreponemal titers. All patients 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 internal mucosal lesions. All patients who have syphilis should be tested for HIV infection.

Treatment

Because latent syphilis is not transmitted sexually, the objective of treating patients with this stage of disease is to prevent complications. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available to guide choice of specific regimens.

The following regimens are recommended for penicillin nonallergic patients who have normal CSF examinations (if performed).

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 HIV-infected persons and pregnant women are discussed later in this report (see Syphilis among HIV-Infected Persons and Syphilis in Pregnancy).

Available data demonstrate no enhanced efficacy of additional doses of penicillin G, amoxicillin, or other antibiotics in early syphilis, regardless of HIV status.

Infants and children aged ≥1 month who have been diagnosed with syphilis should have a CSF examination to exclude neurosyphilis. In addition, birth and maternal medical records should be reviewed to assess whether children have congenital or acquired syphilis (see Congenital Syphilis). Older children with acquired latent syphilis should be evaluated as described for adults and treated using the following pediatric regimens (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.

Recommended Regimens for 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 or Latent Syphilis of Unknown Duration

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)

Other Management Considerations

Patients diagnosed with latent syphilis who demonstrate any of the following criteria should have a prompt CSF examination:

- Neurologic (e.g., auditory disease, cranial nerve dysfunction, acute or chronic meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense) or ophthalmic signs or symptoms (e.g., iritis and uveitis);
- evidence of active tertiary syphilis (e.g., aortitis and gumma); or
- serologic treatment failure.

If a patient misses a dose of penicillin in a course of weekly therapy for late syphilis, the appropriate course of action is unclear. Pharmacologic considerations suggest that an interval of 10–14 days between doses of benzathine penicillin for late syphilis or latent syphilis of unknown duration might be acceptable before restarting the sequence of injections. Missed doses are not acceptable for pregnant patients receiving therapy for late latent syphilis. 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) titers increase fourfold, 2) an initially high titer (≥1:32) fails to decline at least fourfold (i.e., two dilutions) within 12–24 months of therapy, or 3) signs or symptoms attributable to syphilis develop. In such circumstances, even if the CSF examination is negative, retreatment for latent syphilis should be initiated. In rare instances, despite a negative CSF examination and a repeated course of therapy, serologic titers might fail to decline. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear.

Management of Sex Partners

See General Principles, 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 therapies 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 late latent syphilis or latent syphilis of unknown duration are doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily), both for 28 days. These therapies should be used only in conjunction with close serologic and clinical follow-up. Based on biologic plausibility and pharmacologic properties, ceftriaxone might be effective for treating late latent syphilis or syphilis of unknown duration. However, the optimal dose and duration of ceftriaxone therapy have not been defined, and treatment decisions should be discussed in consultation with a specialist. Some patients who are allergic to penicillin also might be allergic to ceftriaxone; in these circumstances, use of an alternative agent might be required. The efficacy of these alternative regimens in HIV-infected persons has not been well studied.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

See Syphilis Among HIV-Infected Persons.

Tertiary Syphilis

Tertiary syphilis refers to gumma and cardiovascular syphilis but not to all neurosyphilis. Patients who are not allergic to penicillin and have no evidence of neurosyphilis should be treated with the following regimen.

Recommended Regimen

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

Patients who have symptomatic late syphilis should be given a CSF examination before therapy is initiated. Some providers treat all patients who have cardiovascular syphilis with a neurosyphilis regimen. These patients should be managed in consultation with an infectious disease specialist.

Follow-Up

Limited information is available concerning clinical response and follow-up of patients who have tertiary syphilis.

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Patients allergic to penicillin should be treated in consultation with an infectious disease specialist.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

See Syphilis Among HIV-Infected Persons.

Neurosyphilis

Treatment

CNS involvement can occur during any stage of syphilis. However, CSF laboratory abnormalities are common in persons with early syphilis, even in the absence of clinical neurological findings. No evidence exists to support variation from recommended treatment for early syphilis for patients found to have such abnormalities. 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), a CSF examination should be performed.

Syphilitic uveitis or other ocular manifestations frequently are associated with neurosyphilis and should be managed according to the treatment recommendations for neurosyphilis. Patients who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, and optic neuritis) should be treated with the recommended regimen for neurosyphilis; those with eye disease should be managed in collaboration with an ophthalmologist. A CSF examination should be performed for all patients with syphilitic eye disease to identify those with abnormalities; patients found to have abnormal CSF test results should be provided follow-up CSF examinations to assess treatment response.

Recommended Regimen

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 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 late syphilis in the absence of neurosyphilis. 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

Other considerations in the management of patients who have neurosyphilis are as follows:

- All persons who have syphilis 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 (*219,220*). The 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 HIV-infected persons on highly active antiretroviral therapy, normalization of the serum RPR titer predicts normalization of CSF parameters (*220*).

Management of Sex Partners

See General Principles, 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 patients with neurosyphilis (*221,222*). However, the possibility of cross-reactivity between ceftriaxone and penicillin exists. Other regimens have not been adequately evaluated for treatment of neurosyphilis. Therefore, 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, desensitization in consultation with a specialist.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Syphilis During Pregnancy).

HIV Infection

See Syphilis Among HIV-Infected Persons.

Syphilis Among HIV-Infected Persons

Diagnostic Considerations

Although they are uncommon, unusual serologic responses have been observed among HIV-infected persons who have syphilis. Most reports have involved serologic titers that were higher than expected, but false-negative serologic test results and delayed appearance of seroreactivity also have been reported (*223*). Regardless, both treponemal and nontreponemal serologic tests for syphilis can be interpreted in the usual manner for most patients who are coinfected with *T. pallidum* and HIV.

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 disease in HIV-infected persons.

Treatment

Compared with HIV-negative patients, HIV-positive patients who have early syphilis might be at increased risk for neurologic complications (*224*) and might have higher rates of serologic treatment failure with currently recommended regimens. The magnitude of these risks is not defined precisely, but is likely small. No treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in HIV-infected patients than the syphilis regimens recommended for HIV-negative patients (*208*). Careful follow-up after therapy is essential.

Primary and Secondary Syphilis Among HIV-Infected Persons

Treatment

Treatment of primary and secondary syphilis among HIV-infected persons is 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 early syphilis do not result in enhanced efficacy, regardless of HIV status (*208*).

Other Management Considerations

Most HIV-infected persons respond appropriately to standard benzathine penicillin for primary and secondary syphilis. CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in HIV-infected persons, even in those without neurologic symptoms, although the clinical and prognostic significance of such CSF abnormalities with primary and secondary syphilis is unknown. Several studies have demonstrated that among persons infected with both HIV and syphilis, clinical and CSF abnormalities consistent with neurosyphilis are associated with a CD4 count of ≤350 cells/mL and/or an RPR titer of ≥1:32 (*204,225,226*); however, unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.

The use of antiretroviral therapy as per current guidelines might improve clinical outcomes in HIV-infected persons with syphilis (*220,227,228*).

Follow-Up

HIV-infected persons should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.

HIV-infected persons who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or persons who have a sustained fourfold increase in nontreponemal test titer) should be managed in the same manner as HIV-negative patients (i.e., a CSF examination and retreatment). CSF examination and retreatment also should be strongly considered for persons whose nontreponemal test titers do not decrease

fourfold within 6–12 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.

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

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

Latent Syphilis Among HIV-Infected Persons

Treatment

HIV-infected persons with latent syphilis should be treated according to the stage-specific recommendations for HIV-negative persons.

- Treatment of early latent syphilis among HIV-infected persons is benzathine penicillin G, 2.4 million units IM in a single dose.
- Treatment of late latent syphilis or syphilis of unknown duration among HIV-infected persons is benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks.

Other Management Considerations

All HIV-infected persons with syphilis and neurologic symptoms should undergo immediate CSF examination. Some studies have demonstrated that clinical and CSF abnormalities consistent with neurosyphilis are most likely in HIV-infected persons who have been diagnosed with syphilis and have a CD4 count of ≤350 cells/ml and/or an RPR titer of ≥1:32 (*204,225,226*); however unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.

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 nontreponemal titers rise fourfold, a repeat CSF examination should be performed and treatment administered accordingly. If during 12–24 months the nontreponemal titer does not decline fourfold, CSF examination should be strongly considered and treatment administered accordingly.

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy. The efficacy of alternative nonpenicillin regimens in HIV-infected persons has not been well studied. Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy). These therapies should be used only in conjunction with close serologic and clinical follow-up. Limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone might be effective (*229*,*230*). However, the optimal dose and duration of ceftriaxone therapy have not been defined.

Neurosyphilis Among HIV-Infected Persons

Treatment

HIV-infected patients with neurosyphilis should be treated according to the recommendations for HIV-negative patients with neurosyphilis (see Neurosyphilis).

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 gauge response after therapy. Limited data suggest that changes in CSF parameters might occur more slowly in HIV-infected patients, especially those with more advanced immunosuppression (*219,227*). If the cell count has not decreased after 6 months or if the CSF is not normal after 2 years, retreatment should be considered.

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy. HIV-infected, penicillin-allergic patients who have neurosyphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative patients with neurosyphilis. Several small observational studies conducted in HIV-infected patients with neurosyphilis suggest that ceftriaxone 1–2 g IV daily for 10-14 days might be effective as an alternate agent (*218,229,230*).

Syphilis During Pregnancy

All women should be screened serologically for syphilis early in pregnancy. Most states mandate screening at the first prenatal visit for all women (*231*); antepartum screening by nontreponemal antibody testing is typical, but in some settings, treponemal antibody testing is being used. Pregnant women with reactive treponemal screening tests should have confirmatory testing with nontreponemal tests with titers. In populations in which use of prenatal care is not optimal, RPR test screening and treatment (if the RPR test is reactive) should be performed at the time that pregnancy is confirmed (*232*). For communities and populations in which the prevalence of syphilis is high and for patients at high risk, serologic testing should be performed twice during the third trimester (ideally at 28–32 weeks' gestation) and at delivery. Any woman who delivers a stillborn infant after 20 weeks' gestation should be tested for syphilis. No infant should leave the hospital without the maternal serologic status having been determined at least once during pregnancy.

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. Serofast low antibody titers might not require treatment; however, persistent higher titer antibody tests might indicate reinfection, and treatment might be required.

Treatment

Penicillin is effective for preventing maternal transmission to the fetus and for treating fetal infection (*233*). Evidence is insufficient to determine optimal, recommended penicillin regimens (*234*).

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 can be beneficial for pregnant women in some settings (e.g., a second dose of benzathine penicillin 2.4 million units IM administered 1 week after the initial dose for women who have primary, secondary, or early latent syphilis) (*235*). When syphilis is diagnosed during the second half of pregnancy, management should include a sonographic fetal evaluation for congenital syphilis, but 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 (*231*); such cases 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 (*236*). 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. All patients who have syphilis should be offered testing for HIV infection.

Follow-Up

Coordinated prenatal care and treatment are vital. Serologic titers should be repeated at 28–32 weeks' gestation and at delivery as recommended for the disease stage. 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, if clinical signs of infection are present at delivery, or if the maternal antibody titer at delivery is fourfold higher than the pretreatment titer. 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

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

For treatment of syphilis during pregnancy, no proven alternatives to penicillin exist. Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin. Oral step-wise penicillin dose challenge or skin testing might be helpful in identifying women at risk for acute allergic reactions (see Management of Patients Who Have a History of Penicillin Allergy).

Tetracycline and doxycycline usually are not used during pregnancy. Erythromycin and azithromycin should not be used, because neither reliably cures maternal infection or treats an infected fetus (*234*). 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 HIV-infected women should be evaluated for syphilis and receive treatment as recommended. Data are insufficient to recommend a specific regimen for HIV-infected pregnant women (see Syphilis Among HIV-Infected Patients).

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. In communities and populations in which the risk for congenital syphilis is high, serologic testing and a sexual history also should be obtained at 28 weeks' gestation and at delivery. Moreover, as part of the management of pregnant women who have syphilis, information concerning the 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. Serologic testing of the mother's serum is preferred rather than testing of the infant's serum because the serologic tests performed on infant serum can be nonreactive if the mother's serologic test result is of low titer or the mother was infected late in pregnancy (see Diagnostic Considerations and Use of Serologic Tests). Screening can be performed using either a nontreponemal or treponemal test. If either screening test is positive, testing must be performed immediately using the other complimentary test (i.e., nontreponemal test followed by treponemal test or vice-versa). No infant or mother should leave the hospital unless maternal serologic status has been documented at least once during pregnancy; in communities and populations in which the risk for congenital syphilis is high, documentation should also occur at delivery.

Evaluation and Treatment of Infants During the First Month of Life

The diagnosis of congenital syphilis is complicated by the transplacental transfer of maternal nontreponemal and treponemal IgG antibodies to the fetus, which can complicate the interpretation of reactive serologic tests for syphilis in infants. 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 infant; and 4) comparison of maternal (at delivery) and infant nontreponemal serologic titers using the same test conducted preferably by the same laboratory.

All infants 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 infant serum, because umbilical cord blood can become contaminated with maternal blood and yield a false-positive result. Conducting a treponemal test (i.e., TP-PA, FTA-ABS, EIA, or chemiluminescence assay) on a newborn's serum is not necessary. No commercially available immunoglobulin (IgM) test can be recommended.

All infants 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 fluorescent antitreponemal antibody staining is suggested. Darkfield microscopic examination of suspicious lesions or body fluids (e.g., nasal discharge) also should be performed.

The following scenarios describe the evaluation and treatment of infants for congenital syphilis.

Scenario 1

Infants with proven or highly probable disease and

1. an abnormal physical examination that is consistent with congenital syphilis;
2. a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer;[¶] or
3. a positive darkfield test of 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, cranial ultrasound, ophthalmologic examination, and auditory brain stem response)

[¶] The absence of a fourfold or greater titer for an infant 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)/mm3 and/or protein of 150 mg/dL might occur among normal neonates; some specialists, however, recommend that lower values (i.e., 5 WBCs/mm3 and protein of 40 mg/dL) 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. In all other situations, the maternal history of infection with *T. pallidum* and treatment for syphilis must be considered when evaluating and treating the infant.

Scenario 2

Infants who have a normal physical examination and a serum quantitive nontreponemal serologic titer the same or less than fourfold the maternal titer and the

1. mother was not treated, inadequately treated, or has no documentation of having received treatment;
2. mother was treated with erythromycin or another nonpenicillin regimen;[††] or
3. mother received 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. If a single dose of benzathine penicillin G is used, then the infant must be fully evaluated (i.e., by CSF examination, long-bone radiographs, and CBC with platelets), the full evaluation must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed or if the CSF analysis is rendered uninterpretable because of contamination with blood, then a 10-day course of penicillin is required.[§§]

[††] A woman treated with a regimen other than those recommended in these guidelines for treatment should be considered untreated.

[§§] If the infant's nontreponemal test is nonreactive and the provider determines that the mother's risk for untreated syphilis is low, treatment of the infant (single IM dose of benzathine penicillin G 50,000 units/kg for possible incubating syphilis) without an evaluation can be considered.

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

If the mother has untreated early syphilis at delivery, 10 days of parenteral therapy can be considered.

Scenario 3

Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the

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 required.

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 in those whose mother's nontreponemal titers decreased fourfold after appropriate therapy for early syphilis or remained stable or low for late syphilis.

Scenario 4

Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the

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

Recommended Evaluation

No evaluation is required.

Recommended Regimen

No treatment is required; however, **benzathine penicillin G** 50,000 units/kg as a single IM injection might be considered, particularly if follow-up is uncertain.

Evaluation and Treatment of Older Infants and Children

Older infants and children aged ≥1 month who are identified as having reactive serologic tests for syphilis should 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 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, 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 child has no clinical manifestations of disease, the CSF examination is normal, and the CSF VDRL test result is negative, treatment with up to 3 weekly doses of benzathine penicillin G, 50,000 U/kg IM can be considered.

Any child who is suspected of having congenital syphilis or who has neurologic involvement should be treated with aqueous penicillin G. A single dose of benzathine penicillin G, 50,000 units/kg IM after the 10-day course of IV aqueous penicillin can be considered. This treatment also would be adequate for children who might have other treponemal infections.

Follow-Up

All seroreactive infants (or infants whose mothers were seroreactive at delivery) should receive careful follow-up examinations and serologic testing (i.e., a nontreponemal test) every 2–3 months until the test becomes nonreactive or the titer has decreased fourfold. Nontreponemal antibody titers should decline by age 3 months and should be nonreactive by age 6 months if the infant is not infected (i.e., if the reactive test result was caused by passive transfer of maternal IgG antibody) or was infected but adequately treated. The serologic response after therapy might be slower for infants treated after the neonatal period. If these titers are stable or increase after age 6–12 months, the child should be evaluated (e.g., given a CSF examination) and treated with a 10-day course of parenteral penicillin G.

Treponemal tests should not be used to evaluate treatment response, because the results for an infected child can remain positive despite effective therapy. Passively transferred maternal treponemal antibodies can be present in an infant until age 15 months; therefore, a reactive treponemal test after age 18 months is diagnostic of congenital syphilis. If the nontreponemal test is nonreactive at this time, no further evaluation or treatment is necessary. If the nontreponemal test is reactive at age 18 months, the infant should be fully (re)evaluated and treated for congenital syphilis.

Infants whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. A reactive CSF VDRL test or abnormal CSF indices that cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis.

Follow-up of children treated for congenital syphilis after the newborn period should be conducted as recommended for neonates.

Special Considerations

Penicillin Allergy

Infants and children who require treatment for syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should be desensitized, if necessary, and then treated with penicillin (see Management of Patients With a History of Penicillin Allergy). Data are insufficient regarding the use of other antimicrobial agents (e.g., ceftriaxone); if a nonpenicillin agent is used, close serologic and CSF follow-up are indicated.

Penicillin Shortage

During periods when the availability of penicillin is compromised, the following is recommended (see http://www.cdc.gov/nchstp/dstd/penicillinG.htm).

1. For infants 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 age and weight) can be considered with careful clinical and serologic follow-up. Ceftriaxone must be used with caution in infants with jaundice. For infants aged ≥30 days, use 75 mg/kg IV/IM a day in a single daily dose for 10–14 days; however, dose adjustment might be necessary based on current weight. For older infants, the dose should be 100 mg/kg a day in a single daily dose. Evidence is insufficient

to support the use of ceftriaxone for the treatment of congenital syphilis. Therefore, ceftriaxone should be used in consultation with a specialist in the treatment of infants with congenital syphilis. Management may include a repeat CSF examination at age 6 months if the initial examination was abnormal.

2. For infants without any clinical evidence of infection (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, CSF examination is not interpretable, CSF examination was not performed, 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 other clinical evidence of infection (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 (see Penicillin Shortage, Number 1). Ceftriaxone dosing must be adjusted according to age and birth weight.

HIV Infection

Evidence is insufficient to determine whether infants who have congenital syphilis and whose mothers are coinfected with HIV require different evaluation, therapy, or follow-up for syphilis than is recommended for all infants.

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 for use, whenever possible, in HIV-infected patients. Of the adult U.S. population, 3%–10% have experienced an immunoglobulin E (IgE)-mediated allergic response to penicillin (*238,239*), such as urticaria, angioedema, or anaphylaxis (i.e., upper airway obstruction, bronchospasm, or hypotension). Readministration of penicillin to these patients 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 patients, unless they undergo acute desensitization to eliminate anaphylactic sensitivity.

Although an estimated 10% of persons who report a history of severe allergic reactions to penicillin continue to remain allergic their entire lives, with the passage of time, most persons who have had a severe reaction to penicillin stop expressing penicillin-specific IgE (*238,239*). These persons can then be treated safely with penicillin. Penicillin skin testing with the major and minor determinants of penicillin can reliably identify persons at high risk for penicillin reactions (*238,239*). Although these reagents are easily generated and have been available for more than 30 years, only benzylpenicilloyl poly-L-lysine (Pre-Pen [i.e., the major determinant]) and penicillin G have been available commercially. These two tests identify an estimated 90%–97% of the currently allergic patients. However, because skin testing without the minor determinants would still miss 3%–10% of allergic patients and because serious or fatal reactions can occur among these minor-determinant–positive patients, caution should be exercised when the full battery of skin-test reagents is not available (Box 2). Manufacturers are working to ensure better availability of the Pre-Pen skin test reagent as well as an accompanying minor determinant mixture.

Recommendations

If the full battery of skin-test reagents is available, including both major and minor determinants (see Penicillin Allergy Skin Testing), patients who report a history of penicillin reaction and who are skin-test negative can receive conventional penicillin therapy. Skin-test–positive patients should be desensitized before initiating treatment.

If the full battery of skin-test reagents, including the minor determinants, is not available, the patient should be skin tested using benzylpenicilloyl poly-L-lysine (i.e., the major determinant) and penicillin G. Patients who have positive test results should be desensitized. One approach suggests that persons with a history of allergy who have negative test results should be regarded as possibly allergic and desensitized. Another approach in those with negative skin-test results involves test-dosing gradually with oral penicillin in a monitored setting in which treatment for anaphylactic reaction can be provided.

If the major determinant (Pre-Pen) is not available for skin testing, all patients with a history suggesting IgE-mediated reactions to penicillin (e.g., anaphylaxis, angioedema, bronchospasm, or urticaria) should be desensitized in a hospital setting. In patients with reactions not likely to be IgE-mediated, outpatient-monitored test doses can be considered.

Penicillin Allergy Skin Testing

Patients at high risk for anaphylaxis, including those who 1) have a history of penicillin-related anaphylaxis, 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, patients should be tested in a monitored setting in which treatment for an anaphylactic reaction is available. If possible, the patient should not have taken antihistamines recently (e.g., chlorpheniramine maleate or fexafenadine during the preceding 24 hours, diphenhydramine HCl during the preceding 4 days, or hydroxyzine or phenathiazines during the preceding 3 weeks).

Procedures

Dilute the antigens either 100-fold for preliminary testing (if the patient has had a life-threatening reaction to penicillin) or 10-fold (if the patient has had another type of immediate, generalized reaction to penicillin within the preceding year).

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 controls. Otherwise, the tests are negative.

Desensitization

Patients 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 IV. Although the two approaches have not been compared, oral desensitization is regarded as safer and easier to perform. Patients should be desensitized in a hospital setting because serious IgE-mediated allergic reactions can occur. Desensitization usually can be completed in approximately 4–12 hours, after which time the first dose of penicillin is administered. After desensitization, patients must be maintained on penicillin continuously for the duration of the course of therapy.

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

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

* Adapted from Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med 1987;107:204–15. Reprinted with permission from G.N. Beall and *Annals of Internal Medicine*.

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

Diseases Characterized by Urethritis and Cervicitis

Urethritis

Urethritis, as characterized by urethral inflammation, can result from infectious and noninfectious conditions. Symptoms, if present, include discharge of mucopurulent or purulent material, dysuria, or urethral pruritis. Asymptomatic infections are common. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *Mycoplasma genitalium* has also been associated with urethritis (*240–243*). If clinic-based diagnostic tools (e.g., Gram-stain microscopy, first void urine with microscopy, and leukocyte esterase) are not available, patients should be treated with drug regimens effective against both gonorrhea and chlamydia. Further testing to determine the specific etiology is recommended because both chlamydia and gonorrhea are reportable to health departments and a specific diagnosis might improve partner notification and treatment. Culture, nucleic acid hybridization tests, and NAATs are available for the detection of both *N. gonorrhoeae* and *C. trachomatis*. Culture and hybridization tests require urethral swab specimens, whereas NAATs can be performed on urine specimens. Because of their

higher sensitivity, NAATs are preferred for the detection of *C. trachomatis* (*197*).

Etiology

Several organisms can cause infectious urethritis. The presence of Gram-negative intracellular diplococci (GNID) on urethral smear is indicative of gonorrhea infection, which is frequently accompanied by chlamydial infection. Nongonoccocal urethritis (NGU), which is diagnosed when examination findings or microscopy indicate inflammation without GNID, 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 (*244*). Complications of NGU among males infected with *C. trachomatis* include epididymitis and Reiter's syndrome. Documentation of chlamydial infection is essential because of the need for partner referral for evaluation and treatment.

In most cases of nonchlamydial NGU, no pathogen can be detected. *M. genitalium,* which appears to be sexually transmitted, is associated with both symptoms of urethritis and urethral inflammation and accounts for 15%–25% of NGU cases in the United States (240–243). *T. vaginalis*, HSV, and adenovirus also can cause NGU, but data supporting other *Mycoplasma* species and *Ureaplasma* as etiologic agents are inconsistent (*244–247*). Diagnostic and treatment procedures for these organisms are reserved for situations in which these infections are suspected (e.g., contact with trichomoniasis, genital lesions, or severe dysuria and meatitis, which might suggest genital herpes) or when NGU is not responsive to therapy. Enteric bacteria have been identified as an uncommon cause of NGU and might be associated with insertive anal intercourse (*244*).

Confirmed Urethritis

Clinicians should attempt to obtain objective evidence of urethral inflammation. However, if clinic-based diagnostic tools (e.g., Gram-stain microscopy) are not available, patients should be treated with drug regimens effective against both gonorrhea and chlamydia.

Urethritis can be documented on the basis of any of the following signs or laboratory tests:

- Mucopurulent or purulent discharge on examination.
- Gram stain of urethral secretions demonstrating ≥5 WBC per oil immersion field. The Gram stain is the preferred rapid diagnostic test for evaluating urethritis and is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC containing GNID.

TABLE 1. Oral desensitization protocol for patients 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

Note: Observation period was 30 minutes before parenteral administration of penicillin.

* Reprinted with permission from the New England Journal of Medicine (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.).

† 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.

- Positive leukocyte esterase test on first-void urine or microscopic examination of first-void urine sediment demonstrating ≥10 WBC per high-power field.

If none of these criteria are present, testing for *N. gonorrhoeae* and *C. trachomatis* using NAATs might identify additional infections (*248*). If the results demonstrate infection with either of these pathogens, the appropriate treatment should be given and sex partners referred for evaluation and treatment. If none of these criteria are present, empiric treatment of symptomatic males is recommended only for men at high risk for infection who are unlikely to return for a follow-up evaluation. Such patients should be treated with drug regimens effective against gonorrhea and chlamydia. Partners of patients treated empirically should be evaluated and treated, if indicated.

Nongonococcal Urethritis

Diagnosis

All patients who have confirmed or suspected urethritis should be tested for gonorrhea and chlamydia. Testing for chlamydia is strongly recommended because of the increased utility and availability of highly sensitive and specific testing methods (e.g., NAATs) and because a specific diagnosis might enhance partner notification and improve compliance with treatment, especially in the exposed partner.

Treatment

Treatment should be initiated as soon as possible after diagnosis. Azithromycin and doxycycline are highly effective for chlamydial urethritis; however, infections with *M. genitalium* respond better to azithromycin (*249,250*). Single-dose regimens have the advantage of improved compliance and directly observed treatment. To maximize compliance with recommended therapies, medications should be dispensed on-site in the clinic, and the first dose should be directly observed.

Recommended Regimens

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Levofloxacin 500 mg orally once daily for 7 days

OR

Ofloxacin 300 mg orally twice a day for 7 days

To minimize transmission, men treated for NGU should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen, provided their symptoms have resolved. To minimize the risk for reinfection, men should be instructed to abstain from sexual intercourse until all of their sex partners are treated.

Persons who have been diagnosed with a new STD should receive testing for other infections, including syphilis and HIV.

Follow-Up

Patients should be instructed to return for evaluation if symptoms persist or recur after completion of therapy. Symptoms alone, without documentation of signs or laboratory evidence of urethral inflammation, are not a sufficient basis for retreatment. Providers should be alert to the possibility of chronic prostatitis/chronic pelvic pain syndrome in male patients experiencing persistent pain (perineal, penile, or pelvic), discomfort, irritative voiding symptoms, pain during or after ejaculation, or new-onset premature ejaculation lasting for >3 months.

Unless a patient's symptoms persist or therapeutic noncompliance or reinfection is suspected by the provider, a test-of-cure (i.e., repeat testing 3–4 weeks after completing therapy) is not recommended for persons with documented chlamydia or gonococcal infections who have received treatment with recommended or alterative regimens. However, because men with documented chlamydial or gonococcal infections have a high rate of reinfection within 6 months after treatment (*251,252*), repeat testing of all men diagnosed with chlamydia or gonorrhea is recommended 3–6 months after treatment, regardless of whether patients believe that their sex partners were treated (*251*).

Partner Referral

A specific diagnosis might facilitate partner referral. Therefore, testing for gonorrhea and chlamydia is encouraged. Because a substantial proportion of female partners of males with nonchlamydial NGU are infected with chlamydia, partner management is recommended for males with NGU regardless of whether a specific etiology is identified. All sex partners within the preceding 60 days should be referred for evaluation, testing, and empiric treatment with a drug regimen effective against chlamydia. Expedited partner treatment and patient referral are alternative approaches to treating partners (*71*).

Recurrent and Persistent Urethritis

Objective signs of urethritis should be present before the initiation of antimicrobial therapy. In persons who have persistent symptoms after treatment without objective signs of urethritis, the value of extending the duration of antimicrobials has not been demonstrated. Persons who have persistent or recurrent urethritis can be retreated with the initial regimen if they did not comply with the treatment regimen or if they were reexposed to an untreated sex partner. Persistent urethritis after doxycycline treatment might be caused by doxycycline-resistant *U. urealyticum* or *M. genitalium*. *T. vaginalis* is also known to cause urethritis in men; a urethral swab, first void urine, or semen for culture or a NAAT (PCR or TMA) on a urethral swab or urine can be performed. If compliant with the initial regimen and re-exposure can be excluded, the following regimen is recommended while awaiting the results of the diagnostic tests.

Recommended Regimens

Metronidazole 2 g orally in a single dose

OR

Tinidazole 2 g orally in a single dose

PLUS

Azithromycin 1 g orally in a single dose (if not used for initial episode)

Studies involving a limited number of patients who experienced NGU treatment failures have demonstrated that Moxifloxacin 400 mg orally once daily for 7 days is highly effective against *M. genitalium* (*253,254*). Men with a low

probability of *T. vaginalis* (e.g., MSM) are unlikely to benefit from the addition of metronidazole or tinidazole.

Urologic examinations usually do not reveal a specific etiology for urethritis. A four-glass Meares-Stamey lower-urinary-tract localization procedure (or four-glass test) might be helpful in localizing pathogens to the prostate (*255*). A substantial proportion of men with chronic nonbacterial prostatitis/chronic pelvic pain syndrome have evidence of urethral inflammation without any identifiable microbial pathogens. Estimates vary considerably depending on the source and sensitivity of the assay, but one study demonstrated that in 50% of men with this syndrome, ≥5 WBCs per high-power field were detected in expressed prostatic secretions (*256*). Referral to a urologist should be considered for men who experience pain for more than 3 months within a 6-month period.

If men require treatment with a new antibiotic regimen for persistent urethritis and a sexually transmitted agent is the suspected cause, all partners in the past 60 days before the initial diagnosis and any interim partners should be referred for evaluation and appropriate treatment.

Special Considerations

HIV Infection

Gonococcal urethritis, chlamydial urethritis, and nongonococcal, nonchlamydial urethritis might facilitate HIV transmission. Patients who have NGU and also are infected with HIV should receive the same treatment regimen as those who are HIV negative.

Cervicitis

Two major diagnostic signs characterize cervicitis: 1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (commonly referred to as mucopurulent cervicitis or cervicitis) and 2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os. Either or both signs might be present. Cervicitis frequently is asymptomatic, but some women complain of an abnormal vaginal discharge and intermenstrual vaginal bleeding (e.g., after sexual intercourse). A finding of leukorrhea (>10 WBC per high-power field on microscopic examination of vaginal fluid) has been associated with chlamydial and gonococcal infection of the cervix. In the absence of inflammatory vaginitis, leukorrhea might be a sensitive indicator of cervical inflammation with a high negative predictive value (*257,258*). Although some specialists consider an increased number of polymorphonuclear leukocytes on endocervical Gram stain as being useful in the diagnosis of cervicitis, this criterion has not been standardized. In addition, it has a low positive-predictive value (PPV) for infection with *C. trachomatis* and *N. gonorrhoeae* and is not available in most clinical settings. Finally, although the presence of GNID on Gram stain of endocervical fluid is specific for the diagnosis of gonococcal cervical infection, it is not a sensitive indicator, because it is observed in only 50% of women with this infection.

Etiology

When an etiologic organism is isolated in the presence of cervicitis, it is typically *C. trachomatis* or *N. gonorrhoeae*. Cervicitis also can accompany trichomoniasis and genital herpes (especially primary HSV-2 infection). However, in most cases of cervicitis, no organism is isolated, especially in women at relatively low risk for recent acquisition of these STDs (e.g., women aged >30 years). Limited data indicate that infection with *M. genitalium* and BV and frequent douching might cause cervicitis (*259–263*). For reasons that are unclear, cervicitis can persist despite repeated courses of antimicrobial therapy. Because most persistent cases of cervicitis are not caused by relapse or reinfection with *C. trachomatis* or *N. gonorrhoeae*, other factors (e.g., persistent abnormality of vaginal flora, douching [or exposure to other types of chemical irritants], or idiopathic inflammation in the zone of ectopy) might be involved.

Diagnosis

Because cervicitis might be a sign of upper-genital–tract infection (endometritis), women who seek medical treatment for a new episode of cervicitis should be assessed for signs of PID and should be tested for *C. trachomatis* and for *N. gonorrhoeae* with the most sensitive and specific test available. Women with cervicitis also should be evaluated for the presence of BV and trichomoniasis, and if these organisms are detected, they should be treated. Because the sensitivity of microscopy to detect *T. vaginalis* is relatively low (approximately 50%), symptomatic women with cervicitis and negative microscopy for trichomonads should receive further testing (i.e., culture or other FDA-cleared method). Although HSV-2 infection has been associated with cervicitis, the utility of specific testing (i.e., culture or serologic testing) for HSV-2 in this setting is unknown. Standardized diagnostic tests for *M. genitalium* are not commercially available.

As discussed, NAAT should be used for diagnosing *C. trachomatis* and *N. gonorrhoeae* in women with cervicitis; this testing can be performed on either vaginal, cervical, or urine samples (*197*). A finding of >10 WBC in vaginal fluid, in the absence of trichomoniasis, might indicate endocervical inflammation caused specifically by *C. trachomatis* or *N. gonorrhoeae* (*264,265*).

Treatment

Several factors should affect the decision to provide presumptive therapy for cervicitis or to await the results of diagnostic tests. Treatment with antibiotics for *C. trachomatis* should be provided for those women at increased risk for this common STD (e.g., those aged ≤25 years, those with new or multiple sex partners, and those who engage in unprotected sex), especially if follow-up cannot be ensured and if a relatively insensitive diagnostic test is used in place of NAAT. Concurrent therapy for *N. gonorrhoeae* is indicated if the prevalence of this infection is >5% (those in younger age groups and those living in certain facilities).

Trichomoniasis and BV should also be treated if detected. For women in whom any component of (or all) presumptive therapy is deferred, the results of sensitive tests for *C. trachomatis* and *N. gonorrhoeae* (e.g., NAATs) should determine the need for treatment subsequent to the initial evaluation.

Recommended Regimens for Presumptive Treatment*

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

* Consider concurrent treatment for gonococcal infection if prevalence of gonorrhea is high in the patient population under assessment.

Recurrent and Persistent Cervicitis

Women with persistent cervicitis should be reevaluated for possible reexposure to an STD. If relapse and/or reinfection with a specific STD has been excluded, BV is not present, and sex partners have been evaluated and treated, management options for persistent cervicitis are undefined; in addition, the utility of repeated or prolonged administration of antibiotic therapy for persistent symptomatic cervicitis remains unknown. Women who receive such therapy should return after treatment so that a determination can be made regarding whether cervicitis has resolved. Research is needed on the etiology of persistent cervicitis including the potential role of *M. genitalium* (*266*). In women with persistent symptoms that are clearly attributable to cervicitis, referral to a gynecologic specialist can be considered.

Follow-Up

Follow-up should be conducted as recommended for the infections for which a woman is treated. If symptoms persist, women should be instructed to return for re-evaluation because women with documented chlamydial or gonococcal infections have a high rate of reinfection within 6 months after treatment. Therefore, repeat testing of all women with chlamydia or gonorrhea is recommended 3-6 months after treatment, regardless of whether their sex partners were treated (*267*).

Management of Sex Partners

Management of sex partners of women treated for cervicitis should be appropriate for the identified or suspected STD. Partners should be notified and examined if chlamydia, gonorrhea, or trichomoniasis was identified or suspected in the index patient; these partners should then be treated for the STDs for which the index patient received treatment. To avoid reinfection, patients and their sex partners should abstain from sexual intercourse until therapy is completed (i.e., 7 days after a single-dose regimen or after completion of a 7-day regimen). Expedited partner treatment and patient referral (see Partner Management) are alternative approaches to treating male partners of women that have chlamydia or gonococcal infections (*68,69,71*).

Special Considerations

HIV Infection

Patients who have cervicitis and also are infected with HIV should receive the same treatment regimen as those who are HIV negative. Treatment of cervicitis in HIV-infected women is vital because cervicitis increases cervical HIV shedding. Treatment of cervicitis in HIV-infected women reduces HIV shedding from the cervix and might reduce HIV transmission to susceptible sex partners (*268–270*).

Chlamydial Infections

Chlamydial Infections in Adolescents and Adults

Chlamydial genital infection is the most frequently reported infectious disease in the United States, and prevalence is highest in persons aged ≤25 years (*93*). Several important sequelae can result from *C. trachomatis* infection in women, the most serious of which include PID, ectopic pregnancy, and infertility. Some women who have uncomplicated cervical infection already have subclinical upper-reproductive–tract infection upon diagnosis.

Asymptomatic infection is common among both men and women. To detect chlamydial infections, health-care providers frequently rely on screening tests. Annual screening of all sexually active women aged ≤25 years is recommended, as is screening of older women with risk factors (e.g., those who have a new sex partner or multiple sex partners). In June 2007, USPSTF reviewed and updated their chlamydia screening guidance and found that the epidemiology of chlamydial

infection in the United States had not changed since the last review (*81,271*). In issuing recommendations, USPSTF made the decision to alter the age groups used to demonstrate disease incidence (i.e., from persons aged ≤25 years to those aged ≤24 years). CDC has not changed its age cutoff, and thus continues to recommend annual chlamydia screening of sexually active women aged ≤25 years.

Screening programs have been demonstrated to reduce both the prevalence of *C. trachomatis* infection and rates of PID in women (*272,273*). Although evidence is insufficient to recommend routine screening for *C. trachomatis* in sexually active young men because of several factors (including feasibility, efficacy, and cost-effectiveness) (*94*), the screening of sexually active young men should be considered in clinical settings with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and STD clinics). Among women, the primary focus of chlamydia screening efforts should be to detect chlamydia and prevent complications, whereas targeted chlamydia screening in men should only be considered when resources permit and do not hinder chlamydia screening efforts in women (*274 275*). An appropriate sexual risk assessment should be conducted for all persons and might indicate more frequent screening for some women or certain men (see MSM).

Diagnostic Considerations

C. trachomatis urogenital infection in women can be diagnosed by testing urine or by collecting swab specimens from the endocervix or vagina. Diagnosis of *C. trachomatis* urethral infection in men can be made by testing a urethral swab or urine specimen. Rectal *C. trachomatis* infections in persons that engage in receptive anal intercourse can be diagnosed by testing a rectal swab specimen. NAATs, cell culture, direct immunofluorescence, EIA, and nucleic acid hybridization tests are available for the detection of *C. trachomatis* on endocervical specimens and urethral swab specimens from men (*197*). NAATs are the most sensitive tests for these specimens and are FDA-cleared for use with urine. Some NAATs are cleared for use with vaginal swab specimens, which can be collected by a provider or self-collected by a patient. Self-collected vaginal swab specimens perform at least as well as with other approved specimens using NAATs (*276,277*), and women find this screening strategy highly acceptable. Rectal and oropharyngeal *C. trachomatis* infection in persons engaging in receptive anal or oral intercourse can be diagnosed by testing at the anatomic site of exposure. Most tests, including NAAT and nucleic acid hybridization tests, are not FDA-cleared for use with rectal or oropharyngeal swab specimens, and chlamydia culture is not widely available for this purpose. However, NAATs have demonstrated improved sensitivity and specificity compared with culture for the detection of *C. trachomatis* at rectal sites (*278–280*) and at oropharyngeal sites among men (*278–281*). Some laboratories have met CLIA requirements and have validated NAAT testing on rectal swab specimens for *C. trachomatis*. Recent evidence suggests that the liquid-based cytology specimens collected for Pap smears might be acceptable specimens for NAAT testing, although test sensitivity using these specimens might be lower than those resulting from the use of cervical swab specimens (*282*); regardless, certain NAATs have been FDA-cleared for use on liquid-based cytology specimens. Persons who undergo testing and are diagnosed with chlamydia should be tested for other STDs.

Treatment

Treating infected patients prevents sexual transmission of the disease, and treating all sex partners of those testing positive for chlamydia can prevent reinfection of the index patient and infection of other partners. Treating pregnant women usually prevents transmission of *C. trachomatis* to infants during birth. Chlamydia treatment should be provided promptly for all persons testing positive for infection; delays in receiving chlamydia treatment have been associated with complications (e.g., PID) in a limited proportion of chlamydia-infected subjects (*283*). Coinfection with *C. trachomatis* frequently occurs among patients who have gonococcal infection; therefore, presumptive treatment of such patients for chlamydia is appropriate (see Gonococcal Infection, Dual Therapy for Gonococcal and Chlamydial Infections). The following recommended treatment regimens and alternative regimens cure infection and usually relieve symptoms.

Recommended Regimens

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Levofloxacin 500 mg orally once daily for 7 days

OR

Ofloxacin 300 mg orally twice a day for 7 days

A meta-analysis of 12 randomized clinical trials of azithromycin versus doxycycline for the treatment of genital chlamydial infection demonstrated that the treatments were

equally efficacious, with microbial cure rates of 97% and 98%, respectively (*284*). These studies were conducted primarily in populations in which follow-up was encouraged, adherence to a 7-day regimen was effective, and culture or EIA (rather than the more sensitive NAAT) was used for determining microbiological outcome. Azithromycin should always be available to treat patients for whom compliance with multiday dosing is uncertain. The clinical significance and transmissibility of *C. trachomatis* detected at oropharyngeal sites is unclear (*285*), and the efficacy of different antibiotic regimens in resolving oropharyngeal chlamydia remains unknown.

In patients who have erratic health-care–seeking behavior, poor treatment compliance, or unpredictable follow-up, azithromycin might be more cost-effective in treating chlamydia because it enables the provision of a single-dose of directly observed therapy (*284*). Erythromycin might be less efficacious than either azithromycin or doxycycline, mainly because of the frequent occurrence of gastrointestinal side effects that can lead to noncompliance. Levofloxacin and ofloxacin are effective treatment alternatives but are more expensive and offer no advantage in the dosage regimen. Other quinolones either are not reliably effective against chlamydial infection or have not been evaluated adequately.

To maximize compliance with recommended therapies, medications for chlamydial infections should be dispensed on site, and the first dose should be directly observed. To minimize disease transmission to sex partners, persons treated for chlamydia should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen. To minimize the risk for reinfection, patients also should be instructed to abstain from sexual intercourse until all of their sex partners are treated.

Follow-Up

Except in pregnant women, test-of-cure (i.e., repeat testing 3–4 weeks after completing therapy) is not advised for persons treated with the recommended or alterative regimens, unless therapeutic compliance is in question, symptoms persist, or reinfection is suspected. Moreover, the validity of chlamydial diagnostic testing at <3 weeks after completion of therapy (to identify patients who did not respond to therapy) has not been established. False-negative results might occur in the presence of persistent infections involving limited numbers of chlamydial organisms. In addition, NAAT conducted at <3 weeks after completion of therapy in persons who were treated successfully could yield false-positive results because of the continued presence of nonviable organisms (*197*).

A high prevalence of *C. trachomatis* infection has been observed in women and men who were treated for chlamydial infection during the preceding several months (*251*,*267*,*286*–*288*). Most post-treatment infections result from reinfection caused by failure of sex partners to receive treatment or the initiation of sexual activity with a new infected partner. Repeat infections confer an elevated risk for PID and other complications. Unlike the test-of-cure, which is not recommended, repeat *C. trachomatis* testing of recently infected women or men should be a priority for providers. Chlamydia-infected women and men should be retested approximately 3 months after treatment, regardless of whether they believe that their sex partners were treated (*251*,*267*). If retesting at 3 months is not possible, clinicians should retest whenever persons next present for medical care in the 12 months following initial treatment.

Management of Sex Partners

Patients should be instructed to refer their sex partners for evaluation, testing, and treatment if they had sexual contact with the patient during the 60 days preceding onset of the patient's symptoms or chlamydia diagnosis. Although the exposure intervals defined for the identification of at-risk sex partners are based on limited evaluation, the most recent sex partner should be evaluated and treated, even if the time of the last sexual contact was >60 days before symptom onset or diagnosis.

Among heterosexual patients, if concerns exist that sex partners who are referred to evaluation and treatment will not seek these services (or if other management strategies are impractical or unsuccessful), patient delivery of antibiotic therapy to their partners can be considered (see Partner Management). Compared with standard partner referral, this approach, which involves delivering a prescription or the medication itself, has been associated with a trend toward a decrease in rates of persistent or recurrent chlamydia (*68*,*69*,*71*). Patients must also inform their partners of their infection and provide them with written materials about the importance of seeking evaluation for any symptoms suggestive of complications (e.g., testicular pain in men and pelvic or abdominal pain in women). Patient-delivered partner therapy is not routinely recommended for MSM because of a high risk for coexisting infections, especially undiagnosed HIV infection, in their partners.

Patients should be instructed to abstain from sexual intercourse until they and their sex partners have completed treatment. Abstinence should be continued until 7 days after a single-dose regimen or after completion of a multiple-dose regimen. Timely treatment of sex partners is essential for decreasing the risk for reinfecting the index patient.

Special Considerations

Pregnancy

Doxycycline, ofloxacin, and levofloxacin are contraindicated in pregnant women. However, clinical experience and published studies suggest that azithromycin is safe and effective (*289–291*). Repeat testing to document chlamydial eradication (preferably by NAAT) 3 weeks after completion of therapy with the following regimens is recommended for all pregnant women to ensure therapeutic cure, considering the severe sequelae that might occur in mothers and neonates if the infection persists. Women aged <25 years and those at increased risk for chlamydia (i.e., women who have a new or more than one sex partner) also should be retested during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant (*81*). Pregnant women diagnosed with a chlamydial infection during the first trimester should not only receive a test to document chlamydial eradication, but be retested 3 months after treatment.

Recommended Regimens

Azithromycin 1 g orally in a single dose

OR

Amoxicillin 500 mg orally three times a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days

OR

Erythromycin base 250 mg orally four times a day for 14 days

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Erythromycin ethylsuccinate 400 mg orally four times a day for 14 days

The frequent gastrointestinal side effects associated with erythromycin can result in noncompliance with the alternative regimens. Although erythromycin estolate is contraindicated during pregnancy because of drug-related hepatotoxicity, the lower dose 14-day erythromycin regimens can be considered if gastrointestinal tolerance is a concern.

HIV Infection

Patients who have chlamydial infection and also are infected with HIV should receive the same treatment regimen as those who are HIV negative.

Chlamydial Infections Among Infants

Prenatal screening and treatment of pregnant women can prevent chlamydial infection among neonates. Pregnant women aged <25 years are at high risk for infection.

C. trachomatis infection of neonates results from perinatal exposure to the mother's infected cervix. Although neonatal ocular prophylaxis with silver nitrate solution or antibiotic ointments does not prevent perinatal transmission of *C. trachomatis* from mother to infant, ocular prophylaxis with these agents does prevent gonococcal ophthalmia and therefore should be administered (see Ophthalmia Neonatorum Prophylaxis).

Initial *C. trachomatis* perinatal infection involves the mucous membranes of the eye, oropharynx, urogenital tract, and rectum, although infection might be asymptomatic in these locations. Instead, *C. trachomatis* infection in neonates is most frequently recognized by conjunctivitis that develops 5–12 days after birth. *C. trachomatis* also can cause a subacute, afebrile pneumonia with onset at ages 1–3 months. Although *C. trachomatis* has been the most frequent identifiable infectious cause of ophthalmia neonatorum, perinatal chlamydial infections (including ophthalmia and pneumonia) have occurred less frequently because of the institution of widespread prenatal screening and treatment of pregnant women.

Ophthalmia Neonatorum Caused by *C. trachomatis*

A chlamydial etiology should be considered for all infants aged ≤30 days who have conjunctivitis, especially if the mother has a history of untreated chlamydia infection.

Diagnostic Considerations

Sensitive and specific methods used to diagnose chlamydial ophthalmia in the neonate include both tissue culture and nonculture tests (e.g., direct fluorescence antibody [DFA] tests, EIA, and NAAT). Most nonculture tests are not FDA-cleared for the detection of chlamydia from conjunctival swabs, and clinical laboratories must verify the procedure according to CLIA regulations. Specimens for culture isolation and nonculture tests should be obtained from the everted eyelid using a dacron-tipped swab or the swab specified by the manufacturer's test kit, and they must contain conjunctival cells, not exudate alone. Specific diagnosis of *C. trachomatis* infection confirms the need for treatment not only for the neonate, but also for the mother and her sex partner(s). Ocular specimens from infants being evaluated for chlamydial conjunctivitis also should be tested for *N. gonorrhoeae*.

Recommended Regimen

Erythromycin base or **ethylsuccinate** 50 mg/kg/day orally divided into 4 doses daily for 14 days*,†

* An association between oral erythromycin and infantile hypertrophic pyloric stenosis (IHIS) has been reported in infants aged <6 weeks who were treated with this drug. Infants treated with erythromycin should be followed for signs and symptoms of IHPS.
† Data on use of other macrolides (e.g., azithromycin and clarithromycin) for the treatment of neonatal chlamydia infection are limited. The results of one study involving a limited number of patients suggest that a short course of azithromycin, 20 mg/kg/day orally, 1 dose daily for 3 days, might be effective (292).

Topical antibiotic therapy alone is inadequate for treatment of chlamydial infection and is unnecessary when systemic treatment is administered.

Follow-Up

Because the efficacy of erythromycin treatment is only approximately 80%, a second course of therapy might be required. Therefore, follow-up of infants is recommended to determine whether initial treatment was effective. The possibility of concomitant chlamydial pneumonia should be considered.

Management of Mothers and Their Sex Partners

The mothers of infants who have chlamydial infection and the sex partners of these women should be evaluated and treated (see Chlamydial Infection in Adolescents and Adults).

Infant Pneumonia Caused by *C. trachomatis*

Characteristic signs of chlamydial pneumonia in infants include 1) a repetitive staccato cough with tachypnea and 2) hyperinflation and bilateral diffuse infiltrates on a chest radiograph. In addition, peripheral eosinophilia (≥400 cells/mm^3) occurs frequently. Wheezing is rare, and infants are typically afebrile. Because clinical presentations differ, initial treatment and diagnostic tests should include *C. trachomatis* for all infants aged 1–3 months who are suspected of having pneumonia (especially those whose mothers have untreated chlamydial infection).

Diagnostic Considerations

Specimens for chlamydial testing should be collected from the nasopharynx. Tissue culture is the definitive standard for chlamydial pneumonia. Nonculture tests (e.g., EIA, DFA, and NAAT) can be used, although nonculture tests of nasopharyngeal specimens have a lower sensitivity and specificity than nonculture tests of ocular specimens. DFA is the only FDA-cleared test for the detection of *C. trachomatis* from nasopharyngeal specimens. Tracheal aspirates and lung biopsy specimens, if collected, should be tested for *C. trachomatis*.

Because test results for chlamydia often are not available in a timely manner, the decision to provide treatment for *C. trachomatis* pneumonia must frequently be based on clinical and radiologic findings. The results of tests for chlamydial infection assist in the management of an infant's illness and can help determine the need for treating the mother and her sex partner(s).

Recommended Regimen

Erythromycin base or **ethylsuccinate** 50 mg/kg/day orally divided into 4 doses daily for 14 days

Follow-Up

The effectiveness of erythromycin in treating pneumonia caused by *C. trachomatis* is approximately 80%; a second course of therapy might be required. Follow-up of infants is recommended to determine whether the pneumonia has resolved, although some infants with chlamydial pneumonia continue to have abnormal pulmonary function tests later in childhood.

Management of Mothers and Their Sex Partners

Mothers of infants who have chlamydia pneumonia and the sex partners of these women should be evaluated and treated according to the recommended treatment of adults for chlamydial infections (see Chlamydial Infection in Adolescents and Adults).

Infants Born to Mothers Who Have Chlamydial Infection

Infants born to mothers who have untreated chlamydia are at high risk for infection; however, prophylatic antibiotic treatment is not indicated, and the efficacy of such treatment is unknown. Infants should be monitored to ensure appropriate treatment if symptoms develop.

Chlamydial Infections Among Children

Sexual abuse must be considered a cause of chlamydial infection in preadolescent children, although perinatally transmitted *C. trachomatis* infection of the nasopharynx, urogenital tract, and rectum might persist for >1 year (see Sexual Assault or Abuse of Children).

Diagnostic Considerations

Nonculture, nonamplified probe tests for chlamydia (EIA and DFA) should not be used because of the possibility of false-positive test results. With respiratory-tract specimens, false-positive results can occur because of cross-reaction of test reagents with *C. pneumoniae*; with genital and anal specimens,

false-positive results might occur as a result of cross-reaction with fecal flora.

Recommended Regimen for Children Who Weigh <45 kg

Erythromycin base or **ethylsuccinate** 50 mg/kg/day orally divided into 4 doses daily for 14 days

Recommended Regimen for Children Who Weigh ≥45 kg but Who Are Aged <8 Years

Azithromycin 1 g orally in a single dose

Recommended Regimens for Children Aged ≥8 years

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Other Management Considerations

See Sexual Assault or Abuse of Children.

Follow-Up

Follow-up cultures are necessary to ensure that treatment has been effective.

Gonococcal Infections

Gonococcal Infections in Adolescents and Adults

In the United States, an estimated 700,000 new *N. gonorrhoeae* infections occur each year (*93*,*293*). Gonorrhea is the second most commonly reported bacterial STD. The majority of urethral infections caused by *N. gonorrhoeae* among men produce symptoms that cause them to seek curative treatment soon enough to prevent serious sequelae, but treatment might not be soon enough to prevent transmission to others. Among women, gonococcal infections might not produce recognizable symptoms until complications (e.g., PID) have occurred. PID can result in tubal scarring that can lead to infertility or ectopic pregnancy.

The prevalence of gonorrhea varies widely among communities and populations; health-care providers should consider local gonorrhea epidemiology when making screening decisions. Although widespread screening is not recommended because gonococcal infections among women are frequently asymptomatic, targeted screening of young women (i.e., those aged <25 years) at increased risk for infection is a primary component of gonorrhea control in the United States. For sexually active women, including those who are pregnant, USPSTF (*82*) recommends that clinicians provide gonorrhea screening only to those at increased risk for infection (e.g., women with previous gonorrhea infection, other STDs, new or multiple sex partners, and inconsistent condom use; those who engage in commercial sex work and drug use; women in certain demographic groups; and those living in communities with a high prevalence of disease). USPSTF does not recommend screening for gonorrhea in men and women who are at low risk for infection (*82*).

Diagnostic Considerations

Because of its high specificity (>99%) and sensitivity (>95%), a Gram stain of a male urethral specimen that demonstrates polymorphonuclear leukocytes with intracellular Gram-negative diplococci can be considered diagnostic for infection with *N. gonorrhoeae* in symptomatic men. However, because of lower sensitivity, a negative Gram stain should not be considered sufficient for ruling out infection in asymptomatic men. In addition, Gram stain of endocervical specimens, pharyngeal, or rectal specimens also are not sufficient to detect infection, and therefore are not recommended. Specific testing for *N. gonorrhoeae* is recommended because of the increased utility and availability of highly sensitive and specific testing methods and because a specific diagnosis might enhance partner notification.

Specific diagnosis of infection with *N. gonorrhoeae* can be performed by testing endocervical, vaginal, urethral (men only), or urine specimens. Culture, nucleic acid hybridization tests, and NAATs are available for the detection of genitourinary infection with *N. gonorrhoeae* (*197*). Culture and nucleic acid hybridization tests require female endocervical or male urethral swab specimens. NAATs allow testing of the widest variety of specimen types including endocervical swabs, vaginal swabs, urethral swabs (men), and urine (from both men and women), and they are FDA-cleared for use. However, product inserts for each NAAT vendor must be carefully examined, because specimen types that are FDA-cleared for use vary by test. NAAT tests are not FDA-cleared for use in the rectum, pharynx, and conjunctiva; however, some public and private laboratories have established performance specifications for using NAAT with rectal and pharyngeal swab specimens, thereby allowing results to be used for clinical management. Laboratories that establish performance specifications for the use of NAATs with nongenital specimens must ensure that specificity is not compromised by cross-reaction with nongonococcal *Neisseria* species. The sensitivity of NAATs for the detection of *N. gonorrhoeae* in genital and nongenital anatomic sites is superior to culture but varies by NAAT type (*197*,*278–281*).

Because nonculture tests cannot provide antimicrobial susceptibility results, in cases of suspected or documented

treatment failure, clinicians should perform both culture and antimicrobial susceptibility testing.

All persons found to have who have gonorrhea also should be tested for other STDs, including chlamydia, syphilis, and HIV.

Dual Therapy for Gonococcal and Chlamydial Infections

Patients infected with *N. gonorrhoeae* frequently are coinfected with *C. trachomatis*; this finding has led to the recommendation that patients treated for gonococcal infection also be treated routinely with a regimen that is effective against uncomplicated genital *C. trachomatis* infection (*294*). Because most gonococci in the United States are susceptible to doxycycline and azithromycin, routine cotreatment might also hinder the development of antimicrobial-resistant *N. gonorrhoeae*. Limited data suggest that dual treatment with azithromycin might enhance treatment efficacy for pharyngeal infection when using oral cephalosporins (*295*,*296*).

Antimicrobial-Resistant *N. gonorrhoeae*

Gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobial therapies (*297*). Quinolone-resistant *N. gonorrhoeae* strains are now widely disseminated throughout the United States and the world (*298*). As of April 2007, quinolones are no longer recommended in the United States for the treatment of gonorrhea and associated conditions, such as PID (*299*). Consequently, only one class of antimicrobials, the cephalosporins, is recommended and available for the treatment of gonorrhea in the United States. The CDC website (http://www.cdc.gov/std/gisp) and state health departments can provide the most current information.

The proportion of isolates in CDC's Gonococcal Isolate Surveillance Project (GISP) demonstrating decreased susceptibility to ceftriaxone or cefixime has remained very low over time; during 1987–2008, only four isolates were found to have decreased susceptibility to ceftriaxone, and 48 isolates had decreased susceptibility to cefixime. In 2008, no isolates demonstrated decreased susceptibility to ceftriaxone; cefixime was not part of test panel during that year (*93*). Although only two cases of suspected treatment failure with ceftriaxone have been reported (*300*), approximately 50 patients are thought to have failed oral cephalosporin treatment (*301–304*).

Most of the treatment failures resulting from use of oral cephalosporins have been reported from Asian countries, although one possible case was reported in Hawaii in 2001 (*305*). To ensure appropriate antibiotic therapy, clinicians should ask patients testing positive for gonorrhea about recent travel to and sexual activity in these countries.

Decreased susceptibility of *N. gonorrhoeae* to cephalosporins and other antimicrobials is expected to continue to spread; therefore, state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations (*297*). GISP, which samples approximately 3% of all U.S. men who have gonococcal infections, is a mainstay of surveillance. However, surveillance by clinicians also is critical. Clinicians who diagnose *N. gonorrhoeae* infection in a patient with suspected cephalosporin treatment failure should perform culture and susceptibility testing of relevant clinical specimens, consult a specialist for guidance in clinical management, and report the case to CDC through state and local public health authorities. Health departments should prioritize partner notification and contact tracing of patients with *N. gonorrhoeae* infection thought to be associated with cephalosporin treatment failure or associated with patients whose isolates demonstrate decreased susceptibility to cephalosporin.

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose

OR, IF NOT AN OPTION

Cefixime 400 mg orally in a single dose

OR

Single-dose injectible **cephalosporin** regimens

PLUS

Azithromycin 1g orally in a single dose

OR

Doxycycline 100 mg a day for 7 days

To maximize compliance with recommended therapies, medications for gonococcal infections should be dispensed on site. Ceftriaxone in a single injection of 250 mg provides sustained, high bactericidal levels in the blood. Extensive clinical experience indicates that ceftriaxone is safe and effective for the treatment of uncomplicated gonorrhea at all anatomic sites, curing 99.2% of uncomplicated urogenital and anorectal and 98.9% of pharyngeal infections in published clinical trials (*306*,*307*). A 250-mg dose of ceftriaxone is now recommended over a 125-mg dose given the 1) increasingly wide geographic distribution of isolates demonstrating decreased susceptibility to cephalosporins in vitro, 2) reports of ceftriaxone treatment failures, 3) improved efficacy of ceftriaxone 250 mg in pharyngeal infection (which is often unrecognized), and 4) the utility of having a simple and consistent recommendation for treatment regardless of the anatomic site involved.

A 400-mg oral dose of cefixime does not provide as high, nor as sustained, a bactericidal level as that provided by the 250-mg dose of ceftriaxone. In published clinical trials, the 400-mg dose cured 97.5% of uncomplicated urogenital and anorectal (95% CI = 95.4%–99.8%) and 92.3% of pharyngeal gonococcal infections (95% CI = 74.9%–99.1%) (*306*,*307*). Although cefixime can be administered orally, this advantage is offset by the limited efficacy of cefixime (as well as other oral cephalosporins) for treating gonococcal infections of the pharynx. Providers should inquire about oral sexual exposure and if reported, treat these patients with ceftriaxone because of this drug's well documented efficacy in treating pharyngeal infection.

Single-dose injectible cephalosporin regimens (other than ceftriaxone 250 mg IM) that are safe and highly effective against uncomplicated urogenital and anorectal gonococcal infections include ceftizoxime (500 mg, administered IM), cefoxitin (2 g, administered IM with probenecid 1 g orally), and cefotaxime (500 mg, administered IM). None of the injectible cephalosporins offer any advantage over ceftriaxone for urogenital infection, and efficacy for pharyngeal infection is less certain (*306*,*307*).

Alternative Regimens

Several other antimicrobials are active against *N. gonorrhoeae*, but none have substantial advantages over the recommended regimens, and they should not be used if pharyngeal infection is suspected. Some evidence suggests that cefpodoxime 400-mg orally can be considered an alternative in the treatment of uncomplicated urogenital gonorrhea; this regimen meets the minimum efficacy criteria for alternative regimens for urogenital infection (demonstrated efficacy of ≥95% in clinical trials with lower 95% CI of >90%) (*307*). In one clinical trial, cefpodoxime 400 mg orally was found to have a urogenital and rectal cure rate of 96.6% (95% CI = 93.9%), but the efficacy of cefpodoxime 400 mg orally at the pharyngeal site was poor (70.3%, 95% CI = 53.0%) (Hall, unpublished data, 2010). Gonococcal strains with decreased susceptibility to oral cephalosporins have been reported in the United States (*308*). With a cure rate of 96.5% (95% CI = 93.6%–98.3%) for urogenital and rectal infection, cefpodoxime proxetil 200 mg orally meets the criteria for an alternative regimen; however, its use is not advised because of concerns about the pharmacodynamics of cefpodoxime using this dose. Efficacy in treating pharyngeal infection with cefpodoxime 200 mg is unsatisfactory (78.9%; 95% CI = 54.5%–94%), as with cefpodoxime at the 400-mg dose.

Treatment with cefuroxime axetil 1 g orally meets the criteria for minimum efficacy as an alternative regimen for urogenital and rectal infection (95.9%; 95% CI = 94.3%–97.2%), but the pharmacodynamics of cefuroxime axetil 1 g orally are less favorable than those of cefpodoxime 400 mg, cefixime 400 mg, or ceftriaxone 125 mg (*309*). The efficacy of cefuroxime axetil 1 g orally in treating pharyngeal infection is poor (56.9%; 95% CI = 42.2%–70.7%).

Spectinomycin, which is useful in persons who cannot tolerate cephalosporins, is expensive, must be injected, and is not available in the United States (updates available at: www.cdc.gov/std/treatment) (*310*). However, it has been effective in published clinical trials, curing 98.2% of uncomplicated urogenital and anorectal gonococcal infections. Spectinomycin has poor efficacy against pharyngeal infection (51.8%; 95% CI = 38.7%–64.9%) (*306*).

Azithromycin 2 g orally is effective against uncomplicated gonococcal infection (99.2%; 95% CI = 97.3%–99.9%), but concerns over the ease with which *N. gonorrhoeae* can develop resistance to macrolides should restrict its use to limited circumstances. Although azithromycin 1 g meets alternative regimen criteria (97.6%; 95% CI = 95.7%–98.9%), it is not recommended because several studies have documented treatment failures, and concerns about possible rapid emergence of antimicrobial resistance with the 1-g dose of azithromycin are even greater than with the 2-g dose (*311*–*313*). *N. gonorrhoeae* in the United States is not adequately susceptible to penicillins, tetracyclines, and older macrolides (e.g., erythromycin) for these antimicrobials to be recommended.

Uncomplicated Gonococcal Infections of the Pharynx

Most gonococcal infections of the pharynx are asymptomatic and can be relatively common in some populations (*103*,*278*,*279*,*314*). Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites (*315*). Few antimicrobial regimens, including those involving oral cephalosporins, can reliably cure >90% of gonococcal pharyngeal infections (*306*,*307*). Providers should ask their patients about oral sexual exposure; if reported, patients should be treated with a regimen with acceptable efficacy against pharyngeal infection. Chlamydial coinfection of the pharynx is unusual; however, because coinfection at genital sites sometimes occurs, treatment for both gonorrhea and chlamydia is recommended.

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose

PLUS

Azithromycin 1g orally in a single dose

OR

Doxycycline 100 mg a day for 7 days

Follow-Up

Patients diagnosed with uncomplicated gonorrhea who are treated with any of the recommended or alternative regimens do not need a test-of-cure (i.e., repeat testing 3-4 weeks after completing therapy). Patients who have symptoms that persist after treatment should be evaluated by culture for *N. gonorrhoeae*, and any gonococci isolated should be tested for antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis also might be caused by *C. trachomatis* or other organisms.

N. gonorrhoeae infection is prevalent among patients who have been diagnosed with and treated for gonorrhea in the preceding several months (*64,251,252,267*). Most infections result from reinfection rather than treatment failure, indicating a need for improved patient education and referral of sex partners. Clinicians should advise patients with gonorrhea to be retested 3 months after treatment. If patients do not seek medical care for retesting in 3 months, providers are encouraged to test these patients whenever they next seek medical care within the following 12 months, regardless of whether the patients believe that their sex partners were treated. Retesting is distinct from test-of-cure to detect therapeutic failure, which is not recommended.

Management of Sex Partners

Effective clinical management of patients with treatable STDs requires treatment of the patients' recent sex partners to prevent reinfection and curtail further transmission. Patients should be instructed to refer their sex partners for evaluation and treatment. Sex partners of patients with *N. gonorrhoeae* infection whose last sexual contact with the patient was within 60 days before onset of symptoms or diagnosis of infection in the patient should be evaluated and treated for *N. gonorrhoeae* and *C. trachomatis* infections. If a patient's last sexual intercourse was >60 days before onset of symptoms or diagnosis, the patient's most recent sex partner should be treated. Patients should be instructed to abstain from sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms.

For heterosexual patients with gonorrhea whose partners' treatment cannot be ensured or is unlikely, delivery of antibiotic therapy for gonorrhea (as well as for chlamydia) by the patients to their partners can be considered (see Partner Management). Use of this approach (*68,71*) should always be accompanied by efforts to educate partners about symptoms and to encourage partners to seek clinical evaluation. For male patients informing female partners, educational materials should include information about the importance of seeking medical evaluation for PID (especially if symptomatic). Possible undertreatment of PID in female partners and possible missed opportunities to diagnose other STDs are of concern and have not been evaluated in comparison with patient-delivered therapy and partner referral. This approach should not be considered a routine partner management strategy in MSM because of the high risk for coexisting undiagnosed STDs or HIV infection.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Reactions to first generation cephalosporins occur in approximately 5%–10% of persons with a history of penicillin allergy and occur less frequently with third-generation cephalosporins (*239*). In those persons with a history of penicillin allergy, the use of cephalosporins should be contraindicated only in those with a history of a severe reaction to penicillin (e.g., anaphylaxis, Stevens Johnson syndrome, and toxic epidermal necrolysis) (*316*).

Because data are limited regarding alternative regimens for treating gonorrhea among persons who have severe cephalosporin allergy, providers treating such patients should consult infectious disease specialists. Azithromycin 2 g orally is effective against uncomplicated gonococcal infection, but because of concerns over emerging antimicrobial resistance to macrolides, its use should be limited. Cephalosporin treatment following desensitization is impractical in most clinical settings.

Pregnancy

As with other patients, pregnant women infected with *N. gonorrhoeae* should be treated with a recommended or alternate cephalosporin. Because spectinomycin is not available in the United States, azithromycin 2 g orally can be considered for women who cannot tolerate a cephalosporin. Either azithromycin or amoxicillin is recommended for treatment of presumptive or diagnosed *C. trachomatis* infection during pregnancy (see Chlamydial Infections).

HIV Infection

Patients who have gonococcal infection and also are infected with HIV should receive the same treatment regimen as those who are HIV negative.

Suspected Cephalosporin Treatment Failure or Resistance

Suspected treatment failure has been reported among persons receiving oral and injectable cephalosporins (*300–304*). Therefore, clinicians of patients with suspected treatment failure or persons infected with a strain found to demonstrate in vitro resistance should consult an infectious disease specialist, conduct culture and susceptibility testing of relevant clinical

specimens, retreat with at least 250 mg of ceftriaxone IM or IV, ensure partner treatment, and report the situation to CDC through state and local public health authorities.

Gonococcal Conjunctivitis

In the only published study of the treatment of gonococcal conjunctivitis among U.S. adults, all 12 study participants responded to a single 1-g IM injection of ceftriaxone (*317*).

Recommended Regimen

Ceftriaxone 1 g IM in a single dose

Consider lavage of the infected eye with saline solution once. Persons treated for gonococcal conjunctivitis should be treated presumptively for concurrent *C. trachomatis* infection.

Management of Sex Partners

Patients should be instructed to refer their sex partners for evaluation and treatment (see Gonococcal Infections, Management of Sex Partners).

Disseminated Gonococcal Infection (DGI)

DGI frequently results in petechial or pustular acral skin lesions, asymmetrical arthralgia, tenosynovitis, or septic arthritis. The infection is complicated occasionally by perihepatitis and rarely by endocarditis or meningitis. Some strains of *N. gonorrhoeae* that cause DGI can cause minimal genital inflammation. No recent studies have been published on the treatment of DGI.

Treatment

Hospitalization is recommended for initial therapy, especially for patients who might not comply with treatment, for those in whom diagnosis is uncertain, and for those who have purulent synovial effusions or other complications. Examination for clinical evidence of endocarditis and meningitis should be performed. Persons treated for DGI should be treated presumptively for concurrent *C. trachomatis* infection.

Recommended Regimen

Ceftriaxone 1 g IM or IV every 24 hours

Alternative Regimens

Cefotaxime 1 g IV every 8 hours

OR

Ceftizoxime 1 g IV every 8 hours

All of the preceding regimens should be continued for 24–48 hours after improvement begins, at which time therapy can be switched to cefixime 400 mg orally twice daily to complete at least 1 week of antimicrobial therapy. No treatment failures have been reported with the recommended regimens.

Management of Sex Partners

Gonococcal infection frequently is asymptomatic in sex partners of patients who have DGI. As with uncomplicated gonococcal infections, patients should be instructed to refer their sex partners for evaluation and treatment (see Gonococcal Infection, Management of Sex Partners).

Gonococcal Meningitis and Endocarditis

Recommended Regimen

Ceftriaxone 1–2 g IV every 12 hours

Therapy for meningitis should be continued for 10–14 days; therapy for endocarditis should be continued for at least 4 weeks. Treatment of complicated DGI should be undertaken in consultation with an infectious disease specialist.

Management of Sex Partners

Patients should be instructed to refer their sex partners for evaluation and treatment (see Gonococcal Infection, Management of Sex Partners).

Gonococcal Infections Among Infants

Gonococcal infection among infants usually is caused by exposure to infected cervical exudate at birth. It is usually an acute illness that manifests 2–5 days after birth. The prevalence of infection among infants depends on the prevalence of infection among pregnant women, whether pregnant women are screened for gonorrhea, and whether newborns receive ophthalmia prophylaxis. The most severe manifestations of *N. gonorrhoeae* infection in newborns are ophthalmia neonatorum and sepsis, which can include arthritis and meningitis. Less severe manifestations include rhinitis, vaginitis, urethritis, and reinfection at sites of fetal monitoring.

Ophthalmia Neonatorum Caused by *N. gonorrhoeae*

Although *N. gonorrhoeae* causes ophthalmia neonatorum relatively infrequently in the United States, identifying and treating this infection is especially important because ophthalmia neonatorum can result in perforation of the globe of the eye and blindness.

Diagnostic Considerations

Infants at increased risk for gonococcal ophthalmia are those who do not receive ophthalmia prophylaxis and those whose mothers have had no prenatal care or whose mothers have a history of STDs or substance abuse. Gonococcal ophthalmia is strongly suspected when intracellular gram-negative diplococci are identified in conjunctival exudate, justifying presumptive treatment for gonorrhea after appropriate cultures for *N. gonorrhoeae* are obtained. Appropriate chlamydial testing should be done simultaneously. Presumptive treatment for *N. gonorrhoeae* might be indicated for newborns who are at increased risk for gonococcal ophthalmia and who have increased WBCs (but not gonococci) in a Gram-stained smear of conjunctival exudate.

In all cases of neonatal conjunctivitis, conjunctival exudates should be cultured for *N. gonorrhoeae* and tested for antibiotic susceptibility before a definitive diagnosis is made. A definitive diagnosis is vital because of the public health and social consequences of a diagnosis of gonorrhea. Nongonococcal causes of neonatal ophthalmia include *Moraxella catarrhalis* and other *Neisseria* species, organisms that are indistinguishable from *N. gonorrhoeae* on Gram-stained smear but can be differentiated in the microbiology laboratory.

Recommended Regimen

Ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg

Topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is administered.

Other Management Considerations

Simultaneous infection with *C. trachomatis* should be considered when a patient does not improve after treatment. Both mother and infant should be tested for chlamydial infection at the same time that gonorrhea testing is conducted (see Ophthalmia Neonatorum Caused by *C. trachomatis*). Ceftriaxone should be administered cautiously to hyperbilirubinemic infants, especially those born prematurely.

Follow-Up

Infants who have gonococcal ophthalmia should be hospitalized and evaluated for signs of disseminated infection (e.g., sepsis, arthritis, and meningitis). One dose of ceftriaxone is adequate therapy for gonococcal conjunctivitis.

Management of Mothers and Their Sex Partners

The mothers of infants who have gonococcal infection and the mothers' sex partners should be evaluated and treated according to the recommendations for treating gonococcal infections in adults (see Gonococcal Infections in Adolescents and Adults).

DGI and Gonococcal Scalp Abscesses in Newborns

Sepsis, arthritis, and meningitis (or any combination of these conditions) are rare complications of neonatal gonococcal infection. Localized gonococcal infection of the scalp can result from fetal monitoring through scalp electrodes. Detection of gonococcal infection in neonates who have sepsis, arthritis, meningitis, or scalp abscesses requires cultures of blood, CSF, and joint aspirate on chocolate agar. Specimens obtained from the conjunctiva, vagina, oropharynx, and rectum that are cultured on gonococcal selective medium are useful for identifying the primary site(s) of infection, especially if inflammation is present. Positive Gram-stained smears of exudate, CSF, or joint aspirate provide a presumptive basis for initiating treatment for *N. gonorrhoeae*. Diagnoses based on Gram-stained smears or presumptive identification of cultures should be confirmed with definitive tests on culture isolates.

Recommended Regimens

Ceftriaxone 25–50 mg/kg/day IV or IM in a single daily dose for 7 days, with a duration of 10–14 days, if meningitis is documented

OR

Cefotaxime 25 mg/kg IV or IM every 12 hours for 7 days, with a duration of 10–14 days, if meningitis is documented

Prophylactic Treatment for Infants Whose Mothers Have Gonococcal Infection

Infants born to mothers who have untreated gonorrhea are at high risk for infection.

Recommended Regimen in the Absence of Signs of Gonococcal Infection

Ceftriaxone 25–50 mg/kg IV or IM, not to exceed 125 mg, in a single dose

Other Management Considerations

Both mother and infant should be tested for chlamydial infection.

Follow-Up

Follow-up examination is not required.

Management of Mothers and Their Sex Partners

The mothers of infants who have gonococcal infection and the mothers' sex partners should be evaluated and treated according to the recommendations for treatment of gonococcal infections in adults (see Gonococcal Infections).

Gonococcal Infections Among Children

Sexual abuse is the most frequent cause of gonococcal infection in preadolescent children (see Sexual Assault or Abuse of Children). For preadolescent girls, vaginitis is the most common manifestation of this infection; gonococcal-associated PID after vaginal infection is likely less common in preadolescents than adults. Among sexually abused children, anorectal and pharyngeal infections with *N. gonorrhoeae* are common and frequently asymptomatic.

Diagnostic Considerations

Because of the legal implications of a diagnosis of *N. gonorrhoeae* infection in a child, culture remains the preferred method for diagnosis. Gram stains are inadequate for evaluating prepubertal children for gonorrhea and should not be used to diagnose or exlude gonorrhea. NAATs for the detection of *N. gonorrhoeae* can be used under certain circumstances (see Sexual Assault or Abuse of Children)

Recommended Regimen for Children Who Weigh >45 kg

Treat with one of the regimens recommended for adults (see Gonococcal Infections)

Recommended Regimen for Children Who Weigh ≤45 kg and Who Have Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis

Ceftriaxone 125 mg IM in a single dose

Recommended Regimen for Children Who Weigh ≤45 kg and Who Have Bacteremia or Arthritis

Ceftriaxone 50 mg/kg (maximum dose: 1 g) IM or IV in a single dose daily for 7 days

Recommended Regimen for Children Who Weigh >45 kg and Who Have Bacteremia or Arthritis

Ceftriaxone 50 mg/kg IM or IV in a single dose daily for 7 days

Follow-Up

Follow-up cultures are unnecessary if ceftriaxone is used.

Other Management Considerations

Only parenteral cephalosporins (i.e., ceftriaxone) are recommended for use in children; cefotaxime is approved for gonococcal ophthalmia only. No data are available regarding the use of oral cefixime to treat gonococcal infections in children.

All children found to have gonococcal infections should be evaluated for coinfection with syphilis and *C. trachomatis*. (For a discussion of concerns regarding sexual assault, see Sexual Assault or Abuse of Children.)

Ophthalmia Neonatorum Prophylaxis

To prevent gonococcal ophthalmia neonatorum, a prophylactic agent should be instilled into the eyes of all newborn infants; this procedure is required by law in most states. All of the recommended prophylactic regimens in this section prevent gonococcal ophthalmia. However, the efficacy of these preparations in preventing chlamydial ophthalmia is less clear, and they do not eliminate nasopharyngeal colonization by *C. trachomatis*. The diagnosis and treatment of gonococcal and chlamydial infections in pregnant women is the best method for preventing neonatal gonococcal and chlamydial disease. Not all women, however, receive prenatal care, and therefore go untreated. Ocular prophylaxis is warranted for neonates, because it can prevent sight-threatening gonococcal ophthalmia and because it is safe, easy to administer, and inexpensive.

Recommended Regimen

Erythromycin (0.5%) ophthalmic ointment in each eye in a single application

This preparation should be instilled into both eyes of every neonate as soon as possible after delivery. Ideally, ointment should be applied using single-use tubes or ampules rather than multiple-use tubes. If prophylaxis is delayed (i.e., not administered in the delivery room), a monitoring system should be established to ensure that all infants receive prophylaxis. All infants should be administered ocular prophylaxis, regardless of whether they are delivered vaginally or by cesarean section.

Erythromycin is the only antibiotic ointment recommended for use in neonates. Silver nitrate and tetracycline ophthalmic ointment are no longer manufactured in the United States, bacitracin is not effective, and povidone iodine has not been studied adequately. If erythromycin ointment is not available, infants at risk for exposure to *N. gonorrhoeae* (especially those born to a mother with untreated gonococcal infection or who has received no prenatal care) can be administered ceftriaxone 25-50 mg/kg IV or IM, not to exceed 125 mg in a single dose.

Diseases Characterized by Vaginal Discharge

Most women will have a vaginal infection, characterized by discharge, itching, or odor, during their lifetime. With the availability of complementary and alternative therapies and over-the-counter medications for candidiasis, many symptomatic women seek these products before or in addition to an evaluation by a medical provider.

Obtaining a medical history alone has been shown to be insufficient for accurate diagnosis of vaginitis and can lead to the inappropriate administration of medication. Therefore, a careful history, examination, and laboratory testing to determine the etiology of vaginal complaints are warranted. Information on sexual behaviors and practices, gender of sex partners, menses, vaginal hygiene practices (such as douching), and other medications should be elicited. The three diseases most frequently associated with vaginal discharge are BV (caused by the replacement of the vaginal flora by an overgrowth of anaerobic bacteria including *Prevotella* sp., *Mobiluncus* sp., *G. vaginalis*, *Ureaplasma, Mycoplasma*, and numerous fastidious or uncultivated anaerobes) trichomoniasis (caused by *T. vaginalis*), and candidiasis (usually caused by *Candida albicans*). Cervicitis also can sometimes cause a vaginal discharge. Although vulvovaginal candidiasis (VVC) usually is not transmitted sexually, it is included in this section because it is frequently diagnosed in women who have vaginal complaints or who are being evaluated for STDs.

Various diagnostic methods are available to identify the etiology of an abnormal vaginal discharge. Clinical laboratory testing can identify the cause of vaginitis in most women and is discussed in detail in the sections of this report dedicated to each condition. In the clinician's office, the cause of vaginal symptoms might be determined by pH, a potassium hydroxide (KOH) test, and microscopic examination of fresh samples of the discharge. The pH of the vaginal secretions can be determined by narrow-range pH paper; an elevated pH (i.e., >4.5) is common with BV or trichomoniasis. Because pH testing is not highly specific, discharge should be further examined microscopically by first diluting one sample in one to two drops of 0.9% normal saline solution on one slide and a second sample in 10% KOH solution (samples that emit an amine odor immediately upon application of KOH suggest BV or trichomoniasis infection). Cover slips are then placed on the slides, and they are examined under a microscope at low and high power.

The saline-solution specimen might yield motile *T. vaginalis,* or clue cells (i.e., epithelial cells with borders obscured by small bacteria), which are characteristic of BV, whereas the presence of WBCs without evidence of trichomonads or yeast in this solution is suggestive of cervicitis (see Cervicitis). The KOH specimen typically is used to identify the yeast or pseudohyphae of *Candida* species. However, the absence of trichomonads or pseudohyphae in KOH samples does not rule out these infections, because the sensitivity of microscropy is approximately 50% compared with NAAT (trichomoniasis) or culture (yeast).

In settings where pH paper, KOH, and microscopy are not available, alternative commercially available point-of-care tests or clinical laboratory testing can be used to diagnose vaginitis. The presence of objective signs of vulvar inflammation in the absence of vaginal pathogens after laboratory testing, along with a minimal amount of discharge, suggests the possibility of mechanical, chemical, allergic, or other noninfectious irritation of the vulva.

Bacterial Vaginosis

BV is a polymicrobial clinical syndrome resulting from replacement of the normal hydrogen peroxide producing *Lactobacillus* sp. in the vagina with high concentrations of anaerobic bacteria (e.g., *Prevotella* sp. and *Mobiluncus* sp.), *G. vaginalis*, *Ureaplasma, Mycoplasma*, and numerous fastidious or uncultivated anaerobes. Some women experience transient vaginal microbial changes, whereas others experience them for a longer intervals of time. Among women presenting for care, BV is the most prevalent cause of vaginal discharge or malodor; however, in a nationally representative survey, most women with BV were asymptomatic (*318*).

BV is associated with having multiple male or female partners, a new sex partner, douching, lack of condom use, and lack of vaginal lactobacilli; women who have never been sexually active can also be affected. The cause of the microbial alteration that characterizes BV is not fully understood, nor is whether BV results from acquisition of a sexually transmitted pathogen. Nonetheless, women with BV are at increased risk for the acquisition of some STDs (e.g., HIV, *N. gonorrhoeae*, *C. trachomatis*, and HSV- 2), complications after gynecologic surgery, complications of pregnancy, and recurrence of BV. Treatment of male sex partners has not been beneficial in preventing the recurrence of BV.

Diagnostic Considerations

BV can be diagnosed by the use of clinical criteria (i.e., Amsel's Diagnostic Criteria) (*319*) or Gram stain. A Gram stain (considered the gold standard laboratory method for diagnosing BV) is used to determine the relative concentration of lactobacilli (i.e., long Gram-positive rods), Gram-negative and Gram-variable rods and cocci (i.e., *G. vaginalis*, *Prevotella*, *Porphyromonas*, and peptostreptococci), and curved Gram-negative rods (i.e., *Mobiluncus*) characteristic of BV. If a Gram

stain is not available, clinical criteria can be used and require three of the following symptoms or signs:

- homogeneous, thin, white discharge that smoothly coats the vaginal walls;
- presence of clue cells on microscopic examination;
- pH of vaginal fluid >4.5; or
- a fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test).

Detection of three of these criteria has been correlated with results by Gram stain (*320*). Other tests, including a DNA probe-based test for high concentrations of *G. vaginalis* (Affirm VP III, Becton Dickinson, Sparks, Maryland), a prolineaminopeptidase test card (Pip Activity TestCard, Quidel, San Diego, California), and the OSOM BVBlue test have acceptable performance characteristics compared with Gram stain. Although a card test is available for the detection of elevated pH and trimethylamine, it has low sensitivity and specificity and therefore is not recommended. PCR also has been used in research settings for the detection of a variety of organisms associated with BV, but evaluation of its clinical utility is uncertain. Detection of one organism or group of organisms might be predictive of BV by Gram stain (*321*). However, additional evaluations are needed to confirm these associations. Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. Cervical Pap tests have no clinical utility for the diagnosis of BV because of their low sensitivity.

Treatment

Treatment is recommended for women with symptoms. The established benefits of therapy in nonpregnant women are to relieve vaginal symptoms and signs of infection. Other potential benefits to treatment include reduction in the risk for acquiring *C. trachomatis* or *N. gonorrhoeae* (*322*), HIV, and other viral STDs.

Recommended Regimens

Metronidazole 500 mg orally twice a day for 7 days*

OR

Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days

OR

Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days†

* Consuming alcohol should be avoided during treatment and for 24 hours thereafter.

† Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use (refer to clindamycin product labeling for additional information).

Providers should consider patient preference, possible side-effects, drug interactions, and other coinfections when selecting a regimen. Women should be advised to refrain from intercourse or to use condoms consistently and correctly during the treatment regimen. Douching might increase the risk for relapse, and no data support the use of douching for treatment or relief of symptoms.

Alternative Regimens

Tinidazole 2 g orally once daily for 3 days

OR

Tinidazole 1 g orally once daily for 5 days

OR

Clindamycin 300 mg orally twice daily for 7 days

OR

Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days

Alternative regimens include several tinidazole regimens (*323*) or clindamycin (oral or intravaginal) (*324*). Additional regimens include metronidazole (750-mg extended release tablets once daily for 7 days), or a single dose of clindamycin intravaginal cream, although data on the performance of these alternative regimens are limited.

Several studies have evaluated the clinical and microbiologic efficacy of using intravaginal lactobacillus formulations to treat BV and restore normal flora (*325–327*). Further research efforts to determine the role of these regimens in BV treatment and prevention are ongoing.

Follow-Up

Follow-up visits are unnecessary if symptoms resolve. Because recurrence of BV is common, women should be advised to return for evaluation if symptoms recur. Detection of certain BV-associated organisms have been associated with antimicrobial resistance and might determine risk for subsequent treatment failure (*328–333*). Limited data are available regarding optimal management strategies for women with early treatment failure. Using a different treatment regimen might be an option in patients who have a recurrence; however, retreatment with the same topical regimen is another acceptable approach for treating recurrent BV during the early stages of infection (*334*). For women with multiple recurrences after completion of a recommended regimen, metronidazole gel twice weekly for 4-6 months has been shown to reduce recurrences, although this benefit might not persist when suppressive therapy is discontinued (*335*). Limited data suggest that oral nitroimidazole followed by intravaginal boric acid and suppressive metronidazole gel for those women in remission might be an option in women with recurrent BV (*336*). Monthly oral metronidazole administered with fluconazole has also been evaluated as suppressive therapy (*337*).

Management of Sex Partners

The results of clinical trials indicate that a woman's response to therapy and the likelihood of relapse or recurrence are not affected by treatment of her sex partner(s). Therefore, routine treatment of sex partners is not recommended.

Special Considerations

Allergy or Intolerance to the Recommended Therapy

Intravaginal clindamycin cream is preferred in case of allergy or intolerance to metronidazole or tinidazole. Intravaginal metronidazole gel can be considered for women who do not tolerate systemic metronidazole. Intravaginal metronidazole should not be administered to women allergic to metronidazole.

Pregnancy

Treatment is recommended for all pregnant women with symptoms. Although BV is associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm labor, preterm birth, intra-amniotic infection, and postpartum endometritis, the only established benefit of therapy for BV in pregnant women is the reduction of symptoms and signs of vaginal infection. Additional potential benefits include reducing the risk for infectious complications associated with BV during pregnancy and reducing the risk for other infections (other STDs or HIV).

Several trials have been undertaken to determine the efficacy of BV treatment among pregnant women. Two trials demonstrated that metronidazole was efficacious during pregnancy using the 250-mg regimen (*338*,*339*); however, metronidazole administered at 500 mg twice daily can be used. One trial involving a limited number of participants revealed that treatment with oral metronidazole 500 mg twice daily was equally effective as metronidazole gel, with cure rates of 70% using Amsel criteria to define cure (*340*), and a recent trial demonstrated a cure rate of 85% using Gram stain criteria after 4 weeks with oral clindamycin (*341*). Multiple studies and meta-analyses have not demonstrated an association between metronidazole use during pregnancy and teratogenic or mutagenic effects in newborns (*342*,*343*). Regardless of the antimicrobial agent used to treat pregnant women, oral therapy is preferred because of the possibility of subclinical upper-genital–tract infection.

Recommended Regimens for Pregnant Women

Metronidazole 500 mg orally twice a day for 7 days

OR

Metronidazole 250 mg orally three times a day for 7 days

OR

Clindamycin 300 mg orally twice a day for 7 days

Treatment of asymptomatic BV among pregnant women who are at high risk for preterm delivery (i.e., those with a previous preterm birth) has been evaluated by several studies, which have yielded mixed results. Seven trials have evaluated treatment of pregnant women with asymptomatic BV at high risk for preterm delivery; one showed harm (*344*), two showed no benefit (*345*,*346*), and four demonstrated benefit (*338*,*339*,*347*,*348*). Therefore, evidence is insufficient to assess the impact of screening for BV in pregnant women at high risk for preterm delivery (*85*).

Similarly, data are inconsistent regarding whether the treatment of asymptomatic pregnant women with BV who are at low risk for preterm delivery reduces adverse outcomes of pregnancy. Although USPSTF recommends against screening these women (*85*), one trial demonstrated a 40% reduction in spontaneous preterm birth among women using oral clindamycin during weeks 13–22 of gestation (*348*). Several additional trials have shown that intravaginal clindamycin given at an average gestation of later than 20 weeks did not reduce preterm birth, and in three of these trials, intravaginal clindamycin cream administered at 16–32 weeks' gestation was associated with an increase in adverse events (e.g., low birth weight and neonatal infections) in newborns (*346*,*349*–*351*). Providers should be aware that intravaginal clindamycin cream might be associated with adverse outcomes if used in the latter half of pregnancy.

HIV Infection

BV appears to recur with higher frequency in HIV-positive women (*352*). Patients who have BV and also are infected with HIV should receive the same treatment regimen as those who are HIV negative.

Trichomoniasis

Trichomoniasis is caused by the protozoan *T. vaginalis*. Some men who are infected with *T. vaginalis* might not have symptoms; others have NGU. Some women have symptoms characterized by a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation. However, many women have minimal or no symptoms. Because of the high prevalence of trichomoniasis in clinical and nonclinical settings (*64*,*92*,*353*,*354*), testing for *T. vaginalis* should be performed in women seeking care for vaginal discharge. Screening for *T. vaginalis* in women can be considered in those at high risk for infection (i.e., women who have new or multiple partners, have a history of STDs, exchange sex for payment, and use injection drugs).

Diagnosis of vaginal trichomoniasis is usually performed by microscopy of vaginal secretions, but this method has a

sensitivity of only approximately 60%–70% and requires immediate evaluation of wet preparation slide for optimal results. FDA-cleared tests for trichomoniasis in women include OSOM Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge, Massachusetts), an immunochromatographic capillary flow dipstick technology, and the Affirm VP III (Becton Dickenson, San Jose, California), a nucleic acid probe test that evaluates for *T. vaginalis*, *G. vaginalis*, and *C. albicans*. Each of these tests, which are performed on vaginal secretions, have a sensitivity of >83% and a specificity of >97%. Both tests are considered point-of-care diagnostics. The results of the OSOM Trichomonas Rapid Test are available in approximately 10 minutes, whereas results of the Affirm VP III are available within 45 minutes. Although these tests tend to be more sensitive than those requiring vaginal wet preparation, false positives might occur, especially in populations with a low prevalence of disease.

Culture is another sensitive and highly specific commercially available method of diagnosis. Among women in whom trichomoniasis is suspected but not confirmed by microscopy, vaginal secretions should be cultured for *T. vaginalis*. While the sensitivity of a Pap test for *T. vaginalis* diagnosis is poor, use of a liquid-based testing has demonstrated enhanced sensitivity; however, false-positive tests can occur, and confirmatory testing might be needed in some circumstances (*355*). An FDA-cleared PCR assay for detection of gonorrhea and chlamydial infection (Amplicor, manufactured by Roche Diagnostic Corp.) has been modified for *T. vaginalis* detection in vaginal or endocervical swabs and in urine from women and men; sensitivity ranges from 88%–97% and specificity from 98%–99% (*356*). APTIMA *T. vaginalis* Analyte Specific Reagents (ASR; manufactured by Gen-Probe, Inc.) also can detect *T. vaginalis* RNA by transcription-mediated amplification using the same instrumentation platforms available for the FDA-cleared APTIMA Combo2 assay for diagnosis of gonorrhea and chlamydial infection; published validation studies of *T. vaginalis* ASR found sensitivity ranging from 74%–98% and specificity of 87%–98% (*357*–*359*). Laboratories that use the Gen-Probe APTIMA Combo2 test for detection of *N. gonorrhoeae* and *C. trachomatis* can consider adding the *T. vaginalis* ASR to their testing armentarium, as long as the necessary CLIA verification studies have been conducted.

In men, wet preparation is not a sensitive test, and no approved point-of-care tests are available. Culture testing of urethral swab, urine, or semen is one diagnostic option; however, NAATs (i.e., PCR or transcription-mediated amplification [TMA]) have superior sensitivity for *T. vaginalis* diagnosis in men (*356*,*359*). *T. vaginalis* has not been found to infect oral sites, and rectal prevalence appears low in MSM (*360*). Therefore, oral and rectal testing for *T. vaginalis* is not recommended.

Recommended Regimens

Metronidazole 2 g orally in a single dose

OR

Tinidazole 2 g orally in a single dose

Alternative Regimen

Metronidazole 500 mg orally twice a day for 7 days*

* Patients should be advised to avoid consuming alcohol during treatment with metronidazole or tinidazole. Abstinence from alcohol use should continue for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole.

The nitroimidazoles comprise the only class of drugs useful for the oral or parenteral therapy of trichomoniasis. Of these drugs, metronidazole and tinidazole are available in the United States and are cleared by the FDA for the treatment of trichomoniasis. In randomized clinical trials, the recommended metronidazole regimens have resulted in cure rates of approximately 90%–95%, and the recommended tinidazole regimen has resulted in cure rates of approximately 86%–100%. The appropriate treatment of sex partners might increase these reported rates. Randomized controlled trials comparing single 2-g doses of metronidazole and tinidazole suggest that tinidazole is equivalent or superior to metronidazole in achieving parasitologic cure and resolution of symptoms (*361*). Treatment of patients and sex partners results in relief of symptoms, microbiologic cure, and reduction of transmission.

Metronidazole gel is considerably less efficacious for the treatment of trichomoniasis (<50%) than oral preparations of metronidazole. Topically applied antimicrobials (e.g., metronidazole gel) are unlikely to achieve therapeutic levels in the urethra or perivaginal glands; therefore, use of this gel is not recommended. Several other topically applied antimicrobials occasionally have been used for treatment of trichomoniasis; however, these preparations likely are no more effective than metronidazole gel.

Follow-Up

Because of the high rate of reinfection among patients in whom trichomoniasis was diagnosed (17% were reinfected within 3 months in one study), rescreening for *T. vaginalis* at 3 months following initial infection can be considered for sexually active women with trichomoniasis; the benefit of this approach, however, has not been fully evaluated (*64*). No data support rescreening in men diagnosed with *T. vaginalis*. While most recurrent *T. vaginalis* infections are thought to result from having sex with an untreated partner (i.e., reinfection), some

recurrent cases can be attributed to diminished susceptibility to metronidazole. Low-level metronidazole resistance has been identified in 2%–5% of cases of vaginal trichomoniasis (*362*,*363*), but high-level resistance only rarely occurs. Fortunately, infections caused by most of these organisms respond to tinidazole or higher doses of metronidazole. Tinidazole has a longer serum half-life and reaches higher levels in genitourinary tissues than metronidazole. In addition, many *T. vaginalis* isolates have lower minimal lethal concentrations (MLCs) to tinidazole than metronidazole.

If treatment failure occurs with metronidazole 2-g single dose and reinfection is excluded, the patient can be treated with metronidazole 500 mg orally twice daily for 7 days. For patients failing this regimen, treatment with tinidazole or metronidazole at 2 g orally for 5 days should be considered. If these therapies are not effective, further management should be discussed with a specialist. The consultation should ideally include determination of the susceptibility of *T. vaginalis* to metronidazole and tinidazole. Consultation and *T. vaginalis* susceptibility testing is available from CDC (telephone: 404-718-4141; website: http://www.cdc.gov/std).

Management of Sex Partners

Sex partners of patients with *T. vaginalis* should be treated. Patients should be instructed to abstain from sex until they and their sex partners are cured (i.e., when therapy has been completed and patient and partner[s] are asymptomatic). Existing data suggest that patient-delivered partner therapy might have a role in partner management for trichomoniasis; however, no one partner management intervention has shown superiority over another in reducing reinfection rates (*72*,*73*). Although no data are available to guide treatment of the male partners of women with nitroimidazole treatment failure, on the basis of expert opinion, male partners should be evaluated and treated with either tinidazole in a single dose of 2 g orally or metronidazole twice a day at 500 mg orally for 7 days.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Metronidazole and tinidazole are both nitroimidazoles. Patients with an immediate-type allergy to a nitroimidazole can be managed by metronidazole desensitization in consultation with a specialist (*364*–*366*). Topical therapy with drugs other than nitroimidazoles can be attempted, but cure rates are low (<50%).

Pregnancy

Vaginal trichomoniasis has been associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and low birth weight. However, metronidazole treatment has not been shown to reduce perinatal morbidity. Although some trials suggest the possibility of increased prematurity or low birth weight after metronidazole treatment, limitations of the studies prevent definitive conclusions regarding risks for treatment (*367*,*368*). Treatment of *T. vaginalis* might relieve symptoms of vaginal discharge in pregnant women and might prevent respiratory or genital infection of the newborn and further sexual transmission. Clinicians should counsel patients regarding the potential risks and benefits of treatment and communicate the option of therapy deferral in asymptomatic pregnant women until after 37 weeks' gestation. All symptomatic pregnant women should not only be considered for treatment regardless of pregnancy stage, but be provided careful counseling regarding condom use and the continued risk of sexual transmission.

Women can be treated with 2 g metronidazole in a single dose at any stage of pregnancy. Multiple studies and meta-analyses have not demonstrated an association between metronidazole use during pregnancy and teratogenic or mutagenic effects in infants (*342*,*343*,*369*). The safety of tinidazole in pregnant women, however, has not been well evaluated.

In lactating women who are administered metronidazole, withholding breastfeeding during treatment and for 12–24 hours after the last dose will reduce the exposure of the infant to metronidazole. For women treated with tinidazole, interruption of breastfeeding is recommended during treatment and for 3 days after the last dose.

HIV Infection

There is increasing evidence for epidemiologic and biologic interaction between HIV and *T. vaginalis* (*370*–*375*). *T. vaginalis* infection in HIV-infected women might enhance HIV transmission by increasing genital shedding of the virus (*376*,*377*), and treatment for *T. vaginalis* has been shown to reduce HIV shedding (*376*,*377*). For sexually active women who are HIV-positive, screening for trichomoniasis at entry into care with subsequent screening performed at least annually is recommended based on the reported prevalence of *T. vaginalis*, the effect of treatment at reducing vaginal HIV shedding, and the potential complications of upper-genital-tract infections among women who are left untreated (*130*,*370*–*375*). Rescreening 3 months after completion of therapy should be considered among HIV-positive women with trichomoniasis, a recommendation based on the high proportion of recurrent or persistent infection and the association between HIV and *T. vaginalis* infection (*64*,*374*,*378*).

A recent randomized clinical trial involving women coinfected with trichomoniasis and HIV demonstrated that a single dose of metronidazole 2 gm orally was not as effective as 500 mg twice daily for 7 days (*379*). Therefore, a multi-

dose treatment regimen for *T. vaginalis* can be considered in HIV-infected women.

Vulvovaginal Candidiasis

VVC usually is caused by *C. albicans*, but occasionally is caused by other *Candida* sp. or yeasts. Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge. None of these symptoms is specific for VVC. An estimated 75% of women will have at least one episode of VVC, and 40%–45% will have two or more episodes within their lifetime. On the basis of clinical presentation, microbiology, host factors, and response to therapy, VVC can be classified as either uncomplicated or complicated (Box 3). Approximately 10%–20% of women will have complicated VVC that necessitates diagnostic and therapeutic considerations.

Uncomplicated VVC

Diagnostic Considerations

A diagnosis of *Candida* vaginitis is suggested clinically by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, or thick, curdy vaginal discharge. The diagnosis can be made in a woman who has signs and symptoms of vaginitis when either 1) a wet preparation (saline, 10% KOH) or Gram stain of vaginal discharge demonstrates yeasts, hyphae, or pseudohyphae or 2) a culture or other test yields a yeast species. *Candida* vaginitis is associated with a normal vaginal pH (<4.5), and therefore, pH testing is not a useful diagnostic tool. Use of 10% KOH in wet preparations improves the visualization of yeast and mycelia by disrupting cellular material that might obscure the yeast or pseudohyphae. Examination of a wet mount with KOH preparation should be performed for all women with symptoms or signs of VVC, and women with a positive result should receive treatment. For women with negative wet mounts who are symptomatic, vaginal cultures for *Candida* should be considered. If the wet mount is negative and *Candida* cultures cannot be done, empiric treatment can be considered for symptomatic women with any sign of VVC on examination. Identifying *Candida* by culture in the absence of symptoms or signs is not an indication for treatment, because approximately 10%–20% of women harbor *Candida* sp. and other yeasts in the vagina. VVC can occur concomitantly with STDs. Most healthy women with uncomplicated VVC have no identifiable precipitating factors.

Treatment

Short-course topical formulations (i.e., single dose and regimens of 1–3 days) effectively treat uncomplicated VVC. The topically applied azole drugs are more effective than nystatin. Treatment with azoles results in relief of symptoms and negative cultures in 80%–90% of patients who complete therapy.

Recommended Regimens

Over-the-Counter Intravaginal Agents:

Butoconazole 2% cream 5 g intravaginally for 3 days
OR
Clotrimazole 1% cream 5 g intravaginally for 7–14 days
OR
Clotrimazole 2% cream 5 g intravaginally for 3 days
OR
Miconazole 2% cream 5 g intravaginally for 7 days
OR
Miconazole 4% cream 5 g intravaginally for 3 days
OR
Miconazole 100 mg vaginal suppository, one suppository for 7 days
OR
Miconazole 200 mg vaginal suppository, one suppository for 3 days
OR
Miconazole 1,200 mg vaginal suppository, one suppository for 1 day
OR
Tioconazole 6.5% ointment 5 g intravaginally in a single application

Prescription Intravaginal Agents:

Butoconazole 2% cream (single dose bioadhesive product), 5 g intravaginally for 1 day
OR
Nystatin 100,000-unit vaginal tablet, one tablet for 14 days
OR
Terconazole 0.4% cream 5 g intravaginally for 7 days
OR
Terconazole 0.8% cream 5 g intravaginally for 3 days
OR
Terconazole 80 mg vaginal suppository, one suppository for 3 days

Oral Agent:

Fluconazole 150 mg oral tablet, one tablet in single dose

The creams and suppositories in this regimen are oil-based and might weaken latex condoms and diaphragms. Patients and providers should refer to condom product labeling for further information.

Intravaginal preparations of butaconazole, clotrimazole, miconazole, and tioconazole are available over-the-counter (OTC). Women whose condition has previously been diagnosed with VVC are not necessarily more capable of diagnosing themselves; therefore, any woman whose symptoms persist after using an OTC preparation or who has a recurrence of symptoms within 2 months should be evaluated with office-based testing. Unnecessary or inappropriate use of OTC preparations is common and can lead to a delay in the treatment of other

Box 3. Classification of vulvovaginal candidiasis (VVC)

Uncomplicated VVC

- Sporadic or infrequent vulvovaginal candidiasis
  OR
- Mild-to-moderate vulvovaginal candidiasis
  OR
- Likely to be *C. albicans*
  OR
- Non-immunocompromised women

Complicated VVC

- Recurrent vulvovaginal candidiasis
  OR
- Severe vulvovaginal candidiasis
  OR
- Non-albicans candidiasis
  OR
- Women with uncontrolled diabetes, debilitation, or immunosuppression

vulvovaginitis etiologies, which can result in adverse clinical outcomes.

Follow-Up

Patients should be instructed to return for follow-up visits only if symptoms persist or recur within 2 months of onset of the initial symptoms.

Management of Sex Partners

VVC is not usually acquired through sexual intercourse; no data support the treatment of sex partners. A minority of male sex partners might have balanitis, which is characterized by erythematous areas on the glans of the penis in conjunction with pruritus or irritation. These men benefit from treatment with topical antifungal agents to relieve symptoms.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Topical agents usually cause no systemic side effects, although local burning or irritation might occur. Oral agents occasionally cause nausea, abdominal pain, and headache. Therapy with the oral azoles has been associated rarely with abnormal elevations of liver enzymes. Clinically important interactions can occur when these oral agents are administered with other drugs, including astemizole, calcium channel antagonists, cisapride, cyclosporin A, oral hypoglycemic agents, phenytoin, protease inhibitors, tacrolimus, terfenadine, theophylline, trimetrexate, rifampin, and warfarin.

Complicated VVC

Recurrent Vulvovaginal Candidiasis (RVVC)

RVVC, usually defined as four or more episodes of symptomatic VVC in 1 year, affects a small percentage of women (<5%). The pathogenesis of RVVC is poorly understood, and most women with RVVC have no apparent predisposing or underlying conditions. Vaginal cultures should be obtained from patients with RVVC to confirm the clinical diagnosis and to identify unusual species (including nonalbicans species), particularly *Candida glabrata.* Although *C. glabrata* and other nonalbicans *Candidia* species are observed in 10%–20% of patients with RVVC, *C. glabrata* does not form pseudohyphae or hyphae and is not easily recognized on microscopy. Conventional antimycotic therapies are not as effective against these species as they are against *C. albicans*.

Treatment

Each individual episode of RVVC caused by *C. albicans* responds well to short-duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., 7–14 days of topical therapy or a 100-mg, 150-mg, or 200-mg oral dose of fluconazole every third day for a total of 3 doses [day 1, 4, and 7]) to attempt mycologic remission before initiating a maintenance antifungal regimen.

Maintenance Regimens

Oral fluconazole (i.e., 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is the first line of treatment. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.

Suppressive maintenance antifungal therapies are effective in reducing RVVC. However, 30%–50% of women will have recurrent disease after maintenance therapy is discontinued. Routine treatment of sex partners is controversial. *C. albicans* azole resistance is rare in vaginal isolates, and susceptibility testing is usually not warranted for individual treatment guidance.

Severe VVC

Severe vulvovaginitis (i.e., extensive vulvar erythema, edema, excoriation, and fissure formation) is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. Either 7–14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.

Nonalbicans VVC

The optimal treatment of nonalbicans VVC remains unknown. Options include longer duration of therapy (7–14

days) with a nonfluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for 2 weeks. This regimen has clinical and mycologic eradication rates of approximately 70% (*380*). If symptoms recur, referral to a specialist is advised.

Special Considerations

Compromised Host

Women with underlying debilitating medical conditions (e.g., those with uncontrolled diabetes or those receiving corticosteroid treatment) do not respond as well to short-term therapies. Efforts to correct modifiable conditions should be made, and more prolonged (i.e., 7–14 days) conventional antimycotic treatment is necessary.

Pregnancy

VVC frequently occurs during pregnancy. Only topical azole therapies, applied for 7 days, are recommended for use among pregnant women.

HIV Infection

The incidence of VVC in HIV-infected women is unknown. Vaginal *Candida* colonization rates among HIV-infected women are higher than among those for seronegative women with similar demographic characteristics and high-risk behaviors, and the colonization rates correlate with increasing severity of immunosuppression. Symptomatic VVC is more frequent in seropositive women and similarly correlates with severity of immunodeficiency. In addition, among HIV-infected women, systemic azole exposure is associated with the isolation of nonalbicans *Candida* species from the vagina.

On the basis of available data, therapy for VVC in HIV-infected women should not differ from that for seronegative women. Although long-term prophylactic therapy with fluconazole at a dose of 200 mg weekly has been effective in reducing *C. albicans* colonization and symptomatic VVC (*381*), this regimen is not recommended for routine primary prophylaxis in HIV-infected women in the absence of recurrent VVC (*129*). Given the frequency at which RVVC occurs in the immmunocompetent healthy population, the occurrence of RVVC should not be considered an indication for HIV testing among women previously testing HIV negative. Although VVC is associated with increased HIV seroconversion in HIV-negative women and increased HIV cervicovaginal levels in HIV-positive women, the effect of treatment for VVC on HIV acquisition and transmission remains unknown.

Pelvic Inflammatory Disease

PID comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis (*382*). Sexually transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis*, are implicated in many cases; however, microorganisms that comprise the vaginal flora (e.g., anaerobes, *G. vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*) also have been associated with PID (*383*). In addition, cytomegalovirus (CMV), *M. hominis*, *U. urealyticum*, and *M. genitalium* might be associated with some cases of PID (*263*,*384–386*). All women who have acute PID should be tested for *N. gonorrhoeae* and *C. trachomatis* and should be screened for HIV infection.

Diagnostic Considerations

Acute PID is difficult to diagnose because of the wide variation in the symptoms and signs. Many women with PID have subtle or mild symptoms. Delay in diagnosis and treatment probably contributes to inflammatory sequelae in the upper reproductive tract. Laparoscopy can be used to obtain a more accurate diagnosis of salpingitis and a more complete bacteriologic diagnosis. However, this diagnostic tool frequently is not readily available, and its use is not easy to justify when symptoms are mild or vague. Moreover, laparoscopy will not detect endometritis and might not detect subtle inflammation of the fallopian tubes. Consequently, a diagnosis of PID usually is based on clinical findings.

The clinical diagnosis of acute PID is imprecise (*387*,*388*). Data indicate that a clinical diagnosis of symptomatic PID has a positive predictive value (PPV) for salpingitis of 65%–90% compared with laparoscopy. The PPV of a clinical diagnosis of acute PID depends on the epidemiologic characteristics of the population, with higher PPVs among sexually active young women (particularly adolescents), patients attending STD clinics, and those who live in other settings where the rates of gonorrhea or chlamydia are high. Regardlesss of PPV, however, in all settings, no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Combinations of diagnostic findings that improve either sensitivity (i.e., detect more women who have PID) or specificity (i.e., exclude more women who do not have PID) do so only at the expense of the other. For example, requiring two or more findings excludes more women who do not have PID but also reduces the number of women with PID who are identified.

Many episodes of PID go unrecognized. Although some cases are asymptomatic, others are not diagnosed because the patient or the health-care provider fails to recognize the

implications of mild or nonspecific symptoms or signs (e.g., abnormal bleeding, dyspareunia, and vaginal discharge). Because of the difficulty of diagnosis and the potential for damage to the reproductive health of women (even by apparently mild or subclinical PID), health-care providers should maintain a low threshold for the diagnosis of PID (*382*).

The optimal treatment regimen and long-term outcome of early treatment of women with asymptomatic or subclinical PID are unknown. The following recommendations for diagnosing PID are intended to help health-care providers recognize when PID should be suspected and when they need to obtain additional information to increase diagnostic certainty. Diagnosis and management of other common causes of lower abdominal pain (e.g., ectopic pregnancy, acute appendicitis, and functional pain) are unlikely to be impaired by initiating empiric antimicrobial therapy for PID.

Empiric treatment for PID should be initiated in sexually active young women and other women at risk for STDs if they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, and if one or more of the following minimum criteria are present on pelvic examination:

- cervical motion tenderness
  or
- uterine tenderness
  or
- adnexal tenderness.

The requirement that all three minimum criteria be present before the initiation of empiric treatment could result in insufficient sensitivity for the diagnosis of PID. The presence of signs of lower-genital–tract inflammation (predominance of leukocytes in vaginal secretions, cervical exudates, or cervical friability), in addition to one of the three minimum criteria, increases the specificity of the diagnosis. Upon deciding whether to initiate empiric treatment, clinicians should also consider the risk profile of the patient for STDs.

More elaborate diagnostic evaluation frequently is needed because incorrect diagnosis and management of PID might cause unnecessary morbidity. One or more of the following additional criteria can be used to enhance the specificity of the minimum criteria and support a diagnosis of PID:

- oral temperature >101° F (>38.3° C);
- abnormal cervical or vaginal mucopurulent discharge;
- presence of abundant numbers of WBC on saline microscopy of vaginal fluid;
- elevated erythrocyte sedimentation rate;
- elevated C-reactive protein; and
- laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*.

Most women with PID have either mucopurulent cervical discharge or evidence of WBCs on a microscopic evaluation of a saline preparation of vaginal fluid (i.e., wet prep). If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely, and alternative causes of pain should be considered. A wet prep of vaginal fluid offers the ability to detect the presence of concomitant infections (e.g., BV and trichomoniasis).

The most specific criteria for diagnosing PID include:

- endometrial biopsy with histopathologic evidence of endometritis;
- transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia); or
- laparoscopic abnormalities consistent with PID.

A diagnostic evaluation that includes some of these more extensive procedures might be warranted in some cases. Endometrial biopsy is warranted in women undergoing laparoscopy who do not have visual evidence of salpingitis, because endometritis is the only sign of PID for some women.

Treatment

PID treatment regimens must provide empiric, broad spectrum coverage of likely pathogens. Several antimicrobial regimens have been effective in achieving clinical and microbiologic cure in randomized clinical trials with short-term follow-up. However, only a limited number of investigations have assessed and compared these regimens with regard to elimination of infection in the endometrium and fallopian tubes or determined the incidence of long-term complications (e.g., tubal infertility and ectopic pregnancy) after antimicrobial regimens (*389–391*).

All regimens used to treat PID should also be effective against *N. gonorrhoeae* and *C. trachomatis* because negative endocervical screening for these organisms does not rule out upper-reproductive-tract infection. The need to eradicate anaerobes from women who have PID has not been determined definitively. Anaerobic bacteria have been isolated from the upper-reproductive tract of women who have PID, and data from in vitro studies have revealed that some anaerobes (e.g., *Bacteroides fragilis*) can cause tubal and epithelial destruction. BV also is present in many women who have PID (*383*,*391*). Until treatment regimens that do not adequately cover these microbes have been demonstrated to prevent long-term sequelae (e.g., infertility and ectopic pregnancy) as successfully as

the regimens that are effective against these microbes, the use of regimens with anaerobic activity should be considered. Treatment should be initiated as soon as the presumptive diagnosis has been made because prevention of long-term sequelae is dependent on early administration of appropriate antibiotics. When selecting a treatment regimen, health-care providers should consider availability, cost, patient acceptance, and antimicrobial susceptibility (*392*).

In women with PID of mild or moderate clinical severity, outpatient therapy yields short- and long-term clinical outcomes similar to inpatient therapy. The decision of whether hospitalization is necessary should be based on the judgment of the provider and whether the patient meets any of the following suggested criteria:

- surgical emergencies (e.g., appendicitis) cannot be excluded;
- the patient is pregnant;
- the patient does not respond clinically to oral antimicrobial therapy;
- the patient is unable to follow or tolerate an outpatient oral regimen;
- the patient has severe illness, nausea and vomiting, or high fever; or
- the patient has a tubo-ovarian abscess.

No evidence is available to suggest that adolescents benefit from hospitalization for treatment of PID. The decision to hospitalize adolescents with acute PID should be based on the same criteria used for older women. Younger women with mild-to-moderate acute PID have similar outcomes with either outpatient or inpatient therapy, and clinical response to outpatient treatment is similar among younger and older women.

Parenteral Treatment

For women with PID of mild or moderate severity, parenteral and oral therapies appear to have similar clinical efficacy. Many randomized trials have demonstrated the efficacy of both parenteral and oral regimens (*390*,*391*,*393*). Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24–48 hours of clinical improvement. In women with tubo-ovarian abscesses, at least 24 hours of direct inpatient observation is recommended.

Recommended Parenteral Regimen A

Cefotetan 2 g IV every 12 hours

OR

Cefoxitin 2 g IV every 6 hours

PLUS

Doxycycline 100 mg orally or IV every 12 hours

Because of the pain associated with intravenous infusion, doxycycline should be administered orally when possible. Oral and IV administration of doxycycline provide similar bioavailability.

Parenteral therapy can be discontinued 24 hours after clinical improvement, but oral therapy with doxycycline (100 mg twice a day) should continue to complete 14 days of therapy. When tubo-ovarian abscess is present, clindamycin or metronidazole with doxycycline can be used for continued therapy rather than doxycycline alone because this regimen provides more effective anaerobic coverage.

Limited data are available to support the use of other second- or third-generation cephalosporins (e.g., ceftizoxime, cefotaxime, and ceftriaxone), which also might be effective therapy for PID and could potentially replace cefotetan or cefoxitin. However, these cephalosporins are less active than cefotetan or cefoxitin against anaerobic bacteria.

Recommended Parenteral Regimen B

Clindamycin 900 mg IV every 8 hours

PLUS

Gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted.

Although use of a single daily dose of gentamicin has not been evaluated for the treatment of PID, it is efficacious in analogous situations. Parenteral therapy can be discontinued 24 hours after clinical improvement; ongoing oral therapy should consist of doxycycline 100 mg orally twice a day, or clindamycin 450 mg orally four times a day to complete a total of 14 days of therapy. When tubo-ovarian abscess is present, clindamycin should be continued rather than doxycycline, because clindamycin provides more effective anaerobic coverage.

Alternative Parenteral Regimens

Limited data are available to support the use of other parenteral regimens. The following regimen has been investigated in at least one clinical trial and has broad-spectrum coverage (*394*).

Alternative Parenteral Regimens

Ampicillin/Sulbactam 3 g IV every 6 hours

PLUS

Doxycycline 100 mg orally or IV every 12 hours

Ampicillin/sulbactam plus doxycycline is effective against *C. trachomatis*, *N. gonorrhoeae*, and anaerobes in women with tubo-ovarian abscess. One trial demonstrated high short-term clinical cure rates with azithromycin, either as monotherapy

for 1 week (500 mg IV for 1 or 2 doses followed by 250 mg orally for 5–6 days) or combined with a 12-day course of metronidazole (*395*).

Oral Treatment

Outpatient, oral therapy can be considered for women with mild-to-moderately severe acute PID, because the clinical outcomes among women treated with oral therapy are similar to those treated with parenteral therapy (*390*). The following regimens provide coverage against the frequent etiologic agents of PID. Patients who do not respond to oral therapy within 72 hours should be reevaluated to confirm the diagnosis and should be administered parenteral therapy on either an outpatient or inpatient basis.

Recommended Regimen
Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Cefoxitin 2 g IM in a single dose and **Probenecid**, 1 g orally administered concurrently in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

The optimal choice of a cephalosporin is unclear; although cefoxitin has better anaerobic coverage, ceftriaxone has better coverage against *N. gonorrhoeae*. A single dose of cefoxitin is effective in obtaining short-term clinical response in women who have PID. However, the theoretical limitations in coverage of anaerobes by recommended cephalosporin antimicrobials might require the addition of metronidazole to the treatment regimen (*393*). Adding metronidazole also will effectively treat BV, which is frequently associated with PID. No data have been published regarding the use of oral cephalosporins for the treatment of PID.

Alternative Oral Regimens

Although information regarding other outpatient regimens is limited, other regimens have undergone at least one clinical trial and have demonstrated broad spectrum coverage. In a single clinical trial, amoxicillin/clavulanic acid and doxycycline were effective together in obtaining short-term clinical response (*394*); however, gastrointestinal symptoms might limit compliance with this regimen. Azithromycin has demonstrated short-term effectiveness in one randomized trial (*395*), and in another study, it was effective when used combination with ceftriaxone 250 mg IM single dose and azithromycin 1 g orally once a week for 2 weeks (*396*). When considering alternative regimens, the addition of metronidazole should be considered because anaerobic organisms are suspected in the etiology of PID and metronidazole will also treat BV.

As a result of the emergence of quinolone-resistant *Neisseria gonorrhoeae*, regimens that include a quinolone agent are no longer recommended for the treatment of PID. If parenteral cephalosporin therapy is not feasible, use of fluoroquinolones (levofloxacin 500 mg orally once daily or ofloxacin 400 mg twice daily for 14 days) with or without metronidazole (500 mg orally twice daily for 14 days) can be considered if the community prevalence and individual risk for gonorrhea are low. Diagnostic tests for gonorrhea must be performed before instituting therapy and the patient managed as follows if the test is positive.

- If the culture for gonorrhea is positive, treatment should be based on results of antimicrobial susceptibility.
- If the isolate is determined to be quinolone-resistant *N. gonorrhoeae* (QRNG) or if antimicrobial susceptibility cannot be assessed (e.g., if only NAAT testing is available), parenteral cephalosporin is recommended. However, if cephalosporin therapy is not feasible, the addition of azithromycin 2 g orally as a single dose to a quinolone-based PID regimen is recommended.

Follow-Up

Patients should demonstrate substantial clinical improvement (e.g., defervescence; reduction in direct or rebound abdominal tenderness; and reduction in uterine, adnexal, and cervical motion tenderness) within 3 days after initiation of therapy. Patients who do not improve within this period usually require hospitalization, additional diagnostic tests, and surgical intervention.

If no clinical improvement has occurred within 72 hours after outpatient oral or parenteral therapy, further assessment should be performed. Subsequent hospitalization and an assessment of the antimicrobial regimen and diagnostics (including the consideration of diagnostic laparoscopy for alternative diagnoses) are recommended in women without clinical improvement. Women with documented chlamydial or gonococcal infections have a high rate of reinfection within

6 months of treatment. Repeat testing of all women who have been diagnosed with chlamydia or gonorrhea is recommended 3–6 months after treatment, regardless of whether their sex partners were treated (*267*). All women diagnosed with acute PID should be offered HIV testing.

Management of Sex Partners

Male sex partners of women with PID should be examined and treated if they had sexual contact with the patient during the 60 days preceding the patient's onset of symptoms. If a patient's last sexual intercourse was >60 days before onset of symptoms or diagnosis, the patient's most recent sex partner should be treated. Patients should be instructed to abstain from sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms. Evaluation and treatment are imperative because of the risk for reinfection of the patient and the strong likelihood of urethral gonococcal or chlamydial infection in the sex partner. Male partners of women who have PID caused by *C. trachomatis* and/or *N. gonorrhoeae* frequently are asymptomatic.

Sex partners should be treated empirically with regimens effective against both of these infections, regardless of the etiology of PID or pathogens isolated from the infected woman. Even in clinical settings in which only women are treated, arrangements should be made to provide care or appropriate referral for male sex partners of women who have PID (see Partner Management). Expedited partner treatment and enhanced patient referral (see Partner Management) are alternative approaches to treating male partners of women who have chlamydia or gonococcal infections (*68*,*69*).

Prevention

Screening and treating sexually active women for chlamydia reduces their risk for PID (*272*). Although BV is associated with PID, whether the incidence of PID can be reduced by identifying and treating women with BV is unclear (*383*,*391*).

Special Considerations

Pregnancy

Because of the high risk for maternal morbidity and preterm delivery, pregnant women who have suspected PID should be hospitalized and treated with parenteral antibiotics.

HIV Infection

Differences in the clinical manifestations of PID between HIV-infected women and HIV-negative women have not been well delineated. In previous observational studies, HIV-infected women with PID were more likely to require surgical intervention; more comprehensive observational and controlled studies now have demonstrated that HIV-infected women with PID have similar symptoms when compared with uninfected controls (*397*–*399*), except they were more likely to have a tubo-ovarian abscess; both groups of women responded equally well to standard parenteral and oral antibiotic regimens. The microbiologic findings for HIV-positive and HIV-negative women were similar, except HIV-infected women had higher rates of concomitant *M. hominis*, candida, streptococcal, and HPV infections and HPV-related cytologic abnormalities. Regardlesss of these data, whether the management of immunodeficient HIV-infected women with PID requires more aggressive interventions (e.g., hospitalization or parenteral antimicrobial regimens) has not been determined.

Intrauterine Contraceptive Devices

IUDs are popular contraceptive choices for women. Both levonorgestrel and copper-containing devices are marketed in the United States. The risk for PID associated with IUD use is primarily confined to the first 3 weeks after insertion and is uncommon thereafter (*400*,*401*). Given the popularity of IUDs, practitioners might encounter PID in IUD users. Evidence is insufficient to recommend that the removal of IUDs in women diagnosed with acute PID. However, caution should be exercised if the IUD remains in place, and close clinical follow-up is mandatory. The rate of treatment failure and recurrent PID in women continuing to use an IUD is unknown, and no data have been collected regarding treatment outcomes by type of IUD (e.g., copper or levonorgestrel).

Epididymitis

Acute epididymitis is a clinical syndrome consisting of pain, swelling, and inflammation of the epididymis that lasts <6 weeks (*402*). Chronic epididymitis is characterized by a ≥6 week history of symptoms of discomfort and/or pain in the scrotum, testicle, or epididymis. In most cases of acute epididymitis, the testis is also involved in the process — a condition referred to as epididymo-orchitis. Chronic epididymitis has been subcategorized into inflammatory chronic epididymitis, obstructive chronic epididymitis, and chronic epididymalgia (*403*).

Among sexually active men aged <35 years, acute epididymitis is most frequently caused by *C. trachomatis* or *N. gonorrhoeae*. Acute epididymitis caused by sexually transmitted enteric organisms (e.g., *Escherichia coli* and *Pseudomonas* spp.) also occurs among men who are the insertive partner during anal intercourse. Sexually transmitted acute epididymitis usually is accompanied by urethritis, which frequently is asymptomatic.

In men aged >35 years, sexually transmitted epididymitis is uncommon, whereas bacteriuria secondary to obstructive urinary disease (e.g., benign prostatic hyperplasia) is more common. In this older population, nonsexually transmitted epididymitis is associated with urinary tract instrumentation or surgery, systemic disease, and immunosuppression.

Chronic infectious epididymitis is most frequently seen in conditions associated with granulomatous reaction; *Mycobacterium tuberculosis* (TB) is the most common granulomatous disease affecting the epididymis. Up to 25% of patients can have bilateral disease, with ultrasound demonstrating an enlarged hyperemic epididymis with multiple cysts and calcifications. Tuberculous epididymitis should be suspected in all patients with a known history of or recent exposure to TB or in patients whose clinical status worsens despite appropriate antibiotic treatment.

Diagnostic Considerations

Men who have acute epididymitis typically have unilateral testicular pain and tenderness; hydrocele and palpable swelling of the epididymis usually are present. Although the inflammation and swelling usually begin in the tail of the epididymis, they can spread to involve the rest of the epididymis and testicle. The spermatic cord is usually tender and swollen. Testicular torsion, a surgical emergency, should be considered in all cases, but it occurs more frequently among adolescents and in men without evidence of inflammation or infection. Emergency testing for torsion might be indicated when the onset of pain is sudden, pain is severe, or the test results available during the initial examination do not support a diagnosis of urethritis or urinary-tract infection. If the diagnosis is questionable, a urologist should be consulted immediately because testicular viability might be compromised. Radionuclide scanning of the scrotum is the most accurate radiologic method of diagnosis, but it is not routinely available. Although ultrasound is primarily used for ruling out torsion of the spermatic cord in cases of acute scrotum swelling, it will often demonstrate epididymal hyperemia and swelling in men with epididymitis. However, differentiation between testicular torsion and epididymitis must be made on the basis of clinical evaluation, because partial spermatic cord torsion can mimic epididymitis on scrotal ultrasound. Ultrasound provides minimal utility for men with a clinical presentation consistent with epididymitis; a negative ultrasound does not alter physician management of clinical epididymitis. Ultrasound, therefore, should be reserved for patients with scrotal pain who cannot be diagnosed accurately by physical examination, history, and objective laboratory findings.

The evaluation of men for epididymitis should include one of the following:

- Gram stain of urethral secretions demonstrating ≥5 WBC per oil immersion field. Gram stain is the preferred rapid diagnostic test for evaluating urethritis because it is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC containing intracellular Gram-negative diplococci on urethral Gram stain.
- Positive leukocyte esterase test on first-void urine or microscopic examination of first-void urine sediment demonstrating ≥10 WBC per high power field.

Culture, nucleic acid hybridization tests, and NAATs are available for the detection of both *N. gonorrhoeae* and *C. trachomatis*. Culture and nucleic acid hybridization tests require urethral swab specimens, whereas amplification tests can be performed on urine or urethral specimens. Because of their higher sensitivity, amplification tests are preferred for the detection of *C. trachomatis*. Depending on the risk, patients whose conditions are associated with acquiring an STD should receive testing for other STDs.

Treatment

Empiric therapy is indicated before laboratory test results are available. The goals of treatment of acute epididymitis caused by *C. trachomatis* or *N. gonorrhoeae* are 1) microbiologic cure of infection, 2) improvement of signs and symptoms, 3) prevention of transmission to others, and 4) a decrease in potential complications (e.g., infertility or chronic pain). As an adjunct to therapy, bed rest, scrotal elevation, and analgesics are recommended until fever and local inflammation have subsided. Because empiric therapy is often initiated before laboratory tests are available, all patients should receive ceftriaxone plus doxycycline for the initial therapy of epididymitis. Additional therapy can include a fluoroquinolone if acute epididymitis is not found to be caused by gonorrhea by NAAT or if the infection is most likely caused by enteric organisms. For men who are at risk for both sexually transmitted and enteric organisms (e.g., MSM who report insertive anal intercourse), ceftriaxone with a fluoroquinolone are recommended.

Recommended Regimens
Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 10 days
For acute epididymitis most likely caused by enteric organisms
Levofloxacin 500 mg orally once daily for 10 days
OR
Ofloxacin 300 mg orally twice a day for 10 days

Although most patients can be treated on an out-patient basis, hospitalization should be considered when severe pain suggests other diagnoses (e.g., torsion, testicular infarction, or abscess) or when patients are unable or unlikely to comply with an antimicrobial regimen. Because high fever is uncommon and indicates a complicated infection, these patients should be admitted for further evaluation.

Follow-Up

Patients should be instructed to return to their health-care providers if their symptoms fail to improve within 48 hours of the initiation of treatment. Signs and symptoms of epididymitis that do not subside within 3 days requires re-evaluation of the diagnosis and therapy. Swelling and tenderness that persist after completion of antimicrobial therapy should be evaluated comprehensively. Differential diagnoses include tumor, abscess, infarction, testicular cancer, TB, and fungal epididymitis.

Management of Sex Partners

Patients who have acute epididymitis that is confirmed or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be instructed to refer sex partners for evaluation and treatment if their contact with the index patient was within the 60 days preceding onset of their own symptoms.

Patients should be instructed to abstain from sexual intercourse until they and their sex partners have been adequately treated (i.e., until therapy is completed and patient and partners no longer have symptoms).

Special Considerations

HIV Infection

Patients who have uncomplicated acute epididymitis and also are infected with HIV should receive the same treatment regimen as those who are HIV negative. Other etiologic agents have been implicated in acute epididymitis in HIV infection including CMV, salmonella, toxoplasmosis, *Ureaplasma urealyticum*, *Corynebacterium* sp., *Mycoplasma* sp., *and Mima polymorpha*. Fungi and mycobacteria are also more likely to cause acute epididymitis in immunosuppressed men than in immunocompetent men.

Human Papillomavirus (HPV) Infection

More than 100 types of HPV exist, more than 40 of which can infect the genital area. Most HPV infections are asymptomatic, unrecognized, or subclinical. Oncogenic, or high-risk HPV types (e.g., HPV types 16 and 18), are the cause of cervical cancers. These HPV types are also associated with other anogenital cancers in men and women, including penile, vulvar, vaginal, and anal cancer, as well a subset of oropharyngeal cancers (*404*). Nononcogenic, or low-risk HPV types (e.g., HPV types 6 and 11), are the cause of genital warts and recurrent respiratory papillomatosis. Asymptomatic genital HPV infection is common and usually self-limited; it is estimated that more than 50% of sexually active persons become infected at least once in their lifetime (*405*). Persistent oncogenic HPV infection is the strongest risk factor for development of precancers and cancers.

HPV Tests

HPV tests are available for women aged >30 years undergoing cervical cancer screening. These tests should not be used for men, for women <20 years of age, or as a general test for STDs. These HPV tests detect viral nucleic acid (i.e., DNA or RNA) or capsid protein. Four tests have been approved by the FDA for use in the United States: the HC II High-Risk HPV test (Qiagen), HC II Low-Risk HPV test (Qiagen), Cervista HPV 16/18 test, and Cervista HPV High-Risk test (Hologics).

Treatment

Treatment is directed to the macroscopic (i.e., genital warts) or pathologic (i.e, precancerous) lesions caused by infection. Subclinical genital HPV infection typically clears spontaneously, and therefore specific antiviral therapy is not recommended to eradicate HPV infection. In the absence of lesions, treatment is not recommended for subclinical genital HPV infection whether it is diagnosed by colposcopy, acetic acid application, or by laboratory tests for HPV DNA. Treatment also is not recommended for cervical intraepithelial neoplasia 1 (CIN1).

Prevention

Two HPV vaccines are licensed in the United States: a bivalent vaccine (Cervarix) containing HPV types 16 and 18 and a quadrivalent vaccine (Gardasil) vaccine containing HPV types 6, 11, 16, and 18. Both vaccines offer protection against the HPV types that cause 70% of cervical cancers (i.e., types 16 and 18), and the quadrivalent HPV vaccine also protects against the types that cause 90% of genital warts (i.e., types 6 and 11). Either vaccine can be administered to girls aged 11–12 years and can be administered to those as young as 9 years of age (*15*,*16*); girls and women ages 13–26 years who have not started or completed the vaccine series also should receive the vaccine. HPV vaccine is indicated for girls in this

age group, because benefit is greatest if it is administered before the onset of sexual activity. The quadrivalent (Gardasil) HPV vaccine can also be used in males aged 9–26 years to prevent genital warts (*17*). Administering the vaccine to boys before the onset of sexual activity is optimal. Both HPV vaccines are administered as a 3-dose series of IM injections over a 6-month period, with the second and third doses given 1–2 and then 6 months after the first dose. Ideally, the same vaccine product should be used for the entire 3-dose series. HPV vaccine is available for eligible children and adolescents aged <19 years through the Vaccines for Children (VFC) program (available by calling CDC INFO [800-232-4636]).

Women who have received HPV vaccine should continue routine cervical cancer screening because 30% of cervical cancers are caused by HPV types other than 16 or 18. In the United States, the vaccines are not licensed or recommended for use in women >26 years of age. No published data are available on the effectiveness, programmatic requirements, or cost-effectiveness of administering the HPV vaccine in STD clinic settings.

Genital Warts

Of genital warts, 90% are caused by HPV 6 or 11. HPV types 6 or 11 are commonly found before, or at the time of, detection of genital warts (*406*). HPV types 16, 18, 31, 33, and 35 are found occasionally in visible genital warts (usually as coinfections with HPV 6 or 11) and can be associated with foci of high-grade intraepithelial neoplasia, particularly in persons who are infected with HIV infection. In addition to warts on genital areas, HPV types 6 and 11 have been associated with conjunctival, nasal, oral, and laryngeal warts.

Genital warts are usually asymptomatic, but depending on the size and anatomic location, they can be painful or pruritic. Genital warts are usually flat, papular, or pedunculated growths on the genital mucosa. Genital warts occur commonly at certain anatomic sites, including around the introitus in women, under the foreskin of the uncircumcised penis, and on the shaft of the circumcised penis. Genital warts can also occur at multiple sites in the anogenital epithelium or within the anogenital tract (e.g., cervix, vagina, urethra, perineum, perianal skin, and scrotum). Intra-anal warts are observed predominantly in persons who have had receptive anal intercourse, but they can also occur in men and women who do not have a history of anal sexual contact.

Diagnosis of genital warts is usually clinical, made by visual inspection. Genital warts can be confirmed by biopsy, which might be indicated if 1) the diagnosis is uncertain; 2) the lesions do not respond to standard therapy; 3) the disease worsens during therapy; 4) the lesion is atypical; 5) the patient has comprised immunity; or 6) the warts are pigmented, indurated, fixed, bleeding, or ulcerated. Genital warts are usually asymptomatic, but depending on the size and anatomic location, they might be painful or pruritic. The use of HPV DNA testing for genital wart diagnosis is not recommended, because test results would not alter clinical management of the condition.

The application of 3%–5% acetic acid, which causes skin color to turn white, has been used by some providers to detect HPV-infected genital mucosa. However, acetic acid application is not a specific test for HPV infection. Therefore, the routine use of this procedure for screening to detect mucosal changes attributed to HPV infection is not recommended.

Treatment

The primary reason for treating genital warts is the amelioration of symptoms (including relieving cosmetic concerns) and ultimately, removal of the warts. In most patients, treatment can induce wart-free periods. If left untreated, visible genital warts can resolve on their own, remain unchanged, or increase in size or number. Available therapies for genital warts likely reduce, but probably do not eradicate, HPV infectivity. Whether the reduction in HPV viral DNA resulting from treatment reduces future transmission remains unclear. No evidence indicates that the presence of genital warts or their treatment is associated with the development of cervical cancer.

Regimens

Treatment of genital warts should be guided by the preference of the patient, available resources, and the experience of the health-care provider. No definitive evidence suggests that any of the available treatments are superior to any other, and no single treatment is ideal for all patients or all warts. The use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes and should be encouraged. Because of uncertainty regarding the effect of treatment on future transmission of HPV and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.

Factors that influence selection of treatment include wart size, wart number, anatomic site of the wart, wart morphology, patient preference, cost of treatment, convenience, adverse effects, and provider experience. Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy, which can consist of either a single treatment or complete course of treatment. In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. The treatment modality

should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. Most genital warts respond within 3 months of therapy. The response to treatment and any side effects should be evaluated throughout the course of therapy.

Complications occur rarely when treatment is administered properly. Patients should be warned that persistent hypopigmentation or hyperpigmentation occurs commonly with ablative modalities and has also been described with immune modulating therapies (imiquimod). Depressed or hypertrophic scars are uncommon but can occur, especially if the patient has had insufficient time to heal between treatments. Rarely, treatment can result in disabling chronic pain syndromes (e.g., vulvodynia and hyperesthesia of the treatment site) or, in the case of anal warts, painful defecation or fistulas. A limited number of case reports of severe systemic effects resulting from treatment with podophyllin resin and interferon have been documented.

Treatment regimens are classified into patient-applied and provider-applied modalities. Patient-applied modalities are preferred by some patients because they can be administered in the privacy of the patient's home. To ensure that patient-applied modalities are effective, patients must comply with the treatment regimen and must be capable of identifying and reaching all genital warts. Follow-up visits are not required for persons using patient-applied therapy. However, follow-up visits after several weeks of therapy enable providers to answer any questions patients might have about the use of the medication and any side effects they have experienced; follow-up visits also facilitate the assessment of a patient's response to treatment.

Recommended Regimens for External Genital Warts

Patient-Applied:

Podofilox 0.5% solution or gel

OR

Imiquimod 5% cream

OR

Sinecatechins 15% ointment

Provider–Administered:

Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1–2 weeks.

OR

Podophyllin resin 10%–25% in a compound tincture of benzoin

OR

Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90%

OR

Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery.

Podofilox is an antimitotic drug that destroys warts, is relatively inexpensive, easy to use, safe, and self-applied. Podofilox solution should be applied with a cotton swab, or podofilox gel with a finger, to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm^2, and the total volume of podofilox should be limited to 0.5 mL per day. If possible, the health-care provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated. Mild to moderate pain or local irritation might develop after treatment. The safety of podofilox during pregnancy has not been established.

Imiquimod is a topically active immune enhancer that stimulates production of interferon and other cytokines. Imiquimod cream should be applied once daily at bedtime, three times a week for up to 16 weeks (*407*). The treatment area should be washed with soap and water 6–10 hours after the application. Local inflammatory reactions, including redness, irritation, induration, ulceration/erosions, and vesicles, are common with the use of imiquimod, and hypopigmentation has also been described (*408*). Imiquimod might weaken condoms and vaginal diaphragms. The safety of imiquimod during pregnancy has not been established.

Sinecatechin ointment, a green-tea extract with an active product (catechins), should be applied three times daily (0.5-cm strand of ointment to each wart) using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts. This product should not be continued for longer than 16 weeks (*409–411*). The medication should not be washed off after use. Sexual (i.e., genital, anal, or oral) contact should be avoided while the ointment is on the skin. The most common side effects of sinecatechins 15% are erythema, pruritis/burning, pain, ulceration, edema, induration, and vesicular rash. This medication may weaken condoms and diaphragms. No clinical data are available regarding the efficacy or safety of sinecatechins compared with other available anogenital wart treatment modalities. The medication is not recommended for HIV-infected persons, immunocompromised persons, or persons with clinical genital herpes because the safety and efficacy of therapy in these settings has not been established. The safety of sinecatechins during pregnancy also is unknown.

Cryotherapy destroys warts by thermal-induced cytolysis. Health-care providers must be trained on the proper use of this therapy because over- and undertreatment can result in complications or low efficacy. Pain after application of the liquid nitrogen, followed by necrosis and sometimes blistering, is common. Local anesthesia (topical or injected) might facilitate therapy if warts are present in many areas or if the area of warts is large.

Pedophyllin resin 10%–25% should be applied to each wart and allowed to air-dry before the treated area comes into contact with clothing; overapplication or failure to air dry can result in local irritation caused by spread of the compound to adjacent areas. The treatment can be repeated weekly, if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, two guidelines should be followed: 1) application should be limited to <0.5 mL of podophyllin or an area of <10 cm^2 of warts per session and 2) the area to which treatment is administered should not contain any open lesions or wounds. The preparation should be thoroughly washed off 1–4 hours after application to reduce local irritation. The safety of podophyllin during pregnancy has not been established. Podophyllin resin preparations differ in the concentration of active components and contaminants. The shelf life and stability of podophyllin preparations are unknown.

Both TCA and BCA are caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly. TCA solutions have a low viscosity comparable with that of water and can spread rapidly if applied excessively; therefore, they can damage adjacent tissues. A small amount should be applied only to the warts and allowed to dry before the patient sits or stands, at which time a white frosting develops. If pain is intense, the acid can be neutralized with soap or sodium bicarbonate. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate (i.e., baking soda), or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.

Surgical therapy has the advantage of usually eliminating warts at a single visit. However, such therapy requires substantial clinical training, additional equipment, and a longer office visit. After local anesthesia is applied, the visible genital warts can be physically destroyed by electrocautery, in which case no additional hemostasis is required. Care must be taken to control the depth of electrocautery to prevent scarring. Alternatively, the warts can be removed either by tangential excision with a pair of fine scissors or a scalpel, by laser, or by curettage. Because most warts are exophytic, this procedure can be accomplished with a resulting wound that only extends into the upper dermis. Hemostasis can be achieved with an electrocautery unit or a chemical styptic (e.g., an aluminum chloride solution). Suturing is neither required nor indicated in most cases if surgical removal is performed properly. Surgical therapy is most beneficial for patients who have a large number or area of genital warts. Both carbon dioxide laser and surgery might be useful in the management of extensive warts or intraurethral warts, particularly for those persons who have not responded to other treatments.

Because all available treatments have shortcomings, some clinics employ combination therapy (simultaneous use of two or more modalities on the same wart at the same time). Data are limited regarding the efficacy or risk of complications associated with use of such combinations.

Alternative Regimens

Alternative regimens include treatment options that might be associated with more side effects and/or less data on efficacy. Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir.

Recommended Regimen for Cervical Warts

For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade SIL must be performed before treatment is initiated. Management of exophytic cervical warts should include consultation with a specialist.

Recommended Regimens for Vaginal Warts

Cryotherapy with liquid nitrogen. The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation.

OR

TCA or BCA 80%–90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white frosting develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.

Recommended Regimens for Urethral Meatus Warts

Cryotherapy with liquid nitrogen

OR

Podophyllin 10%–25% in compound tincture of benzoin. The treatment area and adjacent normal skin must be dry before contact with podophyllin. This treatment can be repeated weekly, if necessary. The safety of podophyllin during pregnancy has not been established. Data are limited on the use of podofilox and imiquimod for treatment of distal meatal warts.

Recommended Regimens for Anal Warts

Cryotherapy with liquid nitrogen

OR

TCA or BCA 80%–90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white frosting develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.

OR

Surgical removal

Intra-anal warts should be managed in consultation with a specialist. Many persons with warts on the anal mucosa also have warts on the rectal mucosa, so persons with anal and/or intra-anal warts might benefit from an inspection of the rectal mucosa by digital examination, standard anoscopy, or high-resolution anoscopy.

Counseling

The following key counseling messages should be conveyed to all patients diagnosed with HPV infection:

- Genital HPV infection is very common. Many types of HPV are passed on through genital contact, most often during vaginal and anal sexual contact. HPV can also be spread by oral sexual contact.
- Most sexually active adults will get HPV at some point in their lives, though most will never know it because HPV infection usually has no signs or symptoms.
- In most cases, HPV infection clears spontaneously, without causing any health problems. Nevertheless, some infections do progress to genital warts, precancers, and cancers.
- The types of HPV that cause genital warts are different from the types that can cause anogenital cancers.
- Within an ongoing sexual relationship, both partners are usually infected at the time one person is diagnosed with HPV infection, even though signs of infection might not be apparent.
- A diagnosis of HPV in one sex partner is not indicative of sexual infidelity in the other partner.
- Treatments are available for the conditions caused by HPV (e.g., genital warts), but not for the virus itself.
- HPV does not affect a woman's fertility or ability to carry a pregnancy to term.
- Correct and consistent male condom use might lower the chances of giving or getting genital HPV, but such use is not fully protective, because HPV can infect areas that are not covered by a condom.
- Sexually active persons can lower their chances of getting HPV by limiting their number of partners. However, HPV is common and often goes unrecognized; persons with only one lifetime sex partner can have the infection. For this reason, the only definitive method to avoid giving and getting HPV infection and genital warts is to abstain from sexual activity.
- Tests for HPV are now available to help providers screen for cervical cancer in certain women. These tests are not useful for screening adolescent females for cervical cancer, nor are they useful for screening for other HPV-related cancers or genital warts in men or women. HPV tests should not be used to screen:
  - men;
  - partners of women with HPV;
  - adolescent females; or
  - for health conditions other than cervical cancer.
- Two HPV vaccines are available, both of which offer protection against the HPV types that cause 70% of cervical cancers (i.e., types 16 and 18); the quadrivalent vaccine (Gardasil) also protects against the types that cause 90% of genital warts (i.e., types 6 and 11). These vaccines are most effective when all doses are administered before sexual contact. Either vaccine is recommended for 11- and 12-year-old girls and for females aged 13–26 years who did not receive or complete the vaccine series when they were younger. The quadrivalent HPV vaccine can be used in males aged 9–26 years to prevent genital warts.

The following are specific counseling messages for those persons diagnosed with genital warts and their partners:

- Genital warts are not life threatening. If left untreated, genital warts might go away, stay the same, or grow in size or number. Except in very rare and unusual cases, genital warts will not turn into cancer.
- It is difficult to determine how or when a person became infected with HPV; genital warts can be transmitted to others even when no visible signs of warts are present, even after warts are treated.
- It is not known how long a person remains contagious after warts are treated. It is also unclear whether informing subsequent sex partners about a past diagnosis of genital warts is beneficial to the health of those partners.
- Genital warts commonly recur after treatment, especially in the first 3 months.
- Women should get regular Pap tests as recommended, regardless of vaccination or genital wart history. Women with genital warts do not need to get Pap tests more often than recommended.
- HPV testing is unnecessary in sexual partners of persons with genital warts.
- If one sex partner has genital warts, both sex partners benefit from getting screened for other STDs.
- Persons with genital warts should inform current sex partner(s) because the warts can be transmitted to other partners. In addition, they should refrain from sexual activity until the warts are gone or removed.
- Correct and consistent male condom use can lower the chances of giving or getting genital warts, but such use is not fully protective because HPV can infect areas that are not covered by a condom.

- The Gardasil vaccine, which has been approved for use in males and females aged 9–26 years, protects against the HPV types that cause 90% of genital warts (i.e., types 6 and 11).

Special Considerations

Pregnancy

Imiquimod, sinecatechins, podophyllin, and podofilox should not be used during pregnancy. Genital warts can proliferate and become friable during pregnancy. Although removal of warts during pregnancy can be considered, resolution might be incomplete or poor until pregnancy is complete. Rarely, HPV types 6 and 11 can cause respiratory papillomatosis in infants and children, although the route of transmission (i.e., transplacental, perinatal, or postnatal) is not completely understood. Whether cesarean section prevents respiratory papillomatosis in infants and children also is unclear (*412*); therefore, cesarean delivery should not be performed solely to prevent transmission of HPV infection to the newborn. Cesarean delivery is indicated for women with genital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding. Pregnant women with genital warts should be counseled concerning the low risk for warts on the larynx (recurrent respiratory papillomatosis) in their infants or children.

HIV Infection

Persons who are HIV-infected are more likely to develop genital warts then persons who are not HIV-infected (*413*); moreover, lesions are more recalcitrant to treatment due to depressed cell-mediated immunity. No data suggest that treatment modalities for external genital warts should be different for HIV-infected persons. However, persons who are immunosuppressed because of HIV or other reasons might have larger or more numerous warts, might not respond as well as immunocompetent persons to therapy for genital warts, and might have more frequent recurrences after treatment (*414–416*). Squamous cell carcinomas arising in or resembling genital warts might occur more frequently among immunosuppressed persons, therefore requiring biopsy for confirmation of diagnosis for suspicious cases. Because of the increased incidence of anal cancer in HIV-infected MSM, screening for anal intraepithelial neoplasia by cytology can be considered (*417*). However, evidence is limited concerning the natural history of anal intraepithelial neoplasias, the reliability of screening methods, the safety and response to treatments, and the programmatic considerations that would support this screening approach.

Squamous Cell Carcinoma in Situ

Persons in whom squamous cell carcinoma in situ of the genitalia is diagnosed should be referred to a specialist for treatment. Ablative modalities usually are effective, but careful follow-up is essential for patient management.

Cervical Cancer Screening for Women Who Attend STD Clinics or Have a History of STDs

Women attending STD clinics for the treatment of genital infection with high-risk types of Human Papillomavirus (HR-HPV) might be at increased risk for cervical cancer; persistence of HR-HPV can cause cervical cancer and its precancerous lesions. One study demonstrated an HR-HPV prevalence of 27% among women receiving treatment in an STD clinic setting; prevalence was highest among persons aged 14–19 and decreased with increasing age (*418*). In an evaluation of women attending STD clinics, over half of women were at increased risk for cervical cancer as a result of HPV infection, cervical disease, or history of cervical disease compared with women without these characteristics (*419*).

Cervical cytology (i.e., a Pap test) is an effective, low-cost screening test for preventing invasive cervical cancer. In a 2004 survey, 49% of all STD clinics in the United States reported providing cervical screening services, and 20% reported use of HPV DNA testing (*419*).

Current guidelines from USPSTF and ACOG recommend that cervical screening begin at age 21 years (*96*,*97*). This recommendation is based on the low incidence of cervical cancer and limited utility of screening in younger women (*98*). ACS recommends that women start cervical screening with Pap tests after 3 years of initiating sexual activity but by no later than age 21 years (*98*). Recommended screening intervals (http://www.cdc.gov/cancer/cervical/pdf/guidelines.pdf) should continue through 65 years according to USPSTF (http://www.ahrq.gov/clinic/uspstf/uspscerv.htm) or 70 years according to ACS (http://cancer.org/docroot/ped/content/ped_2_3x_acs_cancer detection_guidelines_36.asp).

Screening Recommendations

STD clinics that provide routine cervical screening services should follow the available guidelines. However, to ensure the provision of adequate care, follow-up and referral sources must be in place. Cervical screening should be performed using either conventional or liquid-based cytologic tests (i.e., Pap tests) and can include HR-HPV DNA tests in specific circumstances (*420*). For cythopathologic and HPV/DNA

testing, STD clinics should use CLIA certified laboratories (*421*) and those that report cytopathology findings according to the following Bethesda 2001 terminology (*422*): atypical squamous cells (ASC), low-grade squamous intraepithelial lesions (LSIL), and high-grade intraepithelial lesions (HSIL). The ASC category is subdivided into atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells—cannot exclude HSIL (ASC-H).

During appointments in which a pelvic examination for STD screening is performed, the health-care provider should inquire about the result of the patient's most recent Pap test and discuss the following information with the patient:

- the purpose and importance of a Pap test;
- the need for regularly scheduled Pap tests between 21–65 years of age;
- whether a Pap test will be obtained during this clinic visit; and
- if a Pap test will not be obtained during this examination, the names of local providers or referral clinics that can perform Pap tests and adequately follow up results.

If a woman has not had a Pap test during the previous 12 months (2-year intervals for women aged 21–29 years and 3-year intervals for women aged ≥30 years with a history of three normal Pap tests) and cervical screening is indicated, a Pap test should be obtained as part of the routine pelvic examination. Health-care providers should be aware that many women frequently equate having a pelvic examination with having a Pap test; they erroneously believe that a sample for Pap testing was taken, when in reality, only a pelvic examination was performed. Because self-reports of Pap tests often are not accurate, STD clinics should have a protocol for conducting cervical cancer screening and obtaining a Pap test during the routine clinical evaluation of women who do not have clinical-record documentation of a normal Pap test within the preceding 12 months and do not have another provider for screening services.

HPV Tests

HPV tests are available for clinical use and are recommended for the triage of women aged ≥21 years who have abnormal Pap test results (ASC-US). Additionally, these tests can be used in conjunction with a Pap test (adjunct testing) for cervical cancer screening of women aged ≥30 years. These tests should not be used for women aged <20 years for screening or management of abnormal Pap tests or for STD screening. Current FDA-approved HPV tests detect viral nucleic acid (DNA). Several FDA-approved tests for high-risk HPV testing are available for use in the United States. The Hybrid Capture 2 High-Risk HPV DNA test (Qiagen, Gaithersburg, Maryland) and the Cervista HPV High-Risk test (Hologics, Beford, Massachusetts) detect any of 13–14 high-risk HPV types, whereas the Cervista HPV 16/18 test detects type-specific infection with HPV types 16 and 18. The Digene HC2 HPV DNA test (Qiagen, Gaithersburg, Maryland) detects any of 13 high-risk or five low-risk HPV types, although use of this test is not indicated in the STD clinic setting (i.e., only high-risk HPV DNA testing is necessary) (*423*).

High-risk HPV DNA tests are recommended for the triage of women aged ≥21 years who have ASC-US cytology results. In addition, these tests are recommended for routine adjunctive testing (along with cervical cytology) used to screen women aged ≥30 years (*424*).

HPV DNA testing (including HR HPV and HPV 16/18 tests) is not recommended for the following situations (*425–427*):

- deciding whether to vaccinate for HPV;
- conducting STD screening for HPV;
- triaging LSIL;
- testing adolescents aged <21 years; and
- screening for primary cervical cancer as a stand-alone test (i.e., without a Pap test).

Women might benefit from receiving printed information about the value of and indication for cervical cancer screening (i.e., Pap testing), and they should be provided a clinic visit report that states whether a Pap test was obtained during the clinic visit. When available, a copy of the Pap test result should be provided. Women with abnormal screening or diagnostic tests should be referred to clinic settings that employ providers who are experienced in managing these cases (see Follow-Up). Cervical screening programs should screen women who have received HPV vaccination in the same manner as unvaccinated women.

Follow-Up

Among women aged ≥30 years with normal Pap tests and negative tests for HR-HPV, the screening interval can be increased to 3 years. At that time, routine testing with either a Pap test or a Pap and HR-HPV testing can resume (*428*).

If the results of the Pap test are abnormal, follow-up care should be provided according to the *ASCCP 2006 Consensus Guidelines for Management of Abnormal Cervical Cytology* (*429*) (information regarding management and follow-up care is available at http://www.asccp.org). If resources in STD clinics do not allow for follow-up of women with abnormal results, protocols for referral for follow-up and case management should be in place.

- According to American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, women with Pap tests results indicating ASC-H, low- or high-grade

squamous intraepithelial lesion should be referred to a clinician who can perform a colposcopic examination of the lower genital tract and, if indicated, conduct a colposcopically directed biopsy. For women aged <21 years, referral to colposcopy for ASC-US and LSIL is not recommended, because rates of spontaneous clearance are high in this population; repeat Pap testing at 12 and 24 months is recommended for these women.

- For women aged ≥21 years with a Pap test report of ASC-US, three options are available for follow-up management: 1) prompt colposcopy, 2) repeat Pap tests at 6 and 12 months, and 3) a high-risk HR HPV DNA test. Colposcopy is appropriate if the provider has concerns about adherence with recommended follow-up or concerns about other clinical indications. High-grade histological changes (i.e., CIN 2 or higher) after colposcopic evaluation for ASC-US Pap test reports is typically detected in <12% of cases. If repeat Pap tests are used (instead of prompt colposcopy) to follow ASC-US results, tests should be performed at 6- and 12-month intervals until two consecutive negative results are noted, at which time cervical cancer screening at a normal interval for age can be resumed. If subsequent Pap tests demonstrate ASC or a more serious condition, follow-up should be conducted according to ASCCP 2006 Consensus Guidelines (*424*). A third strategy for managing patients with ASC-US Pap test results involves testing for high-risk HPV DNA (*423*,*424*,*430*,*431*). Whereas conducting high-risk HPV testing might not be possible in some STD clinics because of resource limitations, such testing might be appropriate in other public health clinic settings. HPV tests that detect low-risk HPV types are not recommended for use in STD clinics, because they are not beneficial in this setting.
- If indicated, high-risk HPV DNA testing can be performed by 1) collecting a specimen for Pap test and HPV DNA on the same swab, 2) using a supplied swab at the time of the Pap test, if conventional cytology is used, 3) reflex testing (if liquid-based cytology is used and enough residual material is available in the cytology test vial), or 4) scheduling a separate follow-up appointment when the Pap test report results are known. If the high-risk HPV DNA test is negative, a repeat Pap test should be performed at 12 months. If the test is positive, the patient should be referred immediately for colposcopy, and if indicated, directed cervical biopsy.

Because many public health clinics (including most STD clinics) cannot provide clinical follow-up of abnormal Pap tests, women with Pap tests demonstrating low- or high-grade SIL or ASC-US usually need a referral to other local health-care providers or clinics for colposcopy and biopsy. Clinics and health-care providers who offer cervical screening services but cannot provide appropriate colposcopic follow-up of abnormal Pap tests should arrange referral to health-care facilities that will promptly evaluate and treat patients and report evaluation results to the referring clinic or health-care provider. Clinics and health-care providers should develop protocols that identify women who miss follow-up appointments so that these women can be located and scheduled for needed studies and management, and they should reevaluate these protocols routinely. Pap-test results, type and location of follow-up appointments, and results of follow-up appointment should be clearly documented in the clinic record. The establishment of colposcopy and biopsy services in local health departments, especially in circumstances in which referrals are difficult and follow-up is unlikely, should be considered if resources are available.

Other Management Considerations

The following additional considerations are associated with performing Pap tests:

- The Pap test should not be considered a screening test for STDs.
- All women receiving care in an STD-clinic setting should be considered for cervical cancer screening, regardless of sexual orientation (i.e., heterosexual women and those who identify themselves as lesbian or bisexual).
- If a woman is menstruating, a conventional cytology Pap test should be postponed, and the woman should be advised to have a Pap test at the earliest opportunity.
- If specific infections other than HPV are identified, the patient might need to have a repeat Pap test after appropriate treatment for those infections. However, in most instances (even in the presence of some severe infections), Pap tests will be reported as satisfactory for evaluation, and reliable final reports can be produced without the need to repeat the Pap test after treatment is received.
- When it is necessary to repeat the Pap test because the report was interpreted as unsatisfactory, the repeat test must be determined by the laboratory to be satisfactory and negative before screening can be resumed at regularly scheduled intervals.
- The presence of a mucopurulent discharge should not delay the Pap test. The test can be performed after careful removal of the discharge with a saline-soaked cotton swab.

- In the absence of other indications, women who have external genital warts do not need Pap tests more frequently than women who do not have warts.
- The sequence of Pap testing in relation to collection of other cervicovaginal specimens has not been shown to influence Pap test results or their interpretation (*432*).
- Women who have had a total hysterectomy do not require a routine Pap test unless the hysterectomy was performed because of cervical cancer or its precursor lesions. As recommended by ACOG, for women with hysterectomy resulting from CIN 2 or higher, cervical or vaginal cuff screening can be discontinued once three normal Pap tests have been documented. In these situations, women should be advised to continue follow-up with the physician(s) who provided health care at the time of the hysterectomy, if possible. In women whose cervix remains intact after a hysterectomy, regularly scheduled Pap tests should be performed as indicated (*433–435*).
- Health-care providers who receive basic retraining on Pap-test collection and clinics that use simple quality assurance measures are more likely to obtain satisfactory test results as determined by the laboratory. The use of cytobrushes and brooms also improves the number of satisfactory Pap tests.
- Although evidence supports the option of HPV testing for the triage of women with ASC-US Pap test results, this option might not be feasible in an STD clinic because of limited resources.
- Liquid-based cytology is an acceptable alternative to conventional Pap tests, as it has similar test-performance characteristics.

Special Considerations

Pregnancy

Pregnant women should be screened at the same frequency as nonpregnant women; however, recommendations for management differ in this population (*83*,*84*,*424*). A swab and an Ayre's spatula can be used for obtaining Pap tests in pregnant women, but cytobrushes are not recommended.

HIV Infection

Several studies have documented an increased prevalence of SIL in HIV-infected women (*416*,*436*). The following recommendations for Pap test screening among HIV-infected women are consistent with most of the guidelines published by the U.S. Department of Health and Human Services (HHS) (*129*) and are based partially on the opinions of professionals knowledgeable about the care and management of cervical cancer and HIV infection in women.

HIV-positive women should be provided cervical cytology screening twice (every 6 months) within the first year after initial HIV diagnosis and, if both tests are normal, annual screening can be resumed thereafter. HIV-positive women with ASC-H, LSIL, or HSIL on cytologic screening should undergo colposcopic evaluation. Recommendations for management of HIV-positive women with ASC-US vary. HHS recommends a more conservative management approach (i.e., immediate colposcopy), whereas ASCCP recommends that these women be managed like HIV-negative women with ASC-US (i.e., tested for HR HPV DNA) (*424*,*429*).

Adolescents

Prevalence of HR HPV is high among adolescents aged <21 years (*425*). Infections in adolescent patients tend to clear rapidly, and lesions caused by these infections also have high rates of regression to normal. Therefore, ASCCP and ACOG recommend that adolescents with ASC-US or low-grade SIL be managed with repeat cytologic testing at 12 months and 24 months. Only those with HSIL at either follow-up visit or persistence of ASC-US or LSIL at 24 months should be referred for colposcopic evaluation.

Counseling Messages for Women Receiving Cervical Cancer Screening and HPV Testing

When a woman receives abnormal cervical cytology test results, she might experience considerable anxiety, distress, fear, and confusion, which can serve as barriers to follow-up care. Furthermore, a positive HPV DNA test result might exacerbate these feelings and might also elicit partner concerns, worry about disclosure, and feelings of guilt, anger, and stigmatization.

Health-care providers are the most trusted source of information about HPV and abnormal cervical cytology test results. Therefore, they have an important role to play in educating women about high-risk HPV and moderating the psychosocial impact of the diagnosis.

STD clinic providers should offer patients counseling and information both verbally and in print when delivering HPV and Pap test results. Print materials are available at several websites (http://www.cdc.gov/std/hpv/common/; http://www.ashastd.org/hpv/hpv_publications.cfm). The manner in which this information is communicated to patients can influence the psychological effect of this diagnosis, as well as a woman's likelihood of following up with necessary testing or treatment. Providers should frame high-risk HPV in a neutral, nonstigmatizing context and emphasize its common, asymptomatic, and transient nature. Also, the provider should emphasize that

HPV is often shared between partners and can lie dormant for many years; having HPV does not imply infidelity, nor should it necessarily raise concerns about a partner's health.

In counseling women with high-risk HPV infections about partner management, messages should be tailored to the individual woman's circumstances. While no evidence supports either partner notification (PN) or clinical-evaluation referral for partners of patients with high-risk HPV, some women might benefit from having an informed discussion about their diagnosis with their partners. This type of communication can foster partner support and ensure the sharing of information that can inform decision-making (e.g., decisions regarding condom use).

The following specific key messages should be communicated to patients receiving cervical screening:

- The purpose of regular, lifelong cervical cancer screening is to identify cervical cancer precursors, which can be treated before progression to cervical cancer.
- A positive high-risk HPV DNA test or an abnormal cervical cytology test is not indicative of cervical cancer. Appropriate follow-up is necessary to ensure that cervical abnormalities do not progress.
- Some women might have a normal Pap test and a positive high-risk HPV test. A positive high risk HPV DNA test indicates a HPV infection of the cervix, but does not indicate cervical cancer. A normal cervical cytology test indicates that no cellular abnormalities were detected at the time of testing, but women who have HPV infection of the cervix have a higher likelihood of developing cell changes, which could lead to cervical cancer over time. Follow-up evaluation is essential to monitor cervical cytology.
- A Pap test that reveals ASC-US indicates some abnormal areas on the cervix that may require close follow-up or treatment so that they do not progress. Additional testing might be required to confirm these results. It is essential that patients return for all follow-up appointments and recommended tests.

Discussion concerning disclosure of a positive high-risk HPV test to sex partners might be appropriate and can include the following information:

- HPV is very common. It can infect the genital areas of both men and women. It usually has no signs or symptoms.
- Most sexually active persons get HPV at some time in their lives, though most will never know it. Even persons with only one lifetime sex partner can get HPV if their partner was infected.
- While the immune system clears HPV infection most of the time, in some persons, HPV infection does not resolve.
- No clinically validated test exists for men to determine if they have HPV infection. The most common manifestation of HPV infection in men is genital warts. High-risk HPV types seldom cause genital warts.
- Partners who are in a long-term relationship tend to share HPV. Sexual partners of HPV-infected patients also likely have HPV, even though they might have no signs or symptoms of infection.
- Detection of high-risk HPV infection in a woman does not mean that the woman or her partner is engaging in sexual activity outside of a relationship. HPV infection can be present for many years before it is detected, and no method can accurately confirm when HPV infection was acquired.

Prevention measures for current and subsequent sex partners and risk reduction should be discussed. Providers should counsel women about condom use depending on their current circumstances. Consistent condom use by male partners of sexually active women can reduce the risk for cervical and vulvovaginal HPV infection (*25*), and condom use by couples in long-term partnerships might decrease the time required to clear HPV in the infected woman. Skin not covered by a condom remains vulnerable to HPV infection. HPV vaccines are available and recommended for girls and young women aged 9–26 years, even those who have been diagnosed with HPV infection. Male partners can be vaccinated with the quadrivalent vaccine (Gardasil) to prevent genital warts.

Vaccine-Preventable STDs

Several STDs can be effectively prevented through preexposure vaccination with widely available vaccines, including HAV, HBV, and HPV. Vaccines for other STDs (e.g., HIV and HSV) are under development or are undergoing clinical trials. This guidance focuses largely on integrating the use of available vaccines into STD prevention and treatment activities.

Every person being evaluated or treated for an STD should receive hepatitis B vaccination unless already vaccinated. In addition, some persons (e.g., MSM and IDUs) should receive hepatitis A vaccination.

Hepatitis A

Hepatitis A, caused by infection with HAV, has an incubation period of approximately 28 days (range: 15–50 days). HAV replicates in the liver and is shed in high concentrations in feces from 2 weeks before to 1 week after the onset of clini-

cal illness. HAV infection produces a self-limited disease that does not result in chronic infection or chronic liver disease (CLD). However, 10%–15% of patients experience a relapse of symptoms during the 6 months after acute illness. Acute liver failure from hepatitis A is rare (overall case-fatality rate: 0.5%). The risk for symptomatic infection is directly related to age, with >80% of adults having symptoms compatible with acute viral hepatitis and most children having either asymptomatic or unrecognized infection. Antibody produced in response to HAV infection persists for life and confers protection against reinfection.

HAV infection is primarily transmitted by the fecal-oral route, by either person-to-person contact or through consumption of contaminated food or water. Although viremia occurs early in infection and can persist for several weeks after onset of symptoms, bloodborne transmission of HAV is uncommon. HAV occasionally is detected in saliva in experimentally infected animals, but transmission by saliva has not been demonstrated.

In the United States, almost half of all persons with hepatitis A report having no risk factor for the disease. Among adults with identified risk factors, most cases occur among international travelers, household or sexual contacts, nonhousehold contacts (e.g., those encountered through play and daycare), and IDUs (*437*). Because transmission of HAV during sexual activity probably results from fecal-oral contact, measures typically used to prevent the transmission of other STDs (e.g., use of condoms) do not prevent HAV transmission. In addition, efforts to promote good personal hygiene have not been successful in interrupting outbreaks of hepatitis A. Vaccination is the most effective means of preventing HAV transmission among persons at risk for infection (e.g., MSM, illegal drug users, and persons with CLD), many of whom might seek services in STD clinics.

Diagnosis

The diagnosis of hepatitis A cannot be made on clinical grounds alone; serologic testing also is required. The presence of IgM antibody to HAV is diagnostic of acute HAV infection. A positive test for total anti-HAV indicates immunity to HAV infection but does not differentiate current from previous HAV infection. Although usually not sensitive enough to detect the low level of protective antibody after vaccination, anti-HAV tests also might be positive after hepatitis A vaccination.

Treatment

Patients with acute hepatitis A usually require only supportive care, with no restrictions in diet or activity. Hospitalization might be necessary for patients who become dehydrated because of nausea and vomiting and is critical for patients with signs or symptoms of acute liver failure. Medications that might cause liver damage or are metabolized by the liver should be used with caution among persons with hepatitis A.

Prevention

Two products are available for the prevention of HAV infection: hepatitis A vaccine (Table 2) and immune globulin (IG) for IM administration. Hepatitis A vaccines are prepared from formalin-inactivated, cell-culture–derived HAV and have been available in the United States since 1995, initially for persons aged ≥2 years. In 2005, the vaccines were approved by FDA for persons aged ≥12 months, and the vaccine is available for eligible children and adolescents aged <19 years through the VFC program (telephone: 800-232-4636).

Administered IM in a 2-dose series at 0 and 6–12 months, these vaccines induce protective antibody levels in virtually all adults. By 1 month after the first dose, 94%–100% of adults have protective antibody levels; 100% of adults develop protective antibody after a second dose. In randomized controlled trials, the equivalent of 1 dose of hepatitis A vaccine administered before exposure has been 94%–100% effective in preventing clinical hepatitis A (*2*). Kinetic models of antibody decline indicate that protective levels of antibody persist for at least 20 years.

IG is a sterile solution of concentrated immunoglobulins prepared from pooled human plasma processed by cold ethanol fractionation. In the United States, IG is produced only from plasma that has tested negative for hepatitis B surface antigen, antibodies to HIV and HCV, and HCV RNA. In addition, the process used to manufacture IG inactivates viruses (e.g., HBV, HCV, and HIV). When administered IM before or within 2 weeks after exposure to HAV, IG is >85% effective in preventing HAV infections.

A combined hepatitis A and hepatitis B vaccine has been developed and licensed for use as a 3-dose series in adults aged ≥18 years (Table 3). When administered IM on a 0-, 1-, and 6-month schedule, the vaccine has equivalent immunogenicity to that of the monovalent vaccines.

Pre-exposure Vaccination

Persons in the following groups who are likely to be treated in STD clinic settings should be offered hepatitis A vaccine: 1) all MSM; 2) illegal drug users (of both injection and noninjection drugs); and 3) persons with CLD, including persons with chronic HBV and HCV infection who have evidence of CLD.

Prevaccination Serologic Testing for Susceptibility

Approximately one third of the U.S. population has serologic evidence of previous HAV infection, which increases

TABLE 2. Recommended regimens: dose and schedule for hepatitis A vaccines

Vaccine	Age (yrs)	Dose	Volume (mL)	Two-dose schedule (months)*
HAVRIX†	1–18	720 (EL.U.)	0.5	0 (6–12)
	>18	1,440 (EL.U.)	1.0	0 (6–12)
VAQTA§	1–18	25 (U)	0.5	0 (6–18)
	>18	50 (U)	1.0	0 (6–18)

Source: CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-7).
Abbreviations: EL.U = Enzyme-linked immunosorbent assay (ELISA) units; U = units.
* 0 months represents timing of the initial dose; subsequent numbers represent months after the initial dose.
† Hepatitis A vaccine, inactivated, GlaxoSmithKline Biologicals; this vaccine is also licensed for a 3-dose series in children aged 2–18 years, with 360 EL.U, 0.5 mL doses at 0, 1, and 6–12 months.
§ Hepatitis A vaccine, inactivated, Merck & Co., Inc.

with age and reaches 75% among persons aged >70 years. Screening for HAV infection might be cost-effective in populations where the prevalence of infection is likely to be high (e.g., persons aged >40 years and persons born in areas of high HAV endemicity). The potential cost-savings of testing should be weighed against the cost and the likelihood that testing will interfere with initiating vaccination. Vaccination of a person who is already immune is not harmful.

Postvaccination Serologic Testing

Postvaccination serologic testing is not indicated because most persons respond to the vaccine. In addition, the commercially available serologic test is not sensitive enough to detect the low, but protective, levels of antibody produced by vaccination.

Postexposure Prophylaxis

Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of single-antigen vaccine or IG (0.02 mL/kg) as soon as possible. Information about the relative efficacy of vaccine compared with IG postexposure is limited, and no data are available for persons aged >40 years or those with underlying medical conditions. Therefore, decisions to use vaccine or IG should take into account patient characteristics associated with more severe manifestations of hepatitis A, including older age and CLD.

For healthy persons aged 12 months to 40 years, single-antigen hepatitis A vaccine at the age-appropriate dose is preferred over IG because of vaccine advantages, including long-term protection and ease of administration. For persons aged >40 years, IG is preferred because of the absence of information regarding vaccine performance and the more severe manifestations of hepatitis A in this age group; vaccine can be used if IG cannot be obtained. The magnitude of the risk for HAV transmission from the exposure should be considered in decisions to use IG or vaccine. IG should be used for children aged <12 months, immunocompromised persons, persons who have had diagnosed CLD, and persons for whom vaccine is contraindicated.

If IG is administered to persons for whom hepatitis A vaccine also is recommended, a dose of vaccine should be provided simultaneously with IG. The second vaccine dose should be administered according to the licensed schedule to complete the series. The efficacy of IG or vaccine when administered >2 weeks after exposure has not been established (*438*).

Special Considerations

Limited data indicate that vaccination of persons with CLD and of persons with advanced HIV infection results in lower seroprotection rates and antibody concentrations (*4*). In HIV-infected persons, antibody response might be directly related to CD4+ levels.

Hepatitis B

Hepatitis B is caused by infection with the hepatitis B virus (HBV). The incubation period from the time of exposure to onset of symptoms is 6 weeks to 6 months. The highest concentrations of HBV are found in blood, with lower concentrations found in other body fluids including wound exudates, semen, vaginal secretions, and saliva (*439*,*440*). HBV is more infectious and relatively more stable in the environment than other bloodborne pathogens like HCV and HIV.

HBV infection can be self-limited or chronic. In adults, only approximately half of newly acquired HBV infections are symptomatic, and approximately 1% of reported cases result in acute liver failure and death. Risk for chronic infection is inversely related to age at acquisition; approximately 90% of infected infants and 30% of infected children aged <5 years become chronically infected, compared with 2%–6% of persons who become infected as adults. Among persons with chronic HBV infection, the risk for premature death from cirrhosis or hepatocellular carcinoma (HCC) is 15%–25%.

HBV is efficiently transmitted by percutaneous or mucous membrane exposure to blood or body fluids that contain blood. The primary risk factors associated with infection among adolescents and adults are unprotected sex with an infected partner, unprotected sex with more than one partner, MSM, history of other STDs, and illegal injection-drug use. In addition, several studies have demonstrated the horizontal transmission of HBV, including through premastication, as a less common source of transmission (*441*,*442*).

TABLE 3. Recommended doses of currently licensed formulations of adolescent and adult hepatitis B vaccines

	Single-antigen vaccine				Combination vaccine	
	Recombivax HB		Engerix-B		Twinrix*	
Group	Dose (μg)†	Volume (mL)	Dose (μg)†	Volume (mL)	Dose (μg)†	Volume (mL)
Adolescents aged 11–19 years§	5	0.5	10	0.5	NA	NA
Adolescents aged 11–15 years¶	10	1.0	NA	NA	NA	NA
Adults (aged ≥20 years)	10	1.0	20	1.0	20	1.0
Hemodialysis patients and other immunocompromised persons aged < 20 years§	5	0.5	10	0.5	NA	NA
Hemodialysis patients and other immunocompromised persons aged ≥20 years	40**	1.0	40††	2.0	NA	NA

Sources: CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: immunization of infants, children, and adolescents. **MMWR 2005;54(No. RR-16). CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR 2006;55(No. RR-16).**

* Combined hepatitis A and hepatitis B vaccine. This vaccine is recommended for persons aged ≥18 years who are at increased risk for both hepatitis B and hepatitis A virus infections.

† Recombinant hepatitis B surface antigen protein dose, in micrograms.

§ Pediatric formulation administered on a 3-dose schedule; higher doses might be more immunogenic, but no specific recommendations have been made.

¶ Adult formulation administered on a 2-dose schedule.

** Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 months.

†† Two 1.0-mL doses of the adult formulation administered at one site on a 4-dose schedule at 0, 1, 2, and 6 months.

CDC's national strategy to eliminate transmission of HBV infection includes 1) prevention of perinatal infection through routine screening of all pregnant women for HBsAg and immunoprophylaxis of infants born to HBsAg-positive mothers or mothers whose HBsAg status is unknown, 2) routine infant vaccination, 3) vaccination of previously unvaccinated children and adolescents through age 18 years, and 4) vaccination of previously unvaccinated adults at increased risk for infection (*3*,*4*). High vaccination coverage rates, with subsequent declines in acute hepatitis B incidence, have been achieved among infants and adolescents (*4*,*437*,*443*). In contrast, vaccination coverage among most high-risk adult groups (e.g., persons with more than one sex partner in the previous 6 months, MSM, and IDUs) has remained low, and most new infections occur in these high-risk groups (*3*,*108*,*444–446*). STD clinics and other settings that provide services to high-risk adults are ideal sites in which to provide hepatitis B vaccination to adults at risk for HBV infection. All unvaccinated adults seeking services in these settings should be assumed to be at risk for hepatitis B and should be offered hepatitis B vaccination.

Diagnosis

Diagnosis of acute or chronic HBV infection requires serologic testing (Table 4). Because HBsAg is present in both acute and chronic infection, the presence of IgM antibody to hepatitis B core antigen (IgM anti-HBc) is diagnostic of acute or recently acquired HBV infection. Antibody to HBsAg (anti-HBs) is produced after a resolved infection and is the only HBV antibody marker present after vaccination. The presence of HBsAg and total anti-HBc, with a negative test for IgM anti-HBc, indicates chronic HBV infection. The presence of anti-HBc alone might indicate a false-positive result or acute, resolved, or chronic infection.

Treatment

No specific therapy is available for persons with acute hepatitis B; treatment is supportive. Persons with chronic HBV infection should be referred for evaluation to a physician experienced in the management of CLD. Therapeutic agents cleared by FDA for treatment of chronic hepatitis B can achieve sustained suppression of HBV replication and remission of liver disease in some persons. In addition, patients with chronic hepatitis B might benefit from screening to detect HCC at an early stage.

Prevention

Two products have been approved for hepatitis B prevention: hepatitis B immune globulin (HBIG) and hepatitis B vaccine (*3*,*4*). HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically used as PEP either as an adjunct to hepatitis B vaccination in previously unvaccinated persons or alone in persons who have not responded to vaccination. HBIG is prepared from plasma known to contain high concentrations of anti-HBs. The recommended dose of HBIG is 0.06 mL/kg.

Hepatitis B vaccine contains HBsAg produced in yeast by recombinant DNA technology and provides protection from HBV infection when used for both pre-exposure vaccination and PEP. The two available monovalent hepatitis B vaccines for use in adolescents and adults are Recombivax HB (Merck and Co., Inc., Whitehouse Station, New Jersey) and Engerix-B (GlaxoSmithKline Biologicals, Pittsburgh, Pennsylvania). A combination vaccine (hepatitis A and hepatitis B) for use in

TABLE 4. Interpretation of serologic test results* for HBV infection

Serologic marker				
HBsAg†	Total anti-HBc§	IgM¶ anti-HBc	Anti-HBs**	Interpretation
–	–	–	–	Never infected
+††	–	–	–	Early acute infection; transient (up to 18 days) after vaccination
+	+	+	–	Acute infection
–	+	+	–	Acute resolving infection
–	+	–	+	Recovered from past infection and immune
+	+	–	–	Chronic infection
–	+	–	–	False positive (i.e., susceptible); past infection; "low-level" chronic infection§§; passive transfer to infant born to HBsAg-positive mother
–	–	–	+	Immune if concentration is >10 mIU/mL,¶¶ passive transfer after HBIG administration

* Symbol for negative test result, "–"; symbol for positive test result, "+".
† Hepatitis B surface antigen.
§ Antibody to hepatitis B core antigen.
¶ Immunoglobulin M.
** Antibody to HBsAg.
†† To ensure that an HBsAg-positive test result is not a false positive, samples with repeatedly reactive HBsAg results should be tested with an FDA-cleared (and, if appropriate, neutralizing confirmatory) test.
§§ Persons positive for only anti-HBc are unlikely to be infectious except under unusual circumstances involving direct percutaneous exposure to large quantities of blood (e.g., blood transfusion and organ transplantation).
¶¶ Milli-International Units per milliliter.

adults, Twinrix (GlaxoSmithKline Biologicals, Pittsburgh, Pennsylvania), also is available. The recommended HBV dose varies by product and age of recipient (Table 3).

When selecting a hepatitis B vaccination schedule, the health-care provider should consider the need to achieve completion of the vaccine series. Approved adolescent and adult schedules for both monovalent hepatitis B vaccine (i.e., Engerix-B and Recombivax HB) include the following: 0, 1, and 6 months; 0, 1, and 4 months; and 0, 2, and 4 months. A 4-dose schedule of Engerix-B at 0, 1, 2, and 12 months is licensed for all age groups. A 2-dose schedule of Recombivax HB adult formulation (10 μg) is licensed for adolescents aged 11–15 years. When scheduled to receive the second dose, adolescents aged >15 years should be switched to a 3-dose series, with doses two and three consisting of the pediatric formulation (5 μg) administered on an appropriate schedule. Twinrix can be administered to persons aged ≥18 years at risk for both HAV and HBV infections at 0, 1, and 6 months.

Hepatitis B vaccine should be administered IM in the deltoid muscle and can be administered simultaneously with other vaccines. For adolescents and adults, the needle length should be 1–2 inches, depending on the recipient's weight (1 inch for females weighing <70 kg, 1.5 inches for males weighing <120 kg, and 2 inches for males and females weighing >120 kg and >100 kg, respectively). A 22- to 25-gauge needle is recommended. If the vaccine series is interrupted after the first or second dose of vaccine, the missed dose should be administered as soon as possible. The series does not need to be restarted after a missed dose.

In adolescents and healthy adults aged <40 years, approximately 30%–55% acquire a protective antibody response (anti-HBs ≥10 mIU/mL) after the first vaccine dose, 75% after the second, and >90% after the third. Vaccine-induced immune memory has been demonstrated to persist for at least 15–20 years. Periodic testing to determine antibody levels after routine vaccination in immunocompetent persons is not necessary, and booster doses of vaccine are not currently recommended.

Hepatitis B vaccination is generally well-tolerated by most recipients. Pain at the injection site and low-grade fever are reported by a minority of recipients. For children and adolescents, a causal association exists between receipt of hepatitis B vaccination and anaphylaxis: for each 1.1 million doses of vaccine administered, approximately one vaccinee will experience this type of reaction. No deaths have been reported in these patients (*3,4,447*). Vaccine is contraindicated in persons with a history of anaphylaxis after a previous dose of hepatitis B vaccine and in persons with a known anaphylactic reaction to any vaccine component. No evidence for a causal association has been demonstrated for other adverse events after administration of hepatitis B vaccine.

Pre-exposure Vaccination

Hepatitis B vaccination is recommended for all unvaccinated adolescents, all unvaccinated adults at risk for HBV infection, and all adults seeking protection from HBV infection. For adults, acknowledgement of a specific risk factor is not a requirement for vaccination.

Hepatitis B vaccine should be routinely offered to all unvaccinated persons attending STD clinics and to all unvaccinated persons seeking treatment for STDs in other settings. Other settings where all unvaccinated adults should be assumed to be at risk for hepatitis B and should receive hepatitis B vaccination

include correctional facilities, facilities providing drug abuse treatment and prevention services, health-care settings serving MSM, and HIV testing and treatment facilities. All persons who receive clinical services in these settings should be offered hepatitis B vaccine unless they have a reliable vaccination history (i.e., a written, dated record of each dose of a complete series). In all settings, vaccination should be initiated even when completion of the vaccine series cannot be ensured.

Prevaccination Antibody Screening

Prevaccination serologic testing for susceptibility might be considered to reduce the cost of vaccinating adult populations that have an expected high prevalence (20%–30%) of HBV infection (e.g., IDUs and MSM, especially those in older age groups). In addition, prevaccination testing for susceptibility is recommended for unvaccinated household, sexual, and needle-sharing contacts of HBsAg-positive persons (*108*).

Anti-HBc is the test of choice for prevaccination testing; persons who are anti-HBc–positive should be tested for HBsAg. If persons are determined to be HBsAg negative, no further action is required. If persons are determined to be HBsAg positive, the person should be referred for medical follow-up to include counseling and evaluation for antiviral treatment (see Management of HBsAg-Positive Persons). In addition, all household members, sex partners, and needle-sharing partners of HBsAg-positive persons should be vaccinated.

Serologic testing should not be a barrier to vaccination of susceptible persons, especially in populations that are difficult to access. In most cases, the first vaccine dose should be administered immediately after collection of the blood sample for serologic testing. Vaccination of persons who are immune to HBV infection because of current or previous infection or vaccination does not increase the risk for adverse events.

Postvaccination Testing for Serologic Response

Serologic testing for immunity is not necessary after routine vaccination of adolescents or adults. However, such testing is recommended for persons whose subsequent clinical management depends on knowledge of their immune status (e.g., health-care workers or public safety workers at high risk for continued percutaneous or mucosal exposure to blood or body fluids). In addition, postvaccination testing is recommended for 1) HIV-infected persons and other immunocompromised persons to determine the need for revaccination and the type of follow-up testing and 2) sex and needle-sharing partners of HBsAg-positive persons to determine the need for revaccination and for other methods to protect themselves from HBV infection.

If indicated, testing should be performed 1–2 months after administration of the last dose of the vaccine series by using a method that allows determination of a protective level of anti-HBs (i.e., ≥10 mIU/mL). Persons determined to have anti-HBs levels of <10 mIU/mL after the primary vaccine series should be revaccinated with a 3-dose series and provided with anti-HBs testing 1–2 months after the third dose. Persons who do not respond to revaccination should be tested for HBsAg. If HBsAg positive, the person should receive appropriate management (see Management of HBsAg-Positive Persons); if HBsAg negative, the person should be considered susceptible to HBV infection and counseled concerning precautions to prevent HBV infection and the need for HBIG PEP for any known exposure (see Postexposure Prophylaxis).

Postexposure Prophylaxis

Both passive-active PEP (the administration of HBIG and hepatitis B vaccine at separate sites) and active PEP (the administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV (*4*). HBIG alone also has been demonstrated to be effective in preventing HBV transmission, but with the availability of hepatitis B vaccine, HBIG typically is used as an adjunct to vaccination.

Exposure to HBsAg-Positive Source

Unvaccinated persons or persons known not to have responded to a complete hepatitis B vaccine series should receive both HBIG and hepatitis vaccine as soon as possible (preferably ≤24 hours) after a discrete, identifiable exposure to blood or body fluids that contain blood from an HBsAg-positive source (Table 5). Hepatitis B vaccine should be administered simultaneously with HBIG at a separate injection site, and the vaccine series should be completed by using the age-appropriate vaccine dose and schedule (Table 3). Exposed persons who are in the process of being vaccinated but who have not completed the vaccine series should receive the appropriate dose of HBIG (i.e., 0.06 mL/kg) and should complete the vaccine series. Exposed persons who are known to have responded to vaccination are considered protected; therefore, they need no additional doses of vaccine. Persons who have written documentation of a complete hepatitis B vaccine series who did not receive postvaccination testing should receive a single vaccine booster dose. Alternatively, these persons can be managed according to guidelines for management of persons with occupational exposure to blood or body fluids that contain blood (*446*).

Exposure to Source with Unknown HBsAg Status

Unvaccinated persons who have a discrete, identifiable exposure to blood or body fluids containing blood from a source with unknown HBsAg status should receive the hepatitis

TABLE 5. Guidelines for postexposure immunoprophylaxis of unvaccinated persons who have an identifiable exposure to blood or body fluids that contain blood

Cause	Action
Exposure to an HBsAg*-positive source	
Percutaneous (e.g., bite or needlestick) or mucosal exposure to HBsAg-positive blood or body fluids that contain blood	Administer hepatitis B vaccine & HBIG†
Sexual or needle-sharing contact of an HBsAg-positive person	Administer hepatitis B vaccine & HBIG†
Victim of sexual assault/abuse by a perpetrator who is HBsAg positive	Administer hepatitis B vaccine & HBIG†
Exposure to a source with unknown HBsAg status	
Victim of sexual assault/abuse by a perpetrator with unknown HBsAg status	Administer hepatitis B vaccine†
Percutaneous (e.g., bite or needlestick) or mucosal exposure to blood or body fluids that contain blood from a source with unknown HBsAg status	Administer hepatitis B vaccine†

* Hepatitis B surface antigen.
† Immunoprophylaxis should be administered as soon as possible, preferably ≤24 hours. Studies are limited on the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures and 14 days for sexual exposures. The complete, 3-dose hepatitis B vaccine series should be administered.

B vaccine series, with the first dose initiated as soon as possible after exposure (preferably within 24 hours) and the series completed by using the age-appropriate dose and schedule. Exposed persons who are not fully vaccinated should complete the vaccine series. Exposed persons with written documentation of a complete hepatitis B vaccine series require no further treatment.

Special Considerations

Pregnancy

All pregnant women receiving STD services should be tested for HBsAg, regardless of whether they have been previously tested or vaccinated. All HBsAg-positive pregnant women should be reported to state and local perinatal hepatitis B prevention programs. HBsAg-negative pregnant women seeking STD treatment who have not been previously vaccinated should receive hepatitis B vaccination. Additional information regarding management of HBsAg-positive pregnant women and their infants is available at http://www.cdc.gov/mmwr/PDF/rr/rr5416.pdf.

HIV Infection

HIV infection can impair the response to hepatitis B vaccination. HIV-infected persons should be tested for anti-HBs 1–2 months after the third vaccine dose (see Postvaccination Testing for Serologic Response). Modified dosing regimens, including a doubling of the standard antigen dose and administration of additional doses, might increase the response rate (*130*).

Management of HBsAg-Positive Persons

This section provides recommendations for management of all HBsAg-positive persons. Additional recommendations for management of HBsAg-positive persons who are coinfected with HIV are available (*130*).

- All persons with HBsAg-positive laboratory results should be reported to the state or local health department.
- To verify the presence of chronic HBV infection, HBsAg-positive persons should be retested. The absence of IgM anti-HBc or the persistence of HBsAg for 6 months indicates chronic HBV infection.
- Persons with chronic HBV infection should be referred for evaluation to a physician experienced in the management of CLD. Some patients with chronic hepatitis B will benefit from early intervention with antiviral treatment or screening to detect HCC at an early stage.
- Household, sexual, and needle-sharing contacts of chronically infected persons should be identified. Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection (see Prevaccination Antibody Screening) and should receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing. Susceptible persons should complete the vaccine series by using an age-appropriate vaccine dose and schedule.
- Sex partners of HBsAg-positive persons should be counseled to use latex condoms (*448*) to protect themselves from sexual exposure to infectious body fluids (e.g., semen and vaginal secretions), unless they have been demonstrated to be immune after vaccination (anti-HBs ≥10 mIU/mL) or previously infected (anti-HBc positive).
- To prevent or reduce the risk for transmission to others, HBsAg-positive persons should be advised about the risk for transmission to household, sexual, and needle-sharing contacts and the need for such contacts to receive hepatitis B vaccination. HBsAg-positive persons also should be advised to:
  - use methods (e.g., condoms) to protect nonimmune sex partners from acquiring HBV infection from sexual activity until the partner can be vaccinated and immunity documented;
  - cover cuts and skin lesions to prevent spread by infectious secretions or blood;

  - refrain from donating blood, plasma, body organs, other tissue, or semen; and
  - refrain from sharing household articles (e.g., toothbrushes, razors, or personal injection equipment) that could become contaminated with blood. In addition, HBsAg-positive persons should refrain from premasticating food provided to susceptible persons.
- To protect the liver from further harm, HBsAg-positive persons should be advised to:
  - avoid or limit alcohol consumption because of the effects of alcohol on the liver;
  - refrain from starting any new medicines, including OTC and herbal medicines, without checking with their health-care provider; and
  - obtain vaccination against hepatitis A if liver disease is determined to be present.

When seeking medical or dental care, HBsAg-positive persons should be advised to inform their health-care providers of their HBsAg status so that they can be appropriately evaluated and managed. The following counseling messages should be considered for HBsAg-positive persons:

- HBV is not usually spread by hugging, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact.
- Persons should not be excluded from work, school, play, child care, or other settings because they are infected with HBV.
- Involvement with a support group might help patients cope with chronic HBV infection.

Hepatitis C

Hepatitis C virus (HCV) infection is the most common chronic bloodborne infection in the United States; an estimated 3.2 million persons are chronically infected (*449*). Although HCV is not efficiently transmitted sexually, persons at risk for infection through injection-drug use might seek care in STD treatment facilities, HIV counseling and testing facilities, correctional facilities, drug treatment facilities, and other public health settings where STD and HIV prevention and control services are available.

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 for decades after infection.

HCV is transmitted through parenteral exposures to contaminated blood, usually through use of injection drugs (sharing of needles or works) and to a lesser extent through exposures in health-care settings as a consequence of inadequate infection-control practices. Transmission rarely follows receipt of blood, tissues, and organs from HCV-infected donors who were not identified during routine screening activities, which have been mandated in the United States since 1992. Occupational and perinatal exposures, although less efficient, also can result in transmission of HCV.

Sexual transmission of HCV had been considered to occur rarely. However, recent data indicate that sexual transmission of HCV can occur, especially among HIV-infected persons. CDC surveillance data demonstrate that 10% of persons with acute HCV infection report contact with a known HCV-infected sex partner as their only risk for infection (*437*). Specific studies of HCV transmission between heterosexual or homosexual couples have yielded mixed results, but generally have found low but increased rates of HCV infection in partners of persons with HCV infection compared with those whose partners are not HCV-infected (*450–455*). Several studies have revealed that risk increases commensurate with increasing numbers of sex partners among heterosexual persons (*450*,*451*,*456–458*) and MSM (*459–462*), especially if those partners are coinfected with HIV (*459–465*).

Apparent sexual transmission of HCV has recently been reported among HIV-infected MSM in multiple European cities (*464*,*465*) and New York City (*466*). Common practices associated with these clusters of infection include serosorting (i.e., HIV-infected men having sex with one another), group sex, and the use of cocaine and other nonintravenous drugs during sex.

All persons with HIV infection should undergo serologic testing for HCV at initial evaluation (*130*,*131*). HIV-infected MSM can also acquire HCV after initial screening. Liver function tests should be serially monitored for abnormalities that could be caused by acute viral hepatitis or medication toxicity. HIV-infected persons with new and unexplained increases in ALT should be tested for acute HCV infection. To ensure the detection of acute HCV infection among HIV-infected MSM with high-risk sexual behaviors or concomitant ulcerative STDs, routine HCV testing of HIV-infected MSM should be considered. 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 HIV-infected MSM. Suspected

clusters of acute infection should be reported to the appropriate public health authorities. Unprotected sexual contact between HIV-infected partners can facilitate spread of HCV, as the virus can be recovered from the semen of men coinfected with HIV (*467*). Specific prevention practices (e.g., barrier precautions that limit contact with body fluids during sexual contact with other MSM) should be discussed with patients.

Diagnosis and Treatment

Anti-HCV testing is recommended for routine screening of asymptomatic persons based on their risk for infection or based on a recognized exposure (see Hepatitis C, Prevention). For such persons, testing for HCV infection should include the use of an FDA-cleared test for antibody to HCV (i.e., immunoassay, EIA, or enhanced chemiluminescence imunoassay and, if recommended, a supplemental antibody test) (*468*).

Persons counseled and tested for HCV infection and determined to be anti-HCV positive should be evaluated (by referral or consultation, if appropriate) for the presence of active infection, presence or development of CLD, and possible 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 an elevated ALT level is biochemical evidence of CLD. Combination therapy with pegylated interferon and ribavirin is the treatment of choice for patients with chronic hepatitis C. Providers should consult with specialists knowledgeable about management of hepatitis C infection because these experts remain cognizant of the latest advances in the field of antiviral therapy for acute and chronic hepatitis C.

Prevention

No vaccine for hepatitis C is available, and prophylaxis with immune globulin is not effective in preventing HCV infection after exposure. 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 HCV-infected persons by first identifying them and then providing medical management and antiviral therapy, if appropriate.

Most scientific evidence demonstrates that although HCV can be transmitted sexually, such transmission happens rarely. Because incident HCV has not been demonstrated to occur in heterosexual partner-pairs followed over time (*452–454*), condom use might not be necessary in such circumstances. However, heterosexual and homosexual persons, especially those with concurrent HIV infection or with more than one partner, should protect themselves and their partners against transmission of HCV, HBV, HIV, and other pathogens by use of male latex condoms. Condom use is especially important for HIV-infected men, who might spread HCV to other men though unprotected sexual activity (*464–466*).

Providers in STD clinics and other primary-care settings should identify those persons who should be offered HCV counseling and testing. In STD clinics and other settings that serve large numbers of persons at high risk for bloodborne infections (e.g., correctional settings), the major risk factor necessitating screening for HCV infection is past or current injection of illegal drugs. Because both HCV and HIV are transmitted through injection-drug use, about one fourth of all HIV patients are also coinfected with HCV. For this reason, all persons with HIV infection should be offered HCV counseling and testing. Other risk factors for which routine HCV testing is recommended include:

- having had a blood transfusion or solid organ transplant before July 1992;
- having received clotting factor concentrates produced before 1987;
- having been on long-term dialysis; and
- having signs and symptoms of liver disease (e.g., abnormal ALT).

Persons who test negative for anti-HCV who had an exposure previously should be reassured that they are not infected. Those who test positive for anti-HCV (see Diagnosis and Treatment) should be provided information regarding how to protect their liver from further harm; for instance, HCV-positive persons should be advised to avoid drinking alcohol and taking any new medicines (including OTC and herbals) without checking with their clinician.

To reduce the risk for transmission to others, HCV-positive persons should be advised to 1) not donate blood, body organs, other tissue, or semen; 2) not share any personal items that might have blood on them (e.g., toothbrushes and razors); and 3) cover cuts and sores on the skin to keep the virus from spreading by blood or secretions. HCV-positive persons with one long-term, steady sex partner do not need to change their sexual practices. They should discuss the low but present risk for transmission with their partner and discuss the need for counseling and testing. HCV-positive women do not need to avoid pregnancy or breastfeeding.

HCV-positive persons should be evaluated (by referral or consultation, if appropriate) to detect active HCV infection and the presence of CLD. Evaluation should involve testing for liver function, additional assessment of the severity of liver

disease, possible treatment, and the determination for the need of hepatitis A and B vaccination.

Regardless of test results, persons who use or inject illegal drugs should be counseled to stop using and injecting drugs and 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 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;
- safely dispose of syringes after one use;
- get vaccinated for hepatitis A and B if nonimmune; and
- get tested for HIV infection.

Postexposure Follow-Up

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

Special Considerations

Pregnancy

Routine testing for HCV infection is not recommended for all pregnant women. Pregnant women with a known risk factor for HCV infection should be offered counseling and testing. Patients should be advised that approximately six of every 100 infants born to HCV-infected woman 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. The risk is increased, however, by the presence of maternal HCV viremia at delivery and also is greater (2–3 times) if the woman is coinfected with HIV. HCV has not been shown to be transmitted through breast milk, although HCV-positive mothers should consider abstaining from breastfeeding if their nipples are cracked or bleeding. Infants born to HCV-positive mothers should be tested for HCV infection and, if positive, evaluated for the presence of CLD.

HIV Infection

Because of the high prevalence of HIV/HCV coinfection and because of critical clinical management issues for coinfected persons, all persons with HIV infection should undergo serologic testing for HCV. Providers should be aware of the likelihood that HIV-infected MSM will acquire HCV after initial screening. Liver function tests should be serially monitored, and those persons with new and unexplained increases in ALT should be tested for acute HCV infection. To detect acute HCV infection among HIV-infected MSM with high-risk sexual behaviors or concomitant ulcerative STDs, routine HCV testing of HIV-infected MSM should be considered. Because a small percentage of coinfected persons fail to acquire HCV antibodies, HCV RNA should be tested in HIV-positive 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.

Proctitis, Proctocolitis, and Enteritis

Sexually transmitted gastrointestinal syndromes include proctitis, proctocolitis, and enteritis. Evaluation for these syndromes should include appropriate diagnostic procedures (e.g., anoscopy or sigmoidoscopy, stool examination, and culture).

Proctitis is inflammation of the rectum (i.e., the distal 10–12 cm) that can be associated with anorectal pain, tenesmus, or rectal discharge. *N. gonorrhoeae*, *C. trachomatis* (including LGV serovars), *T. pallidum*, and HSV are the most common sexually transmitted pathogens involved. In patients coinfected with HIV, herpes proctitis can be especially severe. Proctitis occurs predominantly among persons who participate in receptive anal intercourse.

Proctocolitis is associated with symptoms of proctitis, diarrhea or abdominal cramps, and inflammation of the colonic mucosa extending to 12 cm above the anus. Fecal leukocytes might be detected on stool examination, depending on the pathogen. Pathogenic organisms include *Campylobacter* sp., *Shigella* sp., *Entamoeba histolytica*, and LGV serovars of *C. trachomatis*. CMV or other opportunistic agents can be involved in immunosuppressed HIV-infected patients.

Proctocolitis can be acquired by the oral route or by oral-anal contact, depending on the pathogen.

Enteritis usually results in diarrhea and abdominal cramping without signs of proctitis or proctocolitis; it occurs among persons whose sexual practices include oral-anal contact. In otherwise healthy persons, *Giardia lamblia* is most frequently implicated. When outbreaks of gastrointestinal illness occur among social or sexual networks of MSM, clinicians should consider sexual transmission as a mode of spread and provide counseling accordingly. Among HIV-infected patients, gastrointestinal illness can be caused by other infections that usually are not sexually transmitted, including CMV, *Mycobacterium avium–intracellulare*, *Salmonella* sp., *Campylobacter* sp., *Shigella* sp., *Cryptosporidium*, *Microsporidium*, and *Isospora*. Multiple stool examinations might be necessary to detect *Giardia*, and special stool preparations are required to diagnose cryptosporidiosis and microsporidiosis. In addition, enteritis can be directly caused by HIV infection.

When laboratory diagnostic capabilities are available, treatment decisions should be based on the specific diagnosis. Diagnostic and treatment recommendations for all enteric infections are beyond the scope of these guidelines.

Treatment for Proctitis

Acute proctitis of recent onset among persons who have recently practiced receptive anal intercourse is usually sexually acquired (*469*,*470*). Such patients should be examined by anoscopy and should be evaluated for infection with HSV, *N. gonorrhoeae*, *C. trachomatis*, and *T. pallidum.* If an anorectal exudate is detected on examination or if polymorphonuclear leukocytes are detected on a Gram-stained smear of anorectal secretions, the following therapy should be prescribed while awaiting additional laboratory tests.

Recommended Regimen

Ceftriaxone 250 mg IM

PLUS

Doxycycline 100 mg orally twice a day for 7 days

Patients with suspected or documented herpes proctitis should be managed in the same manner as those with genital herpes (see Genital HSV Infections). If painful perianal ulcers are present or mucosal ulcers are detected on anoscopy, presumptive therapy should include a regimen for genital herpes and LGV. Appropriate diagnostic testing for LGV should be conducted in accordance with state or federal guidelines, and doxycycline therapy should be administered 100 mg orally twice daily for 3 weeks.

For MSM, treatment for LGV proctitis/proctocolitis with 3 weeks of doxycycline in those with anorectal chlamydia and either 1) proctitis (as detected by proctoscopic examination and the presence of >10 white-blood cells upon high-power field examination of an anorectal smear specimen) or 2) HIV infection can be considered.

Follow-Up

Follow-up should be based on specific etiology and severity of clinical symptoms. Reinfection might be difficult to distinguish from treatment failure.

Management of Sex Partners

Partners of persons with sexually transmitted enteric infections should be evaluated for any diseases diagnosed in the index patient.

Ectoparasitic Infections

Pediculosis Pubis

Persons who have pediculosis pubis (i.e., pubic lice) usually seek medical attention because of pruritus or because they notice lice or nits on their pubic hair. Pediculosis pubis is usually transmitted by sexual contact.

Recommended Regimens

Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes

OR

Pyrethrins with piperonyl butoxide applied to the affected area and washed off after 10 minutes

Alternative Regimens

Malathion 0.5% lotion applied for 8–12 hours and washed off

OR

Ivermectin 250 μg/kg orally, repeated in 2 weeks

Reported resistance to pediculicides has been increasing and is widespread (*471–473*). Malathion can be used when treatment failure is believed to have resulted from drug resistance. The odor and long duration of application for malathion make it a less attractive alternative than the recommended pediculcides. Ivermectin has been successfully used to treat lice, but it has only been evaluated in studies involving a limited number of participants.

Other Management Considerations

The recommended regimens should not be applied to the eyes. Pediculosis of the eyelashes should be treated by applying occlusive ophthalmic ointment to the eyelid margins twice a day for 10 days. Bedding and clothing should be decontaminated (i.e., either dry cleaned or machine-washed and dried using the heat cycle) or removed from body contact for at least 72 hours. Fumigation of living areas is not necessary.

Patients with pediculosis pubis should be evaluated for other STDs.

Follow-Up

Patients should be evaluated after 1 week if symptoms persist. Retreatment might be necessary if lice are found or if eggs are observed at the hair-skin junction. Patients who do not respond to one of the recommended regimens should be retreated with an alternative regimen.

Management of Sex Partners

Sex partners that have had sexual contact with the patient within the previous month should be treated. Patients should abstain from sexual contact with their sex partner(s) until patients and partners have been treated and reevaluated to rule out persistent disease.

Special Considerations

Pregnancy

Pregnant and lactating women should be treated with either permethrin or pyrethrins with piperonyl butoxide; lindane and ivermectin are contraindicated in pregnancy and lactating women.

HIV Infection

Patients who have pediculosis pubis and also are infected with HIV should receive the same treatment regimen as those who are HIV negative.

Scabies

The predominant symptom of scabies is pruritus, but sensitization to *Sarcoptes scabiei* occurs before pruritus begins. The first time a person is infested with *S. scabiei*, sensitization can take several weeks to develop. However, pruritus might occur within 24 hours after a subsequent reinfestation. Scabies in adults frequently is sexually acquired, although scabies in children usually is not.

Recommended Regimens

Permethrin cream (5%) applied to all areas of the body from the neck down and washed off after 8–14 hours

OR

Ivermectin 200ug/kg orally, repeated in 2 weeks

Alternative Regimen

Lindane (1%) 1 oz. of lotion (or 30 g of cream) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after 8 hours

Lindane is not recommended as first-line therapy because of toxicity (*471*). It should only be used as an alternative if the patient cannot tolerate other therapies or if other therapies have failed.

Lindane should not be used immediately after a bath or shower, and it should not be used by persons who have extensive dermatitis, women who are pregnant or lactating, or children aged <2 years. Lindane resistance has been reported in some areas of the world, including parts of the United States (*474*). Seizures have occurred when lindane was applied after a bath or used by patients who had extensive dermatitis. Aplastic anemia after lindane use also has been reported (*471, 474*).

Permethrin is effective and safe and less expensive than ivermectin (*471, 474*). One study demonstrated increased mortality among elderly, debilitated persons who received ivermectin, but this observation has not been confirmed in subsequent studies (*475*).

Other Management Considerations

Bedding and clothing should be decontaminated (i.e., either dry cleaned or machine-washed and dried using the hot cycle) or removed from body contact for at least 72 hours. Fumigation of living areas is unnecessary.

Crusted Scabies

Crusted scabies (i.e., Norwegian scabies) is an aggressive infestation that usually occurs in immunodeficient, debilitated, or malnourished persons (*476*). Patients who are receiving systemic or potent topical glucocorticoids, organ transplant recipients, mentally retarded or physically incapacitated persons, HIV-infected or human T-lymphotrophic virus-1-infected persons, and persons with various hematologic malignancies are at risk for developing crusted scabies. Crusted scabies is associated with greater transmissibility than scabies. No controlled therapeutic studies for crusted scabies have been conducted, and the appropriate treatment remains

unclear. Substantial risk for treatment failure might exist with a single topical scabicide or with oral ivermectin treatment. Combined treatment with a topical scabicide and repeated treatment with oral ivermectin 200 µg/kg on days 1, 2, 8, 9, and 15 are suggested. Additional treatment on days 22 and 29 might be required for severe cases. Ivermectin should be combined with the application of either 5% topical benzyl benzoate or 5% topical permethrin (full body application to be repeated daily for 7 days then 2 times weekly until release from care or cure). Lindane should be avoided because of the risks for neurotoxicity associated with both heavy applications and denuded skin. Fingernails should be closely trimmed to reduce injury from excessive scratching.

Follow-Up

Patients should be informed that the rash and pruritus of scabies might persist for up to 2 weeks after treatment. Symptoms or signs that persist for >2 weeks can be attributed to several factors. Treatment failure can be caused by resistance to medication, although faulty application of topical scabicides also can contribute to persistence — patients with crusted scabies might have poor penetration into thick scaly skin and harbor mites in these difficult-to-penetrate layers. Particular attention must be given to the fingernails of these patients. Reinfection from family members or fomites can occur in the absence of appropriate contact treatment and washing of bedding and clothing. Even when treatment is successful and reinfection is avoided, symptoms can persist or worsen as a result of allergic dermatitis. Finally, the presence of household mites can cause symptoms to persist as a result of cross reactivity between antigens. Retreatment can be considered after 1–2 weeks for patients who are still symptomatic or if live mites are present. Treatment with an alternative regimen is recommended for persons who do not respond to the recommended treatment.

Management of Sex Partners and Household Contacts

Sexual contacts and those that have had close personal or household contact with the patient within the preceding month should be examined and treated.

Management of Outbreaks in Communities, Nursing Homes, and Other Institutional Settings

Scabies outbreaks frequently occur in nursing homes, hospitals, residential facilities, and other communities. Control of an epidemic can only be achieved by treatment of the entire population at risk. Ivermectin can be considered in this setting, especially if treatment with topical scabicides fails. Epidemics should be managed in consultation with an infectious disease specialist.

Special Considerations

Infants, Young Children, and Pregnant or Lactating Women

Infants, young children, and pregnant or lactating women should not be treated with lindane; however, they can be treated with permethrin. Ivermectin is not recommended for pregnant or lactating patients, and the safety of ivermectin in children who weigh <15 kg has not been determined.

HIV Infection

Patients who have uncomplicated scabies and also are infected with HIV should receive the same treatment regimens as those who are HIV negative. HIV-infected patients and others who are immunosuppressed are at increased risk for crusted scabies, for which ivermectin has been reported to be effective in noncontrolled studies involving only a limited number of participants. HIV-infected patients with crusted scabies should be managed in consultation with an infectious disease specialist.

Sexual Assault and STDs

Adults and Adolescents

The recommendations in this report are limited to the identification, prophylaxis, and treatment of STDs and conditions commonly identified in the management of such infections. The documentation of findings, collection of nonmicrobiologic specimens for forensic purposes, and management of potential pregnancy or physical and psychological trauma are beyond the scope of this report.

Examinations of survivors of sexual assault should be conducted by an experienced clinician in a way that minimizes further trauma to the survivor. The decision to obtain genital or other specimens for STD diagnosis should be made on an individual basis. Care systems for survivors should be designed to ensure continuity (including timely review of test results), support adherence, and monitor for adverse reactions to any therapeutic or prophylactic regimens prescribed at initial examination. Laws in all 50 states strictly limit the evidentiary use of a survivor's previous sexual history, including evidence of previously acquired STDs, as part of an effort to undermine the credibility of the survivor's testimony. Evidentiary privilege against revealing any aspect of the examination or treatment also is enforced in most states. Although it rarely occurs, STD diagnoses might later be accessed, and the survivor and clinician

might opt to defer testing for this reason. While collection of specimens at initial examination for laboratory STD diagnosis gives the survivor and clinician the option to defer empiric prophylactic antimicrobial treatment, compliance with follow up visits is traditionally poor (*477*,*478*). Among sexually active adults, the identification of an STD might represent an infection acquired prior to the assault, and therefore might be more important for the psychological and medical management of the patient than for legal purposes.

Trichomoniasis, BV, gonorrhea, and chlamydial infection are the most frequently diagnosed infections among women who have been sexually assaulted. Such conditions are relatively prevalent, and the presence after an assault does not necessarily imply acquisition during the assault. However, a postassault examination presents an important opportunity to identify or prevent STDs. Chlamydial and gonococcal infections in women are of particular concern because of the possibility of ascending infection. In addition, HBV infection can be prevented by postexposure administration of hepatitis B vaccine. Reproductive-aged female survivors should be evaluated for pregnancy, if appropriate.

Evaluating Adults and Adolescents for Sexually Transmitted Diseases

Initial Examination

An initial examination might include the following procedures:

- NAATs for *C. trachomatis* and *N. gonorrhoeae*. These tests are preferred for the diagnostic evaluation of sexual assault victims, regardless of the sites of penetration or attempted penetration (197).
- Wet mount and culture or point-of-care testing of a vaginal-swab specimen for *T. vaginalis* infection. The wet mount also should be examined for evidence of BV and candidiasis, especially if vaginal discharge, malodor, or itching is evident.
- A serum sample for immediate evaluation for HIV infection, hepatitis B, and syphilis. Decisions to perform these tests should be made on an individual basis.

Follow-Up Examinations

After the initial postassault examination, follow-up examinations provide an opportunity to 1) detect new infections acquired during or after the assault; 2) complete hepatitis B vaccination, if indicated; 3) complete counseling and treatment for other STDs; and 4) monitor side effects and adherence to postexposure prophylactic medication, if prescribed.

Examination for STDs can be repeated within 1–2 weeks of the assault. Because infectious agents acquired through assault might not have produced sufficient concentrations of organisms to result in positive test results at the initial examination, testing can be repeated during the follow-up visit, unless prophylactic treatment was provided. If treatment was provided, testing should be conducted only if the survivor reports having symptoms. If treatment was not provided, follow-up examination should be conducted within 1 week to ensure that results of positive tests can be discussed promptly with the survivor and that treatment is provided. Serologic tests for syphilis and HIV infection can be repeated 6 weeks, 3 months, and 6 months after the assault if initial test results were negative and infection in the assailant could not be ruled out (see Sexual Assault and STDs, Risk for Acquiring HIV Infection).

Prophylaxis

Compliance with follow-up visits is poor among survivors of sexual assault (*477*,*478*). As a result, routine preventive therapy after a sexual assault should be encouraged. The following prophylactic regimen is suggested as preventive therapy:

- Postexposure hepatitis B vaccination, without HBIG. This vaccine should be administered to sexual assault survivors at the time of the initial examination if they have not been previously vaccinated. Follow-up doses of vaccine should be administered 1–2 and 4–6 months after the first dose.
- An empiric antimicrobial regimen for chlamydia, gonorrhea, and trichomonas.
- Emergency contraception. (This measure is necessary only when the assault could result in pregnancy in the survivor.)

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose

OR

Cefixime 400 mg orally in a single dose

PLUS

Metronidazole 2 g orally in a single dose

PLUS

Azithromycin 1 g orally in a single dose OR Doxycycline 100 mg orally twice a day for 7 days

For those requiring alternative treatments, refer to the specific sections in this report relevant to the specific agent. The efficacy of these regimens in preventing infections after sexual assault has not been evaluated. Clinicians should counsel patients regarding the possible benefits and toxicities associated with these treatment regimens; gastrointestinal side effects can occur with this combination.

Other Management Considerations

At the initial examination and, if indicated, at follow-up examinations, patients should be counseled regarding 1) symptoms of STDs and the need for immediate examination if symptoms occur and 2) abstinence from sexual intercourse until STD prophylactic treatment is completed.

Risk for Acquiring HIV Infection

HIV seroconversion has occurred in persons whose only known risk factor was sexual assault or sexual abuse, but the frequency of this occurrence is probably low. In consensual sex, the risk for HIV transmission from vaginal intercourse is 0.1%–0.2% and for receptive rectal intercourse, 0.5%–3% (*479*). The risk for HIV transmission from oral sex is substantially lower. Specific circumstances of an assault (e.g., bleeding, which often accompanies trauma) might increase risk for HIV transmission in cases involving vaginal, anal, or oral penetration. Site of exposure to ejaculate, viral load in ejaculate, and the presence of an STD or genital lesions in the assailant or survivor also might increase the risk for HIV.

Children might be at higher risk for transmission, because the sexual abuse of children is frequently associated with multiple episodes of assault and might result in mucosal trauma (see Sexual Assault or Abuse of Children).

Postexposure therapy with zidovudine was associated with a reduced risk for acquiring HIV in a study of health-care workers who had percutaneous exposures to HIV-infected blood (*480*). On the basis of these results and the results of animal studies, PEP has been recommended for health-care workers who have occupational exposures to HIV (*446*). These findings have been extrapolated to other types of HIV exposure, including sexual assault (*78*). If HIV exposure has occurred, initiation of PEP as soon as possible after the exposure likely increases benefit. Although a definitive statement of benefit cannot be made regarding PEP after sexual assault, the possibility of HIV exposure from the assault should be assessed at the time of the postassault examination. The possible benefit of PEP in preventing HIV infection also should be discussed with the assault survivor if the assault poses a risk for HIV exposure.

Several factors impact the medical recommendation for PEP and affect the assault survivor's acceptance of that recommendation, including 1) the likelihood of the assailant having HIV, 2) any exposure characteristics that might increase the risk for HIV transmission, 3) the time elapsed after the event, and 4) the potential benefits and risks associated with the PEP (*78*). Determination of the assailant's HIV status at the time of the assault examination usually in not possible. Therefore, the health-care provider should assess any available information concerning 1) characteristics and HIV risk behaviors of the assailant(s) (e.g., a man who has sex with other men and persons who use injection drugs or crack cocaine), 2) local epidemiology of HIV/AIDS, and 3) exposure characteristics of the assault. When an assailant's HIV status is unknown, factors that should be considered in determining whether an increased risk for HIV transmission exists include 1) whether vaginal or anal penetration occurred; 2) whether ejaculation occurred on mucous membranes; 3) whether multiple assailants were involved; 4) whether mucosal lesions are present in the assailant or survivor; and 5) any other characteristics of the assault, survivor, or assailant that might increase risk for HIV transmission.

If PEP is offered, the following information should be discussed with the patient: 1) the unproven benefit and known toxicities of antiretrovirals; 2) the importance of close follow-up; 3) the benefit of adherence to recommended dosing; and 4) the necessity of early initiation of PEP to optimize potential benefits (i.e., as soon as possible after and up to 72 hours after the assault). Providers should emphasize that PEP appears to be well-tolerated in both adults and children and that severe adverse effects are rare (*481–483*). Clinical management of the survivor should be implemented according to the following guidelines (*78*). Specialist consultation on PEP regimens is recommended if HIV exposure during the assault was possible and if PEP is being considered. The sooner PEP is initiated after the exposure, the higher the likelihood that it will prevent HIV transmission if HIV exposure occurred; however, distress after an assault also might prevent the survivor from accurately weighing exposure risks and benefits of PEP and from making an informed decision to start such therapy. If use of PEP is judged to be warranted, the survivor should be offered a 3–5-day supply of PEP, and a follow-up visit should be scheduled several days later to allow for additional counseling.

Recommendations for Postexposure Assessment of Adolescent and Adult Survivors Within 72 Hours of Sexual Assault[§§]

- Assess risk for HIV infection in the assailant.
- Evaluate characteristics of the assault event that might increase risk for HIV transmission.
- Consult with a specialist in HIV treatment, if PEP is being considered.
- If the survivor appears to be at risk for HIV transmission from the assault, discuss antiretroviral prophylaxis, including toxicity and lack of proven benefit.

[§§] Assistance with PEP-related decisions can be obtained by calling the National Clinician's Post-Exposure Prophylaxis Hotline (PEP Line) (telephone: 888-448-4911).

- If the survivor chooses to start antiretroviral PEP (*78*), provide enough medication to last until the next return visit; reevaluate the survivor 3–7 days after initial assessment and assess tolerance of medications.
- If PEP is started, perform CBC and serum chemistry at baseline (initiation of PEP should not be delayed, pending results).
- Perform HIV antibody test at original assessment; repeat at 6 weeks, 3 months, and 6 months.

Sexual Assault or Abuse of Children

Recommendations in this report are limited to the identification and treatment of STDs. Management of the psychosocial aspects of the sexual assault or abuse of children is beyond the scope of these recommendations.

The identification of sexually transmissible agents in children beyond the neonatal period suggests sexual abuse. The significance of the identification of a sexually transmitted agent in such children as evidence of possible child sexual abuse varies by pathogen. Postnatally acquired gonorrhea; syphilis; and nontransfusion, nonperinatally acquired HIV are usually diagnostic of sexual abuse. Sexual abuse should be suspected when genital herpes is diagnosed. The investigation of sexual abuse among children who have an infection that could have been transmitted sexually should be conducted in compliance with recommendations by clinicians who have experience and training in all elements of the evaluation of child abuse, neglect, and assault. The social significance of an infection that might have been acquired sexually and the recommended action regarding reporting of suspected child sexual abuse varies by the specific organism, as do the recommendations regarding reporting of suspected child sexual abuse (Table 6). In all cases in which an STD has been diagnosed in a child, efforts should be made to detect evidence of sexual abuse, including conducting diagnostic testing for other commonly occurring STDs (*484–486*).

The general rule that sexually transmissible infections beyond the neonatal period are evidence of sexual abuse has exceptions. For example, rectal or genital infection with *C. trachomatis* among young children might be the result of perinatally acquired infection and has, in some cases, persisted for as long as 2–3 years. Genital warts have been diagnosed in children who have been sexually abused, but also in children who have no other evidence of sexual abuse (*487*,*488*). BV has been diagnosed in children who have been abused, but its presence alone does not prove sexual abuse. In addition, most HBV infections in children result from household exposure to persons who have chronic HBV infection.

TABLE 6. Implications of commonly encountered sexually transmitted (ST) or sexually associated (SA) infections for diagnosis and reporting of sexual abuse among infants and pre-pubertal children

ST/SA confirmed	Evidence for sexual abuse	Suggested action
Gonorrhea*	Diagnostic	Report†
Syphilis*	Diagnostic	Report†
Human immunodeficiency virus§	Diagnostic	Report†
*Chlamydia trachomatis**	Diagnostic	Report†
Trichomonas vaginalis	Highly suspicious	Report†
Condylomata acuminata (anogenital warts)*	Suspicious	Report†
Genital herpes*	Suspicious	Report†¶
Bacterial vaginosis	Inconclusive	Medical follow-up

Source: Adapted from Kellogg N, American Academy of Pediatrics Committee on Child Abuse and Neglect. The evaluation of child abuse in children. Pediatrics 2005;116(2):506–12.

* If not likely to be perinatally acquired and rare nonsexual, vertical transmission is excluded.

† Reports should be made to the agency in the community mandated to receive reports of suspected child abuse or neglect.

§ If not likely to be acquired perinatally or through transfusion.

¶ Unless there is a clear history of autoinoculation.

The possibility of sexual abuse should be strongly considered if no conclusive explanation for nonsexual transmission of an STD can be identified.

Reporting

All U.S. states and territories have laws that require the reporting of child abuse. Although the exact requirements differ by state, if a health-care provider has reasonable cause to suspect child abuse, a report must be made. Health-care providers should contact their state or local child-protection service agency regarding child-abuse reporting requirements in their states.

Evaluating Children for Sexually Transmitted Diseases

Examinations of children for sexual assault or abuse should be conducted in a manner designed to minimize pain and trauma to the child. Collection of vaginal specimens in prepubertal children can be very uncomfortable and should be performed by an experienced clinician to avoid psychological and physical trauma to the child. The decision to obtain genital or other specimens from a child to conduct an STD evaluation must be made on an individual basis. The following situations place children at high-risk for STDs and constitute a strong indication for testing.

- The child has or has had symptoms or signs of an STD or of an infection that can be sexually transmitted, even in the absence of suspicion of sexual abuse. Among the signs that are associated with a confirmed STD diagnosis are vaginal discharge or pain, genital itching or odor, urinary symptoms, and genital ulcers or lesions.

- A suspected assailant is known to have an STD or to be at high risk for STDs (e.g., has multiple sex partners or a history of STDs).
- A sibling or another child or adult in the household or child's immediate environment has an STD.
- The patient or parent requests testing.
- Evidence of genital, oral, or anal penetration or ejaculation is present.

If a child has symptoms, signs, or evidence of an infection that might be sexually transmitted, the child should be tested for other common STDs before the initiation of any treatment that could interfere with the diagnosis of those other STDs. Because of the legal and psychosocial consequences of a false-positive diagnosis, only tests with high specificities should be used. The potential benefit to the child of a reliable diagnosis of an STD justifies deferring presumptive treatment until specimens for highly specific tests are obtained by providers with experience in the evaluation of sexually abused and assaulted children.

The scheduling of an examination should depend on the history of assault or abuse. If the initial exposure was recent, the infectious agents acquired through the exposure might not have produced sufficient concentrations of organisms to result in positive test results. A follow-up visit approximately 2 weeks after the most recent sexual exposure can include a repeat physical examination and collection of additional specimens. To allow sufficient time for antibodies to develop, another follow-up visit approximately 12 weeks after the most recent sexual exposure might be necessary to collect sera. A single examination might be sufficient if the child was abused for an extended period and if a substantial amount of time elapsed between the last suspected episode of abuse and the medical evaluation.

The following recommendations for scheduling examinations serve as a general guide. The exact timing and nature of follow-up examinations should be determined on an individual basis and should be performed to minimize the possibility for psychological trauma and social stigma. Compliance with follow-up appointments might be improved when law enforcement personnel or child protective services are involved.

Initial and 2-Week Follow-Up Examinations

During the initial examination and 2-week follow-up examination (if indicated), the following should be performed.

- Visual inspection of the genital, perianal, and oral areas for genital discharge, odor, bleeding, irritation, warts, and ulcerative lesions. The clinical manifestations of some STDs are different in children than in adults. For example, typical vesicular lesions might not be present in the presence of HSV infection. Because this infection can be indicative of sexual abuse, specimens should be obtained from all vesicular or ulcerative genital or perianal lesions compatible with genital herpes and then sent for viral culture.
- Specimen collection for *N. gonorrhoeae* culture from the pharynx and anus in boys and girls, the vagina in girls, and the urethra in boys. Cervical specimens are not recommended for prepubertal girls. For boys with a urethral discharge, a meatal specimen discharge is an adequate substitute for an intraurethral swab specimen. Because of the legal implications of a diagnosis of *N. gonorrhoeae* infection in a child, if culture for the isolation of *N. gonorrhoeae* is done, only standard culture procedures should be performed. Gram stains are inadequate to evaluate prepubertal children for gonorrhea and should not be used to diagnose or exclude gonorrhea. Specimens from the vagina, urethra, pharynx, or rectum should be streaked onto selective media for isolation of *N. gonorrhoeae*, and all presumptive isolates of *N. gonorrhoeae* should be identified definitively by at least two tests that involve different principles (e.g., biochemical, enzyme substrate, or serologic). Isolates should be preserved to enable additional or repeated testing.
- Cultures for *C. trachomatis* from specimens collected from the anus in both boys and girls and from the vagina in girls. The likelihood of recovering *C. trachomatis* from the urethra of prepubertal boys is too low to justify the trauma involved in obtaining an intraurethral specimen. However, a meatal specimen should be obtained if urethral discharge is present. Pharyngeal specimens for *C. trachomatis* are not recommended for children of either sex because the yield is low, perinatally acquired infection might persist beyond infancy, and culture systems in some laboratories do not distinguish between *C. trachomatis* and *C. pneumoniae*. Only standard culture systems for the isolation of *C. trachomatis* should be used. The isolation of *C. trachomatis* should be confirmed by microscopic identification of inclusions by staining with fluorescein-conjugated monoclonal antibody specific for *C. trachomatis*; EIAs are not acceptable confirmatory methods. Isolates should be preserved. Nonculture tests for chlamydia (e.g., nonamplified probes, EIAs, and DFA) are not sufficiently specific for use in circumstances involving possible child abuse or assault. NAATs can be used for detection of *C. trachomatis* in vaginal specimens

or urine from girls. All specimens should be retained for additional testing if necessary. No data are available regarding the use of NAATs in boys or for extragenital specimens (e.g., those obtained from the rectum) in boys and girls. Culture remains the preferred method for extragenital sites.

- Culture and wet mount of a vaginal swab specimen for *T. vaginalis* infection and BV.
- Collection of serum samples to be evaluated immediately, preserved for subsequent analysis, and used as a baseline for comparison with follow-up serologic tests. Sera should be tested immediately for antibodies to sexually transmitted agents. Agents for which suitable tests are available include *T. pallidum*, HIV, and HBV. Decisions regarding the agents for which to perform serologic tests should be made on a case-by-case basis.

Data on use of NAATs for detection of *N. gonorrhoeae* in children are limited, and performance is test dependent (*197*,*486*). Consultation with an expert is necessary before using NAATs in this context to minimize the possibility of cross-reaction with nongonococcal *Neisseria* species and other commensals (e.g., *N. meningitidis*, *N. sicca*, *N. lactamica*, *N. cinerea,* and *Moraxella catarrhalis*). NAATs can be used as an alternative to culture with vaginal specimens or urine from girls, whereas culture remains the preferred method for urethral specimens or urine from boys and for extragenital specimens (pharynx and rectum) from all children. All positive specimens should be retained for additional testing.

HIV infection has been reported in children whose only known risk factor was sexual abuse. Serologic testing for HIV infection should be considered for abused children. The decision to test for HIV infection should be made on a case-by-case basis, depending on the likelihood of infection among assailant(s). Although data are insufficient concerning the efficacy and safety of PEP among both children and adults, treatment is well tolerated by infants and children (with and without HIV infection), and children have a minimal risk for serious adverse reactions because of the short period recommended for prohylaxis. (*78*,*138*). In considering whether to offer antiretroviral PEP, health-care providers should consider whether the child can be treated soon after the sexual exposure (i.e., within 72 hours), the likelihood that the assailant is infected with HIV, and the likelihood of high compliance with the prophylactic regimen. The potential benefit of treating a sexually abused child should be weighed against the risk for adverse reactions. If antiretroviral PEP is being considered, a provider specializing in evaluating or treating HIV-infected children should be consulted.

Recommendations for HIV-Related Postexposure Assessment of Children within 72 Hours of Sexual Assault

- Review HIV/AIDS local epidemiology and assess risk for HIV infection in the assailant.
- Evaluate circumstances of assault that might affect risk for HIV transmission.
- Consult with a specialist in treating HIV-infected children if PEP is considered.
- If the child appears to be at risk for HIV transmission from the assault, discuss PEP with the caregiver(s), including its toxicity and unknown efficacy.
- If caregivers choose for the child to receive antiretroviral PEP (*78,142,489*), provide enough medication to last until the return visit at 3–7 days after the initial assessment, at which time the child should be reevaluated and tolerance of medication assessed; dosages should not exceed those for adults.
- Perform HIV antibody test at original assessment, 6 weeks, 3 months, and 6 months.

Follow-Up Examination After Assault

In circumstances in which transmission of syphilis, HIV, or hepatitis B is a concern but baseline tests are negative, an examination approximately 6 weeks, 3 months, and 6 months after the last suspected sexual exposure is recommended to allow time for antibodies to infectious agents to develop. In addition, results of HBsAg testing must be interpreted carefully, because HBV can be transmitted nonsexually. Decisions regarding which tests should be performed must be made on an individual basis.

Presumptive Treatment

The risk of a child acquiring an STD as a result of sexual abuse or assault has not been well studied. Presumptive treatment for children who have been sexually assaulted or abused is not recommended because 1) the incidence of most STDs in children is low after abuse/assault, 2) prepubertal girls appear to be at lower risk for ascending infection than adolescent or adult women, and 3) regular follow-up of children usually can be ensured. However, some children or their parent(s) or guardian(s) might be concerned about the possibility of infection with an STD, even if the risk is perceived to be low by the health-care provider. Such concerns might be an appropriate indication for presumptive treatment in some settings and might be considered after all specimens for diagnostic tests relevant to the investigation have been collected.

References

1. CDC. Sexually transmitted diseases treatment guidelines, 2006. MMWR 2006;55(No. RR-11).
2. CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-7).
3. CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR 2006;55(No. RR-16).
4. CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: immunization of infants, children, and adolescents. MMWR 2005;54(No. RR-16).
5. Lin JS, Whitlock E, O'Connor E, et al. Behavioral counseling to prevent sexually transmitted infections: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008; 149:497–9.
6. U.S. Preventive Services Task Force. Behavioral counseling to prevent sexually transmitted infections: recommendation statement. Ann Intern Med 2008;149:491–6.
7. Hatcher RA, Trussell J, Nelson AL, et al. Contraceptive technology. 19th ed. New York: Ardent Media; 2007.
8. Kamb ML, Fishbein M, Douglas JM, Jr., et al. Project RESPECT Study Group. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. JAMA 1998;280:1161–7.
9. Gottlieb SL, Douglas JM, Jr., Foster M, et al. Incidence of herpes simplex virus type 2 infection in 5 sexually transmitted disease (STD) clinics and the effect of HIV/STD risk-reduction counseling. J Infect Dis 2004;190:1059–67.
10. Warner L, Klausner JD, Rietmeijer CA, et al. Effect of a brief video intervention on incident infection among patients attending sexually transmitted disease clinics. PLoS Med 2008;5:e135.
11. CDC, Health Resources and Services Administration, National Institutes of Health, NIV Medicine Association of the Infectious Diseases Society of American, HIV Prevention in Clinical Care Working Group. Recommendations for incorporating human immunodeficiency virus (HIV) prevention into the medical care of persons living with HIV. Clin Infect Dis 2004;38:104–21.
12. Wingood GM, DiClemente RJ, Mikhail I, et al. A randomized controlled trial to reduce HIV transmission risk behaviors and sexually transmitted diseases among women living with HIV: The WiLLOW Program. J Acquir Immune Defic Syndr 2004;37(Suppl 2):S58–67.
13. Richardson JL, Milam J, Stoyanoff S, et al. Using patient risk indicators to plan prevention strategies in the clinical care setting. J Acquir Immune Defic Syndr 2004;37(Suppl 2):S88–94.
14. Fisher JD, Cornman DH, Osborn CY, et al. Clinician-initiated HIV risk reduction intervention for HIV-positive persons: Formative Research, Acceptability, and Fidelity of the Options Project. J Acquir Immune Defic Syndr 2004;37(Suppl 2):S78–87.
15. CDC. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;56(No. RR-2).
16. CDC. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59:626–9.
17. CDC. FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59:630–2.
18. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev 2002;(1):CD003255.
19. Ness RB, Randall H, Richter HE, et al. Condom use and the risk of recurrent pelvic inflammatory disease, chronic pelvic pain, or infertility following an episode of pelvic inflammatory disease. Am J Public Health 2004;94:1327–9.
20. Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. Bull World Health Organ 2004;82:454–61.
21. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. Ann Intern Med 2005;143:707–13.
22. Martin ET, Krantz E, Gottlieb SL, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. Arch Intern Med 2009;169:1233–40.
23. Wald A, Langenberg AG, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA 2001;285:3100–6.
24. Koss CA, Dunne EF, Warner L. A systematic review of epidemiologic studies assessing condom use and risk of syphilis. Sex Transm Dis 2009;36:401–5.
25. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med 2006;354:2645–54.
26. Hogewoning CJ, Bleeker MC, van den Brule AJ, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. Int J Cancer 2003;107:811–6.
27. Bleeker MC, Hogewoning CJ, Voorhorst FJ, et al. Condom use promotes regression of human papillomavirus-associated penile lesions in male sexual partners of women with cervical intraepithelial neoplasia. Int J Cancer 2003;107:804–10.
28. Steiner MJ, Cates W Jr, Warner L. The real problem with male condoms is nonuse. Sex Transm Dis 1999;26:459–62.
29. NIAID. Workshop summary: scientific evidence on condom effectiveness for sexually transmitted disease (STD) prevention. 2001. Available at www.niaid.nih.gov/about/organization/dmid/documents/condomreport.pdf.
30. Gallo MF, Grimes DA, Lopez LM, Schulz KF. Non-latex versus latex male condoms for contraception. Cochrane Database Syst Rev 2006;1:CD003550.
31. Macaluso M, Blackwell R, Jamieson DJ, et al. Efficacy of the male latex condom and of the female polyurethane condom as barriers to semen during intercourse: a randomized clinical trial. Am J Epidemiol 2007;166:88–96.
32. French PP, Latka M, Gollub EL, et al. Use-effectiveness of the female versus male condom in preventing sexually transmitted disease in women. Sex Transm Dis 2003;30:433–9.
33. Gross M, Buchbinder SP, Holte S, et al. Use of reality "female condoms" for anal sex by US men who have sex with men. HIVNET Vaccine Preparedness Study Protocol Team. Am J Public Health 1999;89:1739–41.
34. Minnis AM, Padian NS. Effectiveness of female controlled barrier methods in preventing sexually transmitted infections and HIV: current evidence and future research directions. Sex Transm Infect 2005;81:193–200.
35. Padian NS, van der SA, Ramjee G, et al. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. Lancet 2007;370:251–61.
36. Ramjee G, van der SA, Chipato T, et al. The diaphragm and lubricant gel for prevention of cervical sexually transmitted infections: results of a randomized controlled trial. PLoS One 2008;3:e3488.
37. Fihn SD, Boyko EJ, Normand EH, et al. Association between use of spermicide-coated condoms and *Escherichia coli* urinary tract infection in young women. Am J Epidemiol 1996;144:512–20.
38. Padian NS, Buve A, Balkus J, et al. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. Lancet 2008;372:585–99.

39. Cates W, Feldblum P. HIV prevention research: the ecstasy and the agony. Lancet 2008;372:1932–3.
40. Wilkinson D, Tholandi M, Ramjee G, et al. Nonoxynol-9 spermicide for prevention of vaginally acquired HIV and other sexually transmitted infections: systematic review and meta-analysis of randomised controlled trials including more than 5000 women. Lancet Infect Dis 2002;2:613–7.
41. Skoler-Karpoff S, Ramjee G, Ahmed K, et al. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1977–87.
42. Van DL, Govinden R, Mirembe FM, et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. N Engl J Med 2008;359:463–72.
43. Feldblum PJ, Adeiga A, Bakare R, et al. SAVVY vaginal gel (C31G) for prevention of HIV infection: a randomized controlled trial in Nigeria. PLoS One 2008;3:e1474.
44. Peterson L, Nanda K, Opoku BK, et al. SAVVY (C31G) gel for prevention of HIV infection in women: a phase 3, double-blind, randomized, placebo-controlled trial in Ghana. PLoS One 2007;2:e1312.
45. Karim SA, Coletti A, Richardson BS. Safety and effectiveness of vaginal microbicides BufferGel and 0.5% PRO 2000/5 gel for the prevention of HIV infection in women: results of the HPTN 035 trial. In: 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada, 2009.
46. Microbicides Development Programme. Technical fact sheet for scientists (MDP 301). London, 2009. Available at http://www.mdp.mrc.ac.uk.
47. Karim QA, Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 2010;329:1168–74.
48. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet 2007;369:643–6.
49. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet 2007;369:657–66.
50. Auvert B, Taljaard D, Lagarde E, et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med 2005;2:e298.
51. Auvert B, Sobngwi-Tambekou J, Cutler E, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in Orange Farm, South Africa. J Infect Dis 2009;199:14–9.
52. Sobngwi-Tambekou J, Taljaard D, Lissouba P, et al. Effect of HSV-2 serostatus on acquisition of HIV by young men: results of a longitudinal study in Orange Farm, South Africa. J Infect Dis 2009;199:958–64.
53. Sobngwi-Tambekou J, Taljaard D, Nieuwoudt M, et al. Male circumcision and *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis*: observations after a randomised controlled trial for HIV prevention. Sex Transm Infect 2009;85:116–20.
54. Tobian AA, Serwadda D, Quinn TC, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. N Engl J Med 2009;360:1298–309.
55. Millett GA, Flores SA, Marks G, et al. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. JAMA 2008;300:1674–84.
56. UNAIDS, WHO. New data on male circumcision and HIV prevention: policy and programme implications: WHO/UNAIDS technical consultation male circumcision and HIV prevention—research implications for policy and programming. Geneva: Joint United Nations Programme on HIV/AIDS and World Health Organization; 2007.
57. Smith DK, Taylor A, Kilmarx PH, et al. Male circumcision in the United States for the prevention of HIV infection and other adverse health outcomes: report from a CDC consultation. Public Health Rep 2010;125(Suppl 1):72–82.
58. Cheng L, Gulmezoglu AM, Piaggio G, et al. Interventions for emergency contraception (update of 2004 document). Cochrane Database Syst Rev 2008;(2):CD001324.
59. Myer L, Kuhn L, Stein ZA, et al. Intravaginal practices, bacterial vaginosis, and women's susceptibility to HIV infection: epidemiological evidence and biological mechanisms. Lancet Infect Dis 2005;5:786–94.
60. Cohen MS, Gay C, Kashuba AD, et al. Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1. Ann Intern Med 2007;146:591–601.
61. Peterson L, Taylor D, Roddy R, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials 2007;2:e27.
62. Cohen MS, Kashuba AD. Antiretroviral therapy for prevention of HIV infection: new clues from an animal model. PLoS Med 2008;5:e30.
63. Karim QA, Karim SS, Frohlich JA, et al; The CAPRISA 004 Trial Group. Available at Science express/www.sciencexpress.org/19 July 2010/10.1126/science.1193748.
64. Peterman TA, Tian LH, Metcalf CA, et al. High incidence of new sexually transmitted infections in the year following a sexually transmitted infection: a case for rescreening. Ann Intern Med 2006;145:564–72.
65. Hogben M. Partner notification for sexually transmitted diseases. Clin Infect Dis 2007;44(Suppl 3):S160–74.
66. Wilson TE, Hogben M, Malka ES, et al. A randomized controlled trial for reducing risks for sexually transmitted infections through enhanced patient-based partner notification. Am J Public Health 2009;99(Suppl 1):S104–10.
67. Hodge JG, Jr., Pulver A, Hogben M, et al. Expedited partner therapy for sexually transmitted diseases: assessing the legal environment. Am J Public Health 2008;98:238–43.
68. Golden MR, Whittington WL, Handsfield HH, et al. Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection. N Engl J Med 2005;352:676–85.
69. Schillinger JA, Kissinger P, Calvet H, et al. Patient-delivered partner treatment with azithromycin to prevent repeated *Chlamydia trachomatis* infection among women: a randomized, controlled trial. Sex Transm Dis 2003;30:49–56.
70. Trelle S, Shang A, Nartey L, et al. Improved effectiveness of partner notification for patients with sexually transmitted infections: systematic review. BMJ 2007;334(7589):354.
71. Kissinger P, Mohammed H, Richardson-Alston G, et al. Patient-delivered partner treatment for male urethritis: a randomized, controlled trial. Clin Infect Dis 2005;41:623–9.
72. Kissinger P, Schmidt N, Mohammed H, et al. Patient-delivered partner treatment for *Trichomonas vaginalis* infection: a randomized controlled trial. Sex Transm Dis 2006;33:445–50.
73. Schwebke JR, Desmond RA. A randomized controlled trial of partner notification methods for prevention of trichomoniasis in women. Sex Transm Dis 2010;37:392–6.
74. Rothenberg R, Kimbrough L, Lewis-Hardy R, et al. Social network methods for endemic foci of syphilis: a pilot project. Sex Transm Dis 2000;27:12–8.
75. Ogilvie G, Knowles L, Wong E, et al. Incorporating a social networking approach to enhance contact tracing in a heterosexual outbreak of syphilis. Sex Transm Inf 2005;81:124–7.
76. Vest JR, Valadez AM, Hanner A, et al. Using e-mail to notify pseudonymous e-mail sexual partners. Sex Transm Dis 2007;34:840–5.
77. CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR 2006;55(No. RR-14).
78. CDC. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the US Department of Health and Human Services. MMWR 2005;54(No. RR-2).

79. U.S. Preventive Services Task Force. Screening for syphilis infection in pregnancy: reaffirmation recommendation statement. Ann Intern Med 2009;150:705–9.
80. U.S. Prevention Task Force. Screening for hepatitis B virus infection in pregnancy: reaffirmation recommendation statement. Ann Intern Med 2009;150:869–73.
81. U.S. Preventive Services Task Force. Screening for chlamydial infection: recommendation statement. Ann Intern Med 2007;147:128–34.
82. U.S. Preventive Services Task Force. Screening for gonorrhea: recommendation statement. Ann Fam Med 2005;3:263–7.
83. Sadler L, Saftlas A, Wang W, et al. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. JAMA 2004;291:2100–6.
84. Serati M, Uccella S, Laterza RM, et al. Natural history of cervical intraepithelial neoplasia during pregnancy. Acta Obstet Gynecol Scand 2008;87:1296–1300.
85. U.S. Preventive Services Task Force. Screening for bacterial vaginosis in pregnancy to prevent preterm delivery: recommendation statement. Ann Intern Med 2008;148:214–9.
86. Chou R, Smits AK, Huffman LH, et al. Prenatal screening for HIV: A review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2005;143:38–54.
87. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for perinatal care, 6th ed. Washington, DC: American College of Obstetricians and Gynecologists; 2007.
88. CDC. Rapid HIV antibody testing during labor and delivery for women of unknown HIV status: a practical guide and model protocol, 2004. Atlanta, GA: CDC, National Center for HIV, STD, and TB Prevention; 2004.
89. American College of Obstetricians and Gynecologists. Viral hepatitis in pregnancy. ACOG Practice Bulletin No. 86. Obstet Gynecol 2007;110:941–56.
90. Public Health Agency of Canada. Canadian guidelines on sexually transmitted infections. 2006 ed. Centre for Communicable Diseases and Infection Control; 2010. Available at http://www.phac-aspc.gc.ca/std-mts/sti-its/.
91. Meyers D, Wolff T, Gregory K, et al. USPSTF recommendations for STI screening. Am Fam Physician 2008;77:819–24.
92. Forhan SE, Gottlieb SL, Sternberg MR, et al. Prevalence of sexually transmitted infections among female adolescents aged 14 to 19 in the United States. Pediatrics 2009;124:1505–12.
93. CDC. Sexually Transmitted Disease Surveillance, 2008. Atlanta, GA: US Department of Health and Human Services, CDC; 2009.
94. CDC. Male Chlamydia Screening Consultation, Atlanta, Georgia. March 28 – 29, 2006. Meeting Report, May 2007. Available at http://www.cdc.gov/std/chlamydia/ChlamydiaScreening-males.pdf.
95. U.S. Preventive Services Task Force. Human immunodeficiency virus infection. Rockville, MD: Agency for Healthcare Research and Quality; 2007. Available at http://www.ahrq.gov/clinic/uspstf/uspshivi.htm.
96. American College of Obstetricians and Gynecologists (ACOG). Cervical cytology screening. ACOG Practice Bulletin No. 109. Obstet Gynecol 2009;114:1409–20.
97. U.S. Preventive Services Task Force. Screening for cervical cancer: recommendations. In press 2011.
98. Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. BMJ 2009;339:b2968.
99. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. J Low Genit Tract Dis 2003;7:67–86.
100. Chow JM, Joesoef MR, Kent C, et al. Responding to the burden of STD, HIV, and viral hepatitis in correctional populations through program collaboration and integration. Sex Transm Dis 2009;36(2 Suppl):S1–2.
101. Joesoef MR, Weinstock HS, Kent CK, et al. Sex and age correlates of Chlamydia prevalence in adolescents and adults entering correctional facilities, 2005: implications for screening policy. Sex Transm Dis 2009;36(2 Suppl):S67–71.
102. Kahn RH, Voigt RF, Swint E, et al. Early syphilis in the United States identified in corrections facilities, 1999–2002. Sex Transm Dis 2004;31:360–4.
103. Mayer KH, Klausner JD, Handsfield HH. Intersecting epidemics and educable moments: sexually transmitted disease risk assessment and screening in men who have sex with men. Sex Transm Dis 2001;28:464–7.
104. Kent CK, Chaw JK, Wong W, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis 2005;41:67–74.
105. Millett GA, Peterson JL, Wolitski RJ, et al. Greater risk for HIV infection of black men who have sex with men: a critical literature review. Am J Public Health 2006;96:1007–19.
106. Klausner JD, Wong W. Sexually transmitted diseases in men who have sex with men: a clinical review. Curr Infect Dis Rep 2003;5:135–44.
107. Golden MR, Stekler J, Hughes JP, et al. HIV serosorting in men who have sex with men: is it safe? J Acquir Immune Defic Syndr 2008;49:212–8.
108. CDC. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR 2008;57(No. RR-8).
109. Goodenow C, Szalacha LA, Robin LE, et al. Dimensions of sexual orientation and HIV-related risk among adolescent females: evidence from a statewide survey. Am J Public Health 2008;98:1051–8.
110. Eisenberg M. Differences in sexual risk behaviors between college students with same-sex and opposite-sex experience: results from a national survey. Arch Sex Behav 2001;30:575–89.
111. Koh AS, Gomez CA, Shade S, et al. Sexual risk factors among self-identified lesbians, bisexual women, and heterosexual women accessing primary care settings. Sex Transm Dis 2005;32:563–9.
112. Lindley L, Barnett TL, Brandt HM, et al. STDs among sexually active college students: does sexual orientation make a difference? Perspect Sex Reprod Health 2008;40(4):212–17.
113. Fethers K, Marks C, Mindel A, et al. Sexually transmitted infections and risk behaviours in women who have sex with women. Sex Transm Infect 2000;76:345–9.
114. Marrazzo JM, Koutsky LA, Eschenbach DA, et al. Characterization of vaginal flora and bacterial vaginosis in women who have sex with women. J Infect Dis 2002;185:1307–13.
115. Kellock D, O'Mahony CP. Sexually acquired metronidazole-resistant trichomoniasis in a lesbian couple. Genitourin Med. 1996;72:60–61.
116. Kwakwa HA, Ghobrial MW. Female-to-Female Transmission of Human Immunodeficiency Virus. Clin Infect Dis. 2003;36:e40–e41.
117. Berger BJ, Kolton S, Zenilman JM, Cummings MC, Feldman J, McCormack WM. Bacterial vaginosis in lesbians: a sexually transmitted disease. Clin Infect Dis. Dec 1995;21:1402–1405.
118. Marrazzo JM, Koutsky LA, Kiviat NB, et al. Papanicolaou test screening and prevalence of genital human papillomavirus among women who have sex with women. Am J Public Health 2001;91:947–52.

119. Diamant AL, Schuster MA, McGuigan K, et al. Lesbians' sexual history with men: implications for taking a sexual history. Arch Intern Med 1999;159:2730–6.
120. Marrazzo JM, Stine K, Wald A. Prevalence and risk factors for infection with herpes simplex virus type-1 and -2 among lesbians. Sex Transm Dis 2003;30:890–5.
121. Singh D, Fine D, Marrazzo JM. *Chlamydia trachomatis* infection among women reporting sexual activity with women screened in family planning clinics in the Pacific Northwest, 1997 to 2005. Am J Public Health 2010; Aug 19[epub].
122. Marrazzo JM, Antonio M, Agnew K, et al. Distribution of genital Lactobacillus strains shared by female sex partners. J Infect Dis 2009;199:680–3.
123. Smit C, Geskus R, Walker S, et al. Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion. AIDS 2006;20:741–9.
124. Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. J Infect Dis 2008;198:687–3.
125. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 2005;191:1403–9.
126. Pilcher CD, Tien HC, Eron JJ Jr., et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis 2004;189:1785–92.
127. CDC. HIV/AIDS Surveillance Report, 2008. Vol. 20. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2010. Available at http://www.cdc.gov/hiv/topics/surveillance/resources/reports/.
128. CDC. Persons tested for HIV—United States, 2006. MMWR 2008;57:845–9.
129. DHHS. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Washington, DC: US Department of Health and Human Services; 2010. Available at http://AIDSinfo.nih.gov.
130. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. MMWR 2009;58(No. RR-4).
131. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2009;49:651–81.
132. CDC. Protocols for the confirmation of reactive rapid HIV tests. MMWR 2004;53:221–2.
133. Pilcher CD, Eron JJ Jr., Vemazza PL, et al. Sexual transmission during the incubation period of primary HIV infection. JAMA 2001;286:1713–4.
134. Marks G, Crepaz N, Senterfitt JW, et al. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J Acquir Immune Defic Syndr 2005;39:446–53.
135. Myers JJ, Shade SB, Rose CD, et al. Interventions delivered in clinical settings are effective in reducing risk of HIV transmission among people living with HIV: results from the Health Resources and Services Administration (HRSA)'s Special Projects of National Significance Initiative. AIDS Behav 2010;14:483–92.
136. CDC. Incorporating HIV prevention into the medical care of persons living with HIV: recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 2003;52(No. RR-12).
137. CDC. Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydial infection. MMWR 2008;57(No. RR-9).
138. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2010. Available at www.aidsinfo.nih.gov.
139. Bulterys M, Weidle PJ, Abrams EJ, et al. Combination antiretroviral therapy in African nursing mothers and drug exposure in their infants: new pharmacokinetic and virologic findings. J Infect Dis 2005;192:709–12.
140. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Rockville, MD: US Department of Health and Human Services, National Institutes of Health, Health Resources and Services Administration; 2010. Available at http://www.aidsinfo.nih.gov.
141. Read JS. Diagnosis of HIV-1 infection in children younger than 18 months in the United States. Pediatrics 2007;120:e1547–62.
142. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2009. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf.
143. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. MMWR 2009;58(No. RR-11).
144. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999;75:3–17.
145. Lockett AE, Dance DA, Mabey DC, Drasar BS. Serum free media for the isolation of *Haemophilus ducreyi*. Lancet 1991; 338:326.
146. Lewis D. Chancroid: clinical manifestations, diagnosis and management. Sex Transm Infect 2002;79:68.
147. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA 2006;296:964–73.
148. Ryder N, Jin F, McNulty AM, et al. Increasing role of herpes simplex virus type 1 in first-episode anogenital herpes in heterosexual women and younger men who have sex with men, 1992–2006. Sex Transm Infect 2009;85:416–9.
149. Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. Sex Transm Dis 2003;30:797–800.
150. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann Intern Med 1994;121:847–54.
151. Engelberg R, Carrell D, Krantz E, et al. Natural history of genital herpes simplex virus type 1 infection. Sex Transm Dis 2003;30:174–7.
152. Scoular A. Using the evidence base on genital herpes: optimising the use of diagnostic tests and information provision. Sex Transm Infect 2002;78:160–5.
153. Scoular A, Gillespie G, Carman WF. Polymerase chain reaction for diagnosis of genital herpes in a genitourinary medicine clinic. Sex Transm Infect 2002;78:21–5.

154. Wald A, Huang ML, Carrell D, et al. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. J Infect Dis 2003;188:1345–51.
155. Ashley R, Cent A, Maggs V, et al. Inability of enzyme immunoassays to discriminate between infections with herpes simplex virus types 1 and 2. Ann Intern Med 1991;115:520–6.
156. Song B, Dwyer DE, Mindel A. HSV type specific serology in sexual health clinics: use, benefits, and who gets tested. Sex Transm Infect 2004;80:113–7.
157. Whittington WL, Celum CL, Cent A, et al. Use of a glycoprotein G-based type-specific assay to detect antibodies to herpes simplex virus type 2 among persons attending sexually transmitted disease clinics. Sex Transm Dis 2001;28:99–104.
158. Zimet GD, Rosenthal SL, Fortenberry JD, et al. Factors predicting the acceptance of herpes simplex virus type 2 antibody testing among adolescents and young adults. Sex Transm Dis 2004;31:665–69.
159. Morrow R, Friedrich D. Performance of a novel test for IgM and IgG antibodies in subjects with culture-documented genital herpes simplex virus-1 or -2 infection. Clin Microbiol Infect 2006;12:463–9.
160. Leone PA, Trottier S, Miller JM. Valacyclovir for episodic treatment of genital herpes: a shorter 3-day treatment course compared with 5-day treatment. Clin Infect Dis 2002;34:958–62.
161. Wald A, Carrell D, Remington M, et al. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. Clin Infect Dis 2002;34:944–8.
162. Aoki FY, Tyring S, az-Mitoma F, et al. Single-day, patient-initiated famciclovir therapy for recurrent genital herpes: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2006;42:8–13.
163. Chosidow O, Drouault Y, Leconte-Veyriac F, et al. Famciclovir vs. aciclovir in immunocompetent patients with recurrent genital herpes infections: a parallel-groups, randomized, double-blind clinical trial. Br J Dermatol 2001;144:818–24.
164. Bodsworth NJ, Crooks RJ, Borelli S, et al. Valaciclovir versus aciclovir in patient initiated treatment of recurrent genital herpes: a randomised, double blind clinical trial. International Valaciclovir HSV Study Group. Genitourin Med 1997;73:110–6.
165. Fife KH, Barbarash RA, Rudolph T, et al. Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection. Results of an international, multicenter, double-blind, randomized clinical trial. The Valaciclovir International Herpes Simplex Virus Study Group. Sex Transm Dis 1997;24:481–6.
166. Diaz-Mitoma F, Sibbald RG, Shafran SD, et al. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. Collaborative Famciclovir Genital Herpes Research Group. JAMA 1998;280:887–92.
167. Mertz GJ, Loveless MO, Levin MJ, et al; Collaborative Famciclovir Genital Herpes Research Group. Oral famciclovir for suppression of recurrent genital herpes simplex virus infection in women: a multicenter, double-blind, placebo-controlled trial. Arch Intern Med 1997;157:343–49.
168. Reitano M, Tyring S, Lang W, et al; International Valaciclovir HSV Study Group. Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. J Infect Dis 1998;178:603–10.
169. Romanowski B, Marina RB, Roberts JN. Patients' preference of valacyclovir once-daily suppressive therapy versus twice-daily episodic therapy for recurrent genital herpes: a randomized study. Sex Transm Dis 2003;30:226–231.
170. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med 2004;350:11–20.
171. Goldberg LH, Kaufman R, Kurtz TO, et al; Acyclovir Study Group. Long-term suppression of recurrent genital herpes with acyclovir: a 5-year benchmark. Arch Dermatol 1993;129:582–7.
172. Fife KH, Crumpacker CS, Mertz GJ, et al; Acyclovir Study Group. Recurrence and resistance patterns of herpes simplex virus following cessation of ≥6 years of chronic suppression with acyclovir. J Infect Dis 1994;169:1338–41.
173. Wald A, Selke S, Warren T, et al. Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and viral shedding. Sex Transm Dis 2006;33:529–33.
174. Gilbert LK, Wyand F. Genital herpes education and counseling: testing a one-page, FAQ intervention. Herpes 2009;15:51–6.
175. Rosenthal SL, Zimet GD, Leichliter JS, et al. The psychosocial impact of serological diagnosis of asymptomatic herpes simplex virus type 2 infection. Sex Transm Infect 2006;82:154–7.
176. Miyai T, Turner KR, Kent CK, et al. The psychosocial impact of testing individuals with no history of genital herpes for herpes simplex virus type 2. Sex Transm Dis 2004;31:517–21.
177. Watson-Jones D, Weiss HA, Rusizoka M, et al. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. N Engl J Med 2008;358:1560–71.
178. Celum C, Wald A, Hughes J, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet 2008;371(9630):2109–19.
179. Henry RE, Wegmann JA, Hartle JE, et al. Successful oral acyclovir desensitization. Ann Allergy 1993;70:386–8.
180. Posavad CM, Wald A, Kuntz S, et al. Frequent reactivation of herpes simplex virus among HIV-1-infected patients treated with highly active antiretroviral therapy. J Infect Dis 2004;190:693–6.
181. Conant MA, Schacker TW, Murphy RL, et al. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. Int J STD AIDS 2002;13:12–21.
182. Romanowski B, Aoki FY, Martel AY, et al. Efficacy and safety of famciclovir for treating mucocutaneous herpes simplex infection in HIV-infected individuals. Collaborative Famciclovir HIV Study Group. AIDS 2000;14:1211–7.
183. DeJesus E, Wald A, Warren T, et al. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. J Infect Dis 2003;188:1009–16.
184. Reyes M, Shaik NS, Graber JM, et al. Acyclovir-resistant genital herpes among persons attending sexually transmitted disease and human immunodeficiency virus clinics. Arch Intern Med 2003;163:76–80.
185. Erard V, Wald A, Corey L, et al. Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: impact on herpes simplex virus (HSV) disease and drug-resistant HSV disease. J Infect Dis 2007;196:266–70.
186. Brown ZA, Selke S, Zeh, et al. Acquisition of herpes simplex virus during pregnancy. N Engl J Med 1997;337:509–15.
187. Brown ZA, Wald A, Morrow RA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003;289:203–9.
188. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the international acyclovir pregnancy registry, 1984–1999. Birth Defects Res A Clin Mol Teratol 2004;70:201–7.

189. Sheffield JS, Hollier LM, Hill JB, et al. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. Obstet Gynecol 2003;102:1396–1403.
190. Watts DH, Brown ZA, Money D, et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. Am J Obstet Gynecol 2003;188:836–43.
191. Scott LL, Hollier LM, McIntire D, et al. Acyclovir suppression to prevent recurrent genital herpes at delivery. Infect Dis Obstet Gynecol 2002;10:71–7.
192. O'Farrell N. Donovanosis. Sex Transm Infect 2002;78:452–7.
193. Bowden FJ. Donovanosis in Australia: going, going. Sex Transm Infect 2005;81:365–6.
194. Mabey D, Peeling RW. Lymphogranuloma venereum. Sex Transm Infect 2002;78:90–2.
195. Nieuwenhuis RF, Ossewaarde JM, Gotz HM, et al. Resurgence of lymphogranuloma venereum in Western Europe: an outbreak of *Chlamydia trachomatis* serovar l2 proctitis in the Netherlands among men who have sex with men. Clin Infect Dis 2004;39:996–1003.
196. Ward H, Martin I, Macdonald N, et al. Lymphogranuloma venereum in the United Kingdom. Clin Infect Dis 2007;44:26–32.
197. CDC. Guidelines for the laboratory diagnosis of gonorrhea, chlamydia and syphilis. Available at http://www.aphl.org/aphlprograms/infectious/std/Pages/stdtestingguidelines.aspx.
198. Nandwani R, Evans DT. Are you sure it's syphilis? A review of false positive serology. Int J STD AIDS 1995;6:241–8.
199. Association of Public Health Laboratories (APHL). Laboratory Diagnostic Testing for Treponema pallidum. Expert Consultation Meeting Summary Report, January 13–15, 2009, Atlanta, GA. Available at http://www.aphl.org/aphlprograms/infectious/std/Documents/LaboratoryGuidelinesTreponemapallidumMeetingReport.pdf.
200. Romanowski B, Sutherland R, Fick GH, et al. Serologic response to treatment of infectious syphilis. Ann Intern Med 1991;114:1005–9.
201. CDC. Syphilis testing algorithms using treponemal tests for initial screening–four laboratories, New York City, 2005–2006. MMWR 2008;57:872–5.
202. Pope V. Use of treponemal tests to screen for syphilis. Infect Med 2004;21:399–402.
203. Lukehart SA, Hook EW, III, Baker-Zander SA, et al. Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. Ann Intern Med 1988;109:855–62.
204. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis 2004;189:369–76.
205. Jaffe HW, Larsen SA, Peters M, et al. Tests for treponemal antibody in CSF. Arch Intern Med 1978;138:252–5.
206. CDC. Inadvertent use of Bicillin® C-R to treat syphilis infection — Los Angeles, California, 1999–2004. MMWR 2005;54:217–9.
207. Ghanem KG, Erbelding EJ, Wiener ZS, et al. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics. Sex Transm Infect 2007;83:97–101.
208. Rolfs RT, Joesoef MR, Hendershot EF, et al; The Syphilis and HIV Study Group. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. N Engl J Med 1997;337:307–14.
209. Ghanem KG, Erbelding EJ, Cheng WW, et al. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. Clin Infect Dis 2006;42:e45–9.
210. Wong T, Singh AE, De P. Primary syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. Am J Med 2008;121:903–8.
211. Hook EW, III, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. J Infect Dis 1988;158:881–4.
212. Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. N Engl J Med 2005;353:1236–44.
213. Hook EW, III, Martin DH, Stephens J, et al. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. Sex Transm Dis 2002;29:486–90.
214. Hook EW, III, Behets F, Van DK, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. J Infect Dis 2010;201:1729–35.
215. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. N Engl J Med 2004;351:154–8.
216. Mitchell SJ, Engelman J, Kent CK, et al. Azithromycin-resistant syphilis infection: San Francisco, California, 2000–2004. Clin Infect Dis 2006;42:337–45.
217. Su JR, Hook E, Kenney K, et al. Prevalence of the 23S rRNA point mutation in *Treponema pallidum* in the United States and Associated Factors, 2006–2008. 18th International Society for Sexually Transmitted Diseases Research, #OS1.11.03. London, England: June 2009.
218. Marra CM, Boutin P, McArthur JC, et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. Clin Infect Dis 2000;30:540–4.
219. Marra CM, Maxwell CL, Tantalo L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? Clin Infect Dis 2004;38:1001–6.
220. Marra CM, Maxwell CL, Tantalo LC, et al. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. Clin Infect Dis 2008;47:893–9.
221. Hook EW, III, Baker-Zander SA, Moskovitz BL, et al. Ceftriaxone therapy for asymptomatic neurosyphilis. Case report and Western blot analysis of serum and cerebrospinal fluid IgG response to therapy. Sex Transm Dis 1986;13(3 Suppl):S185–8.
222. Shann S, Wilson J. Treatment of neurosyphilis with ceftriaxone. Sex Transm Infect 2003;79:415–6.
223. Kingston AA, Vujevich J, Shapiro M, et al. Seronegative secondary syphilis in 2 patients coinfected with human immunodeficiency virus. Arch Dermatol 2005;141:431–3.
224. CDC. Symptomatic early neurosyphilis among HIV-positive men who have sex with men: four cities, United States, January 2002–June 2004. MMWR 2007;56:625–8.
225. Libois A, De WS, Poll B, et al. HIV and syphilis: when to perform a lumbar puncture. Sex Transm Dis 2007;34:141–4.
226. Ghanem KG. Sensitivity and specificity of lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms reply. Clin Infect Dis 2009;49:162–3.
227. Ghanem KG, Moore RD, Rompalo AM, et al. Neurosyphilis in a clinical cohort of HIV-1-infected patients. AIDS 2008;22:1145–51.
228. Ghanem KG, Moore RD, Rompalo AM, et al. Antiretroviral therapy is associated with reduced serologic failure rates for syphilis among HIV-infected patients. Clin Infect Dis 2008;47:258–65.

229. Dowell ME, Ross PG, Musher DM, et al. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. Am J Med 1992;93:481–8.
230. Smith NH, Musher DM, Huang DB, et al. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. Int J STD AIDS 2004;15:328–32.
231. Hollier LM, Harstad TW, Sanchez PJ, et al. Fetal syphilis: clinical and laboratory characteristics. Obstet Gynecol 2001;97:947–53.
232. World Health Organization. The global elimination of congenital syphilis: rationale and strategy for action. Geneva: WHO Department of Reproductive Health and Research; 2005.
233. Alexander JM, Sheffield JS, Sanchez PJ, et al. Efficacy of treatment for syphilis in pregnancy. Obstet Gynecol 1999;93:5–8.
234. Walker GJ. Antibiotics for syphilis diagnosed during pregnancy. Cochrane Database Syst Rev 2001;CD001143.
235. Wendel GD, Jr., Sheffield JS, Hollier LM, et al. Treatment of syphilis in pregnancy and prevention of congenital syphilis. Clin Infect Dis 2002;35(Suppl 2):S200–9.
236. Klein VR, Cox SM, Mitchell MD, et al. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. Obstet Gynecol 1990;75(3 Pt 1):375–80.
237. Katz KA, Klausner JD. Azithromycin resistance in *Treponema pallidum*. Curr Opin Infect Dis 2008;21:83–91.
238. Saxon A, Beall GN, Rohr AS, et al. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med 1987;107:204–15.
239. Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. Am J Med 2008;121:572–6.
240. Manhart LE, Holmes KK, Hughes JP, et al. *Mycoplasma genitalium* among young adults in the United States: an emerging sexually transmitted infection. Am J Public Health 2007;97:1118–25.
241. Ross JD, Jensen JS. *Mycoplasma genitalium* as a sexually transmitted infection: implications for screening, testing, and treatment. Sex Transm Infect 2006;82:269–71.
242. Taylor-Robinson D, Gilroy CB, Thomas BJ, et al. *Mycoplasma genitalium* in chronic non-gonococcal urethritis. Int J STD AIDS 2004;15:21–5.
243. Dupin N, Bijaoui G, Schwarzinger M, et al. Detection and quantification of *Mycoplasma genitalium* in male patients with urethritis. Clin Infect Dis 2003;37:602–5.
244. Bradshaw CS, Tabrizi SN, Read TR, et al. Etiologies of nongonococcal urethritis: bacteria, viruses, and the association with orogenital exposure. J Infect Dis 2006;193:336–45.
245. Madeb R, Nativ O, Benilevi D, et al. Need for diagnostic screening of herpes simplex virus in patients with nongonococcal urethritis. Clin Infect Dis 2000;30:982–3.
246. Martin DH. Nongonococcal urethritis: new views through the prism of modern molecular microbiology. Curr Infect Dis Rep 2008;10:128–32.
247. Schwebke JR, Hook EW, III. High rates of *Trichomonas vaginalis* among men attending a sexually transmitted diseases clinic: implications for screening and urethritis management. J Infect Dis 2003;188:465–8.
248. Geisler WM, Yu S, Hook EW, III. Chlamydial and gonococcal infection in men without polymorphonuclear leukocytes on gram stain: implications for diagnostic approach and management. Sex Transm Dis 2005;32:630–4.
249. Falk L, Fredlund H, Jensen JS. Tetracycline treatment does not eradicate *Mycoplasma genitalium*. Sex Transm Infect 2003;79:318–9.
250. Mena LA, Mroczkowski TF, Nsuami M, et al. A randomized comparison of azithromycin and doxycycline for the treatment of *Mycoplasma genitalium*-positive urethritis in men. Clin Infect Dis 2009;48:1649–54.
251. Fung M, Scott KC, Kent CK, et al. Chlamydial and gonococcal reinfection among men: a systematic review of data to evaluate the need for retesting. Sex Transm Infect 2007;83:304–9.
252. Kissinger PJ, Reilly K, Taylor SN, et al. Early repeat *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections among heterosexual men. Sex Transm Dis 2009;36:498–500.
253. Jernberg E, Moghaddam A, Moi H. Azithromycin and moxifloxacin for microbiological cure of *Mycoplasma genitalium* infection: an open study. Int J STD AIDS 2008;19:676–9.
254. Bradshaw CS, Chen MY, Fairley CK. Persistence of *Mycoplasma genitalium* following azithromycin therapy. PLoS One 2008;3:e3618.
255. Meares EM, Stamey TA. Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest Urol 1968;5:492–518.
256. Nickel JC, Alexander RB, Schaeffer AJ, et al. Leukocytes and bacteria in men with chronic prostatitis/chronic pelvic pain syndrome compared to asymptomatic controls. J Urol 2003;170:818–22.
257. Lusk MJ, Konecny P. Cervicitis: a review. Curr Opin Infect Dis 2008;21:49–55.
258. Marrazzo JM, Martin DH. Management of women with cervicitis. Clin Infect Dis 2007;44 (Suppl 3):S102–10.
259. Korte JE, Baseman JB, Cagle MP, et al. Cervicitis and genitourinary symptoms in women culture positive for *Mycoplasma genitalium*. Am J Reprod Immunol 2006;55:265–75.
260. Gaydos C, Maldeis NE, Hardick A, et al. *Mycoplasma genitalium* as a contributor to the multiple etiologies of cervicitis in women attending sexually transmitted disease clinics. Sex Transm Dis 2009;36:598–606.
261. Schwebke JR, Weiss HL. Interrelationships of bacterial vaginosis and cervical inflammation. Sex Transm Dis 2002;29:59–64.
262. Marrazzo JM, Wiesenfeld HC, Murray PJ, et al. Risk factors for cervicitis among women with bacterial vaginosis. J Infect Dis 2006;193:617–24.
263. Haggerty CL, Totten PA, Astete SG, et al. *Mycoplasma genitalium* among women with nongonococcal, nonchlamydial pelvic inflammatory disease. Infect Dis Obstet Gynecol 2006; Article ID 30184:1–5.
264. Steinhandler L, Peipert JF, Heber W, et al. Combination of bacterial vaginosis and leukorrhea as a predictor of cervical chlamydial or gonococcal infection. Obstet Gynecol 2002;99:603–7.
265. Geisler WM, Yu S, Venglarik M, et al. Vaginal leucocyte counts in women with bacterial vaginosis: relation to vaginal and cervical infections. Sex Transm Infect 2004;80:401–5.
266. Manhart LE. Has the time come to systematically test for *Mycoplasma genitalium*? Sex Transm Dis 2009;36:607–8.
267. Hosenfeld CB, Workowski KA, Berman S, et al. Repeat infection with chlamydia and gonorrhea among females: a systematic review of the literature. Sex Transm Dis 2009;36:478–89.
268. Coleman JS, Hitti J, Bukusi EA, et al. Infectious correlates of HIV-1 shedding in the female upper and lower genital tracts. AIDS 2007;21:755–9.
269. Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis. Sex Transm Dis 2008;35:946–59.
270. Mcclelland RS, Wang CC, Mandaliya K, et al. Treatment of cervicitis is associated with decreased cervical shedding of HIV-1. AIDS 2001;15:105–10.

271. Meyers DS, Halvorson H, Luckhaupt S. Screening for chlamydial infection: an evidence update for the U.S. Preventive Services Task Force. Ann Intern Med 2007;147:135–42.
272. Scholes D, Stergachis A, Heidrich FE, et al. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. N Engl J Med 1996;334:1362–6.
273. Kamwendo F, Forslin L, Bodin L, et al. Decreasing incidences of gonorrhea- and chlamydia-associated acute pelvic inflammatory disease: a 25-year study from an urban area of central Sweden. Sex Transm Dis 1996;23:384–91.
274. Gift TL, Blake DR, Gaydos CA, et al. The cost-effectiveness of screening men for *Chlamydia trachomatis*: a review of the literature. Sex Transm Dis 2008;35(11 Suppl):S51–60.
275. Gift TL, Gaydos CA, Kent CK, et al. The program cost and cost-effectiveness of screening men for chlamydia to prevent pelvic inflammatory disease in women. Sex Transm Dis 2008;35(11 Suppl):S66–75.
276. Schachter J, Chernesky MA, Willis DE, et al. Vaginal swabs are the specimens of choice when screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*: results from a multicenter evaluation of the APTIMA assays for both infections. Sex Transm Dis 2005;32:725–8.
277. Doshi JS, Power J, Allen E. Acceptability of chlamydia screening using self-taken vaginal swabs. Int J STD AIDS 2008;19:507–9.
278. Schachter J, Moncada J, Liska S, et al. Nucleic acid amplification tests in the diagnosis of chlamydial and gonococcal infections of the oropharynx and rectum in men who have sex with men. Sex Transm Dis 2008;35:637–42.
279. Mimiaga MJ, Mayer KH, Reisner SL, et al. Asymptomatic gonorrhea and chlamydial infections detected by nucleic acid amplification tests among Boston area men who have sex with men. Sex Transm Dis 2008;35:495–8.
280. Bachmann LH, Johnson RE, Cheng H, et al. Nucleic acid amplification tests for diagnosis of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* rectal infections. J Clin Microbiol 2010;48:1827–32.
281. Bachmann LH, Johnson RE, Cheng H, et al. Nucleic acid amplification tests for diagnosis of *Neisseria gonorrhoeae* oropharyngeal infections. J Clin Microbiol 2009;47:902–7.
282. Chernesky M, Freund GG, Hook E, III, et al. Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in North American women by testing SurePath liquid-based Pap specimens in APTIMA assays. J Clin Microbiol 2007;45:2434–8.
283. Geisler WM, Wang C, Morrison SG, et al. The natural history of untreated *Chlamydia trachomatis* infection in the interval between screening and returning for treatment. Sex Transm Dis 2008;35:119–23.
284. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. Sex Transm Dis 2002;29:497–502.
285. Bernstein KT, Stephens SC, Barry PM, et al. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* transmission from the oropharynx to the urethra among men who have sex with men. Clin Infect Dis 2009;49:1793–7.
286. Dunne EF, Chapin JB, Rietmeijer CA, et al. Rate and predictors of repeat *Chlamydia trachomatis* infection among men. Sex Transm Dis 2008;35(11 Suppl):S40–4.
287. Kjaer HO, Dimcevski G, Hoff G, et al. Recurrence of urogenital *Chlamydia trachomatis* infection evaluated by mailed samples obtained at home: 24 weeks' prospective follow up study. Sex Transm Infect 2000;76:169–72.
288. Whittington WL, Kent C, Kissinger P, et al. Determinants of persistent and recurrent *Chlamydia trachomatis* infection in young women: results of a multicenter cohort study. Sex Transm Dis 2001;28:117–123.
289. Jacobson GF, Autry AM, Kirby RS, et al. A randomized controlled trial comparing amoxicillin and azithromycin for the treatment of *Chlamydia trachomatis* in pregnancy. Am J Obstet Gynecol 2001;184:1352–4.
290. Kacmar J, Cheh E, Montagno A, et al. A randomized trial of azithromycin versus amoxicillin for the treatment of *Chlamydia trachomatis* in pregnancy. Infect Dis Obstet Gynecol 2001;9:197–202.
291. Rahangdale L, Guerry S, Bauer HM, et al. An observational cohort study of *Chlamydia trachomatis* treatment in pregnancy. Sex Transm Dis 2006;33:106–110.
292. Hammerschlag MR, Gelling M, Roblin PM, et al. Treatment of neonatal chlamydial conjunctivitis with azithromycin. Pediatr Infect Dis J 1998;17:1049–50.
293. Weinstock H, Berman S, Cates W, Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. Perspect Sex Reprod Health 2004;36:6–10.
294. Lyss SB, Kamb ML, Peterman TA, et al. *Chlamydia trachomatis* among patients infected with and treated for *Neisseria gonorrhoeae* in sexually transmitted disease clinics in the United States. Ann Intern Med 2003;139:178–85.
295. Sathia L, Ellis B, Phillip S, et al. Pharyngeal gonorrhoea—is dual therapy the way forward? Int J STD AIDS 2007;18:647–8.
296. Golden M, Kerani R, Shafii T, Whittington W, Holmes K. Does azithromycin co-treatment enhance the efficacy of oral cephalosporins for pharyngeal gonorrhea? Presented at: 18th International Society for STD Research (ISSTDR) Conference, London, UK, June 2009.
297. Workowski KA, Berman SM, Douglas JM, Jr. Emerging antimicrobial resistance in *Neisseria gonorrhoeae*: urgent need to strengthen prevention strategies. Ann Intern Med 2008;148:606–13.
298. Tapsall JW. What management is there for gonorrhea in the postquinolone era? Sex Transm Dis 2006;33:8–10.
299. CDC. Update to CDC's sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. MMWR 2007;56:332–6.
300. Tapsall J, Read P, Carmody C, et al. Two cases of failed ceftriaxone treatment in pharyngeal gonorrhoea verified by molecular microbiological methods. J Med Microbiol 2009;58(Pt 5):683–7.
301. Lo JY, Ho KM, Leung AO, et al. Ceftibuten resistance and treatment failure of *Neisseria gonorrhoeae* infection. Antimicrob Agents Chemother 2008;52:3564–7.
302. Deguchi T, Yasuda M, Yokoi S, et al. Treatment of uncomplicated gonococcal urethritis by double-dosing of 200 mg cefixime at a 6-h interval. J Infect Chemother 2003;9:35–9.
303. Yokoi S, Deguchi T, Ozawa T, et al. Threat to cefixime treatment for gonorrhea. Emerg Infect Dis 2007;13:1275–7.
304. Muratani T, Akasaka S, Kobayashi T, et al. Outbreak of cefozopran (penicillin, oral cephems, and aztreonam)-resistant *Neisseria gonorrhoeae* in Japan. Antimicrob Agents Chemother 2001;45:3603–6.
305. Wang SA, Lee MV, O'Connor N, et al. Multidrug-resistant *Neisseria gonorrhoeae* with decreased susceptibility to cefixime-Hawaii, 2001. Clin Infect Dis 2003;37:84952.
306. Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis 1995;20 Suppl 1:S47–S65.
307. Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhea in adults in the United States. Clin Infect Dis 2007;44 Suppl 3:S84–101.

308. Pandori M, Barry PM, Wu A, et al. Mosaic penicillin-binding protein 2 in *Neisseria gonorrhoeae* isolates collected in 2008 in San Francisco, California. Antimicrob Agents Chemother 2009;53:4032–4.
309. Ison CA, Mouton JW, Jones K, et al. Which cephalosporin for gonorrhoea? Sex Transm Infect 2004;80:386–8.
310. CDC. Notice to Readers: Discontinuation of Spectinomycin. MMWR 2006;55:370.
311. Waters LJ, Boag FC, Betournay R. Efficacy of azithromycin 1 g single dose in the management of uncomplicated gonorrhoea. Int J STD AIDS 2005;16:84.
312. McLean CA, Wang SA, Hoff GL, et al. The emergence of *Neisseria gonorrhoeae* with decreased susceptibility to azithromycin in Kansas City, Missouri, 1999 to 2000. Sex Transm Dis 2004;31:73–8.
313. Chisholm SA, Neal TJ, Alawattegama AB, et al. Emergence of high-level azithromycin resistance in *Neisseria gonorrhoeae* in England and Wales. J Antimicrob Chemother 2009;64:353–8.
314. Linhart Y, Shohat T, Amitai Z, et al. Sexually transmitted infections among brothel-based sex workers in Tel-Aviv area, Israel: high prevalence of pharyngeal gonorrhoea. Int J STD AIDS 2008;19:656–9.
315. Ota KV, Fisman DN, Tamari IE, et al. Incidence and treatment outcomes of pharyngeal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections in men who have sex with men: a 13-year retrospective cohort study. Clin Infect Dis 2009;48:1237–43.
316. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics 2005;115:1048–57.
317. Haimovici R, Roussel TJ. Treatment of gonococcal conjunctivitis with single-dose intramuscular ceftriaxone. Am J Ophthalmol 1989;107:511–4.
318. Koumans EH, Sternberg M, Bruce C, et al. The prevalence of bacterial vaginosis in the United States, 2001–2004: associations with symptoms, sexual behaviors, and reproductive health. Sex Transm Dis 2007;34:864–9.
319. Amsel R, Totten PA, Spiegel CA, et al. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med 1983;74:14–22.
320. Schwebke JR, Hillier SL, Sobel JD, et al. Validity of the vaginal gram stain for the diagnosis of bacterial vaginosis. Obstet Gynecol 1996;88(4 Pt 1):573–6.
321. Fredricks DN, Fiedler TL, Thomas KK, et al. Targeted PCR for detection of vaginal bacteria associated with bacterial vaginosis. J Clin Microbiol 2007;45:3270–6.
322. Schwebke JR, Desmond R. A randomized trial of metronidazole in asymptomatic bacterial vaginosis to prevent the acquisition of sexually transmitted diseases. Am J Obstet Gynecol 2007;196:517–6.
323. Livengood CH, III, Ferris DG, Wiesenfeld HC, et al. Effectiveness of two tinidazole regimens in treatment of bacterial vaginosis: a randomized controlled trial. Obstet Gynecol 2007;110(2 Pt 1):302–9.
324. Sobel J, Peipert JF, McGregor JA, et al. Efficacy of clindamycin vaginal ovule (3-day treatment) vs. clindamycin vaginal cream (7-day treatment) in bacterial vaginosis. Infect Dis Obstet Gynecol 2001;9:9–15.
325. Antonio MA, Meyn LA, Murray PJ, et al. Vaginal colonization by probiotic *Lactobacillus crispatus* CTV-05 is decreased by sexual activity and endogenous Lactobacilli. J Infect Dis 2009;199:1506–13.
326. Mastromarino P, Macchia S, Meggiorini L, et al. Effectiveness of Lactobacillus-containing vaginal tablets in the treatment of symptomatic bacterial vaginosis. Clin Microbiol Infect 2009;15:67–74.
327. Hemmerling A, Harrison W, Schroeder A, et al. Phase 1 dose-ranging safety trial of *Lactobacillus crispatus* CTV-05 for the prevention of bacterial vaginosis. Sex Transm Dis 2009;36:564–9.
328. Ferris MJ, Masztal A, Aldridge KE, et al. Association of Atopobium vaginae, a recently described metronidazole resistant anaerobe, with bacterial vaginosis. BMC Infect Dis 2004;4:5.
329. Bradshaw CS, Tabrizi SN, Fairley CK, et al. The association of *Atopobium vaginae* and *Gardnerella vaginalis* with bacterial vaginosis and recurrence after oral metronidazole therapy. J Infect Dis 2006;194:828–36.
330. Marrazzo JM, Thomas KK, Fiedler TL, et al. Relationship of specific vaginal bacteria and bacterial vaginosis treatment failure in women who have sex with women. Ann Intern Med 2008;149:20–8.
331. Meltzer MC, Desmond RA, Schwebke JR. Association of Mobiluncus curtisii with recurrence of bacterial vaginosis. Sex Transm Dis 2008;35:611–3.
332. Beigi RH, Austin MN, Meyn LA, et al. Antimicrobial resistance associated with the treatment of bacterial vaginosis. Am J Obstet Gynecol 2004;191:1124–9.
333. Nyirjesy P, McIntosh MJ, Steinmetz JI, et al. The effects of intravaginal clindamycin and metronidazole therapy on vaginal mobiluncus morphotypes in patients with bacterial vaginosis. Sex Transm Dis 2007;34:197–202.
334. Bunge KE, Beigi RH, Meyn LA, et al. The efficacy of retreatment with the same medication for early treatment failure of bacterial vaginosis. Sex Transm Dis 2009;36:711–3.
335. Sobel JD, Ferris D, Schwebke J, et al. Suppressive antibacterial therapy with 0.75% metronidazole vaginal gel to prevent recurrent bacterial vaginosis. Am J Obstet Gynecol 2006;194:1283–9.
336. Reichman O, Akins R, Sobel JD. Boric acid addition to suppressive antimicrobial therapy for recurrent bacterial vaginosis. Sex Transm Dis 2009;36:732–4.
337. Mcclelland RS, Richardson BA, Hassan WM, et al. Improvement of vaginal health for Kenyan women at risk for acquisition of human immunodeficiency virus type 1: results of a randomized trial. J Infect Dis 2008;197:1361–8.
338. Hauth JC, Goldenberg RL, Andrews WW, et al. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. N Engl J Med 1995;333:1732–6.
339. Morales WJ, Schorr S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study. Am J Obstet Gynecol 1994;171:345–7.
340. Yudin MH, Landers DV, Meyn L, et al. Clinical and cervical cytokine response to treatment with oral or vaginal metronidazole for bacterial vaginosis during pregnancy: a randomized trial. Obstet Gynecol 2003;102:527–34.
341. Ugwumadu A, Reid F, Hay P, et al. Natural history of bacterial vaginosis and intermediate flora in pregnancy and effect of oral clindamycin. Obstet Gynecol 2004;104:114–9.
342. Burtin P, Taddio A, Ariburnu O, et al. Safety of metronidazole in pregnancy: a meta-analysis. Am J Obstet Gynecol 1995;172(2 Pt 1):525–9.
343. Piper JM, Mitchel EF, Ray WA. Prenatal use of metronidazole and birth defects: no association. Obstet Gynecol 1993;82:348–52.
344. Odendaal HJ, Popov I, Schoeman J, et al. Preterm labour—is bacterial vaginosis involved? S Afr Med J 2002;92:231–4.

345. Carey JC, Klebanoff MA, Hauth JC, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 2000;342:534–40.
346. Vermeulen GM, Bruinse HW. Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a randomised placebo-controlled double-blind trial. Br J Obstet Gynaecol 1999;106:652–7.
347. McDonald HM, O'Loughlin JA, Vigneswaran R, et al. Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (*Gardnerella vaginalis*): a randomised, placebo controlled trial. Br J Obstet Gynaecol 1997;104:1391–7.
348. Hay P, Ugwumadu AHN, Manyonda IT. Oral clindamycin prevents spontaneous preterm birth and mid trimester miscarriage in pregnant women with bacterial vaginosis. Int J STD AIDS 2001;12(Suppl 2):70–1.
349. Lamont RF, Duncan SL, Mandal D, et al. Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora. Obstet Gynecol 2003;101:516–22.
350. McGregor JA, French JI, Jones W, et al. Bacterial vaginosis is associated with prematurity and vaginal fluid mucinase and sialidase: results of a controlled trial of topical clindamycin cream. Am J Obstet Gynecol 1994;170:1048–59.
351. Joesoef MR, Hillier SL, Wiknjosastro G, et al. Intravaginal clindamycin treatment for bacterial vaginosis: effects on preterm delivery and low birth weight. Am J Obstet Gynecol 1995;173:1527–31.
352. Jamieson DJ, Duerr A, Klein RS, et al. Longitudinal analysis of bacterial vaginosis: findings from the HIV epidemiology research study. Obstet Gynecol 2001;98:656–63.
353. Van Der PB, Williams JA, Orr DP, et al. Prevalence, incidence, natural history, and response to treatment of *Trichomonas vaginalis* infection among adolescent women. J Infect Dis 2005;192:2039–44.
354. Sutton M, Sternberg M, Koumans EH, et al. The prevalence of *Trichomonas vaginalis* infection among reproductive-age women in the United States, 2001–2004. Clin Infect Dis 2007;45:1319–26.
355. Lara-Torre E, Pinkerton JS. Accuracy of detection of *Trichomonas vaginalis* organisms on a liquid-based papanicolaou smear. Am J Obstet Gynecol 2003;188:354–6.
356. Van Der PB, Kraft CS, Williams JA. Use of an adaptation of a commercially available PCR assay aimed at diagnosis of chlamydia and gonorrhea to detect *Trichomonas vaginalis* in urogenital specimens. J Clin Microbiol 2006;44:366–73.
357. Hardick A, Hardick J, Wood BJ, et al. Comparison between the Gen-Probe transcription-mediated amplification *Trichomonas vaginalis* research assay and real-time PCR for *Trichomonas vaginalis* detection using a Roche LightCycler instrument with female self-obtained vaginal swab samples and male urine samples. J Clin Microbiol 2006;44:4197–9.
358. Huppert JS, Mortensen JE, Reed JL, et al. Rapid antigen testing compares favorably with transcription-mediated amplification assay for the detection of *Trichomonas vaginalis* in young women. Clin Infect Dis 2007;45:194–8.
359. Nye MB, Schwebke JR, Body BA. Comparison of APTIMA *Trichomonas vaginalis* transcription-mediated amplification to wet mount microscopy, culture, and polymerase chain reaction for diagnosis of trichomoniasis in men and women. Am J Obstet Gynecol 2009;200:188–97.
360. Francis SC, Kent CK, Klausner JD, et al. Prevalence of rectal *Trichomonas vaginalis* and *Mycoplasma genitalium* in male patients at the San Francisco STD clinic, 2005–2006. Sex Transm Dis 2008;35:797–800.
361. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. Cochrane Database Syst Rev 2003;(2):CD000218.
362. Schmid G, Narcisi E, Mosure D, et al. Prevalence of metronidazole-resistant *Trichomonas vaginalis* in a gynecology clinic. J Reprod Med 2001;46:545–9.
363. Schwebke JR, Barrientes FJ. Prevalence of *Trichomonas vaginalis* isolates with resistance to metronidazole and tinidazole. Antimicrob Agents Chemother 2006;50:4209–10.
364. Pearlman MD, Yashar C, Ernst S, et al. An incremental dosing protocol for women with severe vaginal trichomoniasis and adverse reaction to metronidazole. Am J Obstet Gynecol 1996;174:934–6.
365. Kurohara ML, Kwong FK, Lebherz TB, et al. Metronidazole hypersensitivity and oral desensitization. J Allergy Clin Immunol 1991;88:279–80.
366. Helms DJ, Mosure DJ, Secor WE, et al. Management of *Trichomonas vaginalis* in women with suspected metronidazole hypersensitivity. Am J Obstet Gynecol 2008;198:370–7.
367. Klebanoff MA, Carey JC, Hauth JC, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic *Trichomonas vaginalis* infection. N Engl J Med 2001;345:487–93.
368. Kigozi GG, Brahmbhatt H, Wabwire-Mangen F, et al. Treatment of Trichomonas in pregnancy and adverse outcomes of pregnancy: a subanalysis of a randomized trial in Rakai, Uganda. Am J Obstet Gynecol 2003;189:1398–1400.
369. Caro-Paton T, Carvajal A, Martin dD, I, et al. Is metronidazole teratogenic? A meta-analysis. Br J Clin Pharmacol 1997;44:179–82.
370. Van Der PB, Kwok C, Pierre-Louis B, et al. *Trichomonas vaginalis* infection and human immunodeficiency virus acquisition in African women. J Infect Dis 2008;197:548–54.
371. Moodley P, Wilkinson D, Connolly C, et al. Influence of HIV-1 coinfection on effective management of abnormal vaginal discharge. Sex Transm Dis 2003;30:1–5.
372. Moodley P, Wilkinson D, Connolly C, et al. *Trichomonas vaginalis* is associated with pelvic inflammatory disease in women infected with human immunodeficiency virus. Clin Infect Dis 2002;34:519–22.
373. McClelland RS, Sangare L, Hassan WM, et al. Infection with *Trichomonas vaginalis* increases the risk of HIV-1 acquisition. J Infect Dis 2007;195:698–702.
374. Kissinger P, Secor WE, Leichliter JS, et al. Early repeated infections with *Trichomonas vaginalis* among HIV-positive and HIV-negative women. Clin Infect Dis 2008;46:994–9.
375. Kissinger P, Amedee A, Clark RA, et al. *Trichomonas vaginalis* treatment reduces vaginal HIV-1 shedding. Sex Transm Dis 2009;36:11–6.
376. Tuomala RE, O'Driscoll PT, Bremer JW, et al. Cell-associated genital tract virus and vertical transmission of human immunodeficiency virus type 1 in antiretroviral-experienced women. J Infect Dis 2003;187:375–84.
377. Wang CC, Mcclelland RS, Reilly M, et al. The effect of treatment of vaginal infections on shedding of human immunodeficiency virus type 1. J Infect Dis 2001;183:1017–22.
378. Niccolai LM, Kopicko JJ, Kassie A, et al. Incidence and predictors of reinfection with *Trichomonas vaginalis* in HIV-infected women. Sex Transm Dis 2000;27:284–8.

379. Kissinger P, Mena L, Levison J, et al. A randomized treatment trial: single versus 7-day dose of metronidazole for the treatment of *Trichomonas vaginalis* among HIV-infected women. J Acquir Immune Defic Syndr 2010;55:565-71.
380. Sobel JD, Chaim W, Nagappan V, et al. Treatment of vaginitis caused by *Candida glabrata*: use of topical boric acid and flucytosine. Am J Obstet Gynecol 2003;189:1297–1300.
381. Vazquez JA, Peng G, Sobel JD, et al. Evolution of antifungal susceptibility among Candida species isolates recovered from human immunodeficiency virus-infected women receiving fluconazole prophylaxis. Clin Infect Dis 2001;33:1069–75.
382. Wiesenfeld HC, Sweet RL, Ness RB, et al. Comparison of acute and subclinical pelvic inflammatory disease. Sex Transm Dis 2005;32:400–5.
383. Ness RB, Kip KE, Hillier SL, et al. A cluster analysis of bacterial vaginosis-associated microflora and pelvic inflammatory disease. Am J Epidemiol 2005;162:585–90.
384. Cohen CR, Mugo NR, Astete SG, et al. Detection of *Mycoplasma genitalium* in women with laparoscopically diagnosed acute salpingitis. Sex Transm Infect 2005;81:463–66.
385. Jurstrand M, Jensen JS, Magnuson A, et al. A serological study of the role of *Mycoplasma genitalium* in pelvic inflammatory disease and ectopic pregnancy. Sex Transm Infect 2007;83:319–23.
386. Short VL, Totten PA, Ness RB, et al. Clinical presentation of *Mycoplasma genitalium* infection versus *Neisseria gonorrhoeae* infection among women with pelvic inflammatory disease. Clin Infect Dis 2009;48:41–7.
387. Peipert JF, Ness RB, Blume J, et al. Clinical predictors of endometritis in women with symptoms and signs of pelvic inflammatory disease. Am J Obstet Gynecol 2001;184:856–63.
388. Gaitan H, Angel E, Diaz R, et al. Accuracy of five different diagnostic techniques in mild-to-moderate pelvic inflammatory disease. Infect Dis Obstet Gynecol 2002;10:171–80.
389. Haggerty CL, Ness RB, Amortegui A, et al. Endometritis does not predict reproductive morbidity after pelvic inflammatory disease. Am J Obstet Gynecol 2003;188:141–8.
390. Ness RB, Soper DE, Holley RL, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. Am J Obstet Gynecol 2002;186:929–37.
391. Ness RB, Hillier SL, Kip KE ea. Bacterial vaginosis and risk of pelvic inflammatory disease. Obstet Gynecol 2004;44 (Supp 3):S111–22.
392. Smith KJ, Ness RB, Wiesenfeld HC, et al. Cost-effectiveness of alternative outpatient pelvic inflammatory disease treatment strategies. Sex Transm Dis 2007;34:960–6.
393. Walker CK, Wiesenfeld H. Antibiotic Therapy for Acute Pelvic Inflammatory Disease: The 2006 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis 2007;28(Supp 1):S29–S36.
394. McGregor JA, Crombleholme WR, Newton E, et al. Randomized comparison of ampicillin-sulbactam to cefoxitin and doxycycline or clindamycin and gentamicin in the treatment of pelvic inflammatory disease or endometritis. Obstet Gynecol 1994;83:998–1004.
395. Bevan CD, Ridgway GL, Rothermel CD. Efficacy and safety of azithromycin as monotherapy or combined with metronidazole compared with two standard multidrug regimens for the treatment of acute pelvic inflammatory disease. J Int Med Res 2003;31:45–54.
396. Savaris RF, Teixeira LM, Torres TG, et al. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. Obstet Gynecol 2007;110:53–60.
397. Bukusi EA, Cohen CR, Stevens CE, et al. Effects of human immunodeficiency virus 1 infection on microbial origins of pelvic inflammatory disease and on efficacy of ambulatory oral therapy. Am J Obstet Gynecol 1999;181:1374–81.
398. Irwin KL, Moorman AC, O'Sullivan MJ, et al. Influence of human immunodeficiency virus infection on pelvic inflammatory disease. Obstet Gynecol 2000;95:525–34.
399. Mugo NR, Kiehlbauch JA, Nguti R, et al. Effect of human immunodeficiency virus-1 infection on treatment outcome of acute salpingitis. Obstet Gynecol 2006;107:807–12.
400. Viberga I, Odlind V, Lazdane G, et al. Microbiology profile in women with pelvic inflammatory disease in relation to IUD use. Infect Dis Obstet Gynecol 2005;13:183–90.
401. Grimes DA. Intrauterine device and upper-genital-tract infection. Lancet 2000;356(9234):1013–19.
402. Tracy CR, Steers WD, Costabile R. Diagnosis and management of epididymitis. Urol Clin North Am 2008;35:101–8.
403. Nickel JC, Siemens DR, Nickel KR, et al. The patient with chronic epididymitis: characterization of an enigmatic syndrome. J Urol 2002;167:1701–4.
404. Cogliano V, Baan R, Straif K, et al. Carcinogenicity of human papillomaviruses. Lancet Oncol 2005;6:204.
405. Myers ER, McCrory DC, Nanda K, et al. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol 2000;151:1158–71.
406. Garland SM, Steben M, Sings HL, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. J Infect Dis 2009;199:805–14.
407. Gotovtseva EP, Kapadia AS, Smolensky MH, et al. Optimal frequency of imiquimod (aldara) 5% cream for the treatment of external genital warts in immunocompetent adults: a meta-analysis. Sex Transm Dis 2008;35:346–51.
408. Mashiah J, Brenner S. Possible mechanisms in the induction of vitiligo-like hypopigmentation by topical imiquimod. Clin Exp Dermatol 2008;33:74–6.
409. Tatti S, Swinehart JM, Thielert C, et al. Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. Obstet Gynecol 2008;111:1371–9.
410. Stockfleth E, Beti H, Orasan R, et al. Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. Br J Dermatol 2008;158:1329–38.
411. Gross G, Meyer KG, Pres H, et al. A randomized, double-blind, four-arm parallel-group, placebo-controlled Phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. J Eur Acad Dermatol Venereol 2007;21:1404–12.
412. Silverberg MJ, Thorsen P, Lindeberg H, et al. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol 2003;101:645–52.
413. Dolev JC, Maurer T, Springer G, et al. Incidence and risk factors for verrucae in women. AIDS 2008;22:1213–19.
414. Silverberg MJ, Ahdieh L, Munoz A, et al. The impact of HIV infection and immunodeficiency on human papillomavirus type 6 or 11 infection and on genital warts. Sex Transm Dis 2002;29:427–35.

415. De Panfilis G., Melzani G, Mori G, et al. Relapses after treatment of external genital warts are more frequent in HIV-positive patients than in HIV-negative controls. Sex Transm Dis 2002;29:121–5.
416. Conley LJ, Ellerbrock TV, Bush TJ, et al. HIV-1 infection and risk of vulvovaginal and perianal condylomata acuminata and intraepithelial neoplasia: a prospective cohort study. Lancet 2002;359(9301):108–13.
417. Chiao EY, Giordano TP, Palefsky JM, et al. Screening HIV-infected individuals for anal cancer precursor lesions: a systematic review. Clin Infect Dis 2006;43:223–33.
418. Datta SD, Koutsky LA, Ratelle S, et al. Human papillomavirus infection and cervical cytology in women screened for cervical cancer in the United States, 2003–2005. Ann Intern Med 2008;148:493–500.
419. Selvam N, Barrow R, Shlay J, et al. Should STD clinics participate in cervical cancer screening: (1) Measurement of pap test abnormalities and HPV infection among women attending STD clinics and (2) A survey of cervical cancer screening practices, ISSTDR, Seattle, WA 2007.
420. Arbyn M, Bergeron C, Klinkhamer P, et al. Liquid compared with conventional cervical cytology: a systematic review and meta-analysis. Obstet Gynecol 2008;111:167–77.
421. Stoler MH, Castle PE, Solomon D, et al. The expanded use of HPV testing in gynecologic practice per ASCCP-guided management requires the use of well-validated assays. Am J Clin Pathol 2007;127:335–7.
422. Solomon D, Davey D, Kurman R, et al; Bethesda 2001 Workshop. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002;287:2114–9.
423. Naucler P, Ryd W, Tornberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med 2007;357:1589–97.
424. Wright TC, Jr., Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis 2007;11:201–22.
425. Widdice LE, Moscicki AB. Updated guidelines for Papanicolaou tests, colposcopy, and human papillomavirus testing in adolescents. J Adolesc Health 2008;43(4 Suppl):S41–S51.
426. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. J Natl Cancer Inst 2001;93:293–9.
427. American Society for Colposcopy and Cervical Pathology (ASCCP). HPV Genotyping Clinical Update. Available at: http://www.asccp.org/pdfs/consensus/clinical_update_20090408.pdf.
428. American Society for Colposcopy and Cervical Pathology (ASCCP) Clinical Update for HPV Genotyping, 2009.
429. Wright TC, Jr., Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. J Low Genit Tract Dis 2007;11:223–39.
430. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test. J Natl Cancer Inst 2008;100:492–501.
431. Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med 2007;357:1579–88.
432. Ghanem KG, Koumans EH, Johnson RE, et al. Effect of specimen order on *Chlamydia trachomatis* and *Neisseria gonorrhoeae* test performance and adequacy of Papanicolaou smear. J Pediatr Adolesc Gynecol 2006;19:23–30.
433. Saraiya M, Lee NC, Blackman D, et al. Self-reported Papanicolaou smears and hysterectomies among women in the United States. Obstet Gynecol 2001;98:269–78.
434. Sirovich BE, Welch HG. Cervical cancer screening among women without a cervix. JAMA 2004;291:2990–3.
435. Stokes-Lampard H, Wilson S, Waddell C, et al. Vaginal vault smears after hysterectomy for reasons other than malignancy: a systematic review of the literature. BJOG 2006;113:1354–65.
436. Delmas MC, Larsen C, van BB, et al. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. European Study Group on Natural History of HIV Infection in Women. AIDS 2000;14:1775–84.
437. CDC. Surveillance for acute viral hepatitis. MMWR 2008;57(No. SS-2):1-24.
438. CDC. Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;56:1080–4.
439. Alter HJ, Purcell RH, Gerin JL, et al. Transmission of hepatitis B to chimpanzees by hepatitis B surface antigen-positive saliva and semen. Infect Immun 1977;16:928–33.
440. Villarejos VM, Visona KA, Gutierrez A, et al. Role of saliva, urine and feces in the transmission of type B hepatitis. N Engl J Med 1974;291:1375–1378.
441. Davis LG, Weber DJ, Lemon SM. Horizontal transmission of hepatitis B virus. Lancet 1989;1(8643):889–93.
442. Martinson FE, Weigle KA, Royce RA, et al. Risk factors for horizontal transmission of hepatitis B virus in a rural district in Ghana. Am J Epidemiol 1998;147:478–87.
443. CDC. National, state, and urban area vaccination coverage among children aged 19–35 months—United States, 2004. MMWR 2005;54:717–21.
444. CDC. Hepatitis B vaccination among high-risk adolescents and adults–San Diego, California, 1998–2001. MMWR 2002;51:618–21.
445. MacKellar DA, Valleroy LA, Secura GM, et al. Two decades after vaccine license: hepatitis B immunization and infection among young men who have sex with men. Am J Public Health 2001;91:965–71.
446. CDC. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR 2001;50(No. RR-11).
447. Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics 2003;112:815–20.
448. Minuk GY, Bohme CE, Bowen TJ, et al. Efficacy of commercial condoms in the prevention of hepatitis B virus infection. Gastroenterology 1987;93:710–4.
449. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–14.
450. Brettler DB, Mannucci PM, Gringeri A, et al. The low risk of hepatitis C virus transmission among sexual partners of hepatitis C-infected hemophilic males: an international, multicenter study. Blood 1992;80:540–3.
451. Kao JH, Hwang YT, Chen PJ, et al. Transmission of hepatitis C virus between spouses: the important role of exposure duration. Am J Gastroenterol 1996;91:2087–90.
452. Marincovich B, Castilla J, del RJ, et al. Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. Sex Transm Infect 2003;79:160–2.

453. Tahan V, Karaca C, Yildirim B, et al. Sexual transmission of HCV between spouses. Am J Gastroenterol 2005;100:821–4.
454. Vandelli C, Renzo F, Romano L, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. Am J Gastroenterol 2004;99:855–9.
455. Feldman JG, Minkoff H, Landesman S, et al. Heterosexual transmission of hepatitis C, hepatitis B, and HIV-1 in a sample of inner city women. Sex Transm Dis 2000;27:338–42.
456. Hammer GP, Kellogg TA, McFarland WC, et al. Low incidence and prevalence of hepatitis C virus infection among sexually active non-intravenous drug-using adults, San Francisco, 1997–2000. Sex Transm Dis 2003;30:919–24.
457. Roy KM, Goldberg DJ, Hutchinson S, et al. Hepatitis C virus among self declared non-injecting sexual partners of injecting drug users. J Med Virol 2004;74:62–6.
458. Mele A, Stroffolini T, Tosti ME, et al. Heterosexual transmission of hepatitis C in Italy. J Med Virol 1999;57:111–3.
459. Rauch A, Rickenbach M, Weber R, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. Clin Infect Dis 2005;41:395–402.
460. van de Laar TJ, van der Bij AK, Prins M, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis 2007;196:230–8.
461. Browne R, Asboe D, Gilleece Y, et al. Increased numbers of acute hepatitis C infections in HIV positive homosexual men: is sexual transmission feeding the increase? Sex Transm Infect 2004;80:326–7.
462. Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS 2007;21:983–91.
463. Ghosn J, Pierre-Francois S, Thibault V, et al. Acute hepatitis C in HIV-infected men who have sex with men. HIV Med 2004;5:303–6.
464. van de LT, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology 2009;136:1609–17.
465. Urbanus AT, van de Laar TJ, Stolte IG, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS 2009;23:F1–F7.
466. Fierer DS, Uriel AJ, Carriero DC, et al. Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study. J Infect Dis 2008;198:683–6.
467. Briat A, Dulioust E, Galimand J, et al. Hepatitis C virus in the semen of men coinfected with HIV-1: prevalence and origin. AIDS 2005;19:1827–35.
468. CDC. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. MMWR 2003;52(No. RR-3).
469. Klausner JD, Kohn R, Kent C. Etiology of clinical proctitis among men who have sex with men. Clin Infect Dis 2004;38:300–2.
470. Rompalo AM. Diagnosis and treatment of sexually acquired proctitis and proctocolitis: an update. Clin Infect Dis 1999;28(Suppl 1):S84–S90.
471. Chosidow O. Scabies and pediculosis. Lancet 2000;355 (9206):819–26.
472. Meinking TL, Serrano L, Hard B, et al. Comparative in vitro pediculicidal efficacy of treatments in a resistant head lice population in the United States. Arch Dermatol 2002;138:220–4.
473. Yoon KS, Gao JR, Lee SH, et al. Permethrin-resistant human head lice, Pediculus capitis, and their treatment. Arch Dermatol 2003;139:994–1000.
474. Mounsey KE, Holt DC, McCarthy J, et al. Scabies: molecular perspectives and therapeutic implications in the face of emerging drug resistance. Future Microbiol 2008;3:57–66.
475. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. Lancet 1997;349(9059):1144–5.
476. Roberts LJ, Huffam SE, Walton SF, et al. Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature. J Infect 2005;50:375–81.
477. Ackerman DR, Sugar NF, Fine DN, et al. Sexual assault victims: factors associated with follow-up care. Am J Obstet Gynecol 2006;194:1653–9.
478. Parekh V, Brown CB. Follow up of patients who have been recently sexually assaulted. Sex Transm Infect 2003;79:349.
479. Varghese B, Maher JE, Peterman TA, et al. Reducing the risk of sexual HIV transmission: quantifying the per-act risk for HIV on the basis of choice of partner, sex act, and condom use. Sex Transm Dis 2002;29:38–43.
480. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. N Engl J Med 1997;337:1485–90.
481. Du Mont J., Myhr TL, Husson H, et al. HIV postexposure prophylaxis use among Ontario female adolescent sexual assault victims: a prospective analysis. Sex Transm Dis 2008;35:973–8.
482. Neu N, Heffernan-Vacca S, Millery M, et al. Postexposure prophylaxis for HIV in children and adolescents after sexual assault: a prospective observational study in an urban medical center. Sex Transm Dis 2007;34:65–8.
483. Loutfy MR, Macdonald S, Myhr T, et al. Prospective cohort study of HIV post-exposure prophylaxis for sexual assault survivors. Antivir Ther 2008;13:87–95.
484. Kellogg N. The evaluation of sexual abuse in children. Pediatrics 2005;116:506–12.
485. Girardet RG, Lahoti S, Howard LA, et al. Epidemiology of sexually transmitted infections in suspected child victims of sexual assault. Pediatrics 2009;124:79–86.
486. Black CM, Driebe EM, Howard LA, et al. Multicenter study of nucleic acid amplification tests for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in children being evaluated for sexual abuse. Pediatr Infect Dis J 2009;28:608–13.
487. Jones V, Smith SJ, Omar HA. Nonsexual transmission of anogenital warts in children: a retrospective analysis. ScientificWorldJournal 2007;7:1896–9.
488. Smith EM, Swarnavel S, Ritchie JM, et al. Prevalence of human papillomavirus in the oral cavity/oropharynx in a large population of children and adolescents. Pediatr Infect Dis J 2007;26:836–40.
489. Havens PL. Postexposure prophylaxis in children and adolescents for nonoccupational exposure to human immunodeficiency virus. Pediatrics 2003;111(6 Pt 1):1475–89.

Terms and Abbreviations Used in This Report

AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
anti-HBc	Antibody to hepatitis B core antigen
anti-HCV	Hepatitis C antibodies
ASC-US	Atypical squamous cells of undetermined significance
BCA	Bichloroacetic acid
BV	Bacterial vaginosis
CBC	Complete blood count
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CLD	Chronic liver disease
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CSF	Cerebrospinal fluid
DFA	Direct fluorescent antibody
DGI	Disseminated gonococcal infection
dL	Deciliter
DNA	Deoxyribonucleic acid
EC	Emergency contraception
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EPT	Expedited partner therapy
FDA	Food and Drug Administration
FTA-ABS	Fluorescent treponemal antibody absorbed
gG	Glycoprotein G
GNID	Gram-negative intracellular diplococci
HAART	Highly active antiretroviral therapy
HAV	Hepatitis A virus
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSV	Herpes simplex virus
IFA	Immunofluorescence assay
IgE	Immunoglobulin E
Ig	Immune globulin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscularly
IUD	Intrauterine device
IV	Intravenous or intravenously
KOH	Potassium hydroxide
LGV	Lymphogranuloma venereum
MAC	*Mycobacterium avium* complex
MIC	Minimum inhibitory concentration
MSM	Men who have sex with men
N-9	Nonoxynol-9
NAAT	Nucleic acid amplification test
NGU	Nongonococcal urethritis
Pap	Papanicolaou
PCR	Polymerase chain reaction
PEP	Postexposure prophylaxis
PID	Pelvic inflammatory disease
PO	By mouth
PPV	Positive predictive value
QRNG	Quinolone-resistant *Neisseria gonorrhoeae*
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT-PCR	Reverse transcriptase polymerase chain reaction
RVVC	Recurrent vulvovaginal candidiasis
SIL	Squamous intraepithelial lesion
STD	Sexually transmitted disease
TCA	Trichloroacetic acid
TE	Toxoplasmic encephalitis
TP-PA	*Treponema pallidum* particle agglutation
VDRL	Venereal Disease Research Laboratory
VVC	Vulvovaginal candidiasis
WB	Western blot
WBC	White blood count
WSW	Women who have sex with women

Sexually Transmitted Diseases Treatment Guidelines, 2010

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