Viral Sexually Transmitted Infections

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, nurses, and allied health professionals involved in the care of patients at risk for or with viral sexually transmitted infections.

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Course Objective

The purpose of this course is to enhance clinician knowledge regarding the most common viral sexually transmitted infections in order to ensure that diagnosis and treatment is initiated early, when transmission risk can be minimized.

Learning Objectives

Upon completion of this course, you should be able to:

1. Incorporate key elements of a sexual history, including history of sexually transmitted infections (STIs), into clinical assessments.
2. Identify barrier and nonbarrier approaches to preventing viral STIs.
3. Discuss best practice screening guidelines for viral STIs.
4. Describe the approach to diagnosis, prevention, and management of genital herpes infection.
5. Review clinical recommendations for the diagnosis and management of human papillomavirus (HPV) infection.
6. Analyze the appropriate approach to hepatitis A and hepatitis B diagnosis, prevention, and treatment.
7. Discuss clinical issues related to the transmission, detection, and management of HIV infection.
8. Outline issues related to the diagnosis and treatment of STIs in refugees and immigrants.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Sexually transmitted infections, or STIs, are clinical syndromes and infections caused by pathogens acquired and transmitted through sexual activity. All communities in the United States are impacted by STIs, and all individuals directly or indirectly pay for the costs of these diseases. STIs are public health problems that lack easy solutions, because they are rooted in human behavior and fundamental societal problems. However, clinicians can provide sexual health information, assess patient risks, discuss testing, and provide post-test counseling and medical care. This can empower patients to make health-promoting choices and receive treatment that protects their health and prevents transmission of untreated STIs [1; 2].

This course will address the prominent viral STIs in the United States—referred to as the four Hs: herpes, human papillomavirus (HPV), hepatitis, and human immunodeficiency virus (HIV). The purpose of this course is to enhance clinician knowledge regarding these infections in order to detect and initiate treatment early, when transmission risk can be minimized.

GENERAL STI ASSESSMENT AND PREVENTION COUNSELING

SEXUAL HISTORY TAKING IN PATIENT INTERVIEWS

The "Five Ps" approach elicits sexual history information related to five key areas of interest: partners, practices, prevention of pregnancy, protection against STIs, and past history [1].

Partners

- "Do you have sex with men, women, or both?"
- "In the past two 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?"

Practices

- "To understand your risks for STIs, I need to understand the kind of sex you have had recently."
- "Have you had oral sex, meaning 'mouth on penis/vagina' sex?"
- "Have you had vaginal sex, meaning 'penis in vagina' sex?"
- "Have you had anal sex, meaning 'penis in rectum/anus' sex?"
- If yes to any of the questions above, "Do you use condoms: never, sometimes, or always?"
  - If "never": "Why don't you use condoms?"
  - If "sometimes": "In what situations (or with whom) do you use condoms?"

Prevention of Pregnancy

- "What are you doing to prevent pregnancy?"

Protection against STIs

- "What do you do to protect yourself from STIs and HIV?"

Past History of STIs

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

STI BEHAVIORAL COUNSELING

Intensive behavioral counseling interventions to prevent STIs are recommended for all sexually active adolescents and adults at increased risk for STIs.

Risk Assessment

All sexually active adolescents are considered at increased risk for STIs and should be counseled. Other at-risk groups include adults with current or past-year STIs, with multiple sex partners, or who use condoms inconsistently. African Americans have the highest STI prevalence of any racial/ethnic group, and STI prevalence is higher in American Indians, Alaska Natives, and Latino/as than in white populations. Increased STI prevalence rates are also found in men who have sex with men (MSM), persons with low incomes living in urban settings, current or former inmates, military recruits, persons who exchange sex for money or drugs, persons with mental illness or a disability, current or former injecting drug users (IDUs), persons with sexual abuse history, and patients of public STI clinics [3].

Behavioral Counseling Interventions

Behavioral counseling interventions can reduce the risk of acquiring an STI. Interventions ranging in intensity from 30 minutes to more than 2 hours of contact time are beneficial; evidence of benefit increases with intervention intensity [3]. Interventions can be delivered by primary care clinicians or through referral to trained behavioral counselors. Successful interventions provide basic information on STIs and STI transmission; assess patient risk for transmission; and provide pertinent skills training, such as condom use, communication about safe sex, problem solving, and goal setting. Many successful interventions aim to increase motivation or commitment to safe sex practices [3]. Specific counseling messages for patients diagnosed with genital herpes, HPV, or hepatitis are described in later sections of this course.

BARRIER AND NONBARRIER APPROACHES TO PREVENT OR REDUCE VIRAL STI TRANSMISSION AND INFECTION

VACCINATION

Pre-exposure vaccination is one of the most effective methods for preventing transmission of hepatitis A virus (HAV), hepatitis B virus (HBV), and HPV. These are the only STIs for which vaccination is available for prevention. The specific recommendations for vaccination will be discussed later in this course.

EXTERNAL CONDOMS

When used consistently and correctly, external latex condoms (also referred to as male latex condoms) are highly effective in preventing the sexual transmission of HIV infection and reducing risks for HPV infection and HPV-associated diseases, genital herpes, and hepatitis B when the infected area or site of potential exposure is covered [4; 5; 6].

As U.S. Food and Drug Administration (FDA)-regulated medical devices, condoms are subject to quality-control testing. Each latex condom manufactured in the United States is tested electronically for holes before packaging. The rate of condom breakage during sexual intercourse and withdrawal is approximately 2 per 100 condoms used, with slightly higher rates during anal intercourse [7; 8]. Condom failure to protect against STI or unintended pregnancy is usually caused by inconsistent or incorrect use, instead of condom breakage [9]. Latex condoms should not be used beyond their expiration date or more than five years after the manufacturing date, and users should check the expiration or manufacture date on the packaging before use [1].

External condoms made of materials other than latex fall in two general categories: synthetic and natural membrane condoms. Polyurethane and other synthetic condoms provide protection against STIs/HIV and pregnancy comparable to latex condoms and are used mainly as latex condom substitutes by persons with latex allergy. These condoms are more resistant to deterioration and are compatible with oil-based or water-based lubricants. The preventive efficacy of other synthetic external condoms is not well studied, and the FDA restricts their use to persons with latex sensitivity or allergy [6; 10].

Natural membrane condoms (termed "natural skin" or "lambskin") are made from lamb cecum. The pores, no greater than 1,500 nm in diameter, block passage of sperm but are more than 10 times the diameter of HIV and more than 25 times that of HBV. Therefore, sexual transmission of hepatitis B, herpes simplex, and HIV organisms can occur with natural membrane condoms. These condoms are recommended for preventing pregnancy but not STIs/HIV [10; 11; 12].

Providers should communicate guidance to patients to ensure correct external condom use [1]. Consistent, correct use is essential to prevent STIs/HIV infection, and a new condom should be used with each oral, vaginal, and anal sex act. It is important to carefully handle condoms to avoid damage from fingernails, teeth, or other sharp objects. Condoms should be put on after the penis is erect and before genital, oral, or anal contact. To prevent the condom from slipping off, the condom should be held firmly against the base of the penis during withdrawal, which should occur while the penis is still erect.

Adequate lubrication during vaginal and anal sex will help prevent condom breakage. With latex condoms, patients should be advised to use only water-based lubricants such as K-Y Jelly, Astroglide, Aqua Lube, or glycerin. Oil-based lubricants (e.g., petroleum jelly, shortening, mineral oil, massage oils, body lotions, cooking oil) weaken latex and should not be used, but are compatible with synthetic condoms.

INTERNAL CONDOMS

Several condoms are available for internal use (also referred to as female condoms), including the FC2 Female Condom, Reddy condom, Cupid female condom, and Woman's condom. Internal condoms can protect from acquisition and transmission of STIs, but data are limited compared with external condoms. Internal condoms are more expensive but offer the advantage of being a female-controlled STI/HIV prevention method, and newer versions may have greater acceptability to both men and women. While internal condoms have been used during receptive anal intercourse, the efficacy is unknown [13; 14].

MALE CIRCUMCISION

Male circumcision has been found to reduce the risk for HIV and some STIs in heterosexual men. By various means, penile foreskin is the primary biologic weak point and conduit for HIV infection during heterosexual intercourse [15]. Several controlled studies of heterosexual HIV transmission in sub-Saharan Africa found circumcision reduced the risk for HIV acquisition in men by 50% to 60% and protected against high-risk genital HPV infection and genital herpes [16; 17; 18]. These benefits of circumcision were sustained over time, and the effects were not solely related to reductions in herpes simplex virus type 2 (HSV-2) infection or genital ulcer disease [19; 20].

Several organizations now recommend male circumcision to reduce or prevent penile cancers, urinary tract infections, genital ulcer disease, and heterosexually acquired HIV, including the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the American Academy of Pediatrics, the American Urological Association, and the American College of Obstetrics and Gynecology. Much less data are available to confirm male circumcision benefits in MSM [1].

INEFFECTIVE METHODS

Topical Microbicides and Spermicides

Nonspecific topical microbicides are ineffective in preventing HIV, and spermicides containing nonoxynol-9 (N-9) might disrupt genital or rectal epithelium to increase the risk for HIV infection [21; 22]. In one study, condoms plus N-9 were no more effective than condoms alone for the prevention of STIs, and N-9 alone or in addition to a condom is not recommended for STI prevention [23]. N-9 use may also increase the risk for bacterial urinary tract infection in women [24]. As of 2020, no topical antiretroviral agent has been proven effective in preventing HIV, but vaginal and rectal microbicides using tenofovir and other antiretroviral drugs are under investigation [25].

Cervical Diaphragms

Uncontrolled studies found that diaphragms protected against cervical gonorrhea, chlamydia, and trichomoniasis, but controlled studies found that compared with external condoms, diaphragms plus lubricant did not improve protection against HIV or herpes acquisition [26]. Diaphragms should not be solely relied on for protection against HIV/STIs [27; 28].

Non-Barrier Contraception

Contraceptive methods that are not mechanical barriers provide no protection against HIV or other STIs. Sexually active women who use hormonal contraception, nonhormonal intrauterine devices, or have been surgically sterilized or undergone a hysterectomy should be advised to use condoms to reduce risks for STIs [10].

Genital Hygiene

Vaginal washing and douching after sexual exposure are ineffective in protecting against HIV and STIs. These practices may increase the risk for bacterial vaginosis, some STIs, and HIV infection [1; 29].

SCREENING RECOMMENDATIONS

GENERAL SCREENING RECOMMENDATIONS

STI screening is an essential component of overall efforts to reduce STI acquisition and transmission and of individual risk assessment, but it is underutilized. STIs themselves are biologic markers of risk for additional STIs, particularly for HIV in some patients [30]. As such, all persons seeking evaluation or treatment for a suspected STI should be screened for HIV and other STIs. The Centers for Disease Control and Prevention (CDC) has established guidelines for screening for viral STIs in specific populations (***Table 1***). The decision to recommend specific STI screening is determined by community prevalence and by individual demographics and STI risk factors. Clinicians should provide patients with information regarding all STIs for which they are being tested and of tests available for common STIs (such as genital herpes and HPV) that are not being provided [30].

Risk factors also determine STI screening frequency. STI risk factors that help determine screening frequency for any given person include [1]:

- Presentation in high-risk settings: Adolescent or STI clinics, correctional facilities
- At-risk women: A new sex partner, more than one sex partner, a sex partner with concurrent partners or an STI
- High-risk women: Multiple sex partners, exchanges sex for money or drugs, illicit drug use, history of STI
- Pregnant women at high risk for HIV: Illicit drug use, STIs during pregnancy, multiple sex partners during pregnancy, residence in areas with high HIV prevalence, partner with HIV infection
- Men: Multiple sex partners
- High-risk MSM: HIV infection and persistent risk behaviors, sexual partner has multiple partners

VIRAL STI SCREENING RECOMMENDATIONS						
Infection	**Population Screened**					
	Women	**Pregnant Women**	**Men**	**MSM**	**Persons with HIV**	**Transgender and Gender Diverse People**
Genital herpes	Consider testing during STI evaluation	Not supported without symptoms	Consider testing during STI evaluation	Consider testing if status unknown or if previous undiagnosed genital tract infection	Consider testing during STI evaluation, especially if high risk	—
HPV/ cervical cancer	Age 21 to 29 years: Every three years with cytology Age 30 to 65 years: Every three years with cytology or every five years with cytology plus HPV testing	Same as nonpregnant cis-gender women	—	Digital anorectal rectal exam (anal cytology not recommended)	Within one year of sexual activity or first HIV diagnosis, using standard or liquid-based cytology. Repeat testing in six months.	Follow recommen-dations for persons with a cervix
Hepatitis B	With increased risk	At first prenatal visit for each pregnancy[a] Retest at delivery if high risk	With increased risk	Test for HBsAg, anti-HBc, and anti-HBs	Test for HBsAg, anti-HBc, and anti-HBs	—
HIV	All aged 13 to 64 years (opt-out) and all seeking STI testing and treatment	All during first prenatal visit (opt-out) Retest in third trimester if high risk Rapid testing should be performed at delivery if not previous screened during pregnancy	All aged 13 to 64 years (opt-out) and all seeking STI testing and treatment	At least yearly if: sexually active, HIV status negative or unknown, patient or sex partner(s) had more than one partner since last HIV test Consider more frequent screening (every 3–6 months) with increased risk	—	Test all transgender patients Frequency of repeat screenings should be based on level of risk

[a]Regardless of whether prior testing was performed.
Anti-HBc = antibodies to hepatitis B core antigen, anti-HBs = antibodies to hepatitis B surface antigen, HBsAg = hepatitis B surface antigen, HIV = human immunodeficiency virus, HPV = human papillomavirus, MSM = men who have sex with men.

Source: [31; 32] *Table 1*

- Persons with HIV: Multiple sex partners
- Hepatitis B: Those born in high prevalence (≥2%) regions, past or current IDU, MSM, immunosuppressive therapy, hemodialysis, HIV-positive status
- Hepatitis B, pregnant women: Same as for nonpregnant women, plus more than one sex partner in past six months, evaluated or treated for an STI, hepatitis B surface antigen (HBsAg)-positive sex partner

HIV SCREENING

Many STIs are screened because they are often asymptomatic during initial infection and likely to be unknowingly transmitted; as such, their detection is essential to avoid serious complications from untreated infection. This is certainly true of HIV infection. All persons seeking STI evaluation or treatment should be screened for HIV infection, regardless of whether or not the patient reports behavioral risk factors. Persons with early syphilis, gonorrhea, or chlamydia are at high risk for HIV infection, and rectal gonorrhea and syphilis are risk markers for HIV [33; 34]. These patients should be screened even with a recently performed HIV test. In all healthcare settings, the CDC recommends HIV screening for patients 13 to 64 years of age; they should be notified that testing will be performed and retain the option to decline or defer testing (opt-out) [32; 35].

HERPES SIMPLEX VIRUS

Genital herpes is the most common ulcerative STI. It is a chronic, lifelong viral infection caused by two strains or types: HSV-1 and HSV-2. Symptomatic HSV-1 usually appears as fever blisters or cold sores on the lips, but it can also infect the genital region through oral-genital or genital-genital contact. Symptomatic HSV-2 typically causes painful, watery skin blisters on or around the genitals or anus [36]. Most cases of recurrent genital herpes are caused by HSV-2, but because the prevalence of oral HSV-1 infection has declined in recent decades, people may have become more susceptible to contracting a genital herpes infection from HSV-1 [3]. It is important for patients to understand that oral herpes lesions can transmit herpes virus to a partner's genitals during oral sex.

In the United States, approximately one in eight persons 14 to 49 years of age is infected with HSV-2. The virus remains for life once infection has occurred, and prevalence rates generally increase with age due to cumulative sexual exposure [37]. Most people infected with genital herpes have not been diagnosed, and many with undiagnosed HSV-2 have minimal or no signs and symptoms, but shed virus intermittently in the anogenital area [38]. As a result, most genital herpes infections are transmitted by people who are unaware they are infected or are asymptomatic when transmitting. The risk of transmission is highest when outbreaks develop with new blisters in the anogenital area [3; 36].

HSV-1 and HSV-2 cannot be cured, and even when infection is dormant, the virus remains sequestered in peripheral nerve ganglia from which it can periodically emerge. Management of genital herpes should address the chronic nature of the disease instead of strictly focusing on treating the genital lesions during acute episodes. Pregnant women, especially those with new-onset genital herpes during pregnancy, may pass the infection to their newborns, causing life-threatening neonatal HSV, an infection that affects the infant's skin, brain, and other organs [3; 36].

Several of the recommended steps in the process of diagnosing and treating patients with STIs are common to all or multiple STIs. All patients should be given detailed information on the natural history, transmission, treatment, and complications relevant to genital herpes (and any other diagnosed STI). Patients should also be provided with clear, accurate written information and directed to appropriate web-based patient information.

SYMPTOMS AND SIGNS

As noted, many cases of primary genital herpes do not cause noticeable symptoms, and many people infected with HSV-2 are unaware they have genital herpes. Primary genital lesions develop four to seven days after contact. The vesicles usually erode to form ulcers that may coalesce. Lesions may occur in the following locations [3; 39; 40]:

- Men: The prepuce, glans penis, and penile shaft
- Women: The labia, clitoris, perineum, vagina, and cervix
- Men or women who engage in receptive rectal intercourse: Around the anus and in the rectum

Those symptomatic during primary (initial) HSV infection may experience painful, prolonged, and bilateral anogenital lesions, regional adenopathy, systemic (flu-like) signs and symptoms, and possibly urinary hesitancy, dysuria, urinary retention, constipation, or severe sacral neuralgia. Scarring may follow healing. The lesions recur in 80% of patients with HSV-2 and in 50% of those with HSV-1. Recurrent lesions are usually much less severe, but some will have severe prodromal symptoms that may involve the buttock, groin, or thigh [39; 40; 41].

DIAGNOSTIC CONSIDERATIONS

HSV testing is performed to diagnose active herpes infection in patients with genital sores or encephalitis, in individuals with suspected previous HSV infection, and in newborns suspected of having neonatal herpes. In symptomatic patients, testing can distinguish primary, active infection from a recurrent infection. Diagnosing genital herpes involves type-specific testing (HSV-1 versus HSV-2) and type-common testing (to identify specific immune protein response to herpes infection). Laboratory testing offsets the difficulties with clinical diagnosis that arise because many infected patients lack the characteristic lesions associated with HSV [42].

Direct Detection of the Virus

In patients seeking medical care for genital ulcers or other mucocutaneous lesions, cell culture and polymerase chain reaction (PCR) testing can detect herpes from a vesicle scraping [42]. Cell culture can distinguish HSV-1 from HSV-2, but it takes at least two days to complete. In addition, false negatives can occur with low viral load in the sample, and sensitivity is low, especially with recurrent or partially healed lesions [42]. PCR has sufficient sensitivity to detect HSV in low virus concentrations, and it is preferred for diagnosing systemic HSV infections, meningitis, central nervous system (CNS) involvement (encephalitis), and neonatal herpes [42; 43; 44].

Serologic Tests

HSV serologic testing is used for persons presenting for general STI evaluation (especially with multiple sex partners), those with HIV infection, and MSM at increased risk for HIV. Serologic HSV antibody testing detects the specific immune protein response to herpes infection. Several days after the primary (initial) HSV infection, immunoglobulin M (IgM) antibody is produced, remaining detectable in serum for several weeks. After HSV IgM, the body begins producing HSV IgG antibody. IgG serum levels rise for several weeks, then slowly decline, stabilize, and remain detectable forever in those with HSV exposure [42; 45]. With type-common antibody testing, positive HSV IgM antibody indicates active or recent infection, while positive HSV IgG antibody indicates previous infection. A significant recent increase in HSV IgG antibodies is a sign of active or recent infection. Negative HSV antibody testing implies HSV exposure is unlikely or the body has had insufficient time to produce HSV antibodies [42; 45].

TREATMENT OF GENITAL HERPES INFECTIONS	
Infection Stage or Patient Group	**Recommended Treatment Regimen**
First clinical episode	Any of the following[a]: Acyclovir 400 mg oral three times per day for 7 to 10 days Valacyclovir 1 g oral twice per day for 7 to 10 days Famciclovir 250 mg oral three times per day for 7 to 10 days
Recurrent: suppressive therapy	Any of the following: Acyclovir 400 mg oral twice per day Valacyclovir 500 mg oral once per day[b] Valacyclovir 1 g oral once per day Famciclovir 250 mg oral twice per day
Recurrent: episodic therapy	Any of the following: Acyclovir 800 mg oral twice per day for 5 days Acyclovir 800 mg oral three times per day for 2 days Valacyclovir 500 mg oral twice per day for 3 days Valacyclovir 1 g oral once per day for 5 days Famciclovir 125 mg oral twice per day for 5 days Famciclovir 1 g oral twice per day for 1 day Famciclovir 500 mg once, followed by 250 mg twice per day for 2 days
Severe disease[c]	Acyclovir 5–10 mg/kg IV every 8 hours clinical improvement, followed by oral antiviral therapy to complete ≥10 days total therapy
During pregnancy[d]	Either of the following: Acyclovir 400 mg oral three times per day Valacyclovir 500 mg oral twice per day
Comorbid HIV Infection	
Daily suppressive therapy	Any of the following: Acyclovir 400–800 mg oral twice to three times per day Valacyclovir 500 mg oral twice per day Famciclovir 500 mg oral twice per day
Episodic infection	Any of the following: Acyclovir 400 mg oral three times per day for 5 to 10 days Valacyclovir 1 g oral twice per day for 5 to 10 days Famciclovir 500 mg oral twice per day for 5 to 10 days
Severe HSV disease	Initiate with acyclovir 5–10 mg/kg IV every 8 hours

[a] Treatment can be extended if healing is incomplete after 10 days of therapy.
[b] Valacyclovir 500 mg once per day might be less effective than other valacyclovir or acyclovir dosing regimens in persons who have very frequent recurrences (i.e., ≥10 episodes per year).
[c] HSV encephalitis requires 21 days of intravenous therapy. Impaired renal function warrants an adjustment in acyclovir dosage.
[d] Treatment recommended starting at 36 weeks' gestation.

Source: [1; 49] *Table 2*

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force recommends against routine serologic screening for genital herpes simplex virus infection in asymptomatic adolescents and adults, including those who are pregnant.

(https://jamanetwork.com/journals/jama/fullarticle/2593575. Last accessed June 15, 2020.)

Strength of Recommendation/Level of Evidence: D (There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.)

HSV antibody tests can also diagnose herpes by detecting HSV-1 or HSV-2 (type-specific) viral type. The most accurate type-specific HSV serologic assays are glycoprotein G (gG)-based [42; 46; 47].

The presence of HSV-1 antibody alone is more difficult to interpret; many with HSV-1 acquired oral HSV infection during childhood, which might be asymptomatic. However, genital HSV-1 is increasing and can be asymptomatic, so typing alone is not a predictor of the likely infection site [38; 48]. General population screening for HSV-1/2 is not indicated, but all patients with HSV-2 should be tested for HIV infection [3].

MANAGEMENT OF GENITAL HERPES

All patients with suspected first-episode genital herpes should be treated presumptively, because treatment success depends on prompt initiation. The choice of presumptive treatment is based on clinical presentation, epidemiologic factors (e.g., population, community incidence), and travel history. Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management (***Table 2***) [1].

Systemic antiviral drugs can reduce symptoms of new onset and recurrent genital herpes episodes and may be used daily as suppressive therapy. However, it is important for patients to understand that antiviral drugs cannot eradicate latent virus or modify the risk, frequency, or severity of recurrences following discontinuation. The three antiviral medications in use for genital herpes are acyclovir, valacyclovir, and famciclovir. Valacyclovir is the valine ester of acyclovir and has enhanced oral absorption. Famciclovir also has high oral bioavailability. Topical antiviral drugs have minimal benefit and are discouraged [50; 51].

First Clinical Episode

Newly acquired genital herpes can cause prolonged clinical illness, with severe genital ulcerations and neurologic involvement. Even patients with mild first-episode herpes symptoms can develop severe or prolonged symptoms, and all patients with an episode of genital herpes should receive antiviral therapy [51; 52].

Established HSV-2 Infection

Almost all patients with symptomatic first-episode genital HSV-2 will subsequently experience recurrent episodes of genital lesions, and intermittent asymptomatic shedding occurs in genital HSV-2 patients, even with dormant infection [53]. Antiviral therapy for recurrent genital herpes can be administered continuously (daily) to suppress recurrence frequency or episodically to ameliorate or shorten active lesion duration [54]. Many patients prefer suppressive therapy, which also decreases the risk of genital HSV-2 transmission to susceptible partners [55].

Suppressive Therapy

In patients with frequent recurrence, suppressive therapy reduces recurrences by 70% to 80%, and many patients report an absence of symptomatic breakouts [50; 52]. Continuous treatment also benefits patients with less frequent recurrences. Safety and efficacy are documented with daily acyclovir therapy taken as long as six years, and valacyclovir or famciclovir for one year [56; 57]. Suppressive therapy also leads to greater improvements in quality of life than episodic treatment [58].

Even in the absence of treatment, the frequency of genital herpes recurrences diminishes over time in many patients and may result in psychologic adjustment to the disease. During suppressive treatment, providers should discuss the need to continue therapy, but treatment discontinuation or laboratory monitoring in healthy patients is unnecessary [1].

Daily treatment with antiviral therapy can decrease HSV-2 transmission rates in infection-discordant heterosexual couples. Such couples should be encouraged to consider suppressive antiviral therapy to prevent transmission, to consistently use condoms, and to avoid sexual activity during recurrences. Suppressive antiviral therapy is also likely to reduce transmission by patients with multiple partners (including MSM) and in HSV-2 seropositive patients without a history of genital herpes [50; 52; 53].

Acyclovir, famciclovir, and valacyclovir have comparable efficacy as episodic genital herpes treatment, while famciclovir appears somewhat less effective in suppressing viral shedding [54; 59]. Important considerations with prolonged treatment include costs and the ease of administration. Allergic and adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. However, desensitization to acyclovir has been described [60].

Episodic Therapy

Effective episodic treatment of recurrent herpes requires initiation of therapy within one day of lesion onset or during the prodromal period before an outbreak. 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 [1].

Severe Disease

Intravenous (IV) acyclovir therapy should be provided for patients with severe HSV disease or complications that require hospitalization, including disseminated infection, pneumonitis, hepatitis, or CNS complications (meningoencephalitis) [1].

Management of Sex Partners

Sex partners of patients with genital herpes can benefit from evaluation and counseling. Symptomatic sex partners should be evaluated and treated in the same manner as patients with HSV-2. Asymptomatic sex partners should be assessed for a history of genital lesions and offered type-specific serologic HSV testing [1].

Comorbid HIV Infection

Anogenital or oral herpes episodes can be prolonged or severe in immunocompromised patients. HSV lesions are common in patients with HIV infection and may be severe, painful, and atypical. While antiretroviral therapy reduces the severity and frequency of symptomatic genital herpes outbreaks, frequent subclinical viral shedding still occurs. Clinical manifestations of genital herpes may worsen during immune reconstitution following initiation of antiretroviral therapy [61; 62].

Suppressive or episodic oral antiviral therapy decreases the clinical manifestations of HSV in patients with HIV infection [63]. HSV type-specific serologic testing may be offered to persons with HIV infection during their initial evaluation if infection status is unknown, and suppressive antiviral therapy may be considered in those who have HSV-2 infection. Suppressive anti-HSV therapy does not decrease the risk of HIV or HSV-2 transmission by patients with HIV to susceptible sex partners [64; 65].

Management of Genital Herpes in Pregnancy

Pregnant women with genital herpes can transmit HSV-2 to the fetus or neonate during delivery via contact with lesions and/or vaginal secretions containing HSV. The virus is rarely transmitted transplacentally. Mothers of neonates with HSV infection tend to have newly acquired genital infection, often without symptoms at the time of delivery. Managing women with genital HSV acquired during late pregnancy requires specialist consultation [66].

During the third trimester, pregnant women without known genital or orolabial herpes should be advised to abstain from vaginal intercourse or receptive oral sex with partners with suspected genital or orolabial herpes, respectively. The efficacy of antiviral treatment to decrease or prevent HSV transmission to pregnant women by infected partners has not been studied. All pregnant women should be questioned about genital herpes history before and at the onset of labor. Patients with a known history of genital herpes should be assessed for prodromal symptoms and examined carefully

for herpetic lesions during labor. Women without genital lesions or prodromal symptoms or signs can deliver vaginally. Cesarean delivery reduces but does not eliminate risk of HSV transmission to the neonate and may be considered for women with active outbreaks [1].

No adverse effects from oral or IV acyclovir to the fetus or newborn have been reported, and acyclovir is safe during breastfeeding and all pregnancy stages [67; 68]. Safety data for prenatal exposure to valacyclovir and famciclovir are limited, but these agents probably pose a low risk. Third trimester antiviral prophylaxis significantly reduces the recurrence of genital herpes at delivery, the need for cesarean delivery due to genital herpes, and detection of HSV-2 at delivery, but it may not prevent transmission to neonates in all cases [69; 70].

PATIENT COUNSELING

Patient and sex partner counseling on the natural history and transmission of genital herpes, methods to prevent sexual and perinatal transmission, and coping strategies for patients with infection are the foundation of clinical management. When the acute illness subsides, many patients benefit from learning about the chronic aspects of the disease. Websites, printed materials, and several other resources are available to assist patients, their partners, and clinicians involved in counseling [71; 72].

Asymptomatic and symptomatic patients should receive the same education and counseling messages, including [1]:

- The natural history of the disease, with an emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and associated risks of sexual transmission
- The effectiveness of suppressive therapy during and after first-episode genital herpes in preventing symptomatic recurrent episodes and future transmission to partners
- Use of episodic therapy to shorten the duration of recurrent episodes
- Importance of informing current and future sex partners about genital herpes
- Sexual transmission of HSV during asymptomatic periods (most frequently in the first 12 months of infection)
- The need to abstain from sexual activity with uninfected partners when lesions or prodromal symptoms are present
- Ineffectiveness of episodic or suppressive therapy to reduce the risk of transmission to partners at risk for HSV-2
- Use of external latex condoms consistently and correctly to reduce, but not eliminate, the risk for genital herpes transmission
- The possibility for HSV infection in the absence of symptoms, including recommendation of type-specific serologic testing of asymptomatic partners to determine whether they are infected or at risk for acquiring HSV
- Risk for neonatal HSV infection
- Increased risk for HIV infection in HSV-2 seropositive persons exposed to HIV

The psychologic impact of HSV-2 diagnosis in patients with asymptomatic or unrecognized genital herpes is usually minimal [73; 74]. However, for some, the emotional effect can be substantial, and some infected patients develop anxiety disproportionate to actual clinical severity. Common concerns include the severity of initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners, and ability to bear healthy children. These patients may benefit from referral to a mental health professional. Clinicians should also dispel the misconception that HSV-1 and HSV-2 cause cancer.

HUMAN PAPILLOMAVIRUS

HPV is the most common STI in the United States. During 2013–2014, the prevalence of genital HPV in adults 18 to 59 years of age was 45.2% in men and 39.9% in women [75]. Around 100 HPV types have been identified, and at least 40 can infect the anogenital area in men and women. HPV types vary by propensity to cause genital warts and recurrent respiratory papillomatosis (HPV types 6

and 11), or cervical, penile, vulvar, vaginal, anal, and oropharyngeal cancers and precancers (HPV types 16 and 18) [36]. Most HPV infections are self-limited, asymptomatic, or unrecognized, and many sexually active persons will be infected with HPV at least once in their lifetime [76].

Persistent oncogenic HPV infection is the greatest risk factor for developing HPV-associated precancers and cancers. In the United States, HPV imposes a high public health burden of cancers and anogenital warts. During 2012–2016, there were an estimated 34,800 cases of newly diagnosed HPV-associated cancers. Of these, the largest number were oropharyngeal cancer (12,600), cervical cancer (9,700), and anal cancer (6,000) [77].

HPV testing is primarily used to screen for cervical cancer and/or identify women who may be at increased risk of cervical cancer. The test determines whether a woman's cervical cells are infected with high-risk oncogenic types of HPV. If long-lasting, the infection can cause changes in cervical cells that could lead to cervical cancer. With high-risk HPV infection now recognized as the cause of almost all cases of cervical cancer, HPV testing has become an essential part of women's health screening [78; 79].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology recommend that women 30 to 65 years of age should be screened with cytology and HPV testing ("cotesting") every five years (preferred) or cytology alone every three years (acceptable).

(https://www.asccp.org/Assets/b75ccc7c-ba43-4942-ac85-aecff6e543d3/635912169968500000/asccp-cervical-cancer-screening-recommendations-pdf. Last accessed June 15, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

Tests that detect oncogenic high-risk HPV infection are used in cervical cancer screening, management, or follow-up of abnormal cervical cytology or histology. These tests should not be used to diagnose genital warts, as a general STI test in male partners of women with HPV [1; 78]. Subclinical genital HPV infection typically clears spontaneously [1].

Part of a standard gynecologic exam is the Papanicolaou (Pap) test, whereby samples of cells from the cervix are examined under a microscope for signs of cervical pre-cancer or cancer [36]. HPV-related precancer is managed based on existing guidance.

PREVENTION

Prevention of high-risk HPV is most effectively achieved through vaccination. The FDA has approved three vaccines that protect against HPV and the diseases and cancers caused by HPV. A bivalent vaccine (Cervarix) and Gardasil were previously available, but are no longer used in the United States. The currently recommended vaccine is nine-valent Gardasil 9, which protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 [80; 81].

HPV types 16 and 18 cause most cervical cancers, and types 6 and 11 cause most genital warts [81]. Gardasil 9 protects against these plus five additional HPV types that account for 15% of cervical cancers [81; 82].

All boys and girls 11 to 12 years of age are now recommended to receive HPV vaccines, as they are most effective when given at younger ages, before the onset of sexual activity and initial exposure to the virus. The earliest approved age is 9 years. The vaccine in clinical use is recommended for girls/women and boys/men. Young sexually active people should still receive the vaccination, because those already infected with one type of HPV may benefit from the protection against other types included in the vaccine. In those who have not received any or all vaccine doses, vaccination is recommended through 26 years of age for all girls/women and boys/men [80]. HPV vaccine is also recommended for those 27 to 45 years of age if desired or if a risk factor is present.

The HPV vaccine is available for eligible children and adolescents younger than 19 years of age through the Vaccines for Children program, and patient-assistance programs are available from the vaccine manufacturers for uninsured persons 19 years of age and older. HPV vaccination is not recommended for use in pregnant women [82; 83]. In 2018, the FDA approved expanded use of Gardasil 9 to include women and men up to 45 years of age [84].

HPV vaccines are given as two or three injections over six months, and the same vaccine product should be used for the entire series. HPV vaccines can be administered regardless of history of anogenital warts, abnormal Pap/HPV tests, or anogenital precancer. Women 21 years of age or older who have received HPV vaccination should continue routine cervical cancer screening, as vaccines do not protect against all cervical cancers.

Safety evaluations have found the HPV vaccines to be well tolerated. Impact-monitoring studies in the United States have demonstrated reductions of genital warts and HPV types contained in the vaccines [85; 86]. The projected impact of vaccinating girls at 12 years of age is a 20% to 66% reduction in lifetime cervical cancer risk, depending on the effectiveness of the vaccine and the duration of protection. Vaccination could also lead to a 21% reduction in low-grade abnormalities on Pap tests over the life of a cohort of vaccinated females. A comparison of HPV prevalence data from the vaccine era (2009–2012) and the prevaccine era (2003–2006) found that the prevalence of the HPV types included in the quadrivalent vaccine decreased by 64% (from 11.5% to 4.3%) among girls 14 to 19 years of age [87]. Considering the modest uptake of this vaccine, the potential impact is significant. HPV vaccination has not been associated with earlier initiation of sexual activity or sexual risk behaviors [88].

GENITAL WARTS

Etiology

Genital warts (condyloma acuminatum) are benign and mainly caused by HPV types 6 and 11. The types affecting the anogenital region are usually transmitted sexually by penetrative vaginal or anal intercourse, but digital, oral, and nonpenetrative genital contact may be involved. The development of genital warts is more common in patients who are immunocompromised. Growth rates vary, but pregnancy, immunosuppression, or maceration of the skin may accelerate the growth and spread of warts [89].

Clinical Features

Anogenital warts appear following an incubation period of one to six months and usually present as flat, papular, or pedunculated growths (often in clusters) on the genital mucosa. While usually asymptomatic, some patients experience itching, burning, pain, or discomfort [90].

Anogenital warts commonly occur around the vaginal introitus, under the foreskin of the uncircumcised penis, and on the shaft of the circumcised penis. Common sites in the anogenital epithelium or within the anogenital tract include the cervix, vagina, urethra, perineum, perianal skin, anus, and scrotum. Intra-anal warts are mostly observed in MSM and others who practice receptive anal intercourse, but they may occur in men and women without histories of anal sexual contact [90].

Diagnosis

The clinical diagnosis of anogenital warts is made by visual inspection and confirmed with biopsy. Biopsy is indicated to rule out anogenital neoplasia if lesions are atypical (e.g., pigmented, indurated, affixed to underlying tissue, bleeding, ulcerated). Especially for patients with immunocompromise, biopsy is indicated when the diagnosis is uncertain; when lesions do not respond to standard therapy; or if the disease worsens during therapy. HPV testing is not recommended for anogenital wart diagnosis, because test results are not confirmatory and do not guide management [90].

RECOMMENDED TREATMENT OF GENITAL WARTS	
Wart Location	**Recommended Treatment**
External anogenital warts (penis, groin, scrotum, vulva, perineum, external anus, perianus)[a]	Patient-applied therapy: Imiquimod 3.75% or 5% cream[b] Podofilox 0.5% solution or gel Sinecatechins 15% ointment[b]
	Provider-administered therapy: Cryotherapy with liquid nitrogen or CryoProbe Surgical removal by tangential scissor or shave excision curettage, laser, or electrosurgery TCA or BCA 80% to 90% solution
Urethral meatus warts	Cryotherapy with liquid nitrogen Surgical removal
Vaginal warts	Cryotherapy with liquid nitrogen[c] Surgical removal TCA or BCA 80% to 90% solution
Cervical warts[d]	Cryotherapy with liquid nitrogen Surgical removal TCA or BCA 80% to 90% solution
Intra-anal warts[e]	Cryotherapy with liquid nitrogen Surgical removal TCA or BCA 80% to 90% solution
[a] Many patients with external anal warts have intra-anal warts; consider anal canal inspection by digital examination, standard anoscopy, or high-resolution anoscopy. [b] May weaken condoms and vaginal diaphragms. [c] Do not use a CryoProbe in the vagina because of risk for vaginal perforation and fistula formation. [d] Consult with a specialist. In women with exophytic cervical warts, a biopsy should be performed before treatment to exclude high-grade squamous intraepithelial lesion. [e] Consult with a specialist. BCA = bichloroacetic acid, TCA = trichloroacetic acid.	
Source: [1]	*Table 3*

Endocervical and anal warts can only be visualized by colposcopy and anoscopy. Visualization and detection of small warts is enhanced before colposcopy by applying a 3% to 5% acetic acid solution for several minutes, which causes the warts to whiten. This procedure should not be used to detect HPV infection [90].

Treatment of Anogenital Warts

Treatment can alleviate symptoms and emotional distress in some patients, particularly those with cosmetic concerns, and it resolves wart(s) in most patients, although it may take several attempts. If left untreated, anogenital warts can resolve spontaneously, remain unchanged, or increase in size or number. In immunocompetent people, genital warts may resolve without treatment within one year. For these patients, an acceptable option is deferred treatment to allow for spontaneous clearance. Available therapies for anogenital warts might reduce, but not eradicate, HPV infectivity. Whether future transmission of HPV is decreased by treatment is unknown [1].

No treatment of genital warts is clearly more efficacious than others. Therapy selection is based on wart size, number, and anatomic site; patient preference; costs; convenience; adverse effects; and provider experience (***Table 3***). Some clinicians combine therapies, such as provider-administered cryotherapy along with patient-applied topical therapy [90].

Treatment involves topical therapy (mostly patient-applied) or provider-administered mechanical removal. Some patients prefer to apply treatment themselves for privacy reasons. To ensure patient-applied treatment is effective, all anogenital warts should be accessible and identified during the clinic visit, and patients should be instructed on proper application technique. Follow-up after several weeks allows providers to answer questions about medication use, address side effects, and assess treatment response [1].

Recommended Regimens for External Anogenital Warts

Recommended topical therapies for external anogenital warts include patient-applied imiquimod, an immune enhancer that stimulates production of interferon and other cytokines; podophyllotoxin, an antimitotic drug that causes wart necrosis; sinecatechins, a green tea extract with catechins the active constituent; and clinician-applied trichloroacetic acid (TCA) or bichloroacetic acid (BCA), caustic agents that destroy warts by chemical coagulation of proteins [90].

Soft, non-keratinized warts respond well to podophyllotoxin and TCA. Keratinized lesions are better suited for physical ablative methods such as cryotherapy, excision or electrocautery, or TCA. Imiquimod is suitable for both keratinized and non-keratinized warts. Patients with a low number of smaller warts can be treated with ablative therapy or topical podophyllotoxin from the outset. With patient-applied therapy, clinicians should provide a demonstration on lesion finding and treatment application. Very large wart lesions generally respond better to surgical treatment [90].

Patient-applied treatments differ in recommended application and possible side effects. Imiquimod is applied three times per week (5% cream) or daily (3.75% cream) at bedtime for up to 16 weeks. Local reactions can include redness, irritation, induration, ulceration/erosions, or vesicles, and imiquimod may worsen psoriasis, vitiligo, and other inflammatory or autoimmune skin diseases [91; 92; 93; 94].

Podophyllotoxin is applied twice daily for three days, followed by four days without therapy; this is repeated for up to four cycles. Mild-to-moderate pain or local irritation may develop [90].

Sinecatechins is applied three times daily for up to 16 weeks [95]. Patients should be advised to avoid sexual contact with treated areas during therapy. Common side effects are erythema, pruritus/burning, pain, ulceration, edema, induration, or vesicular rash. Safety and efficacy is not known in patients with genital herpes or HIV and other immune-impaired conditions [96].

TCA and BCA are widely used but have not been studied extensively. A small amount is applied to the warts and allowed to dry before the patient sits or stands. Treatment can be repeated weekly, if needed [1].

Mechanical removal options include cryotherapy, electrocauterization, and laser or surgical excision. Cryotherapy employs thermal-induced cytolysis for wart destruction and requires proper training to avoid over- or undertreatment and resultant complications or inefficacy. Pain is common following liquid nitrogen treatment from necrosis or blistering, and local anesthesia can help facilitate therapy [1].

Surgical therapy can eliminate most warts in a single visit, but recurrence may occur. After local anesthesia is applied, anogenital warts are physically destroyed by electrocautery, and no additional hemostasis is required. Warts can also be removed by tangential excision with a pair of fine scissors or scalpel, by carbon dioxide (CO_2) laser, or by curettage. Because most warts are exophytic, the wound is not deeper than the upper dermis. Hemostasis can be achieved with an electrocautery unit or, in cases of very minor bleeding, a chemical styptic (e.g., an aluminum chloride solution). Most cases do not need suturing. As noted, with large or extensive warts, surgical therapy, including CO_2 laser, is most beneficial, especially for intraurethral warts and in patients lacking response to other treatments [90].

Alternative Regimens

Alternative approaches for anogenital warts have less supportive data and potentially greater side effects. Options include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Patient-applied podophyllin resin is no longer recommended because of potentially severe systemic toxicity; however, provider-administered podophyllin resin 10% to 25% may be considered with strict adherence to recommended use [1; 97; 98].

Follow-Up

Change to a new treatment modality is indicated if the patient fails to show substantial improvement or experiences severe side effects. Complications are rare when treatment is administered properly, but persistent hypo- or hyperpigmentation can occur with cryotherapy, electrocautery, and imiquimod cream. Depressed or hypertrophic scars are uncommon but can occur, especially with insufficient healing time between treatments. Rarely, treatment can result in chronic pain syndromes such as vulvodynia, hyperesthesia of the treatment site, or painful defecation or fistulas (with anal warts) [1].

Treatment During Pregnancy

Podophyllotoxin, podophyllin, and sinecatechins should not be used during pregnancy. Imiquimod appears to pose low risk but should be avoided until more data are available. Anogenital warts can proliferate and become friable during pregnancy, and although removal of warts 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 is not completely understood. Whether cesarean delivery prevents respiratory papillomatosis in offspring is also unclear, and cesarean delivery should not be performed solely to prevent transmission of HPV. Cesarean delivery is indicated for women with anogenital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding. Pregnant women with anogenital warts should be counseled about the low but present risk for warts on the larynx of their infants or children (recurrent respiratory papillomatosis) [1; 99].

Treatment in the Presence of HIV Co-Infection and Other Causes of Immunosuppression

Patients with HPV who have HIV infection or are immunosuppressed are more likely to develop anogenital warts, to present with larger or more numerous lesions, to lack treatment response, and to have more frequent recurrences after treatment [100; 101]. Despite this, treatment should not be altered for patients with HIV. Squamous cell carcinomas inside of, or resembling, anogenital warts are more frequent in immunosuppressed patients, requiring biopsy for diagnostic confirmation in suspicious cases [102; 103]. Biopsy of an atypical wart might reveal high-grade squamous intraepithelial lesions or cancer of the anogenital tract. In this instance, specialist referral for treatment is recommended [1].

MANAGEMENT OF SEX PARTNERS

Patients should be advised to inform current sex partner(s) about having genital warts, because the HPV types that cause warts can be transmitted sexually. Partners should receive counseling regarding the possibility they may already have HPV despite no visible signs of warts. However, HPV testing of sex partners of persons with genital warts is not recommended. Instead, partner(s) may benefit from a physical examination to detect genital warts and tests for other STIs. The duration of viral persistence after warts have resolved is unknown, and no recommendations can be made for informing future sex partners about a genital warts diagnosis [1].

KEY COUNSELING MESSAGES FOR PATIENTS WITH HPV

All patients with HPV should be educated regarding transmission, treatment, and follow-up [1]. Educational messages may include:

- HPV infection is very common and usually infects the anogenital area, but it may infect the mouth or throat. Most sexually active people acquire HPV at some point, but many are unaware of it.
- Sex partners tend to share HPV, and determining which partner transmitted the original infection is not possible. Diagnosis of HPV does not mean the patient or partner is having sex outside the relationship.
- Most persons who acquire HPV clear the infection without treatment or health problems. HPV infection that does not resolve can lead to genital warts, precancers, and cancers of the cervix, anus, penis, vulva, vagina, head, and neck.
- The HPV types that cause genital warts and cancer often differ.
- Many types of HPV are transmitted through vaginal and anal sex. HPV can also be transmitted by genital-to-genital contact without penetration, oral sex, and, rarely, by pregnant woman to an infant during delivery.
- In women, having HPV does not usually interfere with getting pregnant or carrying a pregnancy to term. However, some HPV-related precancers or cancers, and their treatment, may reduce the ability to get pregnant or have delivery without complications.
- Treatment is available for conditions caused by HPV, but not for the virus itself.
- No HPV test can determine which HPV infections will resolve and which will progress, but in certain circumstances, HPV tests can determine an increased risk for cervical cancer. These tests are not used to detect other HPV-related problems, in women younger than 25 years of age, or in men of any age.

Key counseling messages for patients with anogenital warts include [1]:

- Untreated genital warts may resolve, remain the same, or increase in size or number.
- Women with genital warts do not need Pap tests more often than other women.
- The time of HPV acquisition cannot be determined, and warts can develop months or years after acquiring HPV.
- HPV types that cause genital warts can be transmitted to others, even when visible signs of warts are absent. Sex partners tend to share HPV, even when signs of HPV appear in only one or neither partners.
- Although genital warts are common and benign, receiving this diagnosis can be intensely upsetting to some.
- Genital warts can be treated but not cured. Because the virus persists, genital warts can recur after treatment, especially in the first three months.
- Patients with genital warts benefit from testing for other STIs, because genital warts can be sexually transmitted. Sexual activity with new partners should be avoided until the warts are gone or removed.
- Condoms used consistently and correctly might lower the chances of transmitting genital warts, but HPV can infect areas not covered by a condom.
- Vaccines are available to prevent genital warts and wart-causing types of HPV but will not treat existing HPV or genital warts.

VIRAL HEPATITIS

Hepatitis is an inflammatory state of the liver. Most cases of hepatitis are caused by viral infection; other causes include exposure to chemicals, over-the-counter or prescription drugs, heavy alcohol use, inherited diseases, autoimmune disease, and fatty buildup in the liver [104]. In all patients with symptoms that suggest acute viral hepatitis, clinicians should assess the patient and, if necessary, refer for hospital admission. Tests should be performed to assess hepatitis severity, including liver function tests, coagulation tests, and hepatitis serology (i.e., anti-HAV IgM, HBsAg, hepatitis C virus [HCV] antibodies/RNA, and hepatitis E serology/PCR) [105].

HEPATITIS A VIRUS

Hepatitis A is an RNA virus that is highly common in areas with poor sanitation (typically developing countries), where it mainly affects children; it is less common is the United States and other developed countries [105]. HAV replicates in the liver. Starting two to three weeks after exposure, anti-HAV IgM is detectable, but levels then decline. Anti-HAV IgG levels begin to rise three to four weeks after exposure and remain elevated throughout life [36].

HAV is primarily transmitted through the fecal-oral route, most commonly through contaminated food or water; fecal-oral contact during sexual activity is also a transmission risk. Efforts to promote good personal hygiene have not succeeded in curtailing HAV outbreaks. Bloodborne transmission is uncommon, and transmission by saliva is not documented [106; 107]. In the United States, risk data were missing for 46.6% of reported cases in 2017. The most common risk factors reported were injection drug use, person-to-person and foodborne outbreaks, and sexual/household contact with a hepatitis A patient [108]. Signs of HAV infection include jaundice (with pale stools and dark urine) and liver enlargement/tenderness.

Clinical Presentation

More than 70% of adults are symptomatic during acute HAV infection, but most children are asymptomatic or have mild, nonspecific symptoms and little or no jaundice [1]. Most symptomatic patients follow a clinical course of a prodromal phase, icteric illness, and recovery. Rarely, patients may develop fulminant infection during acute HAV infection [105].

Prodromal Illness

After an average 28-day incubation (range: 15 to 45 days), patients can experience nonspecific flu-like symptoms (e.g., malaise, myalgia, fatigue), often with right upper abdominal pain. This phase lasts 3 to 10 days.

Icteric Illness

The icteric phase is characterized by jaundice (mixed hepatic and cholestatic) and is associated with anorexia, nausea, and fatigue that usually lasts one to three weeks. This phase can persist 12 or more weeks in a minority of patients who have cholestatic symptoms (e.g., itching, deep jaundice). Fever is rare. Up to 10% of patients experience symptomatic relapse in the six months following acute illness.

In patients with acute HAV infection, acute liver failure develops in 0.4%, but 15% may require hospital care. The overall mortality is <0.1%, which rises to 40% with acute liver failure; these patients should be considered for liver transplantation [105].

Diagnostic Considerations

Diagnosis of HAV infection requires serologic testing [1; 105]. Diagnosis is confirmed by positive serum anti-HAV IgM, which usually remains positive for 45 to 60 days. As noted, HAV-IgG does not distinguish current from past infection and remains positive for life.

Treatment

Most patients with symptomatic acute HAV infection can be managed as outpatients, with emphasis on rest and oral hydration. Hospitalization is necessary for patients who become dehydrated from nausea and vomiting or who have signs of hepatic decompensation, including changes in personality or level of consciousness. Medications that may damage, or are metabolized by, the liver should be used with caution in persons with HAV infection [1; 105].

Vaccines

Vaccination is the most effective means of preventing HAV transmission among persons at risk for infection. HAV vaccines are prepared from formalin-inactivated, cell-culture-derived HAV. Two monovalent vaccines (Havrix and VAQTA) are FDA-approved for persons 12 months of age or older [1; 109].

HAV vaccines are given IM in a two-dose series at 0 and 6 to 18 months. Protective antibody levels are induced in 94% to 100% of adults by one month after the first dose, and in 100% after the second dose. Kinetic models of antibody decline indicate that protective antibody levels persist for more than 20 years [109].

HAV vaccine should be offered to the following persons seeking STI services [1]:

- All MSM
- Injection and non-injection illicit drug users
- Those with chronic liver disease, including chronic HBV and HCV infection and evidence of chronic liver disease

A combined HAV/HBV vaccine (Twinrix) is FDA-approved for use as a three-dose series in adults 18 years of age or older at risk for hepatitis A and hepatitis B infections. When administered IM on a 0-, 1-, and 6-month schedule, the vaccine has equivalent immunogenicity to that of the monovalent vaccines [110; 111; 112].

Pre-Vaccination Serologic Testing

Around one-third of the U.S. population has serologic evidence of previous HAV infection, and prevalence increases with age. The potential cost savings of pre-vaccination susceptibility testing should be weighed against the cost and probability that testing will interfere with initiating vaccination. Serologic testing should not be a barrier to vaccination of at-risk populations, and vaccinating a person already immune is not harmful. When a history of at least two-dose HAV vaccination is documented, no further vaccination or serologic testing is needed [113].

Post-Exposure Prophylaxis

When given within two weeks of HAV exposure, intramuscular (IM) immunoglobulin is more than 85% effective in preventing HAV infection [114]. Persons exposed to HAV who have not previously been vaccinated should receive a single dose of monovalent hepatitis A vaccine or immunoglobulin (0.02 mL/kg) as soon as possible; efficacy is not established more than two weeks post-exposure [109]. There is limited information on vaccine versus immunoglobulin post-exposure efficacy, and no data are available on patients older than 40 years of age or with medical comorbidities. The decision to use the vaccine versus immunoglobulin should be informed by patient risk for more severe HAV infection (e.g., older age, chronic liver disease) and HAV transmission risk from the exposure [109].

Immunoglobulin is indicated for use in children younger than 12 months of age, patients with immune compromise or chronic liver disease, and when vaccination is contraindicated. Immunoglobulin is also preferred for persons older than 40 years of age, due in part to the greater severity of hepatitis A in this age group. In these cases, the vaccine can be used if immunoglobulin cannot be obtained [109]. For healthy persons 1 to 40 years of age, the vaccine is preferred to immunoglobulin because of the advantages in long-term protection and ease of use [1]. The combined HAV/HBV vaccine may be considered in eligible persons [1].

Counseling Following Confirmed Acute HAV Infection

It is crucial that all patients with diagnosed HAV infection receive information and counseling [105]. Clinicians should provide detailed explanations, verbally and in writing, of the condition, with emphasis on long-term health implications for the patient and partner(s). Pregnant women should be advised of the increased risk for miscarriage/premature labor and to seek medical advice if symptoms develop. All patients should avoid handling food and unprotected sexual intercourse until they are considered noninfectious. Partner notification is necessary for at-risk sexual contacts (oro-anal, digital/rectal, or penetrative anal sex) within two weeks before and up to one week after the onset of jaundice.

HEPATITIS B VIRUS

Hepatitis B is a DNA virus with eight distinct genotypes (A-H) that vary by geographic distribution, pathogenicity, and treatment susceptibility. Left undetected and untreated, HBV can cause serious liver disease resulting in lifelong infection, permanent liver scarring (cirrhosis), cancer, liver failure, and death [105].

Transmission

After an incubation period of 40 to 160 days, HBV concentrations are highest in the blood and present (but in lower concentrations) in wound exudates, semen, vaginal secretions, and saliva. HBV is efficiently transmitted by percutaneous or mucous membrane exposure to infected blood or body fluids. HBV is more infectious and more stable in the environment than other bloodborne pathogens, including HCV and HIV [1].

Routes of HBV transmission include [36; 105; 115]:

- MSM (unvaccinated/non-immune): Higher risk with multiple partners, sex workers, unprotected anal or oro-anal sex
- Heterosexual contact: Partners of patients with acute HBV, sex workers
- Vertical (infected mother to infant)
- Parenteral: Unscreened blood/blood products, shared drug injection equipment, non-sterile acupuncture and tattoo needles, workplace needlestick injuries
- Sporadic: Adults with Down syndrome and other developmental disabilities placed in institutions (route of transmission poorly understood)
- Premastication (e.g., shared chewing gum)

Clinical Course and Patient Presentation

Signs and symptoms of patients in the prodromal and icteric phases of acute HBV infection are similar to hepatitis A, but can be more severe and prolonged in symptomatic patients. Acute HBV infection is asymptomatic in almost all infants and children and in 10% to 50% of adults [105].

Chronic HBV infection usually occurs without physical signs, but some patients may develop fatigue or loss of appetite. After years of infection, signs of chronic liver disease may develop, including spider nevi, finger clubbing, jaundice, and hepatosplenomegaly. Severe cases can develop thinning skin, bruising, ascites, asterixis ("liver flap"), and encephalopathy [116].

Acute liver failure occurs in less than 1% of symptomatic acute cases; prognosis is worse than in hepatitis A. Pregnant women have increased rates of miscarriage/premature labor and risk of vertical transmission. Mortality is less than 1% in acute infection [116].

Chronic infection (longer than six months) occurs in 5% to 10% of symptomatic patients. Risk is inversely related to age when infected; chronic HBV infection develops in roughly 90% of those infected as infants, 25% to 50% infected before the age of 5 years, and 5% of those infected as adults [117]. Risk of premature death from cirrhosis or hepatocellular carcinoma is 15% to 25% with chronic HBV infection [116; 117].

Diagnosis

Diagnosis of acute or chronic HBV infection requires serologic testing [1; 117]. HBsAg is present in 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), produced after an infection resolves, is the only HBV antibody marker present after vaccination. Presence of HBsAg and total anti-HBc, with a negative test for IgM anti-HBc, indicates chronic HBV infection. Presence of anti-HBc alone can reflect acute, resolved, or chronic infection or a false-positive result.

All persons with confirmed HBsAg should be reported to the state or local health department. In addition, patients with HBsAg should be retested to assess chronic HBV infection, confirmed by the absence of IgM anti-HBc or the persistence of HBsAg for six months.

Treatment

In patients with severe acute HBV infection, antiviral agents can prevent acute liver failure and improve morbidity and mortality [105; 117]. Otherwise, treatment is supportive for patients with acute HBV. Patients with chronic HBV should receive specialist management. Drugs FDA approved for treating chronic hepatitis B can achieve durable suppression of HBV replication and remission of liver disease [1; 117; 118].

Prevention

The national strategy for eliminating transmission of HBV infection includes [117; 119; 120]:

- Preventing perinatal infection by routinely screening all pregnant women for HBsAg and infants born to mothers with HBsAg
- Routine infant vaccination
- Vaccinating unvaccinated children and adolescents through 18 years of age
- Vaccinating unvaccinated adults at increased risk for infection

High vaccination rates and subsequent declines in the incidence of acute HBV infection have been achieved in infants and adolescents [120; 121]. In addition, the aging of vaccinated children and adolescents has likely led to improved vaccination coverage and lower acute HBV infection rates in adults younger than 30 years of age [122]. However, coverage of adults 30 years of age and older in high-risk groups (e.g., multiple sex partners, MSM, IDUs) remains low, and these groups account for the highest rates of preventable acute infections [119; 123]. Settings that provide STI services should vaccinate those who are unvaccinated, as adults seeking STI services are considered at increased risk for HBV infection.

Two product types are approved for HBV prevention: hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) [119; 120]. HBIG protects for three to six months against HBV infection and is used in post-exposure prophylaxis as an adjunct to hepatitis B vaccination (in unvaccinated persons) or in persons without vaccine response.

Hepatitis B vaccine contains HBsAg produced in yeast by recombinant DNA and protects from HBV infection as pre-exposure vaccination and post-exposure prophylaxis. Available monovalent hepatitis B vaccines are [117]:

- Recombivax HB
- Engerix-B
- Heplisav-B

Pediarix is a combination HBV/diphtheria, tetanus, DTaP, and IPV vaccine for infants 6 weeks to 7 years of age [117]. As discussed, Twinrix is a combination HAV/HBV vaccine for patients 18 years of age or older.

Hepatitis B vaccines differ by vaccination schedule; some require three injections over 4 or 6 months, while others require four injections over 12 months. Selection should consider the need to achieve completion of the vaccine series and likelihood of extended follow-up [1].

In adolescents and healthy adults younger than 40 years of age, 30% to 55% achieve a protective antibody response (i.e., anti-HBs ≥10 mIU/mL) after the first vaccine dose, 75% after the second, and more than 90% after the third. Vaccine-induced immune memory is demonstrated to persist for at least 30 years [117]. Periodic testing to determine antibody levels is not necessary, and booster doses of the vaccine are not currently recommended [121; 124; 125].

Hepatitis B vaccination is generally well tolerated by most patients; injection-site pain and low-grade fever are reported in a minority. In children and adolescents, anaphylaxis has been reported in 1 patient for every 1.1 million vaccines, but no deaths have been reported in these patients. Vaccination is contraindicated in patients with previous anaphylactic reaction to hepatitis B vaccination or any vaccine component. No other adverse events with hepatitis B vaccine have been demonstrated [119; 120].

HBV vaccination is recommended for the following unvaccinated persons [120]:

- Children and adolescents
- All adults who are IDUs, MSM, or with multiple sex partners
- All adults wanting protection from HBV

As noted, hepatitis B vaccine should be routinely offered to all unvaccinated persons attending STI clinics and those seeking STI evaluation or treatment in correctional facilities, drug-abuse treatment and prevention programs, federally qualified health centers, and settings that serve MSM.

Pre-Vaccination Serologic Testing

Pre-vaccination serologic testing for susceptibility may reduce the costs of completing the vaccine series in populations with a high prevalence of HBV infection (e.g., older IDUs, MSM). Susceptibility testing is recommended for the unvaccinated household, sexual, and needle-sharing contacts of HBsAg-positive persons. Vaccination of those immune to HBV due to current/past infection or vaccination is not harmful and does not increase the risk for adverse events [123].

Anti-HBc is the test of choice for pre-vaccination testing, and those who test anti-HBc-positive should be tested for HBsAg. If HBsAg negative, no further action is required. Persons who are HBsAg-positive should be referred to a specialist in hepatitis B infection management [1].

Post-Vaccination Serologic Testing for Response

Post-vaccination serologic testing for immunity is not necessary after routine vaccination of most healthy adolescents or adults. Such testing is recommended for persons whose clinical management depends on confirming their immune status, including healthcare and public safety workers at high risk for exposure to blood or body fluids. Post-vaccination testing is also recommended for persons with HIV and other immunocompromising conditions and sex and needle-sharing partners of HBsAg-positive persons. If indicated, anti-HBs testing should be performed one to two months after the last dose of the vaccine series [1].

Post-Exposure Prophylaxis

Passive-active post-exposure prophylaxis (i.e., HBIG plus HBV vaccine at separate IM sites) and active post-exposure prophylaxis (i.e., hepatitis B vaccination alone) are both highly effective in preventing transmission after exposure to HBV. HBIG alone is effective in preventing HBV transmission, but it is typically combined with hepatitis B vaccine.

Unvaccinated persons should receive HBIG plus hepatitis vaccine as soon as possible (within 24 hours) after exposure to blood or body fluids from a person with known HBsAg, and the full HBV vaccine series should be completed. Persons exposed during the vaccine process should receive HBIG and complete the series [126].

Unvaccinated persons exposed to blood or body fluids from a person with unknown HBsAg status should receive the hepatitis B vaccine series, with the first dose initiated preferably less than 24 hours after exposure [126].

Key Counseling Messages

Sex partners of patients with HBV infection should be advised to use latex condoms for protection from sexual exposure unless they demonstrate immunity post-vaccination (anti-HBs ≥10 mIU/mL) or from previous infection (anti-HBc positive). To minimize transmission risk to others through infected blood or bodily fluids, patients with HBV should:

- Use condoms until sex partner is vaccinated and immunity documented
- Cover cuts and skin lesions
- Not donate blood, plasma, body organs, tissue, or semen
- Not share toothbrushes, razors, or injection equipment

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Association for the Study of Liver Diseases, patients with hepatitis B should be counseled regarding transmission to others. For casual sex partners or steady partners who have not been tested or have not completed the full immunization series, barrier protection methods should be utilized.

(https://www.aasld.org/sites/default/files/2019-06/HBVGuidance_Terrault_et_al-2018-Hepatology.pdf. Last accessed June 15, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

In addition, to protect the liver from further harm, patients with HBV are advised to:

- Avoid or limit alcohol consumption.
- Not start new medications, including over-the-counter/herbal medications, without checking with a healthcare provider.
- Obtain hepatitis A vaccination.

When seeking medical or dental care, patients should disclose their HBsAg status so they can be appropriately evaluated and managed.

HBV is not usually spread by hugging, coughing, contaminated food or water, shared eating utensils or drinking glasses, or casual contact. It is important that patients with HBV not be excluded from work, school, play, childcare, or other settings because of their infection. Support group involvement can help patients cope with chronic HBV infection.

Pregnancy

Regardless of previous testing or vaccination, all pregnant women should be tested for HBsAg at the first prenatal visit. Those at high risk should also be tested at delivery and receive hepatitis B vaccination. All pregnant women with HBsAg should be reported to state and local perinatal hepatitis B prevention programs and referred to a specialist [1].

HIV Co-Infection

HIV infection and other immune suppressing conditions can impair hepatitis B vaccine response. Persons with HIV infection should be tested for anti-HBs one to two months after the third vaccine dose. Modified dosing regimens, including doubling the standard antigen dose and adding additional doses, might increase the response rate [1].

HEPATITIS C VIRUS

HCV is primarily transmitted parenterally, such as through sharing drug-injection equipment. Aside from patients with genital ulcerative disease, STI-related proctitis, or sex partner(s) with HIV infection, sexual transmission of HCV is very infrequent [1]. The CDC recommends one-time hepatitis C screening of all adults 18 years of age and older and all pregnant women during each pregnancy. Screening is not necessary in settings in which the prevalence of HCV infection is less than 0.1% [127]. No vaccine exists for HCV, and no effective pre- or postexposure prophylaxis is available.

Since 2013, the United States has witnessed an unprecedented opioid overdose epidemic, caused in large part by the injection of illicit opioids. This epidemic has led to an increase in HCV infections among the injecting population and concern about increases in both HIV and HCV infections in communities disproportionately affected by the opioid crisis. However, identifying HCV infection in this population is challenging. A retrospective study from 2015–2016 was conducted in four urban emergency departments in the United States [128].

The emergency departments adopted opt-out universal hepatitis C screening for all adult patients by offering HCV antibody (anti-HCV) screening to patients who were unaware of their status. Of the 14,252 patients who were tested, staff identified an overall 9.2% prevalence of positive results for anti-HCV. In the cohort born between 1945–1965, the prevalence of positive results was 16.0% among non-Hispanic blacks and 12.2% among non-Hispanic whites. In persons born after 1965, the prevalence of positive results was 15.3% among whites and 3.2% among blacks. The authors of the study suggest that the opt-out method may help improve HCV infection awareness and surveillance and mitigate the age-associated differences in racial/ethnic prevalences of HCV infection in hard-to-reach populations [128].

HIV/AIDS

As of 2016, an estimated 1.1 million individuals 13 years of age or older were living with HIV or acquired immune deficiency syndrome (AIDS) in the United States [129]. The CDC estimates that approximately 14% of these individuals are unaware of their infection [129].

SIGNS AND SYMPTOMS

The clinical manifestations of HIV disease are determined by the stage of primary infection and the chronicity and degree of the resultant cellular immunodeficiency state. Acute, primary HIV infection may be asymptomatic, but most often it is manifest by a subacute viral syndrome of malaise and fatigue, fever, sore throat, rash, myalgia, headache, and lymphadenopathy—clinical features similar in many respects to that seen with Epstein-Barr virus mononucleosis, cytomegalovirus (CMV), and certain types of herpes simplex infections [130]. A variety of atypical symptoms and signs may be seen, including aseptic meningitis syndrome, genital ulcers, and ulcerations involving the gingiva, palate, or buccal mucosa. The acute illness usually resolves in less than 14 days but may follow a protracted course over many weeks [130].

Early in the chronic phase of HIV infection, when the CD4 lymphocyte population is only modestly depressed and declining slowly, patients are often asymptomatic or may exhibit generalized lymphadenopathy and recurrent oropharyngeal candidiasis (thrush). During this stage, a reservoir of HIV is established throughout the lymphoid tissue system, including the spleen. Gradually, wandering (infected) macrophages disseminate the virus to certain internal organs, notably the brain, kidney, and adrenal glands.

Chronic HIV disease follows a variable course but eventually leads to a variety of clinical manifestations, some of which are directly related to the impact of chronic infection on vital organs. Common syndromes include HIV encephalopathy and dementia, peripheral neuropathy, interstitial nephropathy, a variety of skin eruptions, and signs of adrenal insufficiency.

The late clinical manifestations of HIV disease are most frequently the result of AIDS that follows progressive depletion of CD4+ T lymphocytes to levels <200 cells/mcL. AIDS-defining illnesses include secondary, opportunistic infections and certain malignancies usually encountered only in clinical settings of severely impaired cellular immunity.

Opportunistic infections are very common in persons with undiagnosed or poorly treated chronic HIV infection and are of two types. The first type is infection newly acquired by exposure to micro-organisms normally nonpathogenic, or of low pathogenicity, for persons with a healthy immune system. Examples are *Pneumocystis jiroveci*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and atypical mycobacteria, all of which are commonly associated with inhalational exposures and transient colonization of the respiratory tract in healthy individuals. The second type is reactivation of latent infection acquired earlier in life, which typically remains dormant throughout life. Examples of this type are CMV, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, and *H. capsulatum*. The advent of an opportunistic infection may serve as the herald sign of unrecognized, undiagnosed chronic HIV infection/AIDS.

Clinically, these infections tend to present in one of several distinct syndromes, with useful differential diagnosis considerations:

- Pneumonia: *Pneumocystis jiroveci* pneumonia (PJP), *Mycobacterium avium* complex (MAC), cryptococcosis, histoplasmosis
- Meningoencephalitis: Toxoplasmosis, cryptococcosis, tuberculosis
- Gastrointestinal disease (diarrhea): Common bacterial dysentery, cryptosporidiosis, fungal and atypical mycobacterial infection
- Fever of unknown origin (often with abdominal complaints, hepatosplenomegaly, and/or lymphadenopathy): CMV, MAC, tuberculosis, histoplasmosis

Late clinical manifestations related to HIV-induced malignancy include Kaposi sarcoma of the skin or respiratory tract and lymphoma presenting as lymphadenopathy, splenomegaly, or focal gastrointestinal disease.

Without satisfactory antiretroviral therapy, the usual patient with HIV/AIDS experiences a slow, inexorable wasting illness punctuated by periods of feverishness and diarrhea, becoming increasingly anorectic, malnourished, and lethargic. Late clinical signs include muscle wasting and weakness, anemia and thrombocytopenia, lymphadenopathy, pulmonary infiltrates, and neurologic abnormalities (such as dementia, peripheral neuropathy, and tremors). The median survival of patients with advanced HIV/AIDS (CD4 count <50 cells/mcL) is approximately 12 to 18 months. Patients succumb to complications of uncontrolled infection, malignancy, or critical organ failure (such as uremia or adrenal insufficiency).

TESTING

The initial testing for HIV generally consists of an FDA-approved, fourth-generation antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen to identify both established and acute infections [131]. If this test is reactive, repeat testing is recommended to differentiate HIV-1 antibodies from HIV-2 antibodies. If this second test is nonreactive, testing with an FDA-approved HIV-1 nucleic acid test is indicated [131]. It is important to note that HIV-2 is not reliably identified by usual immunoblot antibody tests. Additional testing specific to HIV-2 should be considered if HIV-1 test results are atypical or inconsistent with clinical findings, especially for persons from (or with recent travel to) West Africa [132].

Other available tests, including enzyme-linked immunosorbent assay, may be used if the preferred combination immunoassay is not available. The HIV-1 Western blot and HIV-1 immunofluorescence assay, previously recommended to make a laboratory diagnosis of HIV-1 infection, are no longer part of the recommended testing algorithm [131].

SEXUAL TRANSMISSION PREVENTION

HIV has been isolated from blood, seminal fluid, spermatozoa, pre-ejaculate, vaginal secretions, urine, cerebrospinal fluid, saliva, tears, and breast milk of infected individuals. No cases of HIV infection have been traced to saliva or tears (though traces of the virus are present in these fluids) [133]. The virus is found in greater concentration in semen than in vaginal fluids, leading to a hypothesis that male-to-female transmission could occur more easily than female-to-male. Sexual behavior that involves exposure to blood is likely to increase transmission risks. Transmission could also occur through contact with infected bowel epithelial cells in anal intercourse, in addition to access to the bloodstream through breaks in the rectal mucosa.

Posing the highest risk of infection is unprotected receptive anal intercourse, followed by unprotected receptive vaginal intercourse and unprotected insertive anal intercourse (particularly for uncircumcised men) [134; 135]. Risk is reduced through the use of latex condoms. For the wearer, latex condoms provide a mechanical barrier limiting penile exposure to infectious cervical, vaginal, vulvar, or rectal secretions or lesions. Likewise, the partner is protected from infectious pre-ejaculate, semen, and penile lesions. As discussed, natural membrane condoms (made from lamb cecum)

contain small pores and do not block HIV passage. It is estimated that latex condom use reduces the risk of HIV transmission by approximately 70% to 80% [136; 137; 138]. Although abstinence from sexual contact is the sole way to absolutely prevent sexual transmission, sexual activity in a mutually monogamous relationship in which neither partner is HIV-infected and no other risk factors are present is considered safe [139]. However, men who identify publicly as heterosexual and generally have committed relationships with women, but who also engage in sexual activity with other men, may be a transmission bridge to heterosexual women [140]. To better understand the actual extent of this behavior and its impact on HIV transmission, more research is necessary.

Numerous studies have demonstrated that oral sex can result in the transmission of HIV and other STIs. While the risk of HIV transmission through oral sex is much smaller than the risk from anal or vaginal sex, there are several co-factors that can increase this risk, including oral ulcers, bleeding gums, genital sores, and the presence of other STIs. Prevention includes the use of latex condoms, a natural rubber latex sheet, plastic food wrap, a cut open condom, or a dental dam, all of which serve as a physical barrier to transmission [141].

Pre-Exposure Prophylaxis

In 2012, the FDA approved the first medication for the prevention of sexually transmitted HIV infection, the combination drug Truvada (emtricitabine/tenofovir DF) [142]. In 2019, another combination drug—Descovy (emtricitabine/tenofovir)—was approved to prevent HIV infection [143]. In conjunction with safer sex practices, these agents have been found to be partially effective as pre-exposure prophylaxis in high-risk patients. The Chemoprophylaxis for HIV Prevention in Men study, also known as iPrEx, studied the effect of once daily Truvada in 2,499 HIV-seronegative men or transgender women who have sex with men compared with placebo [144]. Researchers found that persons receiving Truvada experienced a 44% reduction in the incidence of HIV after a median of 1.2 years compared with placebo. Pre-exposure prophylaxis was most effective among participants at particularly high risk for HIV (i.e., self-reports of unprotected receptive anal intercourse). Research has indicated that Descovy is similarly effective [143].

In 2017, the CDC and the U.S. Department of Health and Human Services updated its clinical practice guidelines for pre-exposure prophylaxis for the prevention of HIV infection [145]. This guideline outlines indications for prophylaxis as one prevention option for HIV transmission. The most important first step in determining if an individual is a candidate for pre-exposure prophylaxis is a thorough history, including sexual and injection drug activities. All candidates will be adults without an acute or established HIV diagnosis. Pre-exposure prophylaxis is indicated for high-risk MSM, meaning those who have had any male sex partners in the past six months, are not in a monogamous partnership with a recently tested, HIV-negative man, and have one of the following [145]:

- Anal sex without condoms (receptive or insertive) in the past six months
- Any STI diagnosed or reported in the past six months
- An ongoing sexual relationship with an HIV-positive man
- High number of sex partners
- Commercial sex work

Prophylaxis is also recommended for high-risk heterosexual adults who have had sex with an opposite sex partner(s) in the past six months, are not in a monogamous partnership with a recently tested, HIV-negative partner, and one of the following [145]:

- Is a man who has sex with both women and men (behaviorally bisexual)

- Infrequently uses condoms during sex with one or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (IDU or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner
- Any STI diagnosed or reported in the past six months
- Commercial sex work
- In high HIV prevalence area or network

IDUs are also considered candidates for pre-exposure prophylaxis if they meet certain criteria. The guideline states that persons who have injected drugs not prescribed by a clinician in the past six months may be candidates for prophylaxis if they also are positive for one of the following factors [145]:

- Any sharing of injection or drug preparation equipment in the past six months
- Been in a methadone, buprenorphine, or buprenorphine/naloxone treatment program in the past six months
- Increased risk of sexual acquisition (based on the previously outlined criteria)

As of 2020, only fixed-dose combination tenofovir and emtricitabine (Truvada or Descovy) taken daily is approved for pre-exposure prophylaxis, and it is considered the recommended first-line option [142; 145]. However, because tenofovir alone has been proven effective in trials with IDU and heterosexually active men and women, it is the alternative option for these populations [145]. No other antiretroviral regimens should be used for pre-exposure prophylaxis.

All patients prescribed pre-exposure prophylaxis must have a negative HIV test prior to initiating treatment and every three months thereafter. In addition, patients should be advised regarding possible side effects and the continued necessity for safe sex practices. Eligible patients should also be screened for hepatitis B and have a confirmed creatinine clearance of 60 mL per minute or greater [145].

MANAGEMENT

Combination antiretroviral therapy, or cART, combines seven major classes of agents: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), integrase strand transfer inhibitors (INSTIs), chemokine (C-C motif) receptor 5 (CCR5) antagonists, and gp120 attachment inhibitors. Initiated in 1995 in the United States, antiretroviral therapy regimens have been effective in dramatically decreasing HIV-related morbidity and mortality and should be considered for all HIV-infected persons who qualify for such therapy. In addition to combination therapy, the sequencing of drugs and the preservation of future treatment options are also important. Two types of combination regimens are recommended as initial therapy: INSTI-based regimens or a PI-based regimen. The goal of these regimens is to effectively reduce HIV-associated morbidity, prolong the duration and quality of survival, restore and preserve immunologic function, and prevent HIV transmission while also avoiding drug resistance [146]. A significant proportion of patients starting cART are infected with drug-resistant strains of HIV, which may lead to suboptimal virologic responses. Therefore, pre-treatment genotypic resistance testing should be used to guide selection of the most optimal initial regimen [146].

Antiretroviral therapy should be initiated immediately for all patients infected with HIV in order to reduce the risk of disease progression and limit transmission [146]. There is growing evidence that early initiation of cART is effective in preventing clinical events (e.g., non-AIDS malignancies, infection, AIDS-defining illness) regardless of pre-treatment CD4 count [147; 148]. Advances in the development of antiretroviral medications and combination tablets makes adherence to therapy more effective, more convenient, and better tolerated than regimens used in the past. Deferral of therapy may be considered in patients with high CD4 counts (e.g., more than 500 cells/mcL) if adherence will be very difficult or impossible,

comorbidities complicate or prohibit antiviral therapy, or a patient is considered a long-term non-progressor [146].

For treatment-naïve patients, initial recommended therapy generally consists of one of three INSTIs (bictegravir, dolutegravir, raltegravir) plus two NRTIs or DTG/3TCs (dolutegravir and lamivudine) [146]. For most patients, these INSTI-containing regimens will be highly effective and have relatively infrequent adverse effects and few drug interactions. In several head-to-head comparisons between boosted PI- and INSTI-containing regimens, the INSTI-based regimens were better tolerated and caused fewer treatment discontinuations [146]. These regimens result in maximum reduction of viral load for the longest period of time. When used as initial therapy, these regimens will achieve the goal of no detectable virus in the majority of patients after four to six months [146].

STIs IN IMMIGRANTS AND REFUGEES

A variety of persons migrate to the United States, including legal immigrants granted the indefinite or time-limited right to live in the United States by immigration authorities; undocumented immigrants who have not been granted such a right; and refugees who are unable or unwilling to return to their country of origin due to fears of persecution based on their race or ethnicity, religion, nationality, political opinion, or gender identity or sexual orientation. For simplicity, all three groups are referred to as immigrants [149].

Recent immigrants underuse health services, especially undocumented immigrants, who typically lack health insurance and may avoid seeking medical attention out of fear of being deported. Compared with the United States, many countries of origin have much higher rates of STIs, including hepatitis A (poor sanitation), hepatitis B (sexual contact), and HIV (sexual contact, maternofetal transmission).

Procedurally, STI risk assessment, screening, diagnostic testing, and treatment of recent immigrants are the same as with native-born persons. The process should be nonjudgmental and culturally sensitive during all contacts [149]. In practice, clinicians should be aware of the stigma, discrimination, and complex, stressful circumstances many immigrants experience. In addition to language barriers that require an interpreter, many experience social isolation from loss of social support and cultural identity. Some may have health belief systems, practices, or taboos that impact clinical care. Torture and rape are highly prevalent in some immigrant populations and place these persons at high risk for STIs and/or hepatitis. Post-traumatic stress disorder and other mental health conditions may be prevalent and can influence behaviors and interaction with the health system. A history of female genital mutilation can alter the appearance of the genital structure, making specimen collection and visualization of the cervix very difficult. Some immigrants have cultural sensitivities toward opposite-sex healthcare providers or discussion of sex practices or condom use. Patient history of traditional/herbal medicine should be taken to minimize toxicities and drug interactions [149]. By taking these factors into account when assessing and treating patients, clinicians may improve the sexual health of recent immigrants.

CONCLUSION

Described as hidden epidemics of substantial health and economic consequence, many Americans are reluctant to address sexual health concerns that include STIs because of the biologic and social characteristics of these diseases and associated stigma. However, all communities in the United States are impacted by STIs. Clinicians have an opportunity to identify patients at risk for viral STIs and intervene early in order to limit transmission and debilitating effects of the diseases.

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