COURSE #94182 — 5 CONTACT HOURS/CREDITS RELEASE DATE: 07/01/23 EXPIRATION DATE: 06/30/26

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.
- Receive your Certificate(s) of Completion by mail, fax, or email.

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.

Division Planners

John M. Leonard, MD
John V. Jurica, MD, MPH
Margo A. Halm, RN, PhD, ACNS-BC
Randall L. Allen, PharmD

Senior Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

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, pharmacists, and allied health professionals involved in the care of patients at risk for or with viral sexually transmitted infections.

Accreditations & Approvals

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Disclosure Statement

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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.

Pharmacy Technician Learning Objectives

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

1. Outline best practices for history taking and STI prevention.
2. Describe recommendations for the diagnosis and management of viral STIs.

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. STI prevalence is increasing throughout the world, a major clinical and public health challenge rooted in the complexities of 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 health and prevents transmission of STIs [1; 2]. Both the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) conduct STI surveillance and provide updated clinical guidance on prevention, diagnosis, and management of STIs [2; 151].

CDC data analysis for the year 2018 provides an indication of how common and costly are STIs in the United States. The CDC estimates that about 20% of the population had an STI on any given day in 2018 [152]. The estimated annual prevalence was 68 million, and half of all new ST's occurred among young adults 15 to 24 years of age. The estimated annual economic burden of new STI's was $16 million in direct medical costs; of this total, more than $14 million was attributable to three viruses: human immunodeficiency virus (HIV), human papillomavirus (HPV), and herpes simplex virus type 2 (HSV-2). Given the serious health consequences of untreated STIs and that many are unreported, these data illustrate the challenges and highlight the scope of the STI epidemic.

This course will address the prominent viral STIs in the United States—referred to as the four Hs: herpes, HPV, hepatitis, and HIV. The goal is to address knowledge gaps, enhance clinical skills, and highlight best practice guidelines for early diagnosis, treatment, and prevention of STIs.

GENERAL STI ASSESSMENT AND PREVENTION COUNSELING

The prevalence of STIs can be lowered by a consistent, concerted clinical and public health effort to prevent infection and control spread. Strategies for prevention include risk assessment, education, and counseling; limiting the number of sexual partners; and abstinence or use of condoms and barriers to sexual transmission. The importance of abstaining from sexual activity while undergoing treatment should be emphasized to individuals with a confirmed STI. Effective control measures require identification and treatment of asymptomatic sexual partners of known cases and symptomatic individuals who may not seek health care. The CDC encourages clinicians to promote prevention with patient-centered education that focuses on risk reduction measures directed at the individual patient's personal risk [1]. Obtaining a thorough sexual history is essential to primary prevention and control of spread.

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?"

Practical strategies for risk assessment and counseling are provided in the CDC treatment guidelines document [1]. Health providers should use simple, direct language when asking these questions, taking care to exhibit respect, compassion, and a nonjudgmental attitude. Organizations such as the National Network of STI/HIV Prevention Training Centers,

a CDC-funded group, can help providers enhance skills in counseling individuals about prevention. Resources can be found online at https://www.cdc.gov/std/treatment/resources.htm.

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]. In 2022, the FDA cleared the first natural rubber latex condom designed specifically to be used in anal intercourse [150].

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].

PENILE CIRCUMCISION

Penile 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 penile 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 penile 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 Who Have Sex with Women	MSM	Transgender and Gender Diverse People	Persons with HIV
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/anal 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 cisgender women	—	Digital anorectal rectal exam (anal cytology not recommended)	Follow recommendations for persons with a cervix	Within one year of sexual activity or first HIV diagnosis, using standard or liquid-based cytology. Repeat testing in six months.
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
Hepatitis C	All aged 18 years or older, except where infection positivity rate <0.1%	All aged 18 years or older, except where infection positivity rate <0.1%	All aged 18 years or older, except where infection positivity rate <0.1%	All aged 18 years or older, except where infection positivity rate <0.1%	–	Serologic testing at initial evaluation
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 previously 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	Offer testing to 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

Screening for STIs is important because many are asymptomatic at the time of initial infection and are at risk of transmission; as such, early detection is essential to avoid potential complications and prevent spread of disease. This is especially true of HIV infection and transmission. All persons seeking STI evaluation or treatment should be screened for HIV infection, regardless of whether the patient reports behavioral risk factors. Persons with early syphilis, gonorrhea, or chlamydia may also be at risk for HIV infection; rectal gonorrhea and syphilis are risk markers for HIV acquisition [33; 34]. In all healthcare settings, the CDC recommends HIV screening for patients 13 to 64 years of age who are at risk for STI; patients should be notified that testing will be performed and retain the option to decline or defer testing (opt-out) [32; 35]. Persons with high risk are defined as those with an incident STI; sexual partners of persons with STI; persons who have had more than one sexual partner (or whose sexual partners have had mor than one partner) since their most recent HIV test; injection drug users; and persons who exchange sex for money [166].

HERPES SIMPLEX VIRUS

HSV-1 and HSV-2 are highly prevalent global pathogens that commonly cause recurrent oral and genital ulcerations [153; 154]. HSV-2 is the leading cause of genital ulcer disease and the most common ulcerative STI. HSV-2 genital infection is one driver of the HIV epidemic, increasing the risk of HIV acquisition threefold. Less common complications of HSV include aseptic meningitis, keratitis, and neonatal herpes infection, which is associated with long-term neurologic impairment and high mortality [153]. Transmission of HSV-2 occurs through direct contact with mucosal or skin surfaces during sexual exposure or during labor and delivery of the neonate. Public health control strategies for genital HSV infection, including antiviral therapy and condom use, are only partially effective. A decades-long effort to develop preventative and therapeutic vaccines for HSV-2 has been unsuccessful.

Following primary genital infection, HSV-2 enters peripheral skin and mucosal nerve endings and travels retrograde to nerve root ganglia within the sacral plexus, where it is protected from clearance by host immunity. Lumbosacral ganglia serve as a reservoir for subsequent HSV-2 recurrences that lead to subclinical shedding. During reactivation, HSV-2 is propagated down the axon to mucosal surfaces, followed by asymptomatic shedding of virus or recurrent genital ulcers. Although genital herpes is often characterized as a latent infection with infrequent reactivation, studies show that HSV-2 reactivation and mucosal shedding occur frequently in the absence of symptoms, facilitated by genital tract inflammation and a dynamic interaction between HSV-2 and the mucosal immune response that likely contributes to increased risk of HIV acquisition [153].

Herpes simplex belongs to the human herpesvirus family of viruses, which cause persistent, lifelong infection and cannot be cured with antiviral therapy. The two common strains or types of human herpes virus infection are 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. HSV-2 typically causes painful, self-limited genital ulcers in or around the genital tract or anus; in most persons, the infection is subclinical [36]. The virus is shed periodically from genital mucosal surfaces, even in the absence of signs or symptoms, and can be transmitted during periods of shedding [153].

Most cases of recurrent genital herpes worldwide are caused by HSV-2. The prevalence of oral HSV-1 infection in the United States has declined, particularly among children and adolescents; young adults in the United States are now more susceptible to contracting genital herpes infection from HSV-1 [3]. Genital HSV-1 is the leading cause of new-onset genital ulcer disease in high-income countries, particularly among women and among men who have sex with men (MSM) younger than 25 years of age [153]. It is important for patients to understand that oral herpes lesions can transmit herpes virus to a partner's genital area during oral sex.

The worldwide prevalence of HSV-2 infection among persons 15 to 49 years of age is estimated at 490 million people, almost all of which is sexually transmitted. The global and regional burden of genital ulcer disease from HSV-1 and HSV-2 infection has been quantified using a natural history model reflecting the clinical course of disease. This study estimated that 187 million people 15 to 49 years of age (5% of the world's population) had at least one episode of HSV-related genital ulcer disease in 2016 [155]. Of the total, 178 million (95%) had HSV-2, compared with 9 million (5%) from HSV-1. The burden of disease was highest in Africa, and approximately double in women compared with men. Altogether, there were an estimated 8 billion person-days spent with HSV-related genital ulcer disease globally in 2016, with 99% of days due to HSV-2 [155].

In the United States, approximately one in eight persons 14 to 49 years of age is infected with HSV-2. Human infection persists throughout life, and prevalence rates in the population increase by age group due to cumulative sexual exposures [37]. Most people infected with genital herpes go undiagnosed. While many of those who harbor HSV-2 have minimal or no signs and symptoms, viral shedding recurs intermittently from anogenital sites [38]. As a result, most genital herpes infections are transmitted by individuals who are unaware of their infection or asymptomatic when infectious. Risk of transmission is highest when a new crop of vesicles erupts in the anogenital area [3; 36].

There is no curative treatment for HSV-1 or HSV-2; even when infection is dormant, the virus remains sequestered in peripheral nerve ganglia, from which it periodically emerges as new lesions. Management of genital herpes should address the chronic nature of the disease instead of strictly focusing on treating the genital lesions during acute episodes. New-onset or reactivation genital herpes during pregnancy may lead to infection of the newborn, 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 lack specific symptoms or noticeable signs, 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 are observed most often 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. The first episode typically lasts two to three weeks in the absence of antiviral therapy. 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 and resolve within three to five days, but some will have severe prodromal symptoms that may involve the buttock, groin, or thigh [39; 40; 41]. The number of clinical recurrences the initial syndrome decreases over time, from a median of five recurrences in the first year following symptomatic genital HSV-2, to one (or none) per year by year three [153]. For purposes of prevention, clinicians should bear in mind that frequency of asymptomatic shedding is markedly higher than the rate of subsequent symptomatic recurrences.

DIAGNOSTIC CONSIDERATIONS

Diagnostic testing for HSV infection should be considered in patients who present with localized genital vesicular eruption, encephalitis, symptoms suggestive of reactivation HSV infection, and upon suspicion of 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]. If vesicles or pustules are present, these lesions should be unroofed, and the base of the ulcer swabbed to obtain adequate material for virus detection. 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. Soon after the appearance of HSV IgM, the body begins producing anti-HSV IgG antibody. IgG serum levels rise for several weeks, then slowly decline, stabilize, and remain detectable throughout life [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 reactivation or recent primary infection. Negative HSV antibody testing implies HSV exposure is unlikely or the body has had insufficient time to produce HSV antibodies [42; 45].

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/2801311. Last accessed June 14, 2023.)

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 anti-HSV-1 IgG alone is nonspecific and of little diagnostic import because most adults are seropositive, having acquired oral HSV-1 infection during childhood. 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]. Selective serologic screening may be helpful in patients presenting without current symptoms of genital herpes, given that most individuals who have acquired genital HSV are not aware that they have the infection. CDC guidelines suggest that testing be considered in patients presenting for STI screening and/or those who have high-risk sexual behavior, as well as those with HIV infection and MSM at risk for HIV acquisition [1].

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 episodic 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 reduces genital shedding and the risk of transmission and 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].

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*

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

Episodic anogenital or oral herpes in immunocompromised patients can be severe and prolonged. 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].

Chronic 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. In patients with HIV, suppressive anti-HSV therapy reduces the risk of both HSV-2 shedding and genital ulcer disease after initiation of HIV antiretroviral therapy, but it does not reduce the risk of HIV transmission 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].

HSV-2 VACCINE DEVELOPMENT

The goal HSV vaccine development is both preventative and therapeutic. A vaccine should prevent symptomatic genital herpes and asymptomatic infection, reducing risk of transmission to intimate sexual partners and protecting against neonatal herpes. Therapeutic vaccination should reduce the severity of symptoms, accelerate healing of genital ulcers, and eliminate virus shedding (infectivity) in those previously infected with either HSV-1 or HSV-2. Evidence for the feasibility of developing a successful DNA virus vaccine comes from experience with the varicella zoster vaccine, which has been shown to reduce shedding and severity of varicella (chicken pox) in children [157].

Because the global prevalence of genital HSV-2 infection is high, effective prevention strategies are lacking, and HSV-2 genital infection impacts HIV acquisition and transmission, vaccine research has prioritized HSV-2 over HSV-1 prototypes [154]. Most candidate HSV-2 vaccines elicit virus-specific neutralizing antibody and cellular immune responses and are effective preventing disease in animals; however, clinical trial results in humans have been disappointing, as none has proven effective for HSV-2 prevention [156; 157]. Thus, no therapeutic or preventative vaccine for HSV-1 or -2 is available at present.

Many HSV vaccine candidates are in development, including attenuated live virus vaccines, virion subunit vaccines having a component of the cell-binding glycoprotein, DNA and modified mRNA vaccines, and replication defective virus vaccines [158; 159].

One approach, with promising results, involves a previously studied trivalent (glycoprotein C, D, E) vaccine reformulated as an mRNA vaccine. This mRNA formulation elicited higher neutralizing antibody titers and superior CD4 T-cell responses compared to the subunit vaccine alone. While both formulations prevented genital lesions in mice and guinea pigs, the mRNA vaccine was superior at preventing HSV-2 infection of the dorsal root ganglia and reducing viral shedding [159; 160].

PATIENT COUNSELING

Patients and their sex partner(s) should receive counseling on the natural history and transmission of genital herpes, including methods to prevent sexual and perinatal transmission. Patient education combined with strategies for coping with side effects are the foundation of clinical management. When acute illness subsides, many patients benefit from learning about the chronic aspects of the disease. Websites, printed materials, and 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 at-risk 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

Genital HPV is the most common sexually transmitted infection in the United States. Most HPV infections are asymptomatic or unrecognized and clear or become undetectable within one to two years. During 2013–2016, the estimated prevalence of genital HPV in the United States adult population 18 to 59 years of age was 40.0% overall—41.8% in men and 38.4% in women [75]. The prevalence of disease-associated HPV infection was 24.2% in men and 19.9% in women. The CDC estimates that, in 2021, 13 million persons had an incident infection with a disease-associated HPV [1]. Around 200 phylogenetically related HPV genotypes have been identified, including approximately 40 types that infect the anogenital mucosal epithelium.

Although most HPV infections resolve within one to two years, persistent, progressive infection does occur. Progressive infection with some types of HPV produces precancerous tissue injury and, over a period of years, leads to cervical, vaginal, vulvar, penile, anal, or oropharyngeal cancer. Persistent infection with other HPV genotypes, notably types 6 and 11, causes anogenital warts and recurrent respiratory papillomatosis [36]. Of the dozen or more sexually transmitted HPV genotypes with oncogenic potential, HPV types 16 and 18 are responsible for 70% of all cervical cancers and for an even greater percentage of other HPV-attributable cancers [161]. Estimates of the incidence of HPV-attributable cancers are derived from studies that detect and type the virus in cancer tissue.

Chronic, progressive HPV infection is the principal risk factor for developing cervical, anogenital, and oropharyngeal and cancers. The CDC tracks HPV-associated (known or suspected) cancers in the United States. Each year, about 47,200 new cases of cancer are found in parts of the body where HPV infection is found; about 37,300 (79%) of these cancers are attributable to HPV [162]. The most common HPV-attributable cancers are cervical cancer (approximately 11,000 cases per year) and oropharyngeal cancers (14,800 cases per year, most of which occur in men) [161]. The incidence of cervical cancer has been decreasing as a result of preventive measures (particularly HPV vaccination) and early detection and treatment of precancers, whereas the incidence of oropharyngeal cancer has been increasing.

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 recommends that individuals with a cervix initiate cervical cancer screening at 25 years of age and undergo primary HPV testing every five years through 65 years of age. If primary HPV testing is not available, individuals 25 to 65 years of age should be screened with cotesting (HPV testing in combination with cytology) every five years or cytology alone every three years.

(https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21628. Last accessed June 14, 2023.)

Strength of Recommendation: Strong

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 and the associated disease burden caused by HPV can be achieved through prophylactic vaccination. HPV vaccines target the genotypes responsible for most HPV-attributable cancers and are highly effective for prevention of vaccine-type precancers [161]. The FDA has approved three vaccines for protection against HPV diseases and attributable cancers. 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]. The types prevented by nine-valent vaccination account for approximately 90% of HPV-attributable cancers worldwide [161]. 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 [78; 81].

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 individuals 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 [78; 83]. In 2018, the FDA approved expanded use of Gardasil 9 to include women and men up to 45 years of age [84].

HPV vaccine is administered in either two or three doses, depending on the age at which the series is started. Two doses are recommended for most persons who begin the series before 15 years of age, with the second dose given 6 to 12 months after the first [80]. Three vaccine doses are recommended for people who start the series at 15 through 26 years of age and for immunocompromised persons [80]. HPV vaccines can be administered without regard to 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. During clinical trials conducted before vaccine licensure, involving more than 15,000 male and female participants, the nine-valent HPV vaccine was found to be safe and effective [80]. 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].

The National Immunization Survey – Teen monitors vaccination rates among adolescents 13 to 17 years of age [164]. As of 2021, 79% of girls and 75% of boys had received at least one dose of HPV vaccine; prevalence of up-to-date vaccination was 64% and 60%, respectively. Recommendation from a healthcare provider is the strongest predictor of vaccination compliance. Efforts to improve compliance with HPV vaccine recommendations include providing education and messaging that prioritize HPV vaccination as cancer prevention. Clinical care providers are encouraged to discuss and recommend all approved vaccinations for adolescents at the same time [161]. The goal of the WHO is to achieve 90% HPV vaccine compliance by 2035 [165].

Only about 15% of girls 9 to 14 years of age worldwide have been vaccinated against HPV with a recommended three-dose schedule. Because of the global burden of HPV-associated diseases and demonstrated long-lasting efficacy of nine-valent HPV vaccination, a growing number of clinical trials are assessing the efficacy of fewer doses. One study found that geometric mean antibody titers after two doses were noninferior to titers achieved after three doses of nine-valent HPV vaccine, and more than 98% of two-dose recipients had seroconversion to all nine HPV types [161]. In a randomized, double-blind trial among girls/women 15 to 20 years of age in Kenya, one-dose bivalent (HPV16/18) and one-dose nine-valent HPV vaccines were both 97.5% effective in preventing oncogenic HPV infection at 18 months follow-up [163]. Data on outcomes of single-dose HPV vaccination among boys/men are limited. Because current evidence suggests that a single dose has comparable efficacy and duration of protection as a two-dose HPV vaccination schedule, the WHO modified its 2022 recommendations to include an off-label option for single-dose vaccination in those 9 to 20 years of age [165].

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; if 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].

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 may 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 are intended to 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].

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*

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 (CO2) 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 CO2 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 previous 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 common in regions of the world where sanitation and protection of food and water supplies are poor (typically developing countries). Infection rates are highest among children. Hepatitis A is less common is the United States and other developed countries [105]. The gastrointestinal tract serves as the portal of entry, and HAV replication is confined to 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 mode of transmission. In the United States, where prevalence of immunity is low due to the declining incidence of childhood infection, the potential for outbreaks of HAV has increased, including outbreaks spread by sexual contact among MSM. Efforts to promote good personal hygiene have not succeeded in curtailing HAV outbreaks. Bloodborne transmission is uncommon, and transmission by saliva has not been documented [106; 107]. In the United States, risk data were missing for 48% of reported cases in 2020. 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 are 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 encephalopathy (e.g., drowsiness, somnolence, confusion). 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 preferred for prophylaxis 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, with emphasis on long-term health implications for the patient and partner(s). Pregnant women should be advised of the increased risk of miscarriage/premature labor and the importance of seeking medical advice if symptoms develop. All patients should exercise care whenhandling food and avoid 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), hepatocellular cancer, liver failure, and death [105].

Transmission

After an incubation period of 40 to 160 days, high levels of HBV appear in the blood, followed by low levels of virus 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]. Antibody to hepatitis B surface antigen (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) persists after infection has resolved and is the HBV antibody marker used to verify 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 FDA-approved agents are available 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 is effective for prevention of 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; Vaxelis is a similar product for children birth to 4 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. Hepatitis B vaccination is contraindicated in patients with previous anaphylactic reaction to the vaccine itself 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 to HBV 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://journals.lww.com/hep/Fulltext/2018/04000/Update_on_prevention,_diagnosis,_and_treatment_of.34.aspx. Last accessed June 14, 2023.)

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. HCV infection is curable and persons with diagnosed HCV infection should be linked to care and treatment [1].

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 improve HCV infection awareness and surveillance and mitigate the age-associated differences in racial/ethnic prevalence of HCV infection in hard-to-reach populations [128].

HIV/AIDS

In 2021, an estimated 38.4 million people globally were living with HIV, 1.5 million had become newly infected that year, and 650,00 people died of AIDS-related illnesses [82]. About 75% of people with HIV (28.7 million) were receiving antiretroviral therapy. Women and girls accounted for about 49% of all new infections. Since 2010, new infections have declined overall by 32% and among children have declined by 52%. AIDS-related deaths have been reduced by 68% since the peak in 2004 [82]. In 2021, 36,136 people were newly diagnosed with HIV in the United States and dependent areas. Male-to-male sexual contact accounted for 67% of all new diagnoses, heterosexual contact for 22% [129]. The incidence of new cases decreased 7% from 2017 to 2021. According to the CDC, an estimated 1.2 million people in the United States had HIV at the end of 2021; of these people, an estimated 13% were unaware they had HIV [129].

The demographics of HIV (e.g., age, behavioral risk factors, disparities of race and ethnicity) have changed somewhat since the onset of the AIDS pandemic in the early 1980s. Moreover, the impact of HIV falls disproportionally on the poor and certain groups hesitant to seek medical attention or having limited access to care. In the United States in 2020–2021, 57% of all reported new HIV infections were people younger than 35 years of age; 67% of new diagnoses were among MSM and 7% among injection-drug users. Black/African American people accounted for 40% and Hispanic/Latino individuals for 29% of reported new cases. One-quarter of all new HIV infections in the United States occurred in White people, who make up 73% of the population [129].

The risk of acquiring or transmitting HIV varies widely in relation to type of exposure or behavior. Most commonly, people acquire or transmit the infection through anal or vaginal sex, or sharing needles, syringes, or other drug injection equipment. CDC data from 2019 showed that, overall, 7% of people with HIV had sex without using any HIV prevention strategy during the previous 12 months [166]. The prevalence of this risk behavior was 18% among those 18 to 24 years of age and 13% among those 25 to 34 years of age. Among people 18 to 30 years of age without HIV who use injection drugs, a separate survey found that one-third had used a syringe after someone else used it, and 60% had used any injection equipment after someone else used it in the past 12 months.

The advent of effective antiviral therapy highlights the importance of screening and detection of HIV. Antiviral therapy that successfully suppresses HIV replication to undetectable levels reduces morbidity, provides a near-normal life span, and prevents transmission of HIV to others. Early diagnosis and linkage to care are essential for achieving these goals [1]. A 2022 clinical practice review provides guidance on screening, diagnosis, and treatment of HIV [167]. The International Antiviral Society USA Panel has published recommendations for antiviral drug use for treatment and prevention of HIV infection [168]. The National Institutes of Health Office of AIDS Research provides federally approved medical practice guidelines for HIV/AIDS care [146]. The federal *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents* is available online at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv.

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 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 may be asymptomatic or may exhibit generalized lymphadenopathy and recurrent oropharyngeal candidiasis (thrush). During this stage, a reservoir of HIV is established throughout the lymphoid 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 that 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 microorganisms 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 wasting illness punctuated by periods of feverishness and diarrhea, becoming increasingly anorectic, malnourished, and lethargic. Clinical and laboratory features of advanced disease include muscle wasting, weakness, anemia, thrombocytopenia, lymphadenopathy, pulmonary infiltrates, and neurologic complications (e.g., dementia, peripheral neuropathy). The median survival of patients with advanced HIV/AIDS (CD4 count <50 cells/mcL) is about 12 to 18 months. Patients succumb to complications of uncontrolled infection, malignancy, or critical organ failure (such as uremia or adrenal insufficiency).

TESTING

The choice of test to accurately diagnose HIV infection depends on multiple factors, including attention to the natural history of infection and timing of clinical presentation [167]. By days 6 to 8, virus can be detected by a nucleic acid amplification test (NAAT). By about two weeks following infection, viral protein (p24 antigen) can be detected. Combination antigen-antibody assays, which use p24 antigen to identify patients in early stages of infection, are the standard tests in hospital and commercial laboratories [167]. A fourth-generation combination immunoassay, consisting of HIV-1/HIV-2 antibodies and the HIV-1 p24 antigen, is commonly used for the diagnosis of acute HIV and to identify HIV in patients who present long after the initial infection [131].

A CDC algorithm for HIV diagnosis recommends that HIV testing begin with a laboratory-based HIV-1/HIV-2 antigen/antibody combination assay, which, if reactive, is followed by a supplemental antibody assay to differentiate HIV-1 from HIV-2 [77]. If this second (supplemental antibody) test is non-reactive, testing with an FDA-approved HIV-1 nucleic acid test should be performed to determine whether the discordance represents acute infection [1; 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].

An enzyme-linked immunosorbent assay may be used if the preferred combination immunoassay is unavailable. 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 usual 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 of HIV during anal intercourse

occurs from contact with infected bowel epithelial cells or contact with trace amounts of blood and/or infected body fluid released as well as bloodstream access from small breaks in the rectal mucosa.

The highest risk of HIV infection comes from unprotected receptive anal intercourse, followed by unprotected receptive vaginal intercourse and unprotected insertive anal intercourse (particularly for uncircumcised men) [134; 135]. Risk of transmission is reduced using 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 2021, the FDA approved the first injectable agent for the prevention of HIV infection; cabotegravir is given first as two initiation injections administered one month apart, and then every two months thereafter [76]. 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 and cabotegravir are similarly effective [143].

In 2021, the CDC and the U.S. Department of Health and Human Services updated its clinical practice guidelines for pre-exposure prophylaxis/prevention of HIV infection [145]. This guideline outlines indications for prophylaxis as one option for preventing 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, and are not in a monogamous partnership with a recently tested, HIV-negative partner, and have one of the following risk factors [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)

Injection cabotegravir given bimonthly and fixed-dose combination tenofovir and emtricitabine (Truvada or Descovy) taken daily are approved for pre-exposure prophylaxis, and they are 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].

ANTIRETROVIRAL THERAPY

Combination antiretroviral therapy, or cART, consists of two-drug or three-drug regimens selected from several categories of antiviral 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, gp120 attachment inhibitors, and capsid inhibitors. The newest addition to the arsenal is lenacapavir, a first-in-class HIV capsid inhibitor, approved in 2022 to be used in combination with other antiretroviral drugs for the treatment of heavily treatment-experienced adults with multidrug resistant HIV-1 infection [146]. Antiretroviral therapy regimens have been proven effective in dramatically decreasing HIV-related morbidity and mortality and should be considered for all HIV-infected persons. In selecting a cART regimen, one should consider drug sequencing and the impact on future treatment options. 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 dura-

tion 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, pretreatment 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]. Persons with acute infection or newly diagnosed HIV should be referred immediately to an HIV clinical care provider, screened for other STIs, and provided prevention counseling (e.g., advised to reduce the number of partners and to use condoms correctly and consistently) [1]. 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 initial treatment of HIV infection in most newly diagnosed patients, guidelines recommend a INSTI-based therapy combined with NRTIs: one INSTI (bictegravir, dolutegravir, raltegravir) plus tenofovir and either lamivudine or emtricitabine [146; 167; 168]. Factors to consider in selecting the specific drug combination for initial therapy include availability of baseline laboratory results (e.g., CD4 count, HIV RNA level, HIV genotype) and presence of HBV or HCV coinfection. For some patients, treatment may be as simple as a two-drug (dolutegravir-lamivudine) single tablet [167]. INSTI-based regimens are highly effective and safe, with few drug interactions. In studies comparing a boosted PI approach with INSTI-containing regimens, the INSTI-based regimens were better tolerated and caused fewer treatment discontinuations [146]. Guideline-directed cART results in maximum reduction of viral load for the longest period. When used as initial therapy, these regimens achieve the goal of sustained virologic suppression in more than 90% of patients after four to six months [146; 168].

After beginning antiviral therapy, patients require close follow-up and long-term continuity of care to achieve and maintain optimal outcomes. Clinical issues in need of periodic assessment include treatment adherence or adverse effects, STI evaluation, and potential personal or social barriers to maintaining health. The first follow-up visit should occur four to six weeks after initiation of cART, then every three to four months until virologic suppression is achieved, then every six months [167; 168]. More than 85% of patients under consistent follow-up care have sustained virologic suppression indefinitely [167]. As noted, these patients can expect to have a near normal life span.

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.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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