Genital and Perirectal Herpes Simplex Virus Infection

Herpes Simplex Virus (HSV) Type 2

Learning Objectives

Upon completion of this content, the learner will be able to:

1. Describe the epidemiology of genital HSV in the U.S.
2. Describe the pathogenesis of genital HSV.
3. Discuss the clinical manifestations of genital HSV.
4. Identify the common methods used in the diagnosis of genital HSV.
5. Describe patient management for genital HSV.
6. Summarize appropriate prevention counseling messages for genital HSV.
7. Describe public health measures for the prevention of genital HSV.

Lessons

I. Epidemiology: Disease in the U.S.
II. Pathogenesis
III. Clinical manifestations
IV. Diagnosis
V. Patient management
VI. Prevention

Lesson I: Epidemiology: Disease in the U.S.

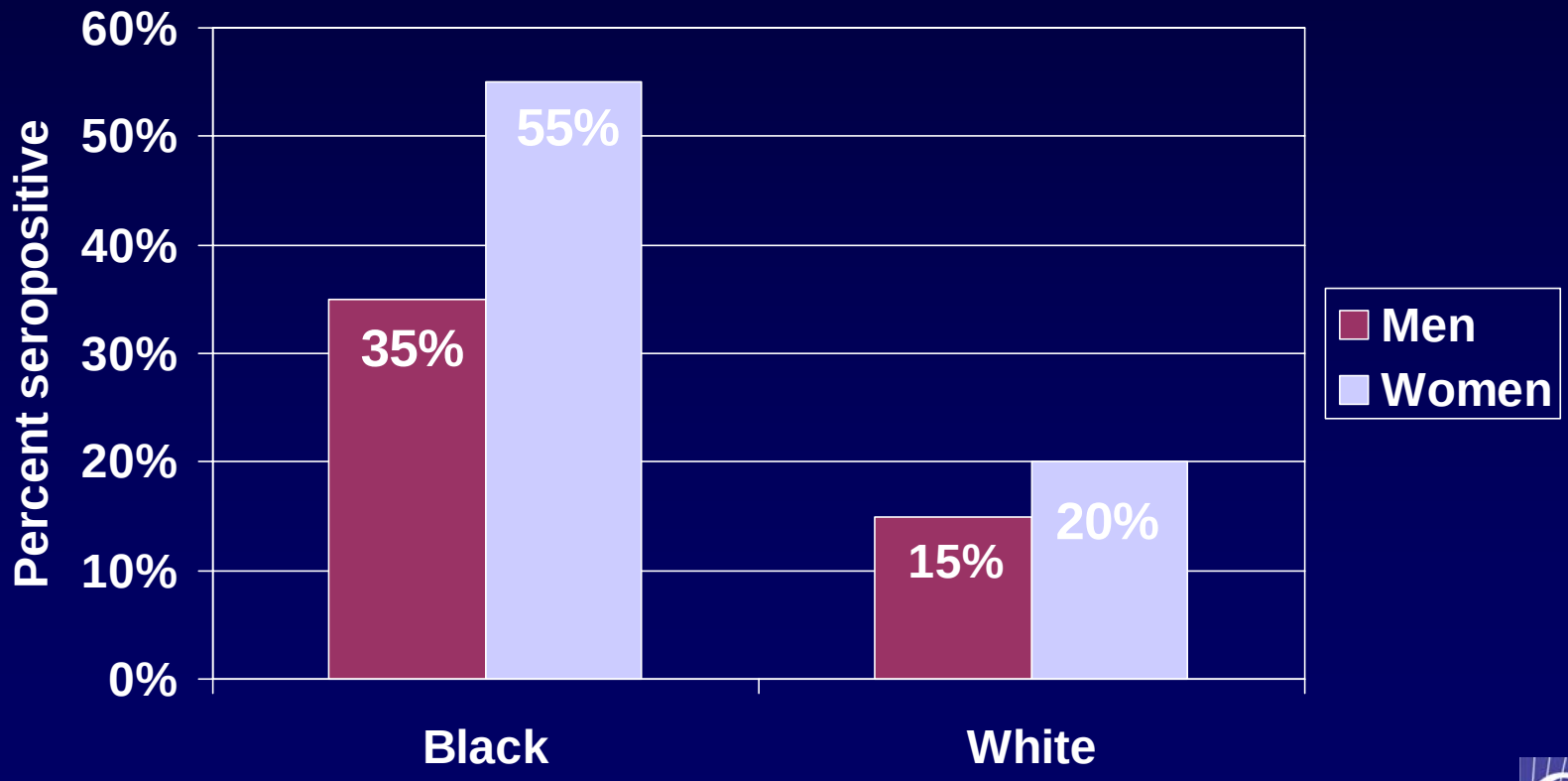
Incidence and Prevalence

- Genital herpes is a recurrent, lifelong viral infection.
- Two HSV serotypes – HSV-1 & HSV-2
- HSV-2 causes the majority of genital and perirectal herpetic outbreaks in the U.S.
- Approximately 1 million new cases occur each year.

Incidence and Prevalence
(continued)

- 50% or more of new cases are asymptomatic or unrecognized.
- In the U.S., 22% of adults over age 12 have HSV-2 antibodies.
- HSV-2 antibodies are not routinely detected until puberty.
- HSV-2 seroprevalence increases with age up to 40 years then levels off.

Seroprevalence of HSV-2 in NHANES, 1988-1994, by Gender and Race, U.S.



Source: Fleming DT et al. NEJM, 337(16):1105-1111, 1997.

CDC STD Prevention

Transmission

- HSV-2 is transmitted sexually and perinatally.
- Most sexual transmission occurs while source case is asymptomatic.
- Efficiency of sexual transmission is greater from men to women than from women to men.

Transmission (continued)

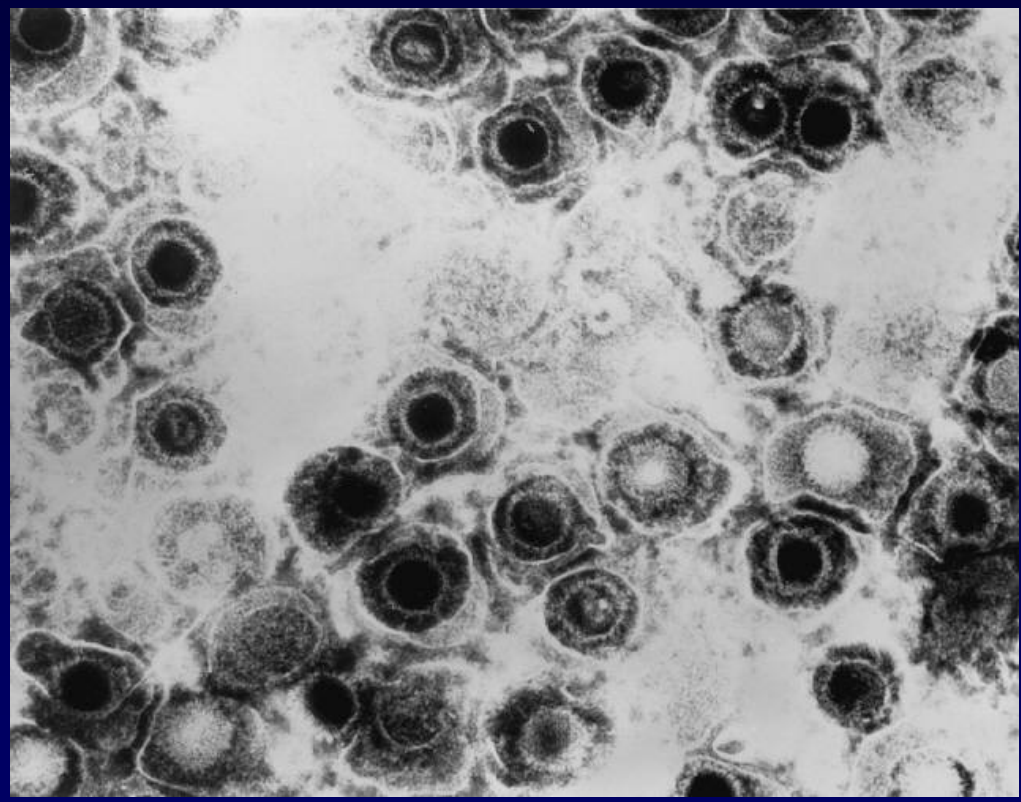
- Likelihood of transmission to others declines with increased duration of infection.
- Incubation period after acquisition is 2-12 days (average is 4 days).
- Genital HSV-2 infection facilitates both acquisition and transmission of HIV infection.

Lesson II: Pathogenesis

Virology

- HSV-1 and HSV-2 are members of the human herpes viruses (herpetoviridae).
- All members of this species establish latent infection in specific target cells.
- Infection persists despite the host immune response, often with recurrent disease.

Transmission electron micrograph of Herpes Simplex Virus



Source: CDC Public Health Image Library/Dr. Erskine Palmer

Pathology

- The virus remains latent indefinitely.
- Reactivation, precipitated by multiple known and unknown factors, induces viral replication.
- The re-activated virus may cause a cutaneous outbreak of herpetic lesions.
- Up to 90% of persons seropositive for HSV-2 antibody have no clinical history of anogenital herpes outbreaks.

Lesson III: Clinical Manifestations

Definitions of Infection Types

First Clinical Episode

- Primary infection
  - First infection **ever** with either HSV-1 or HSV-2
  - Disease is more severe than recurrent disease
  - No antibody present when symptoms appear
- Non-primary infection
  - Newly acquired HSV-1 or HSV-2 infection in an individual **previously seropositive to the other virus**
  - Symptoms usually milder than primary infection
  - Antibody present when symptoms appear

Definitions of Infection Types

Recurrent symptomatic infection

- Disease usually mild and short in duration
- Antibody present when symptoms appear

Asymptomatic infection

- No known history of clinical outbreaks
- Serum antibody is present

Types of Infection

Infection Type	Lesions/ Symptoms	Type-specific antibody at time of presentation	
		HSV-1	HSV-2
First episode, Primary (Type 1 or 2)	+/Severe, bilateral	-	-
First episode, Non-primary Type 2	+/Moderate	+	-
First episode, Recurrence Type 2	+/Mild	+/-	+
Symptomatic, Recurrence Type 2	+/Mild, unilateral	+/-	+
Asymptomatic, Infection Type 2	-	+/-	+

First Episode Primary Infection without Treatment

- Characterized by multiple lesions that are more severe, last longer, and have higher titers of virus than recurrent infections
- Lesion progression:
  - papules → vesicles → pustules → ulcers → crusts → healed
- Illness lasts 2-4 weeks
- Often associated with systemic symptoms including fever, headache, malaise, and myalgia

First Episode Primary Infection without Treatment (continued)

- Local symptoms include pain, itching, dysuria, vaginal or urethral discharge, and tender inguinal adenopathy
- Numerous, bilateral painful genital lesions; last an average of 11-12 days
- Median duration of viral shedding (from the onset of lesions to the last positive culture) is ~12 days
- HSV cervicitis occurs in most primary HSV-2 (~90%) and primary HSV-1 (~70%) infections

Herpes: Primary Complex

Source: Cincinnati STD/HIV Prevention Training Center

Herpes: Genitalis Multiple Ulcer

Source: Cincinnati STD/HIV Prevention Training Center

Herpes: Genitalis External-Labia Minor

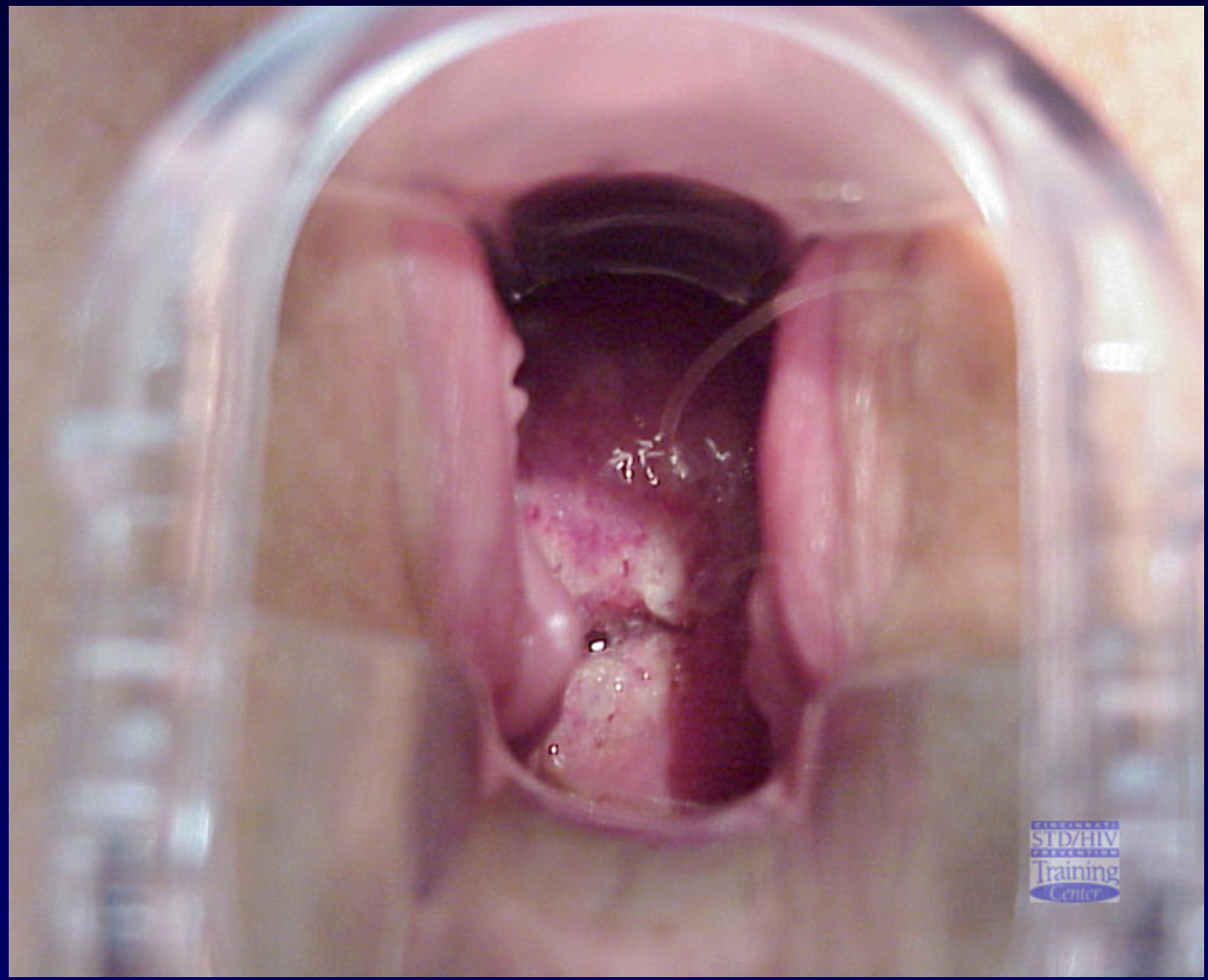
Source: Cincinnati STD/HIV Prevention Training Center

Herpes: Genitalis Clinical Periurethal Lesions on Vestibule

Source: Cincinnati STD/HIV Prevention Training Center

CDC STD Prevention

Herpes: Cervicitis

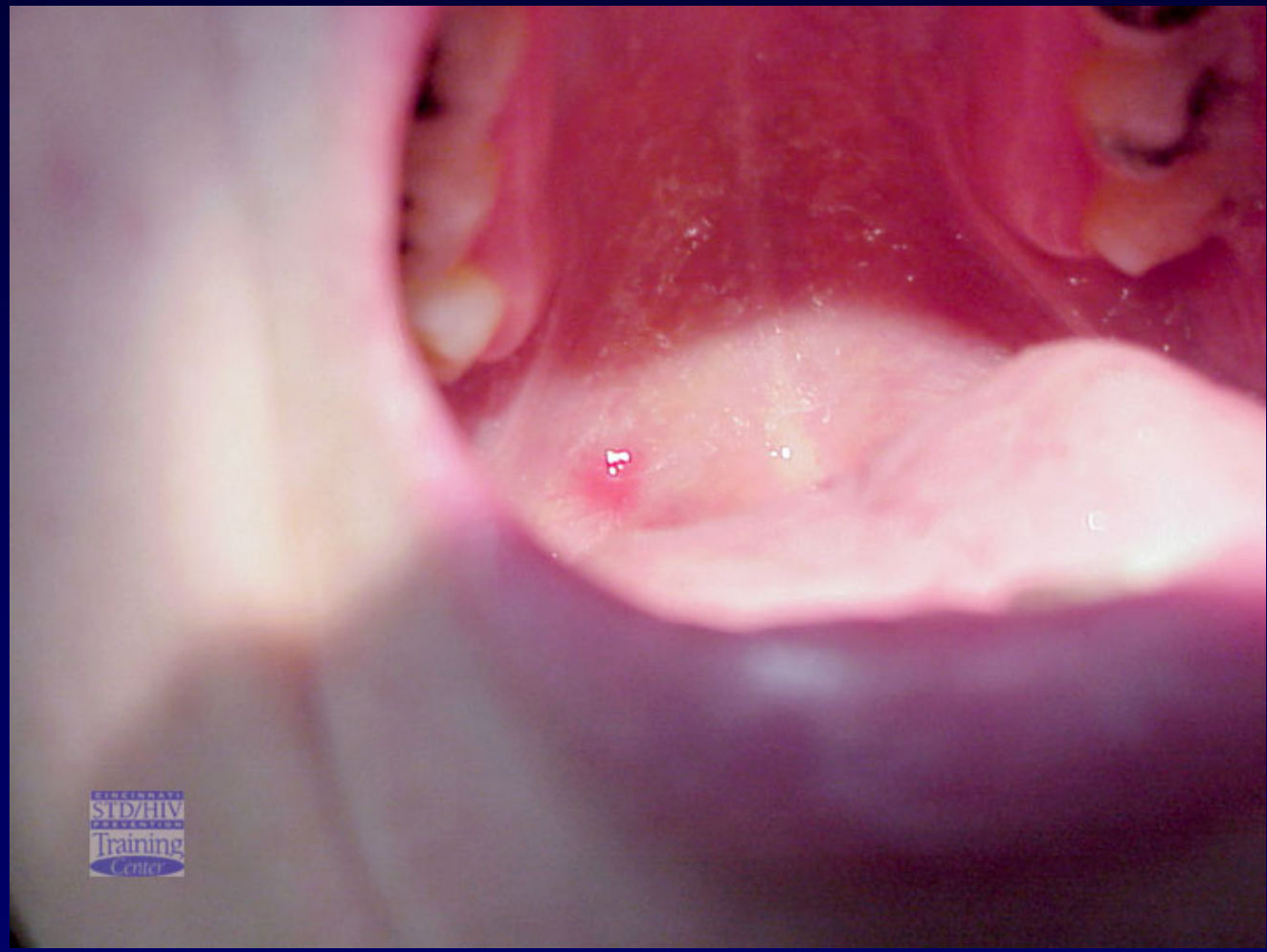


Source: Cincinnati STD/HIV Prevention Training Center

Herpes on the Buttock

Source: Cincinnati STD/HIV Prevention Training Center

Herpes: Possible Oralis Soft Palate



Source: Cincinnati STD/HIV Prevention Training Center

Recurrent Infection Without Treatment

- Prodromal symptoms (localized tingling, irritation) in ~50% begin 12-24 hours before lesions
- Illness lasts 5-10 days
- Symptoms tend to be milder, less severe than in primary infection
- Usually there are no systemic symptoms
- HSV-2 primary infection more prone to recur than HSV-1 primary infection

Asymptomatic Viral Shedding

- Rates of asymptomatic shedding are greater with HSV-2 than HSV-1.
- Most HSV-2 is transmitted during asymptomatic shedding.
- Shedding rates are greatest in the first 3 months after infection.
- Asymptomatic shedding is of briefer duration than during clinical recurrences.

Asymptomatic Viral Shedding
(continued)

- Acyclovir chemosuppression dramatically reduces shedding.

- Most common sites of asymptomatic shedding are vulva and perianal areas in women and penile skin and perianal area in men.

Complications of Genital Infection

- Aseptic meningitis
  - More common in primary than recurrent infection
  - Generally no neurological sequelae
- Rare complications include:
  - Stomatitis and pharyngitis
  - Radicular pain, sacral parathesias
  - Transverse myelitis
  - Autonomic dysfunction

Lesson IV: HSV Diagnosis

HSV Diagnosis

- Clinical diagnosis is insensitive and nonspecific.
- Clinical diagnosis should be confirmed by lab testing:
  - Virologic tests
  - Type-specific serologic tests

Virologic Tests

- Viral culture (gold standard)
  - Preferred test for patients with genital ulcers or other mucocutaneous lesions
- Antigen detection (DFA or EIA)
  - Better than culture for detecting HSV in healing lesions
- Cytology (Tzanck or Pap)
  - Insensitive and nonspecific and should not be relied on for HSV diagnosis
- PCR
  - Preferred test for detecting HSV in spinal fluid

Comparison of Virologic Tests

	Viral culture	Antigen detection (DFA or EIA)	Cytology (Tzanck or Pap)	PCR
Sensitivity (no false-negatives)	80%-90% (primary episode)	>85% (in symptomatic shedders)	50%	
Specificity (no false-positives)	99%		Non-specific	
Test notes	Positive in 80%-90% of primary infection and 30% of recurrent infection; allows for easiest typing; most are positive in 1-3 days, but held 5-7 days	May be better than culture for healing lesions; rapid (2-12 hours)	Identifies typical HSV-infected cells in exfoliated cells or biopsies	Clinical significance of positive result being established

Type-specific Serologic Tests

- Type-specific and nonspecific antibodies to HSV develop during the first several weeks following infection and persist indefinitely.
- Presence of HSV-2 antibody indicates anogenital infection.
- Presence of HSV-1 does not distinguish anogenital from orolabial infection.

Uses of Type-specific Serologic Tests

- To confirm clinical diagnosis
- To diagnose unrecognized infection
- To manage sex partners of persons with genital herpes

Special Diagnostic Considerations

- Establish the etiology of atypical genital ulcer(s) to include mixed infections (e.g., syphilis and chancroid), unusual infections (e.g., LGV, HIV, CMV), and other causes (e.g., cancer).
- Evaluate for acyclovir resistance in patients with persistent genital herpes despite antiviral suppressive therapy.

Lesson V: Patient Management

Principles of Management of Genital Herpes

- Systemic antiviral chemotherapy
  - Partially controls symptoms and signs of herpes episodes
  - Does not eradicate latent virus
  - Does not affect risk, frequency or severity of recurrences after drug is discontinued
- Counseling should include natural history, sexual and perinatal transmission, and methods to reduce transmission.

Antiviral Medications

- Systemic antiviral chemotherapy includes 3 oral medications:
  - Acyclovir
  - Valacyclovir
  - Famciclovir
- Topical antiviral treatment has minimal clinical benefit and is not recommended.

Management of First Clinical Episode of Genital Herpes

- Many patients with first episode present with mild clinical manifestations but later develop severe or prolonged symptoms.

- Antiviral therapy has dramatic effect, especially if symptoms <7 days and no history of oral HSV.

CDC-Recommended Regimens for First Clinical Episode

- Acyclovir 400 mg orally 3 times a day for 7-10 days, or
- Acyclovir 200 mg orally 5 times a day for 7-10 days, or
- Famciclovir 250 mg orally 3 times a day for 7-10 days, or
- Valacyclovir 1 g orally twice a day for 7-10 days

Recurrent Episodes of Genital Herpes

- Most patients with symptomatic, first-episode genital HSV-2 experience recurrent outbreaks.
- Episodic and suppressive treatment regimens are available.
- Treatment options should be discussed with ALL patients.

Episodic Treatment for Recurrent Genital Herpes

- Ameliorates or shortens duration of lesions
- Requires initiation of therapy within 1 day of lesion onset
- Provide patient with a supply of drug or a prescription and instructions to self-initiate treatment immediately when symptoms begin.

CDC-Recommended Regimens for Episodic Therapy

- Acyclovir 400 mg orally 3 times a day for 5 days, or
- Acyclovir 200 mg orally 5 times a day for 5 days, or
- Acyclovir 800 mg orally twice a day for 5 days, or
- Famciclovir 125 mg orally twice a day for 5 days, or
- Valacyclovir 500 mg orally twice a day for 3-5 days, or
- Valacyclovir 1 g orally once a day for 5 days

Suppressive Therapy for Recurrent Genital Herpes

- Reduces frequency of recurrences
- Reduces but does not eliminate subclinical viral shedding
- Periodically (e.g., once a year), reassess need for continued suppressive therapy.

CDC-Recommended Regimens for Suppressive Therapy

- Acyclovir 400 mg orally twice a day,
  or
- Famciclovir 250 mg orally twice a day,
  or
- Valacyclovir 500 mg orally once a day,
  or
- Valacyclovir 1 g orally once a day

Severe Disease

- IV acyclovir should be provided for patients with severe disease or complications requiring hospitalization.
- **CDC-Recommended Regimen**:
  - Acyclovir 5-10 mg/kg IV every 8 hours for 2-7 days or until clinical improvement
  - Follow with oral antiviral therapy to complete at least 10 days total therapy

Allergy, Intolerance, and Adverse Reactions

- Allergic and other adverse reactions to acyclovir, valacyclovir, and famciclovir are rare.
- Desensitization to acyclovir is described by Henry RE, et al., Successful oral acyclovir desensitization. Ann Allergy 1993; 70:386-8.

Herpes and HIV Infection

- HIV-infected patients may have prolonged, severe, or atypical episodes of genital, perianal, or oral herpes.

- Genital ulcers increase the risk of HIV transmission and acquisition.

CDC-Recommended Regimens for Episodic Infection in HIV-Infected Persons

- Acyclovir 400 mg orally 3 times a day for 5-10 days, or
- Acyclovir 200 mg orally 5 times a day for 5-10 days, or
- Famciclovir 500 mg orally twice a day for 5-10 days, or
- Valacyclovir 1 g orally twice a day for 5-10 days

CDC-Recommended Regimens for Daily Suppressive Therapy in HIV-Infected Persons

- Acyclovir 400-800 mg orally twice a day or 3 times a day, or
- Famciclovir 500 mg orally twice a day, or
- Valacyclovir 500 mg orally twice a day

Herpes in Pregnancy

- Risk for transmission to neonate from infected mother is high (30%-50%) among women who acquire genital herpes near the time of delivery and low (<1%) in women with histories of recurrent herpes at term or who acquire genital HSV during the first half of pregnancy.

Herpes in Pregnancy (continued)

- Prevention of neonatal herpes depends on avoiding acquisition of HSV during late pregnancy and avoiding exposure of the infant to herpetic lesions during delivery.

Herpes in Pregnancy (continued)

- Ask all pregnant women if they have a history of genital herpes.
- At the onset of labor:
  - Question all women about symptoms of genital herpes, including prodrome.
  - Examine all women for herpetic lesions.
- Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally.

Herpes in Pregnancy (continued)

- Acyclovir may be administered orally to pregnant women with first-episode genital herpes or severe recurrent herpes and should be administered IV to pregnant women with severe HSV infection.
- The safety of systemic acyclovir, valacyclovir, and famciclovir therapy in pregnant women has not been established.

Lesson VI: Prevention

Patient Counseling and Education

- Goals
  - Help patients cope with the infection
  - Prevent sexual and perinatal transmission
- Psychological impact of infection is often substantial.
- Counsel initially at first visit.
- Education on chronic aspects may be beneficial after acute illness subsides.

Patient Counseling and Education

- Counseling should include:
  - Nature of the infection
  - Transmission
  - Treatment issues
  - Risk-reduction strategies
- Emphasize potential for recurrent episodes, asymptomatic viral shedding, and sexual transmission.

Nature of the Infection

- Sexual transmission of HSV can occur during asymptomatic periods.
- Stressful events may trigger recurrences.
- Prodromal symptoms may precede outbreaks.

Transmission

- Abstain from sexual activity with uninfected partners when lesions or prodromal symptoms are present.
- Inform current sex partners.
- Inform future sex partners before initiating sex.

Treatment Options

Discuss:

- Effectiveness of suppressive and episodic therapy to prevent or shorten the duration of recurrent episodes
- When and how to take antiretroviral medications
- Recognition of prodromal symptoms

Risk Reduction

- Assess client's behavior-change potential.
- Discuss prevention strategies (abstinence, mutual monogamy with an uninfected partner, condoms, limiting number of sex partners, etc.).
- Work with patient to develop individualized risk-reduction plans.

Counseling for Asymptomatic Persons

- Give asymptomatic persons diagnosed with HSV-2 infection by type-specific serologic testing the same counseling messages as symptomatic persons.
- Teach the common manifestations of genital herpes, as many patients will become aware of them with time.

Partner Management

- Symptomatic sex partners
  - Evaluate and treat in the same manner as patients who have genital lesions.
- Asymptomatic sex partners
  - Ask about history of genital lesions.
  - Educate to recognize symptoms of herpes.
  - Offer type-specific serologic testing.

Case Study

Roberta Patterson: History

- 26-year-old woman, presents for her first prenatal visit
- Concerned for her baby because of her husband's history of genital herpes
- States that she is 6 weeks pregnant
- Has never had symptoms of vaginal or oral herpes
- Diagnosed and treated for chlamydia 7 years ago (age 19); no other STD diagnoses reported
- Her 26-year-old husband had his first episode of genital herpes 8 years ago; no other STD diagnoses reported. No visible HSV lesions since they've been sexually active. Reports having had no prodromal symptoms or symptoms of active disease.
- No other sex partners for the last 16 months

Physical Exam

- Vital signs: blood pressure 112/68, pulse 58, respiration 13, temperature 38.5° C
- Cooperative, good historian
- Chest, heart, musculoskeletal, and abdominal exams within normal limits
- Uterus consistent with a 6-week pregnancy
- Normal vaginal exam without signs of lesions or discharge
- No lymphadenopathy

Questions

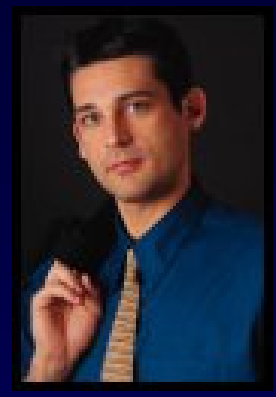
1. Which HSV general education messages should be discussed with Roberta?
2. Given that Roberta's husband Franklin has a history of genital herpes, would it be appropriate to test Roberta for genital herpes using a type-specific serologic test?
3. What other STD screening should be considered for Roberta?

Roberta's Laboratory Results

- HSV gG-based type-specific serologies: HSV-1 negative; HSV-2 positive
- DNA probe for *Chlamydia trachomatis*: negative
- Culture for *Neisseria gonorrhoeae*: negative
- RPR: nonreactive
- HIV antibody test: negative
- Pregnancy test: positive

4. What would you tell Roberta about her HSV infection, based on clinical manifestations and test results?
5. Would routine viral cultures during Roberta's pregnancy be recommended?

Partner Management



Sex Partner and Exposure Information

- Franklin Patterson
- First sexual exposure: 16 months ago
  Last sexual exposure: 1 month ago
- History of genital herpes infection; first episode 8 years ago. No HSV testing or treatment at time of first episode or with subsequent episodes.
- No history of other STDs.

6. Franklin reports genital lesions during Roberta's sixth month of pregnancy. Which laboratory tests should be performed on him?

Franklin's Laboratory Results

- HSV cultures: HSV-1 negative; HSV-2 positive
- DNA probe for *Chlamydia trachomatis*: negative
- Culture for *Neisseria gonorrhoeae*: negative
- RPR: nonreactive
- DFA: negative for *Treponema pallidum*
- HIV antibody test: negative

7. What is an appropriate episodic treatment for Franklin?

Follow-Up

- Roberta had no HSV symptoms during her pregnancy.
- She opted to take the acyclovir treatment in late pregnancy after a discussion with her nurse-midwife that included the following points:
  - The safety of systemic acyclovir therapy in pregnant women has not been established.
  - Preliminary data suggest that acyclovir treatment late in pregnancy might diminish the frequency of HSV occurrence at term that would necessitate an abdominal delivery.
- At onset of labor, she reported no prodromal or other HSV symptoms and no lesions were found on examination.
- After a 14-hour labor, she vaginally delivered a healthy 7.2 lb baby girl.

Questions

8. What questions should ALL women beginning labor be asked?
9. If Roberta has genital herpetic lesions at the onset of labor, should she deliver vaginally or abdominally? What is the risk to the infant?

Questions

10. Roberta is asymptomatic at the time of delivery. Is it medically appropriate for her to deliver vaginally?
11. If Roberta had acquired genital herpes around the time of delivery, would she be more or less likely to transmit genital herpes to her baby during a vaginal delivery than if she had a history of recurrent genital herpes?