Genital and Perirectal Herpes Simplex Virus Infection

Herpes Simplex Virus (HSV) Type 2

Learning Objectives

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.

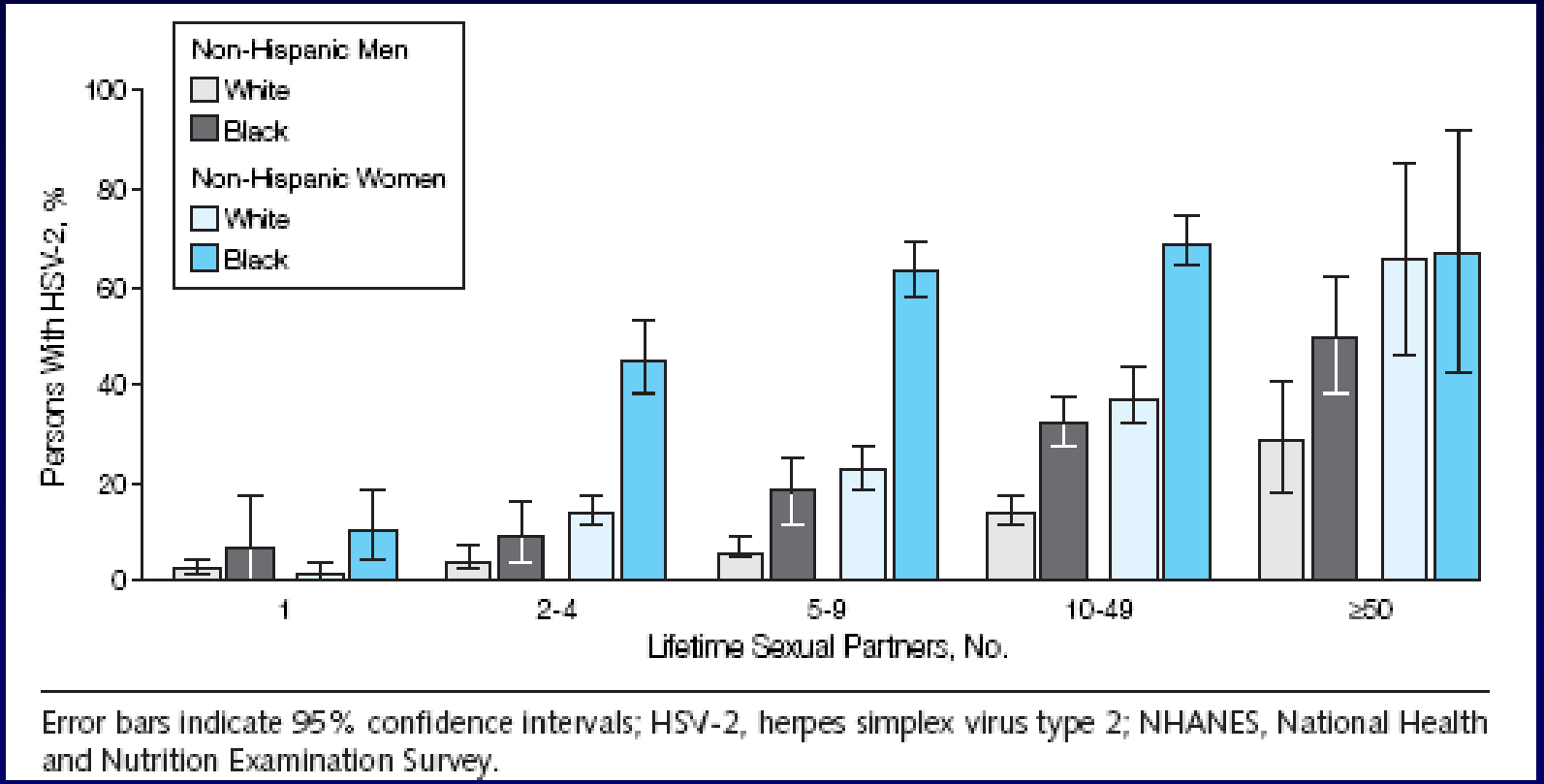
Background and Burden of Disease

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

Background and Burden of Disease (continued)

- In the U.S., 17% of adults aged 14-49 years have HSV-2 antibodies
- HSV-2 antibodies are not routinely detected until puberty
- HSV-2 seroprevalence is higher in women than men in all age groups and varies by race/ethnicity

Age-Adjusted Herpes Simplex Virus Type 2 Seroprevalence According to the Lifetime Number of Sex Partners, by Race/Ethnicity and Sex on NHANES in 1999-2004



Error bars indicate 95% confidence intervals; HSV-2, herpes simplex virus type 2; NHANES, National Health and Nutrition Examination Survey.

Source: Xu F et al. JAMA, 2006; 296(8):964-973.

Transmission

- HSV-2 is transmitted sexually and perinatally
- Majority of genital herpes infections are transmitted by persons who are
  - unaware they are infected with HSV-2 or
  - asymptomatic when transmission occurs
- Efficiency of sexual transmission is greater from men to women than from women to men

Transmission (continued)

- Likelihood of transmission declines with increased duration of infection
- Incubation period after acquisition is 2-12 days (average is 4 days)
- Drying and soap and water readily inactivate HSV; fomite transmission unlikely

HSV-2 and HIV Infection

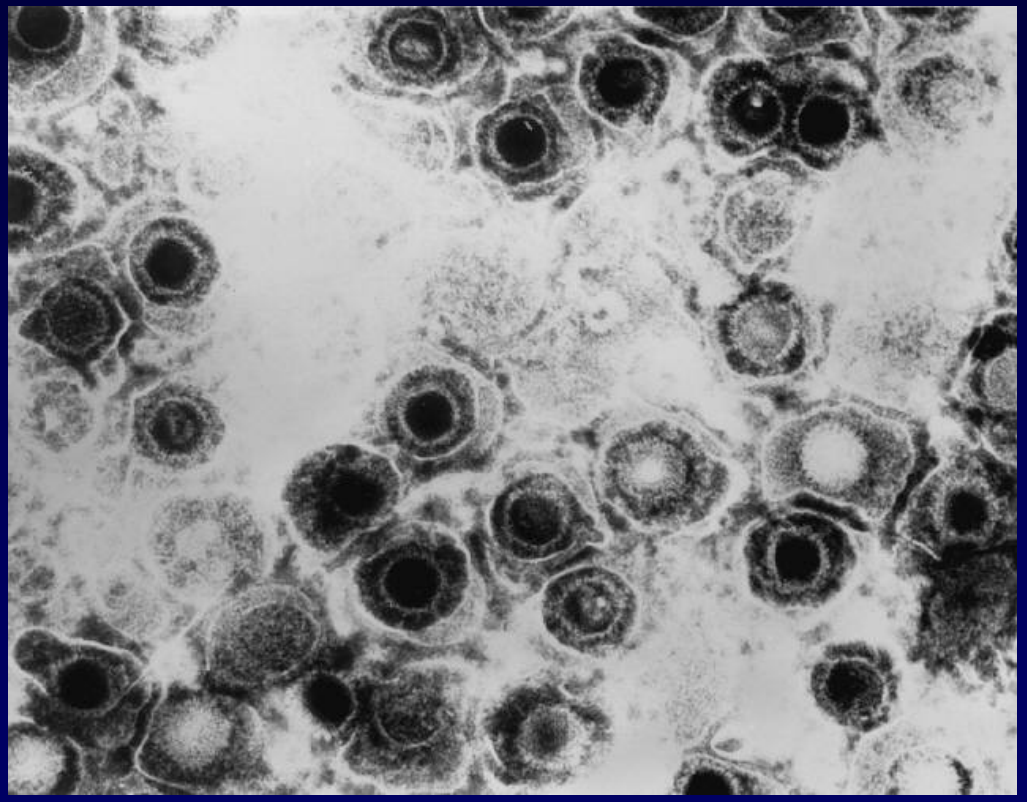
- HSV-2 infection increases the risk of acquiring HIV infection at least 2 fold
- HSV-2 infection is also likely to facilitate transmission of HIV infection from persons co-infected with both viruses

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 is precipitated by multiple known and unknown factors and induces viral replication
- The re-activated virus may cause a cutaneous outbreak of herpetic lesions or subclinical viral shedding
- Up to 90% of persons seropositive for HSV-2 antibody have not been diagnosed with genital herpes

Lesson III: Clinical Manifestations

Definitions of Infection Types

First Clinical Episode

- Primary infection
  - First infection **ever** with either HSV-1 or HSV-2
  - No antibody present when symptoms appear
  - Disease is more severe than recurrent disease

- 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 to new infection may take several weeks to a few months to appear

Definitions of Infection Types

Recurrent symptomatic infection

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

Asymptomatic infection

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

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
- Typical lesion progression:
  - papules → vesicles → pustules → ulcers → crusts → healed
- Often associated with systemic symptoms including fever, headache, malaise, and myalgia
- Illness lasts 2-4 weeks

First Episode Primary Infection without Treatment (continued)

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

Recurrent Infection Without Treatment

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

Genital Herpes: Primary Lesions

Source: Cincinnati STD/HIV Prevention Training Center

Genital Herpes: Multiple Ulcers

Source: Cincinnati STD/HIV Prevention Training Center

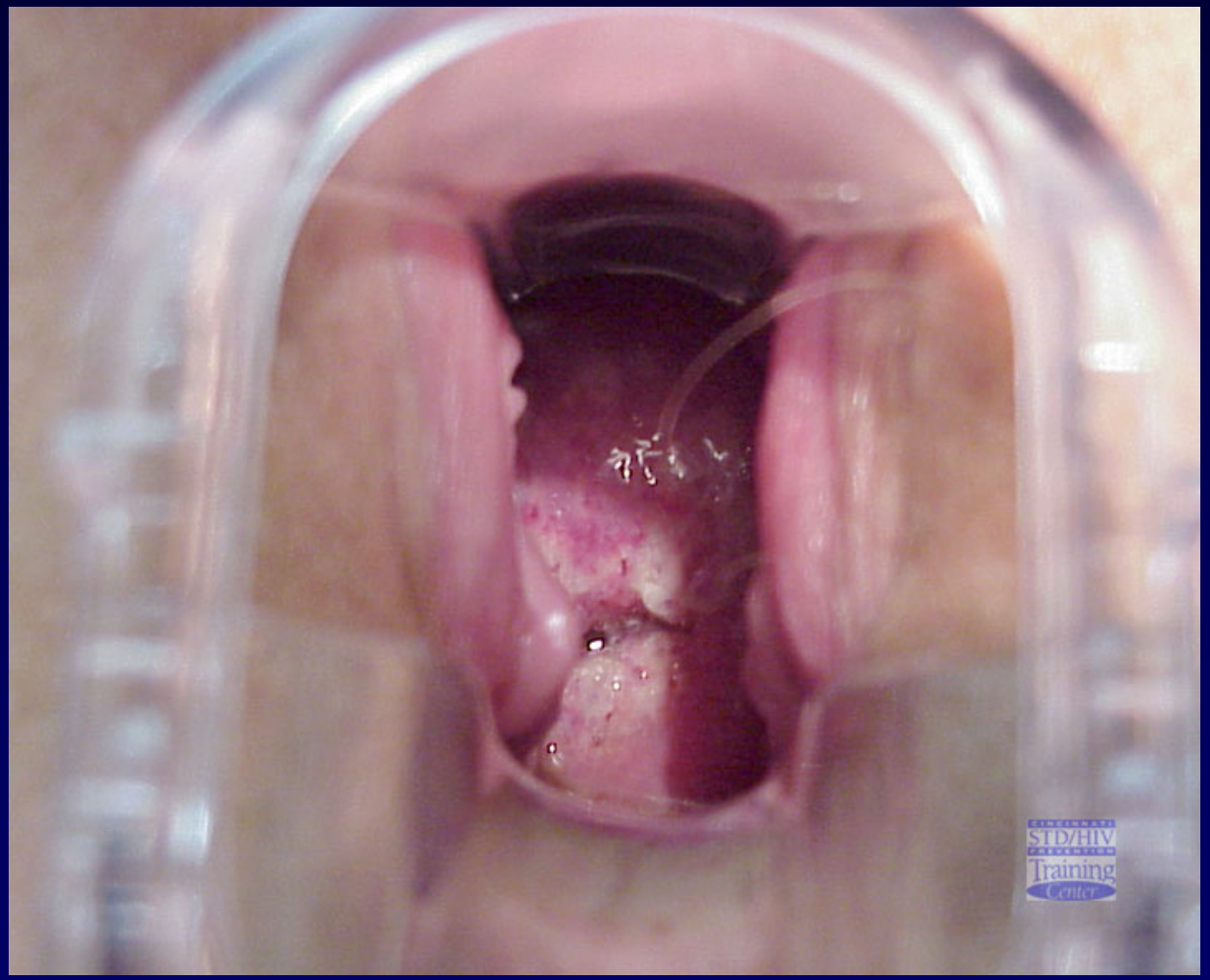
Genital Herpes: Recurrent Ulcer

Source: Cincinnati STD/HIV Prevention Training Center

Genital Herpes: Periurethal Lesions

Source: Cincinnati STD/HIV Prevention Training Center

Genital Herpes: Cervicitis

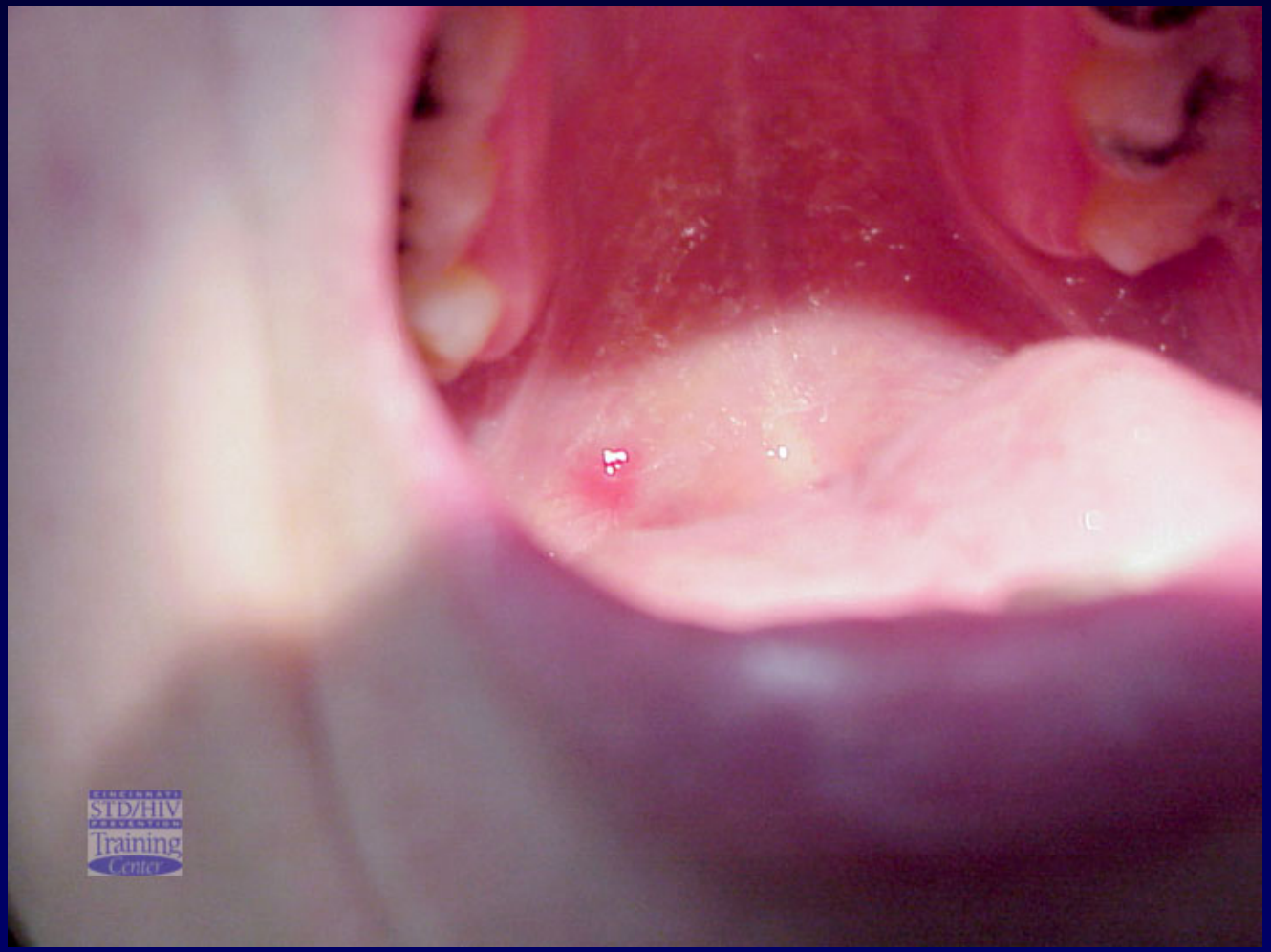


Source: Cincinnati STD/HIV Prevention Training Center

Herpes on the Buttock

Source: Cincinnati STD/HIV Prevention Training Center

Oral Herpes: Soft Palate



Source: Cincinnati STD/HIV Prevention Training Center

Asymptomatic Viral Shedding

- Most HSV-2 is transmitted during asymptomatic shedding
- Rates of asymptomatic shedding greater in HSV-2 than HSV-1
- Rates of asymptomatic shedding are highest in new infections (<2 years) and gradually decrease over time
- Asymptomatic shedding episodes are of shorter duration than shedding during clinical recurrences

Asymptomatic Viral Shedding
(continued)

- Most common sites of asymptomatic shedding are vulva and perianal areas in women and penile skin and perianal area in men
- Antiviral suppressive therapy dramatically reduces, but does not eradicate shedding

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 laboratory testing:
  - Virologic tests
  - Type-specific serologic tests

Virologic Tests

- Viral culture (gold standard)
  - Preferred test if genital ulcers or other mucocutaneous lesions are present
  - Highly specific (>99%)
  - Sensitivity depends on stage of lesion; declines rapidly as lesions begin to heal
  - Positive more often in primary infection (80%–90%) than with recurrences (30%)
  - Cultures should be typed
- Polymerase Chain Reaction (PCR)
  - More sensitive than viral culture; has been used instead of culture in some settings; however PCR tests are not FDA-cleared or widely available
  - Preferred test for detecting HSV in spinal fluid

Virologic Tests
(continued)

- Antigen detection (DFA or EIA)
  - Fairly sensitive (>85%) in symptomatic shedders
  - Rapid (2-12 hours)
  - May be 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

Type-specific Serologic Tests

- Type-specific and nonspecific antibodies to HSV develop during the first several weeks to few months 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

- Type-specific serologic assays might be useful in the following scenarios:
  - Recurrent or atypical genital symptoms with negative HSV cultures
  - A clinical diagnosis of genital herpes without laboratory confirmation
  - A sex partner with herpes
  - As part of a comprehensive evaluation for STDs among persons with multiple sex partners, HIV infection, and among MSM at increased risk for HIV acquisition

Evaluation of Genital Ulcer

- All patients with genital ulcers should be evaluated with a serologic test for syphilis and a diagnostic evaluation for genital herpes
- In settings where chancroid is prevalent, a test for *Haemophilus ducreyi* should also be performed

Lesson V: Patient Management

Principles of Management of Genital Herpes

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

Antiviral Medications

- Systemic antiviral chemotherapy includes 3 oral medications:
  - Acyclovir
  - Valacyclovir
  - Famciclovir
- Topical antiviral treatment is not recommended

Management of First Clinical Episode of Genital Herpes

- Manifestations of first clinical episode may become severe or prolonged

- Antiviral therapy should be used
  - Dramatic effect, especially if symptoms <7 days and primary infection (no prior HSV-1)

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

Suppressive Therapy for Recurrent Genital Herpes

- Reduces frequency of recurrences
  - By 70%-80% in patients with > 6 recurrences per year
  - Also effective in those with less frequent 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

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 800 mg orally twice a day for 5 days, or
- Acyclovir 800 mg orally 3 times a day for 2 days, or
- Famciclovir 125 mg orally twice a day for 5 days, or
- Famciclovir 1000 mg orally twice a day for 1 day, or
- Valacyclovir 500 mg orally twice a day for 3 days, or
- Valacyclovir 1 g orally once a day for 5 days

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 in HIV-Infected Persons

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

- HSV shedding is increased in HIV-infected persons

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

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

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

- Acyclovir 400 mg orally 3 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

Genital Herpes in Pregnancy

- Majority of mothers of infants who acquire neonatal herpes lack histories of clinically evident genital herpes
- Risk for transmission to neonate is high (30%-50%) among women who acquire genital herpes near the time of delivery
- Risk is low (<1%) in women with histories of recurrent herpes at term or who acquire genital HSV during the first half of pregnancy

Genital Herpes in Pregnancy
(continued)

- Prevention of neonatal herpes depends on:
  - ✓ avoiding acquisition of HSV during late pregnancy
  - ✓ avoiding exposure of the infant to herpetic lesions during delivery
- All pregnant women should be asked whether they have a history of genital herpes

Genital Herpes in Pregnancy
(continued)

- At the onset of labor:
  - All women should be questioned carefully about symptoms of genital herpes, including prodromal
  - All women should be examined carefully for herpetic lesions
- Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally

Genital Herpes in Pregnancy
(continued)

- Safety of acyclovir, valacyclovir, famciclovir in pregnancy not definitively established, but no clear evidence for increased birth defects
- Oral acyclovir may be given for first-episode or severe recurrent herpes; IV acyclovir should be used for severe infection
- Suppressive acyclovir late in pregnancy reduces frequency of cesarean sections in women with recurrent genital herpes; many specialists recommend it

Lesson VI: Prevention

Patient Counseling and Education

- Goals
  - Help patients cope with the infection
  - Prevent sexual and perinatal transmission
- Counsel initially at first visit
- Education on chronic aspects may be beneficial after acute illness subsides
- HSV-infected persons may express anxiety about genital herpes that does not reflect the actual clinical severity of their disease

Patient Counseling and Education

- Counseling should include:
  - Natural history of the infection
  - Treatment options
  - Transmission and prevention issues
  - Neonatal HSV prevention issues
- Emphasize potential for recurrent episodes, asymptomatic viral shedding, and sexual transmission

Counseling: Natural History

- Recurrent episodes likely following a first episode; with HSV-2 more than HSV-1
  - Frequency of outbreaks may decrease over time
  - Stressful events may trigger recurrences
  - Prodromal symptoms may precede outbreaks

- Asymptomatic viral shedding is common and HSV transmission can occur during asymptomatic periods

Counseling: Treatment

- Suppressive therapy available and effective in preventing symptomatic recurrences
- Episodic therapy sometimes useful in shortening duration of recurrent episodes
- When and how to take antiviral medications
- Recognition of prodromal symptoms to know when to begin episodic therapy

Counseling: Transmission and Prevention

- Inform current and future sex partners about genital herpes diagnosis
- Abstain from sexual activity with uninfected partners when lesions or prodrome present
- Correct and consistent use of latex condoms might reduce the risk of HSV transmission
- Valacyclovir suppressive therapy decreases HSV-2 transmission in heterosexual couples in which source partner has recurrent herpes

Counseling: Neonatal Herpes Prevention

- Risk of neonatal HSV infection should be explained to all patients, including men
- Pregnant women should inform their prenatal/perinatal providers that they have genital herpes
- Pregnant women without HSV-2 infection should avoid intercourse during third trimester with men who have genital herpes
- Pregnant women without HSV-1 infection should avoid oral sex from a partner with oral herpes

Counseling for Asymptomatic Persons

- Give asymptomatic persons diagnosed with HSV-2 infection 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 other than her husband 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

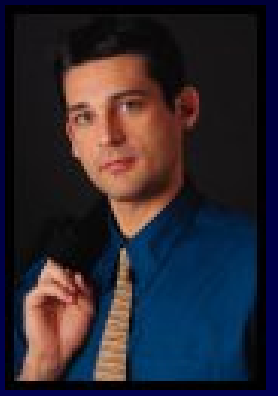
1. Which HSV general education messages should be discussed with Roberta?
2. Given that Roberta's husband Franklin has a history of genital herpes, would it be appropriate to test Roberta for genital herpes using a type-specific serologic test?
3. What other STD screening should be considered for Roberta?

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; no sex partners other than Roberta in past 16 months

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

7. What is an appropriate episodic treatment for Franklin?

Follow-Up

- Roberta had no HSV symptoms during her pregnancy
- Roberta discussed the use of acyclovir treatment in late pregnancy with her certified nurse-midwife, but decided against it because there are no data to support the use of antiviral therapy among HSV seropositive women without a history of clinical genital herpes
- 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 be asked of ALL women beginning labor?
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?