Update on Genital Herpes

Anne Rompalo, MD, ScM
Johns Hopkins University
The Facts...

- Genital herpes is recurrent, incurable
- HSV is rarely fatal
- There are two serotypes—HSV-1, HSV-2
- Most recurrent genital herpes are HSV-2
- At least 50 million are infected in U.S.
- Most HSV-2 infected are not diagnosed
  - They have mild or unrecognized infections
  - But they shed intermittently from the genital tract
- Most transmission occurs during asymptomatic shedding episodes
What’s New?

- More is known about . . .
  - “A-typical” presentations
  - Asymptomatic shedding
  - Genital HSV-1
- New serologic tests are FDA approved and available
  - Proper use of these diagnostics may decrease neonatal HSV transmission
- No new approved drugs (but shorter regimens can be used) and new drugs are in development
- Suppressive therapy prevents transmission
- NIH has vaccine trial underway
Section A: Epidemiology
Genital Herpes—Initial Visits to Physicians’ Offices:

United States, 1966–2003

Data Source: National Disease and Therapeutic Index (IMS Health)
From 1988 to 1994, the overall seroprevalence of HSV-2 was 21.9%
Compared to ’76-80, the age-adjusted seroprevalence increased 30%, with the greatest relative increase among young whites
Women were 45% more likely than men to be infected with HSV-2

- Seroprevalence = 21.3% versus 17.6%; a decrease of 17%
- Largest decreases were in . . .
  - Younger age groups
    - 74% in 14-19 yr olds (From 5.8% to 1.5%)
    - 48% in 20-29 yr olds (From 17.2% to 8.9%)
    - 35% for Males (from 17.2% to 11.2%)
    - 46% in Mexican Americans (from 22.5% to 12.1%)
Tip of the Iceberg

Iceberg represents persons with HSV-2 antibody

90.8% Unrecognized and asymptomatic infection

9.2% Recognized infection

The Clinical Spectrum of HSV-2

- Up to 80-90% of HSV-2 seropositive patients have no clinical history of genital HSV outbreaks
- Most have mild unrecognized disease
- Probably all shed intermittently
Genital Herpes Due to HSV-1:

Data from University of Wisconsin Health Services

- Retrospective review of HSV isolated collected over a nine-year period
- HSV-1 accounted for 78% of all genital herpes isolated in 2001 compared to 31% in 1993
- HSV-1 was more common in persons aged 16 to 21 compared to 22 or older

Source: Sex Transm Dis (2003), 30: 797-800
HSV-2 Incidence/Prevalence

- Most HSV-2 is acquired in third decade of life
- BUT recent studies show earlier acquisition
  - Rates quintupled in white teens and doubled in young adults
- Among teens
  - Seroprevalence is > 5%
    (4.5% white; 9% in black students)
- Among college students
  - Seroprevalence is 1–9%
    with high yearly seroconversion
Summary of Epidemiologic Data, 2005

- High prevalence of HSV-2 in most sexually experienced populations
- Most genital herpes is unrecognized
- HSV-1 accounts for increasing proportion of first genital herpes episodes
Section B

Pathogenesis
Pathogenesis of Genital HSV

- Need mucosal inoculation
- Virus is transported via peripheral nerve axon to nerve cell bodies in dorsal root ganglia
- Virus may remain latent indefinitely in paraspiinous ganglia
- Reactivation, viral replication, centrifugal migration to mucosal surfaces, focal cell necrosis
Histopathologic changes
- Focal necrosis
- Ballooning degeneration of cells
- Production of multi-nucleated giant epithelial cells
- Eosinophilic intra-nuclear inclusions called Cowdry type A bodies
Section C

Clinical Manifestations
Up to 80-90% of HSV-2 sero-positive patients have no clinical history of genital HSV outbreaks. Most have mild unrecognized disease, and probably all shed intermittently.
Types of Infections

- First clinical episode (primary)
  - No infection ever
  - No serum antibody when symptoms appear; serum antibody appears in convalescence
  - Clinically more severe

Continued
First clinical episode (non-primary)
  - First clinically apparent episode with HSV-1 or HSV-2 in person previous seropositive to other virus type
  - Clinically milder
  - 25% with HSV-2 have had a prior asymptomatic primary infection
Types of Infections

- Recurrent or first recognized
  - Antibody is present when symptoms occur although patient may not be aware of previous episodes
  - Generally, there is no or little change in antibody titer in convalescence
  - Disease is mild and short in duration

Types of Infections

- Asymptomatic infection
  - Serum antibody is present
  - No known history of outbreaks
  - Up to 66% with identified asymptomatic HSV-2 can be taught to recognize clinical signs and symptoms of genital outbreaks

### Type Specific Antibody at Time of Presentation

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Lesions/Symptoms</th>
<th>HSV-1</th>
<th>HSV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st episode primary (Type 1 or 2)</td>
<td>+/- severe, bilateral</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>First episode non-primary (Type 2)</td>
<td>+/- moderate</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>First episode recurrence (Type 2)</td>
<td>+/- mild</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Symptomatic recurrence (Type 2)</td>
<td>+/- mild, unilateral</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Asymptomatic infection (Type 2)</td>
<td>–</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>
HSV Lesions

- Macule
- Papule
- Vesicle
- Ulcer
- Crusted lesions
- Healed lesion
Clinical Course of Initial Herpes Virus Infection

Duration Viral Shedding

Symptoms

- Sexual contact
- Lesions noted
- Physician contacted
- New lesion formation common
- Lesions start to heal
- Symptoms gone unless lesions irritated
- Lesions healed

Data Source: Corey, L. (1983) NEJM
Primary Infection

- Often have systemic symptoms
  - Fever, headache, malaise, myalgias (40% men; 70% women)
  - 10% women have urinary retention
  - Symptoms peak within 3–4 days of lesion onset and recede over the next 3–4 days

Continued
Primary Infection

- Local symptoms
  - Pain (95%), itching, dysuria (60%), vaginal (85%), urethral (30%) discharge, tender lymphadenopathy (80%)
  - Lesions are numerous and bilateral; last 11–12 days; full healing takes average of 17–20 days
- Median duration of viral shedding is about 12 days and correlates well with the time from vesicles to crusting
- Inguinal adenopathy peaks in week 2–3 and is often last finding to resolve
- Lymph nodes are firm, nonfluctuant, and tender to palpation
Primary HSV Infection

- Primary HSV cervicitis occurs in ~90% of primary HSV-2 and ~70% of HSV-1
- It may present as mucopurulent cervicitis, or may be asymptomatic
- Cervix will often appear abnormal with ulcerative lesions, erythema, or friability
- Exo- and endocervix may be involved
What about Recurrences?

- Following the initial genital infection
  - HSV becomes latent in the sacral nerve ganglia and can reactivate
  - About 85% of women and nearly all men with symptomatic acquisition of genital HSV-2 will have a recurrence within the first year (average 4–5 bouts/year)
What about Recurrences?

- Following the initial genital infection
  - Recurrent episodes are shorter and more localized
    (may be chronic and unpredictable)
Recurrent Genital HSV

- Triggers for reactivation may or may not be known (trauma, fever, UVL, stress)
- Prodromal symptoms (50%) begin 12–24 hours before lesions and sometimes without lesions
- Duration is shorter (painful lesions last four to six days); shedding is shorter (four days)
Lesions tend to be unilateral

Average of 2–6 recurrences/year—but highly variable

Recurrence probability increases if . . .

- Primary is HSV-2
- Primary is severe/prolonged (>30 days)
Recurrent Genital HSV

- HSV will recur more frequently and after shorter period in men
- Rate of cervical virus shedding in women is 12–20%
Asymptomatic Viral Shedding

- Has been documented in almost all HSV-2 seropositive persons studied
- Most HSV-2 is transmitted during asymptomatic shedding
- Shedding rates are similar in patients with no reported history of genital HSV (2.7%) compared to those with a history (3.0%)
Most common shedding sites
- Women—vulva and perianal areas
- Men—penile skin

Shedding rates are greater with HSV-2 than HSV-1
Reactivation of Genital HSV-2

In Asymptomatic Seropositive Persons

- Prospective study of 53 HSV-2 antibody positive patients with no history of genital HSV versus 90 patients with symptomatic HSV-2
- Genital secretions were sampled daily and cultured for HSV for median 94 days
Of 53 asymptomatic patients, HSV was detected in 38 (72%) by culture and by PCR in an additional four (85%); 33 (62%) subsequently reported typical HSV lesions.

Rate of subclinical shedding was similar in both groups (3.0% of symptomatic patients vs. 2.7% of patients with no reported symptoms).
Among asymptomatic persons

- Duration of recurrences was shorter vs. symptomatic persons (median three vs. five days, p < 0.001)
- Frequency of recurrences was lower (3.0 per year vs. 8.2 per year, p < 0.001)
- Shedding was similar comparing men to women
Diary: No Relationship of Symptoms to Shedding

| Symptoms and Signs         | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|---------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| No symptoms               | X | X | X | X | X | X | X | X | X | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  |
| Itching, burning, tingling|   |   |   |   |   |   |   |   |   | G  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Localized redness or sore spots | |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Sores, blisters, ulcers, crusts | |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Abrasion, skin splits, scratches, fissures | |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Urethral pain or burning |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Abnormal vaginal discharge | |   |   |   |   |   |   |   |   |   | G  | X  | X  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Thigh or buttock pain or sensitivity | |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Swollen groin or lymph nodes |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| HSV culture               | 2 | 2 | 2 | 2 | 2 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

(Note: 'X' indicates presence, 'G' indicates genital herpes, '2' indicates frequency of HSV culture)
Complications of Genital HSV

- Aseptic meningitis
  - More common in primary than in recurrent infection
  - More common with HSV-2 than HSV-1
  - More common in women than in men (35% vs. 11% with primary disease)
Complications of Genital HSV

- Aseptic meningitis
  - May be severe and require hospitalization
  - Usually no neurologic sequelae
  - Recent data suggest that benign recurrent meningitis (Mollaret’s meningitis) is usually caused by HSV-2
Other Complications of Genital HSV

- Stomatitis and pharyngitis
- Radicular pain, sacral paresthesias
- Transverse myelitis
- Autonomic dysfunction—hyperesthesias, neurogenic bladder, constipation, impotence

Continued
Other Complications of Genital HSV

- Disseminated (viremic) infection—occasional in patients with atopic eczema, pregnant women, impaired CMI, neonates
  - High mortality
  - Fulminant hepatitis

- Ocular involvement
  - More common with HSV-1

- Herpetic whitlow
  - More common with HSV-1
Why Is Genital HSV Increasing?

- Frequency of misdiagnosis
- Lack of awareness with unintended spread
- Chronicity of condition with lifelong infectivity
- Occurrence of symptomatic viral shedding
- Lack of cure
- High rate of recurrence—90% recur at least once in first year (60% have four or more)
Section D

Herpes: Diagnosis
Virus Detection Tests Available

- Isolation of virus in culture
- Modified culture techniques
  - Shell vial or spin amplification methods
  - ELVIS™ (Enzyme-Linked Virus-Inducible System)
- Antigen detection
  - Direct fluorescent antibody (FA)
  - EIA (Herpcheck)
- DNA amplification methods
  - Polymerase chain reaction (PCR)
  - TaqMan, LightCycler
Accurate HSV Serology

**Glycoprotein gG tests**

- Western blot
- gG ELISA
- gG-membrane tests
- gG immunoblot

Envelope:
- gB, gC, gD, gE, gG, gH, gI, gK, gL, gM

Tegument:
- VP16

Nucleocapsid:
- VP5, ICP35

DNA core
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>HSV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Approved</strong></td>
<td></td>
</tr>
<tr>
<td>HerpeSelect® ELISA</td>
<td>Focus</td>
</tr>
<tr>
<td>HerpeSelect® Immunoblot</td>
<td>Focus</td>
</tr>
<tr>
<td>POCKit® HSV-2</td>
<td>Diagnology</td>
</tr>
<tr>
<td>Off the market</td>
<td></td>
</tr>
<tr>
<td>Premier™ELISA</td>
<td>Meridian</td>
</tr>
<tr>
<td>Off the market</td>
<td></td>
</tr>
<tr>
<td><strong>Not FDA Approved</strong></td>
<td></td>
</tr>
<tr>
<td>Cobas®-HSV-2</td>
<td>Roche</td>
</tr>
<tr>
<td>QuickVue® HSV-2</td>
<td>Quidel</td>
</tr>
</tbody>
</table>

* The Western blot assay, which is considered the gold standard, is not commercially available. HSV indicates herpes simplex virus; FDA, Food and Drug Administration; ELISA, enzyme-linked immunosorbent assay.
Limitations of gG-Based tests

- Antibodies to gG arise relatively late—first appearing two to three months after infection in 60–70% of newly infected persons.
- Therefore, Western blot detects seroconversion more quickly (not a commercially available test).
- Type specific IgM tests are under development.
Limitations of gG-Based tests

- The sensitivities of these assays for detection of HSV-2 range from 80-98% (false negative results may occur)
- Specificities are high (>96%), but false-positive results can occur, especially in patients with low likelihood of infection
- Therefore, repeat or confirmatory testing may be indicated
Role of Serology in Clinical Management

- Symptomatic—supplements virus detection efforts
  - When lesions are negative for virus
  - When lesions cannot be sampled for virus
  - When lesions are healed or not present

- Subclinical—high-risk patients
  - Partner has genital herpes
  - Sexual history
  - Symptoms suggestive of atypical or undiagnosed herpes
Section E

Herpes: Treatment
Recommended Regimen for First Clinical HSV Episode

- Acyclovir 400 mg PO TID
- Acyclovir 200 mg PO 5 x/day
- Famcyclovir 250 mg PO TID
- Valacyclovir 1 g PO BID

for 7-10 days or until clinical resolution
**Recommended Regimen for Episodic Recurrent HSV**

- Acyclovir 400 mg PO TID
- Acyclovir 200 mg PO five times daily
- Acyclovir 800 mg PO BID
- Famciclovir 125 mg PO BID
- Valacyclovir 1 gm QD for five days
- Valacyclovir 500 mg PO BID for three to five days
Among patients with frequent recurrences (> 6 per year), reduces frequency by up to 93%  
Safe and efficacious  
Discontinue periodically (once a year) and reassess
Recommended Regimens for Daily Suppression of HSV

- Acyclovir 400 mg PO BID
- Famciclovir 250 mg PO BID
- Valacyclovir 500 mg PO once a day
- Valacyclovir 1.0 g QD if recurrence > 10 per year

- Double-blind, placebo-controlled, crossover clinical trial comparing acyclovir 400 mg BID for 70 days, followed by a 14 days washout period, then placebo or in reverse order
- 34 women with HSV 2 of less than two years’ duration
- Daily samples of vulvar cervicovaginal and perianal areas, diary of symptoms
- Sub-clinical shedding occurred on 83 or 1439 days with placebo (5.8%) vs. six of 1611 days on acyclovir (0.37%)
- A 94% reduction
Mechanism of DNA Synthesis Inhibition of Acyclovir and New Drugs

- Helicase-primase complex unwinds HSV-DNA at the replication fork and primes both lagging and leading strands.
- New drugs bind to this complex and inhibit its activity at a different site than acyclovir.
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Section F

Herpes: Prevention
What about Condoms?

- Effect of condoms on reducing the transmission of Herpes Simplex Virus Type 2 from men to women

- Reduction from 8.5% to 0.9% incidence in discordant couples (men → women)

- No protective effect seen in women → men
### Risk of HSV-2 Acquisition in a Prospective Study (N=528)

<table>
<thead>
<tr>
<th>Risk</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each additional sex act per week</td>
<td>1.16</td>
</tr>
<tr>
<td>Condom use &gt;25% vs. ≤ 25%</td>
<td>0.38</td>
</tr>
<tr>
<td>Sex with lesions vs. no sex w/ lesions</td>
<td>2.01</td>
</tr>
<tr>
<td>Acyclovir use by source partner</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Transmission of HSV-2 in a Discordant Couple

Source Partner

- Virus in genital secretions:
  - - + + + + + + + + + + + + + + - - - - - -
- Itching: dot

Exposed Partner

- Cultures:
  +
- Genital lesions:
  . . . . . . . . . . . . . . . . . . .
- HSV-2 serology:
  - +

Date (March 2001): 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 29

Source partner reports irritation during sexual intercourse

Source: CDC
Once Daily Valaciclovir Reduces Transmission of Genital Herpes

- *NEJM* 2004; 350:11-20
Proportion of Susceptible Partners with HSV-2 Infection

**Placebo**
- Percentage with Infection: 3.8%
  - (28/741)
- Statistical Test: *P* = 0.039
- Relative Risk (RR): 0.50 (95% CI: 0.26, 0.94)
- 50% Reduction

**Valaciclovir 500 mg Once Daily**
- Percentage with Infection: 1.9%
  - (14/743)

**Legend**
- Percentage with Infection on the y-axis
- Placebo vs. Valaciclovir on the x-axis

---

72
Frequency of Clinically Symptomatic Genital Herpes in Susceptible Partners

Percentage with Symptoms

Placebo

Valaciclovir 500 mg Once Daily

- 2.3% (17/741)
- 0.5% (4/743)

P = 0.006
RR: 0.23 (95% CI: 0.08, 0.69)

77% Reduction
Conclusions: Valaciclovir 500 mg Once Daily

- Suppressive therapy significantly reduced the rate of transmission of . . .
  - Symptomatic genital herpes by 77%
  - HSV-2 infection by 50%
  - Total HSV acquisitions by 61%
Vaccines?

- HSV-2gD plus adjuvant—Smith Kline, in Phase 3 trials, maybe data next year
  - Information: [www.herpevac.com](http://www.herpevac.com)
  - 1-866-HERP-VAC
- HSV-2 DISC—Paired mutants, single replication cycle
- HSV-2gD—Nucleic acid vaccine
Section G

HSV and HIV: Relations and Affectations
Clinically can be more severe
Requires higher doses of therapy for longer duration
  – Acyclovir 400 mg PO 3-5 x daily
  – Famciclovir 500 mg BID
  – Valacyclovir 1.0 gram PO BID for 5-10 days
Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda

Source: Gray et al., *Lancet* 2001;257:1149
## Acquisition Probabilities per Act

by HSV-2 Status of HIV-Negative Partner

<table>
<thead>
<tr>
<th></th>
<th>Acquisition Probabilities per Act</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HSV-2 Positive</strong></td>
<td>0.0020**</td>
</tr>
<tr>
<td><strong>HSV-2 Negative</strong></td>
<td>0.0004</td>
</tr>
</tbody>
</table>

\[ P = 0.01 \]
Probability of HIV Acquisition per Sex Act by HSV-2 in HIV-Negative Partner and Viral Load of the HIV-Positive Partner

Transmission Probability/1000 Acts

HSV-2 Positive

HSV-2 Negative

Log Viral Load copies/mL

<1700 1700- 12,500- 38,500+

Continued
Probability of HIV Acquisition per Sex Act by HSV-2 Serostatus and Age of HIV-Negative Partner
## Acquisition Probabilities per Act

*by GUD and HSV in HIV-Negative Partner*

<table>
<thead>
<tr>
<th>GUD Status</th>
<th>HSV Status</th>
<th>Acquisition Probabilities per Act</th>
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</thead>
<tbody>
<tr>
<td>GUD+/HSV+</td>
<td></td>
<td>0.0031</td>
</tr>
<tr>
<td>GUD-/HSV+</td>
<td></td>
<td>0.0019</td>
</tr>
<tr>
<td>GUD-/HSV-</td>
<td></td>
<td>0.0004*</td>
</tr>
</tbody>
</table>
Prevalence of HSV-2 and HIV

Prevalence of HSV-2 and HIV

![Graph showing the prevalence of HSV-2 and HIV by age group. The graph displays two lines, one for HSV-2 and another for HIV-1, indicating the percentage prevalence across different age groups.]
HSV-2 and HIV: Rakai Data

- GUD risk factor for HIV acquisition (RR~3.0)
- 45% of GUDs are due to HSV-2 (Multiplex PCR)
- Age and sex-specific prevalence of HSV-2 mirrors that of HIV