Genital Herpes: Framing the Problem, Diagnosing the Disease

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Herpes Simplex Virus

- Mucocutaneous infection, retrograde infection of sensory nerves, continuous slow replication (with clinical latency) in cranial or spinal ganglia and peripheral nerve endings, mucocutaneous recurrences

- HSV-1
  - Mostly orolabial (cold sores, fever blisters)
  - 20%-50% of initial genital herpes in North America and western Europe

- HSV-2
  - Almost entirely genital; oral infection uncommon
  - >90% of recurrent genital herpes
Prevalence of Genital HSV Infection in Adults in the United States

- HSV-2, NHANES-II (1978) 16% (15M age 15-49)
- HSV-2, NHANES-III (1991) 22% (24M age 15-49)
- HSV-2, NHANES 1999-2004 17% (27M age 15-49)
- HSV-2 NHANES 2005-2010 15.3% (27 M age 15-49)
- Genital HSV-1 infection 10 million (??)

- TOTAL >20% >30 million

Bradley et al. JID 2014;209:325-333
Change in HSV-2 Seroprevalence

Table 2. Weighted Herpes Simplex Virus Type 2 Seroprevalence by Age Among Men and Women Aged 14–49 Years: NHANES, 1999–2004 and 2005–2010

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>1999–2004</th>
<th>2005–2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample Size</td>
<td>%</td>
</tr>
<tr>
<td>14–19</td>
<td>4650</td>
<td>1.6</td>
</tr>
<tr>
<td>20–29</td>
<td>2412</td>
<td>10.6</td>
</tr>
<tr>
<td>30–39</td>
<td>2251</td>
<td>22.1</td>
</tr>
<tr>
<td>40–49</td>
<td>2195</td>
<td>26.3</td>
</tr>
<tr>
<td>Total</td>
<td>11 508</td>
<td>17.2</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HSV-2, herpes simplex virus type 2; NHANES, National Health and Nutrition Examination Survey.

Bradley et al. JID 2014;209:325-333
HSV is a Health Inequity Issue

FIGURE 1. Herpes simplex virus type 2 seroprevalence* among persons aged 14–49 years, by age group and race/ethnicity† — National Health and Nutrition Examination Survey, United States, 2005–2008

- 14–19 yrs
- 20–29 yrs
- 30–39 yrs
- 40–49 yrs

Percentage

Race/Ethnicity
- White, non-Hispanic
- Black, non-Hispanic
- Mexican American
Network matters more than Number of Partners

FIGURE 2. Herpes simplex virus type 2 seroprevalence* among persons aged 14–49 years who reported having had sex, by number of lifetime sex partners and race/ethnicity† — National Health and Nutrition Examination Survey, United States, 2005–2008
Decreasing Prevalence of HSV-1 Infection

Table 1. Weighted Herpes Simplex Virus Type 1 Seroprevalence by Age Among Men and Women Aged 14–49 Years: NHANES, 1999–2004 and 2005–2010

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Sample Size</th>
<th>HSV-1 Seroprevalence (%)</th>
<th>95% CI</th>
<th>Sample Size</th>
<th>HSV-1 Seroprevalence (%)</th>
<th>95% CI</th>
<th>% Change</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18</td>
<td>4650</td>
<td>39.0</td>
<td>(36.7, 41.2)</td>
<td>3180</td>
<td>30.1</td>
<td>(27.3, 32.8)</td>
<td>-22.9</td>
<td>(-30.7, -14.2)**</td>
</tr>
<tr>
<td>20–29</td>
<td>2412</td>
<td>54.4</td>
<td>(51.8, 57.0)</td>
<td>2658</td>
<td>49.5</td>
<td>(46.0, 52.9)</td>
<td>-9.1</td>
<td>(-16.4, -1.1)*</td>
</tr>
<tr>
<td>30–39</td>
<td>2251</td>
<td>63.5</td>
<td>(60.7, 66.3)</td>
<td>2592</td>
<td>61.8</td>
<td>(58.6, 65.0)</td>
<td>-2.7</td>
<td>(-9.1, 4.1)</td>
</tr>
<tr>
<td>40–49</td>
<td>2185</td>
<td>65.3</td>
<td>(62.6, 67.9)</td>
<td>2670</td>
<td>63.6</td>
<td>(60.4, 66.7)</td>
<td>-2.6</td>
<td>(-8.6, 3.8)</td>
</tr>
<tr>
<td>Total</td>
<td>11,508</td>
<td>57.9</td>
<td>(56.1, 59.6)</td>
<td>11,100</td>
<td>53.9</td>
<td>(51.6, 56.1)</td>
<td>-6.9</td>
<td>(-11.6, -2.0)**</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HSV-1, herpes simplex virus type 1; NHANES, National Health and Nutrition Examination Survey.

*P ≤ .05.

**P ≤ .01.

Bradley et al. JID 2014;209:325-333
Asymptomatic acquisition of Genital Herpes

HSV-seronegative women, aged 18–30 years, who were in the control arm of the HERPEVAC Trial for Women were followed for 20 months for primary HSV infections.

Results:

3438 evaluable participants

183 became infected with HSV:

HSV-1: 127 (3.7%)

HSV-2: and 56 (1.6%)

The rate of infection for HSV-1 (2.5 per 100 person-years) was more than twice that for HSV-2 (1.1 per 100 person-years). Most infections (74% of HSV-1 and 63% of HSV-2) occurred without recognized signs or symptoms of herpes disease.
Genital Herpes and HIV Transmission

- HSV-2 infection is an important STD in enhancing HIV transmission efficiency; may account for up to half of all HIV infections.

- HSV-2 infected persons have 2–4x increased chance of sexual acquisition of HIV.

- Dual HIV and genital HSV-2 infection increases HIV transmission. HSV reactivation increases seminal HIV levels.

- Consider HSV-2 serologic screening persons with HIV or at high risk for HIV (MSM, intravenous drug users, and their partners).
Relative Risk of HIV Acquisition in HSV-2 Positive vs HSV-2 Negative Persons

HSV-2 increases HIV expression in ectocervical tissue

Rollenhagen et.al. Nature 2014
HSV-2 increases the risk of HIV acquisition, possibly due to increased CD4 T-cell activation in the cervix and an increased expression of HIV susceptibility markers, CCR5 and α4β7.

Zhu, J et al JEM 2007
McKinnon, L.R. Curr. Opin. HIV AIDS 2012
No Effect of HSV-2 suppression on HIV Transmission or Acquisition

Figure 3. Kaplan–Meier Curves for the Modified Intention-to-Treat Analysis. The cumulative probability of genetically linked transmission of HIV-1 is shown for the two study groups.

Celum et al. NEJM 2010
Celum et al. Lancet 2008
HSV is a Spectrum Disease

- Infection results in latency
- Latency → reactivation
- Reactivation = shedding
- Shedding varies in frequency and quantity
- Balance of immune clearance and shedding determines subclinical/disease state
Genital Herpes Clinical Spectrum

- **First episode infection**
  - Primary: First infection with HSV-1 or -2 (~20%)
  - Nonprimary first episode: Prior infection with the opposite HSV type (~40%)
  - First recognized episode of longstanding infection (~40%)

- **Recurrent infection**: Second or subsequent outbreak (HSV-2 >> HSV-1)

- **Subclinical infection**: ~60%–90% of infections
  - Truly asymptomatic
  - Unrecognized
Outbreak Revurrences

- Mean recurrence rate in first year after initial genital HSV-2 infection (N = 457, median FU 391 days)
  - Men 5.2 episodes/yr
  - Women 4.0 episodes/yr

- ≥6 recurrences in first year 38%
- ≥10 recurrences in first year 20%

- Rate gradually declines over several years

- Recurrence after initial genital HSV-1 (N = 83)
  - Mean recurrences 1.3 yr 1, 0.7 yr 2, & beyond
  - 38% had no recurrences

What Triggers Recurrent Outbreaks?

- Oral HSV-1
  - Other infections ('cold sore,' 'fever blister')
  - Actinic/ultraviolet injury
  - Other local trauma (eg, surgery)

- Genital HSV-2
  - *No clearly documented triggers*
  - No good data support stress, diet, menstruation, sex, etc, despite anecdotal reports and strongly held beliefs to the contrary
Asymptomatic Viral Shedding in Transmission and Acquisition of HSV-2
Key Facts for genital HSV-2

- Transmission occurs frequently between outbreaks[1]
- Nearly all shed virus asymptotically*[2]
- Patients cannot predict when AVS will occur[3]
- All are at risk for AVS, regardless of outbreak frequency[3]
- Shedding is a nearly continuous process
- Safer sex practices should be used
  - Even with safer sex, it is still possible to transmit HSV
  - Condoms cannot provide 100% protection against transmission, they do not cover all potential sites of HSV shedding

*Shedding in the absence of lesions
Asymptomatic Viral Shedding

- Asymptomatic viral shedding (AVS) is the presence of HSV on the surface of the skin/mucosa in the absence of signs and symptoms\(^{[1-3]}\)

Asymptomatic Viral Shedding Is Common and Can Occur Frequently

- Most GH patients experience asymptomatic shedding*
- PCR has a ~3-4 times higher detection rate than culture

<table>
<thead>
<tr>
<th>Asymptomatic Shedding</th>
<th>Via Culture†</th>
<th>Via PCR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients with ≥ 1 day</td>
<td>51%-61%</td>
<td>72%-88%</td>
</tr>
<tr>
<td>% of days</td>
<td>2.0%-6.6%</td>
<td>7.8%-27%</td>
</tr>
</tbody>
</table>

PCR = polymerase chain reaction; *shedding in the absence of lesions; †shedding rates can vary based upon time since diagnosis, frequency of recurrences, method of detection, frequency/site of sampling

HSV-2 Shedding and Frequency of Outbreaks

- Those with symptomatic hx detected on 20.1% of day; (18.3%-22.0%) vs. 10.2% (7.7%-13.6%) asymptomatic infection ($P < .001$).

- Subclinical shedding rates were higher in persons with symptomatic infection compared with asymptomatic infection 13.1% (11.5%-14.6%) vs. 8.8% (6.3%-11.5%) ($P < .001$)

- No difference in amount of subclinical shedding detected similar

- Difference in shedding mostly due to lesions

Tornstein et al JAMA 2011
Viral Shedding Patterns Are Unpredictable and Influenced by Therapy

AVS Duration

Mark KE, et al. JID 2008
HSV-2 transmission probability estimates

- Predict transmission is unlikely at viral loads less than $10^4$ HSV DNA copies.
- Most transmissions occur during prolonged episodes with high viral copy numbers.
- Many shedding episodes that result in transmission do not reach the threshold of clinical detection

Up to 70% of Transmission May Occur During Asymptomatic Viral Shedding

- 9.7% of patients infected their partner (14/144)
- Transmission frequently occurs between outbreaks

Summary of Asymptomatic Viral Shedding

- Infection = Shedding
- Asymptomatic viral shedding (AVS) is frequent and difficult to predict when and where
- AVS does decrease with time but remains high over time. Most of the decrease in shedding occurs within the 1st 6-12 mo of infection
- AVS driving force for transmission
Genital Herpes: Diagnosis
Diagnosis of Genital Herpes

- Test all genital ulcers for HSV, including clinically obvious genital herpes
  - Clinical diagnosis insensitive and nonspecific
  - Virus type determines clinical prognosis, transmission, and counseling

- Virologic tests
  - PCR is test of choice
  - Culture: less sensitive after ulceration
  - Direct FA: Some don't provide virus type
  - Cytology (Tzanck prep): Insensitive, no virus type; do not use

- Serologic testing: Use only glycoprotein G (gG)-based assays
Uses of Type-Specific HSV Serology

Definite Indications

- Diagnosis of GUD, recurrent symptoms, etc
- Management of sex partners of persons with herpes
- Persons with or at risk for HIV acquisition

Other Uses

- Selected (all?) pregnant women and their partners
- Patient request
  - Request to test for herpes
  - Comprehensive STD evaluation

Screen All Sexually Active Persons (controversial)?
Type-Specific HSV Serologic Tests

Antibody to HSV-1 or -2 glycoprotein G (gG-1 or gG-2)

- **Western blot**
  - The gold standard but expensive and need reference lab

- **HerpeSelect HSV-1 and HSV-2 ELISA**
  - Sensitivity for HSV-2 ~90%, specificity ~98%
  - Insensitive for HSV-1
  - HSV-2 may be falsely positive at low index values (1.1-3.5). Such low values should be confirmed with another test, such as Biokit or the Western blot

- **HerpeSelect HSV-1 and HSV-2 Differentiation Immunoblot**
  - Same antigen as ELISA, probably similar performance

- **biokitHSV2**
  - Point of care
  - HSV-2 only
Interpreting HSV-2 *HerpeSelect*

- The numerical value is the ratio between the test optical density (OD) and control, *not a titer*
  - <0.9  Negative
  - 0.9–1.1  Equivocal
  - 1.1–3.5  Positive, but influenced by HSV-1
  - >3.5  Unequivocally positive

- **Notes**
  - Varying values below 0.9 are meaningless
  - Some values 1.1–3.5 are false positive if HSV-1 antibody is present
HSV IgM Testing is Not Clinically Useful

- Not type specific
- Does not distinguish early from late infection
- False-positive results common
- There is no valid indication for use in adults
Options for Confirmatory Testing of the HSV-2 ELISA

- BioKit Assay
- Western blot
- Immunoblot
- ELISA avidity assay
- Repeat/convalescent testing

Time to HSV-2 Seroconversion

Days From Primary Episode

Probability of Remaining Seronegative

Western Blot

Focus
Prevention and Available and Emerging Treatments for HSV-2 Infection
Interventions for HSV

- Beneficial
  - oral antiviral therapy in first episodes (Statistically and clinically significant for disease but not transmission)
  - oral antiviral therapy at a start of recurrence (Statistically significant but not clinically significant for disease or transmission)
  - daily antiviral therapy significant to control disease and/or reduce risk of transmission

Wald, Clinical Evidence ‘99
Transmission Reduction: What Can Be Done?

- Advise patients to avoid sexual contact during outbreaks
Transmission Reduction: What Can Be Done?

- Advise patients to avoid sexual contact during outbreaks
- Inform patients about transmission risk during periods of asymptomatic shedding
Transmission Reduction: 
*What Can Be Done?*

- Advise patients to avoid sexual contact during outbreaks
- Inform patients about transmission risk during periods of asymptomatic shedding
- Offer suppressive therapy
Transmission Reduction: What Can Be Done?

- Advise patients to avoid sexual contact during outbreaks
- Inform patients about transmission risk during periods of asymptomatic shedding
- Offer suppressive therapy
- Condoms
Condom Sense

- Condoms appear ~ 30% protective against HSV-2 acquisition in men and in women.
- Evidence for condoms' efficacy will always be measured indirectly.

Transmission Reduction: Disclosure to Sexual Partners

- A recent study found that a strong protective factor against genital HSV-2 acquisition was partner disclosure of genital herpes.
- Median time to transmission nondisclosers: 60 days
  vs
  disclosers: 270 days $P = .03$

Suppressive Antiviral Therapy to Reduce Transmission Risk
CDC Sexually Transmitted Diseases Treatment Guidelines and ACOG Recommend Daily Therapy

**CDC:** Discordant couples should be encouraged to consider suppressive antiviral therapy as a part of a strategy to prevent transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences

**ACOG:** For couples in which 1 partner has HSV-2 infection, suppressive* antiviral therapy should be recommended for the partner with HSV-2 to reduce the rate of transmission

*ACOG recommends valacyclovir 500-1000 mg daily for suppressive therapy.*


Proportion of Susceptible Partners With Overall Acquisition of HSV-2 Infection

- Placebo: 3.6% (27/741)
  - 48% reduction
  - \( P = .054 \)
  - RR: 0.52 (95% CI: 0.27, 0.97)
  - HR for Kaplan-Meyer Analysis
  - \( P = .039 \)

- Valacyclovir: 1.9% (14/743)

Initial Episode

- **Acyclovir**
  - 400 mg t.i.d. or 200 mg 5 times/d for 7 to 10 days

- **Famciclovir**
  - 250 mg t.i.d. for 7 to 10 days

- **Valacyclovir**
  - 1 g b.i.d. for 7 to 10 days

# Treatment Options: Episodic Therapy

<table>
<thead>
<tr>
<th></th>
<th>5-Day Regimens</th>
<th>Shorter Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>400 mg t.i.d.</td>
<td>800 mg t.i.d. for 2 days</td>
</tr>
<tr>
<td></td>
<td>800 mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>Famciclovir</td>
<td>125 mg b.i.d.</td>
<td>1 g b.i.d. for 1 day</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1 g q.d.</td>
<td>500 mg b.i.d. for 3 days</td>
</tr>
</tbody>
</table>

Treatment Options: Suppressive Therapy

Possible dosing regimens¹:

- **Acyclovir**
  400 mg b.i.d.

- **Famciclovir**
  250 mg b.i.d.

- **Valacyclovir**
  500 mg q.d. or (for >10 occurrences/year)
  1 g q.d.

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Workowski KA, et al. 2015. MMWR Recommn Rep 64(RR-3):1–137.
Candidates for Antiviral Suppressive Therapy

<table>
<thead>
<tr>
<th>In HSV 2-Infected Patients</th>
<th>Use Antiviral Suppressive Therapy Primarily to</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Disease</td>
</tr>
<tr>
<td>With new infection</td>
<td>√</td>
</tr>
<tr>
<td>With bothersome outbreaks</td>
<td>√</td>
</tr>
<tr>
<td>Who are immunocompromised</td>
<td>√</td>
</tr>
<tr>
<td>Who are in late pregnancy</td>
<td>√</td>
</tr>
<tr>
<td>Who are distressed by the diagnosis</td>
<td>√</td>
</tr>
<tr>
<td>With a sexual partner who is uninfected or has an unknown HSV status</td>
<td></td>
</tr>
<tr>
<td>With multiple sexual partners</td>
<td></td>
</tr>
</tbody>
</table>
Acyclovir resistance

- Suspect if lesions persist or recur while on antiviral treatment,
- Obtain viral isolate for sensitivity testing
- All acyclovir-resistant strains are resistant to valacyclovir, and the majority are resistant to famciclovir.

Treatment options:

- Foscarnet, 40-80 mg/kg IV q 8 hours until clinical resolution
- IV cidofovir 5 mg/kg once weekly
- Imiquimod topical alternative, as is topical cidofovir gel 1%, however cidofovir must be compounded at a pharmacy. These should be applied to the lesions once daily for 5 consecutive days.
Vaccines
Vaccines

- Prophylactic – failed; primarily glycoprotein based
- Therapeutic: several in trials
  - GEN-003- gD2 and ICP4 with matrix M adjuvant
  - HerpV – 32 HSV Ag complexed with human hsp70 and with QS-21
  - Vical DNA vaccine - vaxfectin liposomes
Sustained Responses at 12m for Both Shedding and Lesion Rates

**Shedding Rates**

- Baseline: 0%
- Post dose 3: -50%
- 6 Months: -52%
- 12 Months: -64%

**Lesion Rates**

- Baseline: 0%
- Post dose 3: -50%
- 6 Months: -64%
- 12 Months: -65%
KM Graph – 20-30% lesion free at 12m
(Historical comparison: Valtrex 34%, Placebo 4%)
Vical HSV DNA Vaccine

HSV-2 Vaccine Candidates

Bivalent

UL46 + gD
Codon-optimized genes

Monovalent

Tegument Protein VP11/12 + Glycoprotein D
Full-length HSV-2 proteins

Vaxfectin® Liposomes

(±)-N-(3-aminopropyl)-N,N-dimethyl-2,3-bis(cis-9-tetradeceneyloxy)-1-propanaminium bromide

1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine
## Secondary Endpoint – Lesion Rate

<table>
<thead>
<tr>
<th>Treatment Group (N)</th>
<th>Prevaccine Lesion Rate [CI]</th>
<th>1st Postvaccine Lesion Rate [CI]</th>
<th>Rate Ratio [CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalent (56)</td>
<td>6.0 [5.3, 6.9]</td>
<td>2.9 [2.4, 3.6]</td>
<td>0.49 [0.31, 0.79]</td>
<td>0.0037</td>
</tr>
<tr>
<td>Monovalent (54)</td>
<td>6.0 [5.3, 6.9]</td>
<td>6.2 [5.4, 7.1]</td>
<td>1.03 [0.70, 1.51]</td>
<td>0.8759</td>
</tr>
<tr>
<td>Placebo (21)</td>
<td>6.4 [5.2, 7.9]</td>
<td>3.5 [2.6, 4.6]</td>
<td>0.54 [0.26, 1.09]</td>
<td>0.0850</td>
</tr>
</tbody>
</table>
What Viral Load is Clinically Meaningful?

- Higher viral loads in presence vs absence of lesions\(^1\)

- > 90% of episodes with viral loads > 10,000 copies/mL are associated with lesions
  - 1,000 shedding episodes among 386 subjects\(^2\):

<table>
<thead>
<tr>
<th>Viral Load (copies/mL)</th>
<th>% of Total Shedding Episodes</th>
<th>% of Episodes Associated with Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10,000</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td>&gt; 10,000</td>
<td>59</td>
<td>91</td>
</tr>
</tbody>
</table>
Conclusions

- Genital herpes is common and under-recognized
- Shedding is the norm
- Treat to control disease and/or transmission
- Therapeutic vaccines on the horizon