Antivirals and Vaccines: What’s old and new in HSV-2 treatment

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Importance of HSV: Why pursue a vaccine?

- Prevention of genital ulcer disease
- Prevention of HSV-2 transmission-sex partners
- Prevention of neonatal herpes
- Interruption of HIV epidemic

- Ideally also prevent HSV-1 infection
  - GUD, neonatal herpes
  - Encephalitis, keratitis, herpes labialis
## HSV-2 Vaccine Strategies

<table>
<thead>
<tr>
<th></th>
<th>Prophylactic</th>
<th>Therapeutic</th>
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<tbody>
<tr>
<td><strong>Target Population</strong></td>
<td>High risk HSV-2 seronegative Adolescent platform</td>
<td>HSV-2 seropositive Adolescent/adults</td>
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<tr>
<td><strong>Goal</strong></td>
<td>Prevent infection –or- Reduce severity of disease</td>
<td>Reduce severity of disease and risk of transmission</td>
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<tr>
<td><strong>Benefit</strong></td>
<td>Individual Societal</td>
<td>Individual Partner Societal</td>
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<tr>
<td><strong>Preferred endpoint</strong></td>
<td>Infection (seroconversion) GUD is historical endpoint</td>
<td>Genital shedding and recurrences</td>
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Prophylactic vaccines

- Most prophylactic vaccines have targeted surface glycoproteins (gD, gB)
  - Subunit vaccines
  - Elicit neutralizing antibody

- Over 20,000 participants enrolled in prophylactic vaccine trials
Genital HSV 1 / 2 Disease Cumulative Incidence Per Protocol Efficacy Cohort

HSV-1 genital disease

HSV-2 genital disease

Infection VE=35% (95% CI=13%-52%)

Belshe et al, NEJM 2012
Vaccine efficacy as a function of elicited gD2 titer

First evidence for correlate of protection against HSV-1 infection

Belshe et al, JID 2014
Poll #1: Therapeutic HSV Vaccine Efficacy

How effective do you think an HSV therapeutic vaccine needs to be to gain support and interest from health care providers and patients (assume it is safe)?

A. 30% reduction in lesions
B. 50% reduction in lesions
C. 75% reduction in lesions
D. 90% reduction in lesions
Therapeutic HSV-2 vaccines: A new paradigm for testing

- Endpoint: Shedding rate pre/post vaccine
- Participant is compared to themselves
- Increased power allows for smaller trials to determine optimal dose in Phase 1/2
GEN-003: Phase 1/2 results

3 doses of vaccine, administered 21 days apart
50ug Matrix M2 adjuvant
Shedding sessions pre, post, and 6 months post vaccine

Relative risk of shedding and lesions after vaccination

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Antigen</th>
<th>10ug</th>
<th>30ug</th>
<th>100ug</th>
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</thead>
<tbody>
<tr>
<td>HSV Shedding rate</td>
<td>0.95</td>
<td>1.59</td>
<td>1.06</td>
<td><strong>0.46</strong></td>
<td><strong>0.68</strong></td>
</tr>
<tr>
<td>HSV shedding 6 months post</td>
<td>1.3</td>
<td>2.22</td>
<td>1.58</td>
<td><strong>0.58</strong></td>
<td>0.88</td>
</tr>
<tr>
<td>HSV lesion rate</td>
<td>1.21</td>
<td>0.90</td>
<td>0.76</td>
<td><strong>0.52</strong></td>
<td>0.53</td>
</tr>
<tr>
<td>HSV lesion rate 6 months</td>
<td>1.32</td>
<td>1.23</td>
<td>0.91</td>
<td><strong>0.33</strong></td>
<td>0.85</td>
</tr>
</tbody>
</table>

Bernstein et al, JID 2017
Therapeutic HSV vaccines in the headlines

Offshore Human Testing Of Herpes Vaccine Stokes Debate Over U.S. Safety Rules

By Marisa Taylor  |  August 28, 2017

Desperate Quest For Herpes Cure Launched ‘Rogue’ Trial

By Marisa Taylor  |  October 19, 2017
Assume a theoretical 3-dose HSV therapeutic vaccine is safe and FDA-approved for use. It requires documentation of HSV-2 infection via genital culture or serology results.

Would you provide this vaccine to your patients in your STD clinic?

A. Yes!!!
B. Yes, if patients provided documentation of HSV-2 infection
C. No, we would not have the resources to test patients or to provide 3 doses
D. No, we don’t see patients with genital HSV
Pipeline for HSV vaccine development, 2017

HSV: candidate approaches
- Live, attenuated, subunit
- “Prime/pull” approach
- Adjuvant: TLR4 agonist

HSV: VCL-HB01
- Therapeutic, DNA
- 57% sustained reduction lesions, but not shedding
- Reduction quantity of HSV

HSV: GEN003
- Therapeutic, subunit
- 50% reduction shedding
- 70% reduction lesions

HSV: COR-1
- Therapeutic, DNA
- Induced T cell responses
- No antibody responses

HSV: HSV529
- Prophylactic, therapeutic
- Live, replication-defective
- Reduced mortality, genital disease, shedding in animals
- Safe

HSV: past trials of gD2/gB2 subunit vaccines did not prevent HSV-2, though gD2 vaccine had 58% efficacy versus HSV-1

Adapted from Gottleib & Johnston, COID 2017
Part 2:

• Changing epidemiology of genital HSV

• Treatment of Genital HSV
Poll #3: HSV in the STD Clinic

In my STD clinic:

A. Genital HSV is one of the leading confirmed diagnoses and requires a lot of clinic resources for diagnostics and treatment

B. Genital HSV is diagnosed clinically and empiric medications are prescribed; impact on clinic operations is small/moderate

C. Genital HSV infection is rarely seen

D. Other
Confirmed First Episode Genital HSV Diagnoses in PHSKC STD clinic: 1994-2014

Dabestani et al, Manuscript in preparation
HSV epidemiology in the USA

HSV-1

HSV-2

Bradley JID 2013
PREP-not only for HIV?

- **Caprisa 004**
  - Intervention: Tenofovir intravaginal gel 12 hours pre and post sexual contact in high risk South African women
  - 55% reduction in HSV-2 seroconversion

- **Partners PREP**
  - Interventions: Daily truvada, TDF testing in heterosexual HIV-negative partners in HIV discordant partnerships in Africa
    - 30% reduction in HSV-2 acquisition

- **iPREX**
  - MSM and transgender women randomized to truvada or placebo in USA, South America, South Africa, Thailand
    - No difference in HSV-2 acquisition rates
    - Decreased proportion with ulcers on truvada (~50%)

- **TDF (oral or gel)** in HSV-2 seropositive women did not decrease HSV-2 shedding or lesions in primary analysis

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Abdool Karim NEJM 2015, Celum Ann Int Med 2014
Marcus PloS One 2014, Bender-Ignacio JID 2015
Poll #4: HSV and PrEP

What do you think will happen to HSV-2 seroprevalence in the setting of PrEP among at risk populations?

A. It will increase, similar to epidemiology for syphilis, GC

B. It will decrease due to secondary preventive effect of truvada for HSV-2 infection

C. No change

D. ??????
Poll #5: Treatment of Genital HSV

For patients with a diagnosis of genital HSV

A. Acyclovir/valacyclovir is stocked in the clinic for first episode or episodic treatment and given at the visit

B. A prescription for episodic therapy is provided

C. A prescription for episodic and suppressive therapy is provided

D. No provision for episodic or suppressive therapy
Genital HSV-2 ≠ HSV-1

- HSV-2
- HSV-1: Session 1
- HSV-1: Session 2

Shedding rate

First episode
Symptomatic
Symptomatic
Asymptomatic

Johnston et al, ISSTDR 2017
Discussion Points

- Impact of genital HSV on STD clinic operations
  - Diagnostics
    - Serology
    - Virologic diagnosis
  - Counseling
  - Treatment
    - First episode
    - Recurrences
Optimizing suppressive HSV Tx

- Safe

- Severity of disease, patient preference, transmission risks are the most important aspects
  - Patients need to be aware it is an option

- 48% decreased risk of HSV-2 transmission among discordant heterosexual couples with symptomatic HSV-2
Optimizing episodic HSV Tx

• Clinically significant benefit (20 - 30%)
  • Decreased duration with therapy

• Self-initiation of therapy important
  • Medication needs to be available to patient
    • Prescription on hand
Poll #6: How do you treat genital HSV-1

A. Managed the same as HSV-2

B. Same treatment for first episode/episodic therapy, no suppressive therapy

C. Suppressive therapy if many outbreaks, but not for prevention of transmission

D. No provision for episodic or suppressive therapy
Advocacy from WHO/NIAID

STI Vaccine Roadmap

- Joint WHO/NIAID technical consultation on STI vaccines
- Global roadmap for STI vaccine development
- Critical next steps from pre-vaccine development through vaccine introduction

Available at: http://www.sciencedirect.com/science/journal/0264410X/32/14

Slide courtesy of S. Gottlieb, WHO
The future of the field

- Define correlates of immunity for prophylactic vaccines
- Understand immune factors controlling shedding and recurrences for therapeutic vaccines
- Advocate for vaccines to prevent and treat HSV-1 and HSV-2
- De-risk vaccine investment for HSV/STI