Herpes Simplex Virus
PD-VAC Presentation
9 September 2014

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Herpes Simplex Virus-1 and -2

• Double stranded DNA virus
• Chronic, lifelong infection, persists in trigeminal (HSV-1) or sacral (HSV-1 & HSV-2) ganglia
• Viral reactivation, transmission, and clinical disease may occur throughout the lifespan
• HSV-1 and HSV-2 cause distinct but overlapping clinical syndromes and can be differentiated from each other
Global burden of disease

<table>
<thead>
<tr>
<th>Infection</th>
<th>Clinical manifestations</th>
<th>Disease estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2</td>
<td>535 million infected, infection rapidly acquired at sexual debut</td>
<td>Genital ulcer disease Neonatal HSV HIV</td>
</tr>
<tr>
<td>HSV-1</td>
<td>&gt;90% of population in LMIC, infection in childhood</td>
<td>Herpes labialis Encephalitis Keratitis GUD Neonatal</td>
</tr>
</tbody>
</table>

Seroprevalence estimates are robust worldwide, updated global estimates pending Disease estimates from HIC, lack of data from LMIC HSV will be included next Global Burden of Disease

HSV-2 prevention strategies

- **Antiviral agents**
  - Acyclovir, valacyclovir, famciclovir
    - Episodic: Decrease length of GUD recurrence
    - Suppressive: Daily antiviral therapy decreases risk of GUD and transmission (50%) among HIV-negative, HSV-2 discordant heterosexual couples in North America

- **Male circumcision**
  - Decreased risk of HSV-2 acquisition in men
  - Decreased risk of GUD in men and female partners

- **Condoms**
  - 30% decreased risk of transmission if used all of the time
  - These strategies are not highly efficacious and are not widely available, unlikely to interrupt HSV-2 epidemic
  - No strategies to prevent HSV-1
Unmet Medical Need: HSV-2 infection

- Prevention of GUD
- Prevention of neonatal herpes
- Prevention of HSV-2 transmission-sex partners
- Interruption of HIV epidemic

- Ideally also prevent HSV-1 infection
  GUD, neonatal herpes
  keratitis, encephalitis, herpes labialis

Impact of HSV-2 vaccine on HIV infection

Model: Impact of a HSV-2 vaccine:
70% coverage, 70% efficacy
10 year duration
Decrease HIV incidence by 30-40%

Zhu Nat Med 2009

Freeman et al, Vaccine 2009
### HSV-2 vaccine strategies

<table>
<thead>
<tr>
<th></th>
<th>Prophylactic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Population</strong></td>
<td>HSV-2 seronegative HSV-1 seropos or seroneg Adolescent platform*</td>
<td>HSV-2 seropositive Adolescent/adults</td>
</tr>
<tr>
<td><strong>Goal</strong></td>
<td>Prevent infection –or- Reduce severity of disease 2(^0) endpoint: HIV acquisition</td>
<td>Reduce severity of disease and risk of transmission</td>
</tr>
<tr>
<td><strong>Preferred endpoint</strong></td>
<td>Infection (seroconversion) Disease has been endpoint</td>
<td>Genital shedding and recurrences</td>
</tr>
</tbody>
</table>

If vaccine also prevents HSV-1 infection, may shift to infant platform

### Prophylactic Vaccines

- Over 20,000 participants enrolled in prophylactic vaccine trials

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

- gD2t subunit vaccine with alum/MPL adjuvant
- Enrolled >8000 HSV seronegative women aged 18-30 in North America
  - Vaccine given at months 0, 1 and 6
  - Control vaccine: hepatitis A
  - Study lasted ~7 years
- Primary endpoint: genital herpes disease
  - 70 cases of genital herpes observed:
    - 32 HSV-1 (VE=58%, 95% CI= 12-80%)
    - 38 HSV-2 (VE=-38%, 95% CI=-167-29%)
- 286 HSV-1 or HSV-2 seroconversions observed:
  - 179 HSV-1 and 108 HSV-2

Vaccine efficacy as a function of ELISA titer

First immune correlate of protection against HSV-1 infection
**Lessons from Herpevac**

- **Immune Correlates**
  - Neutralizing antibody is a correlate of protection against HSV-1 infection
  - CD4+ T cell responses not a correlate. CD8+ T cell responses not detected

- **Efficiency**
  - Phase III trial required >8000 participants due to low attack rate (~1%)
    - Consider cohorts with higher incidence for future studies
  - Systematic review: Incidence rates in SSA: median 16/100 py in women

- **Endpoints:**
  - Infection vs. Disease
  - Frequency of shedding in those infected
  - Use in HSV-1 seropositive and seronegative, prevention of HSV-1

**FEASIBILITY of preventing HSV-1 with HSV-2 based vaccine**

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**Therapeutic HSV-2 vaccines: A new paradigm**

- **Endpoint:** Shedding rate pre/post vaccine
- **Participant is compared to themselves**
- **Efficient design, “derisk” investment for industry**
# HSV vaccines currently in clinical trials: The Pipeline

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Candidate</th>
<th>Adjuvant</th>
<th>Current Phase</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic peptide complex with HHSP 70</td>
<td>HerpV 32 peptides</td>
<td>QS-21</td>
<td>II, therapeutic</td>
<td>17% reduction in shedding</td>
</tr>
<tr>
<td>Recombinant subunit</td>
<td>GEN-003 ICP4, gD2</td>
<td>Matrix-M2</td>
<td>II, therapeutic</td>
<td>I/II: 51% reduction in shedding in 30ug dose</td>
</tr>
<tr>
<td>DNA</td>
<td>VCL-H801 gD, UL46/UL46</td>
<td>Vaxfectin</td>
<td>I/II POC therapeutic</td>
<td>Pending</td>
</tr>
<tr>
<td>Replication defective HSV2</td>
<td>HSV529</td>
<td>NA</td>
<td>I, prophylactic therapeutic</td>
<td>Pending</td>
</tr>
<tr>
<td>DNA vaccine</td>
<td>Coridon gD, codon optimized, Ubiquitin tagged</td>
<td></td>
<td>II, prophylactic therapeutic</td>
<td>Elicited cellular responses in Phase 1</td>
</tr>
</tbody>
</table>

Testing in HIC only to date

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# HSV Vaccines: Preclinical Pipeline

<table>
<thead>
<tr>
<th>Candidate Name/Identifier</th>
<th>Replication competent</th>
<th>Replication incompetent</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>OΔNLS-ICP0</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gE2-deletion</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF10 (HSV-1 mutated for UL43, UL49.5, UL55, UL56, LAT)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD472 (HSV-2 mutated for g34.5, UL43.5, UL55-56, US10-12)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CJ-2-gD2 HSV-2 gD dominant negative</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HSV-2 mutated for TK, prime/pull</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Inactivated HSV-2 in MPL/alum</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HSV-1 glycoprotein B lentiviral vector</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Recombinant HSV-1 gB intranasal</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>gD/gC/gE (Trivalent glycoprotein)</td>
<td></td>
<td>X</td>
<td></td>
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HSV Vaccines: Strengths

• Rich pipeline with novel candidates, variety of platforms
  – Efficacy in phase I/II studies of therapeutic vaccines

• Importance of neutralizing antibody and cellular immune response realized

• Prior experience allows optimization of clinical trials design

HSV Vaccines: Weaknesses

• Only 1 prophylactic candidate in phase I clinical trials
  – Therapeutic vaccines are easier to test, smaller design

• Available animal models do not mimic human disease or immune system

• Lack of standardized assays and experimental endpoints

• Need additional data about immune correlates

• Low perception of disease burden

Knipe et al, Vaccine 2014
Role for WHO

• Raise awareness
• Create global case for HSV vaccine
  – Improved disease surveillance in LMIC
    • Ongoing work for neonatal herpes etc
  – Additional modeling of impact to support development of vaccine
• Development of preferred product characteristics

Role for WHO

• Foster collaboration and alliances across disciplines
  – Public-private partnership to advance vaccines
• Encourage investment
• Advocacy
  – Ensure vaccines are developed for use in LMIC, where HSV-2 infections have highest seroprevalence and greatest synergy with HIV
    • Current focus on vaccines in HIC
    • “Derisk” investment for industry