HSV Vaccine Development: Current Progress and Future Directions

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Outline

- Unmet medical need for an HSV vaccine
- Current HSV vaccine strategies and pipeline
- HSV vaccine development and low- and middle-income countries (LMICs)
- WHO facilitation of HSV vaccine development
Herpes Simplex Virus-1 and -2

- Double-stranded DNA virus
- HSV-1 and HSV-2 cause distinct but overlapping clinical syndromes and can be differentiated from each other
- 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
Global burden of HSV-2 infection: 417 million infected & 19 million new cases in 2012

Large global burden of HSV-1 infection, increasing role of genital HSV-1

- Estimated 3.7 billion people aged 0-49 with HSV-1 globally
- Increasingly important cause of genital herpes in high-income countries (HICs)
  - Decline in HSV-1 seroprevalence in childhood in HICs
  - More adolescents susceptible to HSV-1 at sexual debut, transmission via oral sex
- Preliminary estimates: 239 million adults with genital HSV-1

Looker K et al, unpublished data, 2015
HSV-2 infection increases HIV risk

- HSV-2 infection: 3-fold increased risk of acquiring HIV
  - HSV recruits CD4+ target cells to genital tract
- HSV-2/HIV co-infection: more likely to transmit HIV
  - Higher viral loads; high levels of HIV in HSV lesions

- HIV also increases frequency and severity of HSV recurrences: the infections fuel each other

Neonatal herpes

- Relatively uncommon but devastating
  - 60% fatality rate without treatment
  - Long-term neurologic deficits common even with therapy
- Incidence rate ~10/100,000 in HICs
  - Data in LMICs limited
Other consequences of HSV infection

- Genital ulcer disease (GUD)
  - HSV most common cause of GUD worldwide
  - Estimated 40-80 million people globally with symptomatic genital HSV-2

- Psychosocial / quality of life issues
  - Impact on sexual relationships

- Keratitis, encephalitis, herpes labialis (HSV-1)
Current HSV-2 prevention strategies insufficient

- Antiviral agents: acyclovir, valacyclovir, famciclovir
  - Episodic: Decrease length of GUD recurrence
  - Suppressive: Daily antiviral therapy decreases risk of GUD and transmission (50%) among heterosexual couples in North America; no benefit in decreasing HIV risk
- Male circumcision
- Condoms: 30% decreased transmission risk if used all the time
- These strategies are not highly efficacious and not widely available, unlikely to interrupt HSV-2 epidemic
- No strategies to prevent HSV-1
Why We Need an HSV Vaccine: The Consequences of Genital HSV Infection

- Lifelong recurrent episodes of painful genital lesions
- Increased likelihood of HIV transmission and acquisition
- Risk of vertical transmission to fetus or neonate that can result in neonatal brain damage or death
Why we need an HSV vaccine: Potential benefits

- Prevention of genital ulcer disease
- Prevention of HSV sexual transmission
- Prevention of neonatal herpes/lower mortality in children under five in the neonatal period
- Important tool to interrupt HIV transmission
- Ideally could also impact huge burden of HSV-1
Previous HSV vaccine efforts
Previous prophylactic vaccine trial

- gD subunit vaccine with alum/MPL adjuvant
- Enrolled >8000 HSV-1/2 seronegative women aged 18-30
  - Vaccine given at months 0, 1 and 6
  - Follow-up for 20 months
- 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%)
- Secondary endpoint: HSV infection
  - 286 seroconversion
    - 179 HSV-1
    - 108 HSV-2

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

- First evidence for correlate of protection against HSV-1 infection

Belshe et al, JID 2014
Current vaccination strategies and pipeline
# HSV vaccine strategies

<table>
<thead>
<tr>
<th>Concept</th>
<th>Prophylactic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Population</strong></td>
<td>High risk HSV-2 seronegative 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</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
Benefits of a Prophylactic HSV Vaccine

Individual Benefits
- Decreased risk of infection
- Remains free of negative psychosocial impact
- Decreased risk of acquiring HIV

Societal Benefits
- Decreased cost of medical care
- Interrupt the cycle of transmission
- Decreased risk of maternal transmission of HSV
Benefits of a Therapeutic HSV Vaccine

**Individual Benefits**
- Decreased shedding
- Decreased number of outbreaks
- Decreased probability of transmission to partners

**Societal Benefits**
- Decreased cost of medical care
- Decreased risk of acquiring HIV
- Interrupt the cycle of transmission
- Decreased risk of maternal transmission of HSV and HIV

**Partner Benefits**
- Decreased risk of infection
- Remains free of negative psychosocial impact

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HSV Positive

Vaccine suppresses viral load

HSV Negative Partner
## HSV vaccines currently in clinical trials: The Pipeline

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Company</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>Agenus</td>
<td>HerpV 32 peptides</td>
<td>QS-21</td>
<td>II, therapeutic</td>
<td>17% reduction in HSV shedding</td>
</tr>
<tr>
<td>Recombinant subunit</td>
<td>Genocea</td>
<td>GEN-003 ICP4, gD2</td>
<td>Matrix-M2</td>
<td>II, therapeutic</td>
<td>60 microgram dose + 75 microgram of Matrix-M2 = 55% reduction in shedding</td>
</tr>
<tr>
<td>DNA</td>
<td>Vical</td>
<td>VCL-HB01 gD, UL46/UL46</td>
<td>Vaxfectin</td>
<td>I/II POC therapeutic</td>
<td>Pending</td>
</tr>
<tr>
<td>Replication defective HSV2</td>
<td>Sanofi</td>
<td>HSV529</td>
<td>NA</td>
<td>I, prophylactic therapeutic</td>
<td>Pending</td>
</tr>
<tr>
<td>DNA vaccine</td>
<td>Coridon</td>
<td>Coridon gD, codon optimized</td>
<td>Ubiquitin tagged</td>
<td>II, prophylactic therapeutic</td>
<td>Elicited cellular responses in Phase 1</td>
</tr>
</tbody>
</table>
# HSV Vaccines: Preclinical Pipeline

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>PI/Institution/Company</th>
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<tbody>
<tr>
<td><strong>Subunit</strong></td>
<td></td>
</tr>
<tr>
<td>gD/gC/gE (Trivalent glycoprotein)</td>
<td>Friedman, University of Pennsylvania</td>
</tr>
<tr>
<td>HSV-2 gD with nanoemulsion</td>
<td>NanoBio</td>
</tr>
<tr>
<td><strong>Live attenuated, replicating virus</strong></td>
<td></td>
</tr>
<tr>
<td>0ΔNLS-ICP0</td>
<td>Halford, Southern Illinois University</td>
</tr>
<tr>
<td>AD472 (HSV-2 mutated for g34.5, UL43.5, UL55-56, US10, US11, US12)</td>
<td>MedImmune</td>
</tr>
<tr>
<td>HSV-2 mutated for TK, prime/pull</td>
<td>Iwasaki, Yale University</td>
</tr>
<tr>
<td><strong>Inactivated virus</strong></td>
<td></td>
</tr>
<tr>
<td>Inactivated HSV-2 in MPL/alum</td>
<td>Spector, University of California San Diego</td>
</tr>
<tr>
<td><strong>Live attenuated, non-replicating virus</strong></td>
<td></td>
</tr>
<tr>
<td>HSV-2 deleted in gD</td>
<td>Jacobs and Harold, Albert Einstein College of Medicine</td>
</tr>
<tr>
<td><strong>Peptide</strong></td>
<td></td>
</tr>
<tr>
<td>HerpV mixture of synthetic peptides representing HSV-2 antigens</td>
<td>Agenus</td>
</tr>
<tr>
<td><strong>Prime-boost</strong></td>
<td></td>
</tr>
<tr>
<td>HSV-2 gD, DNA prime followed by a liposome-encapsulated antigen boost</td>
<td>BRM</td>
</tr>
</tbody>
</table>
Therapeutic vaccines likely to be available first

- Encouraging results from current trials
- Advancing to further trials
- Advantages
  - Shorter clinical trial duration
  - Potential path to licensure in 5 years
  - Easy to identify target population
Therapeutic HSV-2 vaccines: A new paradigm for evaluation

- Endpoint: Shedding rate pre/post vaccine
- Participant is compared to themselves
Key questions

- What are the population benefits of a therapeutic vaccine?
- What impact would a therapeutic vaccine have on HIV acquisition and transmission?
- What can we learn from advancing therapeutic vaccines to inform/facilitate development of prophylactic vaccines?
- How will therapeutic vaccine development for HICs be applicable to LMICs?
HSV vaccines and LMICs
HSV burden highest in LMICs with high HIV rates, especially sub-Saharan Africa

Considerations for vaccine strategies for LMICs: Prophylactic vaccines

- Prophylactic vaccines likely the best strategy for LMICs in terms of benefits to individuals and society
  - HSV infection linked to HIV risk, regardless of symptoms
  - Preventing infection ideal

- However:
  - Timeline of development is lengthy
  - Hurdle of previous trials to overcome
Considerations for vaccine strategies for LMICs: Therapeutic vaccines

- Therapeutic vaccines more advanced
  - Timeline to possible licensed vaccine on 5 year horizon
  - Industry investment due to HIC market opportunity
  - Benefits to individual and to society
- Impact on HIV acquisition and transmission unknown
WHO facilitation of HSV vaccine development
Joint WHO and NIAID STI Vaccine Roadmap

- May 2012 - World Health Assembly endorsed the Global Vaccine Action Plan
- April 2013 - WHO and NIAID convened a Technical Consultation on STI Vaccine Development and Introduction
- Focus was five most common STIs
  - HSV
  - *Chlamydia trachomatis*
  - *Neisseria gonorrhoeae*
  - *Trichomonas vaginalis*
  - *Treponema pallidum* (syphilis)
- Identified gaps in knowledge
- Developed a Roadmap to move forward
Global roadmap for STI vaccine development

- Critical next steps from pre-vaccine development through vaccine introduction
Current status of the development pathway of STI Vaccines

Basic Research
- Trichomonas vaginalis
- Treponema pallidum (syphilis)

Preclinical Development
- Chlamydia trachomatis vaccine
- Neisseria gonorrhea vaccine

Clinical Evaluation

Second generation HSV vaccines
- HerpV (synthetic peptide complex with HHSP 70)
- GEN-003 (recombinant subunit)
- VCL-HB01 (DNA vaccine)
- HSV529 (Replication defective HSV2)
- Coridon (DNA vaccine)

First generation HSV vaccines
- Chiron (gD2, gB2 and MF59 adjuvant)
- GSK (gD2 and alum MPL adjuvant)

= therapeutic vaccine
HSV within the STI Vaccine Roadmap: What has been done

- Updated global HSV estimates: HSV-2 estimates published 2015, first ever HSV-1 & neonatal herpes estimates underway
- NIAID workshops and working groups
  - Reagents, animal models, assays, etc.
- WHO Consultation on HSV Vaccine Impact Modelling
  - Recommendations on critical modelling needs, March 2015
- Comprehensive HSV vaccine business case work plan
How can WHO advance HSV vaccine development in the future?

- Preferred product characteristics
- Consensus-building on key endpoints for clinical trials
- Consensus-building on steps needed to evaluate therapeutic vaccines in LMICs
- Better primary data on neonatal herpes in LMICs
- Coordination of updated modeling of the impact of HSV vaccine
  - Incorporating HIV incidence, neonatal herpes, HSV-1 in models
  - Modelling therapeutic and prophylactic vaccines in LMICs
Acknowledgments

- Sami Gottlieb
- Nathalie Broutet
- Birgitte Giersing

- Christine Johnston
- Joshua Schiffer
- Anna Wald

World Health Organization

National Institute of Allergy and Infectious Diseases

NIH
Further Reading