Herpes Simplex Virus (HSV) Vaccine Development Update

Sami Gottlieb, MD, MSPH
World Health Organization

Carolyn Deal, PhD
U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases
Outline

- Epidemiology and roadmap activities
- HSV vaccine pipeline and early clinical trials
- Next steps: opportunities for WHO engagement
Impact of Genital Herpes: The Case for a Vaccine

Leading cause of genital ulcer disease worldwide

HIV-1 acquisition and transmission

Impact on sexual and reproductive health

HSV-2

HIV

Neonatal herpes

World Health Organization

National Institute of Allergy and Infectious Diseases
HSV-2 Estimates: 417 Million Infections Globally in 2012

Large Global Burden of HSV-1 Infection, Increasing Role of Genital HSV-1

3.7 billion*
HSV-1 infection (mostly oral)

*0-49 year-olds

>0.5 billion#
Genital HSV (mostly HSV-2)

#15-49 year-olds

140 million genital HSV-1 infections (mainly HICs)

Better data on neonatal herpes
- WHO global estimates
- Primary data in LMICs

Preferred product characteristics (PPCs)

HSV vaccine value proposition (investment case)
- Updated modelling
- HSV-HIV interaction
WHO Global Neonatal Herpes Estimates: Roughly 14,000 Cases Annually

Looker K et al, Lancet Global Health, 2017
Neonatal Herpes Implications

- Several reasons true numbers may be higher for LMICs
  - Estimates used U.S. transmission risks: took into account prevention measures
  - Higher HIV prevalence areas: increased HSV shedding

- Less infrastructure: neonatal herpes may be missed, 60% fatality rate without treatment

- Need for better primary data in LMICs
  - CHAMPS Network
  - Better understanding of underlying HSV-1 epidemiology/genital HSV-1
HSV Vaccine PPCs: First Expert Consultation Meeting, March 2017

- Overarching strategic public health goals
  - In high prevalence areas, reduce HSV-related HIV infection
  - Globally, reduce HSV disease, including neonatal herpes and effects on sexual and reproductive health

- Separate PPCs for prophylactic and therapeutic vaccines
  - Prophylactic ideal for LMICs but therapeutic available first
  - TVs designed for HICs might also have role in LMICs

- Important considerations related to HSV types, target populations, and infection and disease endpoints
Timeline for developing PPCs for HSV vaccines

Baseline analysis to establish priority public health goals
(29-30th March 2017)

PDVAC PPC Working Group
June 2017

Public Consultation
Q1 2018

PDVAC, Finalise, Update
June 2018

Publish on WHO website
Q4 2018
HSV Vaccine Value Proposition

Reviews and global estimates

Burden of disease and costs (without vaccine)

Vaccine impact modelling

Burden of disease and costs (with vaccine)

PPCs

Vaccine costs Including delivery

Value proposition

Public health and economic rationale
WHO Report

Modelling efforts needed to advance herpes simplex virus (HSV) vaccine development: Key findings from the World Health Organization Consultation on HSV Vaccine Impact Modelling

Sami L. Gottlieb, Birgitte Giersing, Marie-Claude Boily, Harrell Chesson, Katharine J. Looker, Joshua Schiffer, Ian Spicknall, Raymond Hutubessy, Nathalie Broutet, WHO HSV Vaccine Impact Modelling Meeting Working Group

World Health Organization (WHO), Geneva, Switzerland
Imperial College, London, UK
Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA
University of Bristol, UK
University of Washington, Seattle, WA, USA
STIMA: HSV-2 Prevalence Among Women Age 25-49 in Sub-Saharan Africa

Unpublished data, 2017
Updated Meta-Analysis of HSV-2 and HIV Acquisition: 57 Studies

- Prevalent HSV-2 → 3x risk of HIV acquisition
- Highest risk with incident HSV-2
- HSV-2 vaccines have potential for benefit against HIV

Looker et al. Manuscript under review, 2017
Outline

- Epidemiology and roadmap activities
- HSV vaccine pipeline and early clinical trials
- Next steps: opportunities for WHO engagement
HSV Vaccines Currently in Clinical Trials

Currently in development:

- At least 25 including:
  - big pharma
  - biotech
  - academic

- At least 1 including:
  - Sanofi Pasteur

- At least 4 including:
  - Admedus
  - Agenus
  - Genocea
  - Vical

Phases of development:

- Discovery & exploratory stage
- Preclinical stage
- Phase I clinical studies
- Phase II clinical studies
- Phase III clinical studies
- Marketing authorization

Introduction & post-marketing evaluation
# HSV Vaccines Currently in Clinical Trials

<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 shedding; 75% reduction in viral load</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% reduction in lesion rate; 55% reduction in shedding</td>
</tr>
<tr>
<td>DNA vaccine</td>
<td>Vical</td>
<td>VCL-HB01 gD, UL46/UL46</td>
<td>Vaxfectin</td>
<td>II, therapeutic</td>
<td>Significant reduction in viral load; 57% reduction in lesions at 9 months</td>
</tr>
<tr>
<td>Replication defective HSV-2</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>Amedus (Australia)</td>
<td>Amedus gD, codon optimized</td>
<td>Ubiquitin tagged</td>
<td>II, therapeutic</td>
<td>Interim data expected soon</td>
</tr>
</tbody>
</table>
GEN-003: Description

- **Two antigen, subunit vaccine (60 µg each antigen)**
  - GB208: 39.2 kD fragment of Infected Cell Protein 4 (ICP4.2)
  - GB217: gD with transmembrane section removed
- **Matrix-M2™ adjuvant (50 µg per dose)**
  - ISCOM (immune stimulating complexes)-based (Novavax)
  - Mixture of saponin fractions A and C
- **Administered intramuscularly, 0.5 mL**
Design Overview for GEN-003 Clinical Studies to Date

**Data Collected**
- Swabbing
  - Baseline Shedding
  - Follow-up Shedding
- Blood Sample
  - Vaccine Dosing
  - Immune Monitoring
- Lesion Diary
  - Phase 1/2a & Phase 2 – paper diaries during swabbing periods
  - Phase 2b – daily electronic reporting of lesions every day for year

**Scheduled Events**
- Viral Shedding
- T cell and B cell Immunogenicity

**Endpoint**
- Clinical Endpoints

- Inclusion Exclusion criteria
  - Adults 18-50 with genital HSV-2 infection and history of 3-9 recurrences/year
  - Subjects on suppressive antivirals undergo washout period before dosing
- Safety: Independent Data Monitoring Committee

---

Slide source: S. Hetherington
GEN-003-003: Reduction in Viral Shedding After Dose 3

Reduction in Viral Shedding Rate vs. Baseline

- Placebo: 6%
- 60/50 µg: -40%
- 60/75 µg: -27%

p-values:
- vs. baseline: 0.03
- vs. placebo: 0.05

*Poisson model with empiric variance

Slide source: S. Hetherington
GEN-003-003: Genital Lesion Rate Reduction Over 6 Months

![Bar graph showing post-treatment genital lesion rate% for Placebo, 60/50 µg, and 60/75 µg groups.]

- Placebo: Median 5.6, Mean % reduction vs. placebo: 41%
- 60/50 µg: Median 2.7, Mean % reduction vs. placebo: 52%
- 60/75 µg: Median 1.9, Mean % reduction vs. placebo: 66%

Wilcoxon Rank Sum test vs. placebo * p<0.05
Vical Vaccine Candidates

- Bivalent
- Monovalent

UL46 + US6

Codon-optimized genes

Tegument Protein VP11/12
Glycoprotein D

Full-length HSV-2 proteins

Vaxfectin® Liposomes

1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine

Slide source: M. Mammen
Cohort C Design and Endpoints

Comparing swabbing periods – participant serves as own control

- **Primary endpoints**
  - Safety and tolerability
  - Change in shedding rate by UW PCR assay

- **Key secondary endpoints**
  - Change in viral load (shedding)
  - Change in lesion rate
  - Immunogenicity
HSV-2 Replication-Defective Vaccine: dl5-29

- HSV-2 dl5-29 developed by David Knipe (Harvard)
- Deleted for two genes (UL5, UL29) required for virus replication

Dudek & Knipe, Virology 2006
The HSV529 Vaccine Trial

- Phase I randomized, double-blind, placebo-controlled study of replication-defective HSV-2 \( dl5-29 \)

- Healthy adult subjects 18-40 years of age with or without HSV infection

- Objective: To evaluate the safety and immunogenicity of 3 intramuscular injections of HSV529 compared to placebo.

Dropulic L, Cohen J
Sanofi Pasteur
# HSV529 Trial Subject Dosing and Schedule of Events

## Dose and Dosing Schedule

<table>
<thead>
<tr>
<th>Dose pfu*</th>
<th>HSV 1±/ 2+</th>
<th>HSV 1-/2-</th>
<th>HSV 1+/2-</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1 \times 10^7$</td>
<td>Vaccine</td>
<td>Placebo</td>
<td>Vaccine</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>15</td>
<td>5</td>
</tr>
</tbody>
</table>

## Schedule of Events

- **Screening**: Days 0, 30, 180
- **Vaccine Dosing**: Days 0, 30, 180
- **Immune Monitoring**: Days 30, 187
- **Shedding Evaluation**: Days 210, 360
- **Study Day**: Days 0, 30, 180, 210, 360

---

[NIH National Institute of Allergy and Infectious Diseases]
CORE TECHNOLOGY

- Uses a combination of:
  - Intra-dermal delivery
  - Proprietary codon optimisation Coricode®
  - Ubiquitin encoding sequence added to help stimulate the T-cell response Corimmune®
- Core is mix of ubiquitination and non-ubiquitination plasmids
  - 1:1 plasmid combination used clinically to date
- Worldwide, sub-licensable license to NTC plasmid for codon delivery
- Dosed in two clinical studies
  - 20 patient Phase I & 44 patient Phase IIa
HSV-2 VACCINE PHASE IIA STUDY DESIGN

45 day Baseline

0 wk 4 8 Post-vax 24 Post-boost 48

Baseline Post-vax Pre-boost Post-boost

= Dose = Serum & PBMCs measurements = Punch biopsy timing

Slide source: N. Finlayson
VIRAL SHEDDING RATE COMPARED TO BASELINE

- No safety issues raised to date
- 58% decrease in viral shedding post booster
  - Steady decline from baseline
- All follow-up visits completed and results by 1H, CY’17

% Shedding rate reduction F20

<table>
<thead>
<tr>
<th>Reduction in per-person HSV-2 Sheding Rate (days/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to post-vax</td>
</tr>
<tr>
<td>Baseline to post-boost</td>
</tr>
</tbody>
</table>

Slide source: N. Finlayson
Outline

- Epidemiology and roadmap activities
- HSV vaccine pipeline and early clinical trials
- Next steps: opportunities for WHO engagement
Next Steps: Opportunities for WHO Engagement

- Finalize PPCs for prophylactic & therapeutic HSV vaccines
- Support development of HSV vaccine value proposition
- Fill data gaps to inform value proposition and PPCs
  - Coordination of HSV vaccine impact modelling, incorporating HIV, neonatal herpes, HSV-1
  - Collaboration with CHAMPS project to obtain better primary data on neonatal herpes in LMICs
  - Better data on costs of HSV in LMICs
Thank you

World Health Organization

- Nathalie Broutet
- Birgitte Giersing

NIH

- Amanda Coleman
- Hagit David
- Leah Vincent

University of Washington

- Christine Johnston
- Anna Wald

Consultants

- Julian Hickling
- Rebecca Jones
- Sachin Silva