Update on STI vaccines and implications for HIV

Sinead Delany-Moretlwe
SA HIV Clinicians Society Conference 2014
Overview

• The need for STI vaccines

• Current vaccines and applications in the context of HIV
  – E.g. HPV

• Future vaccines
The case for STI vaccines
WHO estimates 499 million new cases of curable STIs in 2008.
Significant global burden of disease associated with curable STIs

• Individual curable STIs, 2008

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia</td>
<td>106 million</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>106 million</td>
</tr>
<tr>
<td>Syphilis</td>
<td>11 million</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>276 million</td>
</tr>
</tbody>
</table>

• Overall, numbers not decreasing compared with 2005 estimate of 448 million

• In all cases, highest incidence in **sub-Saharan Africa region**

• The majority of infections are asymptomatic

Syphilis RPR Positivity - Antenatal Attendees by WHO Region (2008-09)

Viral STIs: large proportion of prevalent STIs

- HSV-2 infection affects an estimated 536 million people globally
- An estimated 291 million women have HPV infection at any point in time
  - Numbers of men likely similar
- Approximately 360 million people suffer chronic HBV infections
  - Most acquired perinatally
- Significant burden in populations with HIV
Neglected STIs are a significant cost to already constrained health systems

- **HPV** cause 3·3 million disability adjusted life years (DALYs)
  - included in estimates of mortality and morbidity due to cancer rather than STIs

- **Syphilis** is responsible for 4·2 million DALYs.
  - Effective screening programmes infant mortality at a cost per DALY that is lower than prevention of a case of perinatal HIV infection.

- **Chlamydia and gonorrhoea** cause 7 million DALYs as a result of cause tubal infertility and, potentially fatal, ectopic pregnancy.

- **Vaginal discharge** prompts women to seek frequent care, which is expensive, often ineffective, and sometimes harmful.
  - Candida and bacterial are not included in the burden of disease calculations.

Source: Low, Lancet 2006
Untreated STIS impact on achieving the Millennium development goals
Epidemiological synergy – STIs increase HIV transmission

• HSV-2
  – 3-fold increase HIV risk
  – Increased shedding in HIV positives

• Urethritis/cervicitis
  – 2-3 fold increased risk
  – More prevalent

• Treatment of curable STIs of limited value for population level reductions in incidence
  – Beneficial for individuals
Currently available vaccines
HPV vaccines are highly effective

- Efficacy = prevention of new infection and/or disease caused by vaccine-associated types (fully vaccinated women aged 16-26)

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine</th>
<th>No of subjects</th>
<th>Endpoints</th>
<th>Vaccine efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munoz, 2010</td>
<td>6/11/16/18</td>
<td>4616/4689</td>
<td>CIN 2/3, (AIS), VIN 2/3, VAIN 2/3, GW</td>
<td>100 (90-100) 95 (70-100)</td>
</tr>
<tr>
<td>Lehtinen, 2011</td>
<td>16/18</td>
<td>5824/5820</td>
<td>CIN3+, (AIS)</td>
<td>100 (85-100)</td>
</tr>
</tbody>
</table>

Vaccine efficacy against non-vaccine types more limited: Bivalent > quadrivalent

Since these initial trials with 3 doses, vaccines have been licensed for two doses
HPV vaccines are safe

• Trials (Lu, 2011)
  – Systematic review and analysis of 44,142 females
  – Safe with no evidence of difference in risk
    • SAE RR: 1.00 (0.91-1.09); vaccine-related SAE RR: 1.82; 0.79-4.20

• Post-licensure (Gee, 2011)
  – Assessment of 600,558 doses of quadrivalent vaccine from 7 managed care organisations
  – No vaccine related risk associated with prespecified outcomes including Guillian-Barre Syndrome, thrombo-embolic disease, appendicitis and allergic reactions

• WHO Global Advisory Committee on Safety continues to monitor (statement March 2014)
HPV vaccines can be used safely in HIV positive populations

Women aged 18-25 years
- Vaccine safe and immunogenic in HIV positive women
- All HIV positive women seroconverted for HPV 16/18
- Antibody levels>natural immunity
- Sustained anti-HPV 16/18 CD4+ T-Cell responses inducted
- No association between immune response and CD4+ count or viral load
- Similar results in other studies of quadrivalent vaccine (Levin 2010, Wilkin 2010)

Denny, Vaccine 2013
Lessons learnt from HPV vaccine implementation – relevance for HIV vaccines

• South Africa 1st dose
  – 91% school coverage,
  – 87% learner coverage,
  – > 340,000 Grade 4 girls were vaccinated in over 15,000 schools in South Africa in the period March 10 - April 23 2014.
  – No major adverse events
Lessons learnt from HPV vaccine implementation – relevance for HIV vaccines

• South Africa 1st dose
  – 91% school coverage,
  – 87% learner coverage,

Should we vaccinate boys?
Who else might benefit?

March 10 - April 23 2014.
  – No major adverse events
Age-dependent decrease in GW in Australian women after vaccine introduction in 2007
Herd immunity: **declines in incidence** of GW in **heterosexual men** after 2007.
No benefits for herd immunity from MSM
No benefits for herd immunity from MSM

Consider targeted vaccination of higher risk populations e.g. HIV positive MSM, HIV positive women

Ali H et al. BMJ 2013;346:bmj.f2032
Longer term - potential value of vaccination for HIV prevention?

- 8 studies
  - RR Women 2.06
  - Association also in M
  - Similar for HR and LR
  - PAF 21-37%

Houlihan, 2012
Progress on future vaccines
HSV-2 vaccines – the need

• Significant morbidity

• Risk of vertical transmission

• Risk of HIV acquisition, transmission and disease progression
Limited prevention options with public health impact
Limited prevention options with public health impact

No benefit of HSV-2 treatment on HIV acquisition and transmission
The immune response to HSV-2

• Animal models limited
  – No good models for recurrences or severity

• Human host/virus interactions poorly understood
  ? Control of viral reactivation
  ? Promotes viral clearance
Early prophylactic vaccine trials

Recombinant glycoproteins

<table>
<thead>
<tr>
<th>gD</th>
<th>gB</th>
<th>gH</th>
<th>gL</th>
</tr>
</thead>
</table>


Early prophylactic vaccine trials

Recombinant glycoproteins

<table>
<thead>
<tr>
<th>gD</th>
<th>gB</th>
<th>gH</th>
<th>gL</th>
</tr>
</thead>
</table>

HSV-2 discordant couples and STD clients

gB2/gD2 + Oil/water | nAb +++ | CD4+ +++ | Did not protect
Early prophylactic vaccine trials

Recombinant glycoproteins

<table>
<thead>
<tr>
<th>gD</th>
<th>gB</th>
<th>gH</th>
<th>gL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- gB2/gD2 + Oil/water
  - nAb +++
  - CD4+ +++
  - Did not protect

- gD2/alum/MPL
  - nAb +++
  - CD4+ +++
  - Protection in subgroup of HSV-1 negative women
• 8323 sexually active HSV-1/HSV-2 negative women
• 3 doses of gD2 vaccine or control

• No protection vs. HSV-2 infection or disease
  – *But significant decrease in HSV-1 infection and genital disease*
  – *Lower antibody titres associated with HSV-1 acquisition*
  – *Magnitude of CD4+ cell response not associated with prevention*
  – *CD8+ responses not detected*
### HSV-2 vaccines: lots in the pipeline

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Name</th>
<th>Construct</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2 functionally mutated for ICP0 [95]</td>
<td>0ΔNL5</td>
<td>Replication-competent whole virus</td>
<td>Preclinical</td>
</tr>
<tr>
<td>HSV-1 functionally mutated for UL43, UL49.5, UL55, UL56, and IAT expression [96]</td>
<td>HF10</td>
<td>Replication-competent whole virus</td>
<td>Preclinical</td>
</tr>
<tr>
<td>HSV2 glycoprotein E deletion mutant [98]</td>
<td>HSV2 gE mutant</td>
<td>Replication-competent whole virus</td>
<td>Preclinical</td>
</tr>
<tr>
<td>HSV-2 functionally mutated for γ34.5, UL43.5, UL55-56 US10, US11, US12 [99]</td>
<td>AD472</td>
<td>Replication-competent whole virus</td>
<td>Preclinical</td>
</tr>
<tr>
<td>HSV-2 functionally mutated for UL5/UL29 [100–102]</td>
<td>ACAM-529/HSV529 CJ2-gD2</td>
<td>Replication-competent whole virus</td>
<td>Preclinical</td>
</tr>
<tr>
<td>HSV-2 glycoprotein D dominant negative, functionally mutated for ICP0/UL9 [104]</td>
<td>ACAM-529/HSV529</td>
<td>Replication-competent whole virus</td>
<td>Preclinical</td>
</tr>
<tr>
<td>HSV-2 functionally mutated for thymidine kinase (TK) [39]</td>
<td>ACAM-529/HSV529 CJ2-gD2</td>
<td>Replication-competent whole virus, followed by topical vaginal application of CXCL9 and CXCL10</td>
<td>Phase I</td>
</tr>
<tr>
<td>HSV-2 functionally mutated for ICP10 [86,113]</td>
<td>ICP10ΔPK</td>
<td>Replication-competent whole virus</td>
<td>No active program, has been in phase I/II, therapeutic</td>
</tr>
<tr>
<td>HSV-2 functionally mutated for ICP47, vhs, γ34.5, US5, UL43 [114]</td>
<td>ImmunoVEXHSV2</td>
<td>Replication-competent whole virus</td>
<td>Phase I</td>
</tr>
<tr>
<td>Inactivated HSV-2 in MPL/alum [105,106]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV-1 glycoprotein B [107]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant secreted HSV-1 glycoprotein B [109]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant HSV-2 gD [45]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant HSV-2 gD [110]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gD2/UL46/UL47 DNA [108]</td>
<td>gD2-Vaxfectin</td>
<td>Plasmid gD2/UL46/UL47 polyvalent DNA with cationic lipid adjuvant</td>
<td>Phase I therapeutic announced</td>
</tr>
<tr>
<td>Modified gD2 DNA [115]</td>
<td></td>
<td>Plasmid gD2 fused to ubiquitin mixed with codon-optimized non-linked gD2</td>
<td>Phase I</td>
</tr>
<tr>
<td>32 unique 35-mer HSV-2 peptides [112]</td>
<td>HerpV</td>
<td>Synthetic peptides, multivalent with heat shock protein adjuvant</td>
<td>Phase II, therapeutic</td>
</tr>
<tr>
<td>gD2 and ICP4 [66]</td>
<td>GEN-003/MM2</td>
<td>Recombinant bivalent proteins with liscamatrix adjuvant</td>
<td>Phase 1b/II, therapeutic</td>
</tr>
</tbody>
</table>
An HSV-2 vaccine has the potential to prevent HIV infection

• Potential to reduce HIV infection, especially in young women
  – Incidence in young women

• Future vaccine trials likely to be conducted in settings like South Africa
  – High prevalence and incidence
  – Need populations that are HSV-1 positive/negative
  – Need to assess potential of different strain effects

• Future trials will focus on demonstrating effects by gender, on seroconversion and shedding
  – Even low prevention effect but high control of reactivation may have benefits for transmission and impact on HIV
• Significant technical difficulties with the development of vaccines for CT, NG, TV and TP
• Some progress with animal studies
Development of vaccines against STIs – importance for HIV

• Decade of vaccines
  – WHO global commitment to fund the development of vaccines for neglected STIs

• Significant benefits for maternal, child and reproductive health

• Existing vaccines already demonstrate benefits for HIV positive populations

• Lessons learned from delivery are critical for the eventual development of an HIV vaccine

• Future vaccines may be an important components of a package for HIV prevention