Immunization in HIV-infected Adults

Marc Mendelson
Division of Infectious Diseases & HIV Medicine
Groote Schuur Hospital, University of Cape Town
Outline of the talk

• Vaccine type as a determinant of response

• Why does HIV present a problem?

• Principles for immunization of adults with HIV

• Missed opportunities to vaccinate
## Types of Vaccine

<table>
<thead>
<tr>
<th>Live attenuated</th>
<th>Inactivated</th>
<th>Toxoid / Other</th>
<th>Polysaccharide</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Hepatitis A</td>
<td>Diphtheria</td>
<td>Hib</td>
</tr>
<tr>
<td>Influenza (intranasal)</td>
<td>Influenza</td>
<td>Hepatitis B (protein)</td>
<td>Hib-conjugate</td>
</tr>
<tr>
<td>Measles</td>
<td>Pertussis (Whole cell)</td>
<td>Human Papillomavirus (VLP)</td>
<td>Meningococcal</td>
</tr>
<tr>
<td>Mumps</td>
<td>Polio (inactivated, IPV)</td>
<td>Pertussis (acellular)</td>
<td>Meningococcal-conjugate</td>
</tr>
<tr>
<td>Rubella</td>
<td>Rabies</td>
<td>Tetanus</td>
<td>Pneumococcal (PPV)</td>
</tr>
<tr>
<td>Polio (Oral)</td>
<td></td>
<td></td>
<td>Pneumococcal-conjugate (PCV)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td></td>
<td></td>
<td>Typhoid</td>
</tr>
<tr>
<td>Varicella</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yellow Fever</td>
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</tbody>
</table>
T-dependent antibody production

DC migration to Regional LN
T-dependent antibody production

Amplification of the Ag-specific T-cell response
T-dependent antibody production
T-dependent antibody production

Lymph Node Germinal Centre

T-cell help

FDC

Massive Clonal Expansion
T-dependent antibody production

Massive Somatic Mutation within variable region of the Ig genes
T-dependent antibody production

Generating of a minority of Ig
With INCREASED affinity for Ag

B cells efficiently compete for binding to small amounts of vaccine Ag on FDCs

Process vaccine antigens into small peptides expressed on B cell surface with MHC class II
T-dependent antibody production

Selection, proliferation & survival of B cells with the highest Ag-specific affinity

Differentiation signals drive plasma cell development & secretion of specific antibodies or memory B cells
HIV-induced immune suppression reduces vaccine responses

- Reduced CD4 T cell help
- Reduced Dendritic cell responses
- Reduced B cell numbers and function
- Reduced antibody production
Principles of immunization in HIV-infected adults

• Vaccination is associated with HIV viral load blip and transient reduction in CD4 count
• Avoid live vaccines if CD4 count < 200 cells/mm$^3$
MMR Vaccination

- Indicated for measles IgG seronegative persons
- Avoid pregnancy for 1 month post-vaccination
- Breast feeding is not contraindicated
- Safe for household contacts
- Contraindicated CD4 <200

Yellow Fever Vaccination

- Increased neurotropic and viscerotropic adverse disease events in persons with CD4 <200
- Well tolerated with seroconversion rate ~ 85% in persons with CD4 >200
- Transient drop in CD4 count and rise in HIV viral load
- Adverse event reporting increases > 60 years age (x6)

Other Live Vaccines

Ty21a Oral Typhoid
- Contraindicated
- Use inactivated Typhoid ViCPS

Varicella Zoster
- Contraindicated if CD4 <200 cells/mm³
- Indicated in clients if CD4 >200 cells/mm³
- Avoid pregnancy for 1 month

Poliomyelitis, oral
- Contraindicated
- Use inactivated vaccine instead
- Contraindicated in household contacts
Principles of immunization in HIV-infected adults

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- Avoid live vaccines if CD4 count < 200 cells/mm$^3$
- Polysaccharide vaccines elicit poor antibody responses
T-independent antibody production

Marginal Zone

Bacterial Polysaccharide Antigens
T-independent antibody production

Non-mutated, low-affinity ‘germline’ Abs
Move towards red pulp of spleen – apoptosis
Short-lived response
Conjugating polysaccharide with protein induces a T-dependent antibody response

Pneumococcal Vaccines

- 10-300 x more susceptible to invasive pneumococcal disease (IPD)
- 25% risk of recurrent IPD within 12 months
- 2-3 fold reduction IPD in persons on ART, but still ~35 x greater than general population

Pneumococcal Polysaccharide Vaccine (PPV-23)

- HIV-infected adults with CD4 >200 cells/mm$^3$ as soon as possible after diagnosis
- Elicits modest antibody responses, lower than healthy controls
- Ugandan RCT
  - increase pneumonia in 6-month period in those not on ART
  - 16% overall reduction all cause mortality
- Meta-analysis – marked heterogeneity in efficacy with no overall benefit

Pneumococcal Conjugate Vaccine (PCV-7, PCV-13)

- Greater immunogenicity than PPV
- Low coverage of IPD-causing strains necessitates use of PPV-23 in addition to PCV
- More durable antibody response on ART
- RCT of PCV-7 vs placebo for reduction of IPD recurrence
  - Vaccine efficacy reduced from 85% in year 1 to 25% in year 2
  - Efficacy 88% in CD4 <200 cells/mm³ group
  - Overall protection regardless of serotype hazard ration 0.76 (95% CI 0.42-1.42)

Meningococcal Conjugate Vaccine

- Increased severity of *N. meningitidis* infection
- Mandatory vaccine for pilgrims to the Hajj
- Conjugate vaccines target subtypes A,C, Y & W-135
- Quadrivalent Conjugate vaccine safe & efficacious
- Decreased response to serotype C
Typhoid Vi Capsular Polysaccharide Vaccine

- HIV increases chance of:
  - fulminant diarrhoea
  - fulminant colitis
  - bacteraemia
  - antibiotic resistance
  - relapsing disease
  - persistent infection

- Serological response decreased in CD4<200
Principles of immunization in HIV-infected adults

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- Avoid live vaccines if CD4 count < 200 cells/mm$^3$
- Polysaccharide vaccines elicit poor antibody responses
- Extra booster doses are commonly employed but often without hard evidence
## Booster doses recommended

<table>
<thead>
<tr>
<th></th>
<th>Safe and well tolerated at all CD4 counts</th>
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</thead>
<tbody>
<tr>
<td><strong>Hepatitis A</strong></td>
<td>Response rates reduced but good clinical efficacy</td>
</tr>
<tr>
<td></td>
<td>Some guidelines suggest 3\textsuperscript{rd} dose</td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>Standard (0, 1, 6m) or rapid (0, 1, 2 and 12m)</td>
</tr>
<tr>
<td></td>
<td>HBsAb &lt;10 iu/L</td>
</tr>
<tr>
<td></td>
<td>3 further double-doses</td>
</tr>
<tr>
<td></td>
<td>HBsAb 10–100 iu/L</td>
</tr>
<tr>
<td></td>
<td>1 additional vaccine dose</td>
</tr>
<tr>
<td></td>
<td>HBsAb &gt;100 iu/L</td>
</tr>
<tr>
<td></td>
<td>Check yearly and boost</td>
</tr>
<tr>
<td><strong>Rabies</strong></td>
<td>Considered safe at all CD4 counts</td>
</tr>
<tr>
<td></td>
<td>3 x intramuscular doses (0, 7 and 28 days)</td>
</tr>
<tr>
<td></td>
<td>± 4\textsuperscript{th} dose if Ab response poor at low CD4 counts</td>
</tr>
</tbody>
</table>
Missed Opportunities
Hepatitis B vaccination

• RCT - Double dose vaccine in CD4 >350 cell/mm$^3$
  – 69% versus 34% serocoversion rate

• Hepatitis B testing only occurs at ART initiation

• Options for vaccinating HBV seronegatives
  – Continue the status quo in Southern Africa
  – Vaccinate high risk groups only – IVDU, MSM, Sex care workers, partners of HBsAg positives
  – Universal HBV vaccination for those not yet infected

Influenza vaccination in HIV

The Swine Flew
Seasonal influenza and HIV

Pre-ART era
- Higher rates of
  - Hospitalization
  - Secondary bacterial infection
- Prolonged illness
- Increased Mortality

Post ART era
- Reduction in cardiopulmonary admissions by 56%
- Risk still > general population

Neuzil et al, JAMA 1999;281:901-7
Neuzil et al, JAIDS 2003;34:304-7
# Fatal pandemic H1N1 in South African HIV-infected patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested</td>
<td>Pregnant</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>COPD</td>
</tr>
<tr>
<td>Median CD4 count</td>
<td>Active TB</td>
</tr>
<tr>
<td>On ART</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Obesity</td>
</tr>
<tr>
<td>- Bilateral infiltrates</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>- Multi-lobar consolidation</td>
<td></td>
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<tr>
<td>- ARDS</td>
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</tbody>
</table>

- Median CD4 count: 58
- On ART: 4
- Oseltamivir: 9
- Chest radiography: - Bilateral infiltrates (10), - Multi-lobar consolidation, - ARDS
How much H1N1 did we miss?
Protective post-vaccination influenza titres

Meta-analysis of influenza vaccine effect on ILI and lab-confirmed cases

Human Papillomavirus (HPV)

- HPV infection rates
  - 66% HIV-infected women
  - 90% MSM
- Higher risk of cervical and anal cancer
- Risk of anal cancer on ART remains 2-fold higher than HIV-uninfected patients

# HPV Vaccines

<table>
<thead>
<tr>
<th></th>
<th>Gardasil</th>
<th>Cervarix</th>
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</thead>
<tbody>
<tr>
<td>HPV strains covered</td>
<td>HPV-6, HPV-11</td>
<td>HPV-16, HPV-18</td>
</tr>
<tr>
<td></td>
<td>HPV-16, HPV-18</td>
<td></td>
</tr>
<tr>
<td>Prevention genital warts</td>
<td>98.8% in women 9-12yrs</td>
<td>Nil</td>
</tr>
<tr>
<td>Prevention CIN</td>
<td>98% cervical precancerous lesions from vaccine strains in HPV-uninfected vs 44% in all study participants</td>
<td>93% of CIN 2 or greater dypslasia in HPV-uninfected vs 30% overall population</td>
</tr>
<tr>
<td>Prevention of AIN in MSM 16-26yrs</td>
<td>95% persistent anal infections 75% high grade AIN from vaccine strains</td>
<td>Not studied</td>
</tr>
</tbody>
</table>

**References:**
- NEJM 2011;364(5):401-11
- Lancet 2009;374:301-14
HPV vaccine efficacy in HIV

• Efficacy will depend on rates of HPV infection
  – HIV-infected women infected with HPV-16 (30%), HPV-18 (12-19%) and both (9%)
  – HIV-infected men – HPV-16 (50%) and HPV-18 (23%)

• Limited data of efficacy in HIV
  – Children with CD4% ≥15 – seroconversion rates >96% to all 4 strains
  – Men ≥18 yrs – without AIN had seroconversion rates >95%
  – Some evidence that seroconversion was less in MSM

Principles of immunization in HIV-infected adults

- Vaccination is associated with HIV viral load blip and transient reduction in CD4 count
- Avoid live vaccines if CD4 count < 200 cells/mm$^3$
- Polysaccharide vaccines elicit poor antibody responses
- Extra booster doses are commonly employed but often without hard evidence
- Either delay vaccination until ART reconstitutes immunity or repeat once CD4 count >200 cells/mm$^3$
Interrupted ART decreases protective antibody titres to neoantigens

Azzoni et al. AIDS 2012;26:1355-62
Summary

- Quantitative and qualitative defects in innate and adaptive immunity limit vaccine responses in HIV

- In patients with CD4 counts $<$200 cells/mm$^3$, avoid live vaccines and if possible reconstitute the immune system prior to vaccination or revaccinate once reconstitution has occurred

- Do not miss the opportunity to limit vaccine-preventable infections in your patients
VACCINES WORK!

IMMUNITY

Vaccines For Adults.org

Call 311 San Francisco Department of Public Health