HIV vaccines (and why this is still an urgent priority)…..

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National Institute for Communicable Diseases,
Johannesburg, South Africa

PD-VAC, WHO HQ, 8-10 Sept 2014

Global summary of the AIDS epidemic | 2013

<table>
<thead>
<tr>
<th>Number of people living with HIV in 2013</th>
<th>Total</th>
<th>Adults</th>
<th>Women</th>
<th>Children (&lt;15 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35.0 million</td>
<td>31.8 million</td>
<td>16.0 million</td>
<td>3.2 million</td>
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<td></td>
<td>[33.1 million – 37.2 million]</td>
<td>[30.1 million – 33.7 million]</td>
<td>[15.2 million – 16.9 million]</td>
<td>[2.9 million – 3.5 million]</td>
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<table>
<thead>
<tr>
<th>People newly infected with HIV in 2013</th>
<th>Total</th>
<th>Adults</th>
<th>Children (&lt;15 years)</th>
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<tbody>
<tr>
<td></td>
<td>2.1 million</td>
<td>1.9 million</td>
<td>240 000</td>
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<td></td>
<td>[1.9 million – 2.4 million]</td>
<td>[1.7 million – 2.1 million]</td>
<td>[210 000 – 280 000]</td>
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<table>
<thead>
<tr>
<th>AIDS deaths in 2013</th>
<th>Total</th>
<th>Adults</th>
<th>Children (&lt;15 years)</th>
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<tbody>
<tr>
<td></td>
<td>1.5 million</td>
<td>1.3 million</td>
<td>190 000</td>
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<td>[1.4 million – 1.7 million]</td>
<td>[1.2 million – 1.5 million]</td>
<td>[170 000 – 220 000]</td>
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</table>

About 6 000 new HIV infections a day - 68% in Africa
HIV prevalence in young pregnant women in rural Vulindlela, South Africa (2009-2012)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=1029)</th>
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<tbody>
<tr>
<td>≤16</td>
<td>8.4</td>
</tr>
<tr>
<td>17-18</td>
<td>18.6</td>
</tr>
<tr>
<td>19-20</td>
<td>25.4</td>
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<tr>
<td>21-22</td>
<td>32.8</td>
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<td>23-24</td>
<td>44.8</td>
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One way to measure progress in fighting AIDS is to compare the number of new HIV infections with the increase in the number of people on antiretroviral therapy (ART) over a given time period. If AIDS advocacy reaches its "tipping point," when the number of new HIV infections falls below the annual increase in people on ART, then treatment works. Vulnerable populations such as teenagers and pregnant women are often seen as being at the "head" of the curve in terms of infection rates. In South Africa, the tipping point may be reached as the number of new HIV infections in young pregnant women falls below the number of new ART initiations. This is why it is essential to achieve high levels of ART initiation, treatment, and viral suppression. Before that happens, ART programs need to be scaled up to meet the needs of the population. To stay on course, countries and donors need to increase financial and technical support to ensure that ART services are sustained.
Potential impact of a vaccine with 60% efficacy and 60-70% coverage in 2050

Without a vaccine, if current trends in the response to HIV/AIDS continue:
- 1.8m

With a vaccine, if current trends in the response to HIV/AIDS continue:
- 535k

Without a vaccine at 50% scale-up of UNAIDS recommendations for treatment and prevention:
- 1.2m
- 365k

With a vaccine at 50% scale-up of UNAIDS recommendations for treatment and prevention:
- 544k
- <165k

Without a vaccine, at full implementation of UNAIDS recommendations:
- 62,049

With a vaccine, at full implementation of UNAIDS recommendations:
- 510,689

HIV Prevention Trial Participants by Region 2013

- North America
- Latin America and the Caribbean
- Western, Central, and Eastern Europe
- Middle East and North Africa
- East, South & Southeast Asia
- Africa
- Oceania
Why is it so difficult to make an HIV vaccine?

• No correlates of protection - no-one has ever recovered from HIV infection
• HIV integrates into human DNA – need sterilizing immunity
• HIV causes immune system dysfunction
• HIV is highly variable with multiple subtypes and CRFs
• Animal models for testing vaccines are sub-optimal
• Antibody neutralization-sensitive sites on HIV are recessed, conformational and covered in sugars

HIV Vaccine Efficacy Trials

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<tbody>
<tr>
<td>VAX 004</td>
<td>Recombinant gp 120 (R/F)</td>
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<td></td>
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<td></td>
<td>No</td>
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<tr>
<td>VAX 003</td>
<td>Recombinant gp 120 (R/F)</td>
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<td>No</td>
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<tr>
<td>Step</td>
<td>rAdS (gp120, nef) (R)</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>RV14</td>
<td>Canavero gp120 (gp, pol, env) (E)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Yes (32%)</td>
</tr>
<tr>
<td>HIVN 505</td>
<td>rAdS (gp, pol, nef) (R) + rAdS (gp120, E)</td>
<td></td>
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<td></td>
<td>No</td>
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NOTE: Phambili (HVTN 503) began to explore a regime similar to STEP in South Africa (not included).

Esparza J. Brief history of the global effort to develop an HIV vaccine.
RV144 - Thai Trial - HIV Vaccine efficacy of 31.2%\(^\text{(p=0.04)}\)

**HIV test, risk assessment and counseling**

- **ALVAC\(^\text{®-HIV (HIV-1 E/B gp120/gp41tm anchor HIV-1B gag, protease)}}**
  - priming at week 0, 4, 12, 24
- **AIDSVAX\(^\text{® B/E gp120 boosting at week 12, 24)**

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**The NEW ENGLAND JOURNAL of MEDICINE**

**Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand**

Supachai Rerk-Ngarm, M.D., Runnree Pil浦suthorn, M.D., D.T.M.H., Soracha Nitisophon, M.D., Ph.D., Jeenrak Koonsawang, Ph.D., Joseph Cho, M.D., Robert Reis, M.D., Salim Paremo, M.D., Chaweechai Hormsal, M.D., Mark de Souza, Ph.D., Elizabeth Aliano, M.D., Michael Berenger, M.D., Sanly Garunthan, M.D., Jim Taratip, Ph.D., John G. Martin, M.D., Carol F. Francis, M.D., D.R., Donald S. Keilin, Ph.D., Deborah L. Bla, M.D., Supaporn Chansuthiwat, M.D., Chraisak Khromboon, M.D., Praphat Thongsilpan, M.D., Ph.D., Morita I. Robbe, M.D., Nelson L. Michael, M.D., Ph.D., Chayraporn Kurnam, M.D., and Jerome H. Kim, M.D., for the MOPH-ThaiVacc Investigators

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**Figure 3. Viral Loads in Subjects with Early HIV-1 Infection.**
Two correlates of protection identified:

- Probability of infection

- Supporting evidence that V2 antibodies are a correlate of risk

2. Isolation of V2 mAbs from RV144 volunteers that recognize residue 169 (Liao et al. Immunity 2013).
Beyond Neutralization: HIV Inhibition at Mucosal Surfaces

Pox-Protein Public-Private Partnership (P5)

P5 is a partnership among Bill & Melinda Gates Foundation, HIV Vaccine Trials Network, NIAID, South African MRC, Novartis, Sanofi Pasteur, and U.S. Military HIV Research Program.

Purpose: To build on the RV144 result and develop and ultimately license HIV pox-protein vaccines with the potential for broad and timely public health impact.

1. Continue to build public-private partnerships critical for success.
2. Work with host countries to support a flexible regulatory strategy in target populations and regions.
3. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.
EVOLUTION OF THE HIV VACCINE CLINICAL TRIAL PIPELINE SINCE 1988

From the IAVI trial database (accessed September 2012)
LOCALLY DEVELOPED CANDIDATE HIV-1 SUBTYPE C VACCINES FOR SOUTH AFRICA – DNA/MVA/protein

Three completed Phase I human clinical trials

• HVTN 073 / SAAVI 102
• HVTN 073E / SAAVI 102E
• HVTN 086 / SAAVI 103

Funding from SAAVI, NRF and DAIDS (NIH, USA)
Part of the HIV Vaccine Trials Network (USA)

Anna-Lise Williamson, Carolyn Williamson, Glenda Gray, Gavin Churchyard, Ken Mayer and the HVTN
New Concepts in Vaccine Design

• HIV Env trimers designed to elicit bnAbs.
• HIV antibody epitope-based vaccines including those designed to bind putative germline ancestors of bnAbs.
• Sequential immunization to mimic viral evolution and drive antibody affinity maturation of bnAbs.
• Conserved/mosaic inserts to drive breadth, depth and coverage of cellular immune responses.
• Replicating adenovirus, poxvirus and Sendai virus vectors designed to mimic the efficacy of live attenuated vaccines and also for mucosal delivery.

Core Cellular assays

• ICS or both ICS and ELISpot
  – Percent responders: total, CD4 + T cells, CD8 + T cells
  – Magnitude of response
  – Number and types of cytokines (minimum of three, preferably four)
• Cellular proliferation in response to vaccine antigen(s) (CFSE cell staining)
  – Percent responders

Manrique et al, ARHR 2014
Core Humoral Assays

- Neutralizing antibodies (TZM-bl assay Tier 1 and Tier 2 isolates)
  - Response rate, magnitude, durability, specificity
- Binding antibodies (Luminex for IgG and IgA)
  - Response rate, magnitude, durability, subclass, specificity, (eg V2, V3 etc)
- ADCC (infected cell targets)

The HIV envelope has at least 5 major sites of vulnerability defined by monoclonal antibodies

Modified from Burton et al., Science 2012
Neutralizing monoclonal antibodies PREVENT HIV infection in animal models

1.8 mg/ml
95 μg/ml
15 μg/ml

HIV-1 bNAbs display unusual genetic and physical properties

- High levels of somatic hypermutation
- Restricted germline gene usage
- Long CDRH3 regions
- Auto-/poly-reactivity

These features pose significant challenges for HIV vaccine development
Ontogeny of BNAbs: How do they develop?

Developmental pathways are likely to differ by epitope

Modified from Burton et al., Science 2012
CD4bs antibodies develop through a process of extensive somatic hypermutation

Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus

V1V2 antibodies with long CDRH3 regions are selected during the initial recombination event
Which pathway is more amenable to HIV vaccine design?

- Requires the engagement of a BCR with a long CDR H3 - these B cells are very rare
- No requirement for long CDR H3, but Ig allele skewing may limit viable BCRs
- Once stimulated, V1V2 BNAbs can develop within months, not years
- May need high levels of affinity maturation take years – hard to achieve through vaccination
- Immunogens may need to recreate antigenic diversity to drive affinity maturation
- Immunogens may need to recreate antigenic diversity to drive affinity maturation

Active versus passive immunity

Vaccination

Person immunized to induce protective antibody response

Passive “vaccination”

Person is infused with protective antibodies

Highly potent antibodies are being tested as drugs to prevent HIV
Passive Immunization – shortcut to an HIV vaccine?

- Plan B!
- Small studies in uninfected and HIV-infected humans with mAbs targeting CD4bs (VRC01, 3BNC117) and V3 glycan (PGT121/10-1074)
- May help to answer important vaccine questions such as can antibodies protect humans from HIV infection, what dose needed at mucosal surfaces, which epitope, which isotype etc
- Large-scale efficacy trials are planned but results only expected in 2020!
First HIV vaccine efficacy results are expected in 2019-2020!

• WHO could play an important role at all stages of the process:
  – Maintain sense urgency for an HIV vaccine
  – Information sharing, advice and consensus building
  – Fostering partnerships to build manufacturing capabilities
  – Endorsement of effective vaccines (and how to handle partially effective ones)
  – Lobbying governments, GAVI, funders and others to ensure access and implementation of effective vaccine