HIV Vaccine Field Advance and Reverses and a Way Forward

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Statement of Need

- An effective HIV vaccine is perhaps the most cost-effective element in a comprehensive program of HIV prevention.
- Despite recent gains, UNAIDS estimates that there are 35 million people living with HIV (PLHA).
- There are 700,000 fewer infections per year than in 2001.
- There are 2.5 million new infections per year.
- There are 1.6 million AIDS-related deaths.
- Global funding is 18.9 billion USD per year, with needs estimated at 22-24 billion USD.
- Low vaccine efficacy (VE) at 50%, requiring 40% coverage.
- Medium VE at 70%, requiring 40% coverage.
- High VE at 90%, requiring 40% coverage.
- There are 46-90 billion USD savings per year in the cost of care for ART.

Source: IAVI Policy Brief, May 2012
Goals of an HIV Vaccine

A. Lower Initial Peak of Viremia
   - PREVENT INFECTION

B. Lower Set Point
   - DELAY PROGRESSION

HIV

Vaccine

HAART
HIV Vaccine Pipeline (cumulative)

**Phase I, Ib, I/II**

58 different products and 23 adjuvants

- Adenovirus serotype vectors
  - Ad5
  - Ad26
  - Ad5HVR48
  - Ad35
- Poxvirus vectors
  - Canarypox
  - Fowlpox
  - MVA
  - NYVAC
- DNAs
  - HIV inserts
  - Cytokine inserts
  - Alphavirus replicon (VEE)
  - VSV
  - Measles
  - Adeno-associated virus vector
  - Envelope subunit
  - Peptide/Lipopeptide

**Evolving criteria to enter pipeline and move to next phase:**
- Informed by previous trials and preclinical research
- Escalating requirements (e.g. breadth, magnitude, character of current speculated relevant response)

**Phase II**

- Env subunit protein
  - Ad5 alone
  - DNA/Ad5
  - DNA ± MVA
  - Pox vector + Subunit

**Efficacy testing**

- Subunit
  - ALVAC+subunit
  - Ad5
  - DNA + Ad5

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Vaccine Concepts with Efficacy Data

2003: AIDSVAX STUDIES
VaxGen Env gp120
Humoral Immunity
• Phase III studies in high-risk subjects in the US/Thailand
• Elicited type-specific Abs but not broadly reactive NAbs
• No efficacy

2005: STEP-PHAMBILI STUDIES
Merck Ad5-Gag/Pol/Nef
Cellular Immunity
• Phase IIb study in high-risk subjects in North/South America
• Elicited cellular immunity by IFN-γ ELISPOT assays
• No efficacy, possible increased HIV-1 acquisition

2007: RV144
Sanofi ALVAC prime, AIDS VAX gp120 boost
Humoral and Cellular Immunity
• Phase III study in low-risk subjects in Thailand
• 31% reduction in HIV-1 acquisition with no viral load effect

2009: VTN 505
VRC DNA prime, Adenovirus type 5 Boost
• Phase Iib study in MSM in US and Caribbean who are Ad5 antibody negative and circumcised
• Stopped for futility at first interim analysis for efficacy

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Phase III HIV Vaccine Trials – Harm & Futility

- AIDSVAX
  (Thai IDUs, 2006)

- STEP
  (Multi-Site Heterosexuals, 2007)

- Phambili/HVTN 503
  (RSA Heterosexuals, 2007)

- HVTN 505
  (Multi-Site MSM and Transgenders, 2013)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDSVAX</td>
<td>0.1% (-30.8%, 23.8%)</td>
</tr>
<tr>
<td>STEP</td>
<td>-0.5% (-2.3%, 1.3%)</td>
</tr>
<tr>
<td>Phambili/HVTN 503</td>
<td>-1.5% (-5.5%, 2.2%)</td>
</tr>
<tr>
<td>HVTN 505</td>
<td>-25.0% (-121.2%, 29.3%)</td>
</tr>
</tbody>
</table>
## Results at 1 year

<table>
<thead>
<tr>
<th>Method</th>
<th>Effect size (CI)</th>
<th>Length of Study</th>
<th>Efficacy at 12 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prime-Boost Vaccine (Thai RV144, 2009)</td>
<td>31% (1, 51)</td>
<td>3.5 y</td>
<td>*60% (22,80)</td>
</tr>
<tr>
<td>1% Tenofovir vaginal Gel (CAPRISA 004, 2010)</td>
<td>39% (6, 60)</td>
<td>2.5 y</td>
<td>50% (15,72)</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in MSM (iPrEx, 2010)</td>
<td>44% (15, 63)</td>
<td>1.2 y</td>
<td>50% (28,66)</td>
</tr>
<tr>
<td>MEDICAL male Circumcision (Orange Farm, 2005; Rakai, 2007)</td>
<td>57% (42, 68)</td>
<td></td>
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</tbody>
</table>

Researchers hope to extend early high effect by adding boost and improving immunogenicity

*Not part of pre specified analysis*
RV 144 Study Design, Vaccination and Follow-up

- Community-based, randomized, double-blind, placebo-controlled trial (V:P 1:1)
- Volunteers: HIV negative, 18-30 years of age
- Excluded: chronic disease, pregnancy or breastfeeding

6-month vaccination schedule

- ALVAC®-HIV (vCP1521) priming at week 0, 4, 12, 24
- AIDSVAX® B/E gp120 boosting at week 12, 24

3 years of follow-up (every 6 mo.)

HIV test, risk assessment and counseling
RV144 – Only link to Clinical Efficacy

Waning durability?

**Modified ITT Population**

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Events</th>
<th>KM Rate (%)</th>
<th>SE (%)</th>
<th>Events</th>
<th>KM Rate (%)</th>
<th>SE (%)</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5</td>
<td>0.06</td>
<td>0.028</td>
<td>11</td>
<td>0.14</td>
<td>0.042</td>
<td>54.46</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>0.15</td>
<td>0.044</td>
<td>30</td>
<td>0.38</td>
<td>0.069</td>
<td>59.95</td>
</tr>
<tr>
<td>18</td>
<td>24</td>
<td>0.31</td>
<td>0.063</td>
<td>43</td>
<td>0.55</td>
<td>0.083</td>
<td>43.97</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>0.41</td>
<td>0.072</td>
<td>50</td>
<td>0.64</td>
<td>0.09</td>
<td>35.7</td>
</tr>
<tr>
<td>30</td>
<td>37</td>
<td>0.48</td>
<td>0.078</td>
<td>58</td>
<td>0.74</td>
<td>0.097</td>
<td>35.96</td>
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<tr>
<td>36</td>
<td>45</td>
<td>0.58</td>
<td>0.086</td>
<td>65</td>
<td>0.84</td>
<td>0.103</td>
<td>30.42</td>
</tr>
<tr>
<td>42</td>
<td>51</td>
<td>0.68</td>
<td>0.096</td>
<td>74</td>
<td>0.96</td>
<td>0.111</td>
<td>29.15</td>
</tr>
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</table>
Follow up Findings Provide Clues

Correlates of Risk (CoR)

Provided clues how RV144 protected

Plasma Anti-V1V2 (inverse)

Plasma Anti-Env IgA (direct)

RV144 Sieve Analysis Reinforces the importance of a region on HIV (Env V2)

Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2

Morgane Rolland1, Paul T. EdleSens2, Brendan B. Larsen1, Sodsai Tovarabut1, Eric Sanders-Buell1, Tomer Hertz2, Allan C. deCamp1, Chris Carrico1, Sergey Mennis3,4, Craig A. Magaret5, Hasan Ahmed6, Michal Juraska7, Lennie Chen8, Philip Konopa1, Snehal Narjya4, Julia N. Stoddard4, Kim Wong8, Hong Zhao7, Wenjie Deng4, Brandon S. Maust2, Meera Bose4, Shana Howell1, Adam Bates1, Michelle Lazzaro1, Annemarie O’Sullivan1, Esther Lei1, Andrea Bradfield1, Grace Itinamun1, Vatcharain Assawadaranachai1, Robert J. O’Connell1, Mark S. deSouza8, Sorachai Nityaphan9, Supachai Rekers-Ngarm1, Merlin L. Robb1, Jason S. McLellan1, Iyelin Geoghe4, Peter D. Kwong6, Jonathan M. Carlson1, Nelson L. Michael1, William R. Schief4,5, Peter B. Gilbert4, James I. Mullins4 & Jerome H. Kim10
CH38 IgA Inhibits ADCC of CM235 Infected Target Cells by RV144 C1 Region mAbs

Adapted from Nature Reviews Immunology 3, 304 (2003)

Tomaras, Ferrari et al. 2013, PNAS, 110; 22, 9019-9024.
Env IgG3 Higher in RV144 vs. VAX003 and V1/V2 IgG3 Significantly Correlates with Decreased Risk of HIV in RV144

Statistical significance is noted as follows: ** p< 0.0005; ** p< 0.005; * p< 0.05.

Yates... Tomaras et al. submitted
GLOBAL STRATEGY: Planned studies are interdependent and will amplify global impact and regional relevance.

Precedent for vaccine efficacy

Focus on regional public health impact

Future amplification of global reach

THAILAND
High risk MSM

US/EUROPE
High risk

SOUTHEAST ASIA
High risk groups (hetero, MSM, IVDU, CSW)

SOUTHERN AFRICA
High risk

RSA
High risk heterosexual

Global co-ordination of proposed trials provides the strongest regulatory strategy for filing in target markets.

TEST OF CONCEPT (TOC) Phase IIb vs Pivotal Phase III
Pox-Protein Public-Private Partnership (P5)

- Established in 2010 to build on the RV144 results
- Seeks to advance and ultimately license HIV pox-protein vaccine candidates that have the potential to achieve a broad public health impact
RV144 F/U Trials in Southern Africa

ALVAC + gp120/MF59

CTM

Phase I/IIa

P5 Licensure track

Efficacy study

Licensure Submission?

- Data meets TPP
- Product suitable

(DNA) NYVAC + gp120/MF59

CTM

Phase I

P5 Research track

Multi-arm adaptive Phase IIb

Others?

CTM

Phase I

rcNYVAC + gp120/MF59

Phase I/IIa

Down-select to 1 candidate?

- Safety
- Duration
- Preliminary efficacy ≥ 70%

rc = replication-competent
AIDS Vaccine Efficacy Consortium (AVEC) Summit for an AIDS-Free Generation in Thailand
Bangkok, August 2013

- Government of Thailand committed to supporting:
  - A future HIV vaccine efficacy study
  - In-country production capability for an efficacious HIV vaccine

U.S. Ambassador to Thailand, Kristie Kenney, Advisor to the Thai Minister of Science and Technology, and the Thai Minister of Public Health address Summit attendees.
**RV144 Follow-up Immunogenicity Studies**

- **RV305**
  - Evaluating re-boosting at Month 0, 6 with AIDSVAX, ALVAC, or combination in volunteers who participated in the RV144 study
  - Intensive systemic and mucosal immunogenicity data
  - Started May 2012; n=162

- **RV306**
  - RV144 vaccine regimen + month 12 boost with ALVAC, AIDSVAX, or combination; Intensive systemic and mucosal data
  - Started September 2013; n=360

- **RV328**
  - AIDSVAX alone for intense assessments
  - Start early 2014; n=40
Heterologous Vector Regimens Partially Resist Heterologous, Repetitive, IR SIVmac251 Challenges
MVA/Ad26 and Ad26/MVA Regimens Lower Early Setpoint Viral Loads Following SIVmac251 Infection

Log SIV RNA

Days Following Infection

Sham

MVA/MVA

DNA/MVA

MVA/Ad26

Ad26/MVA

3x resistance to infection
4/8 : viremia blunted 1 log
3/8 : rapid virologic control
1/8 : persistently uninfected

5.75

6.09

5.47

4.55

3.83
HIV Vaccines are One Tool of Prevention Efforts

Adapted from: A. Fauci, US NIAID/NIH, AIDS Vaccine Conference, 2012
We still need an HIV vaccine

- There is an urgent need for new HIV prevention options, including an AIDS vaccine
- An AIDS vaccine is possible
- An AIDS vaccine should be the simplest and most cost effective prevention strategy
- It will take broad-based partnerships to develop and deliver HIV vaccines to the populations that need them the most.
Acknowledgements

- RV144 volunteers and community members
- Ministry of Public Health, Thailand
- Royal Thai Army
- Faculty of Tropical Medicine, Mahidol University
- AFRIMS – US and Thai Component
- Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH
- Global Solutions for Infectious Diseases
- sanofi pasteur
- The Bill & Melinda Gates Foundation’s Collaboration for AIDS Vaccine Discovery (CAVD)
- Center for HIV/AIDS Vaccine Immunology (CHAVI)
- HIV Vaccine Trials Network (HVTN)
- Fred Hutchinson Cancer Research Center, SCHARP