HIV Vaccines: An update and view of the future

INTEREST Conference
7 May, 2014
Lusaka, Zambia
HIV Vaccine Update

- What we have learned:
  - Efficacy trial results
  - RV 144 correlates

- Adding another boost: preliminary RV305 data

- Future studies
HIV Vaccine Pipeline (cumulative)

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 protein
- Ad5 alone
- DNA/Ad5
- DNA + MVA
- Pox vector + Subunit

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

Efficacy testing
- Subunit
  - ALVAC+subunit
  - Ad5 alone
  - DNA + Ad5
## 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

### 2009: RV144

**Sanofi ALVAC prime, AIDSVAX 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

### 2007: 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

### 2013: VTN 505

**VRC DNA prime, Adenovirus type 5 Boost**
- Phase lib study in MSM in US and Caribbean who are Ad5 antibody negative and circumcised
- Stopped for futility at first interim analysis for efficacy
Step long term HIV results

- Evaluate Adenovirus 5 vaccine with gag/pol/nef
  - stopped for futility with more infections in vaccinees (N=81)

- Long term 172 of 1836 men were infected.

- The adjusted vaccinee vs placebo hazard ratio (HR) for all follow-up time was 1.40 (95% confidence interval [CI], 1.03–1.92; P = .03).

- Vaccine effect differed by baseline Ad5 or circumcision status during first 18 months, but waned and neither was significant for all follow-up time.

- No significant vaccine-associated risk was seen among circumcised, Ad5-negative men (HR, 0.97; P = 1.0) over all follow-up time.
VTN 503 Phambili – long term follow-up

Cumulative HIV Incidence over entire study follow-up
VTN 505 Cumulative MITT Probability of HIV Infection

Late increase is not significant;
Conclusions from non-efficacious studies

1) Adenovirus 5 vaccines have been associated with increased risk of HIV infection

2) Ad5 HIV vaccines should not be tested further

3) Ad5 specific activated CD4+/CCR5+ increased in gut mucosa; may account for susceptibility in Step study

4) Adenoviridae is diverse and utilize different cell receptors, have different tissue tropism and inflammatory profiles

5) Other Ad vectors may proceed with caution: HIV testing and assessment of gut mucosal target cells
Study Design, Vaccination and Follow-up Schedule

- 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

HIV test, risk assessment and counseling
3 years of follow-up (every 6 mo.)
## Effectiveness Recent HIV Prevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prime-boost Vaccine (Thai RV144, 2009)</td>
<td>31% (1, 51)</td>
</tr>
<tr>
<td>1% tenofovir gel (CAPRISA 004, 2010)</td>
<td>39% (6, 60)</td>
</tr>
<tr>
<td>TDF/FTC oral PrEP (iPrEx, 2010)</td>
<td>44% (15, 63)</td>
</tr>
<tr>
<td>Medical male circumcision (Orange Farm, 2005; Rakai, Kisumu, 2007)</td>
<td>57% (42, 68)</td>
</tr>
<tr>
<td>TDF/FTC oral PrEP (TDF2, CDC, 2011)</td>
<td>63% (22, 83)</td>
</tr>
<tr>
<td>TDF oral PrEP (Partners PrEP, 2011)</td>
<td>62% (34, 78)</td>
</tr>
<tr>
<td>TDF/FTC oral PrEP (Partners PrEP, 2011)</td>
<td>73% (49, 85)</td>
</tr>
<tr>
<td>Immediate ART for HIV+ partner (HPTN 052, 2011)</td>
<td>96% (82, 99)</td>
</tr>
</tbody>
</table>

**Efficacy**
RV144 Summary

**Antigen**
- **B gp120**
  - 2 weeks: 31207 (800-204800) (99% responders)
  - 24 weeks: 1758 (200-25600) (99% responders)
- **E gp120**
  - 2 weeks: 14558 (200-204800) (99% responders)
  - 24 weeks: 1000 (100-128000) (99% responders)
- **B p24**
  - 2 weeks: 205 (100-1600) (52% responders)
  - 24 weeks: 149 (100-200) (18% responders)

P<0.0001 compared to placebo group - all Antigens

*: P<0.001 compared to 2 week time-point

Dr. Mark de Souza
## Results at 1 year

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

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

*Not part of pre specified analysis*
All 6 variables together in multivariate analysis, P=0.08

2 individual variables were significant:

- gp70 V1-V2 inversely correlates with infection \[ q = 0.08 \]
  - Estimated Relative Risk = 0.57

- Plasma IgA directly correlates with infection \[ q = 0.08 \]
  - Estimated Relative Risk = 1.54

### Multivariate Logistic Regression: Quantitative Variables RV144 Correlates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>P-value</th>
<th>Q-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA Binding to Envelope Panel</td>
<td>1.54</td>
<td>0.027</td>
<td>0.08</td>
</tr>
<tr>
<td>IgG Avidity A244 gp120</td>
<td>0.81</td>
<td>0.37</td>
<td>0.56</td>
</tr>
<tr>
<td>ADCC AE.HIV-1 Infected CD4 Cells</td>
<td>0.92</td>
<td>0.68</td>
<td>0.68</td>
</tr>
<tr>
<td>Tier 1 Neutralizing Antibodies</td>
<td>1.37</td>
<td>0.22</td>
<td>0.45</td>
</tr>
<tr>
<td>IgG Binding to gp70-V1V2</td>
<td>0.57</td>
<td>0.015</td>
<td>0.08</td>
</tr>
<tr>
<td>CD4+ T Cell Intracellular Cytokines</td>
<td>1.09</td>
<td>0.61</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Case control study: 40 HIV+ vaccinees, 205 HIV- vaccinees; 40 placebo

Multivariate and Cox Analysis confirmed independently

80% power to detect a 53% change in HIV infection per 1 sd change in biomarker

Use q-test to generate hypotheses for future testing
Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2

Morgane Rolland1*, Paul T. Edlefsen2*, Brendan B. Larsen3, Sodsai Tovanabutra1, Eric Sanders-Buell1, Tomer Hertz2, Allan C. deCamp2, Chris Carrico4,5, Sergey Menis4,5, Craig A. Magaret2, Hasan Ahmed2, Michal Juraska2, Lennie Chen3, Philip Konopa3, Snehal Nariya3, Julia N. Stoddard3, Kim Wong3, Hong Zhao3, Wenjie Deng3, Brandon S. Maust3, Meera Bose1, Shana Howell1, Adam Bates1, Michelle Lazzaro1, Annemarie O’Sullivan1, Esther Lei1, Andrea Bradfield1, Grace Ibitumuno1, Vatcharain Assawadarakarn6, Robert J. O’Connell1, Mark S. deSouza6, Sorachai Nitayaphan6, Supachai Rerks-Ngarm7, Merlin L. Robb1, Jason S. McLellan8, Ivelin Georgiev8, Peter D. Kwong8, Jonathan M. Carlson9, Nelson L. Michael1, William R. Schief4,5, Peter B. Gilbert2*, James I. Mullins3* & Jerome H. Kim1*
RV144 vaccine-induced IgG antibodies to V1V2 regions of multiple HIV subtypes correlate with decreased risk

<table>
<thead>
<tr>
<th>Zolla-Pazner….Tomaras</th>
<th>V1V2 Scaffold antigen</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ELISA²</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>gp70.B(Case A2)-V1V2.APorg (primary) §</td>
<td>0.63</td>
<td>0.0179</td>
</tr>
<tr>
<td>gp70.B(Case A2.p623)-V1V2.APorg †</td>
<td>0.62</td>
<td>0.0149</td>
</tr>
<tr>
<td>gp70.B(Case A2)-V1V2.LL †</td>
<td>0.60</td>
<td>0.0084</td>
</tr>
<tr>
<td>gp70.A(92RW020)-V1V2</td>
<td>0.68</td>
<td>0.0521</td>
</tr>
<tr>
<td>gp70.C(97ZA012)-V1V2</td>
<td>0.56</td>
<td>0.0040</td>
</tr>
<tr>
<td>tags.C(1086)-V1V2</td>
<td>0.53</td>
<td>0.0014</td>
</tr>
<tr>
<td>gp70.AE(92TH023)-V1V2</td>
<td>0.62</td>
<td>0.0130</td>
</tr>
<tr>
<td>Score (cross-reactivity)</td>
<td>0.58</td>
<td>0.0073</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BAMA²</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>0.60</td>
<td>0.0059</td>
<td></td>
</tr>
<tr>
<td>0.59</td>
<td>0.0031</td>
<td></td>
</tr>
<tr>
<td>0.61</td>
<td>0.0071</td>
<td></td>
</tr>
<tr>
<td>0.55</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>0.62</td>
<td>0.0039</td>
<td></td>
</tr>
<tr>
<td>0.67</td>
<td>0.0097</td>
<td></td>
</tr>
<tr>
<td>0.56</td>
<td>0.0015</td>
<td></td>
</tr>
</tbody>
</table>

RV144 case-control analysis samples IgA-adjusted weighted logistic regression

– IgG binding to linear peptides of V2 from multiple sub-types also significantly correlated to HIV status, especially when adjusting for IgA

Gottardo…Montefiore et al. PLoS One 2013

*different labs, different techniques, same conclusion*
Protective efficacy of adenovirus/poxvirus vaccines

- Fifty percent of animals infected:
  - One challenge in the control group
  - Three challenges in the Ad26/MVA and MVA/Ad26 groups

- Protection associated with:
  - Env-specific binding ELISA antibody responses ($p < 0.0001$), including V2-specific antibodies ($p < 0.0001$)
  - Tier 1 NAb titers immediately before challenge ($p = 0.0034$)

Barouch et al., Nature, 2012
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.
RV144 and Vax003 V1V2 IgG3 Responses

**Graphs:**
- ConS gp140
- GNE gp120
- AE Con gp140
- 92TH023 gp120
- A244 gp120
- MN gp120

**Bar Graph:**
- % Positive IgG3 Env
  - RV144
  - VAX003

**Legend:**
- ConS gp140
- GNE gp120
- AE Con gp140
- 92TH023 gp120
- A244 gp120
- MN gp120
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
Polyfunctional IgG3 associated with reduced risk of HIV

Mean 4.6
ADCC
ADCVI
ADCP
NK IFN-g
NK CD107a
NK-MIP1b

Chung...Alter
Summary of Correlates

- V1V2 binding remains a strong correlate of risk using different targets, different methods (scaffold binding and peptide array) and in different labs
- Subtype B and E virion capture mediated by RV 144 plasma
- In RV 144 compared to Vax 003:
  - IgG3 more and IgG4 less frequent in RV 144 vaccinees
  - IgG3 binding to V2 a correlate of protection in RV 144
  - IgG3 associated with greater poly-functionality in RV 144
  - Glycosylation of IgG in RV 144 altered favorably
- Evidence for a role of V3 antibody as a correlate of risk
  - Controlling for IgA env binding antibody levels
Building on RV144: Immunogenicity Studies
RV305, RV306 and RV328
RV144, RV305, RV306, and RV328 Schedules

Vaccination Schedules

- RV144: 0, 3, 6, 9 months
- RV305: 0, 6 months
- RV306: 0, 3, 6, 12 months
- RV328: 0, 3, 6, 9, 12 months

- ALVAC®-HIV (vCP1521) or placebo
- AIDSVAX® B/E gp120 or placebo
- No Boost

RV305 Start
Comparison of RV144 Antibody Binding to gp120 A244

Same Samples as in RV305, Visits 8

Karasavvas….Kim et al. AIDS Vaccine 2013
Geometric Mean Titers of IgG Responses to gp70 V1V2 B (Case A2)

Karasavvas….Kim et al. AIDS Vaccine 2013
Summary

- Late boost #1 produces higher peak response vs RV 144
  - Binding to gp 120 and V2 scaffold
  - Tier 1 neutralizing antibody
- Second boost in RV 305 does not achieve same peak binding response for either gp 120 or V2 but is similar to RV 144
- Second boost response is significantly lower than the first boost response for tier 1 neuts but it remains higher than RV 144
- Critical to assess IgG3, breadth of binding recognition and functional capacity at both time points
- Consider evaluating vaccine schedule to enhance boosting
GLOBAL STRATEGY: Planned studies are interdependent and will amplify global impact and regional relevance.

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
**RV144 F/U Trials in Southern Africa – Subtype C**

- **ALVAC + gp120/MF59**
  - **Phase I/IIa**
  - Efficacy study
  - Licensure Submission?
    - Data meets TPP
    - Product suitable

- **(DNA) NYVAC + gp120/MF59**
  - **Phase I**
    - Multi-arm adaptive Phase IIb
    - Down-select from 10 to 4 candidate?
      - Safety
      - Duration
      - Preliminary efficacy ≥ 70%

- **Others?**
  - **Phase I**
    - Multi-arm adaptive Phase IIb

- **rcNYVAC + gp120/MF59**
  - **Phase I/IIa**

**rc = replication-competent**
So what else is there?

- Potent and broadly neutralizing monoclonal antibodies
  - Will be used for PMTC and other settings
  - Delivered via Adeno Associated Virus to express Ab in vivo
  - Will serve as models to “reverse engineer” vaccines

- hCMV vectored vaccines have 50% efficacy for protection in NHP and are under development for human use
  - Persist indefinitely

- Many vaccine platforms optimized for T cell immunity
  - We need proteins and adjuvants to improve humoral immunity

- Inserts which permit testing in all HIV sub-types - mosaics
Heterologous Vector Regimens Partially Resist Heterologous, Repetitive, IR SIVmac251 Challenges

Graph showing the percentage of uninfected cells over the number of IR challenges for different vector regimens: DNA/MVA, MVA/MVA, Ad26/MVA, MVA/Ad26, and Sham.
MVA/Ad26 and Ad26/MVA Regimens Lower Early Setpoint Viral Loads Following SIVmac251 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
Summary

- Progress is being made
  - Correlates to guide new design
    - V2 targets
    - Potential for non-neutralizing effectors
  - Novel approaches coming to human clinical trials
  - Efficacy trials to begin in 2016
  - Pace must accelerate and be integrated into the advent of effective prevention strategies as they emerge
Acknowledgements

- RV144 volunteers and community members
- Dr. Supachai/Punnee/Prasert/Sorachai and the RV 144 team
- Ministry of Public Health, Thailand
- Faculty of Tropical Medicine, Mahidol University
- Royal Thai Army
- AFRIMS – US and Thai Components
- Division of AIDS, NIAID, NIH
- Global Solutions for Infectious Diseases
- Henry M. Jackson Foundation for the Advancement of Military Medicine
- sanofi pasteur
- The Bill & Melinda Gates Foundation’s (CAVD)
- Center for HIV/AIDS Vaccine Immunology (CHAVI)
- NYU School of Medicine
- HIV Vaccine Trials Network (HVTN)
- Fred Hutchinson Cancer Research Center, SCHARP
RV 144 Correlates Acknowledgements

- Bart Haynes
- Georgia Tomaras
- Galit Alter
- David Montefiori
- Susan Zolla-Pazner
- Larry Liao
- Guido Ferrari
- Peter Gilbert
- Jerome Kim
- Rob O’Connell
- Nelson Michael
- Nicos Karasavva
- Morgane Rolland
- Sodsai Tovanabutra
- Rasmi Thomas
- Alexandra Schuetz
- Mangala Rao
- Charla Andrews

NHP 001
- Dan Barouch and colleagues at BIDMC and Ragon
- Mangala Rao