Trials & Tribulations: on the way to cure: where do HIV Vaccines fit in?

Glenda Gray
SA HIV Clinicians Society Conference 2016
13-16 April, 2016
Scope

- Rationale for an HIV vaccine
- RV144 study in Thailand
- P5 programme in RSA
- Janssen HIV vaccine strategy
- VRC01 neutralising antibody study
What we need to end AIDS?

- Innovations in the management of HIV that will impact on community viral load and infectiousness: prevention of secondary transmission
- Innovations in the Prevention of Sexual Acquisition that will be required when secondary transmission is not averted
- HIV Cure: the ultimate control of the HIV epidemic will be in the elimination of viremia in those infected

Gray, G et al Plos Biol, in press 2015
“Ultimately, we believe, the only guarantee of a sustained end of the AIDS pandemic lies in a combination of non-vaccine prevention methods and the development and deployment of a safe and effective HIV vaccine.”
Why so little interest?

• **Scientific:** highly variable virus that integrates into host genome, rapidly establishing latency, evading both humoral & cellular responses
Why so little interest?

- Limited pharmaceutical support

HIV Prevention R&D by Funder Type 2013

Donaldson E, et al, HIVR4P 2014
Imbalance Between Societal Value and Private Sector Economic Value for Vaccines

Societal Valuation

- Greatest cost savings of any medical technology
- Greatest societal benefit regarding reducing effects of an illness

Economic Valuation

- Highest hurdle for safety of any pharmaceutical product
- Highest hurdle for effectiveness of any pharmaceutical product
- High manufacturing costs
- High liability
- Lowest profit margins of any novel pharmaceutical
Imbalance Between Societal Value and Private Sector Economic Value for a HIV vaccine

Societal Valuation
• Only effective way to control HIV
• Every country wants a HIV vaccine especially LMIC
• Even the CIA want an HIV vaccine!

Economic Valuation
• Multiple commercial failures already
• High manufacturing costs
• High liability
• Tiered pricing unlikely to cover the commercial costs
• If effective, likely to be distributed as a commodity
• No assurance platform technology will lead to other money making uses

Bottom Line
- Relying on push or pull mechanisms to effectively provide resources for the private sector to devote a full scale assault on this issue is nil
<table>
<thead>
<tr>
<th>Study/location</th>
<th>Vaccine/s</th>
<th>Risk Group/HIV incidence</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vax003 Thailand</td>
<td>AIDSVAX B/E gp120 in alum</td>
<td>IDUs 3.4%</td>
<td>No VE</td>
</tr>
<tr>
<td>Vax004 US/Europe</td>
<td>AIDSVAX B/B gp120 in alum</td>
<td>MSM/high risk women 2.6%</td>
<td>No VE</td>
</tr>
<tr>
<td>HVTN 502 Americas</td>
<td>MRKAd5 HIV-1 gag/pol/nef</td>
<td>MSM/high risk women 3%</td>
<td>Halted for futility; early transient increased infection in vaccinees</td>
</tr>
<tr>
<td>HVTN 503</td>
<td>MRKAd5 HIV-1 gag/pol/nef</td>
<td>Heterosexual men &amp; women 3.7%</td>
<td>No VE; late increased HIV infection in unblended male vaccinees</td>
</tr>
<tr>
<td>RV144 Thailand</td>
<td>ALVAC-HIV vCP1521, AIDSVAX B/E rgp120 in alum</td>
<td>Heterosexual men and women with variable risk 0.28%</td>
<td>31.2% VE at 42/12; 60% VE @ 12/12</td>
</tr>
<tr>
<td>HVTN 505</td>
<td>DNA, rAD5 (A,B,C)</td>
<td>Circumcised MSM Ad5 neg 1.8%</td>
<td>Halted at interim analysis for futility</td>
</tr>
</tbody>
</table>
Thai Trial (RV144) Primary Results

Vaccine efficacy decreases over time

### Modified Intention-to-Treat Analysis*

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Cumulative Infections</th>
<th>% HIV-1 infection rate (95% CI)</th>
<th>Cumulative Infections</th>
<th>% HIV-1 infection rate (95% CI)</th>
<th>Vaccine Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>12</td>
<td>0.15 (0.07,0.24)</td>
<td>30</td>
<td>0.38 (0.24,0.52)</td>
<td>61</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>0.41 (0.27,0.55)</td>
<td>50</td>
<td>0.64 (0.46,0.82)</td>
<td>36</td>
</tr>
<tr>
<td>36</td>
<td>45</td>
<td>0.58 (0.41,0.75)</td>
<td>65</td>
<td>0.84 (0.63,1.04)</td>
<td>31</td>
</tr>
<tr>
<td>42</td>
<td>51</td>
<td>0.68 (0.49,0.87)</td>
<td>74</td>
<td>0.96 (0.74,1.18)</td>
<td>31</td>
</tr>
</tbody>
</table>

*Vaccine efficacy decreases over time.*

---

**The NEW ENGLAND JOURNAL of MEDICINE**

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

Supachai Berks-Ngarm, M.D., Punnee Pitisutthithum, M.D., D.T.M.H., Sorachai Nitisaphan, M.D., Ph.D., Jarat Krupkungnul, Ph.D., Joseph Chu, M.D., Robert Paris, M.D., Nakorn Premroi, M.D., Chawetsan Nathan, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stabile, Ph.D., Deborah L. Birs, M.D., Supamit Chunsuttiwat, M.D., Chinsak Khamboonruang, M.D., Presert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunavokin, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators.
Defining the correlates of immunity in RV144

- Case Control Study
- Used specimens 2 weeks after the final vaccination

41 vaccine recipients who got HIV > 26 weeks

Case control

40 placebo recipients

205 controls: vaccine recipients who were negative at the end of the study
6 assays emerged to be related to Vaccine Efficacy

The binding of IgG antibodies to the V1V2 region of gp 120

The binding of plasma IgA to env

The avidity of IgG antibodies for env

Antibody Dependent Cellular Cytotoxicity (ADCC)

Neutralising Antibodies

The magnitude of CD4 T cells specific for HIV-1 env

In vaccinees with low plasma IgA responses
Correlates of Risk of HIV Infection
Reported in Haynes et al, NEJM 2012

- IgA antibodies binding to Env
- gp70–V1V2 binding
- NAAb
- ADCC
- IgG avidity
- CD4+ T Cells
- IgA A.con.env03 gp140CF
- IgA C1 biotin
- V2 hotspot
lack of a direct correlation between neutralising antibodies and HIV-1 acquisition

Even at peak antibody response, none of the sera from the vaccinees neutralised a panel of 20 contemporaneous isolates of HIV-1 circulating in Thailand during the course of the trial…..
3 strategies to advance immunization

- P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)
- Multi-clade approach using rAd26/MVA/gp140 trimer
- Neutralising antibody approach using VRC01 (HVTN 703)
2010 Formation of the P5 Partnership

**Purpose:**
To build on RV144 data and ultimately license a pox-protein based HIV vaccine with the potential for broad and timely public health impact.

**Strategy:**
Continue to build public-private partnerships critical for success.
1. Work with host countries to support a flexible regulatory strategy in target populations and regions.
2. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.
Construction of Bivalent Subtype C gp120/MF59

Construction of ALVAC-HIV-C (vCP2438)

Optimize regimen by increasing potency and durability

Booster at 12 months
HVTN Strategy for the Phase 3 Program

HVTN 097
Designed to evaluate RV144 vaccine regimen in RSA and compare immunogenicity to that in Thailand

HVTN 100
A standard phase 1 trial of the clade C products to decide whether to proceed to phase 3

HVTN 702
A Classic phase 3 RCT assessing efficacy and safety aimed at licensure
Peak CD4^+ T Cell Response Rates and Magnitudes are Higher in Prevalence in 097 vs. RV144

<table>
<thead>
<tr>
<th>Response rate:</th>
<th>RV144</th>
<th>HVTN 097</th>
<th>RV144</th>
<th>HVTN 097</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.3%</td>
<td>69.2%</td>
<td>2.5%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>88/175</td>
<td>54/78</td>
<td>1/40</td>
<td>3/78</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.01

P = 1.00
Strong IgG Responses to V1V2, gp120 and gp140 Antigens

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Number of antigens</th>
<th>98.6%</th>
<th>100%</th>
<th>98.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1V2</td>
<td>15</td>
<td>68/69</td>
<td>69/69</td>
<td>68/69</td>
</tr>
<tr>
<td>Gp120</td>
<td>8</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gp140</td>
<td>8</td>
<td></td>
<td></td>
<td>98.6%</td>
</tr>
</tbody>
</table>

Geometric mean of MFI

Number of antigens in compiled analysis:
- V1V2: 15
- Gp120: 8
- Gp140: 8
Comparison of V1V2 IgG responses between 097 and RV144
Summary of HVTN 097

• 097 trial indicates ALVAC vectors are equally immunogenic in RSA populations as compared to Thais.

• We hope that the manufacturing of the Envelope and gag genes separately and the bivalent mixture of vectors in combination with a bivalent clade C gp120 will provide even higher clade C immunogenicity with the proposed 702 regimen as compared to RV144.
## Study Schema: HVTN 100

<table>
<thead>
<tr>
<th>N (total 252)</th>
<th>Primary Vaccine Regimen</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>210</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
</tr>
<tr>
<td>42</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

### Products:
- ALVAC-HIV (vCP2438) expressing HIV-1 env (clade C gp120), clade B (gp41), gag (clade B) & protease (clade B) (Dose: >$1 \times 10^6$ CCID$_{50}$)
- Bivalent subtype C gp120/MF59 containing 100mcg TV1.Cgp120 & 100mcg 1086.Cgp120

Immunogenicity evaluation to be applied to this study to inform advancement into phase 3
**Go/No-Go Criteria:**

**HVTN 100 Must Meet all of the Following Conditions to advance to HVTN 702**

<table>
<thead>
<tr>
<th>Variable Measured at Month 6.5</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Env Ab Response Rate (≥ 2 of 3)</td>
<td>Adequate Ab take to vaccine Env</td>
</tr>
<tr>
<td>Env Ab Magnitude* (≥ 2 of 3)</td>
<td>Non-inferior Ab magnitude vs. RV144</td>
</tr>
<tr>
<td>Env CD4 Response Rate* (1 of 1)</td>
<td>Non-inferior CD4 T cell take vs. RV144</td>
</tr>
<tr>
<td>Env V1V2 Response Rate (≥ 1 of 3)</td>
<td>Adequate to predict achieving VE=50% for 2 years if V1V2 Ab is an immune correlate</td>
</tr>
</tbody>
</table>

* Based on simultaneous assessment of clade C vaccinee samples vs. RV144 vaccinee samples by the same lab
Study Schema: HVTN 702

<table>
<thead>
<tr>
<th>N (total 5400)</th>
<th>Primary Vaccine Regimen</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>2700</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
</tr>
<tr>
<td>2700</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Estimated Total Study duration 72 months:
- Stage 1: 60 months-18 months for enrolment, 24 months of follow-up for HIV-1 uninfected individuals, 18 months follow up for HIV-1 infected individuals
- Stage 2: an additional 12 months of follow up for uninfected individuals
For RV144:
- Observed V1V2 = 64%

For 702:
- Observed VE = 44%
- Observed VE (V1V2 responders) = 69%

To achieve observed VE ≥ 42%, assuming observed VE (V1V2 responders) = 69%

Requirements:
- Require Observed V1V2 ≥ 53%
- Need Observed V1V2 ≥ 61%
3 strategies to advance immunization

- **P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)**
- **Multi-clade approach using rAd26/MVA/gp140 trimer**
- **Neutralising antibody approach using VRC01 (HVTN 703)**
HIV vaccine research program: Janssen and Collaborators

IAVI  Ragon  NIAID/HVTN  BIDMC  Harvard  MHRP
HIV Vaccine Aiming at Protection Against all Clades of HIV-1

Different HIV-1 clades dominate in different geographic regions

1. Vectors that elicit optimal immune responses
   - Low seroprevalent Ad26
   - Ad26.HIV-Gag-Pol
   - Ad26.HIV-Env
   - (MVA.HIV-Gag-Pol-Env)

2. Mosaic inserts for global coverage

3. Trimeric env protein for improved humoral immunity

Adolescents (11-17 years) / Adults (18-65 years) in endemic countries and populations at risk in Western world

Protective Efficacy of a Global HIV-1 Mosaic Vaccine against Heterologous SHIV Challenges in Rhesus Monkeys

Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys

Dan H. Barouch et al., 2010
Ad26/MVA and Ad35/Ad26 SIV Vaccines Partially Protect Against IR SIVmac251 Challenges in Rhesus Monkeys

76-83% reduction of per exposure acquisition risk

- 48 rhesus monkeys
  - Ad26/MVA, MVA/Ad26 (N=16)
  - Ad35/Ad26 (N=16)
  - Sham (N=16)

- Repetitive, intrarectal, heterologous SIVmac251 challenges

- Correlates of protection
  - ELISA \( P < 0.0001 \)
  - NAb \( P = 0.0034 \)

Barouch et al. Nature 2012; 482: 89-93
Ad26/Env SIV Vaccines Partially Protect Against IR SIVmac251 Challenges in Rhesus Monkeys

90% reduction of per exposure acquisition risk for Ad/Env (P=0.001)
50% (6 of 12) show complete protection for Ad/Env (P=0.01)

- 32 rhesus monkeys
  - Ad26/Env (N=12)
  - Ad26/Ad35 (N=12)
  - Sham (N=7)

- Repetitive, intrarectal, heterologous SIVmac251 challenges

- Correlates of protection
  - ELISA  \( P < 0.0001 \)
  - Ab Funct  \( P = 0.004 \)
  - NAb  \( P = NS \)

Barouch et al. Science 2015
A prime-boost vaccine regimen aiming at global coverage

Prime

- Ad26 Mosaic vectors gag-pol-env
- Ad26 Mosaic vectors gag-pol-env

Boost

- Ad26 Mosaic vectors gag-pol-env
- Soluble trimer gp140 env protein
- MVA Mosaic vectors gag-pol-env
- Soluble trimer gp140 env protein

Regimen to be selected after Phase 1/2a
High Level Clinical Development Plan

Phase 1/2a
2014-2016
- USA, Africa, Asia
  - Safety
  - Regimen selection
  - Dose confirmation

Ancillary studies
- Evaluation of alternative schedules
- Evaluation of Mosaic trimer
- Evaluation of tetravalent Ad26

Phase 2b/3
2017-2021
- Africa and Asia
  Efficacy in high risk population
- USA, LatAm, Europe
  Efficacy in high risk population
- Additional trials
  - Lot to lot, bridging

Phase 3/4
2021 +
- Long term efficacy
  - Persistence of Immunity
- Additional trials
  - ≠populations
  - ≠countries
- BLA-MAA submissions?
3 strategies to advance immunization

- **Efficacy Studies**
  - P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)
  - Multi-clade approach using rAd26/MVA/gp140 trimer
  - Neutralising antibody approach using VRC01 (HVTN 703)
## Clinical Use of HIV Antibodies

### Prevention
- Can mAb prevent infection in high risk adults (PrEP)
- Can mAb protect infants during childbirth and breastfeeding
- What level of antibody is needed (ug/ml) to protect
- How long will the antibody work (weeks, months?)

### Treatment
- Does mAb have virologic effect; i.e., lower viremia
- Used for treatment interruption; e.g., ART sparing
- Can mAbs impact the viral reservoir; e.g. used with latency reversing agents
- Can mAbs be used with ART as part of approach to functional cure

Possible that Single mAb could protect

Likely want combinations to maximize effect and avoid escape

---

**Prevention**
- Can mAb prevent infection in high risk adults (PrEP)
- Can mAb protect infants during childbirth and breastfeeding
- What level of antibody is needed (ug/ml) to protect
- How long will the antibody work (weeks, months?)

**Treatment**
- Does mAb have virologic effect; i.e., lower viremia
- Used for treatment interruption; e.g., ART sparing
- Can mAbs impact the viral reservoir; e.g. used with latency reversing agents
- Can mAbs be used with ART as part of approach to functional cure

Possible that Single mAb could protect

Likely want combinations to maximize effect and avoid escape
Neutralising Ab to HIV-1

- V1V2-Glycan – bind to trimer cap
- V3-glycan, N332 supersite
- gp41 MPER – near membrane
- gp120/41 interface – bind to parts of both gp120 and gp41
- CD4 binding site of gp120 – where the virus attaches to CD4

Only antibodies that have advanced to the clinic (VRC01, 3BNC117)

Christina Corbaci, Andrew Ward,
## Neutralisation Activity of VRC01

<table>
<thead>
<tr>
<th>Virus clade</th>
<th>Number of viruses</th>
<th>IC$_{50}$ &lt; 50 µg/mL</th>
<th>IC$_{50}$ &lt; 1 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>22</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>B</td>
<td>49</td>
<td>96%</td>
<td>80%</td>
</tr>
<tr>
<td>C</td>
<td>38</td>
<td>87%</td>
<td>66%</td>
</tr>
<tr>
<td>D</td>
<td>8</td>
<td>88%</td>
<td>50%</td>
</tr>
<tr>
<td>CrRF01_AE</td>
<td>18</td>
<td>89%</td>
<td>61%</td>
</tr>
<tr>
<td>CRF02_AG</td>
<td>16</td>
<td>81%</td>
<td>56%</td>
</tr>
<tr>
<td>G</td>
<td>10</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>CRF07_BC</td>
<td>11</td>
<td>100%</td>
<td>45%</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>Total</td>
<td>190</td>
<td>91%</td>
<td>72%</td>
</tr>
</tbody>
</table>
VRC01 Protects Against Mucosal SHIV-Challenge in Non-Human Primates

20 mg/kg infusion of VRC01: Challenge with SHIV SF162P3

RECTAL CHALLENGE

VAGINAL CHALLENGE

4/4 protected

4/4 protected

0/4 protected

1/4 protected

Days post challenge

Days post challenge

AMP: Two Phase IIB Studies

- HVTN 703/HPTN 081 will enroll 1,500 women in sub-Saharan Africa
- HVTN 704/HPTN 085 will enroll 2,700 MSM and transgender persons in the Americas
- Each ppt. will be randomized to receive VRC01 10 mg/kg or 30 mg/kg or placebo every 8 weeks for 10 doses

www.ampstudy.org
Major Scientific Questions and Issues the Trial will Define

- Do immunogens that elicit lower levels of neutralization, levels that have proven protective in NHP challenge models, protect against HIV acquisition in humans?

- What is the dynamic range in concentration of antibodies and neutralizing activity associated with protection?

- Can lower levels of neutralization activity afford protection or does *in vivo* protection require only high concentrations of CD4 binding site antibodies?

- Are non-neutralizing effector functions as predictive of efficacy as neutralizing activity?

- What are the kinetics and functional (non-neutralizing) activities that are seen at low levels of neutralization for VRC01?
AMP Research Sites
AMP sub-Saharan Africa Sites

- Gabarone, Botswana
- Kisumu, Kenya
- Blantyre, Malawi
- Lilongwe, Malawi
- Maputo, Mozambique
- Harare (3 clinics), Zimbabwe
- Cape Town, RSA
- Durban (2 clinics), RSA
- Johannesburg, RSA
- Soweto, RSA
- Vulindlela, RSA
- Mbeya, Tanzania
# Timeline for AMP in sub-Saharan Africa: Open April 2016

<table>
<thead>
<tr>
<th>AMP sub-Saharan Africa</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAIDS Reviews</td>
<td>2/1/2016 - 3/21/2016</td>
</tr>
<tr>
<td>MCC and RSA EC Reviews</td>
<td>10/2015 - 2/2016</td>
</tr>
<tr>
<td>Trial Opens*</td>
<td>4/1/2016</td>
</tr>
</tbody>
</table>

*Additional SSA National Regulatory Authority & EC reviews continue to Q3 2016, with trainings to be scheduled accordingly.*
Enrollment Projections: AMP in sub-Saharan African women
Develop highly effective strategies to reduce HIV acquisition e.g. HIV vaccine, or novel ways to administer broadly reactive neutralizing antibodies

Develop long acting pre exposure prophylaxis strategies that can be used topically or systemically

 Deliver ARV Treatment "en masse" including implementing highly effective programs to eliminate mother to child transmission
Acknowledgements

• HVTN
  Ken Mayer
• HVTN
  Larry Corey
  Julie McElrath
• VRC
  John Mascola
  Barney Graham
& Funders:
NIAID/BMGF/SAMRC

• J&J/Janssen
  Dan Barouch
  Nelson Michael
• Frank Tomaka
• NICD
  Lynn Morris
  HPTN
• Mike Cohen