Prospects for an AIDS Vaccine: Clinical Development

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INTEREST Workshop

The views expressed are those of the presenter and should not be construed to represent the positions of the U.S. Army or DoD
Past HIV Vaccine Concepts

Only three concepts have completed clinical efficacy testing

2003: AIDSVAX
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

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

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

Phase I and II vaccine trials are necessary BUT
PROGRESS IS MEASURED BY EFFICACY TRIALS ONLY

8 May 2012
Vaccination and Follow-up Schedule

16,395 Infection Free at first injection

6-month vaccination schedule

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

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

(time in years)
RV 144 demonstrated efficacy for HIV acquisition

![Graph showing probability of HIV infection over years for Placebo and Vaccine groups.]

N=16,395
51 vaccine, 74 placebo HIV infected
Est. VE = 31% 95% CI 1-51% (p=0.04)

Rerks-Ngarm et al. (2009, NEJM)
Co-primary Endpoint 2:
No difference in post-infection setpoint viral load

Mean Setpoint Viral Load
Vaccine recipients: $4.3 \log_{10}$
Placebo recipients: $4.2 \log_{10}$
p = 0.24

Observation 1: Once infected, vaccine and placebo behave similarly.
Methodology

Baseline HIV infection risk was classified into 3 levels.

- **High risk:**
  - categorized themselves as high risk, or
  - reported high risk behaviors, e.g. needle sharing, multiple sex partners, sex work, STD symptoms

- **Low risk:**
  - perceived their risk as low, and
  - in previous 6 months reported 0-1 sex partners and no sex with CSWs, casual partners, same gender partner, HIV infected partner, IDU partner or a partner with multiple partners,
  - reported no STD symptoms or incarceration within 6 months of study entry.

- **Moderate risk:**
  - neither low nor high risk.
Comparison of baseline risk to “highest” (ever) risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Baseline</th>
<th></th>
<th>Highest (ever)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>High risk self report</td>
<td>1620</td>
<td>9.9</td>
<td>5613</td>
<td>36.1</td>
</tr>
<tr>
<td>Needle sharing</td>
<td>133</td>
<td>0.8</td>
<td>1250</td>
<td>8.2</td>
</tr>
<tr>
<td>2-4 sex partners</td>
<td>1034</td>
<td>6.3</td>
<td>2745</td>
<td>17.5</td>
</tr>
<tr>
<td>&gt; 4 sex partners</td>
<td>205</td>
<td>1.3</td>
<td>502</td>
<td>3.2</td>
</tr>
<tr>
<td>No condom / casual partner</td>
<td>936</td>
<td>5.7</td>
<td>2490</td>
<td>15.9</td>
</tr>
<tr>
<td>No condom / CSW</td>
<td>62</td>
<td>0.4</td>
<td>291</td>
<td>1.9</td>
</tr>
<tr>
<td>No condom / same gender</td>
<td>169</td>
<td>1.0</td>
<td>429</td>
<td>2.7</td>
</tr>
<tr>
<td>Condom / HIV infected partner</td>
<td>227</td>
<td>1.4</td>
<td>597</td>
<td>3.8</td>
</tr>
<tr>
<td>No Condom / HIV+ partner</td>
<td>29</td>
<td>0.2</td>
<td>143</td>
<td>0.9</td>
</tr>
<tr>
<td>No condom / IDU partner</td>
<td>18</td>
<td>0.1</td>
<td>97</td>
<td>0.6</td>
</tr>
<tr>
<td>No condom / many sex partners</td>
<td>258</td>
<td>1.6</td>
<td>753</td>
<td>4.8</td>
</tr>
<tr>
<td>STD sx</td>
<td>479</td>
<td>2.9</td>
<td>1613</td>
<td>10.4</td>
</tr>
<tr>
<td>IDU in jail</td>
<td>38</td>
<td>0.2</td>
<td>181</td>
<td>1.2</td>
</tr>
<tr>
<td>CSW</td>
<td>86</td>
<td>0.5</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Occupation: entertainment</td>
<td>470</td>
<td>2.9</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>High risk (categorical)</td>
<td>3945</td>
<td>24.1</td>
<td>9187</td>
<td>58.2</td>
</tr>
</tbody>
</table>
Risk behavior changes over time were similar in vaccine and placebo arms.

Both medium and high risk reports declined through the first year;
Risk-stratified Treatment Effects (mITT)

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Endpoints</td>
<td>PY Rate %</td>
</tr>
<tr>
<td>Low</td>
<td>3,865</td>
<td>17</td>
<td>0.135</td>
</tr>
<tr>
<td>Medium</td>
<td>2,369</td>
<td>12</td>
<td>0.157</td>
</tr>
<tr>
<td>High</td>
<td>1,963</td>
<td>22</td>
<td>0.349</td>
</tr>
</tbody>
</table>

- Transmission rates for risk groups were significantly different (p=0.005)
- VE for each risk category was statistically similar.
- These observations are exploratory and hypothesis-generating
Baseline versus time-varying risk

Cumulatively 58.2% reported high risk at some time during the study (ever high risk)

<table>
<thead>
<tr>
<th>Risk Assessment</th>
<th>risk:treatment interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline risk (pre-hoc analysis)</td>
<td>p = 0.36</td>
</tr>
<tr>
<td>High or rising above baseline to medium or high vs low-medium (post-hoc)</td>
<td>p = 0.010</td>
</tr>
</tbody>
</table>

VE for low-medium risk = 68% (p=0.002 95% CI 34-84%)
VE for rising or high risk = 5% (p=NS 95% CI -46-38%)

This may reflect the transient protective effect of the vaccine regimen rather than imply protection only in “lower risk” individuals.
Traditional High Risk Group Analysis

- 19 of 125 (15.2%) infections were in high-risk groups (mITT)
  - Same-gender sex risk (14)
  - CSW (2)
  - IDU (5)

- Equivalent distribution across study arms
Does Vaccine Efficacy Appear Transient?

(Kaplan-Meier-based estimates)

<table>
<thead>
<tr>
<th>month</th>
<th>mITT</th>
<th></th>
<th>PP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Efficacy</td>
<td>Events</td>
<td>Efficacy</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>54%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>60%</td>
<td>21</td>
<td>68%</td>
</tr>
<tr>
<td>18</td>
<td>67</td>
<td>44%</td>
<td>41</td>
<td>41%</td>
</tr>
<tr>
<td>24</td>
<td>82</td>
<td>36%</td>
<td>53</td>
<td>27%</td>
</tr>
<tr>
<td>30</td>
<td>95</td>
<td>36%</td>
<td>62</td>
<td>31%</td>
</tr>
</tbody>
</table>

Efficacy did not decrease with time in a statistically meaningful way
## Frequency and Magnitude of Binding Antibody Responses

### 2 and 24 weeks post-final vaccination

<table>
<thead>
<tr>
<th>Antigen</th>
<th><em>Reciprocal GMT (Range)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 weeks</td>
</tr>
<tr>
<td>B gp120</td>
<td>140/142 (99%)</td>
</tr>
<tr>
<td></td>
<td>31207 (800-204800)</td>
</tr>
<tr>
<td>E gp120</td>
<td>14558 (200-204800)</td>
</tr>
<tr>
<td>B p24</td>
<td>74/142 (52%)</td>
</tr>
<tr>
<td></td>
<td>205 (100-1600)</td>
</tr>
</tbody>
</table>

*P*<0.0001 compared to placebo group - all Antigens

*: P<0.001 compared to 2 week time-point
Model for Early Effect and Low Risk Effect
Post-hoc analyses – generate hypotheses

- Time dependant effects:
  - VE appears to peak early
    - VE = 60% at 12 months after initial vaccination
    - 95% CI 22-80%
  - No vaccine temporal difference for VL effect

- High or rising risk at least once versus those who maintained low or medium risk
  - interaction of risk and acquisition efficacy (\( P = 0.010 \))
  - Few classical high risk participants or events
What we would want next

- Extend the observation of early 60% efficacy by increasing the durability of such protection (additional boosts)
  - Heterosexual risk groups in Asia

- Ensure that we can elucidate correlates/surrogates of protection with more appropriate sample collection.
  - Mucosal collections

- Establish protection in higher incidence populations (additional boosts)
  - Heterosexuals in sub-Saharan Africa
  - MSM in Africa and Asia
Phase 2b, Randomized, Placebo-Controlled Test-of Concept Trial to Evaluate the Safety and **Efficacy** of a Multiclade HIV-1 DNA Plasmid Vaccine Followed by a Multiclade Recombinant Adenoviral Vector Vaccine in HIV-Uninfected, Adenovirus Type 5 Neutralizing Antibody Negative, Circumcised Men and Male-to-Female Transgender Persons Who Have Sex with Men

**Short Title:** VRC DNA/rAd5 Multiclade, Multigene HIV-1 Vaccine Regimen in HIV(-) MSM

**Version 3.0**

Principal Investigator - Scott M. Hammer, M.D.
HVTN 505: Primary Objectives

- **Acquisition** (4 weeks post-boost through month 24)
- Viral load post-infection
- Safety
HVTN 505

| Months | 0 | 1 | 2 | 3 | 6 | 9 | 12 |

CMV-R promoter

- Env A
- Env B
- Env C
- gag B
- pol B
- nef B

rAd5

- Env A
- Env B
- Env C
- gag/pol B

8 May 2012
# HVTN 505: Vaccination Schedule

<table>
<thead>
<tr>
<th>HVTN 505 Groups</th>
<th>Prime</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Day 0</td>
<td>Wk 4</td>
</tr>
<tr>
<td>Wk 8</td>
<td>Wk 24</td>
<td></td>
</tr>
</tbody>
</table>

**Group 1: Vaccine**
- 1100 DNA (4 mg) Day 0
- 1100 DNA (4 mg) Wk 4
- 1100 DNA (4 mg) Wk 8
- 1100 rAd5 (10^{10} PU) Wk 24

**Group 2: Placebo**
- 1100 PBS Day 0
- 1100 PBS Wk 4
- 1100 PBS Wk 8
- 1100 FFB Wk 24

- 80% power to detect 50% reduction in HIV-1 acquisition
- 93% power to detect 1 log_{10} reduction in setpoint VL if VE=0; 84% power if VE=50%
- Time-driven and not event-driven
HVTN 505: Primary Endpoints
Week 28 (4 weeks post-boost) through Month 24

Post-infection diagnosis visit schedule

Weeks 0  2  4  6  8  10  12  14  16  20  24

Diagnosis of HIV Infection Acquisition (VE) endpoint

VL endpoint

VL setpoint = average of all values between week 10 and 20 after diagnosis study visit and prior to ART initiation
What will we learn from HVTN 505?

- Is the rate of HIV acquisition reduced by >50%?
- Is mean VL reduced by >1 log_{10} genome copy/ml?
- Is there a sieve effect or selective escape from vaccine-induced antibody or T cell responses in breakthrough viruses?
- Is there an immune correlate of risk?
Definitions

**Correlate of Risk**- an immune response that predicts whether vaccinees become HIV-1 infected.

It may be causally related to protection from infection, or may be only a surrogate marker for another factor.
Sieve Analysis of RV144 Breakthrough Viruses supports importance of V2 loop
Sieve Analysis of V2

- Comparison of viruses from HIV-1 infected vaccine versus HIV-1 infected placebo recipients
- These are not transmitted/founder viruses—the mean time to last negative visit was ~ 3 months.
- V2 was a major focus of analysis.
- Analysis—collaboration between Dr. Morgane Rolland (MHRP), Dr. Jim Mullins (UW), SCHARP
Results: Sites 169 and 181 Separately

- For each site, VE significantly differs against match vs. mismatched infection
  - Vaccine reduced infection rate 3.77 times more for 181-mm than 181-m.
- Positive VE for 169-matched infection and 181-mismatched infection
- The sieve analysis suggests that the vaccine selectively blocked acquisition with 169-matched and with 181-mismatched virus; but conferred no protection against 169-mismatched or 181-matched virus.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. Infections</th>
<th>Est. VE</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>169m</td>
<td>87</td>
<td>48%</td>
<td>18% to 66%</td>
<td>0.0036</td>
</tr>
<tr>
<td>169mm</td>
<td>23</td>
<td>-45%</td>
<td>-258% to 33%</td>
<td>0.30</td>
</tr>
<tr>
<td>181m</td>
<td>88</td>
<td>-20%</td>
<td>-26% to 45%</td>
<td>0.38</td>
</tr>
<tr>
<td>181mm</td>
<td>22</td>
<td>78%</td>
<td>35% to 93%</td>
<td>0.0028</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>No. Infections</th>
<th>Est. HR / HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>169mm/169m</td>
<td>87/23</td>
<td>2.73</td>
<td>1.08 to 6.92</td>
<td>0.034</td>
</tr>
<tr>
<td>181m/181mm</td>
<td>22/88</td>
<td>3.77</td>
<td>1.19 to 11.92</td>
<td>0.024</td>
</tr>
</tbody>
</table>
The case control correlates data suggest 2 hypotheses:

- Binding to gp70:V1V2 correlates inversely with HIV infection rate?
  - A244 and MN V2 crown linear peptides show similar effects
  - Linear epitope microarray data suggest V2 effect
- Anti-Env IgA M-B correlates directly with HIV infection rate

Sieve analysis suggests a V2 effect

Other secondary analyses identify additional potential inverse correlations

- Cytokine production after stimulation with Env peptides
- IgG binding to gp120 A244 gD-
- IgG binding to gp120 TH023 gD-
Questions

- Will these correlate of risk generalize to....
  - These products in Thai MSM?
  - ALVAC-gp120 engineered for heterosexuals in Africa?
  - Other HIV vaccines such as DNA/Ad5?
  - WARNING—it is textbook (Stan Plotkin’s) knowledge that different vaccines for the same pathogen can have different correlates of risk/protection.

- Is the V2 finding a marker for high Env responders?

- What effector function do binding Ab subserve...mucosal Nab?

- What binding specificities and effector functions do mAb from RV144 vaccine recipients possess?
Vaccine Therapy

- Identification of HIV infection in early acute viremia is feasible

- Destruction of immune system is rapidly progressive and targets HIV specific T cells
  - **Hypothesis:** Early intervention preserves immune function and allows vaccine to induce protective responses

- **HAART with active and passive immunization**

**Develop interventions**

- **time limited strategies to**
  - alter viral set-point durably,
  - reduce latent reservoirs and
  - ultimately obtain a functional cure
Ad26-MVA +/- protein

Barouch et al *Nature* 482:89-93 02 Feb 2012
Immunogenicity and Protective Efficacy of Heterologous Ad26/MVA Regimens in Rhesus Monkeys

- 40 rhesus monkeys immunized with the following vectors expressing SIVsmE543 (E660) Gag, Pol, Env
  - DNA/MVA (N=8)
  - MVA/MVA (N=8)
  - Ad26/MVA (N=8)
  - MVA/Ad26 (N=8)
  - Sham (N=8)

- Monkeys: Mamu-A*01/B*17/B*08 negative, TRIM alleles balanced
- Prime at week 0 (or week 0, 4, 8 for DNA)
- Boost at week 24
- Low-dose, heterologous IR SIVmac251 challenges at week 52 (DB stock)
- Immunogenicity assays prior to challenge
  - ELISA
  - IFN-g ELISPOT
  - Multiparameter ICS

8 May 2012
Heterologous Vector Regimens Partially Resist Heterologous, Repetitive, IR SIVmac251 Challenges
MVA/Ad26 and Ad26/MVA Regimens Lower Early Setpoint Viral Loads Following SIVmac251 Infection

Sham: 5.75
MVA/MVA: 6.09
DNA/MVA: 5.47

MVA/Ad26: 4.55
Ad26/MVA: 3.83

3x resistance to infection
4/8: viremia blunted 1 log
3/8: rapid virologic control
1/8: persistently uninfected
Ad26-MVA correlates analysis

- Acquisition endpoint.
  - envelope binding antibody r=.79 p<.0001.
  - V2 binding antibody r=0.65 p<0.0001
  - neutralization antibody r=.50 p=.0034
  - ADCC r=.38 p=.034

- set point viral load endpoint, Many correlates (N=27);
  - prechallenge gag elispot count and gag elispot breadth were both correlated (r=-.50 p=.006 and r=-.64 p=.0002, respectively) with the endpoint.
  - peak envelope binding antibody r=-.70 followed by prechallenge neutralizing antibody r=.67.
Basic Active Vaccine Therapy Design

VL <50 copies/mL x 6 months

mHAART (6 months)

Day 0 1 mo 2 mo 4 mo 6 mo 7 mo 18 mo 5 years

HIVIS DNA/placebo

MVA-CMDR/placebo

Re-initiation of HAART as clinically indicated

Long-term flu
Basic Active Vaccine Therapy Design

- Objectives
  - Viral set-point
  - Time to
    - Detectable rebound viremia
    - Resumption of HAART
  - Viral Load peak during rebound viremia
  - Peripheral blood CD4 count at set-point
  - Markers of immune activation
  - Gut CD4+CCR5+ T cell preservation
  - GALT and PBMC HIV DNA
Acknowledgements

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- National Institutes of Health (NIH)
- Division of AIDS (DAIDS)
- U.S. Department of Health and Human Services (HHS)

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