HIV Vaccine Efficacy Trials; Lessons and Opportunities for Future Research

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INTEREST Conference
Harare, Zimbabwe
Outline

- Need for an HIV Vaccine
- Efficacy Trials up to date
- Lessons from failed Efficacy trials and opportunities for Research
- Lessons form RV 144 and P5 follow up studies
Vaccines work really well!

Vaccines are among the most successful medical interventions (eradicated or controlled smallpox, polio, measles...)

Before vaccines | % DECREASE | After vaccines
---|---|---
DIPHTHERIA | 100% | 0%
H. INFLUENZA | 99% | 99%
HEPATITIS A | 91% | 91%
HEPATITIS B | 83% | 83%
MEASLES | 99% | 99%
MUMPS | 99% | 99%
PERTUSSIS | 93% | 93%
PNEUMOCOCCAL DISEASE | 74% | 74%
POLIO | 100% | 100%
RUBELLA | 99% | 99%
CONGENITAL RUBELLA | 99% | 99%
SMALLPOX | 100% | 100%
TETANUS | 98% | 98%
VARICELLA | 69% | 69%

Before: 21,053 | After: 0
Before: 28,000 | After: 243
Before: 117,333 | After: 11,049
Before: 46,232 | After: 11,219
Before: 550,217 | After: 41
Before: 162,344 | After: 982
Before: 203,752 | After: 13,506
Before: 14,689 | After: 4,147
Before: 16,314 | After: 0
Before: 47,745 | After: 4
Before: 112 | After: 1
Before: 22,005 | After: 0
Before: 590 | After: 14
Before: 6,085,129 | After: 449,362
A Vaccine Is Essential to End AIDS

Potential impact of an AIDS vaccine as part of the UNAIDS Enhanced Investment Framework (IFE)

* Illustrative vaccine with an assumed efficacy of 70%, not representative of any specific candidate. Coverage in generalized epidemics: routine 10 years old 70%, catch-up 11-14 years old 60%, 15-17 years old 55%, 18-49 years old 50%; in high risk populations in concentrated epidemics: 50%

Modeling project – UNAIDS, Futures Institute, IAVI, AVAC [funded by USAID]
Several new prevention measures have been realized in the last few years.

Although efficacious, the interventions are faced with potential challenges of access and adherence.

HIV vaccine has potential to address some of these challenges.

A clinical trial- RV 144 has shown that an HIV vaccine is possible.
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

- 172 of 1836 men were infected.

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

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

Duerr et al
J Infect dis 2012
Late increase is not significant

There was no increased risk to HIV-1 infection in the vaccine group

Hammer et al.
N Engl J Med 2013
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
Protective efficacy of adenovirus/poxvirus vaccines in Animals

- 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 ($p < 0.0001$)

Barouch et al., Nature, 2012
Protective efficacy of a global HIV mosaic vaccine in animals

Barouch et al. Cell 2013

- Env-specific binding antibodies strongly correlated with protection
- Non-neutralising ADCP response correlated with protection
Ad26/MVA: Clinical Trials

- HIV-V-A002 (MENSCH) – Crucell sponsored phase I
  - Rolls over prior Ad26EnvA vaccine recipients (participants in IPCAVD001) and boosts with MVA product with mosaic sequence inserts (MVAmos)
  - Comparison to MVAmos only arm

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Week 0</th>
<th>Week 12</th>
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<tbody>
<tr>
<td>1 Healthy</td>
<td>12</td>
<td>MVA mos</td>
<td>MVA mos</td>
</tr>
<tr>
<td>2 Healthy</td>
<td>3</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>3 Previously in Ad26.ENVA.01</td>
<td>8-20</td>
<td>MVA mos</td>
<td>MVA mos</td>
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<tr>
<td>4 Previously in Ad26.ENVA.01</td>
<td>2-5</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
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</table>

- All vaccinations complete
- MVA mos vaccine was very well tolerated
- Immunogenicity data in development

Study Site: Brigham and Women’s Hospital, Boston
**HIV-V-A004 = APPROACH**

**APPROACH** = Ad26 and MVA mosaic with gp140 Protein to **PROtect** subjects from **Acquiring** HIV

- Crucell sponsored phase 1b/2a
- 8-arms, 400 subjects
- Ad26/Ad26 with and without gp140 protein vs. Ad26/MVA with and without protein vs. Ad26/protein
- Two dose of gp140 trimeric protein evaluated (alum adjuvant)
- MHRP contributing sites in Uganda (1), Thailand (2)
- IAVI and Ragon Institute contribute sites in Rwanda, Uganda, and South Africa
- Started vaccinations in US: Feb 2015
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

(time in years)
RV144 – Only link to Clinical Efficacy

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>
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<tbody>
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<tr>
<td>12</td>
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<td>0.15</td>
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<td>0.58</td>
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<td>0.84</td>
<td>0.103</td>
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<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>

Waning durability?
Follow up Findings Provide Clues

**Correlates of Risk (CoR)**

Provided clues how RV144 protected

**Plasma Anti-V1V2** (Decreased risk)

**Plasma Anti-Env IgA** (Increased risk)

**RV144 Sieve Analysis**

Reinforces the importance of a region on HIV (Env V2)
Questions that needed answers

- Would additional boosting be required to extend efficacy seen in 1st year?
- Would the approach work against another HIV subtype?
- Would similar efficacy be seen in high risk individuals?
- Would an adjuvant improve magnitude and duration of responses?
- What are immune responses at the mucosa?
Building on RV144: Immunogenicity Studies

RV305, RV306 and RV328
Building on RV144: Immunogenicity Studies

RV305, RV306 and RV328

- **RV144 extended boost study (RV305)**
  - Existing RV 144 uninfected vaccine recipients
  - Objective—Evaluate late boosts
  - Extensive sampling with mucosal collection and biopsy

- **Intensive immunogenicity study (RV306)**
  - ALVAC-HIV (vCP1521) + AIDSVAX B/E
  - Mucosal secretions and gut biopsy
  - 12 month boost

- **AIDSVAX only (RV328)**
  - Provide cells / specimens for analysis of AIDSVAX only responses to compare with ALVAC + AIDSVAX prime boost
  - Extensive sampling
RV144, RV305, RV306, and RV328 Schedules

**Vaccination Schedules**

- **RV 144**
  - Months: 0, 3, 6, 9
  - ALVAC®-HIV (vCP1521) or placebo

- **RV 305**
  - Months: 0, 3, 6
  - AIDSVAX® B/E gp120 or placebo
  - No Boost

- **RV306**
  - Months: 0, 3, 6, 9, 12

- **RV328**
  - Months: 0, 3, 6, 9, 12

**RV305 Start**
Geometric Mean Titers of IgG Responses to gD+ gp120 A244

Karasavvas….Kim et al. AIDS Vaccine 2013
GLOBAL STRATEGY: Planned studies are interdependent and will amplify global impact and regional relevance.

**Precedent for vaccine efficacy**

Focus on regional public health impact

- **THAILAND**
  - High risk MSM
- **RSA**
  - High risk heterosexual
- **US/EUROPE**
  - High risk
- **SOUTHEAST ASIA**
  - High risk groups (hetero, MSM, IVDU, CSW)
- **SOUTHERN AFRICA**
  - High risk

Future amplification of global reach

**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 to build on the success of RV 144 and provide answers to some unanswered questions and incorporate knowledge into next generation vaccine concepts

Logos of participating organizations: Bill & Melinda Gates Foundation, MHRP, National Institute of Allergy and Infectious Diseases, SANOFI PASTEUR, HIV Vaccine Trials Network, Novartis Vaccines, South African Medical Research Council.
What's Next for the Pox-Protein Public-Private Partnership (P5)?

- **2012**: RV144 31% efficacy 2003-2009
  - Thailand Phase IIb/III ALVAC/AIDSVAX Clade B, A/E
  - Analysis of samples & correlates of risk (2009-ongoing)
  - Tests among RV144 participants whether additional boosts of RV144 vaccine extend and increase immune responses

- **2013**: RV305 Start 2012
  - Thailand Phase I & II ALVAC/AIDSVAX Clade B, A/E
  - Test among new participants to explore systemic and mucosal responses to RV144 regimen + boosts

- **2014**: RV306 Start 2013
  - Results: RV305 helped determine which boost combinations increase and optimize immune responses. As with all candidates, duration of immune responses is still an issue. Results for RV306 anticipated in 2015.

- **2015**: RV403 Start 2015
  - Possible Thai efficacy trial Start date uncertain
  - Thailand Phase III Clades B, A/E ALVAC/Protein boost to be determined

**Product/Manufacturing Challenges**

- **2010**: P5 formed to coordinate the follow-up research agenda.
- **2011**: Novartis joined P5 to develop new gp120 protein “boost” component, with a new adjuvant.
- **2014**: Novartis vaccine division sold to GSK, future of gp120 manufacturing becomes less clear.

**Development Track**

- To identify a vaccine candidate for eventual licensure, manufacturing and delivery.

- **2014**: HVTN 097 Start 2014
  - Similar immune response among South Africans to the Thai trial participants.

- **2015**: HVTN 100 Start 2015
  - South Africa Phase VII ALVAC/gp120/MF59 adjuvant Clade C

- **2016**: HVTN 070 Start 2014
  - South Africa Phase III ALVAC/gp120/MF59 adjuvant Clade C

**Research Track**

- To identify ‘correlates of immunity’, biological markers that signify immunity to HIV, which will improve efficiency of future vaccine trials.

- **2012**: Southern Africa Phase III MF59 vs alum adjuvants Clade C
  - HTVN 070 Start 2013

- **2013**: Southern Africa, US and Switzerland Phase III DNA Protein, MF59 AS01B adjuvant Clade C
  - HTVN 097 Start 2013

- **2014**: Southern Africa Phase III DNA, ALVAC Protein, MF59-AS01B adjuvant Clade C
  - HTVN 107 Start 2015

- **2015**: Southern Africa, US Phase VII DNA, Protein, MF59 AS01B adjuvant Clade C
  - HTVN 108 Start 2015

- **2016**: Southern Africa Phase VII DNA Protein, MF59 AS01B adjuvant Clade C
  - HTVN 111 Start 2014

- **2017**: Southern Africa Phase IIb Efficacy study of down-selected vaccine regimens Clade C
  - HTVN 701 Possible Start 2018
Hypothetical Schema of a Vaccine vs. Placebo Trial

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Number</th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 3</th>
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<th>Month 12</th>
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<td>ALVAC + prot</td>
<td>ALVAC + prot</td>
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- HIV negative subjects enrolled and tested for HIV infection for 3-monthly for a maximum of 36 months
- Primary endpoint at 24 months
Acknowledgements

- Ministry RV144 volunteers and community members of Public Health, Thailand
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- Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH
- Global Solutions for Infectious Diseases
- 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
- RV 305 participants

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RV144 Correlates Working Group
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Beth Israel Deaconness Medical Center
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SCHARP
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