Pathway to HIV Vaccine Efficacy Trials

Pox-Protein Public-Private Partnership (P5) and MOSAIC HIV Prophylactic Vaccine (JnJ/Janssen)

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The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.
First Sign of Efficacy: RV144

The Thai HIV Vaccine Study

- First HIV vaccine to show efficacy
  - Major international collaboration with 16,000 Thai volunteers
  - Showed a preventive vaccine IS possible
- Efficacy of ~60% at 1 year; demonstrated 31.2% efficacy at end of study (3.5 years)
RV 144 demonstrated efficacy for HIV acquisition

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*)
## RV144: Higher Efficacy Early in Trial

<table>
<thead>
<tr>
<th>month</th>
<th>Events</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>16</td>
<td>54%</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>60%</td>
</tr>
<tr>
<td>18</td>
<td>67</td>
<td>44%</td>
</tr>
<tr>
<td>24</td>
<td>82</td>
<td>36%</td>
</tr>
<tr>
<td>30</td>
<td>95</td>
<td>36%</td>
</tr>
</tbody>
</table>

Researchers seek to extend and increase the immune response

*not part of pre specified analysis*
RV144: Follow up

- Intensive Laboratory Studies
  - Provides clues as to why vaccine protected some volunteers
    - Target on the HIV envelope (V2)
  - International collaboration with more than 120 scientists
  - Several subsequent studies and papers in *Lancet*, *Nature* and *Cell* confirm V2 as an important potential target

*RV144 continues to inform vaccine development and impact clinical trial design*
Future Directions: Clinical Trials

- RV305A: Rollover vaccination of RV305
- RV306: ALVAC-HIV + AIDSVAX B/E per RV144 with late boost at 12, 15, or 18.
- RV328: AIDSVAX B/E at 0, 1, 6, 12
- RV403: Ph II ALVAC + AIDSVAX B/E L(MPLA)
- RV349: Ph IIb ALVAC + gp120 B/E in ?
- [proposed] Ad26/MVA-mosaic ± protein
RV144 – Its Importance

- RV144 trial provided the test of concept that we could prevent acquisition of infection.
- Major shift from attempting to reduce post acquisition viral load to reducing the frequency of acquisition.
- Surprising finding that a region of the HIV envelope in the V1/V2 variable domain appears to be a major susceptibility point for attacking HIV.
P5 Overview

- **Who We Are:** The Pox-Protein Public-Private Partnership (P5) is a diverse group of organizations committed to building on the success of RV144, the only HIV vaccine clinical trial to date to show efficacy.

- **Our Goal:** The P5 aims to produce an HIV vaccine that can have significant public health impact in Southern Africa and to deepen our understanding of immune responses associated with HIV prevention.
Pox-Protein Public-Private Partnership (P5)

**What's Next for the Pox-Protein Public-Private Partnership (P5)?**

- **RV144**
  - 2012: Analysis of samples & correlates of risk (2009-ongoing)
  - Tests among RV144 participants whether additional boosts of RV144 vaccine extend and increase immune responses
  - Thailand Phase I/II
    - ALVAC/AIDSVAX Clade B, A/E
  - 2014: Novartis vaccine division sold to CER, future of gp120 protein “best” component, with a new adjuvant
  - 2014: Novartis vaccine division sold to CER, future of gp120 protein manufacturing becomes less clear
  - 2018: Possible Thai efficacy trial
    - Start date uncertain
    - Thailand Phase III
      - Clades B, A/E ALVAC/Protein boost to be determined

- **RV305**
  - Start 2012
  - Test among RV144 participants whether additional boosts of RV144 vaccine extend and increase immune responses
  - Thailand Phase I/II
    - ALVAC/AIDSVAX Clade B, A/E

- **RV306**
  - Start 2013
  - Test among new participants to explore systemic and mucosal responses to RV144 regimen + boosts

- **RV403**
  - Start 2015
  - Testing ALVAC-HIV prime and AIDSVAX BE formulated with new adjuvant in Uganda, Mozambique and Thailand.

**Product/Manufacturing Challenges**

- 2009: Manufacturer NOVIA, no longer operational, new manufacturer needs to be identified.

**Development Track**

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

**Research Track**

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

**Possible Thai efficacy trial**

- Start date uncertain

**South Africa Phase III**

- ALVAC/gp120/AS01B
  - Adjuvant Clade C

- **HVTN 097**
  - Start 2013
  - South Africa Phase I/II
    - ALVAC/AIDSVAX Clade B & E

- **HVTN 100**
  - Start 2015
  - South Africa Phase VII
    - ALVAC/gp120/AS01B
    - Adjuvant Clade C

- **HVTN 101**
  - Possible Start 2016
  - Down-selection from these Phase VII trials
  - Southern Africa, US
    - Phase VII
      - DNA Protein, MF59/AS01B
      - Adjuvant Clade C

- **HVTN 109**
  - Start 2015
  - Southern Africa, US
    - Phased V
      - DNA Protein, MF59/AS01B
      - Adjuvant Clade C

- **HVTN 108**
  - Start 2015
  - Southern Africa, US
    - Phased V
      - DNA Protein, MF59/AS01B
      - Adjuvant Clade C

- **HVTN 701**
  - Start 2016
  - Efficacy study of down-selected vaccine regimens
    - Clade C

**P5**

- **RV144**
  - 31% efficacy
  - 2003-2009

**Rationale**

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

**Development Track**

- This track **supports the licensure of a subtype C-based HIV vaccine** similar to the prime-boost regimen pioneered in RV144.

- To improve on efficacy of the RV144 regimen, these trials will test a new adjuvant that could boost the immune response and add a vaccination boost to prolong protection.

**Research Track**

- This track **improves scientific understanding of other possible HIV vaccine regimens**.

- These studies test different pox-protein and related vaccine candidates with a variety of adjuvants as part of the search for next-generation HIV vaccines.
An HIV Vaccine for Southern Africa

- A series of early-stage trials that started in 2015
  - Aims to prolong and improve the level of protection

- The trials in Southern Africa use a vaccine regimen adapted to subtype C
  - The main circulating HIV subtype in the region.

- The P5 aims to produce a licensable HIV vaccine that can have a significant public health benefit in Southern Africa

African HVTN clinical trials sites: Cape Town, Durban (2), Harare, Klerksdorp, Kwa Zulu Natal, Lilongwe, Lusaka, Maputo, Mbeya, Soshanguoe and Soweto (2)
### Ongoing and Planned P5 Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Start (Projected)</th>
<th>Site</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Development Track</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVTN 100</td>
<td>Phase I/II</td>
<td>Q1 2015</td>
<td>South Africa</td>
<td>ALVAC/gp120 MF59 adjuvant</td>
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<tr>
<td>HVTN 702</td>
<td>Phase III</td>
<td>Q3 2016</td>
<td>South Africa</td>
<td></td>
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<tr>
<td><strong>Research Track</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVTN 107</td>
<td>Phase I</td>
<td>Q3 2015</td>
<td>Southern Africa</td>
<td></td>
</tr>
<tr>
<td>HVTN 111</td>
<td>Phase I</td>
<td>Q3 2015</td>
<td>Southern Africa</td>
<td></td>
</tr>
<tr>
<td>HVTN 108</td>
<td>Phase I/II</td>
<td>Q1 2016</td>
<td>US &amp; Southern Africa</td>
<td>Various combinations of ALVAC, gp120 protein, DNA and adjuvants</td>
</tr>
<tr>
<td>HVTN 113</td>
<td>Phase I/II</td>
<td>Q1 2016</td>
<td>Southern Africa</td>
<td></td>
</tr>
<tr>
<td>HVTN 701</td>
<td>Phase IIb</td>
<td>Q2 2018</td>
<td>Southern Africa</td>
<td>Up to three vaccine regimens will be selected from products tested in HVTN 108, 111 and 113</td>
</tr>
</tbody>
</table>
Development Track Objective:
Increase Vaccine Efficacy from 30% to $\geq 50$

- **Scientific rationale and feasibility:**
  - *Trend* of RV144 vaccine efficacy (VE) at 12 mos: 60%
  - Boost may impact protection level/durability
  - Alternative adjuvant may impact magnitude, quality and durability of CD4 T cell and Ab responses

- **VE 50% for 3 years offers a significant public health benefit for regional epidemics**
  - Population modeling data for Benin and rural Zimbabwe suggest that a vaccine with VE$>30\%$ could significantly reduce the number of new infections
  - Thai MOPH modeling supports the rationale for a 50% effective HIV vaccine in high-risk populations
Moving Forward in Thailand

AIDS Vaccine Efficacy Consortium (AVEC)

- Government of Thailand announced commitment to build on RV144 by supporting:
  - Future HIV vaccine efficacy study
  - Flexible biologics manufacturing capability that could support the production of 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.
Development of a Global HIV Vaccine for Prevention: Partners

IAVI  BIDMC  Harvard  MHRP  WRAIR  NIAID/HVTN
An HIV vaccine designed for protection against all HIV subtypes

Different HIV-1 clades dominate in different geographic regions

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

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

Protective Efficacy of a Global HIV-1 Mosaic Vaccine against Heterologous SHIV Challenges in Rhesus Monkeys
Dan H Barouch et al., 2013

Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys
Dan H Barouch et al., 2010
Heterologous Prime-Boost with Adeno and Pox vectors harbouring gag-pol-env Mosaic Inserts Elicit Protective Immunity Against heterologous SHIV-SF162P3 Challenges

<table>
<thead>
<tr>
<th></th>
<th>Ad.mos</th>
<th>MVA.mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad.mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHIV-SF162P3 CHALLENGES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>low-dose IR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>52</td>
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</table>

Note: SHIV challenge model ~100-fold more infectious than HIV in humans

<table>
<thead>
<tr>
<th>P-Value vs Sham*</th>
<th>Per-Exposure Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad/MVA</td>
<td>0.002</td>
</tr>
<tr>
<td>Ad/Ad</td>
<td>0.007</td>
</tr>
<tr>
<td>Sham</td>
<td>N/A</td>
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</table>

*Cox proportional hazard model

Correlates of Protection

<table>
<thead>
<tr>
<th>Assay</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>0.00000012</td>
</tr>
<tr>
<td>ADCP</td>
<td>0.00030</td>
</tr>
<tr>
<td>NAb</td>
<td>0.00072</td>
</tr>
</tbody>
</table>

Barouch et al. Cell 2013
Protective efficacy of Adeno-mosaic prime and GP140 trimer boost in stringent NHP SIV and SHIV models

Protective efficacy of the Ad/Env SIV vaccine against SIVmac251 challenges

Protective efficacy of the Ad/Env HIV-1 vaccine against SHIV-SF162P3 challenges

<table>
<thead>
<tr>
<th>Number of IR Challenges</th>
<th>% Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of IR challenges</th>
<th>% Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
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<table>
<thead>
<tr>
<th>Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad /Env</td>
<td>90%</td>
</tr>
<tr>
<td>Ad Alone</td>
<td>75%</td>
</tr>
<tr>
<td>Env</td>
<td>49%</td>
</tr>
<tr>
<td>Env Alone</td>
<td>17%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad /Env (N=12)</td>
<td>90%</td>
</tr>
<tr>
<td>Ad Alone (N=12)</td>
<td>75%</td>
</tr>
<tr>
<td>Sham (N=7)</td>
<td>75%</td>
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</table>

<table>
<thead>
<tr>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad /Env (N=20)</td>
<td>79%</td>
</tr>
<tr>
<td>Env (N=8)</td>
<td>49%</td>
</tr>
<tr>
<td>Env Alone</td>
<td>17%</td>
</tr>
</tbody>
</table>

Dan 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
- MVA Mosaic vectors gag-pol-env
- Soluble trimer gp140 env proteins
- Soluble trimer gp140 env proteins

Regimen to be selected after Phase 1/2a
Overall Early Clinical Development Plan

Target vaccine regimen will have 2 or 3 components

- Establish safety of each component separate FIH studies
  - HIV-V-A002/IPCAVD006/MENSCH
    - FIH MVA-Mosaic
  - HIV-V-A003/IPCAVD008
    - FIH gp140 with and without Alum
  - HIV-V-A004/IPCAVD009/APPROACH
    - FIH Ad26.HIV and heterologous prime/boost regimens

- Additional Phase 1/2a studies under consideration
MENSCH/HIV-V-A002

FIH safety of MVA-Mosaic (also, FIH of mosaic insert)

A Phase I Study of Modified Vaccinia Ankara with Mosaic HIV Inserts in Healthy, HIV-Uninfected Adults, Some of Whom Have Previously Received an Adenovirus Type 26 ENVA.01 Vaccine

- To assess the safety of MVA Mosaic when given as a late boost to subjects previously vaccinated with Ad26.ENVA (in IPCAVD001) and naïve subjects

- Clinical site: Brigham and Women’s Hospital, Boston

- Population: healthy subjects, aged 18-50 years; N=25 (10 previously received Ad26.ENVA in IPCAVD001 and 15 naïve)

- Funders: BIDMC/Ragon and Crucell/Janssen

- MVA supplied by MHRP, manufacturing supported by DAIDS

- IND sponsor: Crucell/Janssen
MENSCH/HIV-V-A002

Current Status

- Vaccinations completed
- Immunogenicity analyses ongoing
HIV-V-A003

FIH safety of gp140 trimer

A first-in-human study to evaluate the safety, tolerability and immunogenicity of 2 dose levels of trimeric clade C gp140 protein, prior to dosing at Week 24 in HIV-V-A004

- Single-center (Miami Research Associates), randomized, placebo-controlled, double-blind clinical study in healthy HIV-uninfected adult male and female subjects
- Randomized 2:2:1 to one of three groups (gp140 DP, gp140 DP/adjuvant, or placebo, resp.)
- Subjects receive 2 injections 4 weeks apart
- IND sponsor: Crucell/Janssen
HIV-V-A003

Current Status

• Vaccinations completed

• Immunogenicity analyses in Q1 2016
FIH safety of Ad26.Mos.HIV

A Phase 1/2a Study to Evaluate the Safety/Tolerability and Immunogenicity of Homologous Ad26 Mosaic Vector Vaccine Regimens or Ad26 Mosaic and MVA Mosaic Heterologous Vector Vaccine Regimens, with High-Dose, Low-Dose or no Clade C gp140 Protein Plus Adjuvant

- To assess the safety and immunogenicity of the 3 components in several prime boost regimens
- 12 Clinical sites: USA, Rwanda, Uganda, South Africa, Thailand
- Population: healthy subjects, aged 18-50 years; N = 400
- IND sponsor: Crucell/Janssen
HIV-V-A004 = APPROACH

The path or route to the start of a technical climb. Although this is generally a walk or, at most, a scramble it is occasionally as challenging as the climb itself.
HIV-V-A004: Study Design

Healthy volunteers ≥18 to ≤50 yo

400 subjects, equal randomization to one of 7 regimens and placebo

4 wk screening

Wk 0

Wk 12

Wk 24

Wk 48 boost

follow-up

48 wks

All participants will receive Ad26.Mos.HIV at Wk 0 and 12; at Wk 24 and 48 they will receive Ad26.Mos.HIV or MVA.Mos or gp140 or a combination of either Ad26 or MVA with gp140

Note: for a subset of subjects who consent, mucosal samples will be collected (cervicovaginal, ano-rectal, ejaculate); and fecal specimens to evaluate enteric microbiome

Randomizations completed, vaccinations ongoing
High Level Clinical Development Plan

Phase 1/2a
- USA, Africa, Asia
  - Safety
  - Regimen selection
  - Dose confirmation
  - Evaluation of alternative schedules
  - Evaluation of Mosaic gp140
  - Evaluation of tetravalent Ad26

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

Phase 3/4
- Long term efficacy
  - Persistence of Immunity
- Additional trials
  - ≠populations
  - ≠countries
- BLA-MAA submissions?
From APPROACH to Efficacy trials
Developing criteria for regimen selection and Go/no Go

- The optimal regimen is hypothesized to elicit a
  - well balanced immune response with both antibody and T cell immunity
  - broad coverage of HIV clades A, B and C

- For the choice of regimen, emphasis will be on
  - immunological correlates that have been identified to **correlate with a reduced risk of SIV/SHIV infection in NHP**
    and on
  - immunological correlates that have been identified to **correlate with a reduced risk of HIV infection in RV144**

- For the ‘Go/No Go’ criteria, emphasis will be on
  - Antibodies and cellular responses as a measure of **vaccine take**
  - Providing an indication that the elicited antibodies are **functional**

The above is subject to continuous discussions/decisions by all Partners
Env Protein Boost Increased Functionality of Env-Specific Antibody Responses

Integrated Systems Serology Analysis of 150 Distinct Antibody Parameters
Fc Functionality of Env-Specific Antibody Responses Correlates with Protection Against Acquisition of SIVmac251

![Graph showing the correlation between polyfunctionality and challenges. The p-value is 0.004 and the correlation coefficient is 0.56.](image)