Current State of HIV Vaccine Development

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AVAC HVAD Webinar
May 17, 2018

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. The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70–25.
Outline of Talk

1. Background on RV144

2. Where we are with HIV vaccine trials today

3. Preparing for the future: Efficacy trials in a changing prevention landscape

4. Working together: Ongoing stakeholder engagement
RV144, the “Thai Trial”

Conducted 2003 – 2009
Heterosexual men and women aged 18 – 30
8,197 randomized to receive vaccine regimen, 8,198 randomized to receive placebo
Vaccinated over 6 months; followed for 3.5 years
Of Five Completed HIV Vaccine Efficacy Trials, only RV144 Showed Modest Protection

![Graph showing modified intention-to-treat analysis](image)

- **No. at Risk**
  - Placebo: 8198, 7775, 7643, 7441, 7325
  - Vaccine: 8197, 7797, 7665, 7471, 7347

- **Cumulative No. of Infections**
  - Placebo: 30, 50, 65, 74
  - Vaccine: 12, 32, 45, 51

**P = 0.04**

Rerks-Ngarm et al., NEJM 2009
Of Five Completed HIV Vaccine Efficacy Trials, only RV144 Showed Modest Protection

Efficacy: 31.2%

Rerks-Ngarm et al., NEJM 2009
Following Up on RV144

- RV144 vaccine was 31% effective in preventing HIV, but we need a minimum of 50% efficacy to license for non-research use in general population.

- So, how do we get to 50%?

1) Give additional vaccine boosts

2) Understand protective immune responses in more detail so we know what to target for improvement in future vaccines.

M. Robb et al, Lancet ID 2012  60% Efficacy
“Variable” Loops of HIV Envelope

Scaffold: Murine leukemia Virus gp70

Pinter A, Vaccine 1998

Cole KS, J. Virol 2004
People with higher antibodies to V1V2 were less likely to get infected with HIV.

- Estimated Relative Risk High vs Low = 0.29

Haynes et al., NEJM 2012
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Image Credit: Kayann for iStock via Thinkstock
Understanding Immune Responses in More Detail

1) Softcup Cervical Secretions

2) Semen

3) Rectal Secretions

Akapirat et al., PLOS One, 2018
What we have learned from RV144 follow up trials in Thailand to date

RV305 – 162 prior RV144 vaccine recipients received 2 boosts 6-8 years later

1) Late boosting with AIDSVAX increased immune responses above RV144, indicating that memory responses to RV144 were long-lived
2) Boosting with ALVAC alone did not improve responses
3) Antibody functions were improved, and took on more features of neutralizing antibodies
4) Antibodies were detected at mucosal sites
What we have learned from RV144 follow up trials in Thailand to date

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**RV306** – 360 healthy new volunteers received RV144 with one additional boost at month 12, 15, or 18

1) Late boosting improved humoral and cellular immune responses
2) Mucosal responses are detectable
3) Immune responses at month 15 or 18 were higher than with boosting at month 12
4) Durability of responses is unfortunately still short-lived
Building on RV144 in Africa

- RV144: Thailand
- HVTN 097: RV144 regimen
- HVTN 100: Clade C products/MF59 Adjuvant Month 12 boost
- HVTN 702: Phase 3

South Africa

Bill and Melinda Gates Foundation  
DAIDS/NIAID  
GSK, Novartis  
Sanofi-Pasteur  
Republic of South Africa Medical Research Council  
US Military HIV Research Program

www.hvtn.org
HVTN 702 Ongoing Efficacy Trial

### Thailand (RV144)
- **Cost**: $105 million
- **Volunteers**: 16,400
- **Efficacy**: 31% at 3.5 years

*a Not adjusted for inflation and calculated over the course of entire trial.

### South Africa
- **Cost**: $130 million
- **Volunteers**: 5,400
- **Efficacy goal**: >50% at 3 years

*b Estimated
A Parallel Approach: Mosaic Vaccines

Prime

Ad26.Mos4.HIV
Ad26 vectors with Mosaic gag-pol or env inserts

Ad26.Mos1.Gag-Pol
Ad26.Mos2.Gag-Pol
Ad26.Mos1.Env
(clade B-like)
Ad26.Mos2S.Env
(clade C-like)

Boost

gp140 Clade C
Soluble trimer gp140 env proteins

HVTN 705:
2,600 women in southern Africa
Estimated results in 2022
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Image Credit: Kayann for iStock via Thinkstock
### Ongoing or Upcoming Efficacy Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Intervention</th>
<th>Initiated</th>
<th>Expected Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 083</td>
<td>Long Acting Injectable Cabotegravir</td>
<td>December 2016</td>
<td>2021</td>
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<tr>
<td>DISCOVER</td>
<td>PrEP: F/TAF, F/TDF</td>
<td>August 2016</td>
<td>2020</td>
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<tr>
<td>MTN 042</td>
<td>Dapivirine Ring</td>
<td>Planned</td>
<td>?</td>
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<tr>
<td>AMP</td>
<td>VRC01 Antibody</td>
<td>March 2016</td>
<td>2022</td>
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<tr>
<td>PrEPVacc</td>
<td>TDF, DNA, MVA, Protein</td>
<td>Planned</td>
<td>2022</td>
</tr>
</tbody>
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Adapted from AVAC Trial Database, www.avac.org
Future Directions: Expanding Focus to Subtype B

95% of US DoD HIV positive health care beneficiaries have sub-type B HIV

Germany
70% Subtype B

Thailand
95 % Subtype AE
Biology of HIV Transmission May Vary Among TGW, MSM and CW

**CD4+ T cells**

Vaginal vs. Neo-Vaginal

**CD8+ T cells**

Vaginal vs. Neo-Vaginal

**Sigmoid CD4+ CCR5+ Target Cells**

MSM vs. CW vs. TGW
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It Takes a Global Village to Make an HIV Vaccine
Ongoing Results Dissemination is Key to GPP

The Armed Forces Research Institute of Medical Sciences (AFRIMS) invites you to a
Celebration of 25 Years of Thai-US Partnership on HIV Vaccine Development
Century Park Hotel,
Wednesday, May 9, 2018

The follow-on trials to the landmark RV144 Thai vaccine study continue to propel the vaccine field forward. Come learn about recent findings and how they are informing global vaccine development efforts.