HIV Vaccines: Marry HIV efficacy studies to science, but take shots on goal

Nelson L. Michael, M.D., Ph.D.
Colonel, Medical Corps, U.S. Army
Military HIV Research Program
Walter Reed Army Institute of Research

15 March 2016
GVIRF, JNB, RSA

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.
Four concepts, six trials, 30 years….

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccines</th>
<th>Phase</th>
<th>Risk Group</th>
<th>HIV Incidence per 100 Person-Years</th>
<th>Location</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vax003</td>
<td>AIDSVAX B/E gp120 in alum</td>
<td>III</td>
<td>injecting drug users</td>
<td>3.40%</td>
<td>Thailand</td>
<td>no vaccine efficacy</td>
</tr>
<tr>
<td>Vax004</td>
<td>AIDSVAX B/B gp120 in alum</td>
<td>III</td>
<td>high-risk women and MSM</td>
<td>2.60%</td>
<td>United States, Europe</td>
<td>no vaccine efficacy</td>
</tr>
<tr>
<td>HVTN 502</td>
<td>MRKAd5 HIV-1 gag/pol/nerf B</td>
<td>IIb</td>
<td>high-risk women and MSM</td>
<td>3.00%</td>
<td>United States</td>
<td>halted at interim analysis for futility; early transient increased infection in vaccinees</td>
</tr>
<tr>
<td></td>
<td>HVTN 503 HVTN Phambili</td>
<td>IIb</td>
<td>high-risk heterosexual men and women</td>
<td>3.70%</td>
<td>South Africa</td>
<td>no vaccine efficacy; late increased HIV infection in unblinded male vaccinees</td>
</tr>
<tr>
<td>RV144</td>
<td>ALVAC-HIV vCP1521, AIDSVAX B/E rgp120 in alum</td>
<td>III</td>
<td>community risk heterosexual men and women</td>
<td>0.28%</td>
<td>Thailand</td>
<td>31.2% efficacy at 42 months as primary endpoint; 60% efficacy at 12 months</td>
</tr>
<tr>
<td>HVTN 505</td>
<td>DNA, rAd5 (A, B, C)</td>
<td>IIb</td>
<td>circumcised MSM without pre-existing Ad5 antibodies</td>
<td>1.80%</td>
<td>United States</td>
<td>halted at interim analysis for futility</td>
</tr>
</tbody>
</table>

MSM, men who have sex with men; Ad5, adenovirus serotype 5.
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)
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*
High IgA associates with accelerated time to HIV-1 acquisition in the presence of HLA-DQB1*06.
Computational analysis of CD4 ICS reveals association with infection in RV 144 (Gottardo Nat. Biotech 2015)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
<th>q value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functionality score</td>
<td>0.63 (0.43-0.93)</td>
<td>0.019</td>
<td>0.088</td>
</tr>
<tr>
<td>Polyfunctionality score</td>
<td>0.58 (0.39-0.85)</td>
<td>0.006</td>
<td>0.059</td>
</tr>
<tr>
<td>IL4+IL2+CD154+</td>
<td>0.61 (0.42-0.90)</td>
<td>0.011</td>
<td>0.071</td>
</tr>
<tr>
<td>TNF$\alpha$+IFN$\gamma$+IL4+IL2+CD154+</td>
<td>0.57 (0.39-0.86)</td>
<td>0.006</td>
<td>0.059</td>
</tr>
</tbody>
</table>
Systems Serology: A computational method to assess FcR Ig structure and function: IgG3/ADCP = IgG1/ADCP?

Accelerating HIV-1 Vaccine Efficacy Trials

Dan H. Barouch1,* and Nelson L. Michael3,*
1Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA
2Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA 02139, USA
3U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD 20910, USA
*Correspondence: dbarouch@bidmc.harvard.edu (D.H.B.), nmichael@hivresearch.org (N.L.M.)
http://dx.doi.org/10.1016/j.cell.2014.10.046

Despite major advances in HIV-1 therapeutics and prevention strategies, the development of a safe and effective prophylactic HIV-1 vaccine will likely be critical for ending the global HIV-1 epidemic. Yet only four HIV-1 vaccine concepts have been tested for clinical efficacy over the past 30 years. In this Commentary, we describe key hurdles facing the HIV-1 vaccine development field and outline strategies to accelerate efficacy evaluation of novel HIV-1 vaccine candidates.

- Engage industry in public-private partnerships
- Share risk to advance products to efficacy testing
- Coordinate pre-clinical and clinical testing for cross-validation
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.
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, Soshanguye and Soweto (2)
MOSAIC HIV Prophylactic Vaccine

JnJ/Janssen—Overview Development Program

Current partners

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

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
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