HIV and Challenges of Vaccine Development

Richard A. Koup, MD
What Mediates Vaccine-induced Protection?

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>TYPE OF VACCINE</th>
<th>VACCINE-INDUCED PROTECTION</th>
<th>IMMUNE CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>Live</td>
<td>Antibodies, CTL</td>
<td>CTL</td>
</tr>
<tr>
<td>Rabies</td>
<td>Killed virus</td>
<td>Antibodies</td>
<td>Antibodies, CD4, CTL</td>
</tr>
</tbody>
</table>

Vaccine-induced antibodies (neutralizing) most commonly protect against viral infections.

Little evidence that T cells actually mediate protection against viral challenge.

However, once infected, T cells are clearly involved in mediating viral control.

- HSV types 1 and 2
- HIV-1 and HIV-2
- HHV 6

Presented at the 5th INTEREST workshop – 10 – 13 May 2010, Dar-es-Salaam, Tanzania
Therefore

- Efforts should be directed towards developing immunogens that stimulate neutralizing antibodies
- It has been difficult to induce neutralizing antibodies to HIV
  - Variable loops
  - Envelope is heavily glycosylated
  - Shielding of neutralization domains
  - Multiple clades of HIV with only limited cross-neutralization
- Early vaccines generated binding, but not neutralizing, antibodies
History of Efficacy Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>RV 144</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Canarypox/gp120</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>VaxGen gp120</td>
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<tr>
<td>2001</td>
<td>Merck 023/HVTN 502 (STEP)</td>
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<tr>
<td>2002</td>
<td>rAd5 gag/pol/nef</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>HVTN 503 (Phambili)</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>DNA/rAd5 env/gag/pol/nef</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>HVTN 505</td>
<td></td>
</tr>
</tbody>
</table>

- **Enrollment**
- **Follow-up**
- Final analysis
- Interim analysis

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History of Efficacy Trials

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STEP/Phambili Immunogenicity

• Merck rAd5 expressing HIV clade B Gag, Pol, and Nef
• Strong ELISpot and CD8 responses to HIV Gag, Pol, and Nef
• No Env, so no binding or neutralizing antibodies
• Expected result:
  – No effect on acquisition
  – Positive effect on lowering virus load
Lack of Efficacy in the STEP Trial: Merck rAd HIV Vaccine

rAd5 vaccine expressing Clade B Gag, Pol, Nef

Cumulative Number of HIV Infections: MITT population (males)

No Effect on Viral Load

Increased acquisition among Ad5 seropositive volunteers:
1) Unrelated to Ad-specific CD4 T cells as “targets” for infection
2) Associated with lack of circumcision
3) Associated with HSV-2 serostatus (but unrelated to vaccine)
## History of Efficacy Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Timeline</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>2 3 4 1</td>
<td>VaxGen gp120</td>
</tr>
<tr>
<td>1999</td>
<td>....2003</td>
<td>Canarypox/gp120</td>
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<tr>
<td>2004</td>
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<td>2010</td>
<td>1 2 3 4</td>
<td>HVTN 505</td>
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</tbody>
</table>

- **Enrollment**
- **Follow-up**
- ♦ **Final analysis**
- ★ **Interim analysis**

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Modest Efficacy in RV144: An Effect on Acquisition

ALVAC®-HIV (vCP1521)

- Canarypox expressing HIV-1 subtype E gp120 and HIV-1 subtype B gag and protease

AIDSVAX® B/E

- HIV gp120 from subtype E and subtype B

The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Berks-Ngarm, M.D., Penlee Pitsutthiphat, M.D., D.T.M.H., Sorachai Nithiyaphan, M.D., M.P.H., Jarantit Kaewklangwong, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Prempi, M.D., Chanthawat Namvai, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Berenson, M.D., Sanjeev Guranath, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Salkin, Ph.D., Deborah L. Bros, M.D., Suparat Chunsuksri, M.D., Chirawat Khumboonrug, M.D., Prasert Thongchulnonda, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunav Tamb, M.D., and Jerome H. Kim, M.D., for the MOPH–NAP+ Investigators

ABSTRACT

BACKGROUND

The development of a safe and effective vaccine against the human immunodeficiency virus type 1 (HIV-1) is critical to pandemic control.

METHODS

In a multinational, randomized, double-blind, placebo-controlled efficacy trial, we evaluated four priming-injections of a recombinant canarypox vector vaccine (AIDSVAX B/E) plus two booster injections of recombinant glycoprotein 120 subunit vaccine (ALVAC®) in 15,492 Thai men from 18 to 35 years of age. After 2 years, 10,014 subjects were randomized to receive the vaccine and 5,478 to receive placebo. The vaccine group was vaccinated at 4 months and the control group at 5 months. The vaccine group was stratified by HIV-1 subtype and randomization to subtypes E and B and to randomization to subtypes E and A.

RESULTS

In the intent-to-treat analysis involving 15,492 subjects, there was a trend toward lower HIV-1 infection in the vaccine recipients, with a vaccine efficacy of 26.4% (95% confidence interval [CI], 14.8 to 37.5; P = .005). In the per-protocol analysis involving 12,342 subjects, the vaccine efficacy was 26.4% (95% CI, 13.3 to 39.4; P = .001). In the modified intention-to-treat analysis involving 16,395 subjects with the exclusion of 7 subjects who were found to have had HIV-1 infection at baseline, the vaccine efficacy was 33.2% (95% CI, 21.1 to 45.2; P = .002). Vaccination did not affect the degree of viremia or the CD4+ T-cell count in subjects in whom HIV-1 infection was subsequently diagnosed.

CONCLUSIONS

The ALVAC® and AIDSVAX B/E vaccine regimen may reduce the risk of HIV infection in a community-based population with largely heterosexual risk. Vaccination did not affect the viral load or CD4+ T-cell count in subjects with HIV infection. Although the results show only a modest benefit, they offer insight for future research.
Vaccination and Follow-up Schedule

HIV test, risk assessment and counseling

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

Vaccine: Placebo = 1:1

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Efficacy (mITT)

- 52,985 person-years
- 125 infections
- Vaccine infections: 51
- Placebo infections: 74
- VE: 31.2%
- p=0.04
- 95% CI: 1.1, 52.1 (O'Brien-Fleming-adjusted)

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## Summary of Analyses

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>mITT</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (# subjects)</td>
<td>16,402</td>
<td>16,395</td>
<td>12,542</td>
</tr>
<tr>
<td>Person years</td>
<td>52,985</td>
<td>52,985</td>
<td>36,720</td>
</tr>
<tr>
<td>Vaccine/Placebo (event #)</td>
<td>56 / 76</td>
<td>51 / 74</td>
<td>36 / 50</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td>26.4%</td>
<td>31.2%</td>
<td>26.2%</td>
</tr>
<tr>
<td>2-sided p value</td>
<td>0.08</td>
<td>0.04</td>
<td>0.16</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-4.0, 47.9</td>
<td>1.1, 51.2</td>
<td>-13.3, 51.9</td>
</tr>
</tbody>
</table>

- Includes 5 vaccine and 2 placebo recipients who were HIV positive at baseline
- Decreased event numbers, lower precision

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## IFN-γ/IL-2 ICS

### 6 months post-final vaccination

### Frequency (%)

<table>
<thead>
<tr>
<th>Antigen</th>
<th>CD4</th>
<th>CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V</td>
<td>P</td>
</tr>
<tr>
<td>Env Only</td>
<td>45/142 (32)*</td>
<td>1/54 (2)</td>
</tr>
<tr>
<td>Gag Only</td>
<td>0/144</td>
<td>0/56</td>
</tr>
<tr>
<td>Env + Gag</td>
<td>2/142 (1)</td>
<td>0/54</td>
</tr>
<tr>
<td>Any HIV</td>
<td>47/142 (33)*</td>
<td>1/54 (2)</td>
</tr>
</tbody>
</table>

*P <0.0001 compared to placebo

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## Binding Antibody
### 2 weeks post-final vaccination

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Frequency (%)</th>
<th>Reciprocal GMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>B gp120</td>
<td>140/142 (99)</td>
<td>31207 (800-204800)</td>
</tr>
<tr>
<td>E gp120</td>
<td></td>
<td>14558 (200-204800)</td>
</tr>
<tr>
<td>B p24</td>
<td>74/142 (52)</td>
<td>138 (50-1600)</td>
</tr>
</tbody>
</table>

P<0.0001 compared to placebo group - all Antigens

Only Neutralize “Tier 1” Viruses

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Efficacy at 1 year appeared higher

(Kaplan-Meier-based estimates)

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

<table>
<thead>
<tr>
<th>month</th>
<th>PP</th>
<th>Events</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62</td>
<td>31%</td>
</tr>
</tbody>
</table>

Can we build on this early efficacy?
**Pox-Protein Development Plan (Draft)**

**Ongoing RV144 Follow-up in Thailand**

**Studies:**
- RV144i immune correlates studies
- RV305 protein boosting study
- RV306 expanded immunogenicity study

**Objective:**
Determine correlate of protection for use in future trials; optimize the regimen

**Partners/Funders:**
US Army, Thai Gov’t, NIH, sanofi pasteur, Novartis, BMGF

---

**S. Africa ph2b**

**Population:** Heterosexual, high-risk

**Products:**
- ALVAC (sanofi) + gp120 (Polymun)/MF59 (NVD)
- NYVAC (sanofi) + gp140 (Polymun)/MF59 (NVD)

**Objective:**
Extend results & accelerate evaluation of other products using adaptive trial design and first available protein

**Partners/Funders:**
NIH, HVTN, sanofi pasteur, Novartis, BMGF

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**Thailand ph2b**

**Population:** MSM, high-risk

**Products:** ALVAC (sanofi) + gp120/MF59 (NVD)

**Objective:** Confirm result & demonstrate efficacy in target population with potential for licensure

**Partners/Funders:**
US Army, Thai Gov’t, NIH, sanofi, BMGF

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**Africa ph2b**

**Population:** Heterosexual, high-risk

**Products:** ALVAC (sanofi) + gp120/MF59 (NVD)

**Objective:** Extend result & translate vaccine to Africa, other high-risk groups

**Partners/Funders:**
NIH, HVTN, sanofi, Novartis, BMGF, RSA

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**Candidate selection**

- ALVAC is default vector prime
- Proteins boosts TBD
- RV144 immune correlates
- Immune grid
- Cost, product availability

---

**Timeline:**

|------|------|------|------|------|------|------|------|

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RV 144 Correlates Discovery Effort

ADVISORY GROUPS

Implications for future clinical development of this product

Humoral & Innate Immunity

Cellular Immunity

Host Genetics

Animal Models

Scientific Advisory Groups

Product Development Advisory Group

Scientific Steering Committee

Implications for future scientific inquiry into the result and evaluation/design of other candidates and studies

PA H Steering Committee

MHRP - DAIDS Steering Committee

RV144 Steering Committee

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RV144 Correlates Research: Collaborating Institutions

• 35 investigators from 20 institutions working on 32 different assays (~150 total staff)

Two Phases of Correlates Discovery

- **Phase I (2010 - March 2011)**
  - Broad survey of innate, humoral, systems biology, genetic, and cellular assay evaluation/comparison.
  - Multiple Bab, Nab, ADCC, ADCVI approaches
  - Statistical plan

- **Phase II (March 2011 - July 2011)**
  - Case-control
  - Evaluation of a broad range of assays but with downselection to optimize the statistical design
  - 9000+ specimens have been shipped to collaborating labs in the past few weeks.
RV144 Trial: Cellular Immune Analyses
Cellular Immunity WG (McElrath)

T cells:
- Antigen-specific CD4+ & CD8+ T cells
  - Composite assay
    - Intracellular cytokine staining
    - Soluble mediators (Luminex)
    - Transcriptional arrays (PBMC)
  - Proliferation (CFSE)
  - Epitope mapping
- Functional phenotypes

B cells:
- gp140-binding ELISpot
- Functional phenotypes

NK cells:
- Polyfunctionality
- Receptor expression

Monocytes, mDCs:
- Phagocytosis
The Antigen: A244 gD+ gp120
(component of AIDSVAX)

Amino acid sequence inside circles represents A244 gp120 gD(+). (adapted from Leonard, et al., J. Biol. Chem. 265, 10373, 1990).
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Linear V2 Peptide Binding

Panel A

α4β7 binding epitope

Peptide Number

- HIV-infected
- RV144
- VRC vaccine (DNA/Ad5)

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<table>
<thead>
<tr>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
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<th>2007</th>
<th>2008</th>
<th>2009</th>
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<tbody>
<tr>
<td>Enrollment</td>
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<tr>
<td>Follow-up</td>
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</tbody>
</table>

**History of Efficacy Trials**

- **VaxGen gp120**
- **Canarypox/gp120**
- **RV 144**
- **Merck 023/HVTN 502 (STEP)**
- **rAd5 gag/pol/nef**
- **DNA/rAd5 env/gag/pol/nef**
- **HVTN 503 (Phambili)**
- **HVTN 505**

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Phase 2b, randomized, placebo-controlled trial to evaluate the safety and effect on **post-HIV acquisition viremia** of a multiclade HIV-1 DNA plasmid vaccine followed by a multiclade HIV-1 recombinant adenoviral vector vaccine in HIV-uninfected, adenovirus type 5 neutralizing antibody negative, circumcised men who have sex with men.
HVTN 505: Schedule and Endpoints

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Prime</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Wk 4</td>
</tr>
<tr>
<td>Vaccine</td>
<td>675</td>
<td>DNA</td>
</tr>
<tr>
<td>Placebo</td>
<td>675</td>
<td>PBS</td>
</tr>
</tbody>
</table>

Trial was powered for a viral load effect (STEP trial era)

45 HIV infection endpoints

- 90% power to detect $1.0 \log_{10}$ reduction in plasma VL
- 80% power to detect 57% reduction in acquisition

How do the antibody responses compare to RV144? Should the trial size be increased to provide better power to detect an acquisition effect?
Study Design

• Test sera from RV144 and HVTN204 by ELISA against five envelope proteins
  – Sera:
    • 50 vaccinees and 25 placebo recipients from RV144
    • 30 vaccinees from HVTN204 (precursor to HVTN 505)
    • 5 clade B HIV infected donors
  – Time points:
    • 2-4 weeks post final vaccination and 6 months later
  – Proteins:
    • Env B-MN
    • Env E-A244
    • VRC EnvA
    • VRC EnvB
    • VRC EnvC

25 placebo recipients were negative against all proteins. Those data are not included in the subsequent graphs.
Env Antibody Titers: RV144 and HVTN204

Conclusions:
Both products induced predominantly type-specific antibodies
Similar peak titers
Similar loss of titer over six months
Most vaccinees had no neutralizing antibodies
A few had good neutralization against Tier 1 viruses MN and SF162
Rationale for adding acquisition as a primary endpoint in HVTN 505

- RV144 showed that a reduction in acquisition is possible with a vaccine regimen that does not induce broadly neutralizing antibodies.

- The HVTN 505 vaccine regimen induces antibody responses of similar magnitude and function as those induced by the RV144 regimen.

- The HVTN 505 vaccine regimen induces equivalent CD4 T cell responses and CD8 T cell responses that are superior to those in RV144.

- The SIVmac239 homologue of the HVTN 505 vaccine regimen has been shown to reduce acquisition by ~50% in an SIV challenge model.
**HVTN 505: Schedule and Endpoints**

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<tr>
<th>Study Groups</th>
<th>Prime</th>
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<tbody>
<tr>
<td>Vaccine</td>
<td>N</td>
<td>Day 0</td>
</tr>
<tr>
<td></td>
<td>1100</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td>DNA</td>
<td>DNA</td>
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<td>rAd5</td>
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<td>Placebo</td>
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<td>PBS</td>
<td>PBS</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>FFB</td>
</tr>
</tbody>
</table>

What will we learn at primary analysis?

- 66 total and 52 evaluable HIV infection endpoints
- 90% power to detect $1.0 \log_{10}$ reduction in plasma VL
- 80% power to detect 50% reduction in acquisition
HVTN 505 Accrual

Opened - May 29, 2009
First enrollment - June 11, 2009
Original sites activated - September 2, 2009

New sites activated – August 2010

Atlanta
Bethesda
Birmingham
Boston
Fenway
Brigham
Chicago
Los Angeles

Nashville
New York
Columbia
Union Square
Philadelphia
San Francisco
Rochester
Seattle

Annandale
Baylor
Cleveland
Dallas
Denver
East Midtown
Orlando

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Orlando
AIDS Vaccine Clinical Trials - Works in Progress

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Michelangelo’s “Unfinished Atlas”

2003: Vaxgen - lack of protection by gp120 antibodies
2007: STEP - no viral load protection by rAd5 Gag, Pol, Nef (pure CD8 vaccine)
2009: RV144 - 31% fewer infections from canarypox Gag, Pol, Env/gp120 boost
2011: HVTN 505 – DNA/rAd5 expressing Gag, Pol, Nef, and 3 Envs: powered for an acquisition effect

In the battle between antibody and T cell vaccines, antibodies appear to have won

Questions:
1. Future of pure T cell vaccines?
2. Response to Env important but...
3. Neutralizing vs non-neutralizing antibodies?
4. Can other platforms that include Env provide better protection, and if so, by what mechanism?

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## Results from HIV prevention trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Length of Study</th>
<th>Effect size (CI)</th>
<th>12 mo effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Vaccine (Thai RV144)</td>
<td>3.5 y</td>
<td>31% (1, 51)</td>
<td>60</td>
</tr>
<tr>
<td>1% TDF gel (Caprisa, Karim et al.)</td>
<td>2.5 y</td>
<td>39% (6, 60)</td>
<td>50</td>
</tr>
<tr>
<td>TDF/FTC PrEP (iPrEx, Grant et al 2010)</td>
<td>1.2 y</td>
<td>44% (15, 63)</td>
<td></td>
</tr>
<tr>
<td>Circumcision (Orange Farm, Rakai, Kisumu)</td>
<td></td>
<td>57% (42, 68)</td>
<td></td>
</tr>
</tbody>
</table>

![Efficacy Graph]

An HIV vaccine should be considered a component of a comprehensive approach to HIV prevention

__Prof. Glenda Gray, HVTN Conference, Nov 2010__


Presented at the 5th INTEREST workshop – 10 – 13 May 2010, Dar-es-Salaam, Tanzania
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Vaccine trial volunteers!

www.vrc.nih.gov
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