Preventative Vaccine for HIV: An Update and Prospects for the Future

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The views expressed are those of the presenter and should not be construed to represent the positions of the U.S. Army or DoD
Disclosures

- No conflict of interest to disclose
Combination HIV Prevention

Combination HIV Prevention

Vaccine

Circumcision

Microbicides

Condoms

PrEP/PEP

Education

Drug/Alcohol Interventions

STI Treatment

Structural Interventions

HIV Testing and the Care Continuum

Treatment as Prevention

Adherence to Prevention and Treatment

NIAID/DAIDS/VRP CONFIDENTIAL
Impact of an AIDS Vaccine

Number of HIV infections over time

- **Full Scale-Up of Existing Tools**
- **Full Scale-Up + Vax**
- **Current Trend**
- **Current Trend + Vax**
- **50% Scale-Up**
- **50% Scale-Up + Vax**

* An illustrative vaccine with an assumed efficacy of 60%, not representative of any specific candidate in development

The potential impact of an AIDS vaccine as part of the UNAIDS Enhanced Investment Framework Modeling project – UNAIDS, Futures Institute, IAVI, AVAC.

Source: IAVI
### HIV Vaccine Efficacy Trials To Date

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<tbody>
<tr>
<td>VAX 004</td>
<td>Recombinant gp 120 (B/B)</td>
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<td>No</td>
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<tr>
<td>VAX 003</td>
<td>Recombinant gp 120 (B/E)</td>
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<tr>
<td>Step</td>
<td>rAd5 (gag, pol, nef) (B)</td>
<td></td>
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<td></td>
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<td>No</td>
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<tr>
<td>RV 144</td>
<td>Canarypox (gag, pol, env) [E] + recombinant gp 120 (B/E)</td>
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<td></td>
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<td>Yes (31%)</td>
</tr>
<tr>
<td>HVTN 505</td>
<td>DNA (gag, pol, nef) (B) + DNA (env) (A/B/C) + Ad5 (gag, pol) (B) + Ad5 (env) (A/B/C)</td>
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**NOTE:** Phambili (HVTN 503) began to explore a regimen similar to STEP in South Africa (not included)

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Three Strategies

- **Antibody (Ab) alone**
  - **Neutralizing Ab** – classical mechanism of protection
    - Native trimer envelope immunogens + other designs
    - Serial vaccination of different envelope proteins
    - Passive delivery of broadly active neutralizing antibody

  - **Non-neutralizing Ab** – target / mediate killing infected cells
    - Builds on RV 144 - In efficacy testing in VTN 702

- **T cell effectors alone** - CD8 killing of infected cells
  - rCMV programs – 50% protection

- **Both antibody and T-cell responses**
  - Janssen Ad26/protein program with mosaic inserts
Thai Phase III HIV Vaccine Trial (RV144) Summary

**Early (VE = 60%) effect wanes**  
(Robb et al, Lancet ID 2012)

**bAb decreases rapidly**  

### Antigen Reciprocal GMT (Range)

<table>
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<tr>
<th>Antigen</th>
<th>2 weeks</th>
<th>24 weeks</th>
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<tbody>
<tr>
<td>B gp120</td>
<td>31207 (800-204800) (99% responders)</td>
<td>1758 (200-25600)* (99% responders)</td>
</tr>
<tr>
<td>E gp120</td>
<td>14558 (200-204800) (99% responders)</td>
<td>1000 (100-12800)* (99% responders)</td>
</tr>
<tr>
<td>B p24</td>
<td>205 (100-1600) (52% responders)</td>
<td>149 (100-200)* (18% responders)</td>
</tr>
</tbody>
</table>

P<0.0001 compared to placebo group - all Antigens  
*: P<0.001 compared to 2 week time-point

*Dr. Mark de Souza*
Follow up Findings Provide Clues

Correlates of Risk (CoR) Provided clues how RV144 protected

Plasma Anti-V1V2 (Decreased risk of infection)
Plasma Anti-Env IgA (Increased risk)

Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2
Strategies to Amplify RV144 Response

- **Strength**
- **Breadth**
- **Durability**

Potential approaches:
- Multiple boosts
- Modified vectors
- Adjuvants
RV144 CoP Model Predicting Est. VE(0-24) ≥ 50%

**Observed VE = 44%**
*observed VE (V1V2 responders) = 69%*

**702**

To achieve observed VE ≥ 50%, assuming observed VE (V1V2 responders) = 69%

[% V1V2 neg Mo 12]×VE(neg) + [% V1V2 pos Mo 12]×VE(pos) = 0.28×0 + 0.72×0.69 = 0.50
P5 Vaccine Program: Added 12 month boost

- VTN 100 met “go” criteria for VTN 702
- HIV vaccine efficacy in men and women at high risk for HIV-1
- 5400 volunteers, 15 sites
- Enrollment began Oct 2016 and ends in 2018
Ad26/MVA/Protein Mosaic HIV Vaccine

Designed for protection against all HIV subtypes

Non-human primates:

Protection from infection

Reduction of viral load among infected NHP

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

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
The Ad26/Ad26+Env HIV vaccine regimen provides substantial protection against SHIV$_{SF162P3}$ challenges in non-human primates [study designed to mimic APPROACH trial]

<table>
<thead>
<tr>
<th>Vaccine Regimen</th>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
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<tbody>
<tr>
<td>Ad26/Ad26+Env</td>
<td>94%</td>
<td>66%</td>
</tr>
<tr>
<td>Ad26/MVA+Env</td>
<td>87%</td>
<td>42%</td>
</tr>
<tr>
<td>Ad26/Env</td>
<td>84%</td>
<td>33%</td>
</tr>
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</table>

6x IR SHIV challenges

N = 12 per group
APPROACH: Study Conducted in 5 countries

- **US**: 5 sites, 151 subjects
- **Thailand**: 2 sites, 58 subjects
- **Rwanda**: 1 site, 58 subjects
- **Uganda**: 2 sites, 71 subjects
- **South Africa**: 2 sites, 56 subjects
Broadly Neutralizing Antibodies

Approximately 20% of individuals develop broad neutralizing antibodies (bNAb) during untreated HIV infection

How do individuals develop broadly neutralizing antibodies?

Hypothesis: Viral evolution drives Ab maturation

- Studying the interaction between HIV Env evolution and broadly neutralizing antibodies in natural infection may provide guidance for vaccine design
179 samples from 72 individuals prior to ART initiation at 30-2115 days post-RNA+ were assessed for broad neutralizing Ab against a panel of 35 diverse pSVs.

*16 individuals* developed NAbs with >70% breadth (*broad neutralizers*)

*14 individuals* did not elicit NAbs with >30% breadth by year 3 (*non-broad neutralizers*)
Genetic diversification in the founder $env$ after superinfection

RV217-40512: Infection and superinfection

BEAST tree by Morgane Rolland

Sequencing by Sodsai Tovanabutra
Serum characterization of Broad-Neutralizer 40512

- Autologous neutralization of Founder virus by 6 months
- Neutralization of SI virus only after superinfection
- MPER-directed neutralization came up with autologous
- Neutralization Breadth began at superinfection

**Graph:**
- Superinfection
- bNAbs

**Axes:**
- Days: 029, 85, 154, 240, 330, 401, 485, 577, 646, 743, 846, 1142
- Neutralization
  - %Breadth
  - n = 35 viruses
Genetic diversification in the founder \textit{env} after superinfection

\textbf{RV217-40512: Infection and superinfection}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{BEAST tree by Morgane Rolland}
\end{figure}

\textit{Sequencing by Sodsai Tovanabutra}
Implications

- Founder virus triggered all three antibody lineages
- Superinfecting virus triggered maturation
- Later viruses guided maturation to breadth

These viruses (Founder and Superinfecting) are candidate vaccine strains to elicit MPER-directed bNAbs
How Does This Inform Vaccine Development

- Developmental pathways leading to potent and broad neutralizing antibody may guide new designs to achieve **vaccine induced broadly neutralizing Ab**
  - Direct design of envelope protein vaccines
  - Direct the sequencing of delivery of these vaccines
  - Optimize adjuvant selection to enhance B cell maturation and B cell memory
  - Combine strategies to develop multiple target epitope reactivities

- Downside
  - Can this be generalized
  - Will the vaccine be too complicated to make and distribute
Desirable properties of monoclonal antibodies for HIV prevention (PrEP)

- Potent: Safe/effective at low dose (1-5 mg/kg)
- Broad coverage (>90%) of global HIV isolates.
  - May require combination of 2-3 mAbs
  - Long half-life (up to 4-6 months)
- Subcutaneous injection
- Cost comparable to ARV for PreP
VRC01 Human Monoclonal Antibody

- Discovered in a chronically infected individual (HIV+ >15 yrs) and who maintained virologic control without ART

- Potent against 90% of HIV strains across all subtypes
Protective Efficacy of VRC01 in Non-human primate study challenge model

- Infuse VRC01 (SC or IV) and wait 2-5 days
- Rectal challenge with virus: SHIV-BaLP4

VRC01 Dose: 20 mg/kg  5 mg/kg  0.3 mg/kg

What is the serum level of VRC01 at time of SHIV challenge?

AMP=Antibody Mediated Prevention

A phase 2b study to evaluate the efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection

Proof of concept – neutralizing antibody prevents HIV infection
Define the required amount of antibody required
Define the role of mucosal antibody
Define the potential for bNabs as PrEP
## Study Schema for The AMP Study

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in sub-Saharan Africa</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>800</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>800</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Control</td>
<td>800</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2400</strong></td>
<td><strong>1500</strong></td>
<td><strong>3900</strong></td>
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10 infusions total & Infusions every 8 weeks

Study duration: ~22 months
Summary

- **Non-Neutralizing antibody strategy**
  - RV 144 provides the conceptual framework
  - VTN 702 enrolling

- **Combined T cell and antibody vaccine**
  - New Ad26 prime and protein boost
    - mosaic inserts offers global vaccine
  - Pivotal phase 1B study is nearly complete
  - Proof of concept efficacy trial in late 2017

- **Neutralizing antibody**
  - A road map for new vaccine approaches
  - Passive transfer for prevention
    - (AMP) efficacy trial enrolling
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