HIV Vaccine Development: Current Status and Future Directions

Gwynn Stevens, Ph.D.
Senior Director
International AIDS Vaccine Initiative
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Vaccines: The Facts

- **No** effective AIDS vaccine available today
- A safe and effective vaccine is **critical** to the control of HIV globally
- Over **30** clinical trials currently underway in 25 countries
- If all goes well the first vaccine can be expected **after 2023**
- Not the magic bullet, critical component of a comprehensive combination prevention strategy
HIV continues to devastate….

- 33.4 million people living with HIV worldwide
- 7,400 new HIV infections daily
- 25 million AIDS-related deaths to date
- Women bear the brunt of the epidemic, representing almost 60% of HIV-infected adults in Africa and half of adults worldwide
- Since the beginning >60,000,000 HIV Infections

- Remarkable scale up of treatment; however, doesn’t solve problem. Lifetime treatment required and for every (1) person put on treatment, (2) are newly infected.

THE WORLD NEEDS AN HIV VACCINE!

Source: Joint United Nations Programme on HIV/AIDS
Diversity, human and virus, require a combination of preventions

A vaccine will be critical to the control of HIV globally

Scientific obstacles:

- HIV is a difficult retrovirus
- HIV integrates and quickly establishes infection, very narrow window of opportunity
- CD4 T cell destruction begins immediately
- Different modes of transmission
- Enormous genetic diversity/clades, need for regional vaccine
Why Vaccines?

Remember Smallpox:  
HISTORY- Thanks to a Vaccine

Remember Polio?: Almost 
HISTORY-Thanks to a Vaccine

Vaccines are the most effective tool to 
prevent viral diseases!!
The Good News: Unprecedented momentum in the HIV prevention field

MICROBICIDES
- Microbicide gel (CAPRISA 004) reduces HIV infections in women

PRE-EXPOSURE PROPHYLAXIS
- Oral PrEP reduces HIV infections among MSM and transgendered women

VACCINES
- AIDS vaccine shows first efficacy in clinical trials
- Replicating viral vector effective in controlling SIV in animal studies
- Multiple new antibodies and targets on HIV discovered
New prevention technologies will reduce HIV incidence…
but only a vaccine will end the epidemic

Source: Imperial College and BMGF
The AIDS Vaccine Pipeline: Where are we today?

Efficacy Trials Completed

- 2003 VaxGen: gp 120: *No efficacy*
- 2007 Merck: Ad 5-gag-pol-nef: *No efficacy*
- 2009 RV 144: Sanofi + VaxGen: ALVAC + gp120: ~30% efficacy. Proof of concept for a protective vaccine.

Efficacy Trials Underway: Only 1

- NIH-VRC: DNA + Ad-5: *started 2009, results 2014*

Efficacy Trials Planned

- P5: RV-144 F/U: Poxvirus + Protein Boost (B and E): *planned 2014 (SA, Thailand)*
- ACEPP: Adenovirus prime/boost: *planned 2014*

Other Candidates Currently in Clinical Trials

[www.iavi.org](http://www.iavi.org)
**RV144 trial:** First HIV vaccine candidate to show efficacy

**THE TRIAL**

A Phase IIb test-of-concept trial, based on the expected number of HIV infection endpoints, conducted by Thailand Ministry of Public Health and U.S. Army

**THE VOLUNTEERS**

26,675 Thai citizens screened; 16,402 Thai citizens (60% male, 40% female) enrolled

**Prime:** **ALVAC-HIV (vCP1521)**

A live, recombinant, non-replicating canarypox viral vector vaccine encoding clade B gag/pro and clade E env

Vaccine Developer: Sanofi Pasteur

**Boost:** **AIDSVAX gp120 B/E**

A genetically engineered version of HIV gp120 (env) from clade B and E

Vaccine Developer: Genentech; its spinoff, VaxGen, tested AIDSVAX previously; intellectual property rights now owned by Global Solutions for Infectious Diseases

**Dosing schedule:**

<table>
<thead>
<tr>
<th>Initial vaccination</th>
<th>Weeks after initial vaccination</th>
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<tbody>
<tr>
<td>ALVAC-HIV</td>
<td>4</td>
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<tr>
<td>ALVAC-HIV</td>
<td>12</td>
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<td>ALVAC-HIV AIDSVAX</td>
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</table>

**Source:** MHRP
RV144 trial: What do the results mean for the field?

- First demonstration that a candidate AIDS vaccine shows efficacy in humans

- Biomarkers have been defined that will guide testing of follow on candidates
  - IgG: presence of non-neutralizing IgG antibody to V1/V2 loops of HIV envelope correlated to a 43% reduction in HIV acquisition
  - IgA antibodies to HIV envelope in plasma of vaccinees negated the positive effect of vaccination

- May enable researchers to validate animal models and assays

- Follow up trials in planning (P5)

  Demonstrates the vital importance of testing AIDS vaccine candidates in humans

  Cross clade trials need to happen simultaneously, including Africa
An effective HIV vaccine will likely need to engage both arms of the adaptive immune response

1. Broadly neutralizing antibodies to prevent infection and
2. Broad cell mediated immune responses to control infection – prevent disease
Control of HIV

Vaccine designs to elicit cellular immune responses
Evolution of a T cell AIDS Vaccine Paradigm

Old Paradigm:
Vaccine-elicited immunity controls infection below threshold for transmission

New Paradigm:
Vaccine-elicited immunity prevents or aborts infection, or provides early complete control

Slide: Courtesy of Louis Picker, Oregon National Primate Research Center
## History tells us that Live, Replication-competent Viral Vaccines Work

### Vaccine-Preventable Morbidity in the USA

<table>
<thead>
<tr>
<th>Time period</th>
<th>Average number of cases</th>
<th>Baseline cases</th>
<th>Cases 2008</th>
<th>Vaccine usage commenced</th>
<th>% Decrease</th>
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<td>1900-04</td>
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<td>Varicella</td>
<td>164,114</td>
<td>1972</td>
<td>26,924</td>
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### Other live viral vaccines

- Rotavirus
- FluMist
- Zoster
- Yellow Fever
- Newcastle Disease
- Canine Distemper
- Canine parainfluenza
- Canine parvovirus
- Feline panleukopenia
- Bovine parainfluenza virus
- Bovine respiratory syncytial virus
- Rinderpest

Progress on CMI/Vector Component of an HIV Vaccine

- **1st generation** candidates failed to suppress viral load in human efficacy trials
  - Merck: Ad5 vector (STEP trial)
  - Sanofi + Vaxgen: ALVAC (canarypox )+ gp120 (RV-144-Thai trial)

- **2nd generation** Heterologous (Prime-Boost) Vectors show more promise in nonhuman primates and are next candidates for efficacy trials
  - DNA + Ad5 (NIAID Vaccine Research Center-HVTN)
  - Heterologous Adeno Vectors (Crucell, Harvard, NIAID, IAVI)

- **3rd generation Replicating Vectors** show most promise in nonhuman primates and will soon be advancing to clinical trials
Replication-Competent HIV Vaccine Vectors in Development

- Measles virus
  - GSK (Phase I)

- Attenuated VSV
  - Profectus (Phase I)

- Adenovirus 4/7
  - NCI, PaxVax, NIAID

- Vaccinia virus (Tiantan)
  - National Center for AIDS Beijing (Phase I)

- Vaccinia virus (NYVAC+)
  - EuroVac /BMGF

IAVI /Partners

IAVI /Gates

- VSV
- CDV

Oregon Health Sciences Univ.

IAVI /Partners

IAVI /Partners

CMV

IAVI /Partners

SeV

IAVI /Partners

(DNAVEC)
Prevention of HIV
Vaccine designs to elicit broadly neutralizing antibodies
Neutralizing Antibody
~1% of HIV-Infected Subjects are **elite HIV Neutralizers**

Sera screened from >1800 HIV-Infected subjects showed that about 1% were elite neutralizers

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<th>Clade C</th>
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<td>&lt;100</td>
<td>900</td>
<td>300</td>
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Very broad and potent monoclonal antibodies against HIV have now been identified from several HIV+ subjects.

Source: Vaccine Research Center, NIH; IAVI Neutralizing Antibody Consortium
**Targets for HIV Vaccine Design:** Major Sites on HIV identified by broadly neutralizing antibodies against HIV

- V1V2 Peptide-glycan (*PG9/16, CH01*)
- Dual glycan, V3 (*2G12, PGT 120-135*)
- CD4 binding site (*b12, VRC01, PG04, CH31*)
- Membrane proximal domain + lipid (*2F5, 4E10*)
Reverse Engineering: From antibody to antigen

- Immune / infected individual

  - Broadly neutralizing (protective) antibodies
  
  - Molecular characterization of interaction of antibody with pathogen antigen

  - Design immunogens
    To mimic binding site

  - Improve candidate

  - Combination of several immunogens = vaccine

Source: Adapted from Burton, Nat. Rev. Immunol., 2:706, 2002
Broadly neutralizing antibodies protect against hepatitis C virus quasispecies challenge

Mansun Law, Toshiaki Maruyama, Jamie Lewis, Erick Giang, Alexander W Tarr, Zania Stamatakis, Pablo Gastaminza, Francis V Chisari, Ian M Jones, Robert I Fox, Jonathan K Ball, Jane A McKeating, Norman M Kneteman & Dennis R Burton

A Neutralizing Antibody Selected from Plasma Cells That Binds to Group 1 and Group 2 Influenza A Hemagglutinins

What will it take to bring an preventative HIV vaccine to market?

Global engagement
• Governments in developing and developed countries
• Pharmaceutical and biotechnology companies
• The next generation of AIDS vaccine researchers
• Global Health, development and community advocates and activists

Sustained political support
• Understanding of the impact and potential cost-savings of a preventive HIV vaccine by all stakeholders and decision-makers
• Awareness of the impact an HIV vaccine could have for the most vulnerable and marginalized groups

Funding
• Continued availability of financing to get a range of vaccine candidates into clinical trials
• Continued availability of funding to stimulate innovation and reduce up-front risk of investment
Investment in preventive HIV vaccine R&D, 2000–2010

US$ millions

WORLD TOTAL, 2010: US$ 859 million


www.hivresourcetracking.org
A preventive vaccine is the only way to truly end the AIDS epidemic.
Imagine a world without AIDS
IAVI gratefully acknowledges the generous support provided by the following major donors:


As of January 2012