The History of HIV Vaccine Development
a short story on 30 years of research

Dr. Jill Gilmour
International AIDS Vaccine Initiative
Barcelona, 6 October 2013
IAVI is a product-development partnership whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.
# Persevere: Vaccines can take decades to develop

<table>
<thead>
<tr>
<th>Infectious Agent (Disease)</th>
<th>Agent Linked to Disease in …</th>
<th>Vaccine Licensed in U.S. in …</th>
<th>Years Elapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>1953</td>
<td>1963</td>
<td>10</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1965</td>
<td>1981</td>
<td>16</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>Early '80s to mid-'90s</td>
<td>2006</td>
<td>12-25</td>
</tr>
<tr>
<td>(cervical cancer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>1973</td>
<td>2006</td>
<td>33</td>
</tr>
<tr>
<td>(diarrheal disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella zoster</td>
<td>1953</td>
<td>1995</td>
<td>42</td>
</tr>
<tr>
<td>(chickenpox)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td>1906</td>
<td>1948</td>
<td>42</td>
</tr>
<tr>
<td>(whooping cough)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polio</td>
<td>1908</td>
<td>1955</td>
<td>47</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>1889</td>
<td>1981</td>
<td>92</td>
</tr>
<tr>
<td>Typhoid</td>
<td>1884</td>
<td>1989</td>
<td>105</td>
</tr>
<tr>
<td>Malaria</td>
<td>1893</td>
<td>—</td>
<td>116</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV/AIDS)</td>
<td>1983</td>
<td>—</td>
<td>26</td>
</tr>
</tbody>
</table>
HIV integrates into the host cell genome, short window of opportunity before integration.

HIV infects, suppresses, and destroys key cells of the immune system.

HIV antigens required for protection remain undefined.

Natural immune responses do not eradicate HIV; Limitations in the animal models for HIV/AIDS; correlates of protective immunity remain undefined.

HIV isolates worldwide are hypervariable.

AIDS vaccine efficacy trials very complex and long (4-5 years).
The variability of HIV

Genetic variability of global influenza A virus (1996)

Size = Extent of HIV variability

Genetic variability of HIV-1 V2-C5 (Congo, 1996)

Indications that an AIDS vaccine is possible

Immune control is possible:
- Majority of HIV-infected individuals initially suppress viral load

Populations resistant to HIV infection
- Highly exposed, uninfected
- Children of infected mothers
- Long-term non-progressors - control infection for many years

Vaccine candidates in experimental models:
- Live attenuated SIV
- Broadly neutralizing antibodies
- Recent data: CMV vector

First proof of concept in people:
- The RV144 trial: a modest level of protection against HIV infection
An effective AIDS Vaccine will likely need to stimulate **Neutralizing Antibodies** and **Cell Mediated Immunity**.
**Window of Opportunity** to Prevent Infection

Neutralizing Antibodies

Cell-mediated immunity

- **HOURS**
- **DAYS**
- **WEEKS AND YEARS**

HIV crosses mucosal barrier

HIV integrates into T-cell DNA

Infected dormant T cell

Infected activated T cell

Amplification

Established lymphatic tissue reservoir

Partial control

Late responding T cells
Roadmap for Developing an AIDS Vaccine

Solving the Neutralizing Antibody Problem

Solving the Problem of How to Control HIV Infection
## Four waves of AIDS Vaccine development

<table>
<thead>
<tr>
<th>Year</th>
<th>Wave</th>
<th>Key Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Hepatitis B model</td>
<td>Identify the antigen that elicits neutralizing antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significant infrastructure investment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(manufacturing, primates, reagents)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ending the wave: VaxGen: GP120 Efficacy Trial</td>
</tr>
<tr>
<td>1994</td>
<td>Cell-mediated immunity / Public-private partnerships</td>
<td>More than 30 vaccine candidates focused on cell-mediated immunity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of validated preclinical model → required large-scale efficacy trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A need for validated assays and clinical trial capacity in Africa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The beginning of efforts to solve the key scientific challenges</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ending the wave: Merck: Ad 5-gag-pol-nef efficacy trial</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td>Aggressively addressing the key scientific challenges: Neutralizing antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and cell-mediated immunity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iterative, adaptive clinical development and smaller efficacy trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harnessing innovations and clinical research</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investments in next generation of scientists</td>
</tr>
<tr>
<td>2007</td>
<td>arnessing Innovation</td>
<td>Understanding and optimizing RV-144 Results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Advancing BNAb discoveries</td>
</tr>
<tr>
<td>2011</td>
<td>Building on Success</td>
<td></td>
</tr>
</tbody>
</table>
The State of AIDS Vaccine R&D

Major, breakthrough advances in the field of AIDS vaccines:

First demonstration of a vaccine that can protect against HIV
- RV-144, efficacy at approximately 30% (the Thai trial), 60% in first year

2nd generation vaccine candidate shows unprecedented protection in monkey studies
- Prime boost regimens show protection in NHP model
- The replicating viral vector CMV shows control/protection in approximately 60% of monkeys

New neutralizing antibodies to HIV discovered
- New antibodies are extremely potent and bind to broad range of HIV strains
- The antibodies revealed vulnerable targets on HIV that are now being exploited for vaccine design

An AIDS Vaccine IS possible
### AIDS Vaccine Development Efficacy Trials: Summary

<table>
<thead>
<tr>
<th>Vaccine Candidate</th>
<th>Prevention of HIV Infection</th>
<th>Control of HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2003</strong>&lt;br&gt; VaxGen: gp120</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>2007</strong>&lt;br&gt; Merck rAd5: Gag, Pol, Nef</td>
<td>No – more infections in vaccinees than placebo</td>
<td>No</td>
</tr>
<tr>
<td><strong>2009</strong>&lt;br&gt; RV144 (Sanofi/Vaxgen)&lt;br&gt; Canarypox Gag, Pol, Env /gp120 boost</td>
<td>31% efficacy - first signal in humans for benefit by HIV vaccine</td>
<td>No</td>
</tr>
<tr>
<td><strong>2013</strong>&lt;br&gt; VRC: DNA +Ad5 Gag, Pol, Nef plus env A, B, C</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
# HIV Vaccines Tested for Efficacy: Summary

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Pop. Test</th>
<th>Prevent Infection</th>
<th>Control Infection</th>
<th>ENV Bind Abs</th>
<th>Broad Neut Abs</th>
<th>CD4 Help</th>
<th>CD8 CTL</th>
<th>Viral Inhibition</th>
<th>Broad CD8 - CTL</th>
</tr>
</thead>
<tbody>
<tr>
<td>gp120</td>
<td>MSM, IDU</td>
<td>NO</td>
<td>NO</td>
<td>+++</td>
<td>NO</td>
<td>+</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>ALVAC + gp120</td>
<td>Heterosexual</td>
<td>YES- 31%</td>
<td>NO</td>
<td>+++</td>
<td>NO</td>
<td>+++</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Ad5-gag-pol-nef</td>
<td>MSM; Heterosexual</td>
<td>NO</td>
<td>NO</td>
<td>---- no Env</td>
<td>NO</td>
<td>++</td>
<td>+++</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>DNA +Ad5</td>
<td>MSM</td>
<td>NO</td>
<td>NO</td>
<td>++</td>
<td>NO</td>
<td>+++</td>
<td>+++</td>
<td>Yes</td>
<td>NO</td>
</tr>
</tbody>
</table>
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>
</tr>
</thead>
<tbody>
<tr>
<td>ALVAC-HIV</td>
<td>ALVAC-HIV</td>
</tr>
<tr>
<td></td>
<td>ALVAC-HIV AIDSVAX</td>
</tr>
<tr>
<td></td>
<td>ALVAC-HIV AIDSVAX</td>
</tr>
</tbody>
</table>

HIV clade E is predominant in these regions
RV-144: Evidence that an AIDS Vaccine Can Prevent HIV-1 Infection in Humans

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

Supachai Rerks-Ngarm, M.D., Punnee Pitisutthithum, M.D., D.T.M.H., Sanjanit Niyagam, M.D., Ph.D., Jaraput Kewkungwal, Ph.D., Joseph Chiu, M.D., Robert Parkes, M.D., Nisorn Premru, M.D., Chawetsan Narnwil, M.D., Yatti de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjiv Gurunath, M.D., Jim Tarraglia, Ph.D., John C. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablin, Ph.D., Deborah L. Birx, M.D., Supamit Chusnusitiwatt, M.D., Chirasak Khambooonrang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH-TAVEG Investigators


- Modest 31% reduction in infection
- Limited duration

Proof of concept for a protective vaccine
**Lessons from RV144**

Protection from HIV infection is possible
- Highest protection in first 6-12 months
- Antibody titers appear to wane in line with protection
- Correlate of risk associated with V1V2 antibodies
- Little or no protection in self-reported “high risk” subjects

What’s next:
- Improvements to increase duration of efficacy: additional boosters and adjuvants
- Pox-Protein vaccine slated for testing in South Africa and Thailand in 2014-15

Who’s involved:
- Pox-Protein Public Private Partnership (P5): Sanofi Pasteur, Novartis, BMGF, NIH, MHRP and HVTN

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**In South Africa..**

Even if other prevention options are scaled up, 60% coverage with a vaccine like the one used in RV 144 would still result in:
- **773,000** Infections averted
- 34% reduction in incidence
- **1** life saved every **162** vaccinations

with a more effective vaccine, these numbers could be even higher.
HVTN 505: A Phase 2b Clinical Efficacy Trial

Proof of concept study of a multiclade HIV-1 DNA plasmid/recombinant adenoviral prime-boost vaccine in HIV-uninfected men who have sex with men.

Scott Hammer MD, Principal Investigator; Larry Corey MD, HVTN Principal Investigator
HVTN 505 Study Design

<table>
<thead>
<tr>
<th>N</th>
<th>Day 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1250</td>
<td>DNA* (4 mg)</td>
<td>DNA (4 mg)</td>
<td>DNA (4 mg)</td>
<td>rAd5# (10^{10} PU)</td>
</tr>
<tr>
<td>1250</td>
<td>--</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

- **Co-primary endpoints**
  - HIV-1 acquisition – 80% power to detect vaccine efficacy of 50%
  - HIV-1 viral load setpoint – 84% power detect 1.0 log10 VL reduction
- 18-45 year old, MSM and transgender, circumcised, Ad5 titer <18
- HVTN sites in US
**HVTN 505 Results**

<table>
<thead>
<tr>
<th>N</th>
<th>Pre-Week 28*</th>
<th>Week 28+</th>
<th>MITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine (N=1250)</td>
<td>14</td>
<td>27</td>
<td>41</td>
</tr>
<tr>
<td>Placebo (N=1244)</td>
<td>9</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>Total (N=2494)</td>
<td>23</td>
<td>48</td>
<td>71</td>
</tr>
</tbody>
</table>

*All pre-week 28 infections occurred before receipt of Ad5/placebo boost*

- Planned interim futility analysis – April 2013
- Differences in acquisition not statistically significant
- No difference in viral load set point
- Criteria for non-efficacy reached and vaccinations halted
HVTN 505 – Potential implications

- VRC DNA/Ad5 regimen was not efficacious for acquisition or viral load
  - Increased rate of infection in vaccine group is not statistically significant
  - Occurred even before Ad5 administration
  - Unlike Step, occurred in men who were circumcised and Ad5 negative

- Biologic explanation for potential effect seen in Step is still not clear
- Explanation for potential effect in HVTN505 may also be elusive
- Additional efficacy trials with Ad5 products unlikely
- Impact on development of other Ad-based vectors, and by extension other vectors for HIV vaccine development?
AIDS Vaccine Development Today: The Two Major Strategies

1. BUILDING ON RV144: P5 Consortium
   
   **REGIONAL VACCINE STRATEGY**
   Improving on RV144 and verifying correlates

2. DIVERSIFYING THE PORTFOLIO
   
   **GLOBAL VACCINE STRATEGY**
   Diverse approaches toward a globally effective vaccine.

**APPROACH**

Efficacy trial - ALVAC/AIDSVAX or similar with an additional boost:
   a) Heterosexual risk Thailand
   b) MSM Thai population
   c) High-risk heterosexuals in RSA

**APPROACH**

Pursue multi-clade efficacy testing, increase cellular and antibody responses: breadth; durability and levels of protective immunity.
The Global HIV Vaccine Landscape - 2013

- **Basic research**
  - Improving RV-144: CMI + non-neutralizing Ab

- **Applied research**
  - Prime Boost Candidates improve the breadth of vaccine

- **Preclinical development**
  - Replicating Vectors for durable responses to mimic live attenuated

- **Phase I / II**
  - Candidates to Elicit bnAbs
    - HIV ENV trimers
    - Designed Immunogens
    - AAV –bnAb delivery

- **Large-scale Efficacy trials**
  - ALVAC + gp120 Licensure Trial in Thailand (planned 2015)
  - ALVAC + gp120/MF59 Licensure RSA (planned 2015)
  - DNA + NYVAC + gp120 Test of Concept Trial
    - NYVAC + gp120 (planned 2015)
  - DNA + Ad5 (gag-pol, nef-Env A,B,C) : Phase IIb Efficacy (HVTN 505) 2009-2014

- **Vectors**
  - CMV
  - CDV
  - VSV
  - Pox
  - Adeno

- **Antigens**
  - Ad26 + MVA (mosaic antigens)
  - Chimp Ad 63 + MVA HIVconsv (conserved antigens)
  - epDNA + IL12+ Ad35 or chAd63
  - DNA + MVA (Multiple)
  - DNA + Tiantian-VV
  - Electroporated DNA
  - MVA (multiple)

- **Viruses**
  - Measles virus
  - Attenuated VSV
  - Vaccinia virus Tiantan
  - Sendai

- **Clinical Trials**
  - DNA + NYVAC + gp120 Test of Concept Trial
  - NYVAC + gp120 (planned 2015)
Balancing **safety** and **efficacy** in AIDS vaccine design

*Named for Edward Jenner, the Father of Vaccination, these vaccines are based on animal viruses that are related to the disease-causing human viruses*
The Benefits of **Replication**

![Graph showing SIV viral load over time](image)

- **Green line**: Typical course of SIV infection (no vaccine)
- **Orange line**: Single-cycle SIV challenged with SIV
- **Blue line**: Live-attenuated SIV challenged with SIV

Develop novel vaccines through applied research
The **Neutralizing Antibody Challenge**

- Most licensed vaccines elicit neutralizing antibodies
- Neutralizing antibodies protect against SIV/HIV challenge in animal models
- Broadly neutralizing antibodies in humans against HIV exist
- However, no candidate vaccine in pipeline elicits broadly neutralizing antibodies against HIV = the **neutralizing antibody challenge**
IAVI Antibody Project

*What:* The quest to find antibodies that fight a broad range of HIV variants

*How:* A collaborative network

- 1,800 HIV-infected volunteers from 11 countries
- 49 research partners in 16 countries, including three state-of-the-art laboratories and three innovative biotech companies
- IAVI’s research consortia and partners brought in through Innovation Fund engaged in coordinated effort for further discovery
- Science that begins in and continually returns to the developing world
Finding Broadly Neutralizing Sera: Protocol G partners

- Kenya AIDS Vaccine Initiative, College of Health Sciences, University of Nairobi
- Faculty of Tropical Medicine, Mahidol University; Department of Retrovirology, Armed Forces Research Institute of Medical Sciences
- SUNY Downstate Medical Center
- St. Stephen’s AIDS Trust, Chelsea and Westminster NHS Foundation Trust
- Institute of Human Virology, Plateau State Human Virology Research Centre
- CeDReS/CHU Treichville
- MRC/UVRI Uganda Research Unit on AIDS Uganda Virus Research Institute
- Zambia Emory HIV Research Project and the Rwanda-Zambia HIV Research Group, Emory University
- Desmond Tutu HIV Centre, University of Cape Town
- Project San Francisco and the Rwanda-Zambia HIV Research Group, Emory University
- NRL, St. Vincent’s Institute
The results: Advances in quest for broadly neutralizing antibodies against HIV

2009
IAVI and partners

Broad and Potent Neutralizing Antibodies from an African Donor Reveal a New HIV-1 Vaccine Target
Walker, Phogat, et. al

2010
VRC

Rational Design of Envelope Identifies Broadly Neutralizing Human Monoclonal Antibodies to HIV-1
Wu, Yang, et. al
With new antibodies, **new targets**

Conserved determinants in the V1/V2 and V3 loops
- PG9, PG16

CD4 binding site
- b12, VRC01, VRC03, HJ16, PGV04

Mabs from new donors 17, 36 & 39

Glycan shield
- 2G12

MPER
- 2F5, 4E10, Z13e1

Immunogen development is key next step

With antibodies characterized, immunogen design partners carry the work forward and we are searching for new partners.
Reverse Engineering Vaccines: Retrovaccinology

Immune / Infected individual → Human neutralizing mAbs → Molecular characterization of Ab- Ag interaction → Immunogen design and testing → combination of several immunogens = vaccine
An innovative approach: Passive Immunity

**THE FIND**
Multiple broadly neutralizing antibodies against HIV

**THE GOAL**
Elicit those antibodies through vaccination

**INTERIM STEPS**
Prove concept through …

Passive immunization by injecting antibodies

Gene transfer through a vector that produces the antibodies
Strengthen scientific and clinical research capacity in developing countries

HIV vaccine efficacy trials will need to enroll large numbers of people who are at high risk for HIV infection
Accelerate the development and clinical testing of novel vaccine candidates
A global approach: working with developing countries

An innovative approach to the research and development of health products for nations that most need them

- Ensuring that vaccines will be available, accessible and used in countries hardest hit as quickly as possible
- Paradigm shift- to license a vaccine based solely on efficacy trials performed in the developing world

Create an enabling environment for research

- Promoting national ownership and sustainable in-country commitment
- Addressing the social and political context related to AIDS
- Build support and participation in clinical research
- Move to applied design research when appropriate
Building Sustained Capacity and Delivering for Communities in Developing Countries

- Accreditation of 18 clinical laboratories in Eastern and Southern Africa and India
- Support for more than 350 site workers in Eastern and Southern Africa and India
- 1,031 workers have been trained in Good Clinical Practice at labs and clinics in the developing world
- More than 350,000 people received voluntary HIV counseling and testing
A preventive vaccine is the only way to end the AIDS epidemic
IAVI gratefully acknowledges the generous support provided by the following major donors:


And many other generous individuals from around the world

As of June 2013
# AIDS Vaccine Development Efficacy Trials: Summary

<table>
<thead>
<tr>
<th>Completed</th>
<th>Product/Clade/Trial Name/Immunogen</th>
<th>Countries</th>
<th>Number of participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>AIDSVAX BB/VAX003 gp120</td>
<td>Canada, Netherlands, Puerto Rico, US</td>
<td>5,417</td>
<td>No effect</td>
</tr>
<tr>
<td>2003</td>
<td>AIDSVAX B/E VAX004 gp120</td>
<td>Thailand</td>
<td>2,546</td>
<td>No effect</td>
</tr>
<tr>
<td>2007</td>
<td>MRK-Ad5 B Step Gag, Pol, Nef</td>
<td>Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US</td>
<td>3,000</td>
<td>Immunisations halted early for futility; Potential for increased risk of HIV infection among Ad5-seropositive, uncircumcised men</td>
</tr>
<tr>
<td>2007</td>
<td>MRK-Ad5 B Phambili Gag, Pol, Nef</td>
<td>South Africa</td>
<td>801</td>
<td>Immunisations halted based on Step result; Trend for increased risk of HIV infection</td>
</tr>
<tr>
<td>2009</td>
<td>ALVAC-HIV (Vcp1521) and AIDSVAX B/E Thai Prime-Boost/RV 144 Canarypox Gag, Pol, Env/gp120 boost</td>
<td>Thailand</td>
<td>16,402</td>
<td>Modest effect (31.2%) on acquisition; No impact VL</td>
</tr>
<tr>
<td>2013</td>
<td>DNA and Ad5 A/B/C HVTN 505 Gag, Pol, Nef plus envs A, env B, env C</td>
<td>US</td>
<td>2,500</td>
<td>Immunisation halted early for futility; vaccine regimen did not prevent HIV infection nor reduce viral load among vaccine recipients who become infected with HIV; follow-up continues</td>
</tr>
</tbody>
</table>

Ref: AVAC Report 2012 Achieving the end-One year and Counting