HIV vaccine portfolio and research opportunities

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Summary

• Challenges and successes
• Pipeline
• Possible research questions and other potential areas for EDCTP
How different is HIV

Classical Vaccinology

The response to natural infection provides the proof of concept

HIV Vaccinology

No proof of concept
HIV is different

HIV integrates into the host cell genome, short window of opportunity before integration

Correlates of protective immunity remain undefined

Protective immunity against subsequent infection does not appear to occur—documented super infection

HIV antigens required for protection remain undefined

Variability of HIV and escape from immune pressure

Limitations in the animal models for HIV/AIDS
## AIDS vaccine efficacy trial results

<table>
<thead>
<tr>
<th>Year Completed</th>
<th>Product/Clade/Trial Name</th>
<th>Countries</th>
<th>Number of Participants</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>AIDSVAX B/B VAX003</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</td>
<td>Thailand</td>
<td>2,546</td>
<td>No effect</td>
</tr>
<tr>
<td>2007</td>
<td>MRK-Ad5 B Step</td>
<td>Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US</td>
<td>3,000</td>
<td>Immunizations halted early for futility; subsequent data analysis found potential for increased risk of HIV infection among Ad5-seropositive, uncircumcised men.</td>
</tr>
<tr>
<td>2007</td>
<td>MRK-Ad5 B Phambili</td>
<td>South Africa</td>
<td>801</td>
<td>Immunizations halted based on Step result; additional data presented in May 2013.</td>
</tr>
<tr>
<td>2009</td>
<td>ALVAC-HIV (vCP1521) and AIDSVAX B/E Thai Prime-Boost/RV 144</td>
<td>Thailand</td>
<td>16,402</td>
<td>Modest effect (31.2%)</td>
</tr>
<tr>
<td>2013</td>
<td>DNA and Ad5 A/B/C HVTN 505</td>
<td>US</td>
<td>2,500</td>
<td>Immunizations halted early for futility; vaccine regimen did not prevent HIV infection nor reduce viral load among vaccine recipients who became infected with HIV; follow-up continues.</td>
</tr>
</tbody>
</table>
Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

Barton F. Haynes, M.D., Peter B. Gilbert, Ph.D., M. Juliana McElrath, M.D., Ph.D., Susan Zolla-Pazner, Ph.D., Georgia D. Tomaras, Ph.D., S. Munir Alam, Ph.D., David T. Evans, Ph.D., David C. Montefiori, Ph.D., Chitrapol Karnasuta, Ph.D., Ruengrueng Sutthent, M.D., Ph.D., Hua-Xin Liao, M.D., Ph.D., Anthony L. DeVico, Ph.D., George K. Lewis, Ph.D., Constance Williams, B.S., Abraham Pinter, Ph.D., Youyi Fong, Ph.D., Holly Janes, Ph.D., Allan DeCamp, M.S., Yunda Huang, Ph.D., Mangala Rao, Ph.D., Erik Billings, Ph.D., Nicos Karasavvas, Ph.D., Merlin L. Robb, M.D., Viseth Ngauy, M.D., Mark S. de Souza, Ph.D., Robert Paris, M.D., Guido Ferrari, M.D., Robert T. Bailer, Ph.D., Kelly A. Soderberg, Ph.D., Charla Andrews, Sc.M., Phillip W. Berman, Ph.D., Nicole Frahm, Ph.D., Stephen C. De Rosa, M.D., Michael D. Alpert, Ph.D., Nicole L. Yates, Ph.D., Xiaoying Shen, Ph.D., Richard A. Koup, M.D., Punnee Pitutthimeth, M.D., D.T.M.H., Jaranit Kaewkungwal, Ph.D., Sorachai Nitayaphan, M.D., Ph.D., Supachai Rerks-Ngarm, M.D., Nelson L. Michael, M.D., Ph.D., and Jerome H. Kim, M.D.
RV 144 has shown that planned efficacy trials are important and can complement basic research in our efforts to understand protective immune responses.
Broadly neutralizing HmAb

Fig. 1. The envelope of HIV-1 carries spikes. (a) Each spike is made of three molecules of the surface glycoprotein gp120 and three molecules of the transmembrane glycoprotein gp41. Glycoprotein gp120 contains variable V1/V2 and V3 loops, as well as the binding site for CD4. (b) The binding sites of broadly acting and potent HIV-1-specific neutralizing antibodies are shown as colored circles.
**Retrovaccinology:** From antibody to antigen

- Infected individual
- Broadly neutralizing (protective) antibodies
- Molecular characterization of interaction of antibody with pathogen antigen
- Modified antigen
- Combination of several immunogens = vaccine
- Immunogen design and testing

Source: Adapted from Burton, Nat. Rev. Immunol., 2:706, 2002
Other vaccines providing high levels of protection in SHIV model

1. Adeno/pox and Adeno/adeno vector
2. DNA + Ad5
3. Electroporated DNA + IL2 + Ad5
4. CMV-based vaccines
Human clinical trials

Vaccines with high immunogenicity include:

- DNA-MVA
- DNA-NYVAC
- Chip Adeno-MVA
Other research developments

- B cell maturation
- Importance of CD4 T cells
- Transmitted virus
- Elite controllers
- Viral suppression assays
Pipeline

Current to next 3 years in clinic
On-going trials-IAVI database
August 2013

Globally:
36 phase I/IIa and one IIb efficacy trial
  • IIb halted but participant follow up continues
  • 20 prime-boost - DNA + Viral vector (Pox and Adeno)
    DNA: Multiclade, Multigene
    Pox mostly MVA; various adeno, 5,26, 35 etc
  • Improved DNA delivery e.g electroporation
# On-going trials in Africa IAVI report by August 26 2013

<table>
<thead>
<tr>
<th>Title</th>
<th>Phase</th>
<th>Strategy</th>
<th>Product</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extension HVTN 037/SAAVI 102</td>
<td>I</td>
<td>Protein</td>
<td>Sub C gp140</td>
<td>South Africa</td>
</tr>
<tr>
<td>HVTN 073</td>
<td>I</td>
<td>DNA/Viral Vector-Pox</td>
<td>SAAVI DNA-C2/SAAVI MVA-C</td>
<td>South Africa, USA</td>
</tr>
<tr>
<td>HVTN 086, SAAVI 103</td>
<td>I</td>
<td>Viral Vector-Pox/DNA protein</td>
<td>SAAVI MVA-C/SAAVI DNA-C2/Oligomeric gp140/MF59</td>
<td>South Africa</td>
</tr>
<tr>
<td>IAVI S001</td>
<td>I</td>
<td>Viral Vector-Replicating/Viral Vector-Adeno</td>
<td>SeV-G/Ad35-GRIN</td>
<td>Kenya, Tanzania, Uganda, Rwanda</td>
</tr>
<tr>
<td>RV262</td>
<td>I</td>
<td>DNA/Viral Vector-Pox</td>
<td>Pennvax-G/MVA-CMDR</td>
<td>Kenya, Tanzania, Uganda, USA</td>
</tr>
<tr>
<td>TaMovac II</td>
<td>II</td>
<td>DNA/Viral Vector-Pox</td>
<td>HIVIS-DNA/MVA-CMDR</td>
<td>Tanzania, Mozambique</td>
</tr>
</tbody>
</table>
The Global HIV Vaccine Landscape - 2013

Improving RV-144: CMI + non-neutralizing Ab

Prime Boost Candidates- improve the breadth of vaccine

Replicating Vectors- for durable responses to mimic live attenuated

Candidates to Elicit bnAbs

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)

- 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)

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

- HIV ENV trimers
- Designed Immunogens
- AAV –bnAb delivery

Basic research - Applied research - Preclinical development - Phase I / II - Large-scale Efficacy trials
Follow-on Trials Based on RV144: Strategy includes development and research tracks

RV144 FOLLOW-UP: Thailand

**Research Studies:**
- RV305 protein boost in volunteer-subset from RV144
- RV306 expanded immunogenicity of RV144 regimen
- RV328 AIDSVAX B/E study

**Partners/Funders:**
US Army, Thai government, NIH, Sanofi Pasteur, BMGF

LICENSURE TRIAL: Thailand

**Population:** MSM, high-risk

**Products:** ALVAC (Sanofi Pasteur) + gp120/adjuvant (such as MF59)

**Partners/Funders:** US Army, Thai government, NIH, Sanofi Pasteur, BMGF, Novartis

LICENSURE TRIAL: South Africa

**Population:** Heterosexual, high-risk

**Products:** ALVAC (Sanofi Pasteur) + gp120/MF59 (Novartis)

**Partners/Funders:** NIH, HVTN, Sanofi Pasteur, Novartis, BMGF

RESEARCH TRIAL

**Population:** Heterosexual, high-risk

**Products:** DNA + NYVAC (Sanofi Pasteur) + protein/adjuvant (such as MF59) vs. NYVAC (Sanofi Pasteur) +protein/adjuvant

**Partners/Funders:** NIH, HVTN, Sanofi Pasteur, Novartis, BMGF

Source: This schematic comes from the Pox-Protein Public Private Partnership (P5), a collaboration spanning four continents established in 2010 to build on the results of RV144. P5 partners include the US NIAID, the Bill & Melinda Gates Foundation, the HIV Vaccine Trials Network, the US Military HIV Research Program, Sanofi Pasteur and Novartis Vaccines and Diagnostics.
MHRP clinical vaccine development

ALVAC prime and gp 120 boost
  - gag/pol/env
  - env B/E

Ad26 prime and MVA boost
  gag/pol/env with mosaic inserts

DNA prime and MVA boost
  1) Inovio DNA prime
  2) HIVIS/TaMoVac DNA EDCTP funded
IAVI Clinical Trials Program
2013 Plans for Data and New Trials

- Ad35/Ad26 ENV (B003)
- Ad35/Adj. Protein (B002)
- Ad35/epDNA/IL12 (B004)
- Ad35/ Sendai (S001)
- Sendai – next generation
- AAV PG9 (A003)
- X001-Baseline Trial for HIV prototype trimer- Env- Imperial College- Shattock
- Chip Ad 63 + MVA Oxford-EDCTP
- DNA/NYVAC trial
- Chip Ad 63 + MVA HIVconsv -Phase IIb

Manufacturing completed
Regulatory approvals obtained
Manufacturing Completed
Design
Manufacturing
T cell vaccines

– DNA with electroporation + adjuvant
– Viral-vector approaches
  • VSV, novel serotype Ads, Chimp Ad, repAd4, NYVac, MVA, AAV1
– HIV inserts
  • Native, codon optimized, or mosaic, Gag, Pol, and Envs multiclude
Pipeline Summary

- B cell vaccines
- Protein-based immunogens in the following classes:
  - Native trimers or molecules engineered to resemble native trimers
  - Intermediate immunogens: gp120s, gp41, etc.
  - Minimal immunogens: immunogens designed to selectively express subdominant BnAb epitopes (through scaffold displays, etc.)
UK HVC Clinical Strategy

• Core support for GMP material, data management and laboratory
  ❖ Clinical trial costs through grants (EDCTP, MRC)

• D.A.M.P – DNA, Adenovirus, MVA, protein
  ❖ D> DNA-C: ZM96 gag-pol-nef and CN54 env (Geneart)
  ❖ A> Chimp Adenovirus ChAdC63 + SAd30/39 – on hold pending conclusion regarding adenovirus vectors
  ❖ M> MVA-C CN54 gag-pol-nef & env (M. Esteban)
  ❖ P> Protein: recombinant CN54 GP140. (Polymun)
  ❖ Adjuvant: GLA (IDRI)

• Exploratory trials
  ❖ Adding UKHVC adjuvanted protein to DNA/MVA prime (following HIVIS/TaMoVac DNA/MVA as well as the UK HVC DNA MVA); specimens from 40 TM01 ppts being analysed now
  ❖ To assess accelerated schedule after DNA priming giving the MVA/protein at the same time, compared to consecutively in Phase I (spoke 3), or compared to MVA alone in Phase IIa (TaMoVac II)
  ❖ Other combinations – DNA/protein and possibly with Adeno in future
A comprehensive and integrated approach toward an HIV/HCV vaccine

Candidate vaccine
Development & in vitro validation

NH2-IRIQRGGRAFVT1G-CO-NH2-CO-NH2

Lipopeptides

Delivery

Vaccine biodistribution

Developement of an epitope-based vaccine approach that could be employed in prime-boost strategy combined with recombinant viruses aimed to elicit strong, long lasting, polyepitopic T and B-cell responses focused on highly conserved epitopes
Projected Phase I and II VRC01 Clinical Trials
Projected Activity 2012-2018

- **Phase I: Healthy HIV+Adults**
  - NIAID Intramural: VRC CTC

- **Phase I: HIV- Adults**
  - NIAID Intramural: VRC CTC

- **Phase I: Infants born to HIV-infected mothers**
  - Single dose
  - IMPAACT Network: US

- **Phase IIb: Infants born to HIV-infected mothers**
  - Multi-dose
  - IMPAACT Network: International

- **Phase I: Chronically-treated HIV+ adults**
  - ACTG: US

- **Phase I: Acutely-infected HIV+ Adults**
  - USMHRP: Thailand

- **Phase I: HIV- Adults**
  - NIAID Intramural: VRC CTC

- **Phase IIb: High-risk adults**
  - Multi-dose - HVTN

- **Phase IIb: High-risk adults**
  - Multi-dose
Future of CD8 cell based vaccines ??

- gp160/gp120 subunits
- Poxvirus vector + protein
- rAd5-gag/pol/nef
- DNA/rAd5-Env/gag/pol/nef

Relative focus on vaccine effector mechanisms:
- Antibody
- CD8 T cells

Graph showing the trend of focus on vaccine effector mechanisms over time from 1987 to 2013.
Therapeutic vaccines

Aim is to help restore CD4 T cells in cases of therapeutic failures

Better control of HIV and disease progression during treatment interruptions

More recently with the aim of achieving HIV cure

In HIV functional cure the aim is to boost HIV-specific immunity in a shock and kill strategy of the HIV reservoirs.
Pipeline

- Multi-Antigen DNA Vaccine Prime Delivered by In Vivo Electroporation + IL12
- Synthetic peptides
- p24-RT-Nef-p17 fusion protein in proprietar adjuvant AS01B
- Tat protein vaccine
- Autologous dendritic cells pulsed with autologous, inactivated HIV–
- DNA/MVA
- MVA.HIVconsv
- DNA + lipopeptide vaccine (LIPO-5)
- NYVAC
Research priorities
Vaccine design

- Does EDCTP support vaccine design?
- Should EDCTP partner to move forward products designed to prevent against a broad spectrum of strains (e.g. conserved epitopes, mosaic, multi-clade, multi-gene)?
- Should priority be products that will induce broad NAb?
- How about CD4 and CD8 responses?
- Should EDCTP partner to advance passive delivery of Ab e.g gene transfer?
Epidemiology

• Should priority be support and identification of suitable populations with high incidence e.g. special groups such as fishing communities, sexworkers, MSM, etc
• Should we pioneer newer methods of following populations e.g. virtual cohorts using biometric identifications
• How about evaluate cost effective methods for measuring incidence
• The need for social/behavioural studies for risk assessment, retention etc
Clinical trials

Phase I and II

• What products to move forward- go/no go criteria
• How should trials be designed to answer relevant basic science questions e.g bNAb generation, assays development, effect of co-infection and immune activation on immune responses
• Small trials in high risk groups to conduct sieve analyses
• Should we support cross laboratory standardization
• Should EDCTP support advancing potent broadly Nab into clinical studies of passive immunotherapy
• How about prophylactic vaccines in infants born to HIV positive mothers
Clinical trials

Phase IIb/III

• What is the go/no go criteria
• If there are no vaccines to test should EDCTP support mock vaccine trials and diversification to conduct other clinical trials
• Should EDCTP partner to advance pox-protein under P5 in East Africa
• Can EDCTP partners with others to enlarge trials and to have enough power
Basic sciences

Within existing or new cohorts and planned trials

• Should EDCTP support studies to better understand protective immune responses e.g. acute/early infection events, development of broadly Nab. etc
Therapeutic vaccines

Recent interest as part of functional cure

- Should EDCTP support these studies
- There are unknowns such as viral reservoirs in African patients
Other

• Regulatory support including issues of vaccine manufacture and production relevant for some countries
• Capacity development including support to young investigators
• Networking/Advocacy including supporting the new AAVP
Acknowledgement

- **Research ideas:** Pat Fast, Carolyn Williamson, Omu Anzala, Glenda Gray, Jill Gilmour

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  - IAVI (Wyne Koff, Jill Gilmour)
  - NIAID (Carl Dieffenbach)
  - SAAVI (Anne-Lise Williamson)
  - MHRP (Merlin Robb)
  - UK HVC (Jonathan Weber, Robin Shattock, Sheena McCormack)
  - VRC (Barney Graham)
  - Karolinska (Eric Sandstrom)
  - ANRS (Yves Levy and Cécile Peltekian)