Is an HIV Vaccine Possible?

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Mechanism of Action

Vaccines:

Exposure → Infection → Disease

→ Death

→ Recovery
Immune response to pathogens

Innate immunity:
- Epithelial barriers
- Phagocytes
- NK cells

Adaptive immunity:
- B lymphocytes
- Antibodies
- T lymphocytes
- Effector T cells

Time after infection:
- Hours: 0, 6, 12
- Days: 1, 3, 5
HIV Vaccine Research & Development

• Road has been arduous, will continue to be difficult

• Correlates of immunity and correlates of protection are not fully known.
What are the challenges

• The virus impairs the immune systems
• Viral diversity
• The correlates of immunity or protection not fully known
• Funding
• Keeping communities interested
HOW HIV WORKS

HIV attaches to host CD4 cell

HIV's RNA

Reverse transcriptase

DNA is made from HIV's RNA via reverse transcriptase

DNA

HIV DNA is integrated into host DNA

Viral components are reproduced

HIV virus is assembled

HIV virus is distributed
Heterogeneity of HIV
HIV-1 Subtypes And Distribution (Africa)
Is the discovery of an HIV vaccine possible?

- Basic and Epidemiology research in HIV/AIDS has been pointing to this fact.

- RV144 trial in Thailand demonstrated for the first time modest protection against HIV infection. (Canary-pox-vector prime plus protein-subunit boost)

- Discovery of potent and broadly neutralizing antibodies
Exposed Seronegative Cohorts

• Repeated unprotected sexual HIV exposure
  – Sex workers ♀ ♂
  – Discordant couples

• Repeated intravenous HIV exposure
  – IDU

• Continuous HIV exposure
  – Fetal or perinatal exposure

• Single accidental exposure
  – Health care workers
HIV Immune Responses in ESN

• Studies have been able to demonstrate
  – T-Helper Cells (CD4)
  – CTL Cells (CD8)
  – HIV Specific mucosal immunoglobulin A

• Neonates of HIV infected mothers generate both (T Helper and cytotoxic T cells)
Factors in ESN

• The CCR 5 delta 32 deletion occurs in less 2% of humans.

• HLA Class I & II (HLA-B57, HLA-B27)
Natural History AIDS

- Incubation time to AIDS is ten years

- Slow progression
  - Viral factors (Nef deletion)
  - Host factors (HLA B57), immune response
Natural History of HIV-1
Slow Progressors to AIDS

- **Elite Controllers**
  - >50 copies/ml of RNA
  - Not ARVs
  - Infrequent exposed of viremia

- **Viremic controllers**
  - >2000 copies/ml of RNA
  - Not on ARVs
  - Occassional exposed of viremia

(Elite Neutralizers)
Immune Responses in Controllers

- Gag specific CTL and CD4 T helper responses.
- Demonstrable levels of neutralizing antibodies.
- Genetic factors
New and exciting discovery

- Broadly neutralizing antibodies.
- Revealed vulnerable targets on the virus that are now being exploited for vaccine design.
Antibody Attack on Targets: What we knew and what’s NEW

Cell Membrane

Viral Membrane

"Trimer" "PG9" and "PG16"

CD4bs "b12"

4E10" gp120

CCR 5 Glycan shield "2G12"

MPER "2F5" and

Wyatt and Sodroski Science 1998
Huang et al Science 2005
Phogat, Wyatt Curr Pharm Design 2007
RV 144
Study Vaccines

• ALVAC®-HIV (vCP1521)
  • Recombinant canarypox vector vaccine genetically engineered to express HIV-1 gp120 (subtype E: 92TH023) linked to the transmembrane anchoring portion of gp41 (subtype B: LAI), and HIV-1 gag and protease (subtype B: LAI).

• AIDSVAX® B/E
  • Bivalent HIV gp120 envelope glycoprotein vaccine containing a subtype E envelope from the HIV-1 strain CM244 and a subtype B envelope from the HIV-1 strain MN.
The ADCC mechanism: bridging the gap between innate and adaptive immunity
The new frontier

• HIV Vaccine research and development
A Balanced Approach

Hypothesis generation
Understanding mechanisms of disease

Vaccine Development

Hypothesis testing
New breakthroughs

Laboratory-based research
Hypothesis driven research

Clinical research
Discovery research

KAVI
KENYA AIDS VACCINE INITIATIVE
Balancing safety and efficacy in HIV vaccine design

SAFETY VERSUS EFFICACY IN AIDS VACCINE DESIGN

A large percentage of AIDS vaccine candidates in preclinical and clinical testing today are represented in the green part of the arc. To date these have not been effective. Replicating viral vectors may be an improvement over current candidates since they retain many of the traits that make viruses immunogenic. Given safety concerns, their development raises novel questions for regulatory agencies.

SAFETY CONCERNS PROHIBIT DEVELOPING LIVE-ATTENUATED AIDS VACCINES
- Live-attenuated virus
- Jennerian vaccines*

EFFICACY
- Replicating viral vectors
- Nonreplicating viral vectors
- Inactivated virus

MAJORITY OF AIDS VACCINE CANDIDATES IN CLINICAL TRIALS
- Naked DNA
- Proteins
- Virus-like particles

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

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Time after infection:
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Early Events in HIV Infection

- Blood or mucosal exposure
  
- Regional spread 18-72 hours
  
- Systemic Dissemination between 4 and 12 days
  
- Infection of immunoprivileged sites & sequestration
  
- Latency
Both antibody (Env-specific) and T cell responses (broad) should be induced

Blood or mucosal exposure
Regional spread 18-72 hours
Systemic Dissemination between 4 and 12 days

CD8 T cells
How do adaptive immune responses control virus infection?

- Antibody: +++ in Isolated virion, +/− in Virus-infected cell, - in Latency or extracellular sequestration.
- T cells: - in Isolated virion, +++ in Virus-infected cell, - in Latency or extracellular sequestration.

Virus-infected cell and Latency or extracellular sequestration involve virus replication and spread, regulated by immune responses.
T cell-mediated control of HIV-1 Infection

- **Regional spread**: 18-72 hours
- **Systemic Dissemination**: between 4 and 12 days
- **Latency**: Infection of immunoprivileged sites & sequestration
Mechanism of Action

Vaccines:

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Vaccine-induced CD8 T cells can affect disease expression.
Prevention of HIV-1 acquisition is the new standard.
Ongoing Projects at KAVI

- Three HIV vaccine trials
- Three projects on Mucosal immunology
- Establishing KAVI as a center of mucosal immunology
Ongoing Phase 1 clinical trials

PaedVac

- Funded by EDCTP
- MVA + EPI vaccination vs EPI vaccination (alone)
- Safety, immunogenicity & interference with EPI vaccines
- Infants vaccinated at 20 weeks - single IM injectio
- Immunogenicity data not yet out
- Antibody titres to EPI being conducted
Ongoing Phase 1 clinical trials

Protocol B002

- Recombinant Fusion protein (F4co) in adjuvant (ASO1B or ASO1E) + replication incompetent Ad35-GRIN
- F4co [p24-RT-Nef-p17 of HIV-1 clade B Gag, Pol, Nef)]
- Ad35-GRIN [with HIV-1 clade A gag, RT, integrase, nef)]
- Phase 1, double blind, randomized placebo controlled
- 140 participants (112 vaccine/28 placebo)
Ongoing Phase 1 clinical trials

Protocol B003

- Different combinations of recombinant Ad26 vector & recombinant Ad35 (HIV-1 sub-type A env gene)
- Heterologous or homologous
- Multi-centre – Boston (USA), Rwanda, S/Africa
- KAVI-Kangemi
The Questions ??

- Would an HIV vaccine be useful if it was less than 100% effective?

- Would a vaccine still be needed if current prevention programs and antiretroviral therapy (ART) are significantly expanded while the vaccine is still being developed?

- Would a vaccine result in cost-savings?
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 (cervical cancer)</td>
<td>Early '80s to mid-'90s</td>
<td>2006</td>
<td>12-25</td>
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<tr>
<td>Rotavirus (diarrheal disease)</td>
<td>1973</td>
<td>2006</td>
<td>33</td>
</tr>
<tr>
<td>Varicella zoster (chickenpox)</td>
<td>1953</td>
<td>1995</td>
<td>42</td>
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<tr>
<td>Pertussis (whooping cough)</td>
<td>1906</td>
<td>1948</td>
<td>42</td>
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<tr>
<td>Polio</td>
<td>1908</td>
<td>1955</td>
<td>47</td>
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<tr>
<td>Haemophilus influenza</td>
<td>1889</td>
<td>1981</td>
<td>92</td>
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<td>Typhoid</td>
<td>1884</td>
<td>1989</td>
<td>105</td>
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<tr>
<td>Malaria</td>
<td>1893</td>
<td>—</td>
<td>116</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV/AIDS)</td>
<td>1893</td>
<td>—</td>
<td>28</td>
</tr>
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*Founding donors of IAVI

And many other generous individuals from around the world