Progress Towards an HIV Vaccine – Lessons Learned from HIV Prevention

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Opportunities for Preventing HIV Infection

**Unexposed**
- Behavioral, structural
  - Male circumcision, condoms

**Exposed (precoital/coital)**
- Vaccine, topical microbicides, PrEP

**Exposed (postcoital)**
- Vaccine, Pep

**Infected**
- Treatment of HIV, reduced infectivity

HIV Incidence Reduction by Prevention Technologies

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size (95% CI)</th>
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<tr>
<td>ARV treatment for prevention</td>
<td>96% (73-99)</td>
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<tr>
<td>PrEP for discordant couples</td>
<td>73% (49-85)</td>
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<tr>
<td>PrEP for heterosexual men &amp; women</td>
<td>63% (21-84)</td>
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<tr>
<td>Medical male circumcision</td>
<td>54% (38-66)</td>
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<td>PrEP for MSMs</td>
<td>44% (15-63)</td>
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<tr>
<td>Sexually transmitted diseases treatment</td>
<td>42% (21-58)</td>
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<tr>
<td>Microbicide</td>
<td>39% (6-60)</td>
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<tr>
<td>HIV vaccine</td>
<td>31% (1-51)</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>0% (-41-41)</td>
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Treating HIV-infected People with Antiretrovirals Significantly Reduces Transmission to Partners

Findings Result from NIH-funded International Study

- HPTN 052
- 1,763 HIV-serodiscordant couples in 9 countries
- 96% reduction in HIV transmission when ART started in HIV-infected partner at CD4 count of 350-550 compared to <250
Why it is Essential to Develop a Safe and Effective HIV Vaccine

- A highly effective vaccine is the only prevention strategy that can achieve the necessary population coverage to end the HIV epidemic
- Other than male circumcision, all other biomedical prevention approaches are heavily adherence dependant
HIV Transmission Simplified

Transmitting Virus

Activated CD4^+ T cell

Infected Activated CD4^+ T cell

Replicating Virus
Non-Vaccine Mechanisms of HIV Prevention

- Prevent contact with HIV
  - Condoms, avoiding exposure to HIV
  - Needle and syringe exchange

- Reduce/eliminate infectivity from the source
  - Treatment as prevention

- Reduce the number/density of susceptible cells at the site of exposure
  - Male circumcision
  - Pre-exposure and post-exposure prophylaxis
  - Microbicides
HIV Prevention Simplified

Prevent contact with HIV

- Barrier methods

Reduce/eliminate infectivity from the source

- ART as prevention reduces the amount of virus in secretions
Reduce the Number of Susceptible Cells at the Site of Exposure

- Male circumcision
  - Removal of target cells
- Pre- and post-exposure prophylaxis and microbicides
  - Block virus replication and spread from the site of entry
Early Events in HIV Infection: Opportunities for Intervention

Male Circumcision

No Targets, No Infection

Lamina propria
‘Resting’ CD4+ T cells
Infected ‘resting’ CD4+ T cells

Dissemination

HIV virions
Crossing the barrier
Infected cell

Macrophage

CD4+ T cell
Activated CD4+ T cell
Infected activated CD4+ T cell

Lymphoid tissue
Late-responding CTLs
PD-1+CD8+ T cells
Establishment of lymphoid-tissue central memory
Immune activation
Partial control
Sustained HIV production
Regulatory T cells

Hours
Days

Weeks
Years
Early Events in HIV Infection: Opportunities for Intervention
What Could A Vaccine Do To Prevent Infection?

- Block HIV from coming into contact with target cells and tissues
- Reduce the number of susceptible cells and overall susceptibility of target cells
- Controlling the spread of HIV from infected cells
- Eliminating any infected cells that occur within the vaccinated host or enter the host as part of the inoculum
Where Could a Vaccine Prevent Establishment of Infection?

Antibodies sequester and inactivate incoming virus

- Lamina propria
- Lymphoid tissue

Adapted from: AT Vaccine Action Plan, 2005
Where Could a Vaccine Prevent Establishment of Infection?

- Antibodies prevent binding of virus to cells
- Vaccine response could result in decreased numbers of activated CD4 cells in target tissues
- Host responses to vaccine create intracellular resistance
Where Could a Vaccine Prevent Establishment of Infection?

- Cellular immunity kills infected cells and prevents establishment and spread.
Classical Vaccinology

The response to natural infection provides the proof of concept

HIV Vaccinology
New Approaches in HIV Vaccinology
Alternative Open Reading Frames

CD8 T Cell Recognition of Cryptic Epitopes is a Ubiquitous Feature of AIDS Virus Infection

Journal of Virology

November 2010, Volume 84, No. 21

CD8 T Cell Response and Evolutionary Pressure to HIV-1 Cryptic Epitopes Derived From Antisense Transcription

THE JOURNAL OF EXPERIMENTAL MEDICINE
VOLUME 207 NUMBER 1 JANUARY 18, 2010
New Approaches in HIV Vaccinology
Targeting Endogenous Retroviruses

Strong Human Endogenous Retrovirus-specific T Cell Responses are Associated with Control of HIV-1 in Chronic Infection


Journal of Virology

July 2011, Volume 85, No. 14
New Approaches in HIV Vaccinology
Persistent Vectors

Profound Early Control of Highly Pathogenic SIV by an Effector Memory T Cell Vaccine

Epitopes Targeted by Broadly Neutralizing Human Monoclonal Antibodies

Membrane proximal region

CD4 binding site

Unique glycan side chains on outer domain

V2/V3 loops quaternary epitope

Adapted from Schief et al., 2009.
Does HIV Have an Achilles Heel?

Epitopes Targeted by Broadly Neutralizing Human Monoclonal Antibodies

Membrane proximal region

CD4 binding site

Unique glycan side chains on outer domain

V2/V3 loops quaternary epitope

Adapted from Schief et al., 2009.
Critical Challenge in the Development of an HIV Vaccine

Neutralizing Epitope → Immunogen
Vector-mediated Gene Transfer Engenders Long-lived Neutralizing Activity and Protection Against SIV Infection in Monkeys

Johnson P.R., Schnepp B.C., Zhang J., Connell M.J., Greene S.M., Yuste E., Desrosiers R.C., and Clark K.R.

Dimeric 2G12 as a Potent Protection Against HIV-1

First Signal of Efficacy in an HIV Vaccine Clinical Trial

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

S Rerks-Ngarm, JH Kim et al. for the MOPH–TAVEG Investigators
Building on the Results on the Thai Trial

- Determine, if possible, the correlates of immune protection
- If correlates are identified, maximize induction of relevant responses in subsequent trials
- Focus future trials on prevention of acquisition
- Conduct trials with improved vectors and inserts in high-incidence populations
- Develop relevant NHP acquisition model, concentrating particularly on early events
A partnership of public and private entities has been formed to understand and build on the results of RV144 by advancing clinical development of pox-prime protein-boost vaccine concepts in trials in high(er) incidence populations.

The goals of this partnership are to:
- Extend and confirm the RV 144 efficacy results in high incidence populations in Southern Africa and Thailand, advancing the candidates toward licensure and broader public health impact.

P5 will be informed by RV 144 follow-up correlates analyses and immunogenicity studies.
Our Common Goal: Controlling and Ultimately Ending the HIV/AIDS Pandemic