Development of HIV Vaccine Candidates for Prevention and Treatment

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Vaccines are One Part of HIV Prevention Efforts

- Treatment as Prevention
- HIV Vaccine
- PrEP
- PMTCT
- STI Treatment
- Male Circumcision
- Microbicides
- HIV Testing/Counseling
- Education
- Drug/Alcohol Treatment
- Harm Reduction
- Blood Screening

Adapted from: A. Fauci, US NIAID/NIH, AIDS Vaccine Conference, 2012
Challenges for HIV Vaccine Development

Preventative Efficacy trials to date

Preventative Efficacy Trials going forward

Therapeutic Vaccine Efforts
HIV “hides” proteins on its surface

Trimeric HIV-1-Env Structures Define Glycan Shields from Clades A, B, and G
Guillaume B.E. Stewart-Jones… Peter D. Kwong
Cell 2016
HIV Hides from Antibodies

Latency & Integration

Cell → HIV

HIV Integrated into Human DNA
HIV Hides from Antibodies

Latency & Integration

Cell

HIV

HIV Integrated into Human DNA

Reservoir Sites
Challenges for HIV Vaccine Development

**Preventative Efficacy trials to date**

Preventative Efficacy Trials going forward

**Therapeutic Vaccine Efforts**
AIDS Vaccine Fails in Trials

Clinical trials suspended after dismal results for most promising vaccine

Jane Yager, Newser Staff
Sep 22, 2007 8:25 AM CDT

(Newser) – Heavy hopes riding on an HIV vaccine were dashed as the vaccine proved so ineffective in a clinical trial that manufacturer Merck has ended the trial early. The vaccine had shown promise in animal and small-scale human tests but neither prevented nor reduced the severity of infection in a large-scale trial, the New York Times reports.

Failed efficacy trials
VAX003 – Thailand
VAX004 – Americas
STEP – Americas
Phambili – South Africa (halted early)
The NEW ENGLAND JOURNAL of MEDICINE

Oct 20, 2009

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

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, 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*

Thai Ministry of Public Health
Faculty of Tropical Medicine, Mahidol University
Royal Thai Army

US Military HIV Research Program
Armed Forces Research Institute of Medical Sciences
Division of AIDS, National Institutes of Health, USA
Sanofi-Pasteur, GSID
USAMMDA
RV144 - Participants

men and women ages 18-30
Heterosexual, at “community risk”
8,197 randomized to receive vaccine regimen, 8,198 received placebo

ALVAC
ALVAC + AIDSVAX

Inserts matched to subtype AE circulating recombinant forms prevalent in Thailand
RV144 – Trial Results

Efficacy: 31.2%
Efficacy at 1 year appeared higher

60% Efficacy

M. Robb et al, Lancet ID 2012
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., Chitrartrorn Karnasuta, Ph.D., Ruengpueng 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 Nguay, 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 Pitisuttithum, 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.
“Variable Loops” of HIV Envelope

Scaffold: Murine leukemia Virus gp70

Pinter A, Vaccine 1998

Cole KS, J. Virol 2004
Cumulative Infection Rates With V1V2-gp70 Scaffold Assay

- Estimated Relative Risk High vs Low = 0.29
Failure Of Latest HIV Vaccine Test: A 'Huge Disappointment'

April 26, 2013
RICHARD KNOX, NPR

The largest current study of an AIDS vaccine, involving 2,500 people, is being stopped. After an oversight committee took a preliminary peek at the results this past Monday, they concluded there was no way the study would show that the vaccine prevents HIV infection... So they pulled the plug on HVTN-505.
RV305: 162 people who received RV144 Vaccines

ALVAC + AIDSVAX

ALVAC

0 1 2 3 4 5 6 42
month

6 - 8 years

Bang Lamung Hospital, MOPH

RV306: 360 healthy, low-risk HIV- people

ALVAC + AIDSVAX

ALVAC

0 1 2 3 4 5 6 12 15 18 24
month

Vaccine Trial Center, Mahidol University
Royal Thai Army
RIHES, Chiang Mai University
Challenges for HIV Vaccine Development

Preventative Efficacy trials to date

Preventative Efficacy Trials going forward

Therapeutic Vaccine Efforts
Building on RV144 in Africa

RV144 → HVTN 097 → HVTN 100 → HVTN 702

RV144 regimen → Clade C products/MF59 Adjuvant Month 12 boost → Phase 3

Thailand → South Africa → Southern Africa

Bill and Melinda Gates Foundation
DAIDS/NIAID
GSK, Novartis
Sanofi-Pasteur
Republic of South Africa Medical Research Council
US Military HIV Research Program
Parallel Vaccine Strategies: Poxviridae

Family of double stranded DNA, enveloped viruses

Pox Viruses Tested in Humans

- Vaccinia
- Canary pox (ALVAC)
- Fowlpox (FP)
- Modified Vaccinia Ankara (MVA)
- NYVAC (18 genes deleted from Copenhagen strain of vaccinia)
GOVX-B11: DNA / MVA Vaccine

* Immuno-gold staining for native Env

VLPs expressed by DNA prime

VLPs expressed by MVA boost

GOVX-B11

RV144

% Responders

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<thead>
<tr>
<th>CD4</th>
<th>CD8</th>
<th>Env Ab</th>
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<tr>
<td>60</td>
<td>20</td>
<td>80</td>
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% Responders

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<td>10</td>
<td>90</td>
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2013

Heterologous vector-based prime-boost regimens delivering mosaic antigens afford partial protection against SHIV-SF162P3 repetitive intra-rectal challenges.
Substantial increase of humoral immunity by \textbf{gp140 boost} affording partial protection in stringent SHIV-SF162P3 and SIVmac251 challenge models.
Proof-of-Concept studies in Nonhuman Primates

2015

Substantial increase of humoral immunity by **gp140 boost** affording partial protection in stringent SHIV-SF162P3 and **SIVmac251** challenge models.
Mosaic Approach Aims at Global Coverage of All HIV Subtypes

Prime
- Ad26 Mosaic vectors gag-pol-env
- Ad26 Mosaic vectors gag-pol-env

Boost
- Ad26 Mosaic vectors gag-pol-env
- Soluble trimer gp140 env proteins
- MVA Mosaic vectors gag-pol-env
- Soluble trimer gp140 env proteins

Ongoing Phase 1 includes sites at Mahidol University and Royal Thai Army

Regimen to be selected after Phase 1/2a

Janssen
BIDMC
Harvard
MHRP
WRAIR
IAVI
NIAID/HVTN
**Adjuvants** to improve quality, magnitude and duration of immune response

**Proteins** to elicit more potent broadly neutralizing antibodies to native trimeric HIV envelope

**Novel vectors** to elicit stronger T cell responses:
- Replicating MVA
- Cytomegalovirus: CD8+ cells recognized 3-fold > epitopes than other vectors

Hansen…Picker Nature 2011
World Health Organization expanded guidelines to recommend TDF PrEP to all high risk populations in Nov 2015

1. Increase trial size to accommodate decreased HIV incidence
2. Identify populations with lower PrEP uptake for alternative trial designs

RV438 Cohort
Study of High Risk MSM / TG

Thai MOPH

Mahidol U. Royal Thai Army

n = 500 per site followed 18 months
Vaccine Efficacy Testing in the PrEP Era

1. Vaccine + PrEP

PrEP-willing

2. Vaccine + PrEP-placebo

PrEP-unwilling

2a. Vaccine

Vaccine-placebo

3. Vaccine-placebo + PrEP

PrEP-willing

4. Vaccine-placebo + PrEP-placebo

PrEP-unwilling

4a. Vaccine-placebo
Vaccine Efficacy Testing in the PrEP Era

1. Vaccine + PrEP
2. Vaccine + PrEP-placebo
2a. Vaccine
3. Vaccine-placebo + PrEP
4. Vaccine-placebo + PrEP-placebo
4a. Vaccine-placebo

PrEP-willing

PrEP-unwilling

Evaluate efficacy of Vaccine-Alone:
- Compare 2+2a vs. 4+4a
Vaccine Efficacy Testing in the PrEP Era

1. Vaccine + PrEP
2. Vaccine + PrEP-placebo
   - PrEP-willing
   - PrEP-unwilling

2a. Vaccine
3. Vaccine-placebo + PrEP
4. Vaccine-placebo + PrEP-placebo
   - PrEP-willing
   - PrEP-unwilling

Evaluate efficacy of PrEP Alone:
- Compare 3 vs. 4
Vaccine Efficacy Testing in the PrEP Era

1. Vaccine + PrEP
   - PrEP-willing
     - Vaccine
6a. Vaccine-placebo
   - PrEP-unwilling
     - Vaccine-placebo
4. Vaccine-placebo + PrEP-placebo

Evaluate efficacy of Vaccine+PrEP:
- Compare 1 vs. 4
Challenges for HIV Vaccine Development

Preventative Efficacy trials to date

Preventative Efficacy Trials going forward

**Therapeutic Vaccine Efforts**
T Cell Responses are required for HIV Control

- **Correlate**: Virologic Control
- **Immunological parameter**: Gag Breadth (memory T cells), Gag Magnitude (memory T cells)
- **P-value**: 0.0002, 0.0058

**Viral Load per vaccine group**
(day 84 post infection)

- **DNA**
- **MVA**
- **MVA**
- **Ad26**
- **MVA**
- **Ad26**

**Antigen**: SIVsmE543 Gag-Pol-Env

**N=40**

*The horizontal lines represent mean set point log viral loads.*

**P = 0.0037**, Wilcoxon rank-sum tests.

**Barouch et al., 2012**
RV405 Therapeutic Vaccine Study in HIV+ Volunteers on ART

Ad26/ placebo  Ad26/ placebo  MVA/ placebo  MVA/ placebo

-4 0 12 24 48 60  Study Week 84 96

Ad26 + MVA Vaccines (n=24)

Randomized 2:1

Placebo Vaccines (n=12)

Pl*  ART  ATI

Institutes and Collaborators: Janssen, BIDMC, Harvard, OI, MHRP, WRAIR, Thai Red Cross AIDS Research Centre
An HIV Vaccine is Still Urgently Needed

- Can improve adherence issues
- Even partially efficacious vaccines can reduce population burden in high risk areas (e.g. > 50% in Thailand, >30% in Benin and rural Zimbabwe)
- May help achieve functional cure in HIV+, alone or in combination with other therapies