Preventive and therapeutic HIV vaccines

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Disclosures

• No conflicts to declare
Background

• FAQ: by patients and colleagues

• Publication about “promising results”, especially in the non-medical press

• Vaccines are by far the most effective weapon in epidemics

• Most clinical vaccine trials were not very convincing, but vaccine trials have a revival
<table>
<thead>
<tr>
<th>Year</th>
<th>VAX003</th>
<th>VAX004</th>
<th>RV144 ALVAC/AIDSVAX</th>
<th>STEP MRKAD5</th>
<th>Phambili</th>
<th>HVTN 505 DNA-Ad5</th>
<th>HVTN 704/HPTN 085 VRC01</th>
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<th>HVTN 702 ALVAC Protein</th>
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After several years of early-phase research, the HIV vaccine field is moving into a new era of efficacy trials.
Questions

• What would you guess was the effectiveness of the 2017/2018 Influenza vaccine?

A. 20%
B. 40%
C. 60%
D. 80%
E. >90%
Questions

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A. 20%
B. 40%
C. 60%
D. 80%
E. >90%
SEASONAL FLU VACCINE EFFECTIVENESS

<table>
<thead>
<tr>
<th>FLU SEASON</th>
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<td>2016-17*</td>
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<td>2017-18**</td>
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Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD) - www.cdc.gov/flu
Questions

• What would you guess was the one year effectiveness of the first, large published HIV vaccine trial in Thailand?

A. 20%
B. 40%
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E. >90%
Questions

• What would you guess was the one year effectiveness of the first, large published HIV vaccine trial in Thailand?

A. 20%
B. 40%
C. 60%
D. 80%
E. >90%
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*
4 priming injections of a recombinant canarypox vector vaccine ALVAC-HIV [vCP1521]

+ 2 booster injections of a recombinant glycoprotein 120 subunit vaccine AIDSVAX B/E
4 priming injections of a recombinant canarypox vector vaccine ALVAC-HIV [vCP1521] + 2 booster injections of a recombinant glycoprotein 120 subunit vaccine AIDSvax B/E

“prime-boost” schedule based on the dual ability of canarypox viruses to induce cellular responses and prime for an antibody responses that could be boosted with recombinant envelope proteins
A Sound Rationale Needed for Phase III HIV-1 Vaccine Trials


“We have a concern about the wisdom of the U.S. government’s sponsoring a recently initiated phase III trial in Thailand...”

Burton DR et al., Science. 2004 Jan 16;303(5656):316
4 priming injections of a recombinant canarypox vector vaccine ALVAC-HIV [vCP1521] +
2 booster injections of a recombinant glycoprotein 120 subunit vaccine AIDSVAX B/E

26,676 screened ➔ 16,402 enrolled ➔ 12,542 received all doses
132 HIV seroconversions (56 verum vs 76 placebo)
"Thai-Trial" (RV144)

Phase III: RV144 Sanofi ALVAC prime, AIDSVAX gp120 boost

Modified Intention-to-Treat Analysis

Probability of HIV-1 Infection (%)

Years

Placebo
Vaccine

P=0.04

"Thai-Trial" (RV144)

Phase III: RV144 Sanofi ALVAC prime, AIDSVAX gp120 boost

Est. VE = 31.2%; 95% CI 1.1-52.1%

"Thai-Trial" (RV144)
The receipt of vaccine did not have a significant effect on the viral load in subjects who were found to have early HIV-1 infection
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., Chitraporn 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 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 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.
The binding of IgG antibodies to variable regions 1 and 2 (V1V2) of HIV-1 envelope proteins (Env) correlated inversely with the rate of HIV-1 infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>P-value</th>
<th>Q-value</th>
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<tbody>
<tr>
<td>IgA Binding to Envelope Panel</td>
<td>1.54</td>
<td>0.027</td>
<td>0.08</td>
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<tr>
<td>IgG Avidity A244 gp120</td>
<td>0.81</td>
<td>0.37</td>
<td>0.56</td>
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<tr>
<td>ADCC AE.HIV-1 Infected CD4 Cells</td>
<td>0.92</td>
<td>0.68</td>
<td>0.68</td>
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<tr>
<td>Tier 1 Neutralizing Antibodies</td>
<td>1.37</td>
<td>0.22</td>
<td>0.45</td>
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<tr>
<td>IgG Binding to gp70-V1V2</td>
<td>0.57</td>
<td>0.015</td>
<td>0.08</td>
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<tr>
<td>CD4+ T Cell Intracellular Cytokines</td>
<td>1.09</td>
<td>0.61</td>
<td>0.68</td>
</tr>
</tbody>
</table>

The first study showing that a biomarker predicted the outcome

Additional Boost of AIDSVAX B/E Further Increased RV305 IgG but not IgA Antibodies

RV305/RV305a Vaccination Schedule

AIDSVAX B/E Group

ALVAC-HIV Group

ALVAC-HIV (VCP1521)

AIDSVAX B/E (gp120 MN and gp120 A244 – 600 µg)
Additional boost of AIDSVAX B/E increased levels of IgG responses to gp120 in all groups
A comparison between HIV and influenza virus illustrates the extraordinary scale of HIV variation, and underscores the importance of exploring innovative HIV vaccine strategies. Modified from Korber B et al., Br Med Bull. 2001;58:19-42.
High Level Target Product Profile Goal: A prophylactic vaccine offering protection against all clades of HIV-1 through an heterologous prime boost regimen.
Theory behind therapeutic vaccines

- Deliver non-infectious HIV antigens
- Antigens processed and presented to CD4-, CD8- and B-cells
- Elimination / reduction of latent HIV reservoir due to enhanced immune response
- Induction of a bnAb

Types of therapeutic vaccines

• DNA and RNA encoding for HIV antigens

• Viral vectors: canarypox (ALVAC), Modified Vaccinia Ankara strain (MVA), adenoviruses, lentiviruses

• HIV protein or peptide vaccines

• Dendritic cell vaccines

Problems of therapeutic and preventive vaccinations

• Lots of new, attractive methods (not just in the HIV field), some show very promising results in animal studies

• To prove the efficacy in humans
  – Therapeutic vaccines: treatment interruptions, biomarkers, endpoints?
  – Preventive vaccines: different vaccine in different regions, minimal incidence rate (e.g. 3% per year) required?
HIV reservoir and cure research

Casper Rokx
Erasmus University Medical Center
Rotterdam, the Netherlands
Conflict of interest

• None related to this conference

• Outside this conference:
  – Involved in grants from Gilead, Merck
  – Advisory boards for Gilead, ViiV
  – Travel reimbursement of Gilead, Merck, ViiV
  – Lectures for Gilead, ViiV, Virology Education
The purpose is to understand the factors involved to come to an HIV cure

• The answer for cure is in the reservoir

• HIV Reservoir
  – Where is it?
  – How to measure it?
  – What does it?

• Cure strategies
  – How to target the reservoir?
  – Pitfalls? (And challenges for you!)
Definition of the HIV reservoir  
(non peer reviewed)

The integrated HIV-DNA in the host genome of long lived human mononuclear cells that is BOTH capable to produce a virus that is replication competent AND successful in host immunity evasion

Natural course of the reservoir

- HIV reservoir:
  - Where is it?
  - How to measure it?
  - What does it?

Volberding PA et al., Lancet. 2010 Jul 3;376(9734):49-62
Where is it?

- Blood
- Lymph node
- Gut

How to measure it?

What does it?

<table>
<thead>
<tr>
<th>class</th>
<th>DNA</th>
<th>US RNA</th>
<th>MS RNA</th>
<th>proteins</th>
<th>particle</th>
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<td>+</td>
<td>-</td>
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</table>

The cure hypothesis

- Manipulation:
  - Decrease reservoir starting point
  - Improve reservoir reduction

Hill AL et al., Proc Natl Acad Sci U S A. 2014 Sep 16;111(37):13475-80
From PrEP, TasP and T&T to cure

1. Intervene in acute HIV (up to 6 months from seroconversion)

Walker BD et al., abstract #13, CROI 2016
From PrEP, TasP and T&T to cure

1. Intervene in acute HIV (up to 6 months from seroconversion)
2. Manipulate hiding HIV in the reservoir and target the host
   - Massive interventions (allogeneic-SCT)
   - Genetic interventions
   - Immunological interventions
   - Viral/host interventions

**Timeline Berlin patient**

- First bone marrow transplantation (CCR5 Δ32 homozygous donor)
- Second bone marrow transplantation (same donor)

Kent SJ et al., Lancet Infect Dis. 2013 Jul;13(7):614-21
Genetic interventions

- Genetic interventions
  - Target host(-virus) interaction (CCR5 receptor)
  - Target integrated virus

Fear of off target effects in the host genome but also in society

Immune interventions

- Infuse anti-HIV antibodies (VRCO1)
- Monkey studies to the rescue!
- T-cell/innate cell activators or infuse host Abs

Viral/host interaction
Shock and Kill

Monotherapy:
Shocking works (a little), killing not yet

Margolis DM et al., Science. 2016 Jul 22;353(6297):aaf6517
Challenges / Pitfalls

• Which patients (acute vs. chronic)?
• What biomarkers to measure?
• When to measure biomarkers (viral kinetics)?
• Combination strategies?
• Are immune cells up for it?
• Drug distribution?
• What to sample?

Future directions

• New LRAs (+ combinations + host immunity boosting)

• Biomarkers for reservoir and cure and penetration of our interventions

• Different interventions in chronic and acute HIV?

• We need a team
  – Ongoing translational research
  – (International) collaboration
  – Young and old. Basic and clinical scientists.
MCQ

• What percentage of HIV-DNA in the reservoir is replication competent?
  A. ~90%
  B. ~50%
  C. ~10%
  D. ~1%

• Does measuring integrated HIV-DNA underestimate or overestimate the size of the replication competent reservoir?
  A. Underestimate
  B. Overestimate
  C. It does not under, nor overestimate the size

• What percentage of patients do you think finds it very important to be cured of HIV?
  A. ~25%
  B. ~50%
  C. ~75%
  D. ~99%

Verduld et al., IAS 2012
Prospects

‘I like to refer to my rebirth after being cured as my “cure birthday”’