Progress in HIV Vaccine Development

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Outline

• A short history of HIV vaccine design and development

• Describe the status of advanced clinical development of a safe and effective preventive HIV vaccine

• Describe advances in search for immunogens that induce neutralizing antibodies to block viral entry and prevent infection
Evolution of Approaches to HIV-1 Vaccine Development

1983 ➔ Monomeric envelope glycoproteins ➔ T-cell based vaccines ➔ Ab-based vaccines

2016
Challenges in HIV-1 Vaccine Development (1)

• HIV Pathogenesis
  – Rapid and dramatic early events during acute infection

• Extraordinary genetic diversity of Env
  – Rapid replication and mutation rate and potential for viral escape

• Induction of broadly active neutralizing antibodies
  – Sites of neutralization on virion surface are shielded

• Definition of immune correlates of protection

• Need for protection against mucosal and blood challenges

• Multiple candidate immunogens and adjuvants
  – Subtypes, gene inserts, protein, selecting the optimal combination & dose
  – Vector choice and immunity
Challenges in HIV-1 Vaccine Development (2)

- Community preparedness, engagement and partnership
- Vaccine induced seroreactivity
  - Potential for social harm
- Manufacturing
- Cost
- Changing prevention landscape & increasing uptake of PrEP
  - A welcome development which inevitably will make HIV vaccine trials larger and more complex
    - Decreasing HIV incidence – which is a success – affects study design and conduct of phase 2b/3 efficacy trials of preventive vaccines
    - Hence the importance of defining correlates of protection
HIV-1 Vaccine Efficacy Studies

• Since 1987, more than 200 vaccine products have been tested but only 5 have advanced to efficacy trials

• Diverse approaches to inducing protective immunity
  – cell-mediated immune responses
  – eliciting neutralizing antibodies
  – combined humoral and cellular responses
## HIV-1 Vaccine Efficacy Studies (1)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Vaccine Regimen and Strategy</th>
<th>Study Population</th>
<th>Results</th>
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<tbody>
<tr>
<td>VAX004 1998-2003</td>
<td>AIDSVAX bivalent gp120 B/B</td>
<td>MSM and heterosexual women in US, Canada, Netherlands (N=5417)</td>
<td>No vaccine efficacy</td>
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<tr>
<td>VAX003 1999-2003</td>
<td>AIDSVAX bivalent gp120 B/E</td>
<td>Male and female IDU in Thailand (N=2546)</td>
<td>No vaccine efficacy</td>
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<tr>
<td>Step Study/ HVTN 502 2004-2009</td>
<td>Recombinant Ad5 (Clade B gag/pol/nef)</td>
<td>MSM and high risk women in US, Canada, Caribbean, South America, Australia (N=3000)</td>
<td>No vaccine efficacy; Early &amp; transient increased infection in uncircumcised &amp;/or Ad5 positive MSM</td>
</tr>
<tr>
<td>Phambili / HVTN 503 2006-2009</td>
<td>Recombinant Ad5 (Clade B gag/pol/nef)</td>
<td>Heterosexual men and women in South Africa (N=801)</td>
<td>No efficacy. Late increase in HIV acquisition in unblinded male vaccine recipients.</td>
</tr>
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Flynn NM, Forthal DN, Harro CD et al., J. Infect. Dis, 20015; 191: 654
Buchbinder SP, Mehrotra DV, Duerr A et al. Lancet 2008; 372:1881
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<td>RV144 2003-2010</td>
<td>ALVAC vcp1521 + AIDSVAX gp120 B/E</td>
<td>Heterosexual men and women with variable risk of HIV in Thailand (N=16402)</td>
<td>31.2% vaccine efficacy over entire follow-up 60% vaccine efficacy at 12 month</td>
</tr>
<tr>
<td>HVTN 505 2009-</td>
<td>Multiclade, multigene DNA prime + rAd5 boost</td>
<td>Circumcised and rAd5 seronegative MSM/TGW (N=2500)</td>
<td>Vaccinations stopped at interim analysis for futility</td>
</tr>
</tbody>
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Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S et al. NEJM 2009; 361:2209
Hammer SM, Sobieszczyk ME, Janes H et al NEJM 2013; 369:2083
Thai Trial (RV144) Primary Results

Vaccine efficacy decreases over time

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Cumulative Infections</th>
<th>% HIV-1 infection rate (95% CI)</th>
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<th>% HIV-1 infection rate (95% CI)</th>
<th>Vaccine Efficacy (%)</th>
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<tr>
<td>12</td>
<td>12</td>
<td>0.15 (0.07,0.24)</td>
<td>30</td>
<td>0.38 (0.24,0.52)</td>
<td>61</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>0.41 (0.27,0.55)</td>
<td>50</td>
<td>0.64 (0.46,0.82)</td>
<td>36</td>
</tr>
<tr>
<td>36</td>
<td>45</td>
<td>0.58 (0.41,0.75)</td>
<td>65</td>
<td>0.84 (0.63,1.04)</td>
<td>31</td>
</tr>
<tr>
<td>42</td>
<td>51</td>
<td>0.68 (0.49,0.87)</td>
<td>74</td>
<td>0.96 (0.74,1.18)</td>
<td>31</td>
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Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S et al. NEJM 2009; 361:2209
Post-RV144 Era: Search to Determine Correlates of Risk & Protection

- Major findings:
  - IgG3 response to V1-V2 correlated with decreased risk of acquisition
  - IgA response to Env correlated with increased risk of acquisition
  - Non-neutralizing binding antibodies
  - Antibody dependent cellular cytotoxicity (ADCC)
  - Polyfunctional CD4+ cells
  - No CD8+ cell response
  - No neutralization

- Could the results be reproduced and improved upon?
Association Between Higher V1V2 Antibody Titers and HIV Acquisition in RV144

Vaccinees with the highest IgG binding antibody titers more likely to be protected than those with lower titers

HVTN 505: HIV Acquisition & Viral Load Setpoint
Blinded Follow-up: Data through April 22, 2013

Lessons Learned from HVTN 505

- Major disappointment but provided a clear answer to the question
- Demonstrated value of internet/social media in recruitment
  - Created a challenge in informing participants of DSMB recommendation and study outcome before word spread
- Correlates analysis concordant with RV144 results
  - Humoral responses benchmarked against RV144 revealed important differences

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<th>IgG3 Ab to V1/V2</th>
<th>IgA to Env</th>
<th>ADCC</th>
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<tr>
<td>505 vs RV144</td>
<td>Lower</td>
<td>Higher</td>
<td>Lower</td>
</tr>
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</table>

- Implemented plan to provide free TDF/FTC to participants who wished to start PrEP while study continued (HVTN/Gilead/DAIDS)

Pathways forward: How do these data lead to next steps for HIV vaccines?
What to Expect in the Next Few Years: Current Strategies & Efficacy Studies

**P5* Clade C approach using ALVAC & gp120/MF59**
Can non-neutralizing antibody approaches lead to effective vaccine efficacy in high risk populations?

**Multi-clade approach using rAd26/MVA/gp140 trimer**
To test vaccines with mosaic gene inserts to circumvent the viral diversity and attain cross-clade coverage

**Neutralizing Ab approach using VRC01**
Can antibodies prevent HIV infection in humans (AMP study)?
To identify most appropriate envelope epitopes for immunogen design

*Pox Protein Public Private Partnership*
Building on RV144: The Pox-Protein Public-Private Partnership

• Licensure Track
  – South African trial: goal to reproduce and build on success in Thailand, in support of local licensure
  – ALVAC [Clade C] prime + ALVAC (Clade C) +protein boost with MF59 adjuvant

• Research Track
  – To amplify the findings of the RV144 trial: increase strength, breadth and durability of responses
  – South African trials: assess impact of different priming, alternate dosing, vectors and adjuvants
Design and test vaccines with mosaic gene inserts to circumvent the viral diversity and attain cross-clade coverage.
HIV Vaccine Aiming at Protection Against all Clades of HIV-1

**Different HIV-1 clades dominate in different geographic regions**

- **Vectors that elicit optimal immune responses**
  - Low seroprevalent Ad26
  - Ad26.HIV-Gag-Pol
  - Ad26.HIV-Env
  - (MVA.HIV-Gag-Pol-Env)

- **Mosaic inserts for global coverage**

- **Trimeric env protein for improved humoral immunity**

Adolescents (11-17 years) /Adults (18-65 years) in endemic countries and populations at risk in Western world

Challenge of Eliciting a Neutralizing Antibody

Challenge of inducing broadly reactive neutralizing antibodies

- HIV-1 Env is highly glycosylated and glycans shield critical neutralizing antibody target sites
- Difficult interactions b/w neutralizing antibodies and viral epitopes

Figure courtesy of Dennis Burton.
What Can we Learn from HIV-infected Individuals who Develop Neutralizing Antibodies

- Broadly neutralizing Ab are produced by a minority (~20%) of infected individuals
  - These antibodies appear 2-3 years after infection & neutralize a wide variety of HIV isolates in vivo
  - The evolving B-cell response lags behind the rapidly diversifying virus and antibodies do not control established infection
  - Do not appear to affect the clinical course of patient

- **New technologies** for detecting and isolating B cells that make HIV-1 specific bnAbs
  - ~30 bnAbs recovered from HIV-infected individuals

- Isolation of these antibodies allows one to define where they bind to the virus and what epitope the immunogen/vaccine should be targeting

Ackerman & Alter, NEJM 2013; Koff, Vaccine 2012; Hraber, AIDS 2014
Selected Broadly Neutralizing Abs & their Site of Attachment on the Viral Envelope

Peter Kwong, Jonathan Stuckey
Adapted from Fauci & Marston. Science. 2015
Role of Antibodies in HIV-1 Prevention

Structure-based Vaccine Design

Immune pathways of antibody evolution

Vaccine development

Passive Immunization
- Direct infusion of IgG
- Gene-based Ab (AAV)
HIV Antibodies for HIV-1 Prevention: Key Questions

• Do broadly neutralizing antibodies actually offer protection against acquisition of HIV infection?
  – Passive antibody prevention of HIV/SHIV in NHP for >20 years
  – No direct evidence in humans

• Can broadly neutralizing antibodies be induced by vaccine immunogens?
Plans for Clinical Trials of Neutralizing Monoclonal Antibodies

**N332 Glycan Supersite:**
PGT121, PGT128, 10-1074

**CD4 Binding Site:**
VRC01, PG04, CH31, 3BNC117, 12A12, CH103, VRC07-523

**Trimer (gp120/41):**
8ANC195, PGT151, 35022

**V1V2 Glycan:**
PG6, PG16, CH01-04, PGT141-45, PGDM1400, CAP256-VRC26

**gp41 MPER:**
2F5, 4E10, 10e8

Thanks to the Subramaniam, Kwong, and Wilson groups.
VRC01: CD4 Binding Site Antibody

Gray: gp120
Red: CD4 binding site (CD4bs)
Purple & Green: VRC01 attached to the CD4bs

Photo: NIAID/NIH Vaccine Research Center (VRC)

Panel of 190 Diverse Viral Isolates

- Red: IC_{50} < 1 μg/ml
- Green: IC_{50} 1-50 μg/ml
- Black: IC_{50} > 50 μg/ml

Thanks to Barney Graham and Wu et al. Rational design of envelope identifies broadly neutralizing human monoclonal Antibodies to HIV. Science. 2010
Zhou et al. Science 2010
Antibody Potency/Breadth
In Vitro Neutralization Profiles

(190 Diverse strains of HIV-1)

Antibody Potency/Breadth
In Vitro Neutralization Profiles

% viruses resistant

More potent

IC80 Titer (µg/ml)

Mark Louder, Bob Bailer et al.

Variation in breadth of coverage
Pharmacokinetics of VRC01 Monoclonal Antibody in Healthy Adults

Plasma levels following single infusion of 20 mg/kg I.V.

Phase IIB prevention study: q 8 week dosing

Ledgerwood et al, Clinical & Experimental Immunology, 2015
Phase 2b Efficacy study of mAb VRC01
Antibody Mediated Prevention

Can passively infused monoclonal antibody prevent HIV-1 infection in high risk adults?
AMP Study

• Conducted by DAIDS Networks internationally (HVTN and HPTN)
• Placebo controlled trial of VRC01 mAb administered IV every 2 months
  – 10 mg/kg IV and 30 mg/kg IV based on Phase I studies and NHP prevention data
  – 10 infusions over 20 months per subject = 39,000 infusions total
• Two cohorts
  – 2400 MSM + TG in North and South America
  – 1500 Women in sub-Saharan Africa
• Powered to detect a prevention efficacy (PE) of 60% and to associate VRC01 plasma level with protection
• Open to accrual
Monoclonal Antibody Passive Transfer Studies as a Guide to Vaccine Design

- Define the level of antibody needed to prevent infection
  - Pertains to passive IgG infusion, or options for genetic immunization (AAV, mRNA) to provide medium to long-term protective antibody levels
- Translate that into SQ administration to achieve this level of mAbs
- Develop next generation of mAb: more potent, longer half-life
- Proof of concept that neutralizing mAb can protect will provide a benchmark for vaccine development: i.e. what antibody level does a vaccine need to achieve
- Identify most appropriate envelope epitopes for immunogen design
Desired Characteristics of Second Generation mAbs for Prevention of HIV

• More breadth to cover the extraordinary viral diversity
  – Potentially administer two mAbs in combination
• More potent than current generation mAbs
• Longer half-life
  – Clinical studies with VRC01LS underway
• Administered by SQ injection every 3-4 months
• Cost and manufacturing comparable to ARTs and PrEP
Combining mAbs to Improve Potency and Breadth

>98% coverage with 2 mAbs

Rui Kong et al. J. Virol. 2015;89:2659-2671
HIV Antibodies for HIV-1 Prevention: Key Questions

• Do broadly neutralizing antibodies actually offer protection against acquisition of HIV infection?
  – Passive antibody prevention of HIV/SHIV in NHP for >20 years
  – No direct evidence in humans

• Can broadly neutralizing antibodies be induced by vaccine immunogens?
Co-evolution of Virus and Antibody in an HIV Infected Individual

Liao HX. Haynes BF. Nature, 2013; 496: 469
Implications for Vaccine Design by Studying Virus and Antibody Co-evolution in an Individual with bnAbs

Florian Klein et al. Science 2013;341:1199-1204
How to Induce Broadly Neutralizing Antibodies by Vaccination

- Convert neutralizing epitopes to immunogens that would induce production of broadly neutralizing antibodies
- B-cell lineage immunogen design: use repetitive immunization to selectively stimulate the germline antibodies of bnAb lineages to trigger the desired lineage
- Engage the naïve B-cell repertoire residing in bone marrow and secondary lymphoid tissue
- Stimulate B-cell “evolution” until bnAb producing cells are elicited
Generation of bnAbs

Conformational epitope: co-crystal structure of epitope bound to broadly neutralizing antibody

Target

Structure

Engaging the Naive B-Cell Repertoire

B-Cell Lineage Immunogen Design

Broadly Neutralizing Antibodies

Evolution from germline cell to mutated cell with high-affinity antibodies with increased breadth

HIV-1 viral spike

Trimeric heterodimer of HIV envelope

Engaging the naive B-cell repertoire: naive, germline, unmutated

Naive B cell

Antibody

Broadly neutralizing antibodies

HIV

• B-cell-lineage-based approach to vaccine design

• Plans for phase 1 clinical study are underway

Haynes, Bradley. JAMA, 2015; 313:2419
Conclusions and Future Directions

• There is considerable energy in the HIV vaccine field

• Test of concept studies of both neutralizing and non-neutralizing antibody approaches are getting off the ground and set the stage for the entire field for the next decade

• As prevention technologies intersect, opportunities emerge to test strategies in combination to achieve incremental reduction in HIV incidence
  – PrEP + vaccines
  – PrEP + monoclonal antibodies
  – Improved delivery methods

• Studies become more complex but also more relevant and applicable to diverse populations in greatest need of prevention interventions
Acknowledgments

- Barney Graham & John Mascola (VRC)
- Larry Corey (HVTN)
- Scott Hammer (Columbia)
- Bart Haynes (Duke)

Special thanks and appreciation to the many thousands of volunteers around the globe who have rolled up their sleeves to participate in HIV vaccine trials and to those who will follow to achieve the goal of an effective and safe HIV vaccine