HIV Vaccine Awareness Update

May 16, 2019
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Director, Vaccine Research Program
Presentation Outline

- Mission: Preventative vaccine

- Key HIV Vaccination Trials:
  - 2-pronged Strategy
  - Empiric and rationale design
  - Ongoing efficacy trials

- Passive Antibody efficacy trials (broadly neutralizing Ab)

- Addressing HIV Vaccine Development Challenges
VRP Mission: safe and effective HIV vaccine

**VRP:** Dedicated and talented team of scientists and administrators who support preclinical, translational, and clinical research portfolios with the goal of ending the HIV epidemic.

**What:** Promote research programs, vaccine developers, investigators and laboratorians working to discover and test novel vaccine candidates and strategies - regardless of the funding environment.

**How:** Use science and data-based decision making relying on the peer review system, overseeing iterative processes and using a staged and milestone driven approach.
Preventative Vaccines: Overview
RV144: First to show prevention of HIV infection

First Efficacy Signal (31%) in an HIV vaccine trial

**Immune Correlates analysis:** non-neutralizing Abs correlate with reduced risk of HIV-1 infection

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>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>
Current NIH HIV Vaccine Strategies: The Way Forward

Empirical

RV144 Thai Trial

Theoretical

Broadly Neutralizing Antibodies

Vaccines to improve potency and durability of non-neutralizing anti-Env V2 Abs

Vaccines that induce bNAbs

Immunophylaxis with bNAbs

HVTN702: Phase 2b/3 Clade C ALVAC + gp120 in MF59

HVTN705: Phase 2b Mosaic Ad26 + gp140

Phase 1/2a: Alternative Viral Vectors and Env Proteins

Phase 1: rENV Immunogens for bNAbs, alternative adjuvants

HVTN703/704: Phase 2b AMP Trials VRC01 mAb

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HVTN703/704: Phase 2b AMP Trials VRC01 mAb
## Study Schema: HVTN 702

<table>
<thead>
<tr>
<th>N (total 5400)</th>
<th>Primary Vaccine Regimen</th>
<th>Booster</th>
<th>2nd Booster</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
<td>Month 3</td>
</tr>
<tr>
<td>2700</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV+ Bivalent C gp120/MF59®</td>
</tr>
<tr>
<td>2700</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Study Opened:** Oct 2016 in South Africa, (n=5,400)

**Number Currently enrolled (vaccinated):** >5,100

**Estimated Enrollment Completion:** May 2019
Janssen Collaboration: Preventive HIV “Mosaic” Vaccine for Global Coverage


1. Vectors to elicit both humoral and cellular immune responses
   - Ad26 Mosaic
   - MVA-Mosaic

2. Mosaic inserts for global coverage (Gag-Pol-Env)

3. Trimeric env proteins to boost humoral immunity
   - Clade C gp140
   - Mosaic gp140
Study Schema: HVTN 705
Phase 2b Proof of Concept Trial

- **HVTN705**, opened in sub-Saharan Africa (SSA) Nov 2017:
  - 2450 (94%) enrolled

- Evaluate vaccine efficacy Ad26.Mos4.HIV + clade C gp140 regimen

- Population:
  - Moderate-high risk subjects in Southern Africa
  - Limited to female subjects
Different Mechanisms of Protective Humoral Immunity

Antigen recognition - Neutralization - Binding

Fc-mediated - Complement fixation - FcRn - Fcγ (ADCC, ADCP)

AMP - VRC01 bNAb

HVTN702: ALVAC/gp120
HVTN705: rAd26/gp140

Efficacy could be additive: Possible that both neutralization and Fc-mediated effector functions contribute to protection
Broadly neutralizing Abs (bNAbs)

We know:

- Develop in ~ 20-25% infected pts (humans *can* make them)
- bNAb targets: 5 different vulnerable sites on HIV-1 envelope
- Develop slowly (adults: several years, infants: one year)
- Highly specialized Abs: eg autoreactive, highly mutated, long loop CDRH3
- Prevent infection in NHP SHIV challenge animal model

We DON’T know:

- Do bNAbs protect humans? Currently testing (AMP)
- Can vaccines can elicit bNAbs? May need multiple components
Most effective vaccines induce Neutralizing Antibodies against the virus

- **Hepatitis B**
  - HBsAg

- **Influenza A**
  - Hemagglutinin (HA)
    - e.g., H1, H3

- **HIV-1**
  - gp160

Antibodies bind to viral surface protein
From natural infection: Human repertoire produced broadly neutralizing antibodies

Recognition that bNAb development requires extensive SHM

Recognition of the 5 epitopic targets for bNAbs

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Recognition of the 5 epitopic targets for bNAbs
AMP Americas Trial: HVTN704
AMP Africa Trial: HVTN703

Phase 2b studies to evaluate the efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection
VRC01 Human Monoclonal Antibody

- Discovered in an individual who was HIV infected for a long time (>15 years), who maintained virologic control without ART

- Developed by John Mascola and colleagues at the Vaccine Research Center/NIH

- bNAb that blocks CD4 binding

Photo: NIAID/NIH Vaccine Research Center (VRC)
AMP Study Schema

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection

VRC01 Ab
10 or 30 mg/kg IV or placebo every 8 weeks, 10 doses

High Risk Women
N=1900
Sub-Saharan Africa

MSM/TG
N=2700
North and South Americas

Estimate efficacy of prevention of infection in each of two separate cohorts
Study duration: 92 weeks

Study Enrollment Completed in Oct 2018
Fusion Peptide vaccination with Trimer Boost: shows cross-neutralizing antibodies in NHP!

NHP mAb Neutralizes 59% of 208 viral strains: Geo IC$_{50}$ mean = 3.12 µg/ml

Kong, Duan, Sheng, Xu, Acharya, Chen, Cheng, Chuang, et al. (Submitted)
HIV Vaccine bNAb immunogens: Near Clinical Testing (2017-2020)

2017
- Q1: EnvSeq1 4 x gp120 CH505 proteins (HVTN115)

2018
- Q1: EnvSeq2 M5 protein (HVTN-115 Part B)
- Q3: CH505 TF transient protein (HVTN123)
- Q4: EnvSeq2 M5 protein (HVTN-115 Part B)

2019
- Q2: MPER Liposome (HVTN-133)
- Q3: CH505 M5 G485Y (HVTN-TBD)
- Q4: CH505 M5 G485Y (HVTN-TBD)
- Q1: A244 in SLE individuals (HVTN-121)

2020
- Q1: CH505 TF Infant Study (HVTN-115)
- Q1: A244 protein vs. mRNA (HVTN-TBD)

2020
- Q1: eOD-GT8 60mer (IAVI-G001)

2020
- Q1: BG505 SOSIP (IAVI-W001)
- Q1: BG505 SOSIP Adjuvant Comparison Study (HVTN-137)
- Q4: BG505 D5-SOSIP.664 – VRC 4571 (VRC-018)

2020
- Q1: Env Fusion Peptide conjugated to ITTbc (VRC-TBD)
- Q1: HIV Trimer 2 (VRC-TBD)
- Q1: Diverse FP (VRC-TBD)
- Q1: A246 Core gp120 7-mer (HVTN-TBD)

2020
- Q1: Mosaic SOSIP-based trimers (Imperial College – TBD)
- Q1: SOSIP-based trimers (Imperial College-TBD)
- Q1: Consensus M SOSIP native like trimer (ConM) (Imperial College-TBD)
- Q1: Consensus S Linker-based trimer (ConS) (Imperial College-TBD)
Virus-Neutralizing Antibody Co-evolution

Co-Evolution of HIV Transmitted-Founder Virus and Evolving Neutralizing (CD4bs) & Apex & V3-glycan & MPER

“The Arms Race”

Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus


Nature 496: 469-476, 2013
Sequential HIV Immunization Strategy

Source: Burton Nature Reviews Immunology 2019
## Summary: Efficacy Studies and Timelines

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Trial</th>
<th>Location</th>
<th>Population</th>
<th>N</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVAC + gp120/MF59</td>
<td>HVTN702</td>
<td>South Africa</td>
<td>Men and Women</td>
<td>5400</td>
<td>June 2022</td>
</tr>
<tr>
<td>Ad26Mosaic + gp140/alum</td>
<td>HVTN705</td>
<td>Sub-Saharan Africa</td>
<td>Women</td>
<td>2600</td>
<td>June 2022</td>
</tr>
<tr>
<td>VRC01 10 mg/kg 30 mg/kg</td>
<td>HVTN703</td>
<td>Sub-Saharan Africa</td>
<td>Women</td>
<td>1900</td>
<td>September 2020</td>
</tr>
<tr>
<td></td>
<td>HVTN704</td>
<td>Americas, Lausanne</td>
<td>Men (MSM &amp; Transgender)</td>
<td>2700</td>
<td>September 2020</td>
</tr>
</tbody>
</table>

*estimated timeline for primary analysis

Watch for early Phase studies to elicit neutralizing Abs
Addressing HIV Vaccine Development Challenges

- Interoperable platform technology
- Identify immune correlates in protective vaccine studies
- Use correlates to advance vaccine candidates
- Prequalify vaccines for Registration/Marketing
- Increase capacity and efficiency of manufacturing
- Incentivize/de-risk Industry

Public-Private Partnerships

Community
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