RSA & HIV vaccine efficacy studies

Glenda Gray
15 March 2016
3 strategies that are advancing

**Efficacy Studies**

- P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)
- Multi-clade approach using rAd26/MVA/gp140 trimer
- Neutralising antibody approaches
Thai Trial (RV144) Primary Results

Prime: ALVAC vCP1521
Boost: ALVAC vCP1521 plus VAXGEN Env protein (B/E)
Schedule: 0, 1, 3, 6 months; 16,000+ volunteers; 1:1 vaccine: placebo; follow-up for 3 years

Modified Intention-to-Treat Analysis

Vaccine efficacy (%)

Data from Robb et al, Lancet Infectious Diseases, 2012.
The Strategy for the ALVAC/Protein Phase 3 Program

- Construct Bivalent Subtype C gp120/MF59
- Add Booster at 12 months
- Optimize regimen for regional relevance, increased potency, and durability
- Construct ALVAC-HIV-C (vCP2438)
HVTN 100

Primary objectives

• To **evaluate the safety and tolerability** of 2 doses of ALVAC-HIV (vCP2438) followed by 2 doses of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 in HIV-seronegative low risk South African adults

• To **evaluate the immunogenicity** of 2 doses of ALVAC-HIV (vCP2438) followed by 2 doses of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 in HIV-seronegative low risk South African adults at the month 6.5 timepoint (2 weeks after completion of the primary immunization series)
# HVTN 100 Schema

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Primary vaccine regimen</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>1</td>
<td>210</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Total</td>
<td>252</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HVTN 100 Clinic Sites

- Cape Town—Emavundleni
- Klerksdorp
- Soweto–Baragwanath
- eThekwini and Isipingo
- Shoshanguve
HVTN 100 Current Status

- Primary vaccination series (Months 0, 1, 3, 6) complete for all participants
- Follow-up ongoing
- Booster vaccinations (Month 12) just beginning
- Primary immunogenicity assays (Month 6.5 samples) ongoing
- Interim safety and immunogenicity analyses (to Month 6.5) in process
Go Decision Timeline

HVHN 100 Assays & Data Analysis
Dec-15 - Apr-16

Go/No Go Decision & Funder Confirmation
May 16 - Jun 16

Jan-16  Feb-16  Mar-16  Apr-16  May-16  Jun-16

12/1/2015  6/30/2016
# HVTN 100 Go/No-Go Criteria for HVTN 702: Must Meet **all** of the Following Conditions

<table>
<thead>
<tr>
<th>Variable Measured at Month 6.5</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Env Ab Response Rate (≥ 2 of 3)</td>
<td>Adequate Ab take to vaccine Env</td>
</tr>
<tr>
<td>Env Ab Magnitude* (≥ 2 of 3)</td>
<td><em>Non-inferior</em> Ab magnitude vs. RV144</td>
</tr>
<tr>
<td>Env CD4 Response Rate* (1 of 1)</td>
<td><em>Non-inferior</em> CD4 T cell take vs. RV144</td>
</tr>
<tr>
<td>Env V1V2 Response Rate (≥ 1 of 3)</td>
<td>Adequate to predict achieving VE=50% for 2 years if V1V2 Ab is an immune correlate</td>
</tr>
</tbody>
</table>

* Based on assessment of immune responses from HVTN 100 vaccinees vs. RV144 vaccinees using the same assays run in the same labs
Primary objectives

• To evaluate the preventive vaccine efficacy (VE) of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 for the prevention of HIV infection in HIV-seronegative South African adults over 24 months from enrollment

• To evaluate the safety and tolerability of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 in adults in South Africa
# HVTN 702 Schema

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Primary vaccine regimen</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2700</td>
<td>ALVAC-HIV (vCP2438) ALVAC-HIV (vCP2438) ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59</td>
</tr>
<tr>
<td>2</td>
<td>2700</td>
<td>Placebo Placebo Placebo + Placebo</td>
<td>Placebo + Placebo Placebo + Placebo Placebo + Placebo</td>
</tr>
<tr>
<td>Total</td>
<td>5400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HVTN 702 Design Features (i)

• Evaluates Stage 1 vaccine efficacy (VE) to 24 months after 1st vaccination
• If evidence of positive VE, evaluates VE durability to 36 months after 1st vaccination
• Continuous monitoring for harm
• Sequential monitoring for non-efficacy/efficacy futility
• Monitoring for high efficacy
HVTN 702 Design Features (ii)

- 90% power to detect Vaccine Efficacy (VE) of 50% (enrollment through 24 months)
- = 90% power to reject null hypothesis (VE ≤ 25%)

<table>
<thead>
<tr>
<th>True Average VE(0-24)</th>
<th>Power to reject null: VE(0-24) ≤ 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>7</td>
</tr>
<tr>
<td>40%</td>
<td>45</td>
</tr>
<tr>
<td><strong>50%</strong></td>
<td><strong>90</strong></td>
</tr>
<tr>
<td>60%</td>
<td>100</td>
</tr>
<tr>
<td>70%</td>
<td>100</td>
</tr>
<tr>
<td>80%</td>
<td>100</td>
</tr>
</tbody>
</table>
HVTN 702 Clinic Sites

- Cape Town—Emavundleni
- Cape Town—Khayelitsha
- Soweto—Baragwanath
- Soweto—Kliptown
- Klerksdorp
- Rustenberg
- Brits
- Shoshanguve Medunsaa
- Tembisa
- Ladysmith
- eThekwini
- Isipingo
- Verulam
- Mthatha
- Brits
- Shoshanguve Meduna
- Klerksdorp
- Rustenberg
- Brits
- Shoshanguve Meduna
- Tembisa
- Ladysmith
- eThekwini
- Isipingo
- Verulam
- Mthatha
HVTN 702 Partnership

- Bill & Melinda Gates Foundation
- Division of AIDS, National Institute of Allergy and Infectious Diseases, US National Institutes of Health
- GlaxoSmithKline Vaccines
- HIV Vaccine Trials Network
- Medical Research Council of South Africa
- Sanofi Pasteur
3 strategies that are advancing

Efficacy Studies

- P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)
- Multi-clade approach using rAd26/MVA/gp140 trimer
- Neutralising antibody approaches
HIV vaccine research program: Janssen and Collaborators

- BIDMC
- Harvard
- MHRP
- IAVI
- Ragon
- NIAID/HVTN
HIV Vaccine Aiming at Protection Against all Clades of HIV-1

Different HIV-1 clades dominate in different geographic regions

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

1. Potent priming Vectors
   - Low seroprevalent Ad26
   - Ad26.HIV-Gag-Pol
   - Ad26.HIV-Env
   - (MVA.HIV-Gag-Pol-Env)

2. Mosaic inserts for global coverage

3. Trimeric env protein for improved humoral immunity

Protective Efficacy of a Global HIV-1 Mosaic Vaccine against Heterologous SHIV Challenges in Rhesus Monkeys

Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys

Dan H. Barouch et al., 2010
A prime-boost vaccine regimen aiming at global coverage starting 2017-2021

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

**Boost**
- Soluble trimer gp140 env protein
- (+/-)

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

**Boost**
- MVA Mosaic vectors gag-pol-env
- (+/-)

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

**Boost**
- Soluble trimer gp140 env protein
- (+/-)

Timeline:
- 0 months: Prime
- 3 months: Prime
- 6 months: Boost
- 12 months: Boost

HIV VACCINE TRIALS NETWORK
Ad26/Env SIV Vaccines Partially Protect Against IR SIVmac251 Challenges in Rhesus Monkeys

90% reduction of per exposure acquisition risk for Ad/Env (P=0.001)
50% (6 of 12) show complete protection for Ad/Env (P=0.01)

- 32 rhesus monkeys
  - Ad26/Env (N=12)
  - Ad26/Ad35 (N=12)
  - Sham (N=7)

- Repetitive, intrarectal, heterologous SIVmac251 challenges

- Correlates of protection
  - ELISA  P < 0.0001
  - Ab Funct  P = 0.004
  - NAb  P = NS

Barouch et al. Science 2015
3 strategies that are advancing

**Efficacy Studies**

- P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)
- Multi-clade approach using rAd26/MVA/gp140 trimer
- Neutralising antibody approaches
**Neutralizing Ab to HIV-1**

- V1V2-Glycan – bind to trimer cap
- V3-glycan, N332 supersite
- gp41 MPER – near membrane
- gp120/41 interface – bind to parts of both gp120 and gp41
- CD4 binding site of gp120 – where the virus attaches to CD4

*Only antibodies that have advanced the clinic (VRC01, 3BNC117)*

Christina Corbaci, Andrew Ward,
VRC01 Protects Against Mucosal SHIV-Challenge in Non-Human Primates

20 mg/kg infusion of VRC01: Challenge with SHIV SF162P3

RECTAL CHALLENGE

4/4 protected

0/4 protected

Days post challenge

VAGINAL CHALLENGE

4/4 protected

1/4 protected

Days post challenge

AMP Trial Objectives

1. To determine whether and how the VRC01 broadly neutralizing mAb can prevent HIV infection
2. To develop a marker(s) of VRC01 that correlates with the level of protection against HIV infection
3. To provide insight into the mechanistic correlates of protection

Application: Help design candidate HIV vaccines and define immunogenicity study endpoints in Phase I/II trials for evaluating these candidate vaccines
AMP: Two Phase IIB Studies

- HVTN 703/HPTN 081 will enroll 1,500 women in sub-Saharan Africa
- HVTN 704/HPTN 085 will enroll 2,700 MSM and transgender persons in the Americas
- Each ppt. will be randomized to receive VRC01 10 mg/kg or 30 mg/kg or placebo every 8 weeks for 10 doses

www.ampstudy.org
Major Scientific Questions and Issues the Trial will Define

- Do immunogens that elicit lower levels of neutralization, levels that have proven protective in NHP challenge models, protect against HIV acquisition in humans?
  
  What is the dynamic range in concentration of antibodies and neutralizing activity associated with protection?

  Can lower levels of neutralization activity afford protection or does in vivo protection require only high concentrations of CD4 binding site antibodies?

  Are non-neutralizing effector functions as predictive of efficacy as neutralizing activity?

  What are the kinetics and functional (non-neutralizing) activities that are seen at low levels of neutralization for VRC01?
AMP Research Sites
AMP sub-Saharan Africa Sites

- Gabarone, Botswana
- Kisumu, Kenya
- Blantyre, Malawi
- Lilongwe, Malawi
- Maputo, Mozambique
- Harare (3 clinics), Zimbabwe
- Cape Town, RSA
- Durban (2 clinics), RSA
- Johannesburg, RSA
- Soweto, RSA
- Vulindlela, RSA
- Mbeya, Tanzania
Timeline for AMP in sub-Saharan Africa: Open April 2016

<table>
<thead>
<tr>
<th>AMP sub-Saharan Africa</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAIDS Reviews</td>
<td>2/1/2016 - 3/21/2016</td>
</tr>
<tr>
<td>MCC and RSA EC Reviews</td>
<td>10/2015 - 2/2016</td>
</tr>
<tr>
<td>Trial Opens*</td>
<td>4/1/2016</td>
</tr>
</tbody>
</table>

*Additional SSA National Regulatory Authority & EC reviews continue to Q3 2016, with trainings to be scheduled accordingly.
Enrollment Projections: AMP in sub-Saharan African women

- Number enrolled, by month
- Cumulative enrollment

HIV VACCINE TRIALS NETWORK
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  HPTN
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