Planned Vaccine Trials to Follow-up on RV 144

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MHRP
Planned studies are mutually reinforcing and will amplify public health impact and regional relevance.

Strategy for achieving potential licensure in target markets and having the broadest public health impact.

Precedent for vaccine efficacy
Focus on regional public health impact

Future amplification of global reach

Mutually reinforcing studies strengthen and support public health benefit in target populations and the translation of the platform globally.

RV144

THAILAND
High Risk MSM

US/EUROPE

SOUTHEAST ASIA

SOUTHERN AFRICA

Republic of South Africa (RSA)
High Risk
Heterosexual

High Risk MSM
RV144 FOLLOW-UP: Thailand/SEA Studies:
- RV144i immune correlates studies
- RV305 protein boost
- RV306 expanded immunogenicity of ALVAC
- RV328 AIDSVAX only
Partners/Funders: US Army, Thai Gov’t, NIH, sanofi pasteur, BMGF

DEVELOPMENT: Thailand Phase IIb
Population: MSM, high-risk
Products: ALVAC (sanofi) + gp120/adjuvant, 12 month boost
Partners/Funders: US Army, Thai Gov’t, NIH, sanofi, BMGF

DEVELOPMENT: Southern Africa Phase IIb
Population: Heterosexual, high-risk
Products: ALVAC (sanofi) + gp120/adjuvant
Partners/Funders: NIH, HVTN, sanofi, protein manufacturer, BMGF, RSA

RESEARCH: Southern Africa Phase IIb
Population: Heterosexual, high-risk
Products: DNA + NYVAC (sanofi) + protein/adjuvant versus NYVAC (sanofi) + protein/adjuvant
Partners/Funders: NIH, HVTN, sanofi pasteur, protein manufacturer, BMGF
Next steps for ALVAC + gp120: Immunogenicity

• **RV144 extended boost study (RV305)**
  - Existing RV 144 uninfected vaccine recipients
  - Objective—Evaluate late boosts
  - Extensive sampling with mucosal collection and biopsy

• **AIDSVAX only (RV328)**
  - Provide cells / specimens for analysis of AIDSVAX only responses to compare with ALVAC + AIDSVAX prime boost
  - Extensive sampling

• **Intensive immunogenicity study (RV306)**
  - ALVAC-HIV (vCP1521) + AIDSVAX B/E
  - Mucosal secretions and gut biopsy
  - 12 month boost
Critical path bridging study – possible design

<table>
<thead>
<tr>
<th>Group</th>
<th>V / P</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>12</th>
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<tbody>
<tr>
<td>I</td>
<td>60-100/10</td>
<td>ALVAC</td>
<td>ALVAC</td>
<td>ALVAC+AI DSVAX</td>
<td>ALVAC+AID SVAX</td>
<td>ALVAC+AID SVAX</td>
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<tr>
<td>II</td>
<td>60-100/10</td>
<td>ALVAC</td>
<td>ALVAC</td>
<td>ALVAC+gp 120 in MF59</td>
<td>ALVAC+gp1 20 in MF59</td>
<td>ALVAC+gp1 20 in MF59</td>
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<td>gp120 in MF59</td>
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</table>

Non-inferiority of new gp120 in MF59 to AIDSVAX boost
- Safety
- Immunogenicity with emphasis on hypothesized correlates
RV 349: Thai Efficacy Trial – draft design

- 1 vaccine regimen vs. placebo

Hypothetical Schema of a Vaccine vs. Placebo Trial

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Number</th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
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<tbody>
<tr>
<td>V</td>
<td>2333</td>
<td>ALVAC</td>
<td>ALVAC</td>
<td>ALVAC + prot</td>
<td>ALVAC + prot</td>
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<tr>
<td>P</td>
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<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
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<tr>
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</table>

- HIV negative subjects enrolled and tested for HIV infection for 3-monthly for a maximum of 36 months
- Primary endpoint at 24 months
Thai ALVAC/gp120 efficacy trial: RV349

Statistical Considerations

- Incidence: control arm 2 year infection rate = 6% (3/100 PY)
- 2.5% level, one-sided test with 95% power to detect a halving of the hazard of infection
- 20% loss to follow-up over 2 years (RV144 = 10% over 3.5 years)
- Sample size estimate: 3465 (N = 3500)
- 58 treatment arm infections
- Interim efficacy assessment @ 2/3 information time
- Futility (CP < 10%) every 6 months (as with RV144)
Relevant HVTN phase I/II Trials

- HVTN 097: RV144 regimen in South Africa (n=80)

- HVTN 095: Combined NYVAC-vector vaccine and microbicides Phase 1 trial

- HVTN 096: NYVAC-vector vaccine Phase 1 trial with AIDSVAX

- Bridging study to compare new ALVAC C/gp120 subtype C in South Africans to ALVAC/AIDSVAX (B/E): HVTN 097
Assumptions for African Trials - proposed

• Overall Assumptions
   Power = 0.80,
   1-sided alpha = 0.025
   Drop out = 5%
   Transmission rate = 4%

• Development Trial
   H0: VE(0-24) <= 25%
   H1: VE(0-24) = 50%
   # of infections = 70 – 232
   Stage 1 is 0-24 months; stage 2 (24-36 months) only if VE < 25% rejected

• Research Trial
   H0: VE(0-18) <= 0%
   H1: VE(0-18) = 40%
   # of infections = 102 – 262
### Hypothetical Schema of Licensure Trial

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Number Subjects</th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 3</th>
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<tr>
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<td>ALVAC</td>
<td>ALVAC</td>
<td>ALVAC + gp120</td>
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</table>

- **One vaccine regimen (modification of RV144 regimen) vs. placebo**
- **HIV negative subjects enrolled and tested for HIV monthly for a maximum of 36 months**
• Accelerated evaluation of alternative regimens
  - Identify promising vaccine candidates
  - Fill the immunological space
    - candidates eliciting different immune responses
  - Identify biomarkers that define reduction in acquisition of HIV infection
  - For trials with multiple vaccine arms
    - Head to head comparisons
    - Provide greater sample size and heterogeneity in immune responses
    - Provide greater power (relies on the assumption that the immune correlate is common to the vaccine arms)
### Schema for a Phase 2b Research Trial

- Designs with 1, 2, or 3 vaccine regimens vs. a shared placebo group

#### Hypothetical Schema of 3-Vaccine Arm Trial

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Number Subjects</th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
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</thead>
<tbody>
<tr>
<td>Vaccine 1</td>
<td>1700</td>
<td>NYVAC</td>
<td>NYVAC</td>
<td>NYVAC + gp120</td>
<td>NYVAC + gp120</td>
<td>gp120</td>
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<tr>
<td>Vaccine 2</td>
<td>1700</td>
<td>DNA</td>
<td>DNA</td>
<td>NYVAC + gp120</td>
<td>NYVAC + gp120</td>
<td>gp120</td>
</tr>
<tr>
<td>Vaccine 3</td>
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<td>Novel prime or placebo</td>
<td>Novel prime</td>
<td>Novel prime and protein boost</td>
<td>Novel prime and protein boost</td>
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<tr>
<td>Placebo</td>
<td>1700</td>
<td>Placebo</td>
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Vaccine Efficacy Trial Plans

- Multiple candidates are emerging which have immunogenicity and safety data supporting efficacy testing.
- Cohorts with high incidence, follow-up required for:
  - Multiple sub-types
  - Multiple risk groups
- Pox-protein prime-boost is the most advanced
  - Hypothesis for correlate and limited efficacy
- DNA/Ad in efficacy testing may yield new directions
- DNA/MVA and Ad/MVA and other designs offer opportunities for global testing
  - Multiple subtype or mosaic inserts
Develop cohorts and capacity to conduct efficacy trials

- **High incidence cohort definition:** populations with incidence of 5% (lower bound of CI >3%)
  - Efficient recruiting and high retention (80% at 24 months)
  - Adequate community interest to support an HIV vaccine efficacy trial.

- **Research capacity development:** Through cohort development and phase I/II clinical vaccine trials, establish
  - Human capacity
  - Institutional infrastructure to support efficacy trials
    - Safety labs
    - Immunogenicity and PBMC cryopreservation
    - Mucosal collections
  - Capacity for at least 200 participants
Cohort Development

MHRP cohort development

- Thailand: MSM and Transgender
- Uganda: female sex workers and MSM
- Tanzania: female sex workers
- Kenya: female sex workers
- Nigeria: female sex workers and MSM
- Mozambique: general female population
Methods

- Recruit based on work (sex work or bar/service industry)
- Enroll using Audio-Computer Assisted Self Interview (ACASI)
  - Sex work: exchange goods, services or money for sex
  - Unprotected sex with HIV positive partner
  - Three partners in three months
  - Sexually transmitted infection in last three months
- N = 2000;
  - Thailand (MSM and TG),
  - Uganda, Kenya and Tanzania (FSW)
Cohort Development - background

RV 217 data

• Incidence in RV 217 cohort study in Pattaya,
  - MSM – 6.11 (95% CI – 2.91-9.3)
  - TG – 7.23 (95% CI – 3.14-11.3)

• Incidence in East Africa
  - FSW – 2.57 (95% CI – 1.76-3.4)
  - Kenya – 3.2
  - Tanzania – 2.35
  - Uganda – 1.93
Coordinating Development and Efficacy Trials – Methods

- Risk reduction counseling and condoms to be provided
- Access to other prevention modalities provided or promoted
  - HAART for discordant couples
  - Male Circumcision
  - PrEP
  - Condoms
- Advent of and adherence to these new prevention modalities will require adjustment in efficacy designs
  - Large community based trials
  - Less invasive sampling
  - BUT possibly better chance for success
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