HVTN P5 Vaccine Trials

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“Considerations for a Pan-African HIV Vaccine Development Agenda”
Kigali, Rwanda
16-17 March 2015
To fully characterize the safety, immunogenicity, and efficacy of HIV vaccine candidates with the goal of developing a safe, effective vaccine as rapidly as possible for prevention of HIV infections globally.
Building and Expanding on the Results of RV144 in Southern Africa

- Phase 3 program: RV144 regimen
- Correlates program: other promising vaccine regimens
  - DNA, Protein, NYVAC, ALVAC, adjuvants
The Strategy for the ALVAC/Protein Phase 3 program

- Construction of ALVAC-HIV-C (vCP2438)
- Construction of Bivalent Subtype C gp120/MF59
- Booster at 12 months

Optimize regimen by increasing potency & durability
**Study Schema: HVTN 100**

<table>
<thead>
<tr>
<th>N (total 252)</th>
<th>Primary Vaccine Regimen</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>210</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
</tr>
<tr>
<td>42</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Products:**
- ALVAC-HIV (vCP2438) expressing HIV-1 env (clade C gp120), clade B (gp41), gag (clade B) & protease (clade B) (Dose: >1 X 10^6 CCID₅₀)
- Bivalent subtype C gp120/MF59 containing 100mcg TV1.Cgp120 & 100mcg 1086.Cgp120

**Immunogenicity evaluation to be applied to this study to inform advancement into phase 3**
Scientific Objectives of Phase 1/2 testing in HVTN 100

• To demonstrate immune responses to the clade C vaccine are comparable to that in RV144 vaccine and sufficient to extend results of RV144

• To determine if levels of V1V2 antibody responses to clade C vaccine will enable testing of the V1V2 hypothesis as a vaccine Correlate of Protection (CoP)
“Go” criteria

• Adequate overall clade C vaccine response rate
  • Env Ab binding response rate to vaccine insert

• Clade C vaccine immune effectors not inferior to those from RV144 in terms of:
  • Ab binding magnitude to env vaccine insert HIV strains
  • CD4 T cell ICS response rate to Env PTE peptides

• The V1V2 binding antibody response rate will be sufficient to test if the RV144 Correlate of Risk is a clade C vaccine-induced Correlate of Protection
### Study Schema: HVTN 702

#### Primary Vaccine Regimen

<table>
<thead>
<tr>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV+ Bivalent Subtype C gp120/ MF59®</td>
<td>ALVAC-HIV+ Bivalent Subtype C gp120/ MF59®</td>
<td>ALVAC-HIV+ Bivalent Subtype C gp120/ MF59®</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo + Placebo</td>
<td>Placebo + Placebo</td>
<td>Placebo + Placebo</td>
</tr>
</tbody>
</table>

**Estimated Total Study duration 72 months:**

- Stage 1: 60 months-18 months for enrolment, 24 months of follow-up for HIV-1 uninfected individuals, 18 months follow-up for HIV-1 infected individuals
- Stage 2: an additional 12 months of follow-up for uninfected individuals
Overall Strategy for Correlates Discovery

- Conduct a series of harmonized Phase 1 trials of priming and boosting regimens
  - Select regimens that are:
    - most likely to reduce HIV acquisition
    - most diverse to move forward to Phase 2b
  - Select up to three regimens to discover correlates of protection
A Matrix of Prime/Boosts

- **Phase 1-2a trials (2015)**
  - Prime-boost vaccine regimen similar to that used in RV144 adjusted to target Clade C
  - Multiple vaccine candidates

<table>
<thead>
<tr>
<th>Prime-Boost Combinations</th>
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<tbody>
<tr>
<td><strong>Regimen</strong></td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>E</td>
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<tr>
<td>F</td>
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</table>

<table>
<thead>
<tr>
<th>Env Dose and Adjuvant Types</th>
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<tbody>
<tr>
<td><strong>Option</strong></td>
</tr>
<tr>
<td>i</td>
</tr>
<tr>
<td>ii</td>
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<tr>
<td>iii</td>
</tr>
</tbody>
</table>
Strategy for the Correlates Program

- Construction of DNA
- Construction of ALVAC-HIV-C
- Construction of NYVAC
- Formulation of bivalent Clade C gp 120/MF59
- Formulation of bivalent Clade C gp 120/alum
- Formulation of bivalent Clade C gp 120/AS01B
- Booster at 12 months

Increase potency, durability & diversity
## Candidate Vaccine Products

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>PRODUCT DESCRIPTION</th>
<th>DEVELOPER</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVAC-C</td>
<td>Expressing ZM96 gp120 (clade C strain) linked to gp41, and gag and pro (clade B LAI strain).</td>
<td>Sanofi Pasteur</td>
</tr>
<tr>
<td>NYVAC-C</td>
<td>Bivalent highly attenuated vaccinia virus expressing clade C ZM96 gp140 and ZM96 Gag-CN54 Pol-Nef fusion proteins</td>
<td>Sanofi Pasteur</td>
</tr>
<tr>
<td>Gp120 protein + MF59</td>
<td>Clade C TV1 gp120 Env and clade C 1086 gp120 Env with MF59 adjuvant</td>
<td>Novartis Vaccines</td>
</tr>
<tr>
<td>Gp120 protein + ASO1B</td>
<td>Clade C TV1 gp120 Env and clade C 1086 gp120 Env with ASO1B adjuvant</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>DNA-C</td>
<td>Trivalent DNA expressing clade C ZM96 Gag and gp140, and a CN54 Pol-Nef fusion construct. This DNA product produces virus like particles and trimeric configurations of gp140</td>
<td>IPPOX Foundation</td>
</tr>
</tbody>
</table>
How are the trials going to identify a CoR/CoP for HIV vaccines?

- **The Correlates Program focus**
  - Next-generation clade C-adapted vaccines
  - Potent priming immunogens and adjuvants eliciting unique immunological responses

- **Phase 2b trial**
  - Does not qualify vaccines for licensure
  - Advances the field by expanding knowledge of factors contributing to HIV vaccine protective efficacy

- **The Design**
  - Efficiently evaluate vaccine safety and efficacy
  - Validate previously identified immune correlates of risk (CoR)
  - Identify additional CoR/CoP
Potent Priming Immunogens Elicit Distinct Immunological Profiles

- NYVAC+protein
  - Potent Ab responses
- DNA/NYVAC+protein
  - Potent T-cell responses
- DNA-protein
  - Induction of novel priming for potent Ab and T-cell boost responses
- Coadministration of ALVAC and gp120 from baseline
  - Modulation of IgA responses
Potent Adjuvants with a Track Record

- **MF59** = Squalene + Polysorbate 80 + Sorbitan Trioleate
  - An oil-in-water emulsion, squalene internal oil phase and a external aqueous phase. The two non-ionic surfactants serve to stabilize the emulsion
  - Increased vaccine potency and efficacy (Hep B, flu)
  - Antigen sparing
  - Expands Ab repertoire

- **AS01B** = liposome of MPL + QS21
  - Monophosphoryl Lipid A (MPL) is a preparation derived from *Salmonella minnesota*, R595.
    - a TLR4 agonist already used in vaccines for Hep B and HPV (AS04)
  - QS21 is a purified extract derived from the Soap bark tree; contains water-soluble triterpene glucoside compounds (saponins).
  - Improved vaccine efficacy with malaria vaccine RTS,S
  - Reported effects include expansion of the Ab repertoire
2-Step Down Selection Process

Start with M HIV Vaccine Regimens

Step 1: Screening based on:
• Safety
• Adequate immune responses based on a core set of immune assays: Month 6.5 samples

Screening Succeeded

STOP: Vaccine regimen removed

Screening Failed

Step 2: Selection based on immune responses from a full set of immune assays: Month 6.5, 12 samples
• Select regimens with unique and best-ranked immune responses

Compare each regimen to the ALVAC-gp120 C/C in MF59 regimen being tested in the Phase 3 program

Screening Succeeded

For remaining regimens, determine the unique and ‘best’ regimens to select

STOP: Vaccine regimen removed

Screening Failed

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Step 1 of the Down Selection

- Each vaccine regimen must have positive safety data and sufficient immune response rates and levels, as summarized in the following table

<table>
<thead>
<tr>
<th>Required Immune Response Benchmarks</th>
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<tbody>
<tr>
<td><strong>Required</strong></td>
</tr>
<tr>
<td><strong>2/3 required</strong></td>
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</table>
Step 2 of the Down Selection

- Two sets of immune responses will form the basis for the down selection:
  - A set based on published correlates of vaccine efficacy to prevent HIV infection in the RV144 Thai trial
  - An inclusive set that the HIV vaccine field hypothesizes are relevant for achieving prevention of HIV infection
- The HVTN statistical group develops statistical methods for guiding the down selection decision based on the multivariate immune response data
- Computer simulation studies are used to fine-tune the statistical methods to achieve an appropriate balance of:
  - high probability of selecting promising and distinctive vaccine regimens
  - low probability of selecting poor or redundant vaccine regimens
The Down-Selection Approach Will be Refined Up Until the Phase I Trial Data Analysis

- Statistical methods for analyzing immune response data are developed and validated on additional HVTN vaccine trial data sets over time
- Laboratory immune assays are developed and refined
  - e.g. panels of HIV Envelope reagents for measuring immune responses are developed and refined
- New knowledge accrues about immune correlates of vaccine efficacy in the:
  - RV144 Thai trial
  - non-human primate challenge trials

The down selection approach will be revised over time based on broad discussion with stakeholders in the HIV vaccine field

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Timeline for P5 Correlates Program

**HVTN 113 Phase 1/2a**
DNA/ALVAC+bivalent gp120 AS01b/MF59

**HVTN 108 Phase 1/2a**
DNA+bivalent gp120 AS01b/MF59

**HVTN 109 Phase 1/2a**
DNA/NYVAC+bivalent gp120 AS01b/MF59

**HVTN 701 Phase 2b**
Up to 3 active arms

REGIMEN SELECTION

REGULATORY REVIEW

ENROLLMENT

FOLLOW-UP

PROTOCOL DEVELOPMENT

PRIMARY IMMUNOGENICITY REPORT

HVTN Site Expansion Necessary to Support Upcoming Studies

- Total of 12 sites being developed in Southern Africa
  - Malawi
  - Mozambique
  - Zambia
  - Zimbabwe
  - Tanzania
  - South Africa
Acknowledgments

• BMGF
• DAIDS/NIAID
• EuroVacc
• FHCRC (HVTN)
• GSK

• IPPOX
• Military HIV Research Program
• Novartis
• RSA-MRC
• Sanofi Pasteur

Study Participants and Site Staff
THANK YOU!

HIV VACCINE
TRIALS NETWORK