Development of HIV Vaccine Candidates for Prevention and Treatment

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The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.
Points to Consider

- VTN 097 tested the RV 144 vaccine in South Africans
  - VTN 097 equal to or exceeded RV 144

- VTN 100 met all “go” criteria
  - it exceeded RV 144 responses for clade C targets

- The VTN 702 is the ALVAC/gp 120 prime boost efficacy trial for RSA
  - regimen is intended to support licensure
Points to Consider

• Will it be efficacious only in subtype C epidemics
  • How will this question be evaluated
    • A strong correlate of protection (determinant)
      • In vitro assays demonstrating breadth sufficient?
    • A correlate of risk (association only)
      • Compare clade specific to subtype C vaccine in multiple regions with other clades
      • Non-inferiority versus placebo controlled

• Future Efficacy Trials Competing for High Risk subjects
  • AMP VTN 703 – VRC broadly neutralizing mAb
  • Long acting PrEP agents
  • Janssen program (Ad26 and protein)
Shifting Focus of HIV Vaccines

- gp160/gp120 subunits
- Poxvirus vector + protein
- rAd5-gag/pol/nef
- DNA/rAd5-Env/gag/pol/nef

Relative focus on vaccine effector mechanisms:
- Antibody
- CD8 T cells

Acquisition effect:
- 0
- ↓ 31.2%
- ↑ 31.5%
Thai Trial (RV144) Primary Results

The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-ngaon, MD, D.T.M.H., Sorachai Nityaphan, M.D., Ph.d.,\nJaranit Kaewungwal, Ph.d., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premtri, M.D., Chawetsan Namwat, M.D.,\nMark de Souza, Ph.d., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.d.,\nJohn G. MeNeil, M.D., Donald P. Francis, M.D., Ph.d., Donald Stabein, Ph.d., Deborah L. Birx, M.D.,\nSupamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.d.,\nMerlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.d., Prayura Kunasol, M.D., and Jerome H. Kim, M.D.,\nfor the MOPH-TAVEG Investigators*

Modified Intention-to-Treat Analysis*

Estimated VE Over Time with 95% Confidence Bands

Articles
Risk behaviour and time as covariates for efficacy of the HIV vaccine regimen ALVAC-HIV (vCP1521) and AIDSVAX B/E: a post-hoc analysis of the Thai phase 3 efficacy trial RV 144

Merlin L Robb, MD, Supachai Rerks-ngaon, MD, Sorachai Nityaphan, MD, Prof Punnee Pitsutitthum, MD, Jaranit Kaewungwal, Ph.d, Prayura Kunasol, MD, Chirasak Khamboonruang, MD, Prof Prasert Thongcharoen, MD, Patricia Morgan, MS, Michael Benenson, MD, Robert M Paris, MD, Joseph Chiu, MD, Elizabeth Adams, MD, Donald Francis, MD, Sanjay Gurunathan, MD, Jim Tartaglia, Ph.d, Peter Gilbert, PhD, Don Stabein, PhD, Nelson L Michael, MD, Dr Jerome H Kim, MD.
Efficacy at 1 year appeared higher

60% Efficacy

M. Robb et al, Lancet ID 2012
<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA to Env</td>
<td>1.54 (1.05-2.25)</td>
<td>0.03</td>
</tr>
<tr>
<td>gp70-V1V2 binding</td>
<td>0.57 (0.36-0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>CD4 T cells (COMPASS) Lin et al, Nature Biotechnology 2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 6 marker** functionality</td>
<td>0.62 (0.42-0.91)</td>
<td>0.014</td>
</tr>
<tr>
<td>• 6 marker polyfunctionality</td>
<td>0.57 (0.38-0.84)</td>
<td>0.005</td>
</tr>
<tr>
<td>• 5 marker*** polyfunctionality</td>
<td>0.58 (0.39-0.86)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**6 markers: IL-2, TNFa, IFNg, IL-4, CD40L, IL-17

***5 markers: IL-2, TNFa, IFNg, IL-4, CD40L
The Strategy for the HVTN 100 ALVAC/Protein Phase 2b/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 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>

Total: 252
Primary vaccination series (Months 0, 1, 3, 6) complete for all participants

Booster vaccinations (Month 12) ongoing

Interim safety to 6.5 months

Primary immunogenicity assays (Month 6.5 samples)

Go/No-Go Criteria

Subjects and investigators, are still blinded to treatment group

- All of these analyses are from samples blinded to the laboratories and by individual
HVTN 100 Per Protocol Cohort. Contemporary assays: same labs, same time.

CoP assays

- 185 HVTN100 Vaccinees
- 37 HVTN100 Placebo
- 201 RV144 Vaccinees (Archived)
- 24 RV144 Placebos (Archived)
All “Go” criteria met - will proceed with VTN 702

HVTN 100 Go/No-Go Criteria for HVTN 702: Must Meet all of the Following Conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Observed RV144 Regimen Response</th>
<th>Minimum Observed Response of New Regimen</th>
<th>Go Criteria Threshold (LL of 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Env Ab Response Rate (≥ 2 of 3 antigens)</td>
<td>Resp Rate = 92%, 94%, 98%</td>
<td>82%</td>
<td>≥75%</td>
</tr>
<tr>
<td>Env Ab Magnitude (≥ 2 of 3 antigens)</td>
<td>GMs = 6.31, 6.42, 8.05</td>
<td>GMs=5.92, 6.02, 7.67</td>
<td>GM ratio (new/RV144) ≥50%*</td>
</tr>
<tr>
<td>Env CD4 Response Rate (1 of 1)</td>
<td>Resp Rate = 72%</td>
<td>Resp Rate = 53%</td>
<td>Difference within 30%*</td>
</tr>
<tr>
<td>Env V1V2 Response Rate (≥ 1 of 3 antigens)</td>
<td>Resp Rate = 64%</td>
<td>Resp Rate = 63%</td>
<td>≥ 56%</td>
</tr>
</tbody>
</table>

* Non-inferior to RV144 responses
To achieve observed VE ≥ 50%, assuming observed VE (V1V2 responders) = 69%

Based upon RV306 we expect a boost in V1V2 with month 12 booster
Large-Scale HIV Vaccine Trial to Launch in South Africa
Timeline for P5 Efficacy Trial

**HVTN 100** Phase 1-2  n=252
1. ALVAC/ALVAC-gp120
2. Placebo

**HVTN 702** Phase 3  n=5,400
1. ALVAC/ALVAC-gp120
2. Placebo

- Protocol Development
- RSA Regulatory Review
- Enrollment
- Follow-up

- Interim Safety Report
- Phase 3 Go/No Go Decision
- 1st – 3rd Efficacy/Futility Analyses
- Final Stage 1 Efficacy Analysis
HIV vaccine program: Current Collaborators

- BIDMC/Harvard
- HVTN
- IAVI
- MHRP
- NIAID
- Ragon Institute
High Level Target Product Profile

- HIV global vaccine offering protection against acquisition of HIV-1 through heterologous prime/boost regimen
  - **Viral vectors** with mosaic HIV-1 gag, pol and env transgenes to induce both cellular and humoral HIV specific immunity
  - Soluble gp140 envelope trimeric **protein(s)** to boost HIV specific humoral immunity
Prophylactic Vaccine Aiming at Protection Against all Clades of HIV-1

1. Vectors that elicit optimal immune responses

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

3. Trimeric env proteins for improved humoral immunity
Proof-of-concept studies in NHPs

Heterologous vector-based prime-boost regimens delivering SIV or HIV-mosaic antigens afford partial protection against SIVmac251 and SHIV-SF162P3 repetitive intra-rectal challenges.

<table>
<thead>
<tr>
<th>Vaccine Regimen</th>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26/MVA</td>
<td>83%</td>
<td>12%</td>
</tr>
<tr>
<td>Ad35/Ad26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (N=1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine Regimen</th>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26/MVA</td>
<td>90%</td>
<td>16%</td>
</tr>
<tr>
<td>Ad/MVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad/Ad</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Proof-of-concept studies in NHPs

Substantial increase of humoral immunity by **gp140 boost** affording partial protection in stringent **SIVmac251** and **SHIV-SF162P3** challenge models.

<table>
<thead>
<tr>
<th></th>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26/Env</td>
<td>90%</td>
<td>50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admos/Env</td>
<td>79%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Heterologous prime-boost HIV vaccine aiming at global coverage: *in Phase 1/2a and tested in NHP challenge study*

<table>
<thead>
<tr>
<th>Prime</th>
<th>Boost</th>
</tr>
</thead>
</table>
| **Ad26.Mos.HIV**<br>Ad26 vectors with Mosaic gag-pol or env inserts<br>Ad26.Mos1.Gag-Pol<br>Ad26.Mos2.Gag-Pol<br>Ad26.Mos1.Env (clade B-like) | **gp140 Clade C**<br>Soluble trimer gp140 env protein and/or<br><br>**Ad26.Mos.HIV**<br>gag-pol-env<br><br>**MVA-Mosaic**<br>MVA vectors with Mosaic gag-pol-env inserts<br>MVA-Mosaic 1<br>MVA-Mosaic 2<br><br>**gp140 Clade C**<br>Soluble trimer gp140 env protein

Regimen to be selected after Phase 1/2a
Proof-of-concept studies in NHPs

• Heterologous prime-boost regimens delivering SIV antigens afford partial protection against SIVmac251 repetitive intra-rectal challenges (Nature 2012)

• Heterologous prime-boost regimens delivering mosaic antigens afford partial protection against SHIV-SF162P3 repetitive intra-rectal challenges (Cell 2013)

• Substantial increase of humoral immunity by gp140 boost affording partial protection in stringent SHIV-SF162P3 and SIVmac251 challenge models (Science 2015)

• Challenge study evaluating regimens as in current Phase 1/2a confirmed high level of protection (study recently completed)
**APPROACH Trial Design:** a multicenter, randomized, parallel group, placebo-controlled, double-blind clinical trial in healthy HIV-uninfected adults

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Month 0 (baseline)</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 48 Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 7</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>Ad26.Mos.HIV</td>
<td>gp140 (250 µg/adj)</td>
<td>gp140 (250 µg/adj)</td>
</tr>
<tr>
<td>Group 8</td>
<td>50</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

*Adj=AdjuPhos

12 month follow-up
Current Thinking Efficacy Plans

• A Phase 2b Proof of Concept/Efficacy trial HPX2008, to be performed in sub-Saharan Africa (SSA), commencing in 2017

• 2 Phase 3 Efficacy trials (timing TBD)
  - HPX3001: SSA/South Africa
  - HPX3002: Americas, SE Asia, Europe
The optimal regimen is hypothesized to elicit a well balanced immune response with both antibody and T cell immunity. This includes broad coverage of HIV clades A, B and C.

For the choice of regimen, emphasis will be on immunological correlates that have been identified to correlate with a reduced risk of SIV/SHIV infection in NHP and on immunological correlates that have been identified to correlate with a reduced risk of HIV infection in RV144.

For the criteria to move into PoC, emphasis will be on antibodies and cellular responses as a measure of vaccine take. This includes providing an indication that the elicited antibodies are functional.

Choice of regimen and decision to move to Ph2b in Q4 2016

The above is subject to continuous discussions/decisions by all Partners.
# Long History of Antibodies to Prevent Viral Infections

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Concentrated human gamma globulin</td>
</tr>
<tr>
<td>Polio</td>
<td>Concentrated human gamma globulin</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus Immune Globulin</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Immune serum globulin (ISG)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B Immune Globulin</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies Immune Globulin</td>
</tr>
<tr>
<td>RSV</td>
<td>mAb (palivizumab) for prophylaxis of high risk infants</td>
</tr>
<tr>
<td>VZIG</td>
<td>Varicella Zoster Immune Globulin</td>
</tr>
</tbody>
</table>

**mAbs in development:** Rabies, Ebola, HCV
• **Provide proof-of-principle that bNAbs can prevent HIV infection in humans**

• Determine the minimal dose of antibody (including levels at mucosal surfaces)

• Identify the best viral epitopes to target

• Assess the importance of antibody isotypes

• Provide additional correlates of protection
VRC01 Blocks Attachment to CD4

CD4 binding site on gp120 is functionally conserved: All viruses must bind CD4

VRC01 neutralize ~ 90% of diverse viral isolates
A phase 2b study to evaluate the efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection
# Study Schema for The AMP Study

## REGIMEN

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in sub-Saharan Africa</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>800</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>800</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Control</td>
<td>800</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2400</strong></td>
<td><strong>1500</strong></td>
<td><strong>3900</strong></td>
</tr>
</tbody>
</table>

- 10 infusions total & Infusions every 8 weeks
- Study duration: ~22 months
The Main Hypotheses of the Trial

- Administration of this broadly neutralizing antibody will reduce acquisition of HIV infection in these high risk populations;
- The level of VRC01 antibody required for protection will vary by type of sexual exposure and not by clade;
- The concentration of antibody in serum will be directly associated with the rate of protection; that is, higher levels of antibodies will give greater rates of protection than lower levels; and
- Breakthrough isolates will have greater resistance to neutralization and will exhibit molecular signatures associated with escape from neutralization.
Summary

• Animal studies provide proof-of-concept for mAbs but we need efficacy data in humans

• Currently only 2 mAbs tested in humans (VRC01 and 3BNC117) with many others in the pipeline (VRC07, PGT121/10-1074, CAP256-VRC26.25 and PGDM1400). PG9 also in Phase I trial as VIP

• Broader and more potent antibodies are being engineered

• Possibilities to extend half-life of mAb

• Antibodies may be more useful for prevention than treatment and will provide a benchmark for vaccines
**Adjuvants** to improve quality, magnitude and duration of immune response

**Proteins** to elicit more potent broadly neutralizing antibodies to native trimeric HIV envelope

**Novel vectors** to elicit stronger T cell responses:

- Replicating MVA

- Cytomegalovirus:
  - CD8+ cells recognized 3-fold > epitopes than other vectors

Novel Early Vaccine Development Continues
An HIV Vaccine is Still Urgently Needed

- Can mitigate adherence issues with PrEP
- Even partially efficacious vaccines (e.g. > 50% in Thailand, >30% in Benin and rural Zimbabwe) can reduce population burden in high risk areas
- Therapeutic vaccines including passive mAbs
  - May contribute to achieve functional cure in HIV+,
  - Very early NHP research and development
  - Likely **different correlates of protection** in this setting versus preventative vaccines
- Will be tested in the coming year in cohorts with HAART starting in acute/early infection
- Likely require combination with other agents to activate the latent pool
An HIV Vaccine is Still Urgently Needed

- Prevention efficacy trials will need to incorporate
  - Larger populations as universal testing and treatment and PrEP gain broader implementation = lower incidence

- Plan for success
  - Do not repeat the 7 years between RV 144 and VTN 702
  - Will subtype E vaccine tested in RSA show similar responses to those in VTN 100
  - Will a combination product be sufficient or will a product for each region need to be prepared?
  - Will placebo be required?
  - Plan the study designs and make necessary products available for follow-up testing
Volunteers Globally

- HVTN 100 and 702 protocol team- sites, SHARP, labs, safety, ops, PPD, oversight
  - Larry Corey, Glenda Gray, Linda-Gail Bekker, Julie McElrath, Jim Kublin, Peter Gilbert
  - Sanofi Pasteur and GSK/Novartis Vaccines
  - DAIDS/NIAID/NIH

- VTN 703 team including the PTN

- RV 144 and RV 306 team
  - Thai MOPH, Thai RTA, AFRIMS, DAIDS/NIAID/NIH
  - Dr.Supachai, Dr. Punnee, Sandy Vasan, RobO’Connell, Nicos Karasava

- Janssen Ad26/protein prime-boost team
  - Maria Grazia-Pau and Frank Tomaka