This graphic shows the big picture of AIDS vaccine concepts and clinical trials in process and on the horizon. It is an intentionally simplified representation of a complex field. Some approaches are not listed, and related arenas like therapeutic vaccines and cure research are omitted.

### Current Preclinical Research

Basic discovery and animal trials of vaccines, vectors, adjuvants, inserts

### Development Programs

<table>
<thead>
<tr>
<th>Development programs</th>
<th>Current Clinical Trials</th>
<th>Proposed Future Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P5</strong> ALVAC + Protein Licensure Phase I/II</td>
<td></td>
<td>HVTN 702 Efficacy Trial</td>
</tr>
<tr>
<td><strong>P5</strong> ALVAC + AIDSVAX Follow-on/Phase II</td>
<td></td>
<td>Possible Thai Efficacy Trial</td>
</tr>
<tr>
<td>Ad26.Mos.HIV Phase I/II</td>
<td></td>
<td>Possible Efficacy Trial</td>
</tr>
</tbody>
</table>

### Additional Approaches

- **P5** Pox-protein + Various Adjuvants Phase I/II
- DNA + MVA Phase I
- DNA + AIDSVAX Phase I
- Electroporated DNA Phase II
- Ad35 Vector Phase I
- Chimp-Adenovirus Vector Phase I
- SeV-G Phase I
- rAd26 + Mosaic Phase I
- Tiantan Phase IIa
- LIPO-5 Phase II

### Neutralizing Antibodies

<table>
<thead>
<tr>
<th>Neutralizing Antibodies</th>
<th>Proposed Future Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC07-523 CAP256-VRC26</td>
<td>HVTN 703/HPTN 081 Efficacy Trial</td>
</tr>
<tr>
<td>PGT121 PGDM1400</td>
<td>Proposed combination antibody approaches</td>
</tr>
<tr>
<td>10-1074</td>
<td></td>
</tr>
</tbody>
</table>

### Proposed Future Trials

- HVTN 701 Efficacy Trial
- HVTN 703/HPTN 081 Efficacy Trial
AIDS Vaccine Research: An overview

Development Programs

P5

Product/Manufacturing

Development Track
South Africa

RV144
31% efficacy
2003-2009
ALVAC/AIDSVAX
Clade B, A/E
Thailand

RV305
Additional boosts among RV144 participants

RV306
RV144 + boosts among new participants

RV144-like regimen
Uganda, Mozambique, Thailand

RV403
Possible Thai efficacy trial
Start date uncertain
ALVAC/protein
Clade B, A/E

2009: New manufacturer needed to replace AIDSVAX
2010: P5 formed
2011: Novartis joins P5
2014: Novartis vaccine division sold to GSK

RESULTS: Showed similar immune responses to RV144

HVTN 097
Phase Ib
ALVAC/AIDSVAX
Clade B/E

HVTN 100
Phase I/II
ALVAC/gp120
Clade C

HVTN 107
Phase I
MVA Mosaic boost
USA

HVNV-V-A002
HIV-V-A003

Phase I/II
Dose-escalation gp140 + adjuvant
USA

Ad26.Mos.HIV + Ad26, MVA or gp140 boost
Rwanda, South Africa, Thailand, Uganda, USA

HVTV 108
Phase I and II
Pox-protein candidates with varying primes, boosts, adjuvants
Clade C

HVTV 109

HVTV 113

HVTV 111
Phase IIb
Down-selected regimens
Clade C

HVTV 702
Estimated Start 2016/2017
Phase III
ALVAC/gp120
Clade C

HVTV 701
Possible Start 2018

Research Track
Focus: Southern Africa

Janssen

STATE OF THE FIELD

- Pox-Protein Public-Private Partnership trials began in Southern Africa early 2015, testing canarypox-protein based vaccine candidates in two tracks. Key components:
  - Research track: Small trials of altered pox-protein regimens beginning; will down-select for future proof-of-concept efficacy trial.

- Janssen, a division of Johnson & Johnson, is conducting a global development program of Ad26 vector + mosaic immunogen vaccine strategy designed to act against a range of HIV subtypes.

ADVOCATE’S CHECKLIST

✓ TRACK TIMELINES
Vaccine timelines are long; ensure possible delays are minimized
  - Ensure down-selection criteria are explicit and used.

✓ FOLLOW PHARMA
Industry involvement is essential
  - Track industry engagement and encourage Janssen and others to expand human and financial resources.

✓ SUSTAIN SUPPORT
Countries have had mixed HIV research experiences
  - Meaningfully engage in-country stakeholders to avoid misinformation and sustain support.
A range of vaccine approaches are being tested in early phase clinical trials. The table provides highlights of this area of HIV vaccine research. For full information on clinical trials, please visit www.avac.org/pxrd.

<table>
<thead>
<tr>
<th>Vaccine strategy</th>
<th>Trials and products</th>
<th>Why</th>
<th>Sponsors / Developers</th>
</tr>
</thead>
</table>
| DNA                | • DNA + modified vaccinia Ankara (MVA) boost candidates being tested in two Phase I trials.  
                       • DNA + AIDSVAX candidate being tested in two Phase I trials for various outcomes.  
                       • DNA delivered through electroporation in Phase II TAMOVAC-02 trial. | DNA vaccines induce anti-HIV antibodies that last. This kind of durability is important and is one reason these candidates are being explored.  | Geovax  
                       HVTN  
                       IAVI |
| DNA + MVA          |                                                                                      |                                                                      |                       |
| DNA + AIDSVAX      |                                                                                      |                                                                      |                       |
| Adenovirus vectors | • Ad35 being tested in various regimens in Phase I trials in Africa, Europe, and USA.  
                       • Chimp-Adenovirus vector being tested as therapeutic vaccine in Phase I trial. | Adenovirus vectors are effective in eliciting T-cell responses; Ad5 is not moving forward, but other Ad-based vectors are progressing through early clinical trials.  | IrsiCaixa  
                       University of Oxford |
| Replicating vectors| • SeV-G vaccine in Phase I study in Kenya, Rwanda and the UK using a replicating vector based on the Sendai virus plus a boost with an Ad35-vectorized vaccine.  
                       • Replicating Ad26 (rcAd26) + mosaic insert being tested through oral administration in Phase I does-escalation in USA.  
                       • Tiantan vector, a vaccinia virus, tested in Phase IIa trial in China, in combination with DNA prime; analyzing results. Phase IIb trial planned with gp145 protein in partnership with NIH. | Replicating vectors provide ongoing stimulation to the immune system increasing the amount of cellular immune responses generated, thus potentially increasing the immunogenicity of the vaccine being studied.  | IAVI  
                       China CDC |
| Lipopeptides       | • LIPO-5 candidate being tested in prime-boost combination in proof-of-concept Phase II trial in HIV-infected individuals. | Prime-boost combination using lipopeptide has elicited T-cell responses important to immune responses.  | Inserm-ANRS |

**STATE OF THE FIELD**

**ADVOCATE’S CHECKLIST**

- **PUSH FOR PROMISE**
  Early trial results will yield important data
  - Push for comparison across candidates and prioritization of most promising vaccines to move forward.

- **UNDERSTAND PATHWAYS**
  Many early phase trials are not on a clear path to licensure
  - Push for this information and for stakeholder involvement in discussions and decision-making.
Neutralizing Antibodies

**HIV trimer target** | **Antibody** | **Research highlights**
--- | --- | ---
**CD4 binding site** | 3BNC117 | Phase I dose escalation trial in HIV-positive individuals not on ART who received the safety in all groups and sustained viral load reductions highest dose; further treatment and prevention studies planned (Germany, US)
| VRC01 | Preliminary Phase I dose escalation results have shown impact on viral load; HVTN 104 Phase I trial in HIV-negative adults ongoing with follow-on efficacy trial planned; Phase 1 infant safety trial being explored; planned treatment trials to look at VRC01 + ART in acute infection (US)
| VRC07-523 | A variant of VRC01, which in animal testing has shown increased potency, indicating clinical relevance for preventing HIV infection at lower doses

**V1/V2-glycan** | CAP256-VRC26 | Currently in preclinical testing for development for treatment and prevention (South Africa)
| PG9 | Ongoing Phase 1 trial establishing safety and optimal doses of AAV vector gene-transfer approach (UK)
| PGDM1400 | Identified in animal studies as exceptionally broad and potent with cross-clade neutralization coverage of 83% at low doses

**V3-glycan** | 10-1074 | Animal studies have shown potency in reducing viral load, moving to clinical testing in 2015 as possible treatment and/or component of a cure strategy (US)
| PGT121 | Reduction in viral load has been shown in animal studies; in manufacturing process for future clinical studies as possible treatment and/or component of cure strategy (US)

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**STATE OF THE FIELD**

- Neutralizing antibodies are potent immune cells that block HIV activity.
- Identification of broadly neutralizing antibodies (bNAb) has defined discreet targets on HIV envelope glycoprotein, or trimer.
- Data from small-scale animal and human studies show bNAb generally safe, tolerable and reduce viral load.
- Future directions include multiple bNAb in combination, to target different sites on HIV trimer and may be able to block a wider breadth of HIV strains.

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**ADVOCATE’S CHECKLIST**

- **EXPLORE FEASIBILITY**
  - bNAb research is generating excitement, but still mostly upstream and conceptual
  - Explore feasibility of bNAb as scalable, cost-effective options for prevention and treatment as research progresses.
- **EDUCATE STAKEHOLDERS**
  - Clinical trials will become increasingly complex
  - Ensure communities who may be impacted by bNAb trials understand the science and can play a meaningful role.
- **ENGAGE DECISION MAKERS**
  - Research pathways of bNAb-inducing preventive vaccines are still unknown
  - Remain vigilant around promising antibodies and prioritization for vaccine development.

*See Pw Wire Volume 8 No 2 for additional pipeline information (www.avac.org/pwwire/vol8no2)*
Overview of the HVTN RSA Phase 3 Program

The HVTN is supported through a cooperative agreement with the National Institute of Allergy and Infectious Diseases.
Pox-Protein Public-Private Partnership (P5)

P5 is a partnership among Bill & Melinda Gates Foundation, HIV Vaccine Trials Network, NIAID, South African MRC, Novartis, Sanofi Pasteur, and U.S. Military HIV Research Program.

Purpose:
To build on the RV144 result and develop and ultimately license HIV pox-protein vaccines with the potential for broad and timely public health impact.

1. Continue to build public-private partnerships critical for success.
2. Work with host countries to support a flexible regulatory strategy in target populations and regions.
3. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.
Advancing the Findings of RV144 in a Clade C Region of the World (P5 Partnership)

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

Although protective efficacy was 31.2% at the primary analysis, 42 months after first vaccination, the highest efficacy was observed at 6-12 months.
And this journey has begun. As of 15 May, HVTN 100 has enrolled 182 participants, and we expect to complete enrolment in June.
The Strategy for the ALVAC/Protein Phase 3 Program

Construction of Bivalent Subtype C gp120/MF59

Optimize regimen by increasing potency and durability

Construction of ALVAC-HIV-C (vCP2438)

Booster at 12 months
Strategy for the Phase 3 Program

HVTN 097 Designed to evaluate RV144 vaccine regimen in RSA and compare immunogenicity to that in Thailand

HVTN 100 A standard phase 1 trial of clade C products to decide whether to proceed to phase 3

HVTN 702 A classic phase 3 RCT assessing efficacy and safety aimed at licensure

Underpinned by community, regulatory and government stakeholder engagement
**Study Schema: HVTN 100**

### Primary Vaccine Regimen

<table>
<thead>
<tr>
<th>N (total 252)</th>
<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>210</td>
<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>42</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo + Placebo</td>
<td>Placebo + Placebo</td>
<td>Placebo + 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: $>1 \times 10^6$ CCID$_{50}$)
- 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**
Go/No-Go Criteria: 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>Non-inferior Ab magnitude vs. RV144</td>
</tr>
<tr>
<td>Env CD4 Response Rate* (1 of 1)</td>
<td>Non-inferior 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 simultaneous assessment of clade C vaccinee samples vs. RV144 vaccinee samples by the same lab
To achieve observed VE \( \geq 42\% \), assuming observed VE (V1V2 responders) = 69%.

<table>
<thead>
<tr>
<th>Month</th>
<th>Observed V1V2 Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>64%</td>
</tr>
<tr>
<td>18</td>
<td>Observed VE = 44%</td>
</tr>
<tr>
<td></td>
<td>Observed VE (V1V2 responders) = 69%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Month</th>
<th>Require Observed V1V2</th>
<th>Need Observed V1V2</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>53%</td>
<td>61%</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RV144

702
Timelines

Projected timelines for P5 Phase 3 Program in the Republic of South Africa

HVTN 100 Ph1-2
1. ALVAC/ALVAC-gp120
2. Placebo

HVTN 702 Ph3
1. ALVAC/ALVAC-gp120
2. Placebo

*Interim efficacy/futility analyses are endpoint driven—timepoints shown are approximate.*
## Study Schema: HVTN 702

<table>
<thead>
<tr>
<th>N (total 5400)</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>2700</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
</tr>
<tr>
<td>2700</td>
<td>Placebo</td>
<td>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
Modest Efficacy Can Reduce Infections Significantly But High Efficacy Is Needed to Get Close to “Zero”

[Graph: New infections at varying vaccine efficacy levels - IFE full]

Illustrative vaccine with an assumed efficacy of 70%, not representative of any specific candidate. Coverage in generalized epidemics: routine 10 years old 70%, catch-up 11-14 years old 60%, 15-17 years old 55%, 18-49 years old 50%; in high risk populations in concentrated epidemics: 50%
# Target Product Profile

<table>
<thead>
<tr>
<th>Area</th>
<th>Base Case</th>
<th>Desired Up-side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Prevention of HIV infection</td>
<td></td>
</tr>
<tr>
<td>Product</td>
<td>Sanofi ALVAC recombinant canarypox prime containing HIV genes/ NVD bivalent Env protein with MF59</td>
<td></td>
</tr>
<tr>
<td>Launch Date</td>
<td>Earliest possible regional approval in Republic of South Africa (RSA) or Thailand</td>
<td>Fast-track review by regional authority WHO pre-qualification at launch; Article 58</td>
</tr>
<tr>
<td>Target Population</td>
<td>Primary: Seronegative adults at high risk for acquiring HIV infection</td>
<td>Inclusion of seronegative adolescents</td>
</tr>
<tr>
<td>Efficacy</td>
<td>≥ 50% reduction in laboratory confirmed HIV infection rate at 24 months after first administration</td>
<td>≥ 70% reduction in HIV infection rate</td>
</tr>
<tr>
<td>Safety</td>
<td>Well tolerated, adverse event profile comparable to standard adult vaccines.</td>
<td></td>
</tr>
<tr>
<td>Dosage and Administration</td>
<td>ALVAC: each dose contains &gt;10^6 CCID&lt;sub&gt;50&lt;/sub&gt; after reconstitution</td>
<td>Fewer doses, shorter dosing schedule (6 months), 50 mcg dose each Env protein</td>
</tr>
<tr>
<td></td>
<td>Env protein: bivalent recombinant Env protein with MF59 adjuvant, at a dose of 100 mcg of each Env protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary dosing: months 0 &amp;1 ALVAC, months 3 &amp; 6 ALVAC and Env protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Booster: month 12 ALVAC and Env protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All administrations will be intramuscular</td>
<td></td>
</tr>
<tr>
<td>Protection</td>
<td>Duration of protection 24 months from first administration</td>
<td>36 months from first administration</td>
</tr>
<tr>
<td>Stability / Shelf Life</td>
<td>At least 24 months</td>
<td></td>
</tr>
<tr>
<td>Presentation / Formulation</td>
<td>ALVAC: Lyophilized powder (stored at 2-8°C) and saline for injection.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Env protein: 3 component vials (2 Env proteins stored -80 C; MF59 stored 2-8°C).</td>
<td>1. All components stored 2-8°C</td>
</tr>
<tr>
<td></td>
<td>Extemporaneous mixing of thawed proteins and MF59 adjuvant for a single injection</td>
<td>2. Single vial containing both Env proteins with MF59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Multi-dose presentation</td>
</tr>
<tr>
<td>Price &amp; COGS</td>
<td>TBD</td>
<td></td>
</tr>
</tbody>
</table>
Training the Site Leadership

Regional Workshop, 2 days

Selected topics, developed by experienced site staff:

- Community Education and Recruitment
- Study operations
- HIV Vaccine Science
- Communications & Media Relations
- Staff leadership

- Timing: 6-12 months prior to first trial start date
Training the Community staff

Regional Workshop, 2 days

- Selected topics, developed by experienced southern African site staff:
  - HVTN Overview
  - Recruitment strategies for Phase I trials
  - HIV Vaccines 101
  - Working with Community Advisory Boards
  - Intro to Good Participatory Practice
  - Developing outreach materials and key messages
- Timing: 6-12 months prior to first trial start date
Training the Clinic Staff: Core Competencies

Regional Training, 2 days

- Selected topics:
  - Informed Consent in vaccine trials
  - Adverse Event Evaluation and Reporting
  - Risk Reduction Counseling for vaccine trials
  - Vaccine-Induced Seropositivity
  - Pharmacist training for vaccine trials
- Timing: 4-8 weeks prior to first trial start date
Training the Clinic Staff: Protocol-specific

Regional Training, 3 days

- Selected topics:
  - Scheduling within visit windows
  - Study materials review
  - Safety monitoring
  - Randomization
  - Case Report Form completion
  - Enrollment/follow-up visit scenarios

- Timing: 3-6 weeks prior to first trial start date
HVTN P5 Programs

April 2015
Overall Strategy for Phase 1 Correlates Program

- Conduct a series of harmonized Phase 1 trials of priming and boosting regimens
- Select regimens that achieve sufficient immunological potency for the hypothesis of reducing HIV acquisition based upon correlates of risk
- Select the regimens that are also most diverse to move forward to Phase 2b
  - The final outcome to select up to four regimens to discover correlates of protection
Importance of an Immune Correlate

• Finding an immune correlate is a central goal of vaccine research
  • One of the 14 ‘Grand Challenges of Global Health’ of the NIH & Gates Foundation (for HIV, TB, Malaria)

• Immune correlates useful for:
  • Shortening trials and reducing costs
  • Guiding iterative development of vaccines between basic and clinical research
  • Guiding regulatory decisions
  • Guiding immunization policy
  • Bridging efficacy of a vaccine observed in a trial to a new setting

✓ Pearl (2011, International Journal of Biostatistics) suggests that bridging is the reason for a surrogate endpoint
HVTN Site Expansion Necessary to Support Phase I Program

- Total of 13 sites in southern Africa
  - Malawi
  - Mozambique
  - Zambia
  - Zimbabwe
  - Tanzania
  - South Africa
HVTN 108 (111) – Major questions

• What are the immune responses elicited by vaccine regimens containing DNA and adjuvanted protein without a pox vector?
  • When DNA is administered alone as a prime followed by DNA + protein/adjuvant boost?
  • When DNA and protein/adjuvant are co-administered at each vaccination?
HVTN 108 Hypotheses

• Protocol specific hypotheses:
  • Co-administration of DNA + gp120s will elicit higher levels of Env binding Abs of higher avidity that are more durable than those induced by the DNA-prime / DNA+gp120 boost regimen
  • DNA-prime / DNA+gp120 boost will induce binding Abs against Env in 100% of vaccinees

• Cross-protocol hypotheses:
  • DNA-prime / DNA+gp120 boost will induce a polyfunctional CD4+ T-cell response pattern that differs qualitatively from the ALVAC-prime / ALVAC + gp120 boost regime
  • Co-administration of DNA+gp120 boost will induce lower levels of IgA binding Abs than the ALVAC-prime / ALVAC + gp120 boost regimen
## HVTN 108 - Study Schema

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Dose of each protein</th>
<th>Deltoid</th>
<th>Month 0 (Day 0)</th>
<th>Month 1 (Day 28)</th>
<th>Month 3 (Day 84)</th>
<th>Month 6 (Day 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>100mcg</td>
<td>Left</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Protein + MF59</td>
<td>Protein + MF59</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>100mcg</td>
<td>Left</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Protein + AS01B</td>
<td>DNA</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>20mcg</td>
<td>Left</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Protein + AS01B</td>
<td>DNA</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>100mcg</td>
<td>Left</td>
<td>DNA</td>
<td>DNA</td>
<td>Placebo</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Protein + MF59</td>
<td>Protein + MF59</td>
<td>Placebo</td>
<td>Protein + MF59</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>100mcg</td>
<td>Left</td>
<td>DNA</td>
<td>DNA</td>
<td>Placebo</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Protein + AS01B</td>
<td>Protein + AS01B</td>
<td>Placebo</td>
<td>Protein + AS01B</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>20mcg</td>
<td>Left</td>
<td>DNA</td>
<td>DNA</td>
<td>Placebo</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Protein + AS01B</td>
<td>Protein + AS01B</td>
<td>Placebo</td>
<td>DNA</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>20mcg</td>
<td>Left</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Protein + AS01B</td>
<td>Protein + AS01B</td>
<td>Placebo</td>
<td>Protein + AS01B</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td></td>
<td>Left</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Total</td>
<td>334</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HVTN 113 – Major questions

• How does priming with DNA versus priming with ALVAC affect HIV specific immune responses when followed by ALVAC + protein boosting?
HVTN 113 Hypotheses

• Protocol specific hypotheses:
  • DNA-prime / ALVAC + gp120 boost will elicit CD4+ T-cell responses of higher response rates and magnitudes than the ALVAC-prime / ALVAC + gp120 boost regimen
  • ALVAC-prime / ALVAC + gp120 boost will induce IgG binding antibodies more rapidly than the DNA-prime / ALVAC + gp120 boost regimen

• Cross-protocol hypothesis:
  • ALVAC-prime / ALVAC + gp120 boost will induce a polyfunctional CD4+ T-cell response pattern that differs qualitatively from the CD4+ responses in the DNA-prime / DNA+gp120 boost
## HVTN 113 – Study Schema

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Dose of each protein</th>
<th>Deltoid</th>
<th>Month 0 (Day 0)</th>
<th>Month 1 (Day 28)</th>
<th>Month 3 (Day 84)</th>
<th>Month 6 (Day 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>100mcg</td>
<td>Left</td>
<td>DNA</td>
<td>DNA</td>
<td>ALVAC</td>
<td>ALVAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>-</td>
<td>-</td>
<td>Protein + MF59</td>
<td>Protein + MF59</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>100mcg</td>
<td>Left</td>
<td>DNA</td>
<td>DNA</td>
<td>ALVAC</td>
<td>ALVAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>-</td>
<td>-</td>
<td>Protein + AS01&lt;sub&gt;B&lt;/sub&gt;</td>
<td>Protein + AS01&lt;sub&gt;B&lt;/sub&gt;</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>20mcg</td>
<td>Left</td>
<td>DNA</td>
<td>DNA</td>
<td>ALVAC</td>
<td>ALVAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>-</td>
<td>-</td>
<td>Protein + AS01&lt;sub&gt;B&lt;/sub&gt;</td>
<td>Protein + AS01&lt;sub&gt;B&lt;/sub&gt;</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>100mcg</td>
<td>Left</td>
<td>ALVAC</td>
<td>ALVAC</td>
<td>ALVAC</td>
<td>ALVAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>-</td>
<td>-</td>
<td>Protein + AS01&lt;sub&gt;B&lt;/sub&gt;</td>
<td>Protein + AS01&lt;sub&gt;B&lt;/sub&gt;</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>20mcg</td>
<td>Left</td>
<td>ALVAC</td>
<td>ALVAC</td>
<td>ALVAC</td>
<td>ALVAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>-</td>
<td>-</td>
<td>Protein + AS01&lt;sub&gt;B&lt;/sub&gt;</td>
<td>Protein + AS01&lt;sub&gt;B&lt;/sub&gt;</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>N/A</td>
<td>Left</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>-</td>
<td>-</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>270 (250 vaccinees; 20 placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overview of HVTN 703 / HPTN 081
Role of Antibodies in HIV Prevention and Treatment

Structure-based Vaccine Design

Immune pathways of antibody evolution

- Passive Transfer
  - Direct IgG
  - Gene vector (AAV)

Vaccine development
CD4 binding site antibody: VRC01

Up to 90% breadth
Mean IC50 = 0.3 ug/ml
Covers all clades

Wu et al. Science (2010)
<table>
<thead>
<tr>
<th>Virus clade</th>
<th>Number of viruses</th>
<th>IC_{50} &lt; 50 µg/mL</th>
<th>IC_{50} &lt; 1 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>22</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>B</td>
<td>49</td>
<td>96%</td>
<td>80%</td>
</tr>
<tr>
<td>C</td>
<td>38</td>
<td>87%</td>
<td>66%</td>
</tr>
<tr>
<td>D</td>
<td>8</td>
<td>88%</td>
<td>50%</td>
</tr>
<tr>
<td>CrRF01_AE</td>
<td>18</td>
<td>89%</td>
<td>61%</td>
</tr>
<tr>
<td>CRF02_AG</td>
<td>16</td>
<td>81%</td>
<td>56%</td>
</tr>
<tr>
<td>G</td>
<td>10</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>CRF07_BC</td>
<td>11</td>
<td>100%</td>
<td>45%</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>Total</td>
<td>190</td>
<td>91%</td>
<td>72%</td>
</tr>
</tbody>
</table>
Passive Antibody Prevention

- NHP studies tell us that physiologically achievable levels of Ab could prevent HIV-1 infection:
  *But no direct proof in humans*

- Learn from Proof of Concept in Humans:
  - What type of Ab response can prevent HIV-infection?
  - What level of antibody is needed to prevent infection?
    - Pertains to passive IgG infusion, or vectored delivery
  - Convert mAb levels to serum level of neutralization needed to protect: (e.g. neut titer 1:50, 1:500)
  - Provides a benchmark for vaccine development; i.e. what antibody level does a vaccine need to achieve
PROTOCOL
HVTN 703 / HPTN 081

A phase 2b study to evaluate the efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection
HVTN 703 / HPTN 081

- A phase 2b trial to determine if intravenous (IV) administration of VRC01 as a means of preventing HIV-1 acquisition in two high risk populations:
  - (1) men who have sex with men (MSM) and transgender women who engage in high risk sexual behavior in the US and South America (Clade B).
  - (2) women in Sub-Saharan Africa (Clade C) who are at high risk of HIV acquisition through heterosexual sex.
  - These populations have been selected because of VRC01’s capacity to neutralize a broad range of both Clade C and Clade B viruses and because levels of antibodies required for protection from acquisition may vary by anatomic site and type of sexual exposure.
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.
Inform Future HIV Vaccine Immunogen Design

• 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 \textit{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?
we

our participants
Acknowledgments

- BMGF
- DAIDS/NIAID
- EuroVacc
- FHCRC (HVTN)
- GSK
- HCRISA
- CT Immunology lab
- IPPOX
- US-MHRP
- Novartis
- RSA-MRC
- Sanofi Pasteur
- SCHARP
HIV Prophylactic Vaccine
Overview Development Program

HIV Vaccine Awareness Day
May 18, 2015

Frank L Tomaka, MD
Clinical Leader, HIV Vaccines

Infectious Diseases
and Vaccines

Melinda, Goddess of Healing
Melinda’s artwork reflects her journey living with HIV.
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
**HIV vaccine regimen: viral vector platforms**

- **Adenovirus 26**
  - Ad26.Mos.HIV Vaccine
  - Insert Mosaic genes that encode(s) HIV protein(s)
  - Production on complementing PER.C6® cells

- **Modified Vaccinia Ankara**
  - MVA-Mosaic
  - Production on permissive CEF cells
  - MVA-Mosaic vaccines deliver HIV transgenes inside human cells.
  - The human body produces the HIV proteins that induce anti-HIV Immune responses.

- **Ad26.Mos.HIV and MVA-Mosaic vaccines are cleared from the body.**
HIV vaccine regimen: protein platform

DNA encoding trimeric envelope protein Clade C gp140

PER.C6®

Production on complementing PER.C6® cells

Clade C gp140 mixed with Aluminum Phosphate

Aluminum Phosphate as adjuvant

PER.C6®

Vaccine

Clade C gp140 protein will boost anti-HIV immune response

Aluminum Phosphate will enhance, sustain and direct the immunogenicity of the vaccine
Why Mosaic Inserts?

• There is worldwide diversity of HIV-1 = Multiple clades

• Mosaic inserts are genes that have been engineered to code for HIV-1 gag, pol, env proteins which elicit immune responses across clades

• In monkeys, when compared to consensus or natural HIV-1 sequences, mosaic HIV-1 gag, pol and env antigens expressed in our Ad26 vectors markedly enhanced the breadth of immune responses

• Also, the monkeys that were vaccinated with either Ad26 and Ad35, or Ad26 and MVA with mosaic Gag, Pol and Env inserts, were partially resistant to acquisition of simian HIV, a per-exposure risk reduction of more than 87%
A prime-boost vaccine regimen aiming at global coverage

<table>
<thead>
<tr>
<th>Prime</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26 Mosaic vectors gag-pol-env</td>
<td>Ad26 Mosaic vectors gag-pol-env</td>
</tr>
<tr>
<td>Ad26 Mosaic vectors gag-pol-env</td>
<td>MVA Mosaic vectors gag-pol-env</td>
</tr>
</tbody>
</table>

Soluble trimer gp140 env protein

Prime +/-

Boost +/-

or

Regimen to be selected after Phase 1/2a
Heterologous Prime-Boost with Mosaic Inserts Elicit Protective Immunity Against SHIV-SF162P3 Challenges

**Note:** SHIV challenge model ~100-fold more infectious than HIV in humans

<table>
<thead>
<tr>
<th>P-Value vs Sham*</th>
<th>Per-Exposure Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad/MVA</td>
<td>0.002</td>
</tr>
<tr>
<td>Ad/Ad</td>
<td>0.007</td>
</tr>
<tr>
<td>Sham</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Cox proportional hazard model

**Correlates of Protection**

<table>
<thead>
<tr>
<th>Assay</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>0.00000012</td>
</tr>
<tr>
<td>ADCP</td>
<td>0.00030</td>
</tr>
<tr>
<td>NAb</td>
<td>0.00072</td>
</tr>
</tbody>
</table>

**Barouch et al. Cell 2013**
Protective efficacy of the Ad-based prime/GP140 boost in stringent NHP SIV and SHIV models

Protective efficacy of the Ad/Env SIV vaccine against SIVmac251 challenges

Protective efficacy of the Ad/Env HIV-1 vaccine against SHIV-SF162P3 challenges

<table>
<thead>
<tr>
<th></th>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad /Env</td>
<td>90%</td>
<td>50%</td>
</tr>
<tr>
<td>Ad Alone</td>
<td>75%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Barouch et al, submitted 2015

<table>
<thead>
<tr>
<th></th>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad /Env</td>
<td>79%</td>
<td>40%</td>
</tr>
<tr>
<td>Env Alone</td>
<td>49%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Barouch et al, submitted 2015
Overall Early Clinical Development Plan

Target vaccine regimen will have 2 or 3 components

- Establish safety of each component separate FIH studies
  - HIV-V-A002/MENSCH
  - HIV-V-A003
  - HIV-V-A004/APPROACH
- Ancillary studies to assess alternative schedules and other proteins under consideration
Overall Early Clinical Development Plan

• FIH safety of MVA-Mosaic in HIV-V-A002/MENSCH

  – To assess the safety of MVA Mosaic when given as a late boost to subjects previously vaccinated with Ad26.ENVA and naïve subjects
  – Clinical site: Brigham and Women’s Hospital, Boston
  – Population: healthy subjects, 18-50 yo; N=25
  – Funders: BIDMC/Ragon and Crucell/Janssen

Study started in October 2014
Vaccinations complete
No unexpected safety events
The study consists of a screening period of 4 weeks, a vaccination period of 12 weeks and a follow-up period of 40 weeks after 2nd dose ➔ subjects will be actively followed for 12 months.

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Week 0</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Healthy</td>
<td>12</td>
<td>MVA mos</td>
<td>MVA mos</td>
</tr>
<tr>
<td>2 Healthy</td>
<td>3</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>3 Previously in Ad26.ENVA.01</td>
<td>8-20</td>
<td>MVA mos</td>
<td>MVA mos</td>
</tr>
<tr>
<td>4 Previously in Ad26.ENVA.01</td>
<td>2-5</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Subjects not from IPCAVD001 randomly assigned to Groups 1-2. Subjects previously enrolled in IPCAVD001 stratified block randomization to ensure a balance between the different prior regimens that were given, placed into Groups 3-4.
Overall Early Clinical Development Plan

- FIH safety of gp140 protein in HIV-V-A003
  - To assess the safety of GP140 with Aluminum phosphate
  - Clinical site: single site in USA
  - Population: healthy subjects, 18-50 yo; N= 50

Study started in December 2014
Vaccinations complete
No unexpected safety events
# HIV-V-A003 Trial Design

<table>
<thead>
<tr>
<th>Grp</th>
<th>n</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>gp140 50 mcg</td>
<td>gp140 50 mcg</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>gp140 50 mcg/adj</td>
<td>gp140 50 mcg/adj</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>placebo</td>
<td>placebo</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>gp140 250 mcg</td>
<td>gp140 250 mcg</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>gp140 250 mcg/adj</td>
<td>gp140 250 mcg/adj</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>placebo</td>
<td>placebo</td>
<td>Follow-up</td>
<td></td>
</tr>
</tbody>
</table>

Adjuvant (adj)=aluminum phosphate

All subjects followed to Week 48
Overall Early Clinical Development Plan

- FIH safety of Ad26.Mos.HIV in HIV-V-A004/APPROACH
  - To assess the safety and immunogenicity of the 3 components in prime boost regimens
  - Clinical sites: USA, Uganda, Rwanda, South Africa, Thailand
  - Population: healthy subjects, 18-50 yo; N= 400

Study started in December 2014
Enrollment ongoing
HIV-V-A004/APPROACH: Study Design

Healthy volunteers ≥18 to ≤50 yo

400 subjects, equal randomization to one of 7 regimens and placebo

Wk 0

Wk 12

Wk24

Wk48 boost

follow-up

4 wk screening

48 wks

All participants will receive Ad26.Mos.HIV at Wk 0 and 12; at Wk 24 and 48 they will receive Ad26.Mos.HIV or MVA.Mos or gp 140 or a combination of either Ad26 or MVA with gp140

Note: for a subset of subjects who consent, mucosal samples will be collected (cervicovaginal, ano-rectal, ejaculate)
## HIV-V-A004/APPRAOCH: Treatment Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Week 0 (baseline)</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 5</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>Ad26.Mos.HIV</td>
<td>MVA-Mosaic + gp140 DP (50 µg+adjuvant)</td>
<td>MVA-Mosaic + gp140 DP (50 µg+adjuvant)</td>
</tr>
<tr>
<td>Group 8</td>
<td>50</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo + Placebo</td>
<td>Placebo + Placebo</td>
</tr>
</tbody>
</table>
# Clinical site selected for HIV-V-A004/APPROACH

## US
1. University of Colorado, Anshultz Medical Campus  
   Dr. Cambell
2. Miami Research Associates (MRA)  
   Dr. Sheldon
3. Brigham and Womens Hospital (BWH)  
   Dr. Baden

## Thailand
4. Armed Forces Research Institute of Medical Sciences (AFRIMS)  
   Dr. Nitapayan
5. Vaccine Trial Centre (Mahidol)  
   Dr. Pitisuttithum

## Uganda
6. Makerere University Walter Reed Project (MUWRP)  
   Dr. Kibuuka
7. Uganda Virus Research Institute (UVRI)  
   Dr. Mpendo

## South Africa
8. Desmund Tutu HIV Centre (DTHC)  
   Dr. Roux
9. AURUM - Klerksdorp site  
   Dr. Craig
10. Perinatal HIV Research Centre (PHRU)  
    Dr. Lazarus
11. Centre for the AIDS Programme of Research in South Africa (CAPRISA)  
    Dr. Garrett

## Rwanda
12. Projet San Francisco (PSF)  
    Dr. Karita

## Additional Sites:
- Optimal Research (ABL)
- Tekton-Cenetron
# Ongoing non-human primate study #13-19: study design (similar to APPROACH)

**Aim:** To determine the best vaccine boost components to achieve broad humoral and cellular immunogenicity and to protect against SHIV$_{SF162P3}$ challenge in rhesus macaques.

<table>
<thead>
<tr>
<th>Gr (#)</th>
<th>0 Mo (2Dec13)</th>
<th>3 Mo (24Feb 2014)</th>
<th>6 Mo (19May 2014)</th>
<th>12 Mo (1Dec 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}+$ protein</td>
<td>Ad26$_{mos}+$ protein</td>
</tr>
<tr>
<td>II (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>protein</td>
<td>protein</td>
</tr>
<tr>
<td>III (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>MVA$_{mos}+$ protein</td>
<td>MVA$_{mos}+$ protein</td>
</tr>
<tr>
<td>IV (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>MVA$_{mos}$</td>
<td>MVA$_{mos}$</td>
</tr>
<tr>
<td>V (n=12)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>VI (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
</tr>
</tbody>
</table>

- Ad26$_{mos}$ = Ad26.mos1Gag-Pol + Ad26.mos1Env + Ad26.mos2Gag-Pol (5x10$^{10}$ vp in total)
- Protein (clade C gp140) dosed with adjuvant (250 µg protein + 425 µg AdjuPhos)
- Placebo = saline

**Vaccinations completed. Challenge with SHIV-SF162P3 to start in May 2015**
Regimen selection
Immunogenicity responses properties

- Identify the relevant immune responses (Human and NHP experience)
  - from human (ALVAC+protein)
  - from NHP (Ad26+MVA/Ad26/Protein)

- Responses should be of sufficient magnitude

- Responses should be broad: against multiple clades

- Responses should be durable
Efficacy Program

- **Two Efficacy Trials**

1. In Sub-Saharan/South Africa, SE Asia (primarily Clades C, A, D, E)

1. In North and South America, Europe (primarily Clades B, F)

- Specific countries/sites to be identified later this year/early next year
High Level Clinical Development Plan

Phase 1/2a (2014-2016)
- USA, Africa, Asia
  - Safety
  - Regimen selection
  - Dose confirmation
- Ancillary studies
  - Evaluation of alternative schedules
  - Evaluation of Mosaic trimer

Phase 2b/3 (2017-2021)
- Africa and Asia
  - Efficacy in high risk population
- USA, LatAm, Europe
  - Efficacy in high risk population
- Additional trials
  - Lot to lot, bridging

Phase 3/4 (2021+)
- Long term efficacy
  - Persistence of Immunity
- Additional trials
  - ≠populations
  - ≠countries

BLA-MAA submissions?
Aknowledgements

• Beth Israel Deaconess, Harvard Medical School
  - Dan Barouch
  - Peter Abbink
  - Joseph Nkolola
  - Katy Stephenson
  - Michael Seaman

• Brigham & Women’s, Harvard Medical School
  - Lindsey Baden
  - Raphael Dolin

• IAVI
  - Wayne Koff
  - Fran Priddy
  - Pat Fast

• MHRP
  - Julie Ake
  - Nelson Michael
  - Merlin Robb

• Ragon Institute
  - Bruce Walker
  - Galit Alter

• Janssen
  - Iedo Beeksma
  - Jenny Hendriks
  - Ad Knaapen
  - Lorenz Scheppler
  - Frank Tomaka
  - Danielle van Manen
  - Frank Wegmann
  - Mo Weijtens
  - Hanneke Schuitemaker
  - Maria Grazia Pau

• DAIDS, NIAID, NIH, HVTN
  - Michael Pensiero
  - Mary Marovich
  - Larry Corey
  - Bernie Moss