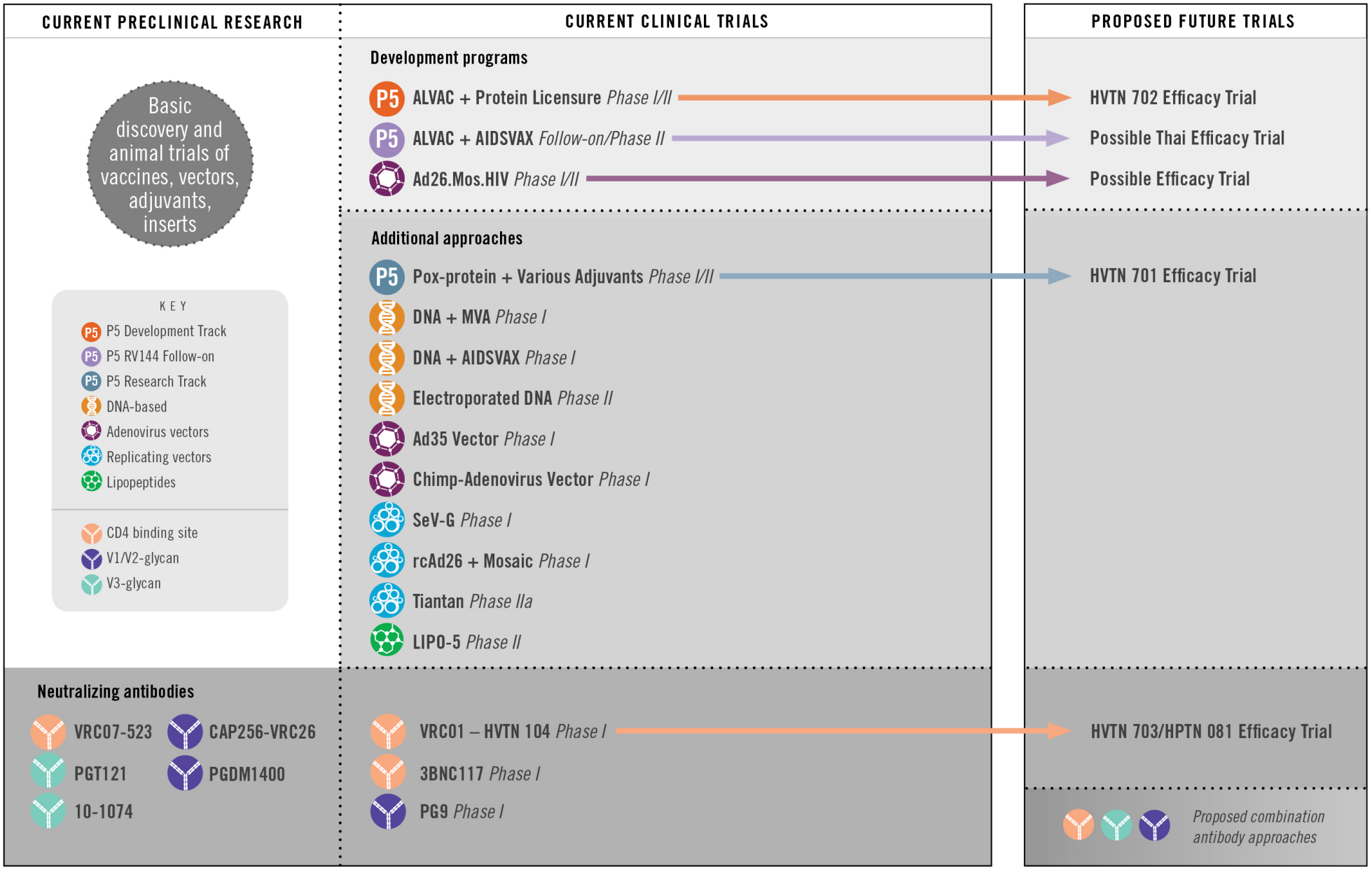
AIDS Vaccine Research: An overview

MAY 2015

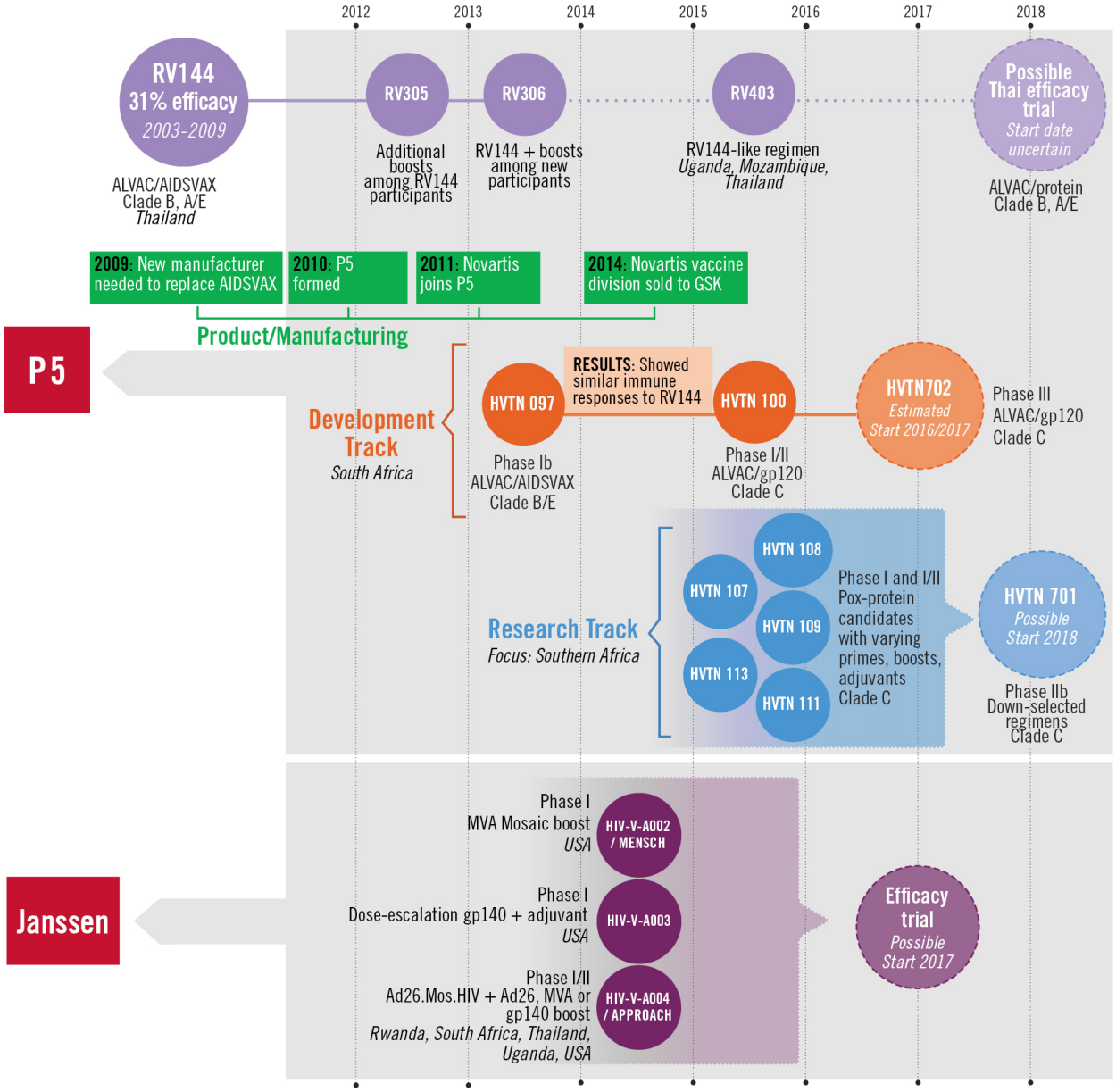
This graphic shows the big picture of AIDS vaccine concepts and clinical trials in process and on the horizon. It is an intentionally simplified representation of a complex field. Some approaches are not listed, and related arenas like therapeutic vaccines and cure research are omitted.



AIDS Vaccine Research: An overview

MAY 2015

Development Programs



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:
  - Development track: Efficacy trial of ALVAC/protein candidate for licensure—possible start 2016/2017.
  - 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.

Additional Vaccine Approaches

STATE OF THE FIELD

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*.

Vaccine strategy	Trials and products	Why	Sponsors / Developers
DNA **DNA + MVA** **DNA + AIDSVAX**	• 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 candiates are being explored.	Geovax HVTN IAVI
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 progress-ing 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-vectored 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

ADVOCATE'S CHECKLIST

✓ PUSH FOR PROMISE

Early trial results will yield important data

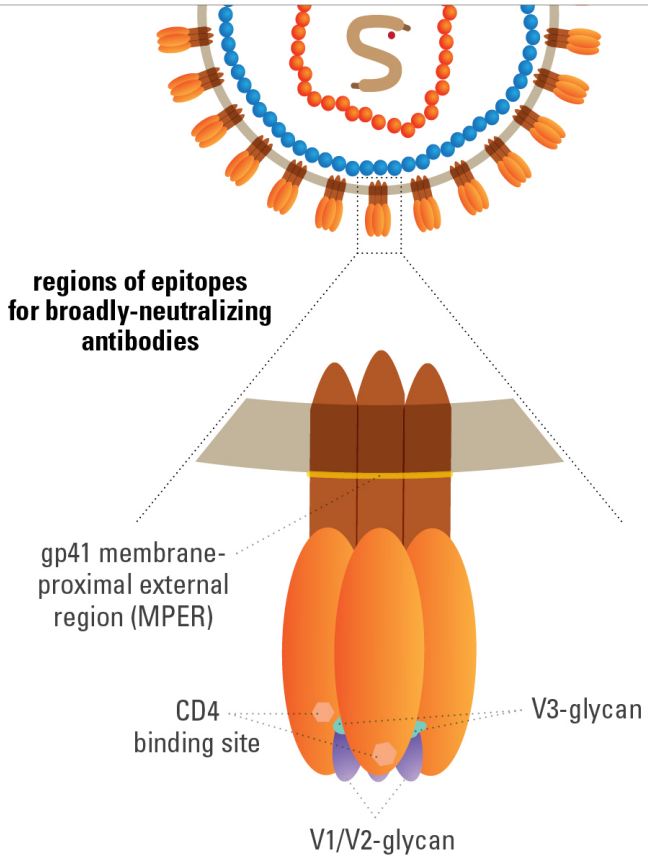
- Push for comparison across candidates and prioritization of most promising vaccines to move forward.

✓ 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 I 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 I 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)

** See Px Wire Volume 8 No 2 for additional pipeline information (www.avac.org/pxwire/vol8no2).*

STATE OF THE FIELD

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

ADVOCATE'S CHECKLIST

✓ **EXPLORE FEASIBILITY**

bNAb research is generating excitement, but still mostly upstream and conceptual

- Explore feasibility of bNAbs 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.

HIV VACCINE
TRIALS NETWORK

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.

NOVARTIS

MHRP U.S. MILITARY HIV RESEARCH PROGRAM

HIV VACCINE TRIALS NETWORK

BILL & MELINDA GATES foundation

National Institute of Allergy and Infectious Diseases

SANOFI PASTEUR

MRC SOUTH AFRICA SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

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.

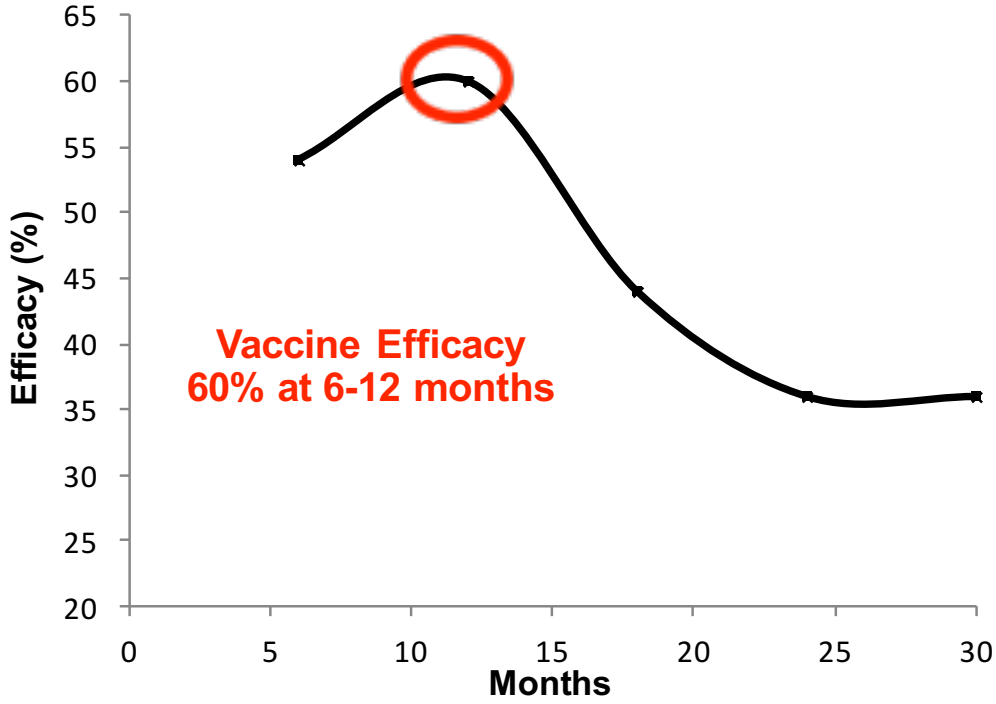
1. Continue to build public-private partnerships critical for success.
2. Work with host countries to support a flexible regulatory strategy in target populations and regions.
3. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.

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)

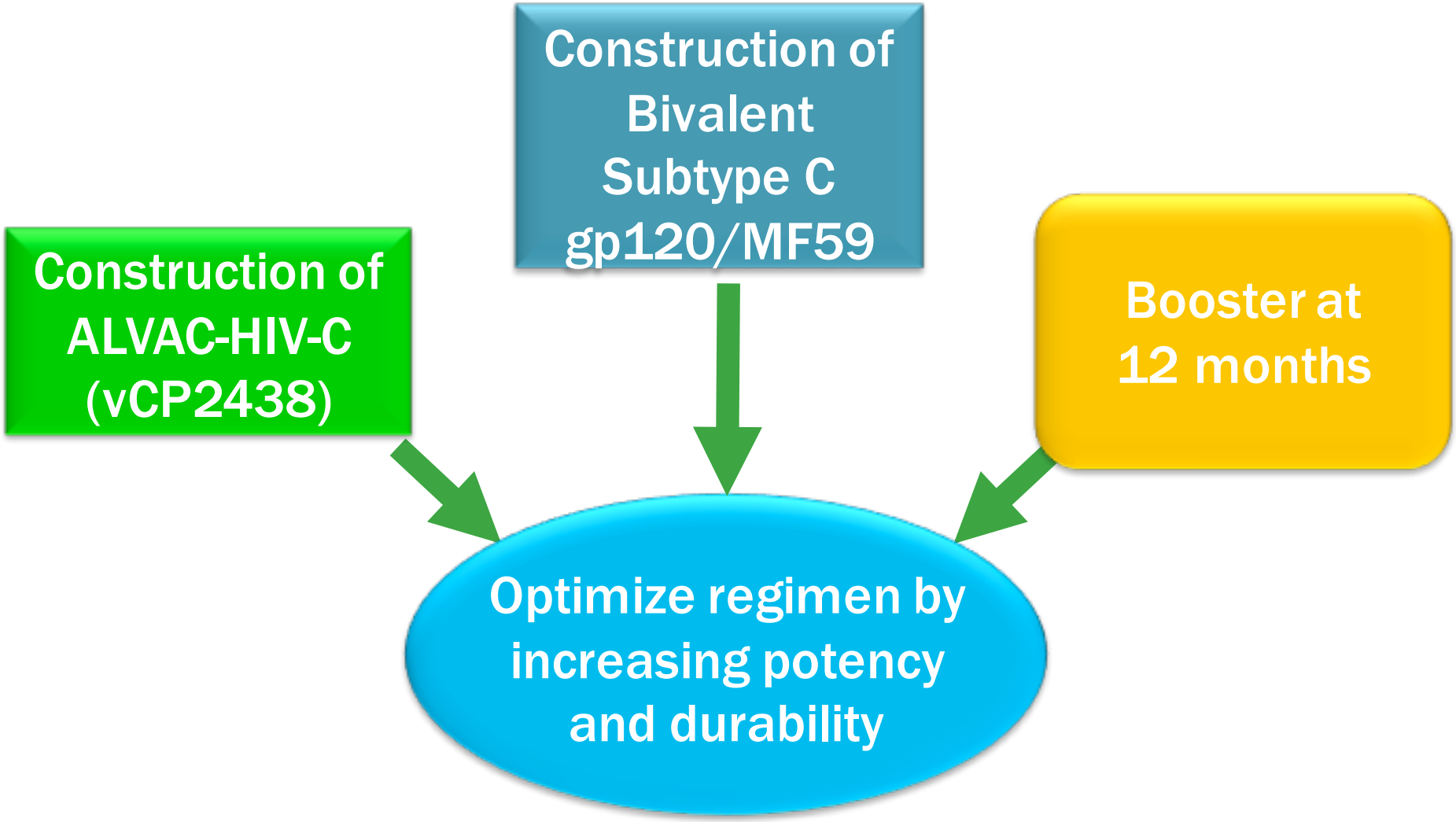
Schedule: 0,1,3,6 months; 16,000 volunteers; 1:1 vaccine: placebo; follow-up for 3 years



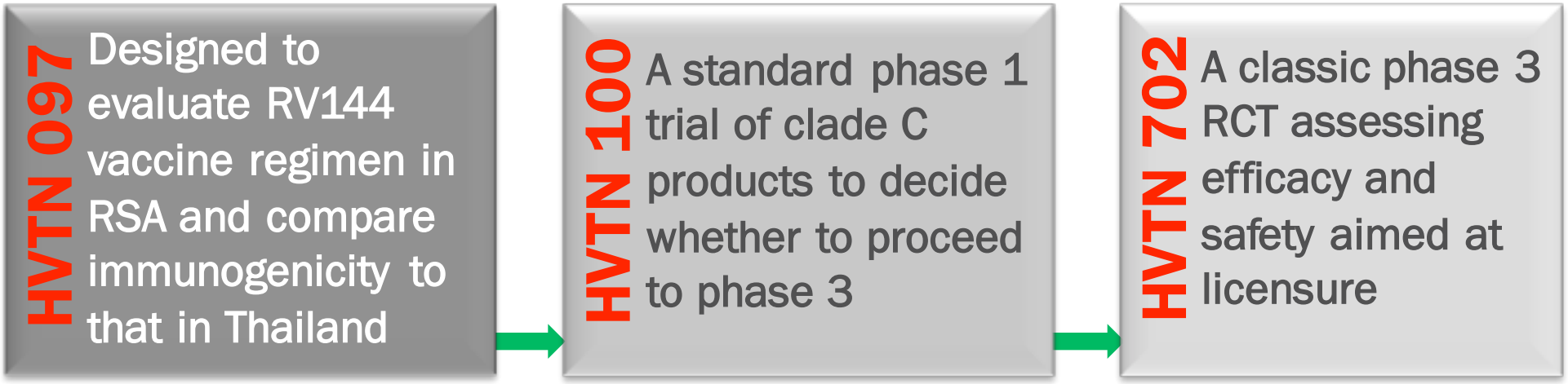
Although protective efficacy was 31.2% at the primary analysis, 42 months after first vaccination, the highest efficacy was observed at 6-12 months.

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



Strategy for the Phase 3 Program



Underpinned by community, regulatory and government stakeholder engagement


ALVAC-HIV Active
HVT02/HVTN097
1 vial, 1 dose IM Lyophilized
Store at 2°C to 8°C. Do not
Manufactured by IDT Biologika
DAIDS/NIH USA
For Clinical Trial Use Only
0.4% NaCl
HVTN097
Lot No. 001
1 dose IM Solution
at 2°C to 8°C. Do not freeze
Clinical Trial Use Only

Study Schema: HVTN 100

N (total 252)	Primary Vaccine Regimen				Booster
	Month 0	Month 1	Month 3	Month 6	Month 12
210	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®
42	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo

Products:

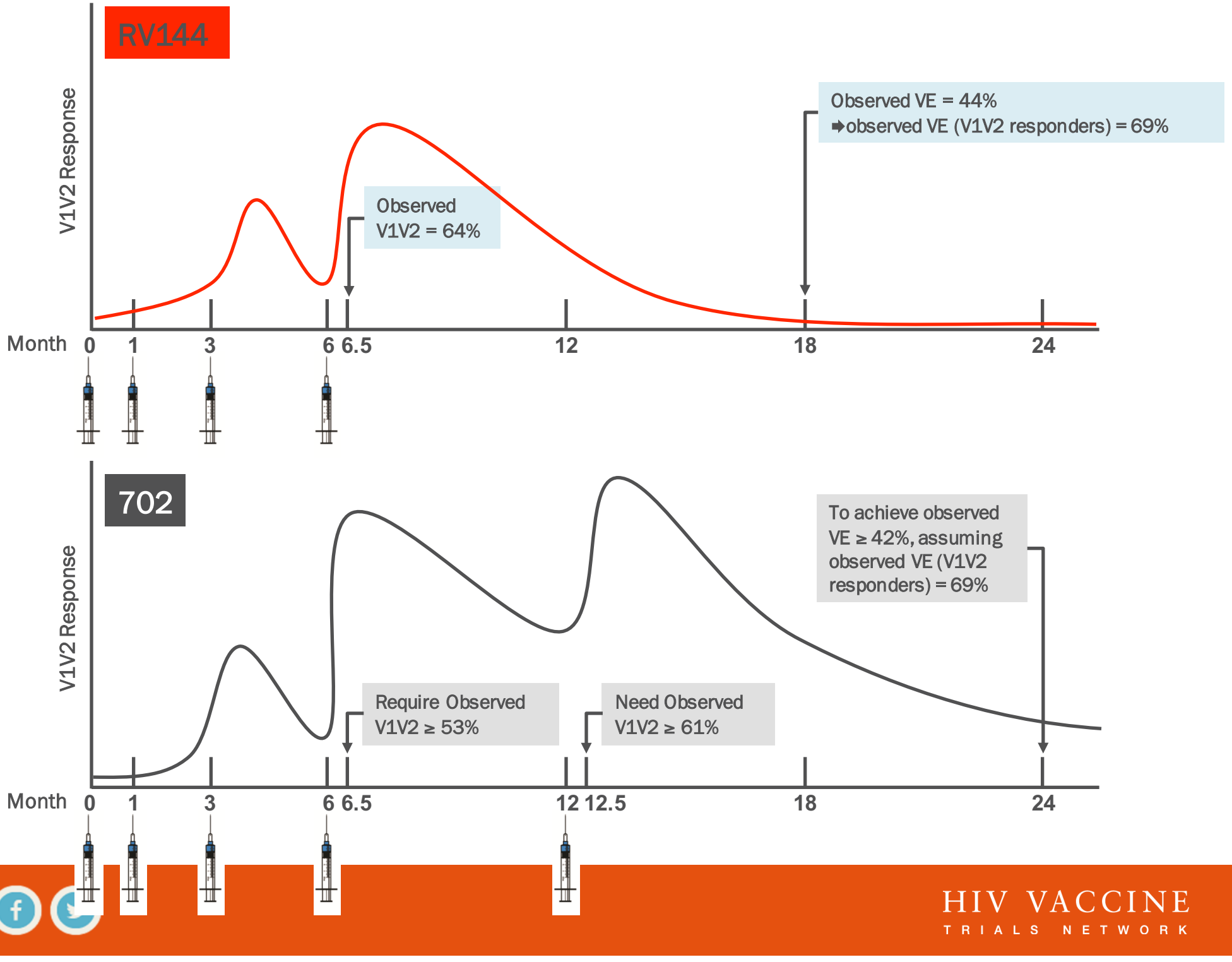
- ALVAC-HIV (vCP2438) expressing HIV-1 env (clade C gp120), clade B (gp41), gag (clade B) & protease (clade B) (Dose: >1 X 10^6 $CCID_{50}$)
- Bivalent subtype C gp120/MF59 containing 100mcg TV1.Cgp120 & 100mcg 1086.Cgp120

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

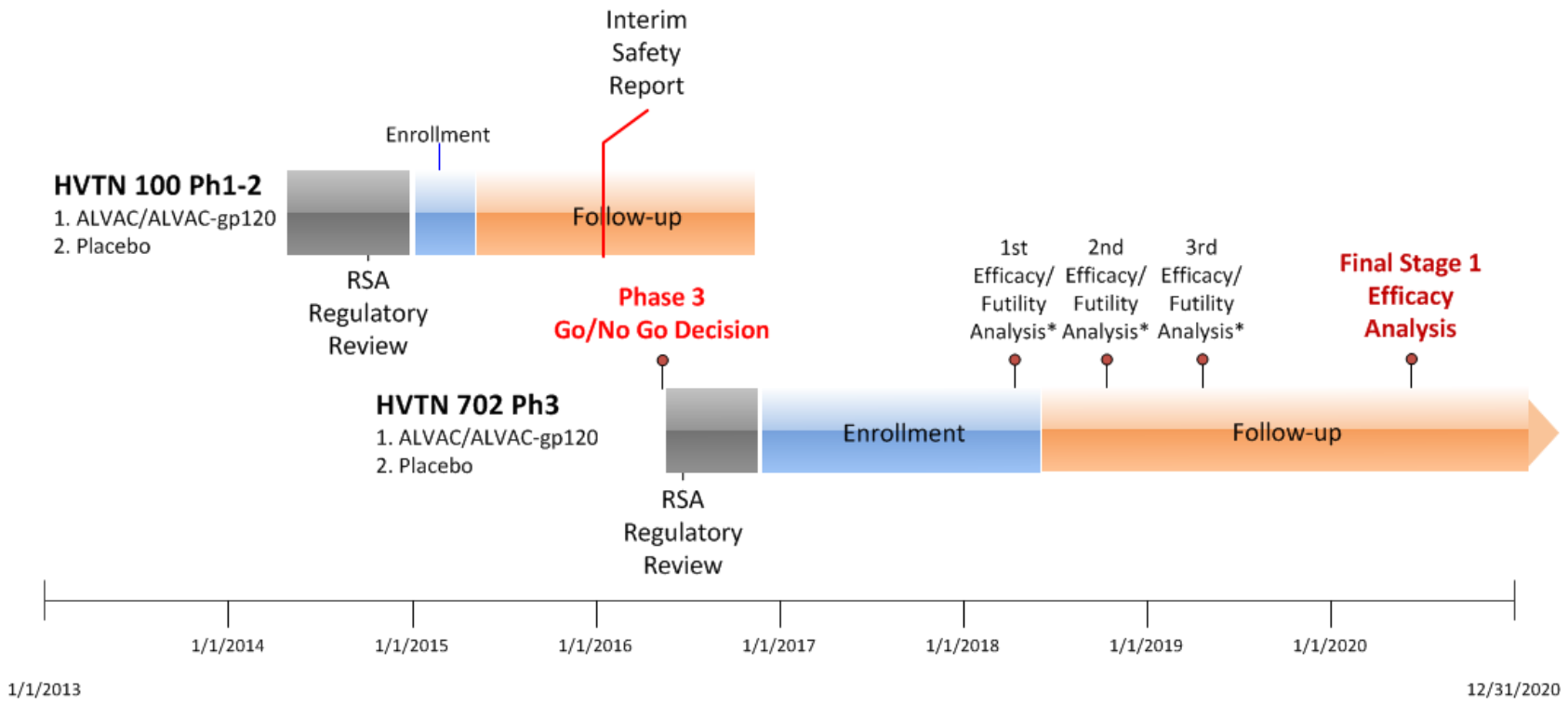
Variable Measured at Month 6.5	Rationale
Env Ab Response Rate (≥ 2 of 3)	Adequate Ab take to vaccine Env
Env Ab Magnitude* (≥ 2 of 3)	*Non-inferior* Ab magnitude vs. RV144
Env CD4 Response Rate* (1 of 1)	*Non-inferior* CD4 T cell take vs. RV144
Env V1V2 Response Rate (≥ 1 of 3)	Adequate to predict achieving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

* Based on simultaneous assessment of clade C vaccinee samples vs. RV144 vaccinee samples by the same lab


RV144
V1V2 Response
Observed VE = 44%
➡observed VE (V1V2 responders) = 69%
Observed
V1V2 = 64%
Month
0
1
3
6
6.5
12
18
24
702
V1V2 Response
To achieve observed VE ≥ 42%, assuming observed VE (V1V2 responders) = 69%
Require Observed V1V2 ≥ 53%
Need Observed V1V2 ≥ 61%
Month
0
1
3
6
6.5
12
12.5
18
24

Timelines

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



*Interim efficacy/futility analyses are endpoint driven—timepoints shown are approximate.

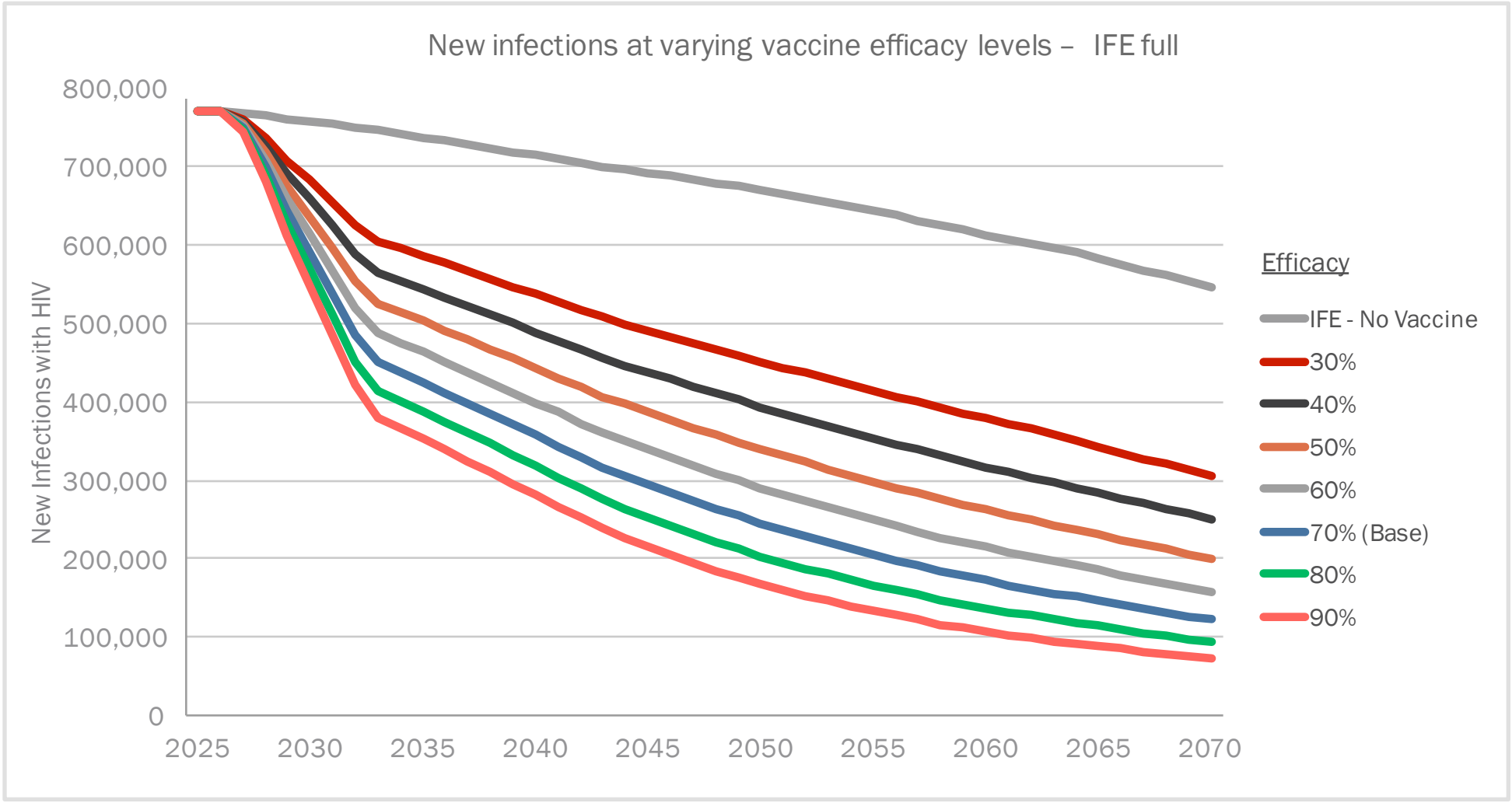
Study Schema: HVTN 702

N (total 5400)	Primary Vaccine Regimen				Booster
	Month 0	Month 1	Month 3	Month 6	Month 12
2700	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®
2700	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo

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"



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%

Modeling project – UNAIDS, Futures Institute, IAVI, AVAC [funded by USAID]

Target Product Profile

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


BAZOOKA

SITE TRAINING AND SUPPORT

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

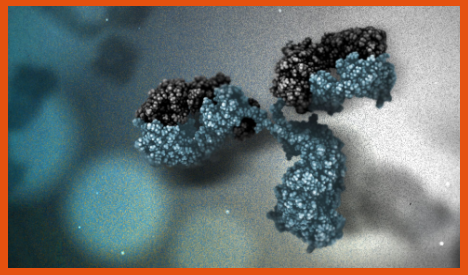
Training the Clinic Staff: Protocol-specific

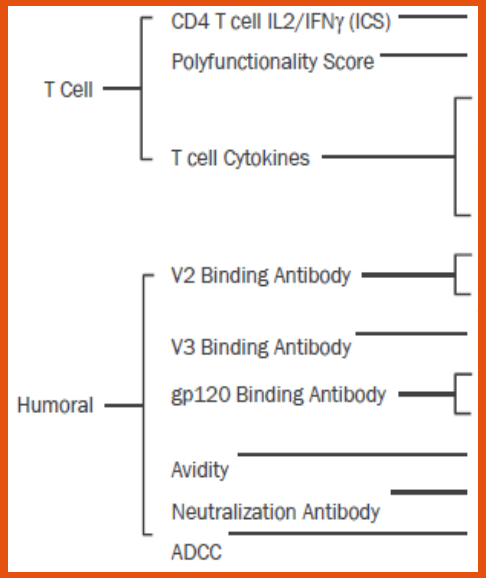
Regional Training, 3 days

- 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

HIV VACCINE
TRIALS NETWORK

HVTN P5 Programs





Click to edit Master subtitle style

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

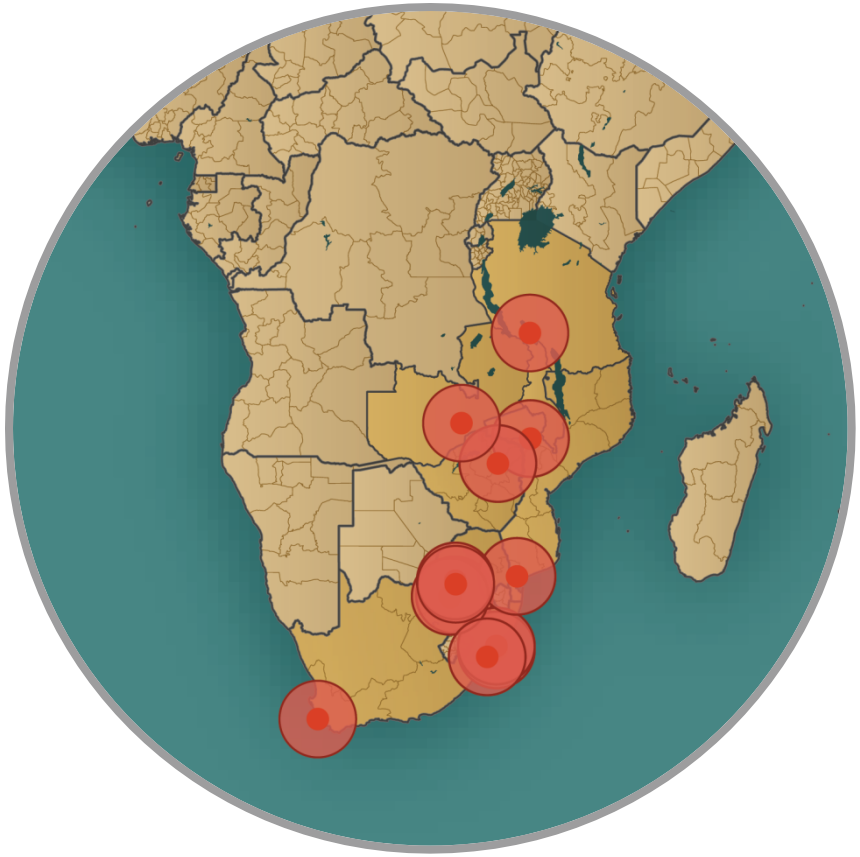
- Finding an immune correlate is a central goal of vaccine research
  - One of the 14 'Grand Challenges of Global Health' of the NIH & Gates Foundation (for HIV, TB, Malaria)

- 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

Group	N	Dose of each protein	Deltoid	Month 0 (Day 0)	Month 1 (Day 28)	Month 3 (Day 84)	Month 6 (Day 168)	
1	30	100mcg	Left	DNA	DNA	DNA	DNA	DNA-prime DNA+protein boost
			Right	Placebo	Placebo	Protein + MF59	Protein + MF59	
2	50	100mcg	Left	DNA	DNA	DNA	DNA	
			Right	Placebo	Placebo	Protein + $AS01_B$	Protein + $AS01_B$	
3	50	20mcg	Left	DNA	DNA	DNA	DNA	
			Right	Placebo	Placebo	Protein + $AS01_B$	Protein + $AS01_B$	
4	30	100mcg	Left	DNA	DNA	Placebo	DNA	DNA+protein coadmin
			Right	Protein + MF59	Protein + MF59	Placebo	Protein + MF59	
5	50	100mcg	Left	DNA	DNA	Placebo	DNA	
			Right	Protein + $AS01_B$	Protein + $AS01_B$	Placebo	Protein + $AS01_B$	
6	50	20mcg	Left	DNA	DNA	Placebo	DNA	
			Right	Protein + $AS01_B$	Protein + $AS01_B$	Placebo	Protein + $AS01_B$	
7	50	20mcg	Left	Placebo	Placebo	Placebo	Placebo	Protein prime-boost
			Right	Protein + $AS01_B$	Protein + $AS01_B$	Placebo	Protein + $AS01_B$	
8	24		Left	Placebo	Placebo	Placebo	Placebo	
			Right	Placebo	Placebo	Placebo	Placebo	
Total	334 (310 vaccinees; 24 placebo)							

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

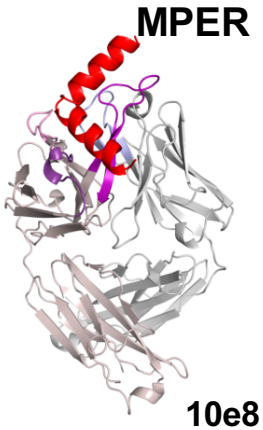
Group	N	Dose of each protein	Deltoid	Month 0 (Day 0)	Month 1 (Day 28)	Month 3 (Day 84)	Month 6 (Day 168)
1	50	100mcg	Left	DNA	DNA	ALVAC	ALVAC
			Right	-	-	Protein + MF59	Protein + MF59
2	50	100mcg	Left	DNA	DNA	ALVAC	ALVAC
			Right	-	-	Protein + $AS01_B$	Protein + $AS01_B$
3	50	20mcg	Left	DNA	DNA	ALVAC	ALVAC
			Right	-	-	Protein + $AS01_B$	Protein + $AS01_B$
4	50	100mcg	Left	ALVAC	ALVAC	ALVAC	ALVAC
			Right	-	-	Protein + $AS01_B$	Protein + $AS01_B$
5	50	20mcg	Left	ALVAC	ALVAC	ALVAC	ALVAC
			Right	-	-	Protein + $AS01_B$	Protein + $AS01_B$
6	20	N/A	Left	Placebo	Placebo	Placebo	Placebo
			Right	-	-	Placebo	Placebo
Total	270 (250 vaccinees; 20 placebo)						

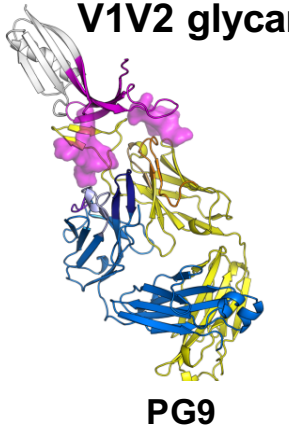
HIV VACCINE
TRIALS NETWORK

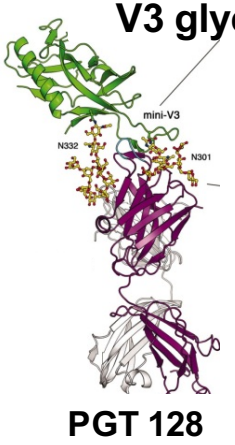
Overview of HVTN 703 / HPTN 081

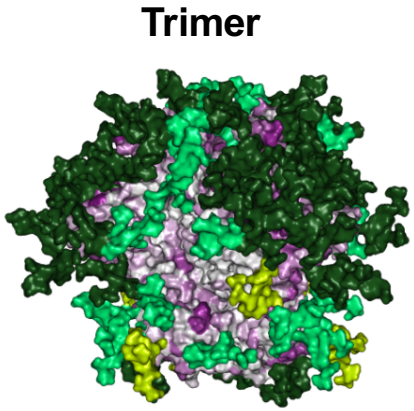
Role of Antibodies in HIV Prevention and Treatment

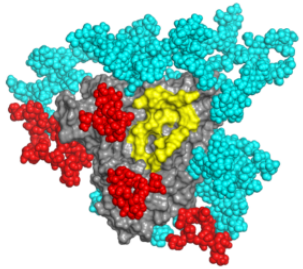
HIV VACCINE TRIALS NETWORK



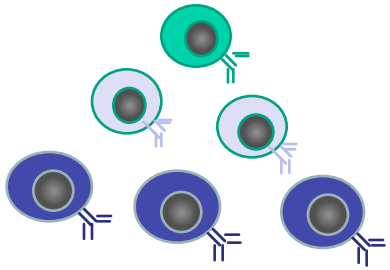




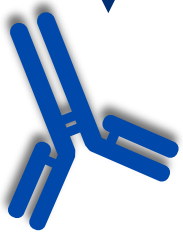




Structure-based Vaccine Design



Immune pathways of antibody evolution

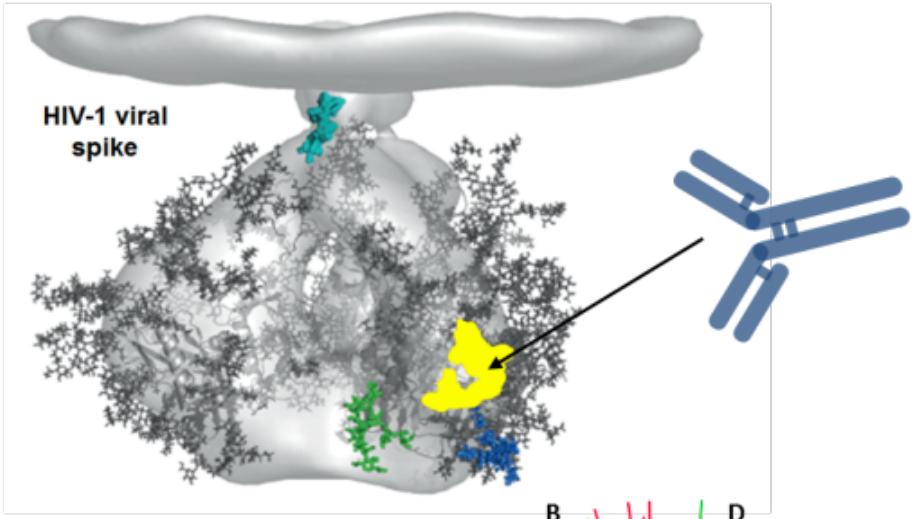


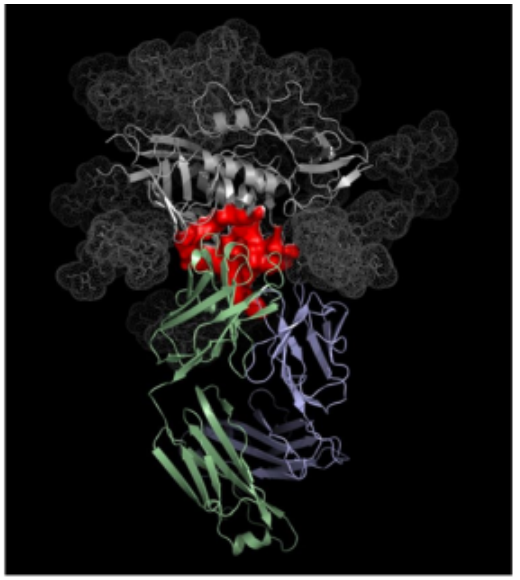
Passive Transfer
- Direct IgG
- Gene vector (AAV)

Vaccine development

HIV VACCINE
TRIALS NETWORK

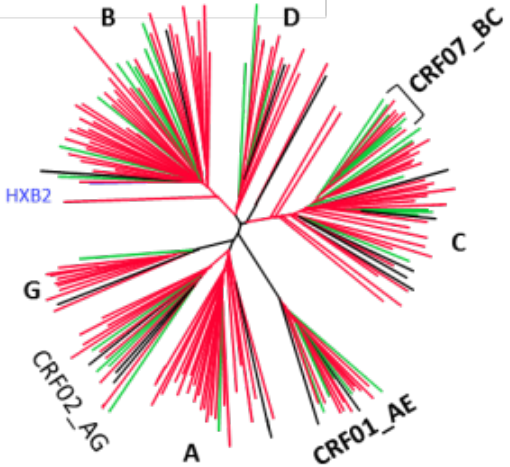
CD4 binding site antibody: VRC01





gp160 protein tree:

190 HIV-1 Isolates



— IC_{50} < 1 µg/ml
— IC_{50} 1-50 µg/ml
— IC_{50} > 50 µg/ml

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

Wu et al. Science (2010)
Zhou et al. Science (2010)

HIV VACCINE
TRIALS NETWORK

Virus clade	Number of viruses	IC_{50} < 50 µg/mL	IC50 < 1 µg/mL
A	22	100%	95%
B	49	96%	80%
C	38	87%	66%
D	8	88%	50%
CrRF01_AE	18	89%	61%
CRF02_AG	16	81%	56%
G	10	90%	90%
CRF07_BC	11	100%	45%
Other	18	83%	78%
Total	190	91%	72%

HIV VACCINE TRIALS NETWORK

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 *in vivo* protection require only high concentrations of CD4 binding site antibodies?

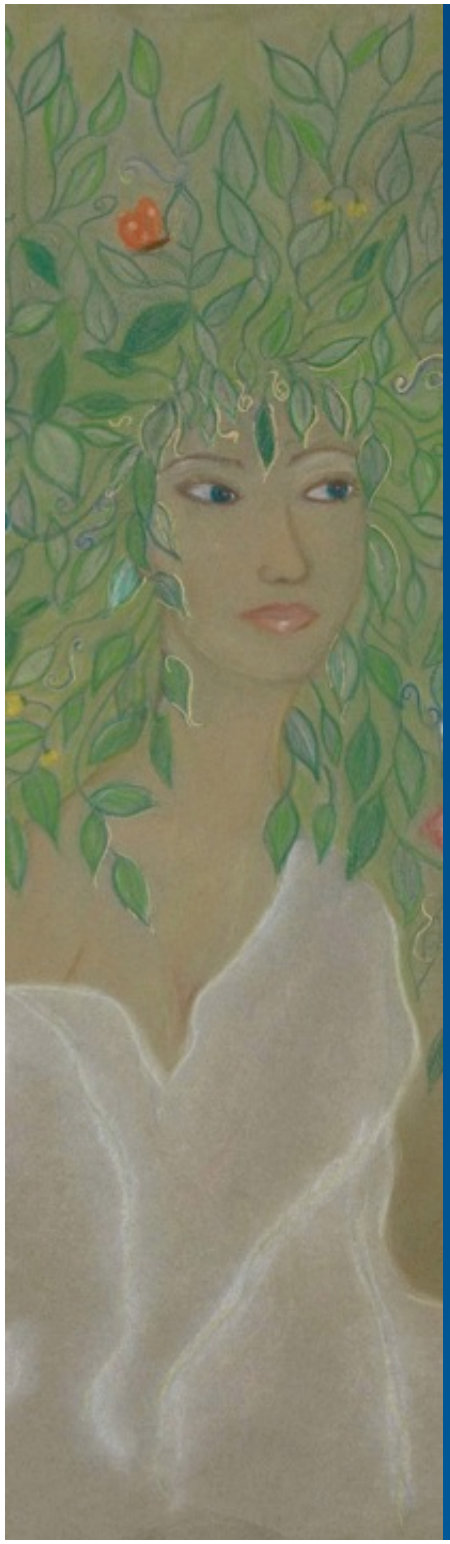
  ☐ Are non-neutralizing effector functions as predictive of efficacy as neutralizing activity?

  ☐ 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

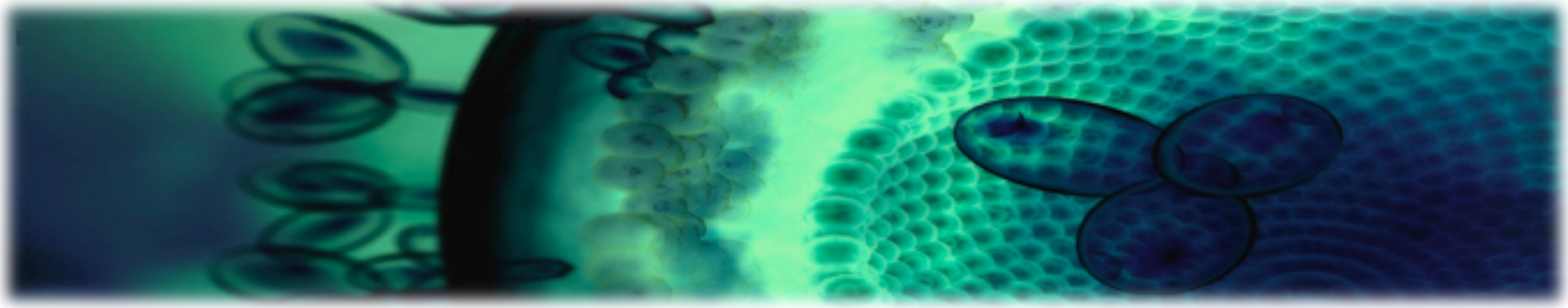
Infectious Diseases
and Vaccines

Melinda, *Goddess of Healing*
Melinda's artwork reflects her journey living with HIV.

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

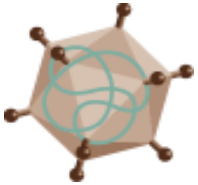
High Level Target Product Profile

- 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

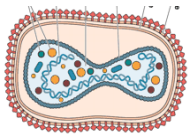


HIV vaccine regimen: viral vector platforms

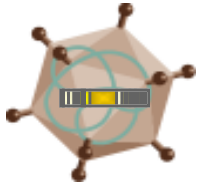
Adenovirus 26



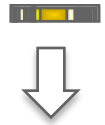
Modified Vaccinia Ankara



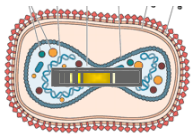
Ad26.Mos.HIV Vaccine



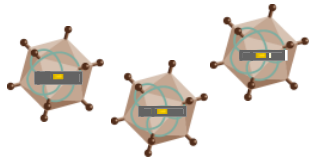
Insert Mosaic genes that encode(s) HIV protein(s)



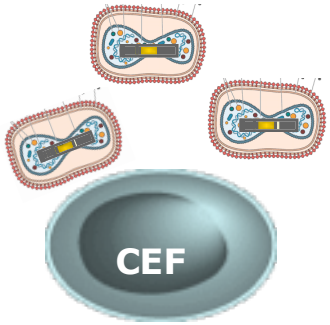
MVA-Mosaic



Production on complementing PER.C6® cells

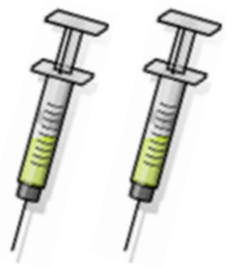


Production on permissive CEF cells



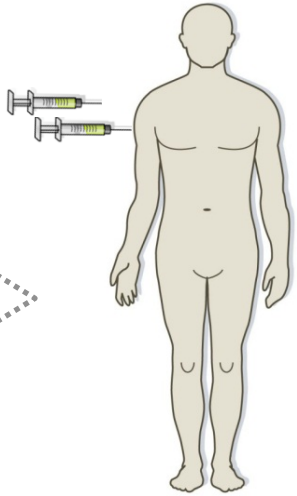
Ad26.Mos.HIV

MVA-Mosaic



Vaccine

Ad26.Mos.HIV and MVA-Mosaic **cannot replicate** in normal human cells.



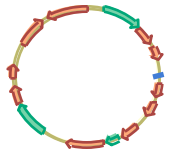
Ad26.Mos.HIV and MVA-Mosaic vaccines **deliver** HIV transgenes inside human cells.

The human body produces the HIV proteins that induce anti-HIV Immune responses.

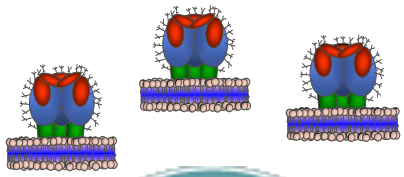
Ad26.Mos.HIV and MVA-Mosaic vaccines **are cleared** from the body.

HIV vaccine regimen: protein platform

DNA encoding trimeric envelope protein **Clade C gp140**



Production on complementing PER.C6® cells



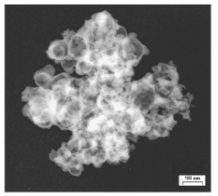


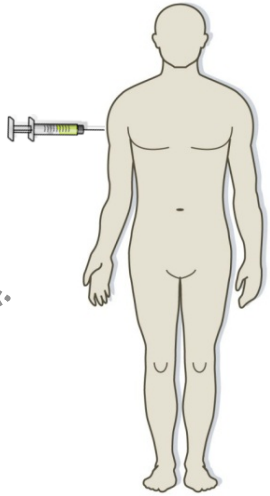
Figure 1. Bright field transmission electron micrograph of the nanostructured aluminum phosphate.

Aluminum Phosphate as adjuvant

Clade C gp140 mixed with Aluminum Phosphate

Vaccine

Clade C gp140 protein will boost anti-HIV immune response

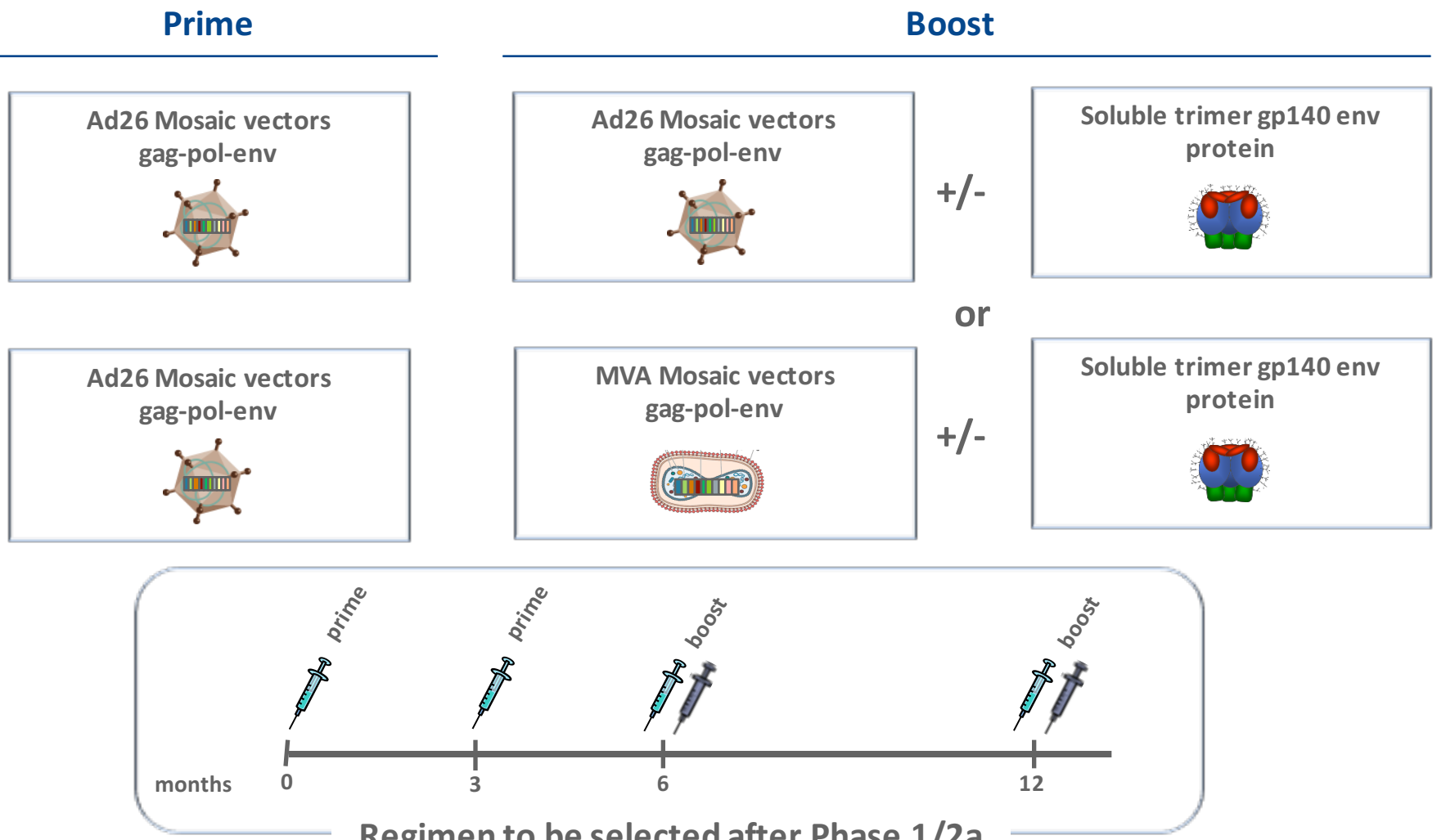


Aluminum Phosphate will enhance, sustain and direct the immunogenicity of the vaccine

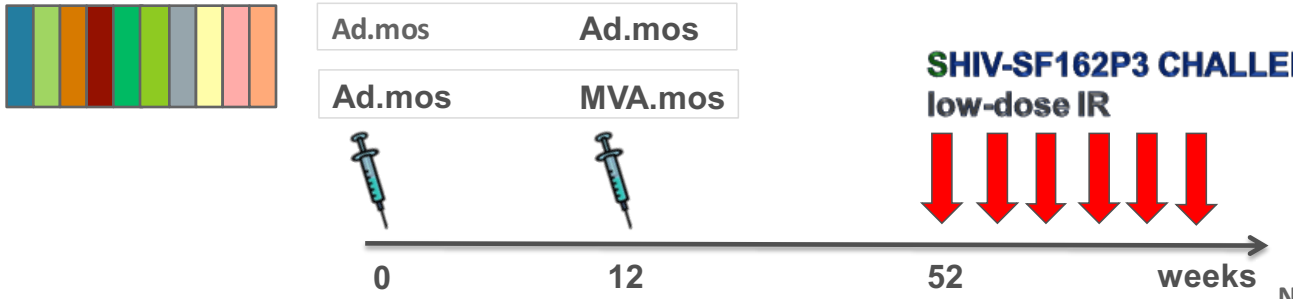
Why Mosaic Inserts?

- 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%

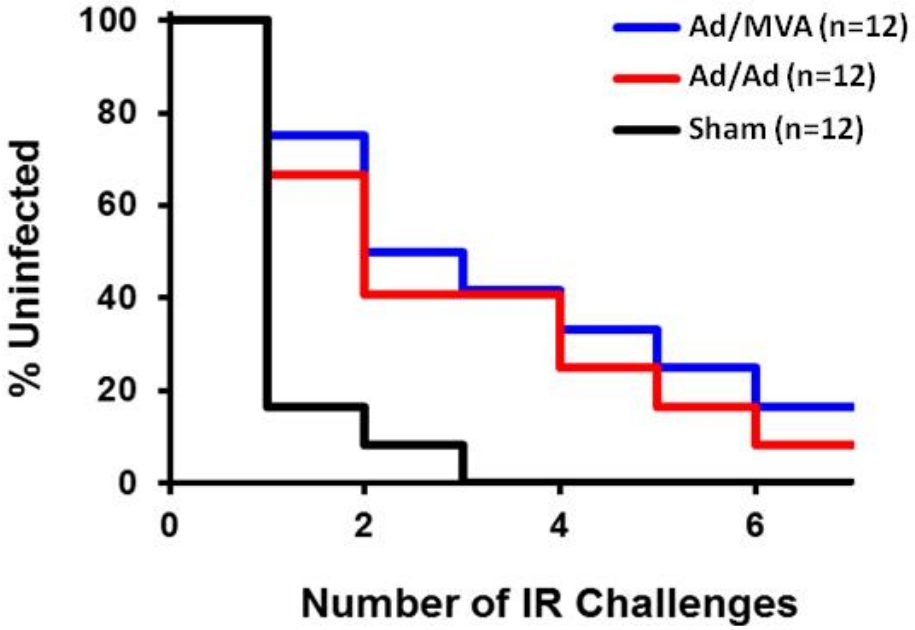
A prime-boost vaccine regimen aiming at global coverage



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



Barouch et al. Cell 2013

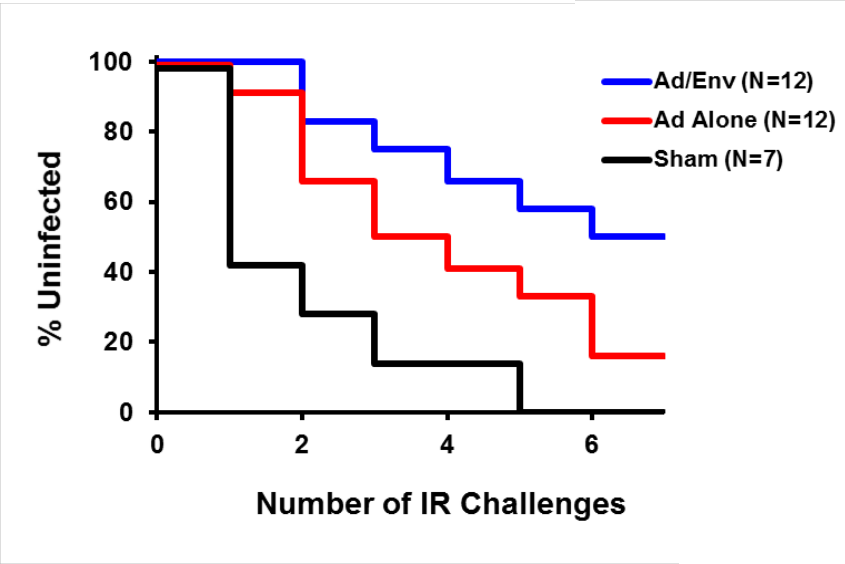
	P-Value vs Sham*	Per-Exposure Risk Reduction
Ad/MVA	0.002	90%
Ad/Ad	0.007	87%
Sham	N/A	N/A

*Cox proportional hazard model

Correlates of Protection	
Assay	P-Value
ELISA	0.00000012
ADCP	0.00030
NAb	0.00072

Protective efficacy of the Ad-based prime/GP140 boost in stringent NHP SIV and SHIV models

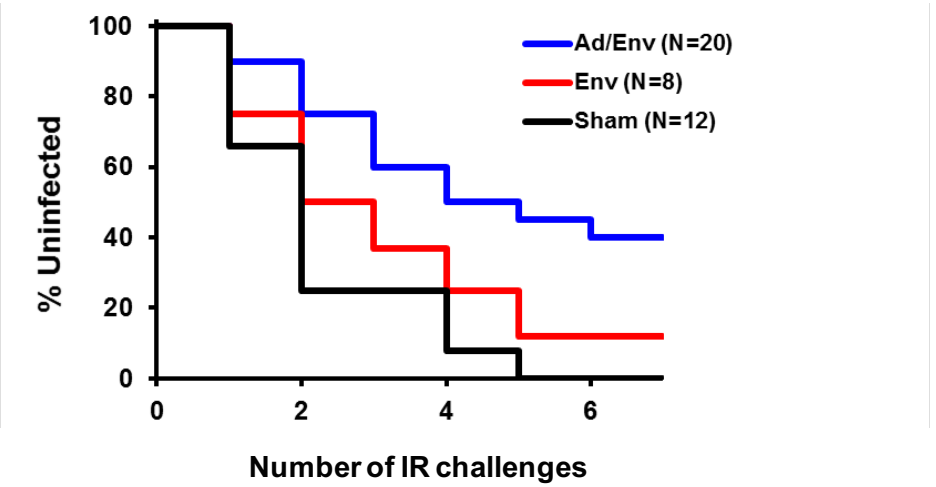
Protective efficacy of the Ad/Env SIV vaccine against SIVmac251 challenges



	Per-Exposure Risk Reduction	Full Protection after 6 challenges
Ad /Env	90%	50%
Ad Alone	75%	17%

Barouch et al, *submitted 2015*

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

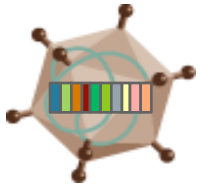


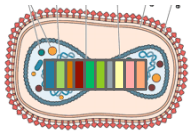
	Per-Exposure Risk Reduction	Full Protection after 6 challenges
Ad /Env	79%	40%
Env Alone	49%	12%

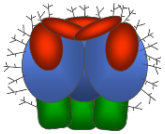
Barouch et al, *submitted 2015*

Overall Early Clinical Development Plan

Target vaccine regimen will have 2 or 3 components


Adeno

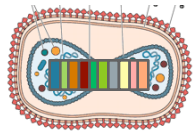

MVA


Protein

- 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

HIV-V-A002 - Trial design

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.

15 HIV neg (unvaccinated) and 25 previously vaccinated with Adv26

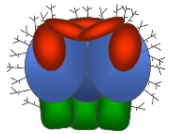
	Population	N	Week 0	Week 12
1	Healthy	12	**MVA mos**	**MVA mos**
2	Healthy	3	**placebo**	**placebo**
3	Previously in Ad26.ENVA.01	8-20	**MVA mos**	**MVA mos**
4	Previously in Ad26.ENVA.01	2-5	**Placebo**	**Placebo**

40 weeks → **Follow-up**

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

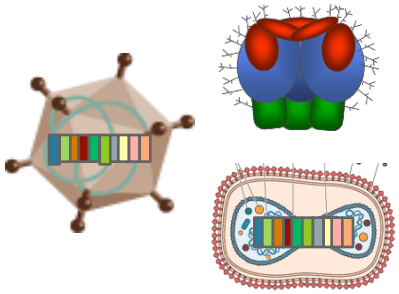
Grp	n	Week 0	Week 4	Week 8	Week 12
1	10	gp140 50 mcg	gp140 50 mcg	Follow-up	
2	10	gp140 50 mcg/adj	gp140 50 mcg/adj	Follow-up	
3	5	placebo	placebo	Follow-up	
4	10		gp140 250 mcg	gp140 250 mcg	Follow-up
5	10		gp140 250 mcg/adj	gp140 250 mcg/adj	Follow-up
6	5		placebo	placebo	Follow-up

Adjuvant (adj)=aluminum phosphate

All subjects followed to Week 48

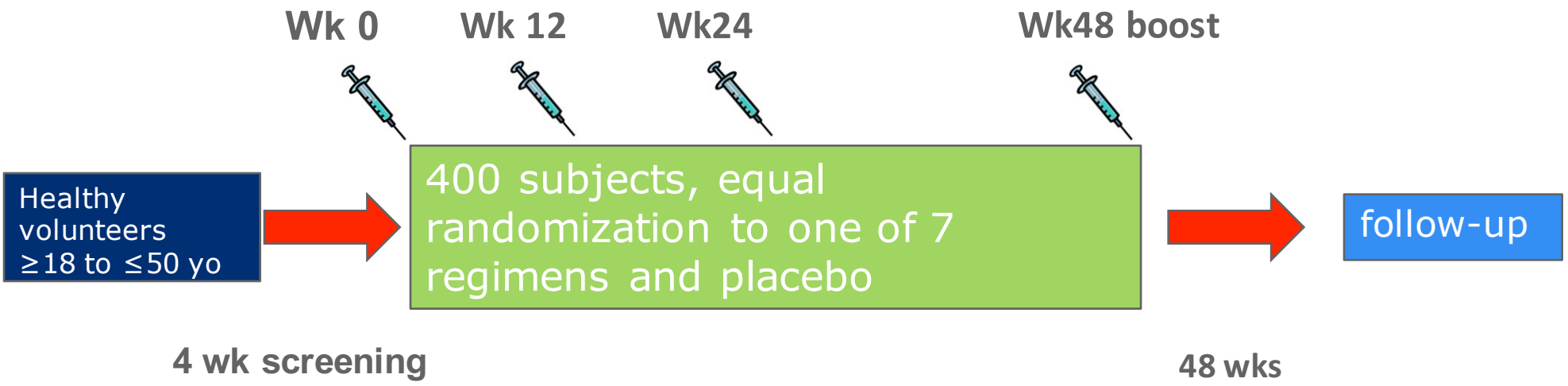
Overall Early Clinical Development Plan

- 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



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/APPROACH: Treatment Groups

Group	N	Week 0 (baseline)	Week 12	Week 24	Week 48
Group 1	50	Ad26.Mos.HIV	Ad26.Mos.HIV	Ad26.Mos.HIV + gp140 DP (250 µg+adjuvant)	Ad26.Mos.HIV + gp140 DP (250 µg+adjuvant)
Group 2	50	Ad26.Mos.HIV	Ad26.Mos.HIV	Ad26.Mos.HIV + gp140 DP (50 µg+adjuvant)	Ad26.Mos.HIV + gp140 DP (50 µg+adjuvant)
Group 3	50	Ad26.Mos.HIV	Ad26.Mos.HIV	Ad26.Mos.HIV + Placebo	Ad26.Mos.HIV + Placebo
Group 4	50	Ad26.Mos.HIV	Ad26.Mos.HIV	MVA-Mosaic + gp140 DP (250 µg+adjuvant)	MVA-Mosaic + gp140 DP (250 µg+adjuvant)
Group 5	50	Ad26.Mos.HIV	Ad26.Mos.HIV	MVA-Mosaic + gp140 DP (50 µg+adjuvant)	MVA-Mosaic + gp140 DP (50 µg+adjuvant)
Group 6	50	Ad26.Mos.HIV	Ad26.Mos.HIV	MVA-Mosaic + Placebo	MVA-Mosaic + Placebo
Group 7	50	Ad26.Mos.HIV	Ad26.Mos.HIV	gp140 DP (250 µg+adjuvant) + Placebo	gp140 DP (250 µg+adjuvant) + Placebo
Group 8	50	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

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:

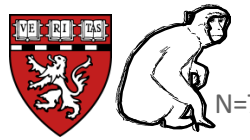
Optimal Research (ABL)

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

Collaboration with Prof. Dan Barouch, BIDMC, Harvard



Gr (#)	0 Mo (2Dec13)	3 Mo (24Feb 2014)	6 Mo (19May 2014)	12 Mo (1Dec 2014)
I (n=12)	$Ad26_{mos}$	$Ad26_{mos}$	$Ad26_{mos}$ + protein	$Ad26_{mos}$ + protein
II (n=12)	$Ad26_{mos}$	$Ad26_{mos}$	protein	protein
III (n=12)	$Ad26_{mos}$	$Ad26_{mos}$	MVA_{mos} + protein	MVA_{mos} + protein
IV (n=12)	$Ad26_{mos}$	$Ad26_{mos}$	MVA_{mos}	MVA_{mos}
V (n=12)	Placebo	Placebo	Placebo	Placebo
VI (n=12)	$Ad26_{mos}$	$Ad26_{mos}$	$Ad26_{mos}$	$Ad26_{mos}$

- $Ad26_{mos}$ = 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

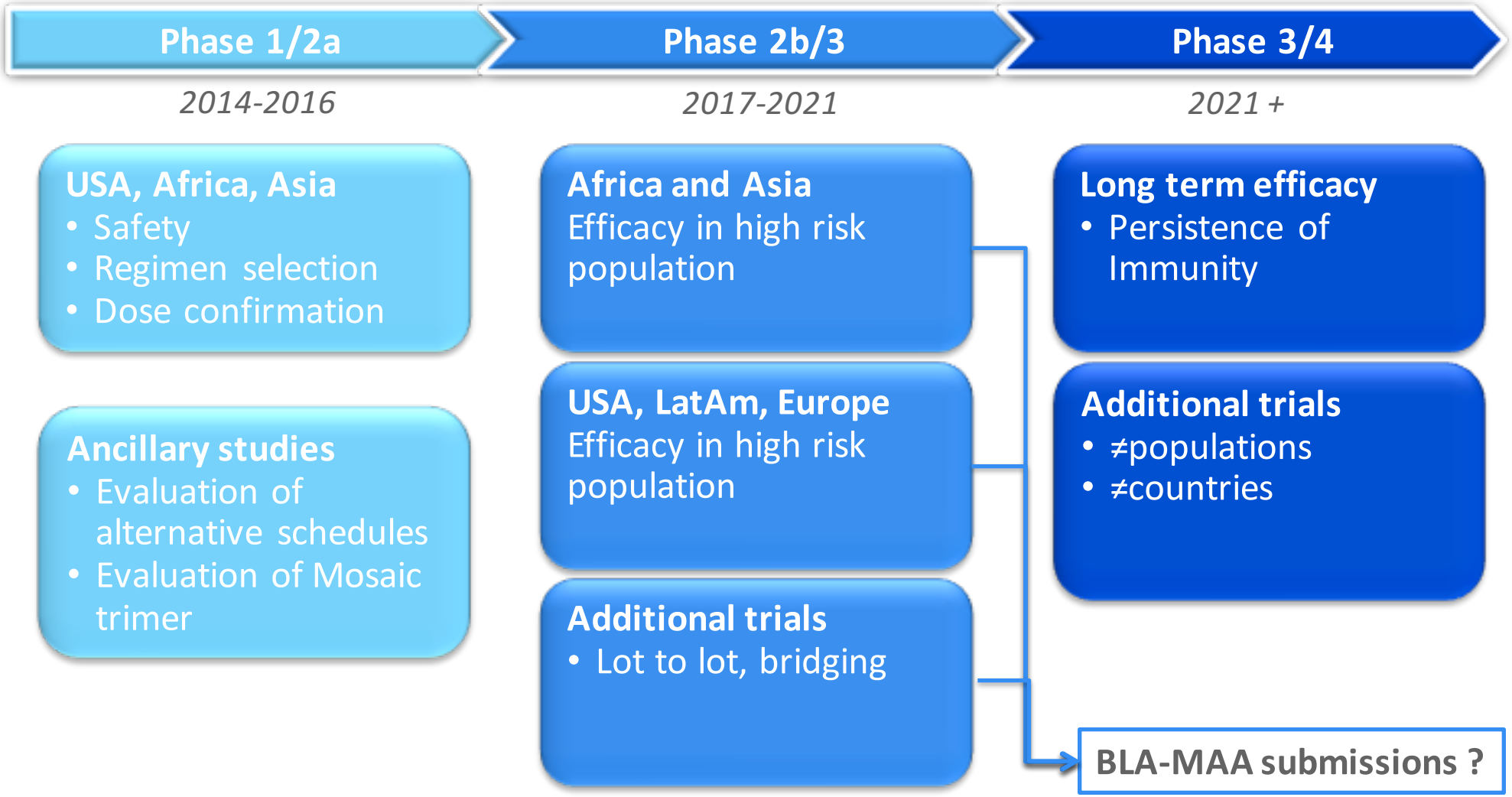
- **Two Efficacy Trials**

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



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
- DAIDS, NIAID, NIH, HVTN
  - Michael Pensiero
  - Mary Marovich
  - Larry Corey
  - Bernie Moss
- Janssen
  - Iedo Beeksma
  - Jenny Hendriks
  - Ad Knaapen
  - Lorenz Scheppler
  - Frank Tomaka
  - Danielle van Manen
  - Frank Wegmann
  - Mo Weijtens
  - Hanneke Schuitemaker
  - Maria Grazia Pau