Trials & Tribulations: on the way to cure: where do HIV Vaccines fit in?

Glenda Gray

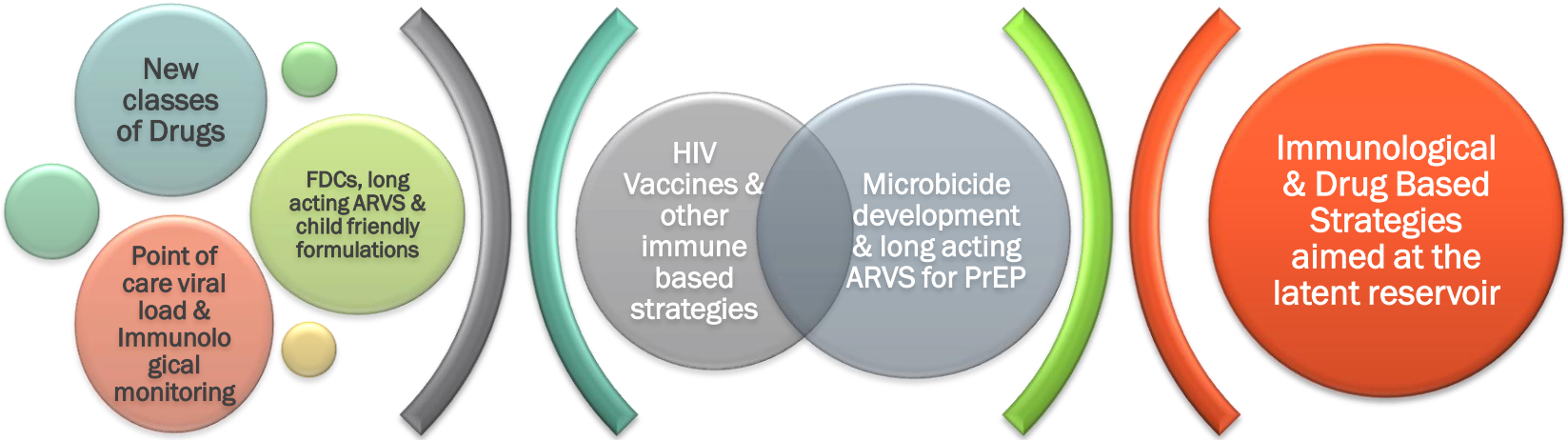
SA HIV Clinicians Society Conference 2016

13-16 April, 2016

Scope

- Rationale for an HIV vaccine
- RV144 study in Thailand
- P5 programme in RSA
- Janssen HIV vaccine strategy
- VRC01 neutralising antibody study

What we need to end AIDS?



Innovations in the management of HIV that will impact on community viral load and infectiousness: prevention of secondary transmission

Innovations in the Prevention of Sexual Acquisition that will be required when secondary transmission is not averted

HIV Cure: the ultimate control of the HIV epidemic will be in the elimination of viremia in those infected

Gray, G et al Plos Biol, in press 2015

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

FEBRUARY 6, 2014

Ending AIDS — Is an HIV Vaccine Necessary?

Anthony S. Fauci, M.D., and Hilary D. Marston, M.D., M.P.H.

In the past decade, according to the 2013 Global Report of the Joint United Nations Program on HIV/AIDS (UNAIDS), the numbers of AIDS-related deaths and new human immunodeficiency virus (HIV) infections have fallen by about one third from their peaks — accomplishments made possible by the accelerated implementation of effective prevention and treatment tools.

Of particular note, the scale-up of antiretroviral therapy (ART) averted 5.4 million deaths in low- and middle-income countries between 1995 and 2012. HIV prevention efforts have expanded from a narrow agenda of providing condoms and clean needles to use of a comprehensive toolkit of preventive interventions that have had a profoundly positive effect on the pandemic. For example, improved approaches to the prevention of mother-to-child transmission have averted the deaths of more than 1 million children worldwide. The rate of male acquisition of HIV can be diminished by two thirds through voluntary medical male circumcision. Preexposure prophylaxis with antiretroviral medication, when adhered to, significantly reduces the risk of HIV infection. Finally,

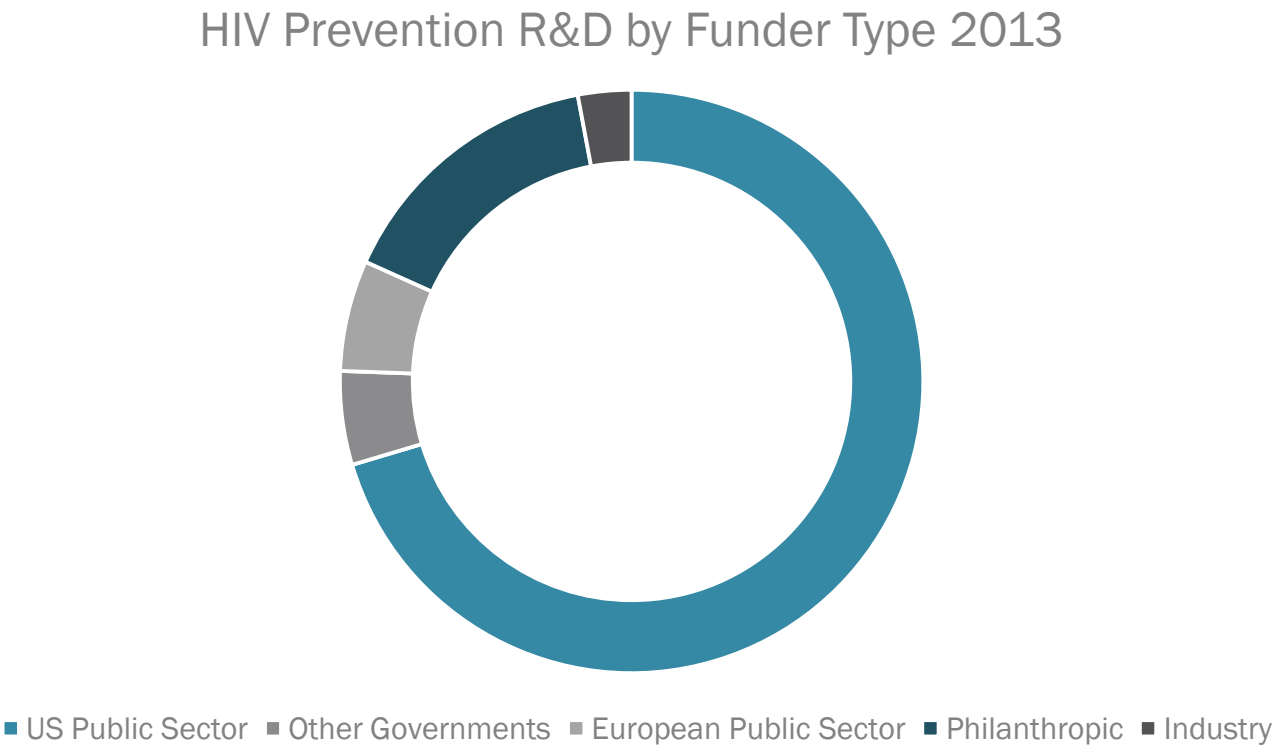
"Ultimately, we believe, the only guarantee of a sustained end of the AIDS pandemic lies in a combination of non-vaccine prevention methods and the development and deployment of a safe and effective HIV vaccine."

Why so little interest?

- **Scientific:** highly variable virus that integrates into host genome, rapidly establishing latency, evading both humoral & cellular responses

Why so little interest?

- Limited pharmaceutical support

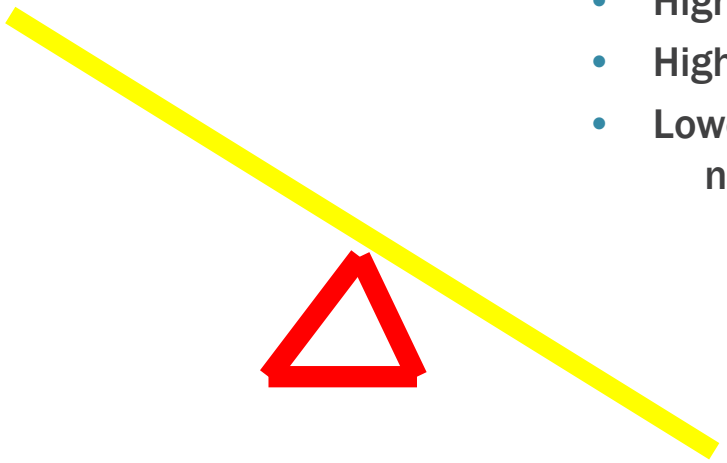


Donaldson E, et al, HIVR4P 2014

Imbalance Between Societal Value and Private Sector Economic Value for Vaccines

Societal Valuation

- Greatest cost savings of any medical technology
- Greatest societal benefit regarding reducing effects of an illness



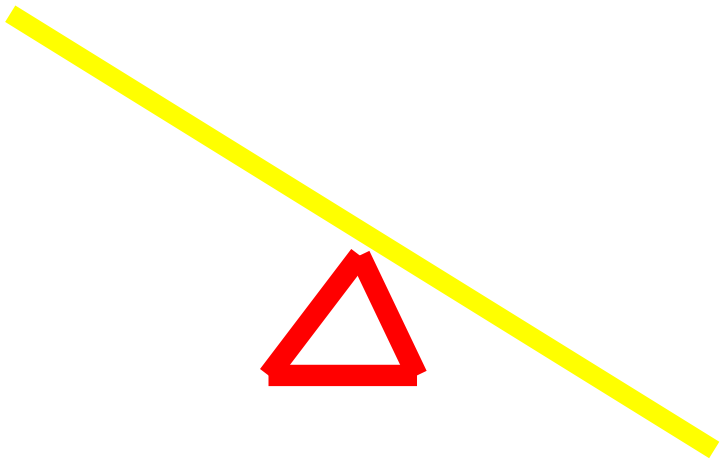
Economic Valuation

- Highest hurdle for safety of any pharmaceutical product
- Highest hurdle for effectiveness of any pharmaceutical product
- High manufacturing costs
- High liability
- Lowest profit margins of any novel pharmaceutical

Imbalance Between Societal Value and Private Sector Economic Value for a HIV vaccine

Societal Valuation

- **Only effective way to control HIV**
- **Every country wants a HIV vaccine especially LMIC**
- **Even the CIA want an HIV vaccine!**

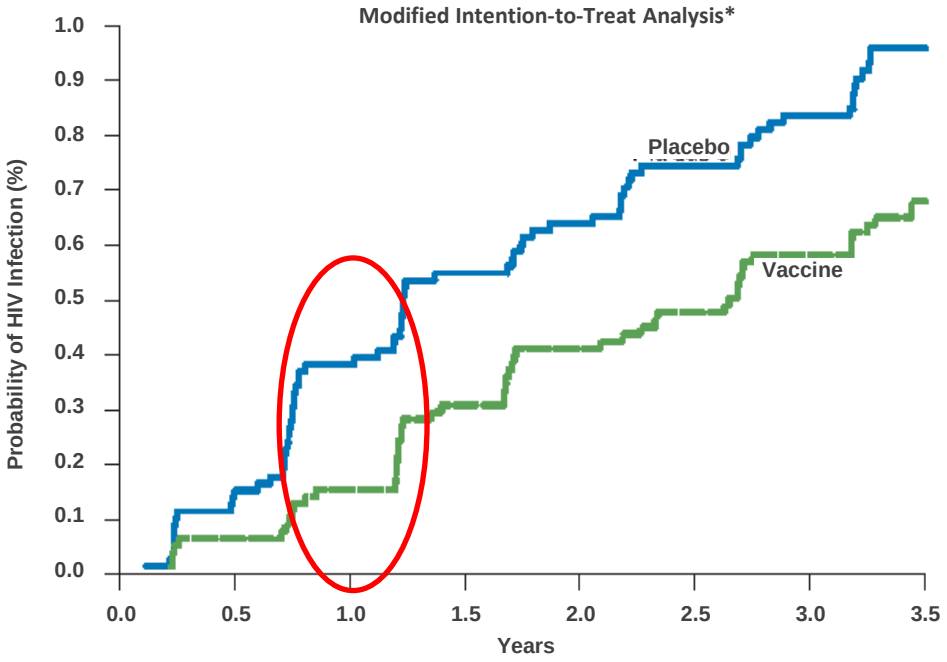


Economic Valuation

- Multiple commercial failures already
- High manufacturing costs
- High liability
- Tiered pricing unlikely to cover the commercial costs
- If effective, likely to be distributed as a commodity
- No assurance platform technology will lead to other money making uses
- Bottom Line
  - Relying on push or pull mechanisms to effectively provide resources for the private sector to devote a full scale assault on this issue is nil

Study/ location	Vaccine/s	Risk Group/HIV incidence	Result
Vax003 Thailand	AIDSVAX B/E gp120 in alum	IDUs 3.4%	No VE
Vax004 US/Europe	AIDSVAX B/B gp120 in alum	MSM/high risk women 2.6%	No VE
HVTN 502 Americas	MRKAd5 HIV-1 gag/pol/nef	MSM/high risk women 3%	Halted for futility; early transient increased infection in vaccinees
HVTN 503	MRKAd5 HIV-1 gag/pol/nef	Heterosexual men & women 3.7%	No VE; late increased HIV infection in unblended male vaccinees
RV144 Thailand	ALVAC-HIV vCP1521, AIDSVAX B/E rgp120 in alum	Heterosexual men and women with variable risk 0.28%	31.2% VE at 42/12; 60% VE @ 12/12
HVTN 505	DNA, rAD5 (A,B,C)	Circumcised MSM Ad5 neg 1.8%	Halted at interim analysis for futility

Thai Trial (RV144) Primary Results



Vaccine efficacy decreases over time

	Vaccine		Placebo		
Time (mo)	Cumulative Infections	% HIV-1 infection rate (95% CI)	Cumulative Infections	% HIV-1 infection rate (95% CI)	Vaccine Efficacy (%)
12	12	0.15 (0.07,0.24)	30	0.38 (0.24,0.52)	61
24	32	0.41 (0.27,0.55)	50	0.64 (0.46,0.82)	36
36	45	0.58 (0.41,0.75)	65	0.84 (0.63,1.04)	31
42	51	0.68 (0.49,0.87)	74	0.96 (0.74,1.18)	31

The NEW ENGLAND JOURNAL of MEDICINE

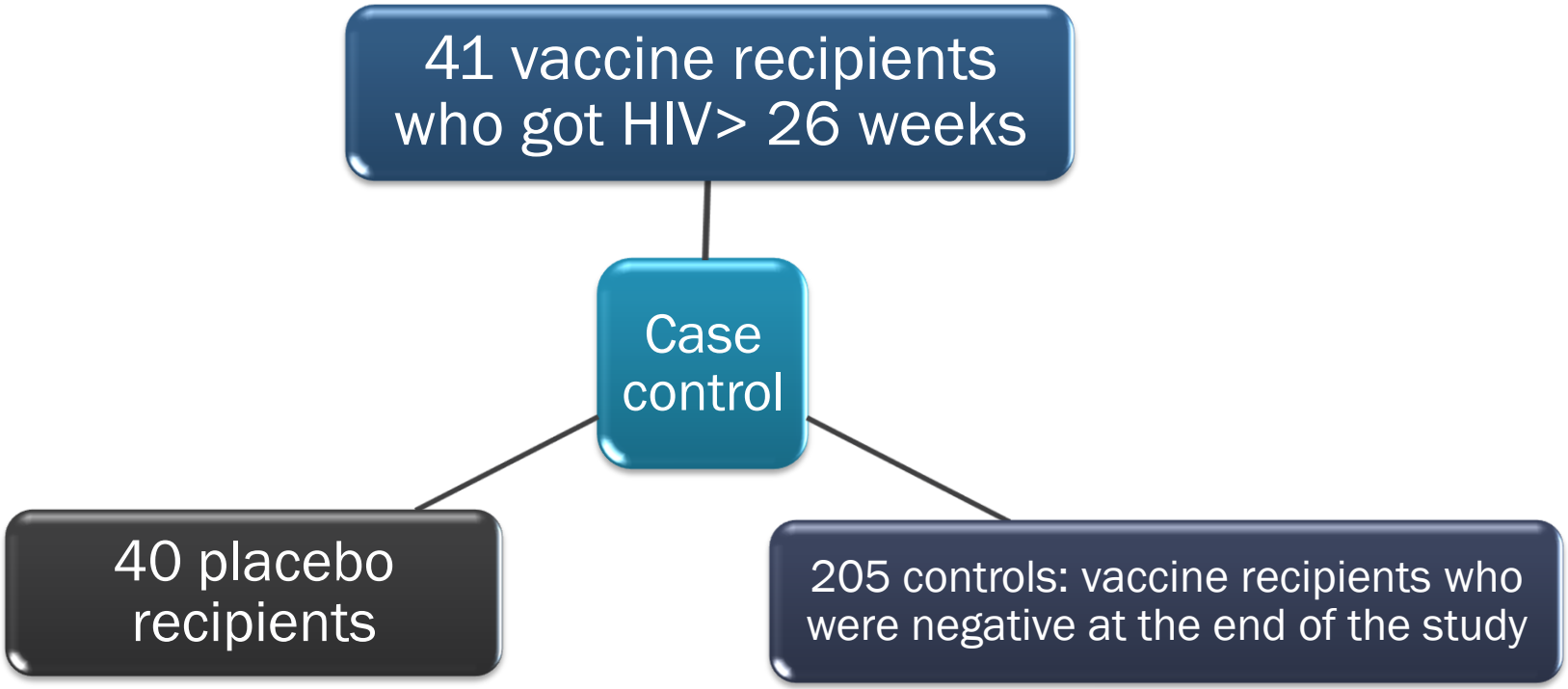
ESTABLISHED IN 1812 DECEMBER 3, 2009 VOL. 361 NO. 23

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

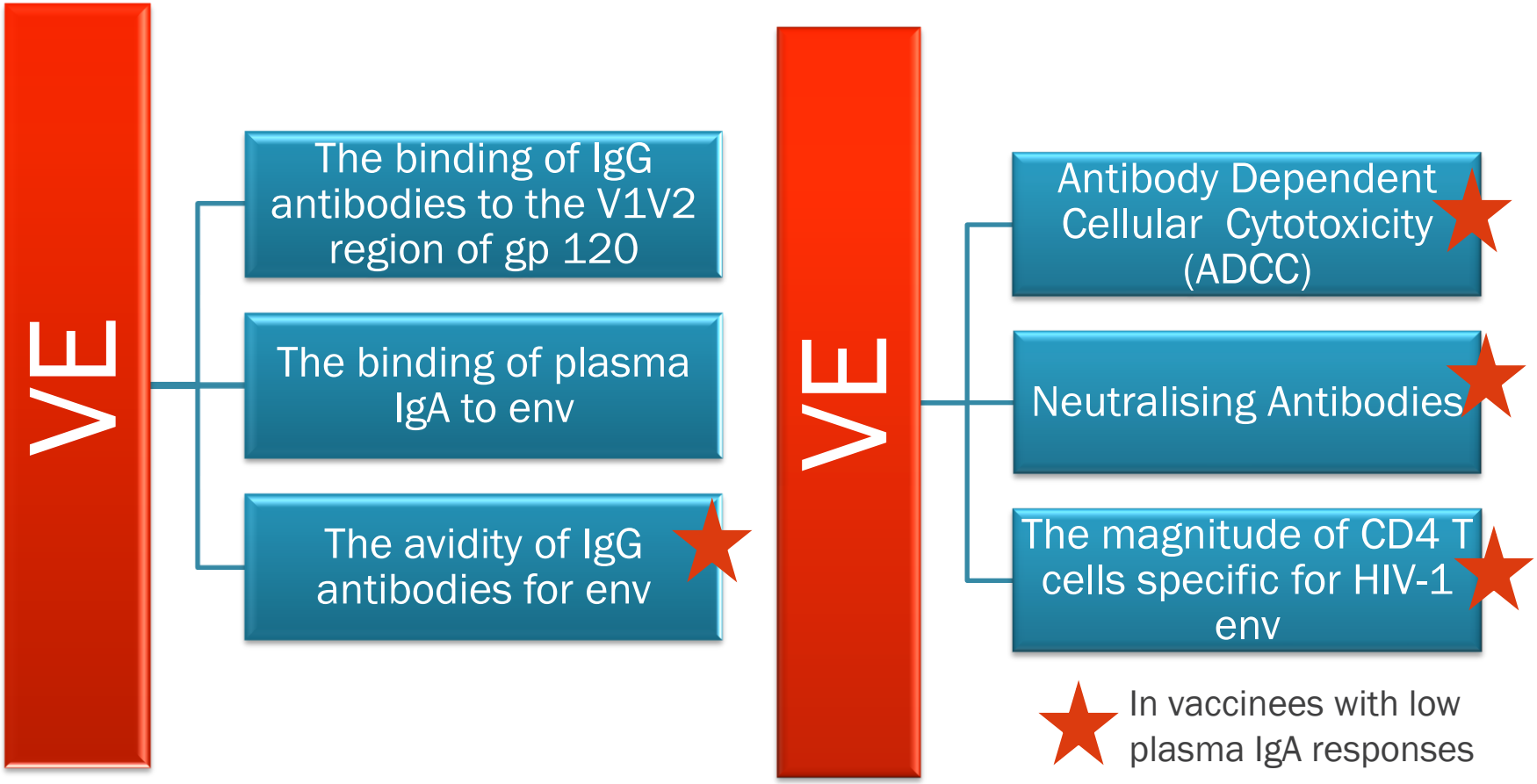
Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D. Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*

Defining the correlates of immunity in RV144

- Case Control Study
- Used specimens 2 weeks after the final vaccination

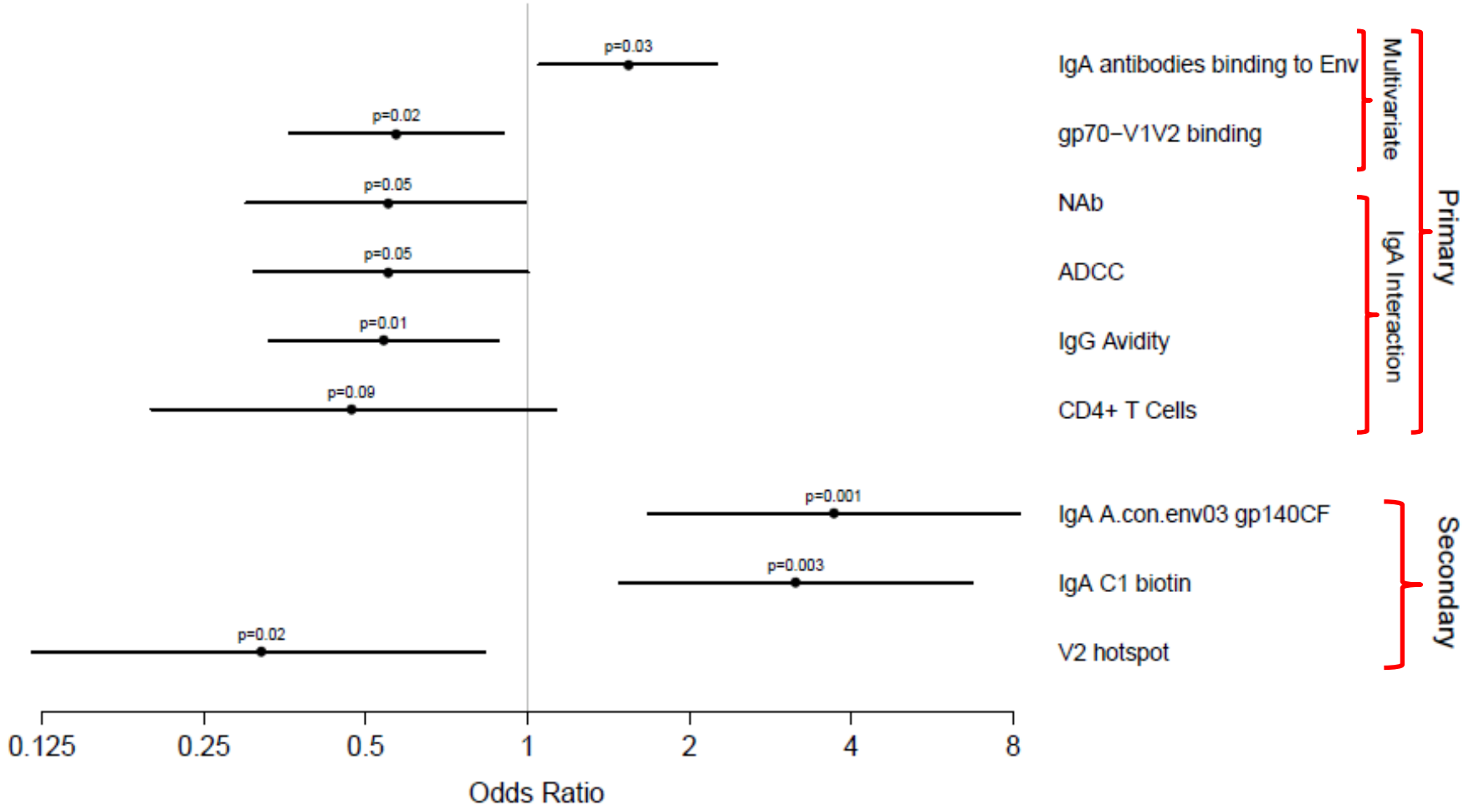


6 assays emerged to be related to Vaccine Efficacy



Correlates of Risk of HIV Infection

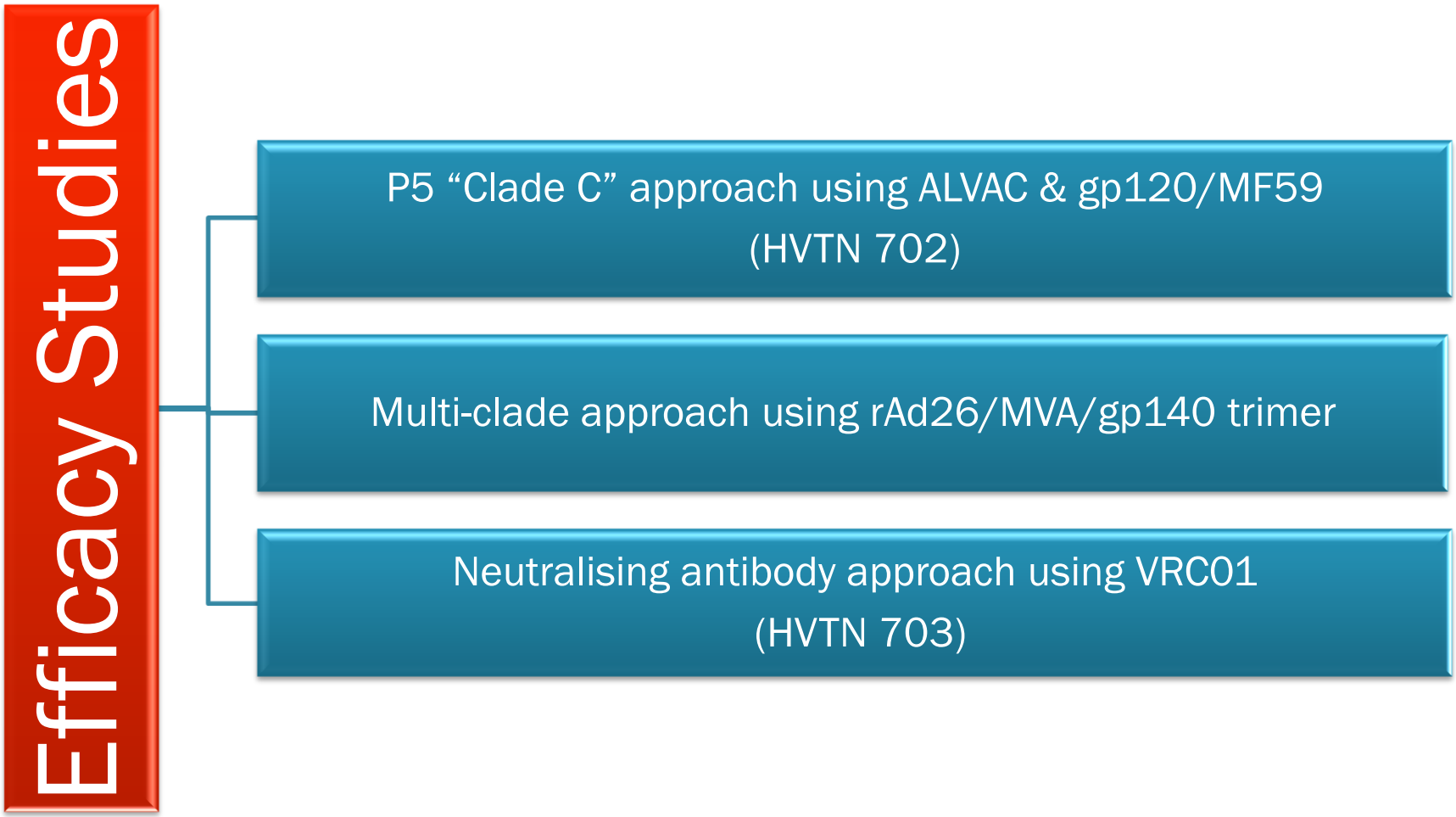
Reported in *Haynes et al, NEJM 2012*



lack of a direct correlation between neutralising antibodies and HIV-1 acquisition

Even at peak antibody response, none of the sera from the vaccinees neutralised a panel of 20 contemporaneous isolates of HIV-1 circulating in Thailand during the course of the trial…..

3 strategies to advance immunization



2010 Formation of the P5 Partnership

Purpose:

To build on RV144 data and ultimately license a pox-protein based HIV vaccine with the potential for broad and timely public health impact.

Strategy:

Continue to build public-private partnerships critical for success.

1. Work with host countries to support a flexible regulatory strategy in target populations and regions.
2. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.

NOVARTIS gsk MHRP U.S. MILITARY HIV RESEARCH PROGRAM

HIV VACCINE TRIALS NETWORK

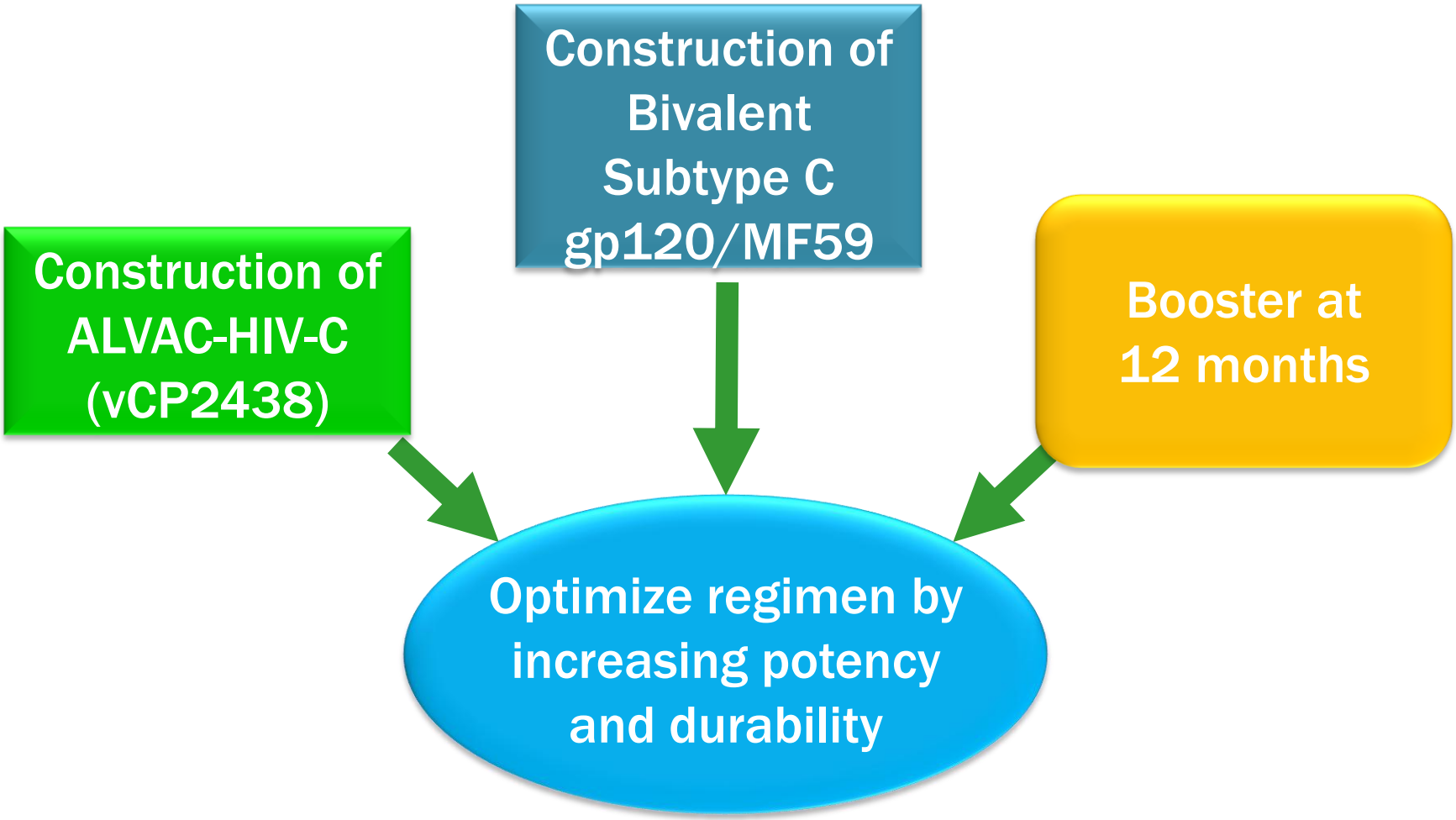
BILL & MELINDA GATES foundation

National Institute of Allergy and Infectious Diseases

SANOFI PASTEUR

MRC SOUTH AFRICA SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

The Strategy for the ALVAC/Protein Phase 3 Program



HVTN Strategy for the Phase 3 Program

HVTN 097

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

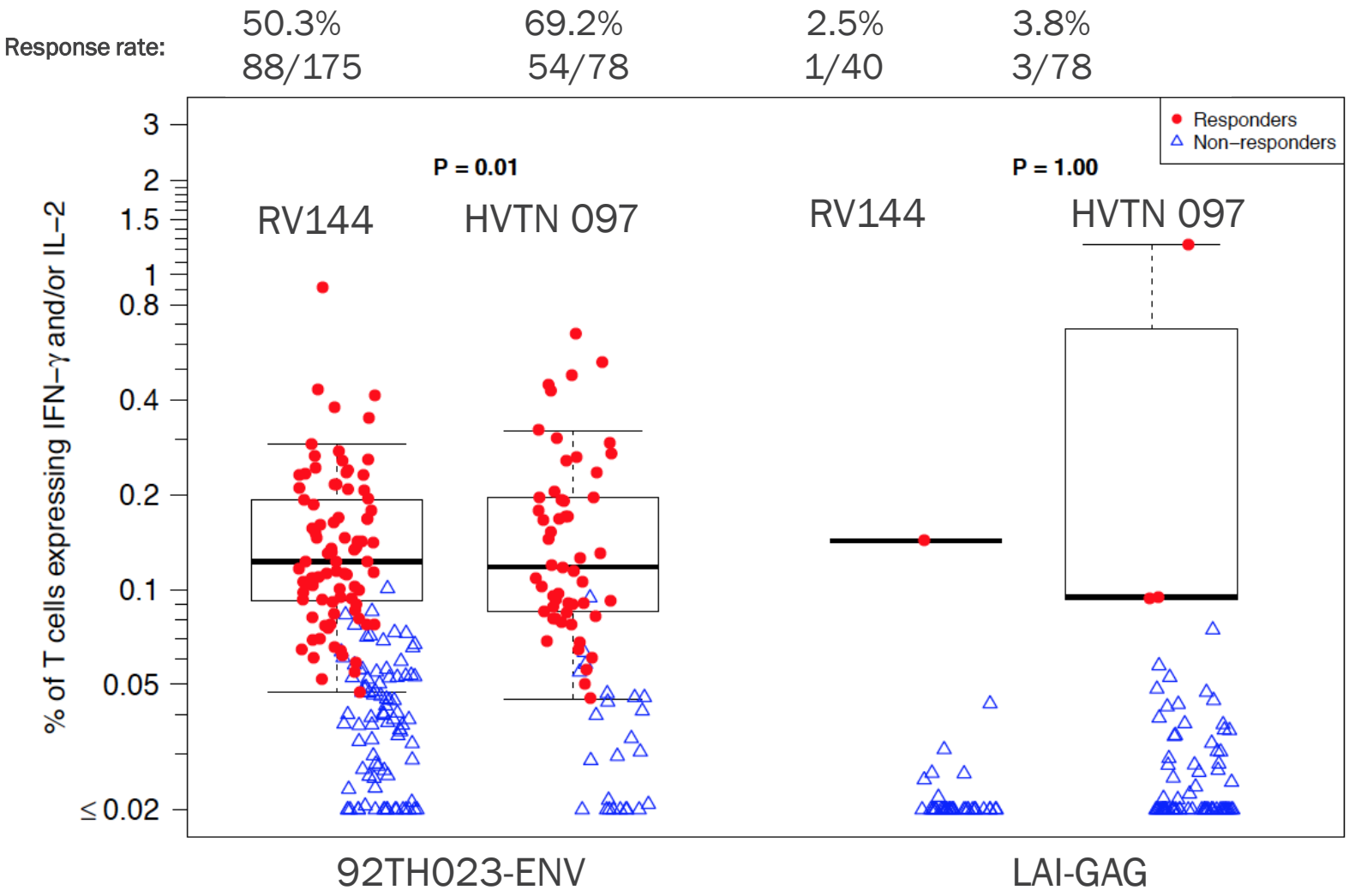
HVTN 100

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

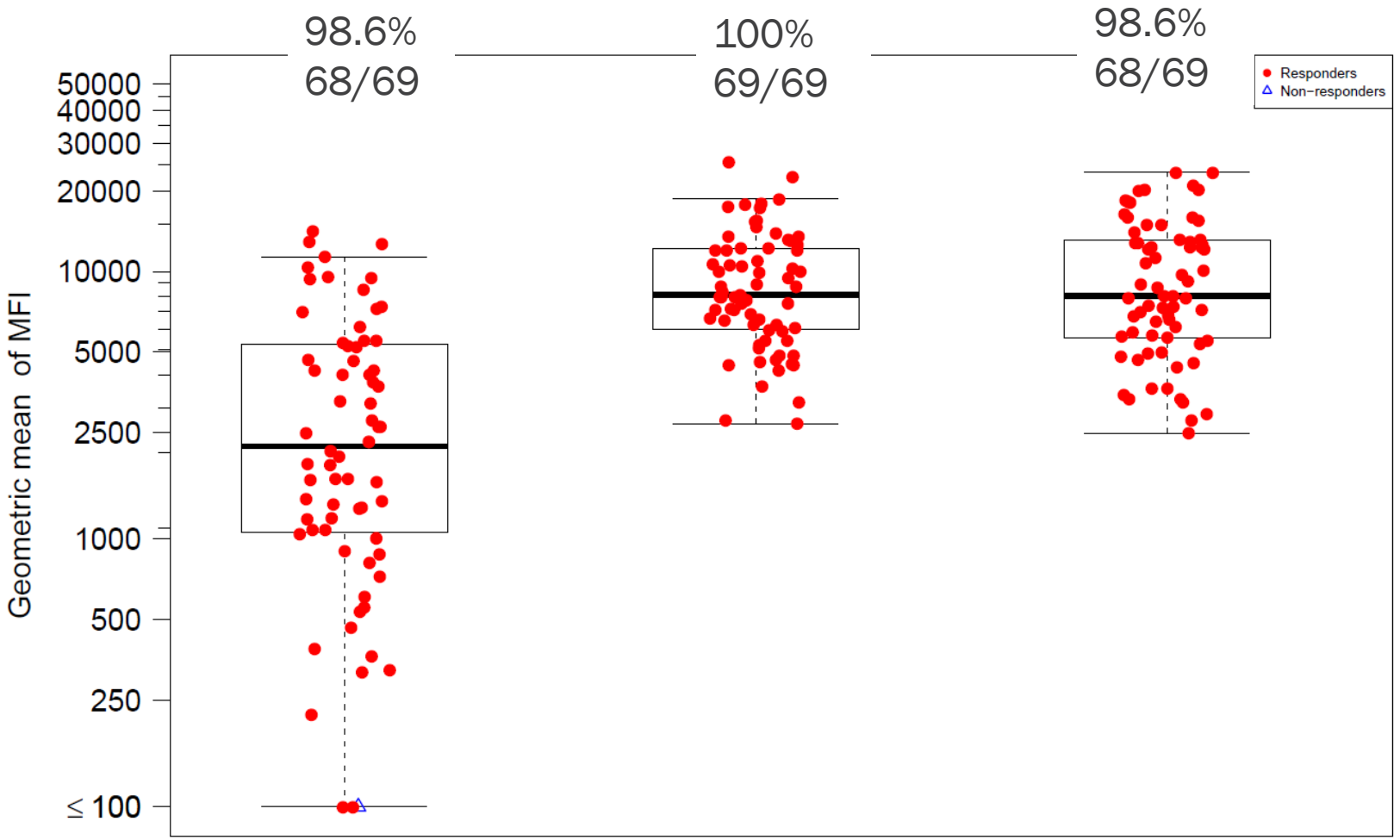
HVTN 702

A Classic phase 3 RCT assessing efficacy and safety aimed at licensure

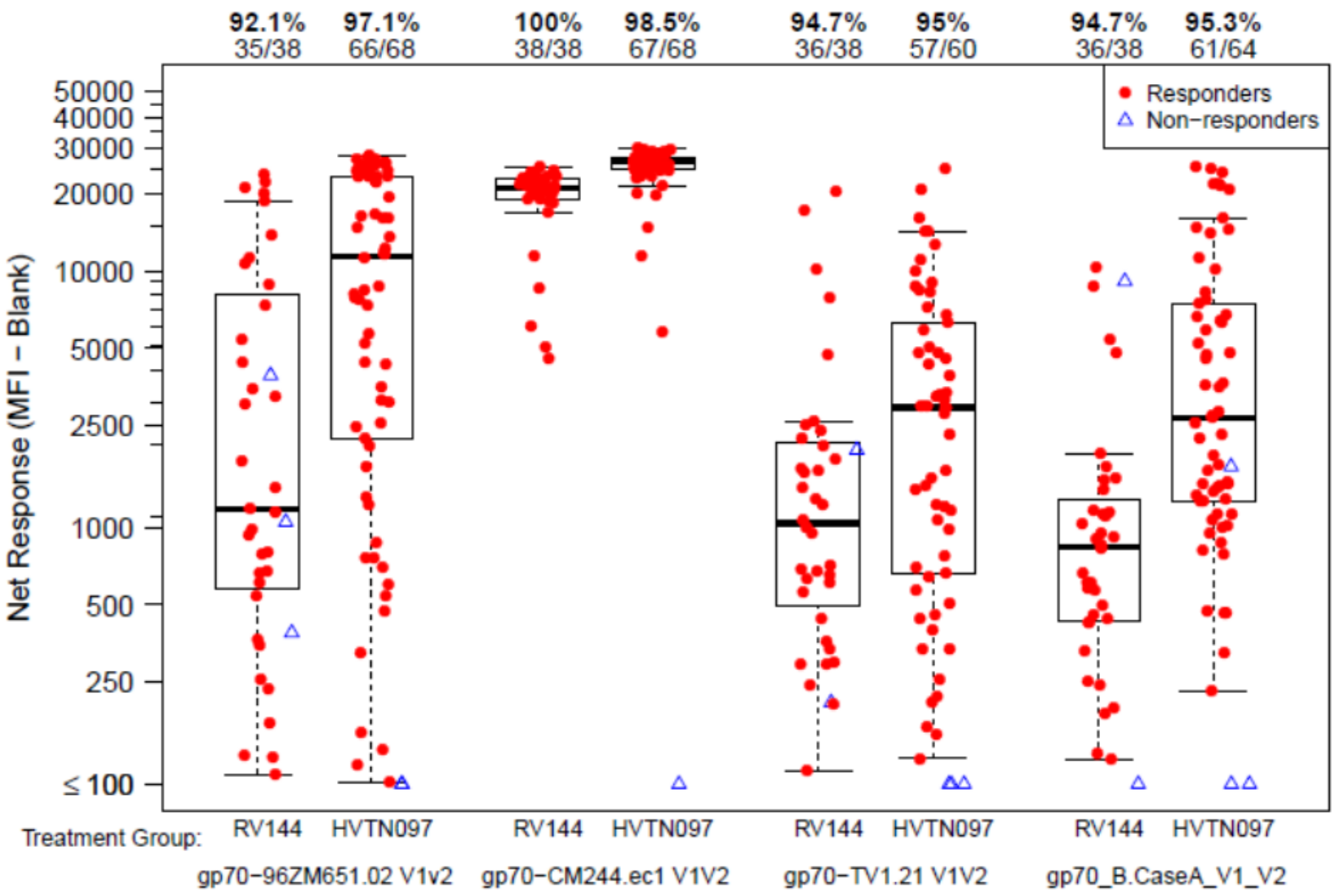
Peak CD4+ T Cell Response Rates and Magnitudes are Higher in Prevalence in 097 vs. RV144



Strong IgG Responses to V1V2, gp120 and gp140 Antigens



Comparison of V1V2 IgG responses between 097 and RV144



Summary of HVTN 097

- 097 trial indicates ALVAC vectors are equally immunogenic in RSA populations as compared to Thais.
- We hope that the manufacturing of the Envelope and gag genes separately and the bivalent mixture of vectors in combination with a bivalent clade C gp120 will provide even higher clade C immunogenicity with the proposed 702 regimen as compared to RV144.

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: HVTN 100 Must Meet all of the Following Conditions to advance to HVTN 702

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

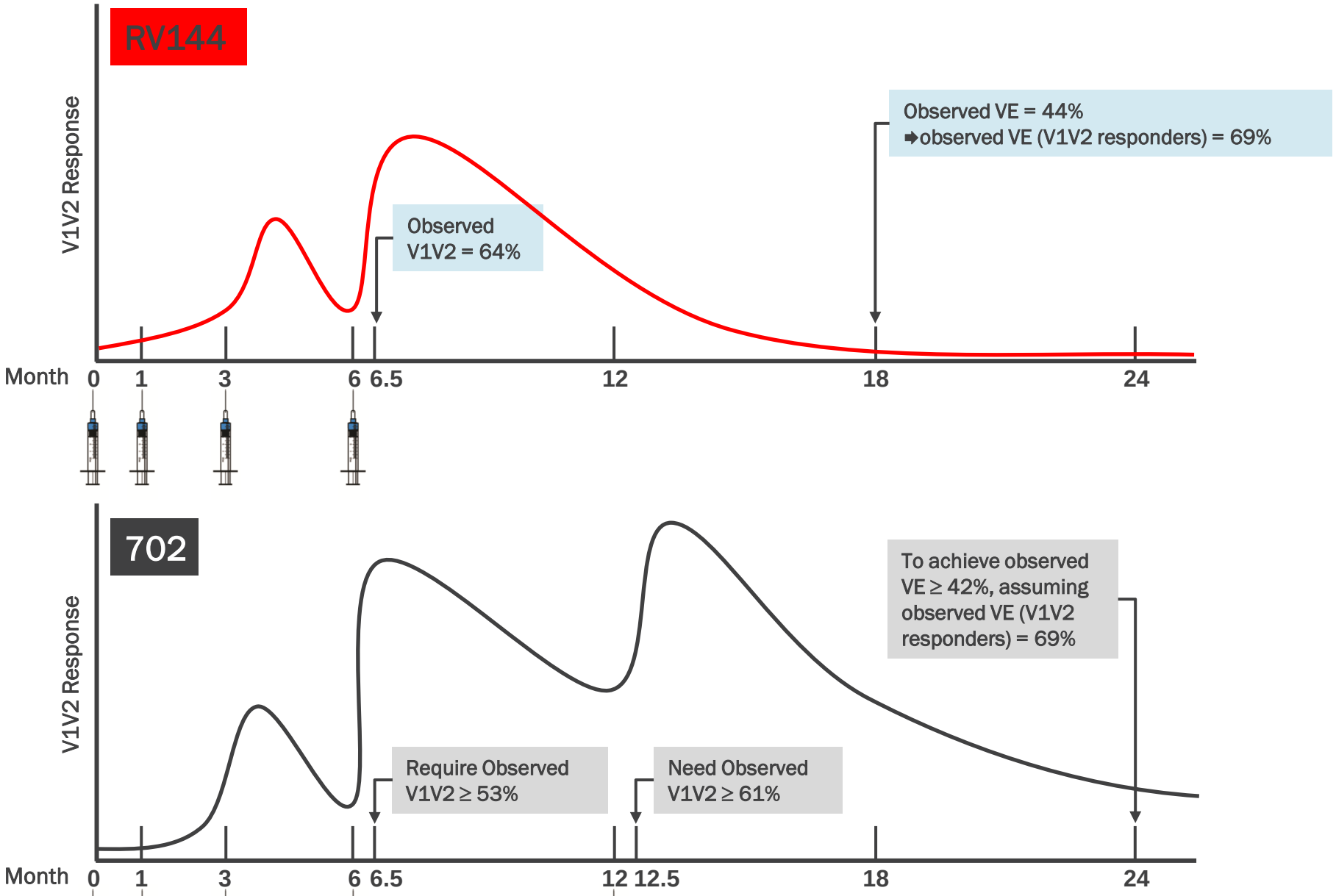
* Based on simultaneous assessment of clade C vaccinee samples vs. RV144 vaccinee samples by the same lab

Study Schema: HVTN 702

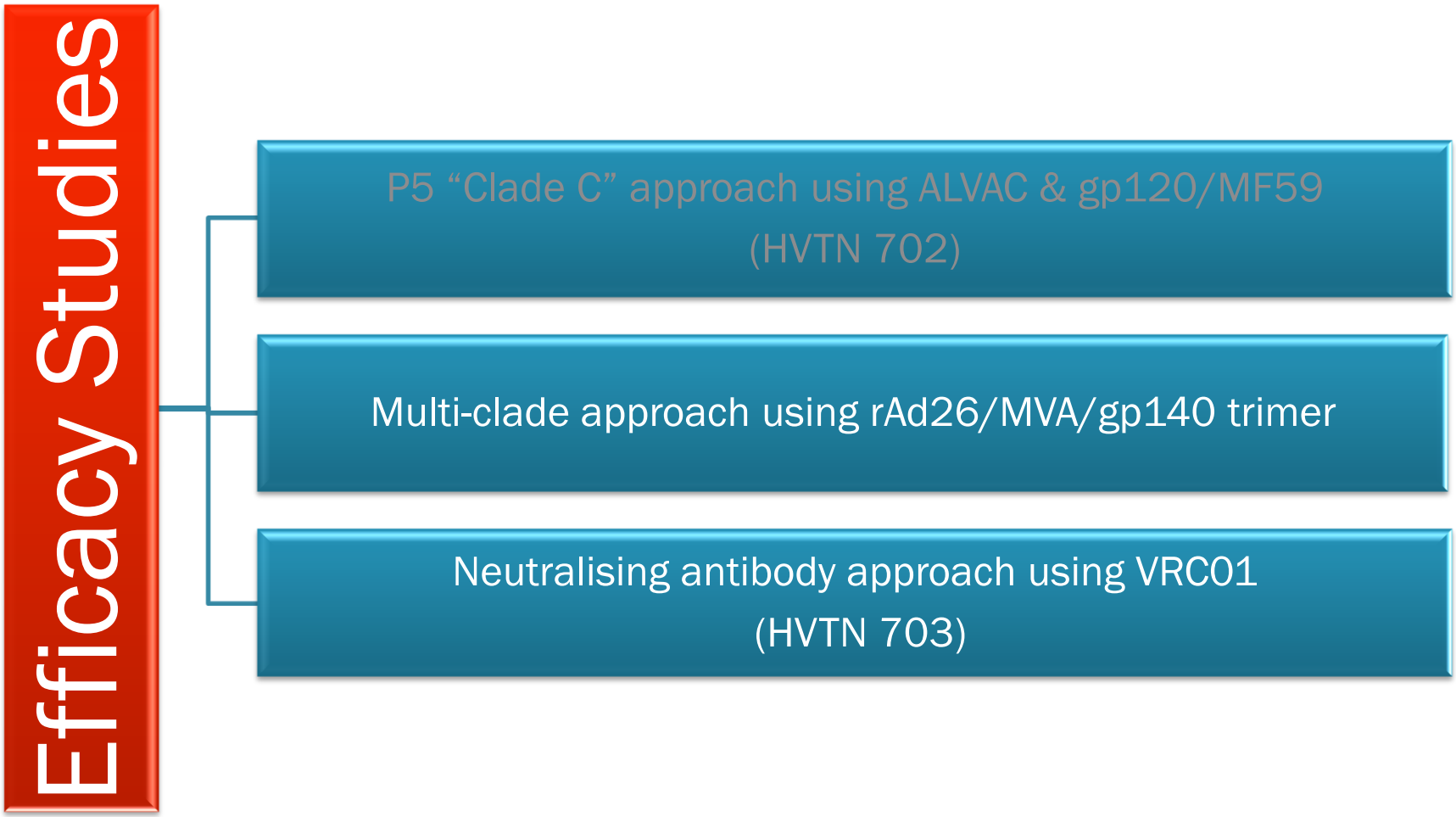
N (total 5400)	Primary Vaccine Regimen				Booster
	Month 0	Month 1	Month 3	Month 6	Month 12
2700	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®
2700	Placebo	Placebo	Placebo + Placebo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


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

3 strategies to advance immunization



HIV vaccine research program: Janssen and Collaborators

BIDMC
Harvard

MHRP

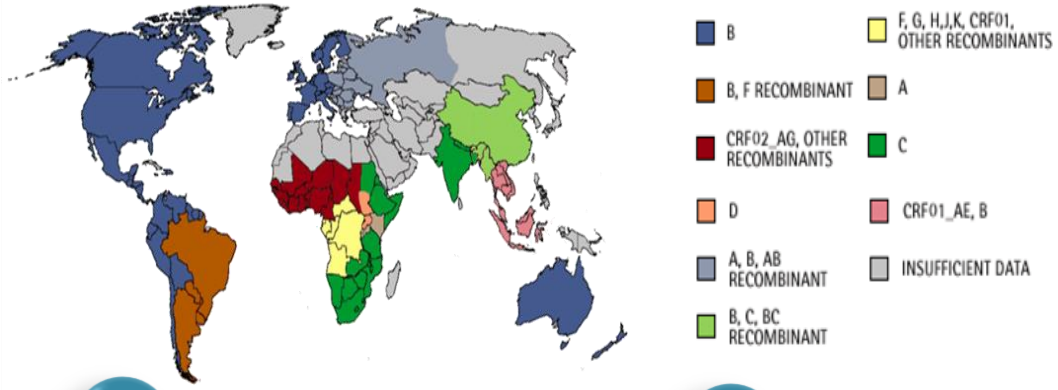
IAVI

Ragon

NIAID/HVTN

HIV Vaccine Aiming at Protection Against all Clades of HIV-1

Different HIV-1 clades dominate in different geographic regions



Adolescents (11-17 years) /Adults (18-65 years) in endemic countries and populations at risk in Western world

1

Vectors that elicit optimal immune responses

Low seroprevalent Ad26
Ad26.HIV-Gag-Pol
Ad26.HIV-Env

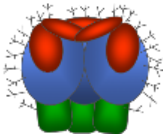
(MVA.HIV-Gag-Pol-Env)

2

Mosaic inserts for global coverage

3

Trimeric env protein for improved humoral immunity



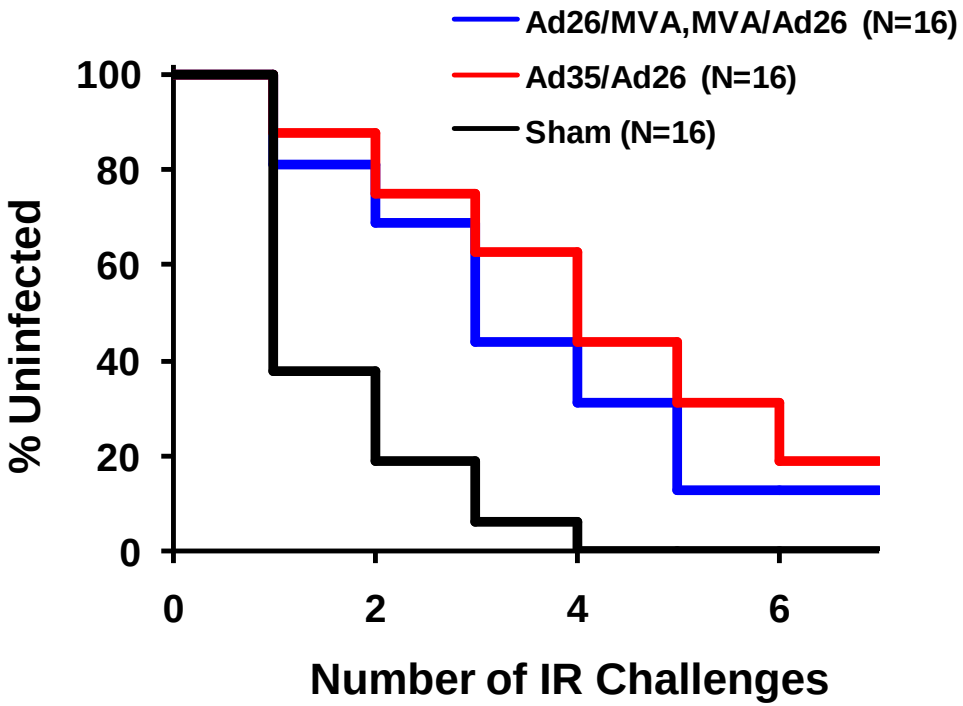
Protective Efficacy of a Global HIV-1 Mosaic Vaccine against Heterologous SHIV Challenges in Rhesus Monkeys — Cell

nature medicine
Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys
Dan H Barouch et al., 2010

Ad26/MVA and Ad35/Ad26 SIV Vaccines Partially Protect Against IR SIVmac251 Challenges in Rhesus Monkeys

76-83% reduction of per exposure acquisition risk

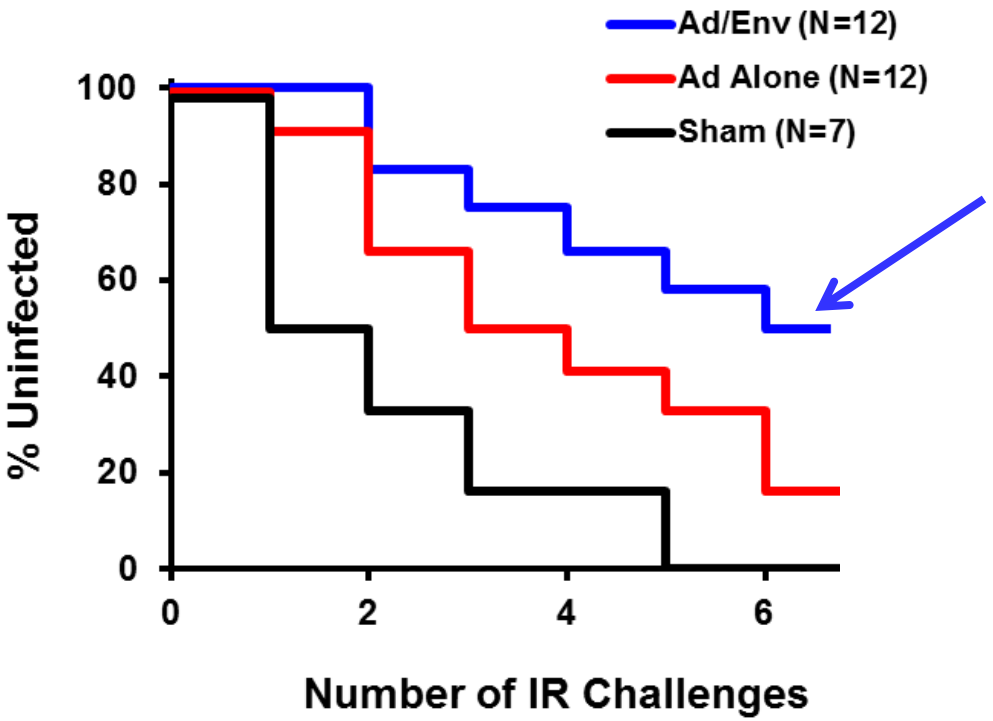
- 48 rhesus monkeys
  - Ad26/MVA, MVA/Ad26 (N=16)
  - Ad35/Ad26 (N=16)
  - Sham (N=16)
- Repetitive, intrarectal, heterologous SIVmac251 challenges
- Correlates of protection
  - ELISA P < 0.0001
  - NAb P = 0.0034



Ad26/Env SIV Vaccines Partially Protect Against IR SIVmac251 Challenges in Rhesus Monkeys

90% reduction of per exposure acquisition risk for Ad/Env (P=0.001)
50% (6 of 12) show complete protection for Ad/Env (P=0.01)

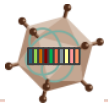
- 32 rhesus monkeys
  - Ad26/Env (N=12)
  - Ad26/Ad35 (N=12)
  - Sham (N=7)
- Repetitive, intrarectal, heterologous SIVmac251 challenges
- Correlates of protection
  - ELISA P < 0.0001
  - Ab Funct P = 0.004
  - NAb P = NS



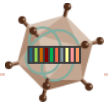
A prime-boost vaccine regimen aiming at global coverage

Prime

Ad26 Mosaic vectors
gag-pol-env

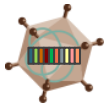


Ad26 Mosaic vectors
gag-pol-env



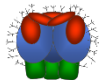
Boost

Ad26 Mosaic vectors
gag-pol-env



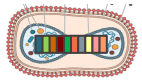
+/-

Soluble trimer gp140 env protein



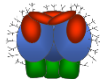
or

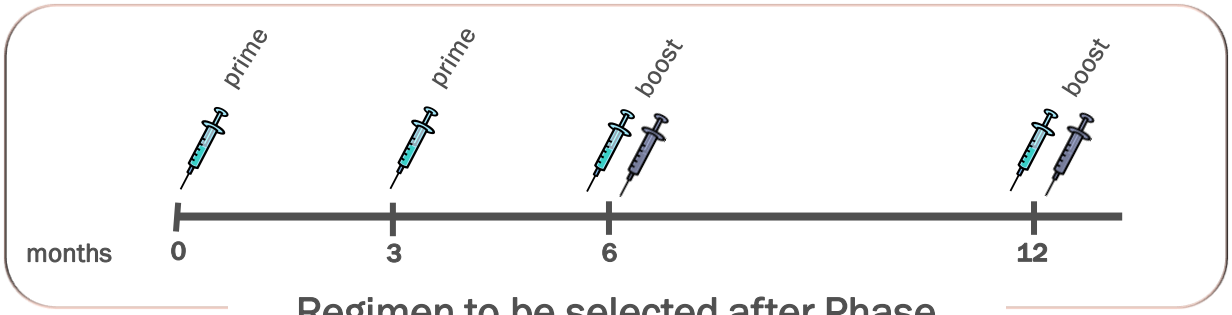
MVA Mosaic vectors
gag-pol-env



+/-

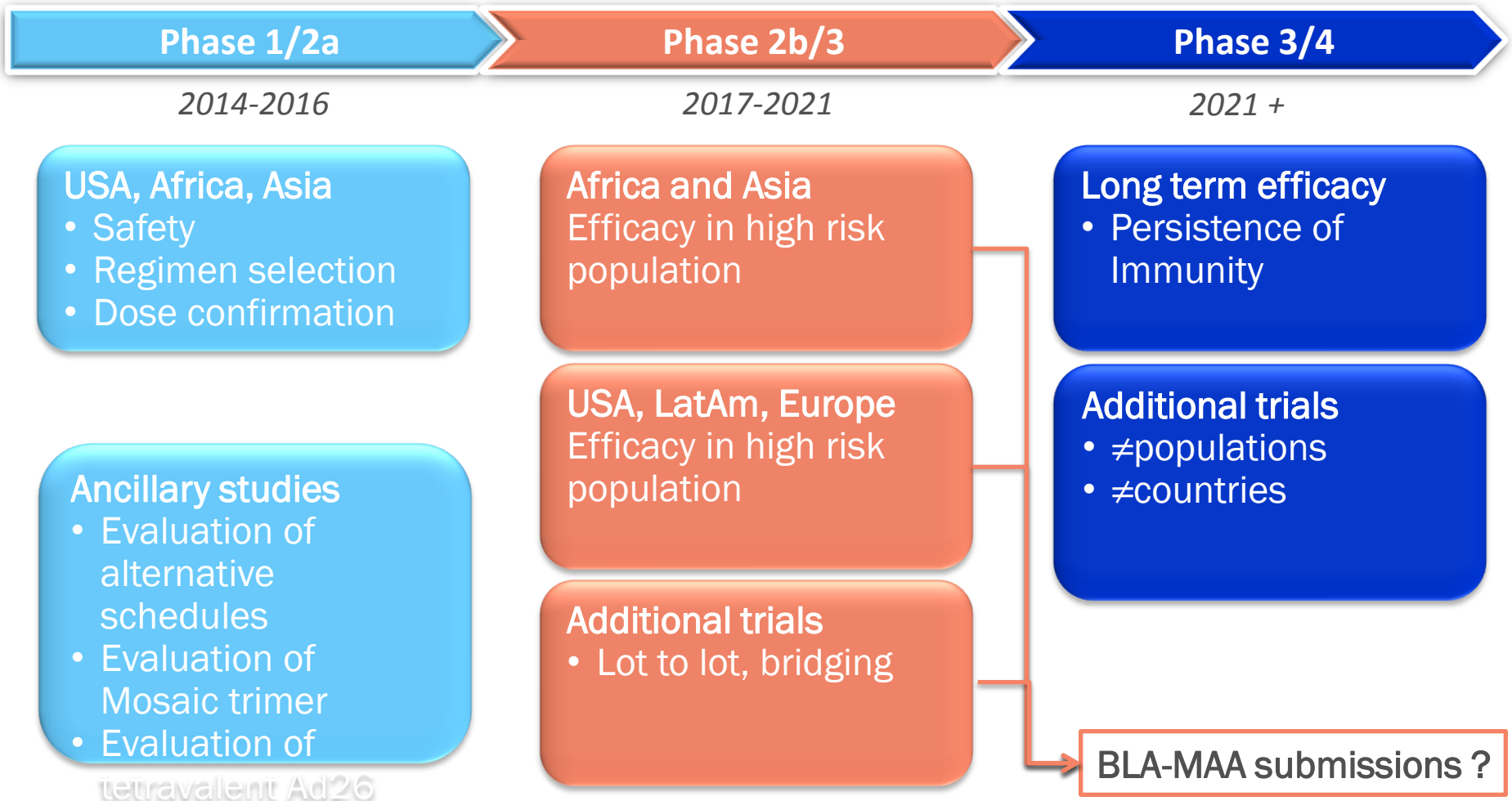
Soluble trimer gp140 env protein



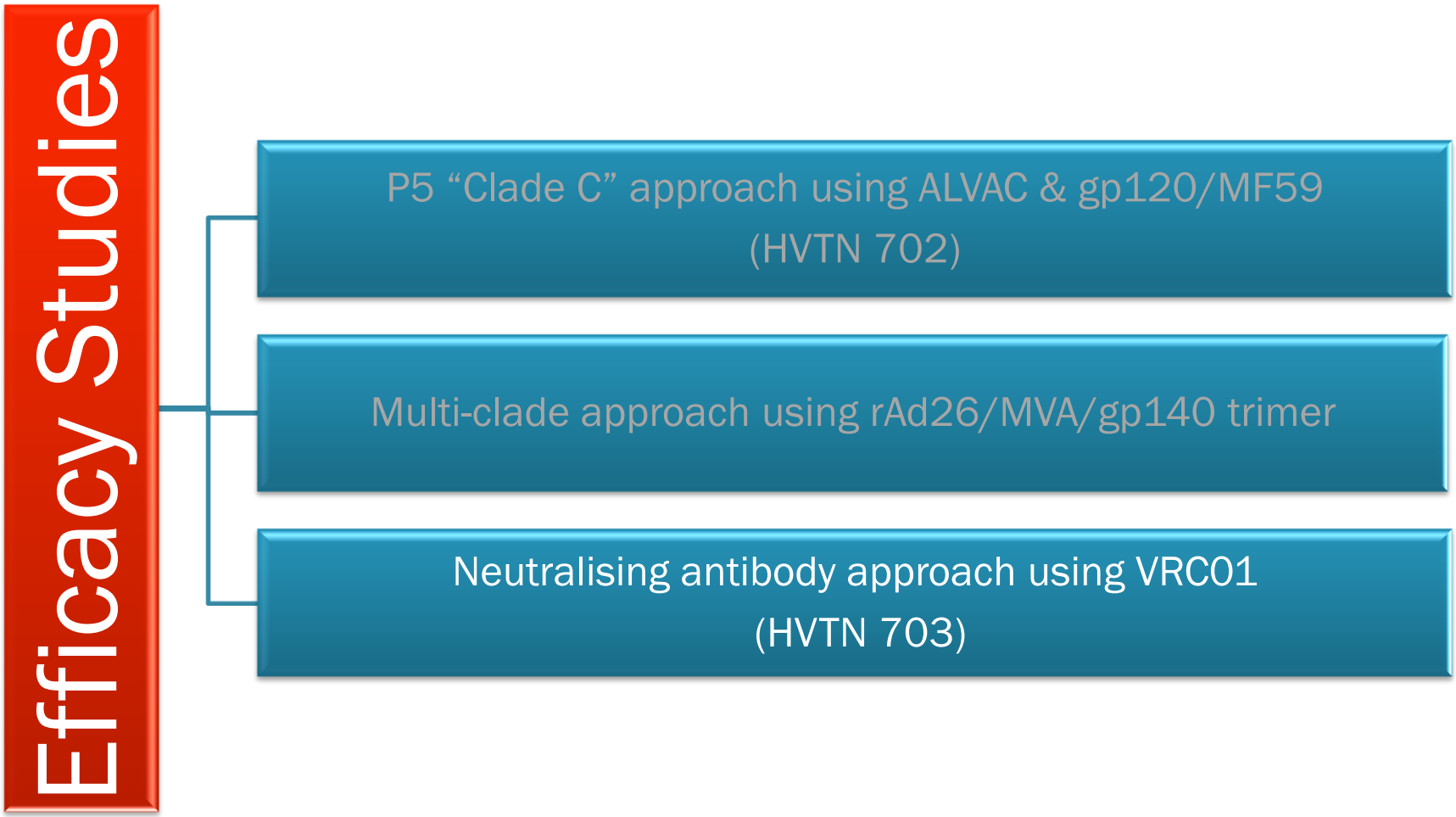


Regimen to be selected after Phase 1/2a

High Level Clinical Development Plan



3 strategies to advance immunization



Clinical Use of HIV Antibodies

Prevention

- Can mAb prevent infection in high risk adults (PrEP)
- Can mAb protect infants during childbirth and breastfeeding
- What level of antibody is needed (ug/ml) to protect
- How long will the antibody work (weeks, months?)

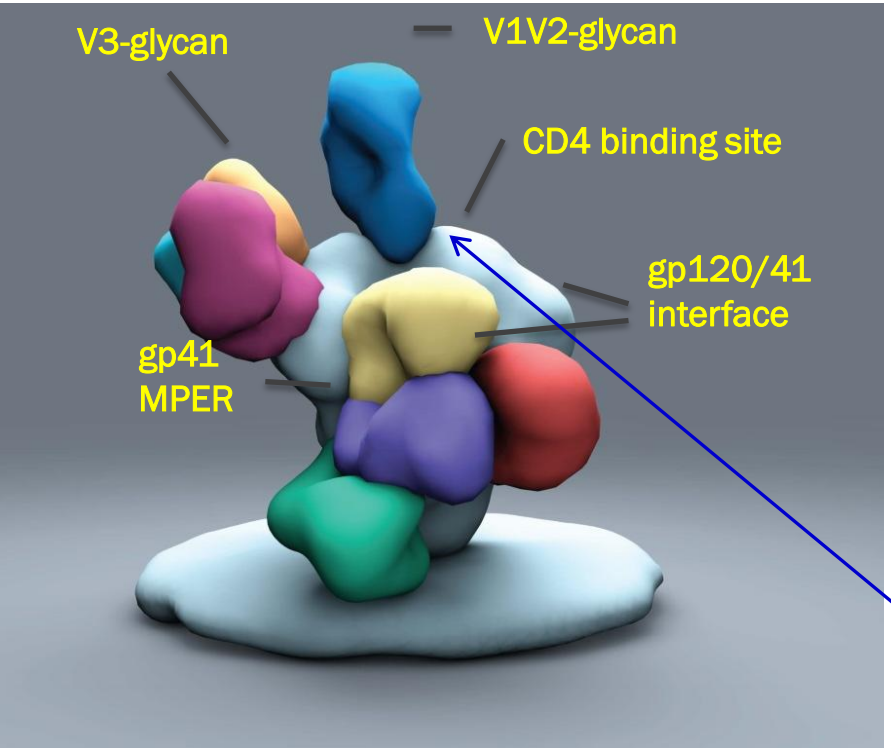
Possible that Single mAb could protect

Treatment

- Does mAb have virologic effect; i.e., lower viremia
- Used for treatment interruption; e.g., ART sparing
- Can mAbs impact the viral reservoir; e.g. used with latency reversing agents
- Can mAbs be used with ART as part of approach to functional cure

Likely want combinations to maximize effect and avoid escape

Neutralising Ab to HIV-1



- **V1V2-Glycan – bind to trimer cap**
- **V3-glycan, N332 supersite**
- **gp41 MPER – near mebrante**
- **gp120/41 interface – bind to parts of both gp120 and gp41**
- **CD4 binding site of gp120 – where the virus attaches to CD4**

Only antibodies that have advanced to the clinic (VRC01, 3BNC117)

Christina Corbaci, Andrew Ward,

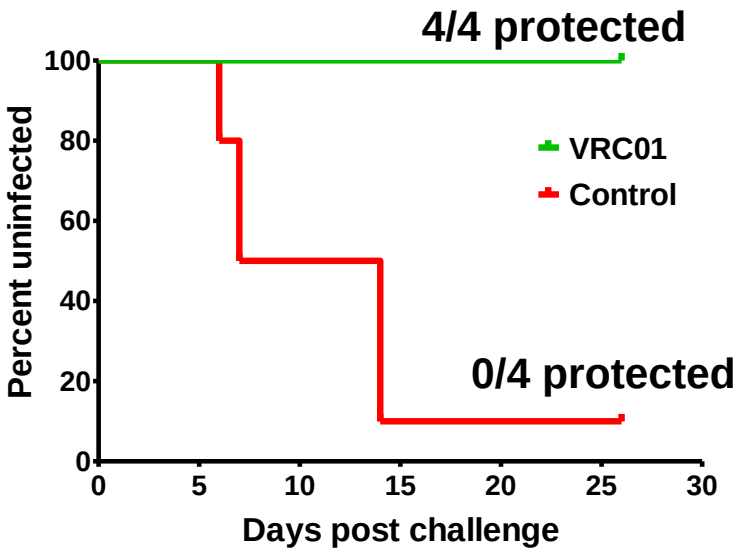
Neutralisation Activity of VRC01

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%

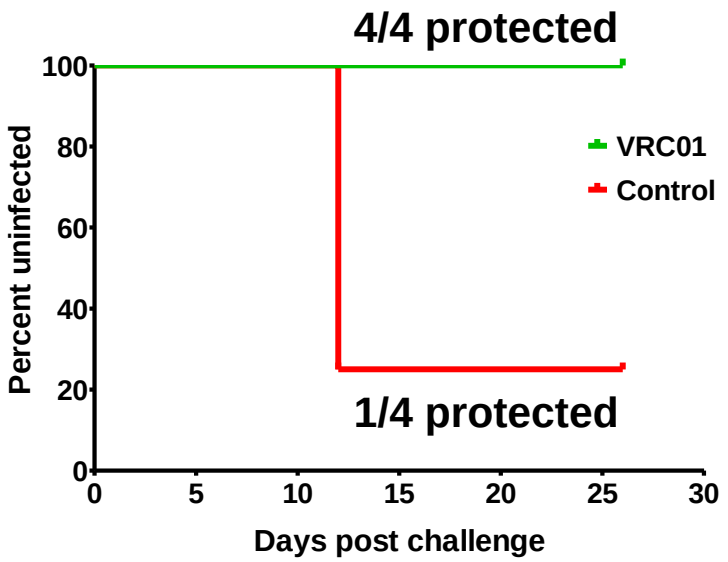
VRC01 Protects Against Mucosal SHIV-Challenge in Non-Human Primates

20 mg/kg infusion of VRC01: Challenge with SHIV SF162P3

RECTAL CHALLENGE



VAGINAL CHALLENGE



- Pegu et al. Science Transl Med (2014)
- Ko et al. Nature (2014)
- Rudicell et al. J Virol (2014)

AMP: Two Phase IIB Studies

- HVTN 703/HPTN 081 will enroll 1,500 women in sub-Saharan Africa
- HVTN 704/HPTN 085 will enroll 2,700 MSM and transgender persons in the Americas
- Each ppt. will be randomized to receive VRC01 10 mg/kg or 30 mg/kg or placebo every 8 weeks for 10 doses

www.ampstudy.org

Major Scientific Questions and Issues the Trial will Define

- Do immunogens that elicit lower levels of neutralization, levels that have proven protective in NHP challenge models, protect against HIV acquisition in humans?

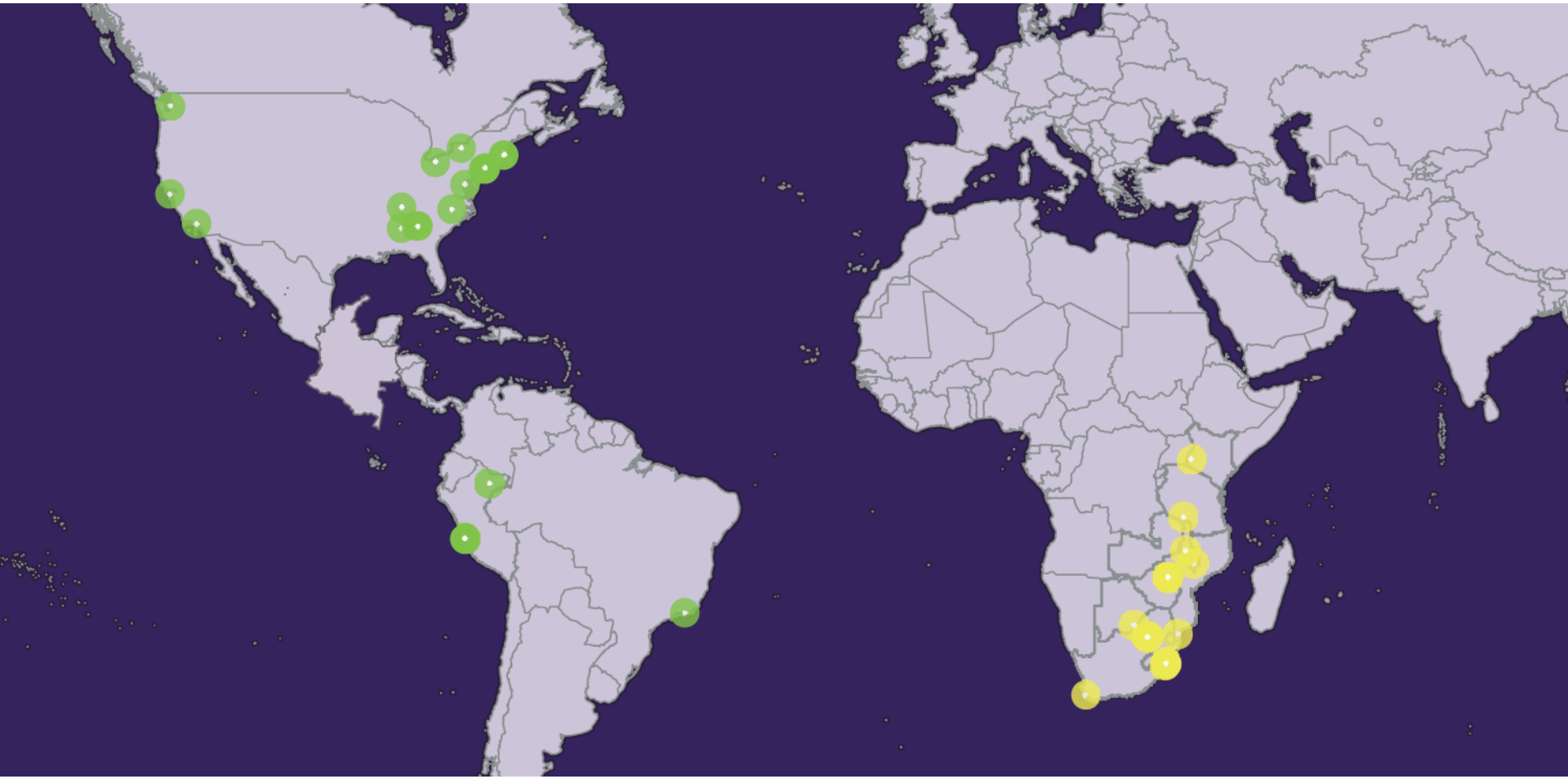
  ☐ What is the dynamic range in concentration of antibodies and neutralizing activity associated with protection?

  ☐ 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?

AMP Research Sites



AMP sub-Saharan Africa Sites

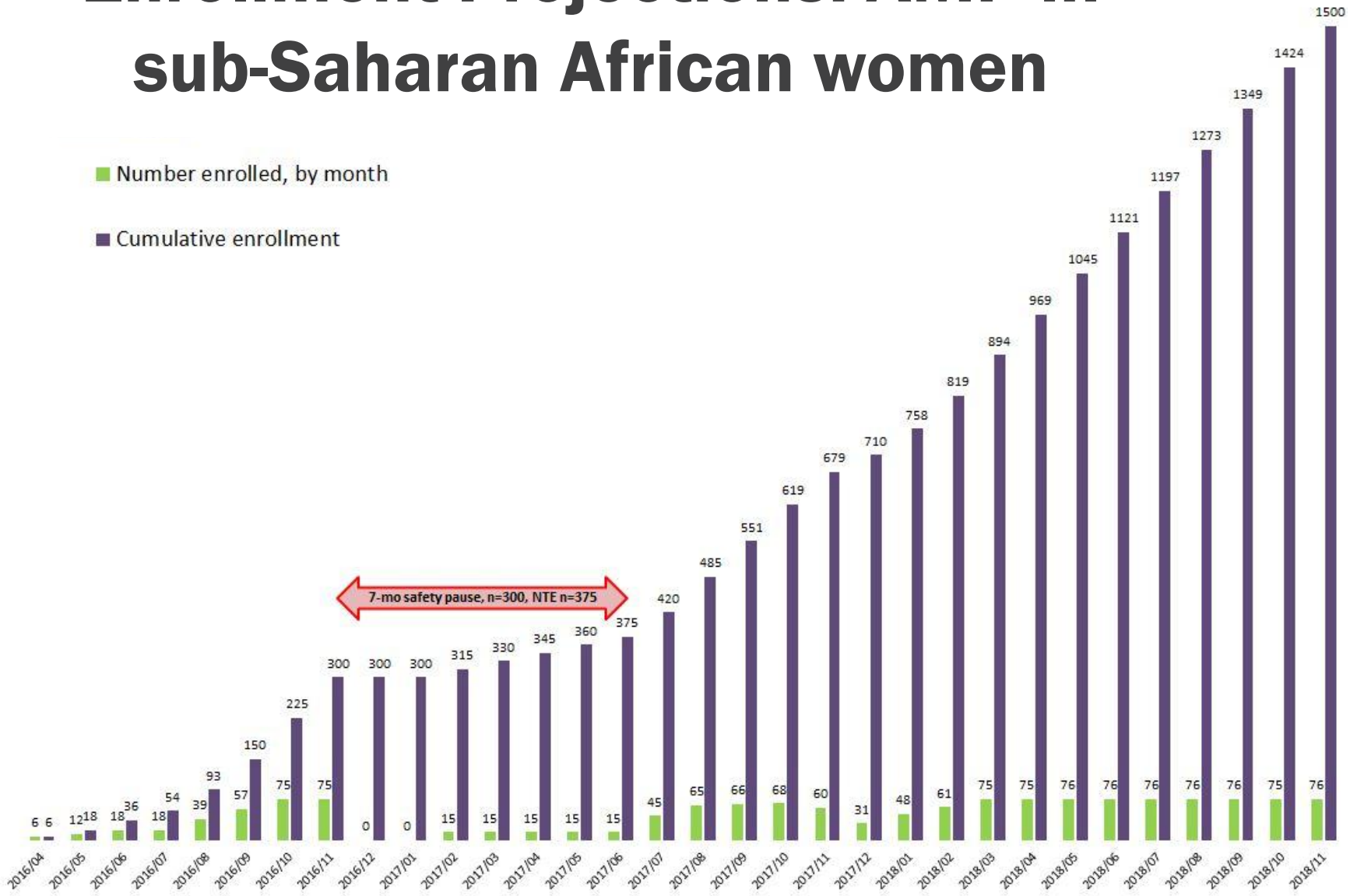
- Gabarone, Botswana
- Kisumu, Kenya
- Blantyre, Malawi
- Lilongwe, Malawi
- Maputo, Mozambique
- Harare (3 clinics), Zimbabwe
- Cape Town, RSA
- Durban (2 clinics), RSA
- Johannesburg, RSA
- Soweto, RSA
- Vulindlela, RSA
- Mbeya, Tanzania

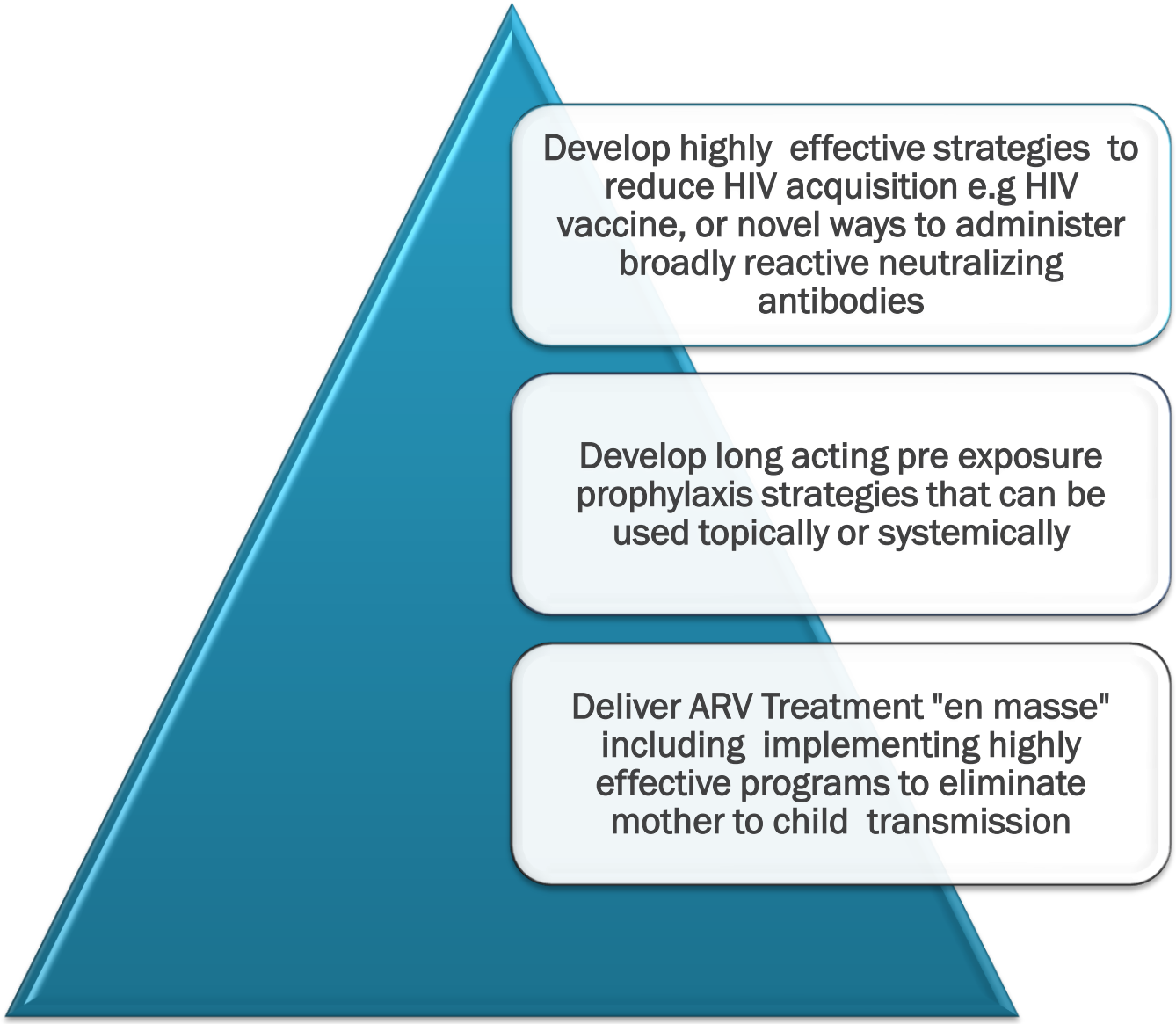
Timeline for AMP in sub-Saharan Africa: Open April 2016

AMP sub-Saharan Africa	Dates
DAIDS Reviews	2/1/2016 - 3/21/2016
MCC and RSA EC Reviews	10/2015 - 2/2016
RSA Community & Protocol Trainings	2/2016 - 3/2016
Trial Opens*	4/1/2016

**Additional SSA National Regulatory Authority & EC reviews continue to Q3 2016, with trainings to be scheduled accordingly.*

Enrollment Projections: AMP in sub-Saharan African women




Develop highly effective strategies to reduce HIV acquisition e.g HIV vaccine, or novel ways to administer broadly reactive neutralizing antibodies
Develop long acting pre exposure prophylaxis strategies that can be used topically or systemically
Deliver ARV Treatment "en masse" including implementing highly effective programs to eliminate mother to child transmission


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
factured by IDT Biologika
DS/NIH USA
Clinical Trial Use Only

Acknowledgements

- HVTN

Ken Mayer

- HVTN

Larry Corey

Julie McElrath

- VRC

John Mascola

Barney Graham

& Funders:

NIAID/BMGF/SAMRC

- J&J/Janssen

Dan Barouch

Nelson Michael

- Frank Tomaka
- NICD

Lynn Morris

HPTN

- Mike Cohen