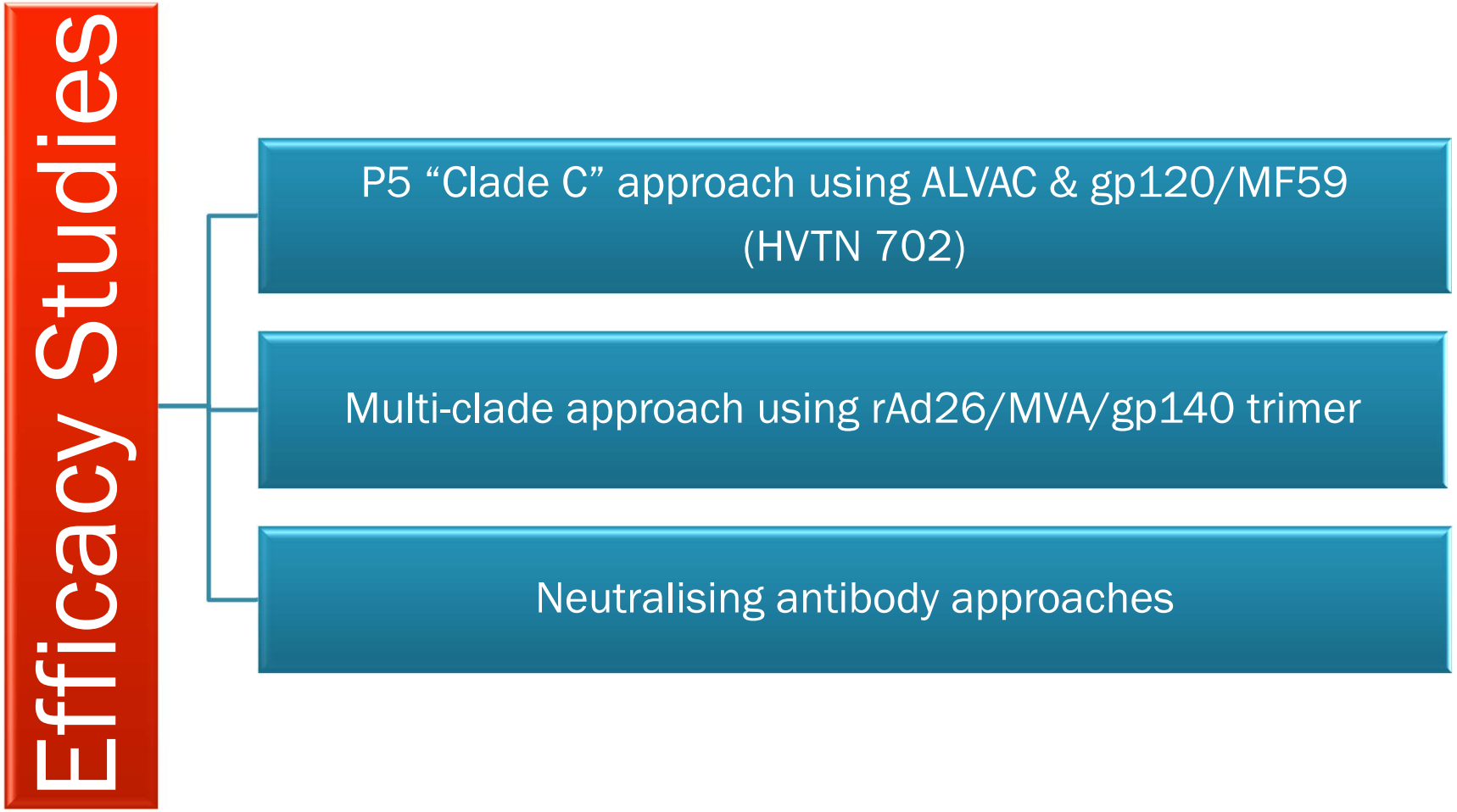
RSA & HIV vaccine efficacy studies

Glenda Gray

15 March 2016

3 strategies that are advancing



Thai Trial (RV144) Primary Results

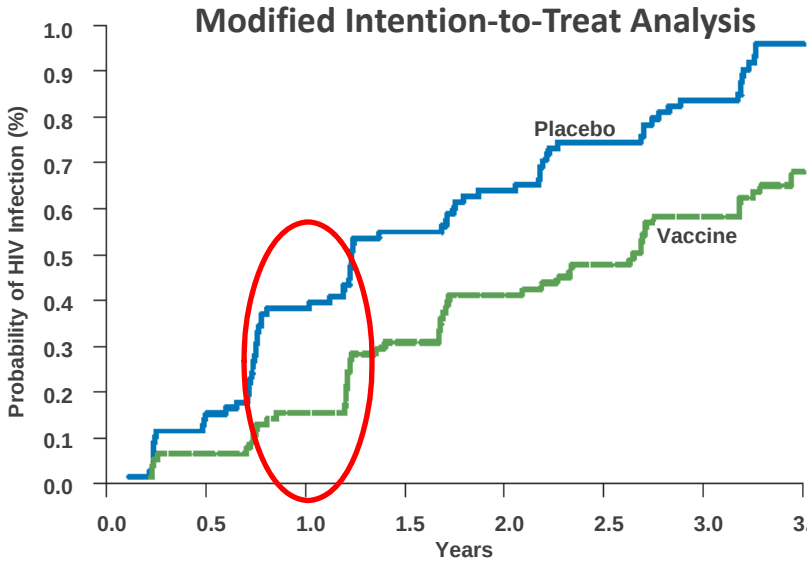
The NEW ENGLAND JOURNAL of MEDICINE

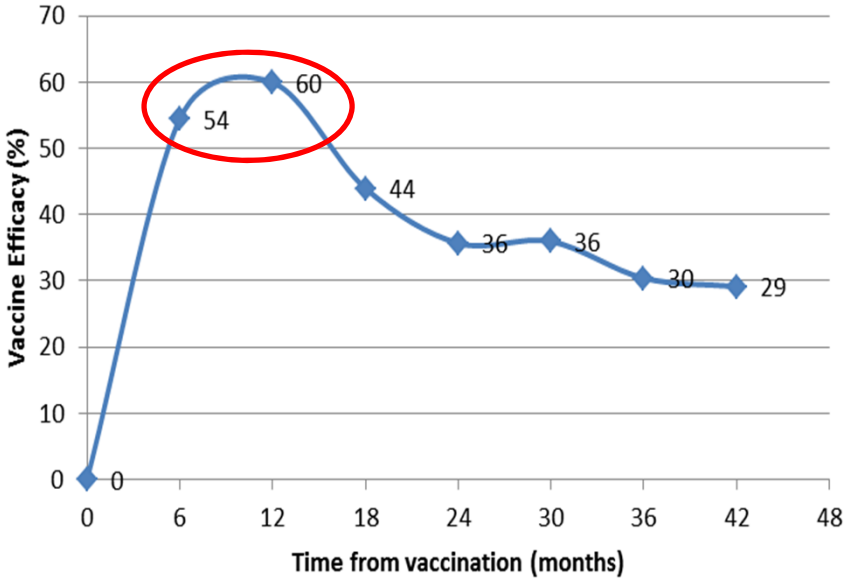
ESTABLISHED IN 1812 DECEMBER 3, 2009 VOL. 361 NO. 23

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., Suparnit 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*

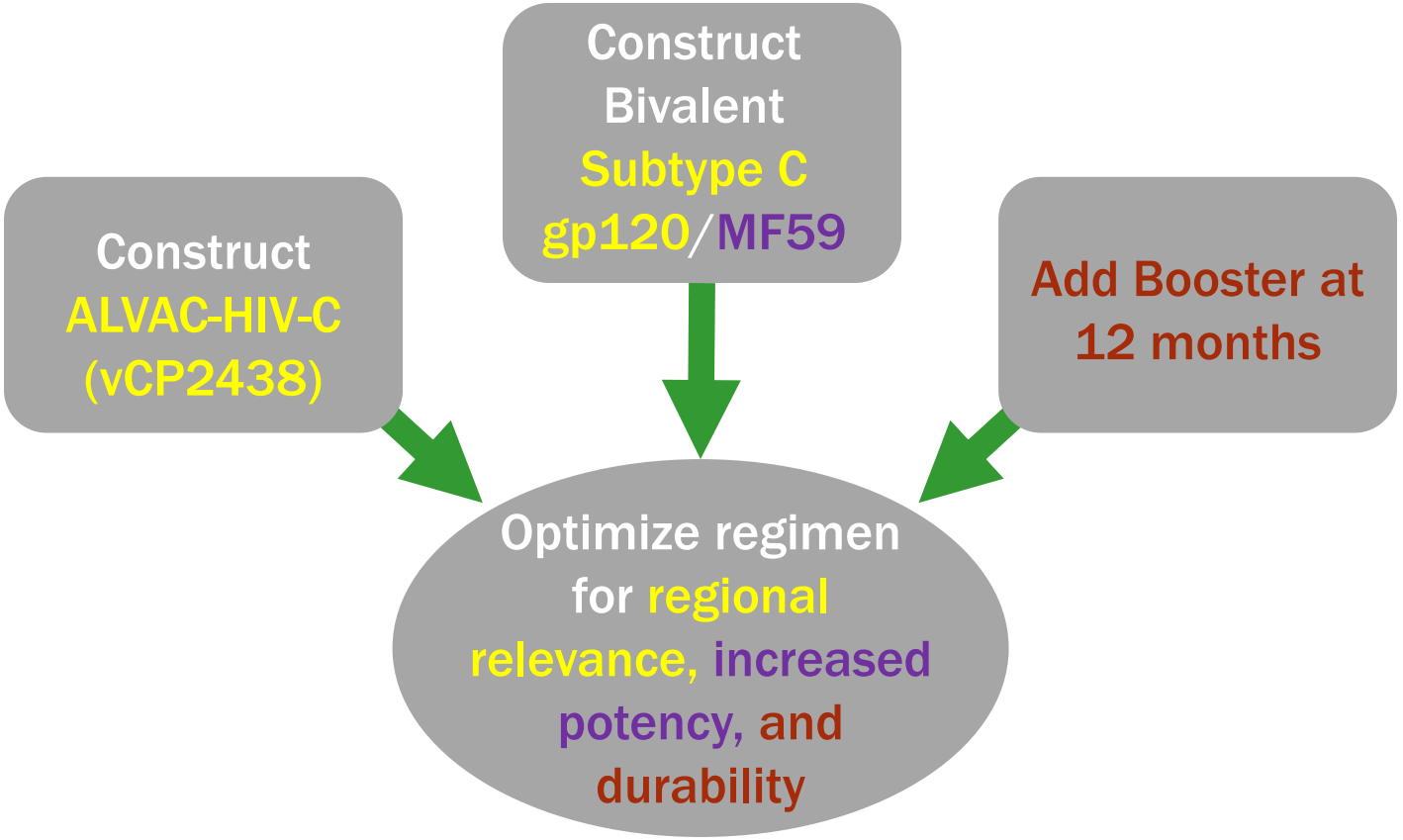
Prime:	ALVAC vCP1521
Boost:	ALVAC vCP1521 plus VAXGEN Env protein (B/E)
Schedule:	0,1,3,6 months; 16,000+ volunteers; 1:1 vaccine: placebo; follow-up for 3 years





Data from Robb et al, Lancet Infectious Diseases, 2012.

The Strategy for the ALVAC/Protein Phase 3 Program



HVTN 100

Primary objectives

- To **evaluate the safety and tolerability** of 2 doses of ALVAC-HIV (vCP2438) followed by 2 doses of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 in HIV-seronegative low risk South African adults

- To **evaluate the immunogenicity** of 2 doses of ALVAC-HIV (vCP2438) followed by 2 doses of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 in HIV-seronegative low risk South African adults at the month 6.5 timepoint (2 weeks after completion of the primary immunization series)

HVTN 100 Schema

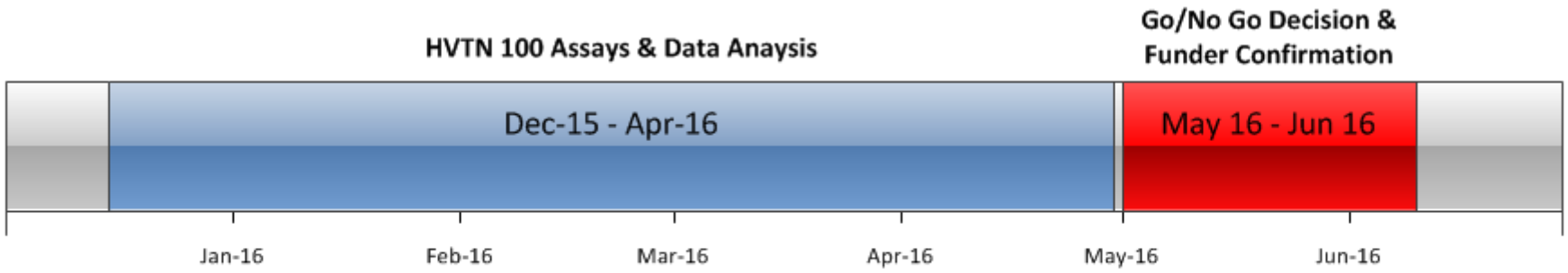
Group	N	Primary vaccine regimen				Booster
		Month 0	Month 1	Month 3	Month 6	Month 12
1	210	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59
2	42	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo
Total	252					

HVTN 100 Clinic Sites

HVTN 100 Current Status

- Primary vaccination series (Months 0, 1, 3, 6) complete for all participants
- Follow-up ongoing
- Booster vaccinations (Month 12) just beginning
- Primary immunogenicity assays (Month 6.5 samples) ongoing
- Interim safety and immunogenicity analyses (to Month 6.5) in process

Go Decision Timeline



12/1/2015

6/30/2016

HVTN 100 Go/No-Go Criteria for HVTN 702: 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 assessment of immune responses from HVTN 100 vaccinees vs. RV144 vaccinees using the same assays run in the same labs

HVTN 702

Primary objectives

- To evaluate the preventive vaccine efficacy (VE) of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 for the prevention of HIV infection in HIV-seronegative South African adults over 24 months from enrollment
- To evaluate the safety and tolerability of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 in adults in South Africa

HVTN 702 Schema

Group	N	Primary vaccine regimen				Booster
		Month 0	Month 1	Month 3	Month 6	Month 12
1	2700	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59
2	2700	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo
Total	5400					

HVTN 702 Design Features (i)

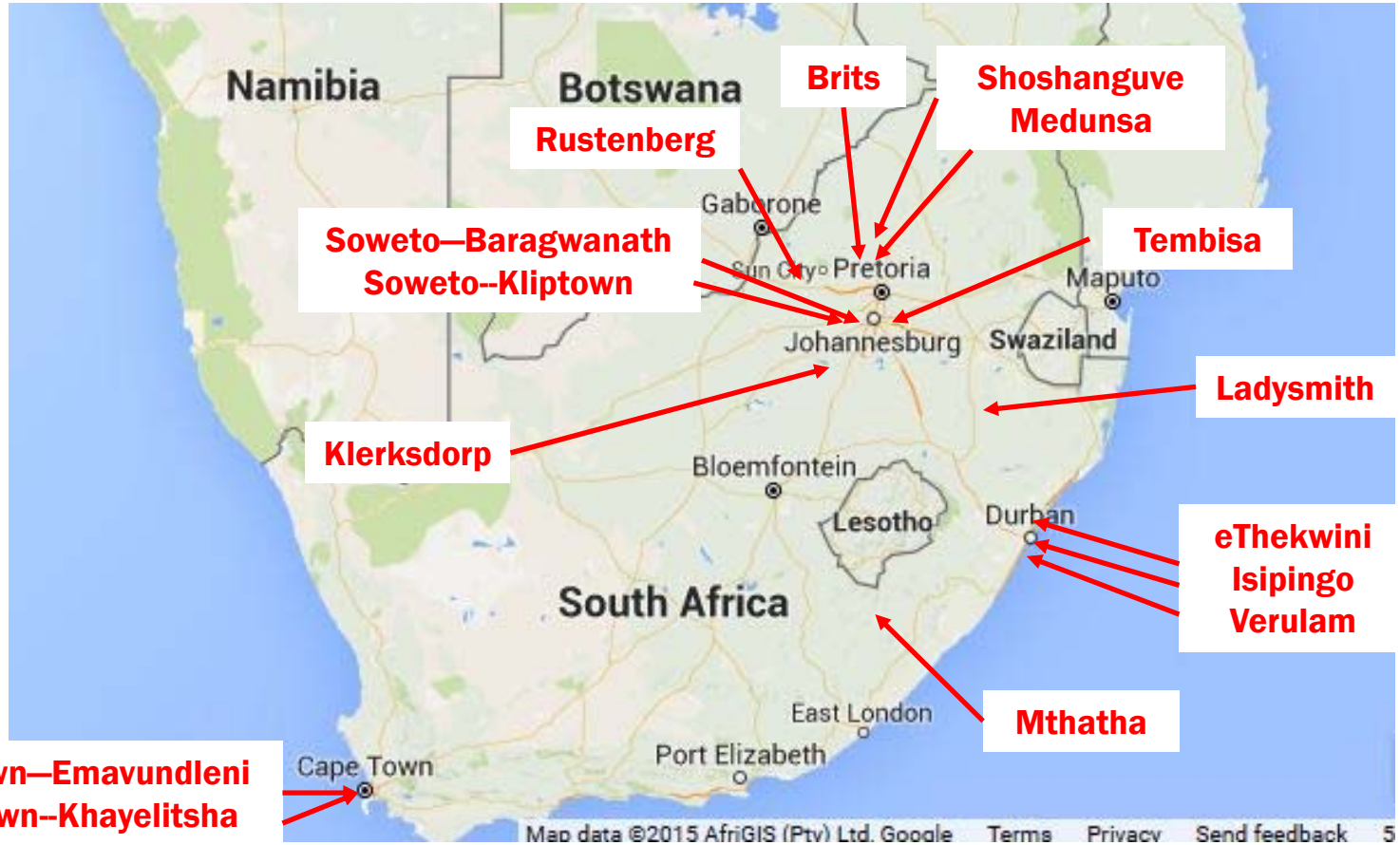
- Evaluates Stage 1 vaccine efficacy (VE) to 24 months after 1st vaccination
- If evidence of positive VE, evaluates VE durability to 36 months after 1st vaccination
- Continuous monitoring for harm
- Sequential monitoring for non-efficacy/ efficacy futility
- Monitoring for high efficacy

HVTN 702 Design Features (ii)

- 90% power to detect Vaccine Efficacy (VE) of **50%** (enrollment through 24 months)
- = 90% power to reject null hypothesis (VE ≤ 25%)

True Average VE(0-24)	Power to reject null: VE(0-24) ≤ 25%
30%	7
40%	45
50%	90
60%	100
70%	100
80%	100

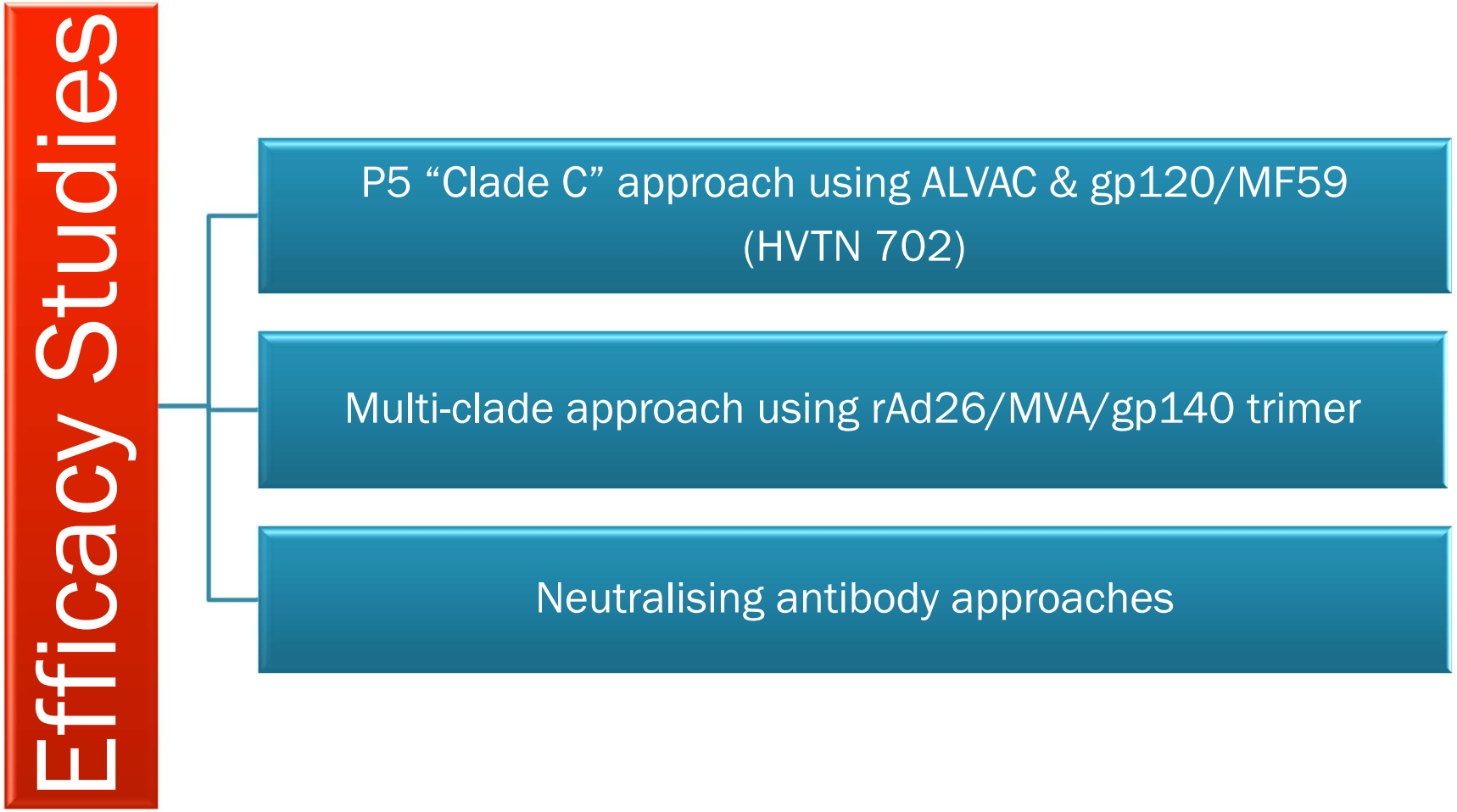
HVTN 702 Clinic Sites



HVTN 702 Partnership

- Bill & Melinda Gates Foundation
- Division of AIDS, National Institute of Allergy and Infectious Diseases, US National Institutes of Health
- GlaxoSmithKline Vaccines
- HIV Vaccine Trials Network
- Medical Research Council of South Africa
- Sanofi Pasteur

3 strategies that are advancing



HIV vaccine research program: Janssen and Collaborators

BIDMC
Harvard

MHRP

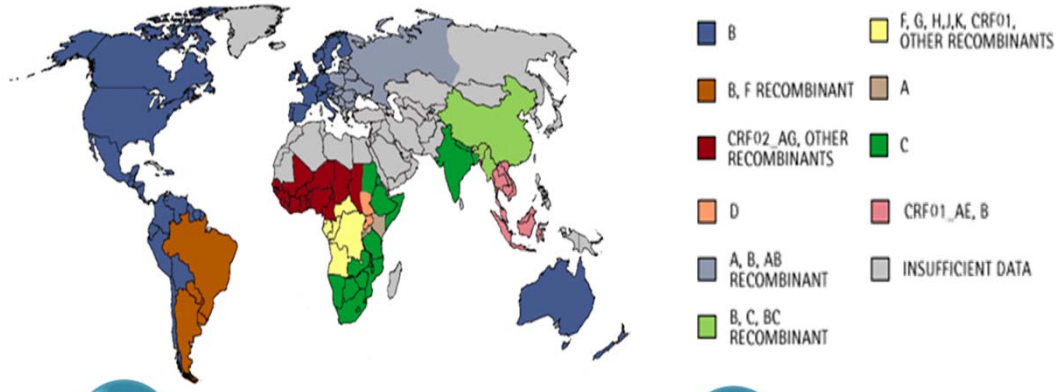
IAVI

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

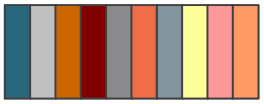
Potent priming Vectors

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

(MVA.HIV-Gag-Pol-Env)

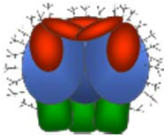
2

Mosaic inserts for global coverage



3

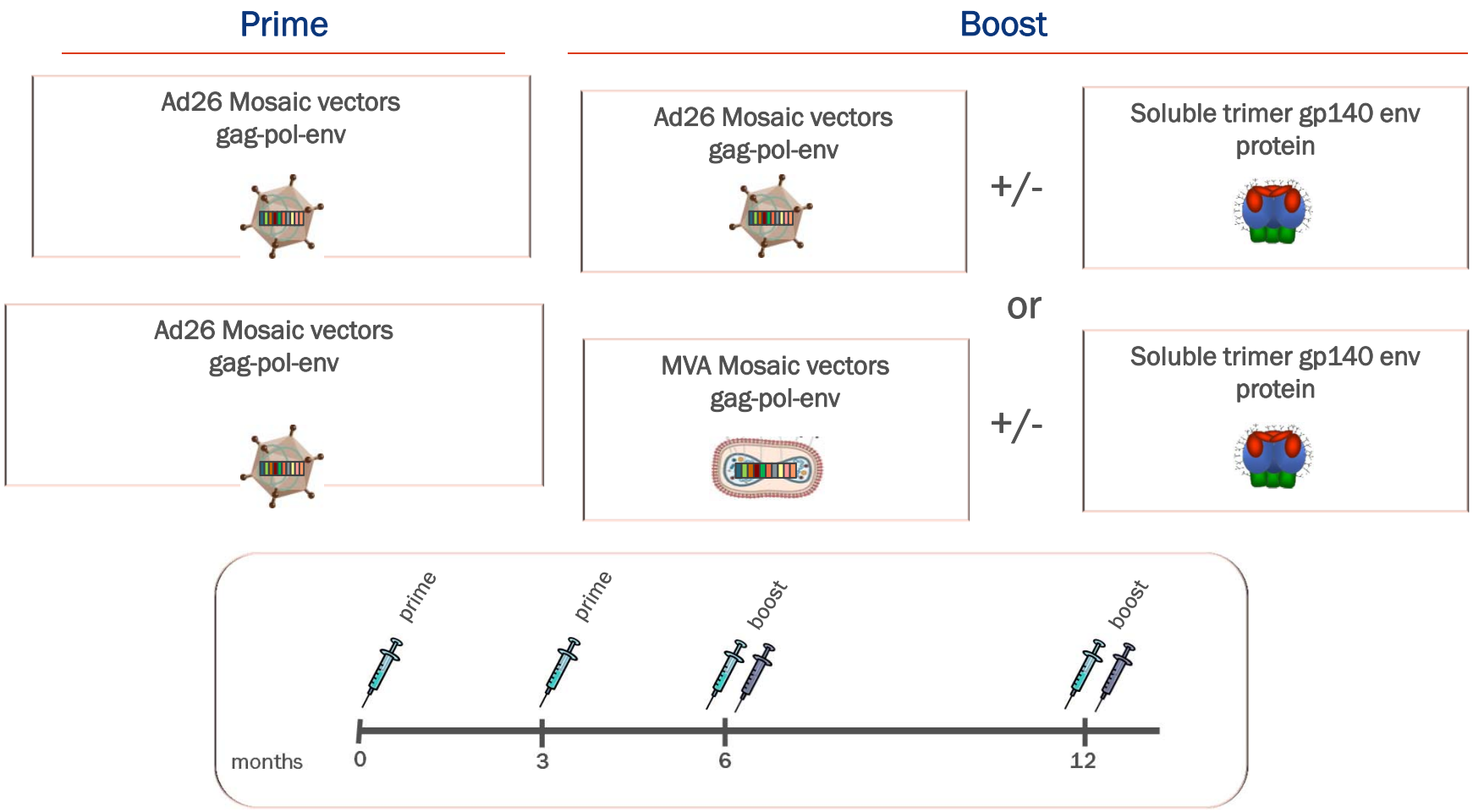
Trimeric env protein for improved humoral immunity



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

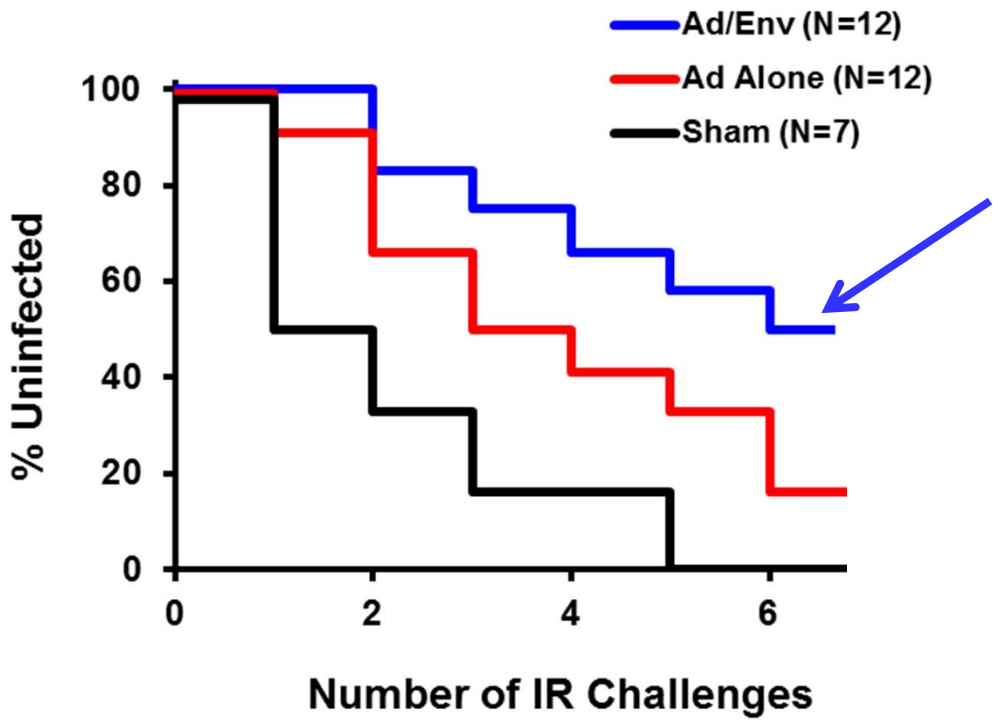
A prime-boost vaccine regimen aiming at global coverage starting 2017-2021



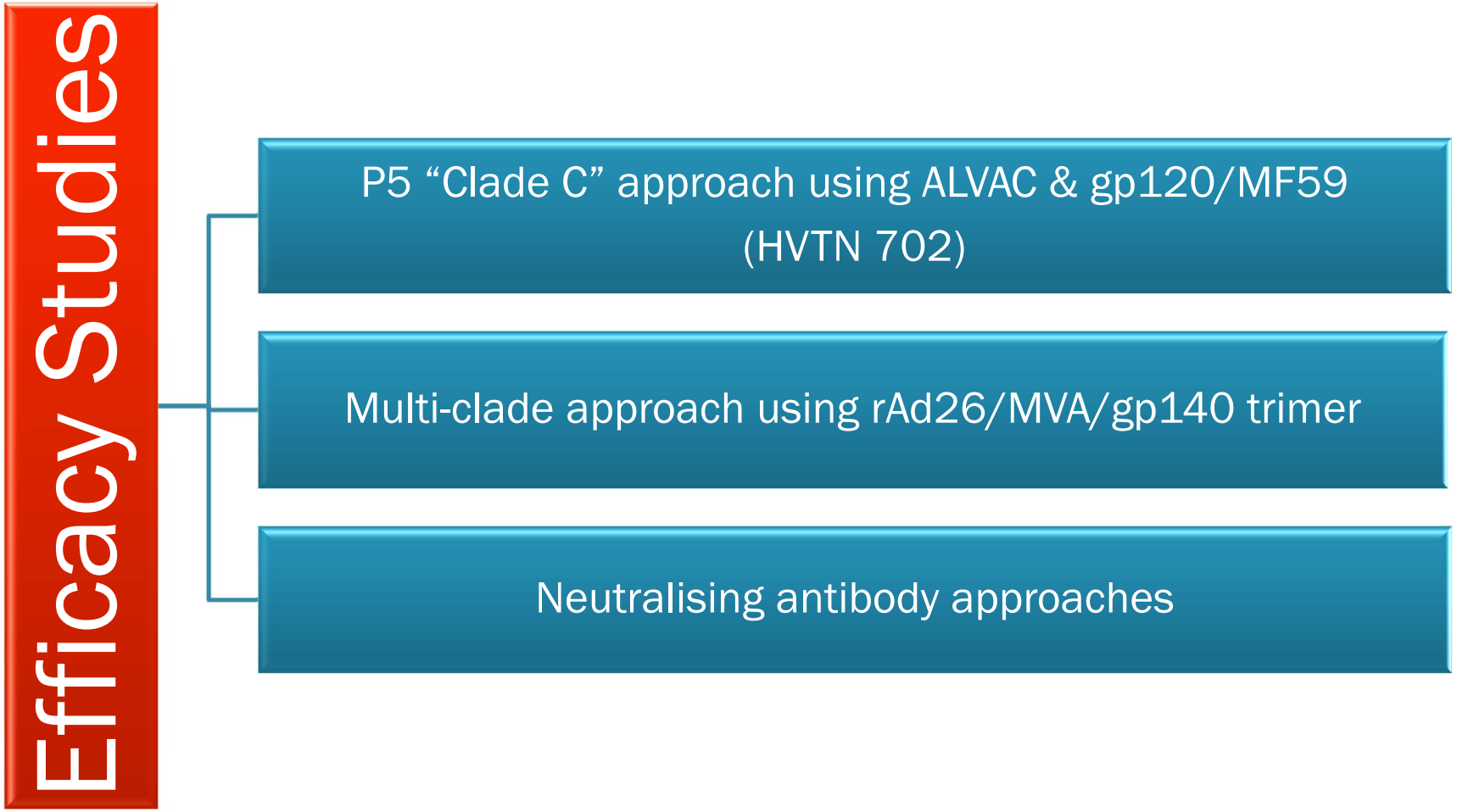
Ad26/Env SIV Vaccines Partially Protect Against IR SIVmac251 Challenges in Rhesus Monkeys

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)

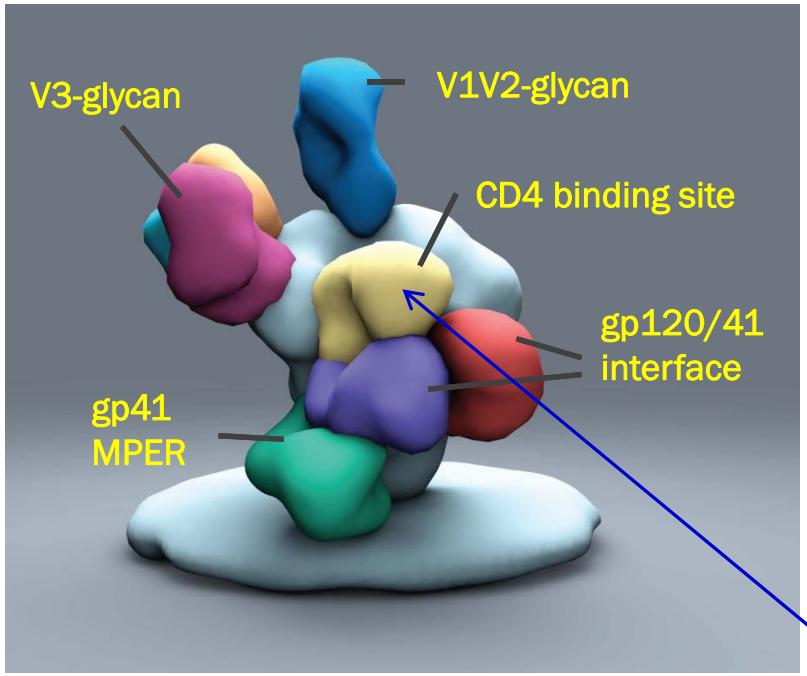
- 32 rhesus monkeys
  - Ad26/Env (N=12)
  - Ad26/Ad35 (N=12)
  - Sham (N=7)
- Repetitive, intrarectal, heterologous SIVmac251 challenges
- Correlates of protection
  - ELISA P < 0.0001
  - Ab Funct P = 0.004
  - NAb P = NS



3 strategies that are advancing



Neutralizing Ab to HIV-1



Christina Corbaci, Andrew Ward,

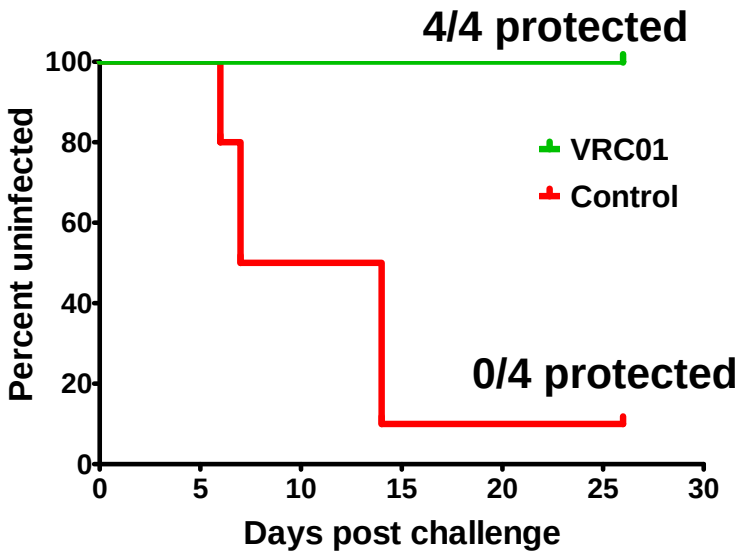
- V1V2-Glycan – bind to trimer cap
- V3-glycan, N332 supersite
- gp41 MPER – near membrane
- gp120/41 interface – bind to parts of both gp120 and gp41
- CD4 binding site of gp120 – where the virus attaches to CD4

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

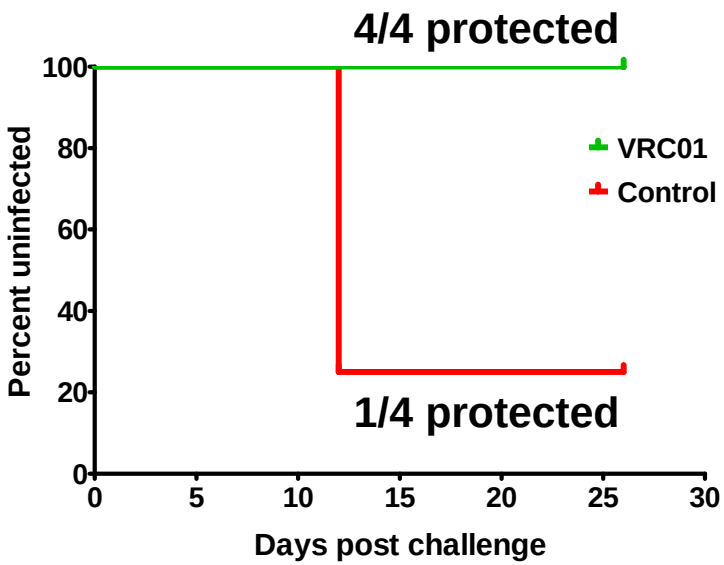
VRC01 Protects Against Mucosal SHIV-Challenge in Non-Human Primates

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 Trial Objectives

1. To determine whether and how the VRC01 broadly neutralizing mAb can prevent HIV infection
2. To develop a marker(s) of VRC01 that correlates with the level of protection against HIV infection
3. To provide insight into the mechanistic correlates of protection

Application: Help design candidate HIV vaccines and define immunogenicity study endpoints in Phase I/II trials for evaluating these candidate vaccines

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?

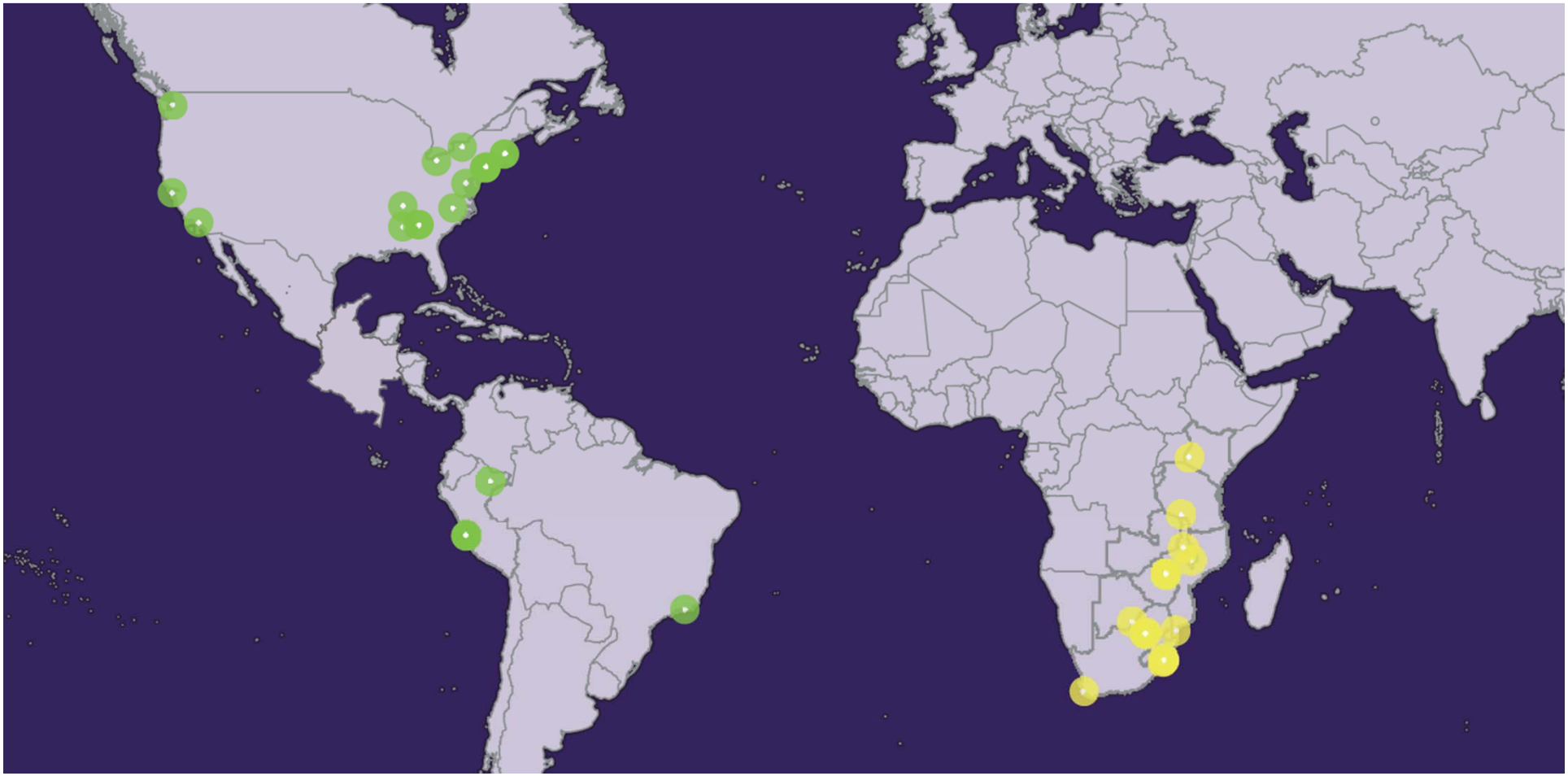
  ☐ What is the dynamic range in concentration of antibodies and neutralizing activity associated with protection?

  ☐ 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

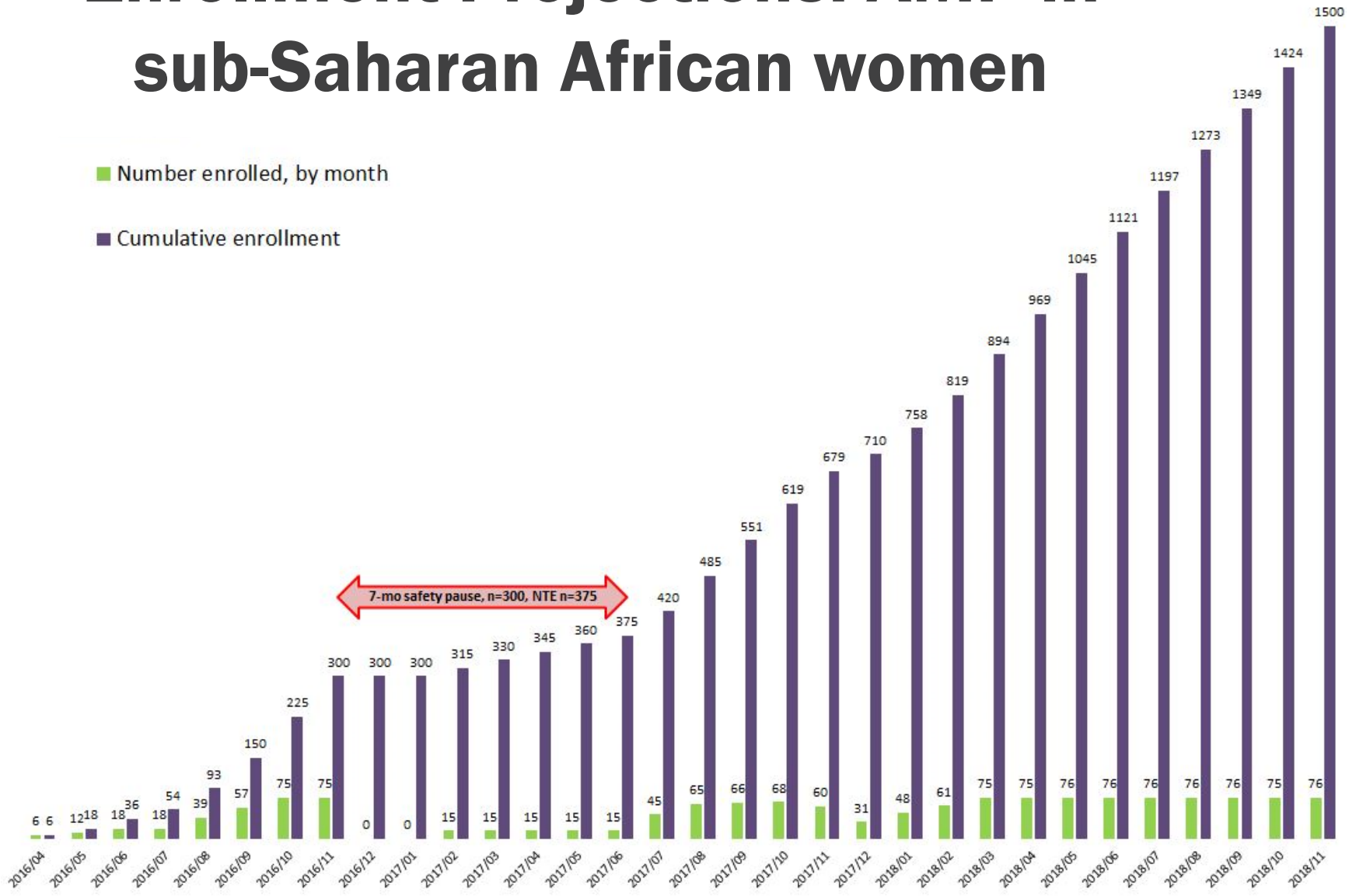
- Gabarone, Botswana
- Kisumu, Kenya
- Blantyre, Malawi
- Lilongwe, Malawi
- Maputo, Mozambique
- Harare (3 clinics), Zimbabwe
- Cape Town, RSA
- Durban (2 clinics), RSA
- Johannesburg, RSA
- Soweto, RSA
- Vulindlela, RSA
- Mbeya, Tanzania

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



Acknowledgements

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Dan Barouch

Nelson Michael

- Frank Tomaka
- NICD

Lynn Morris

HPTN

- Mike Cohen