Beyond RV 144 Efficacy Results and The Future Plan

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For the TAVEG-MOPH

Sponsor : Military HIV Research Program , NIH

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- Background
- Where we are after the RV 144 efficacy results
  - ADCC
  - Correlate of risk
  - IgG and IgA binding antibodies
- Extension study of RV 144-RV305,306
- Future plan for Thailand

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

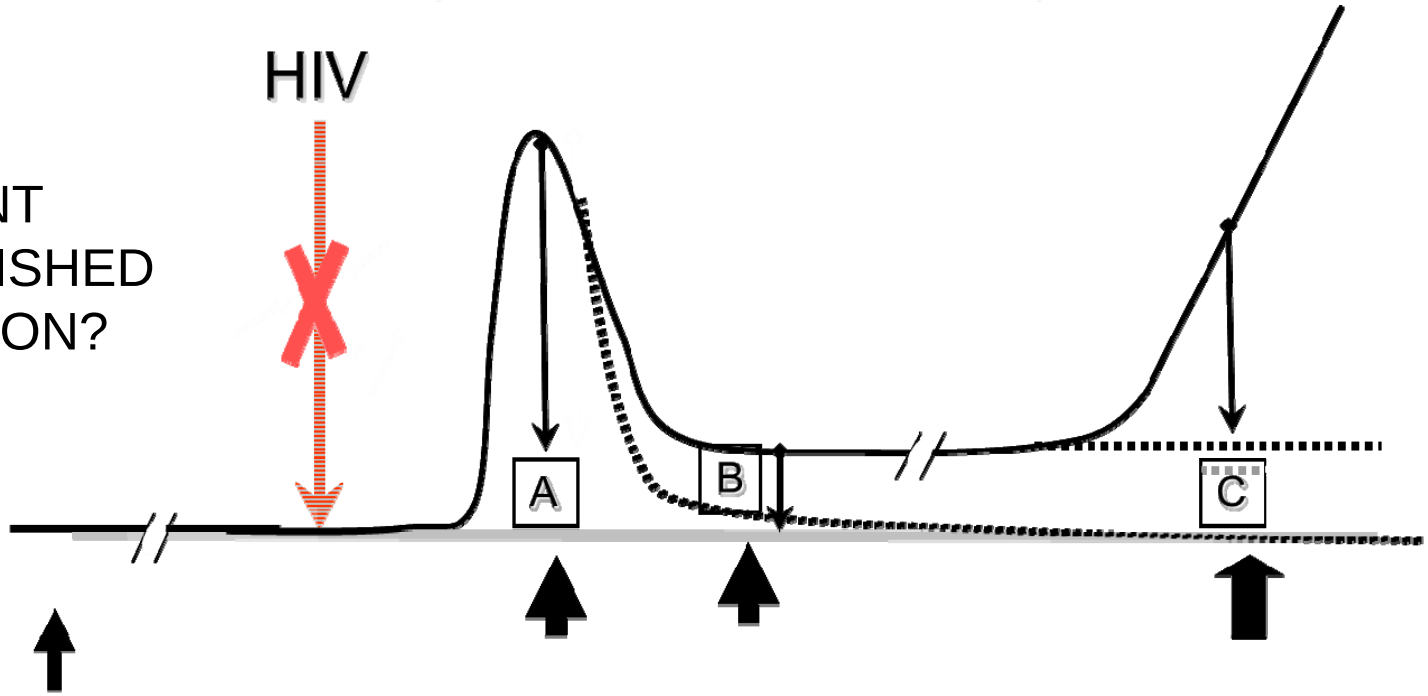
CURRENT CONCEPTS

An HIV Vaccine — Evolving Concepts

Margaret I. Johnston, Ph.D., and Anthony S. Fauci, M.D.

CLASSIC PREVENTIVE VACCINES ARE DESIGNED TO MIMIC THE EFFECTS OF natural exposure to microbes. They provide a high level of long-lasting protection against infection in the vast majority of recipients and serve as free-standing preventive measures. Although a classic preventive vaccine remains the ultimate goal of efforts to develop a vaccine for protection against the human im-

PREVENT
ESTABLISHED
INFECTION?
*****



A. Lower Initial Peak of Viremia

B. Decrease viral set point

C. Delay Progression

Immune responses against HIV

Jhonston M and Fauci A. NEJM,2007,May17;356(20):2073

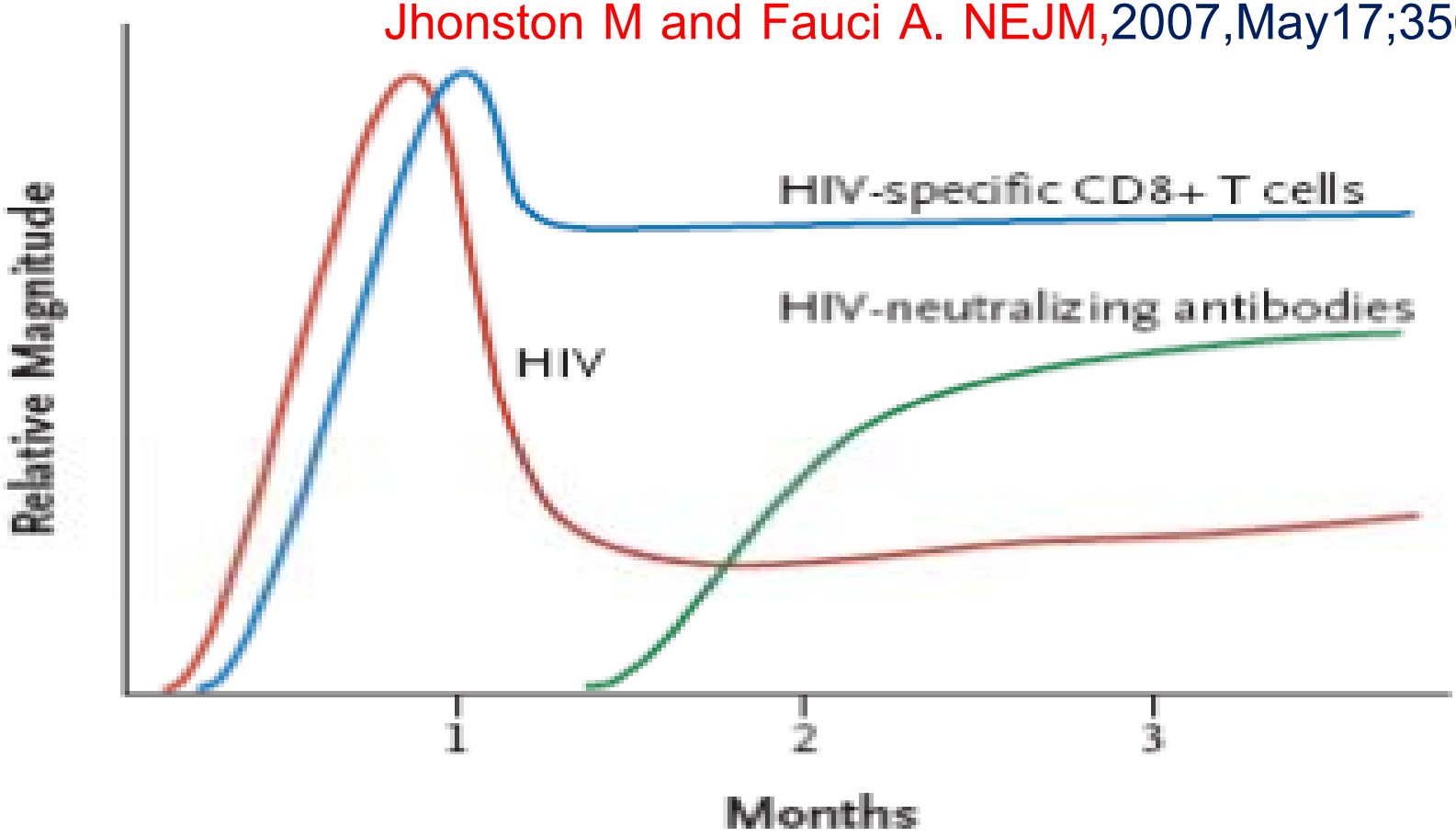
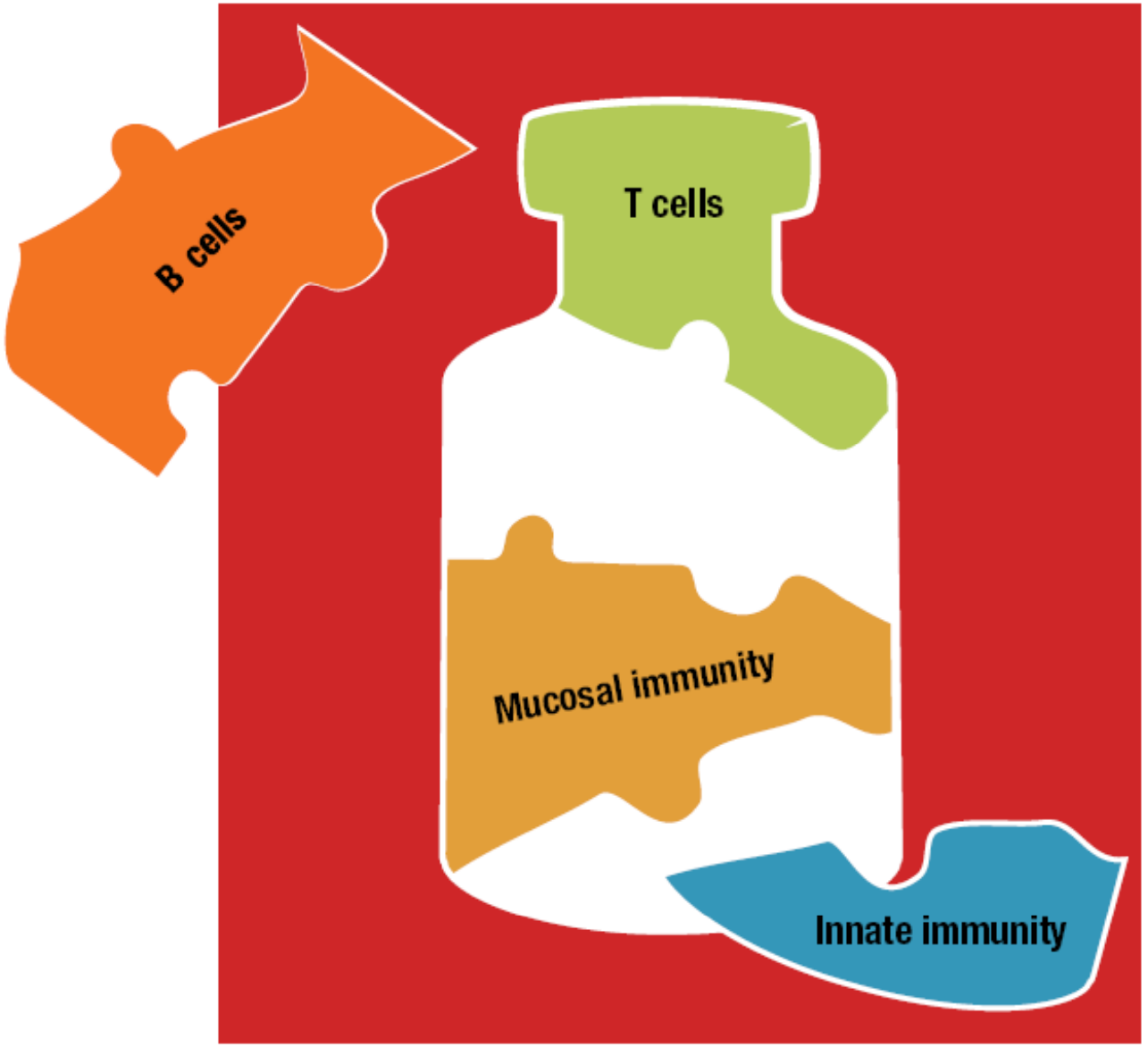
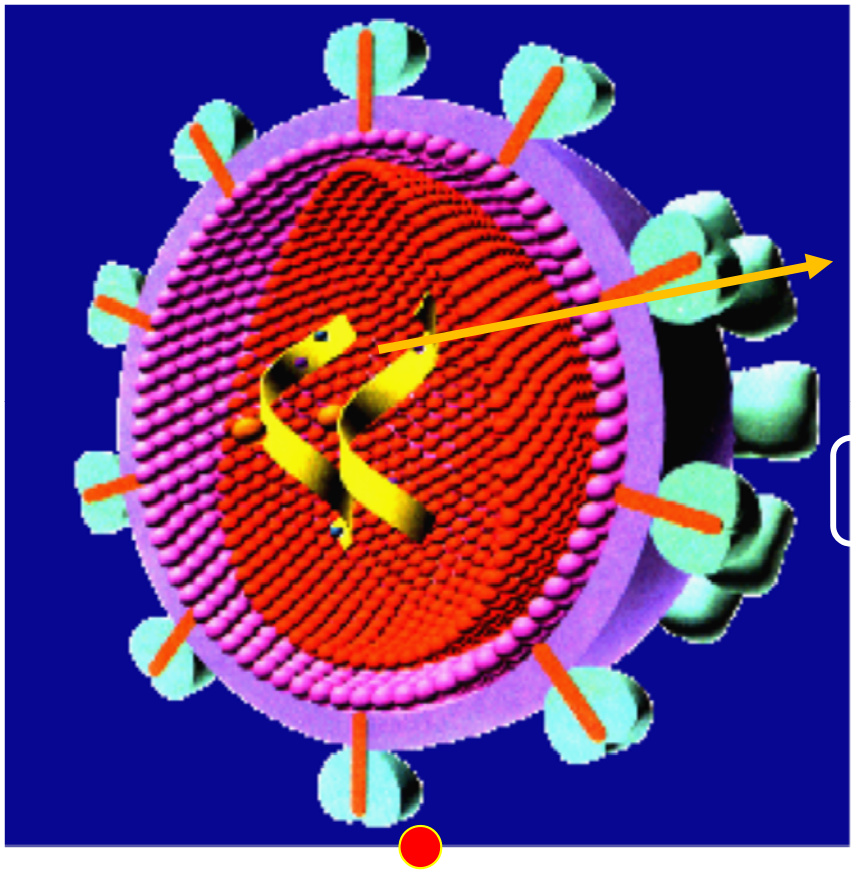
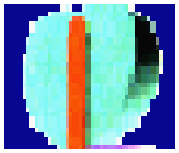


Figure 3. Immune Responses to HIV Infection, Showing Plasma HIV Levels, HIV-Specific CD8+ T Cells, and HIV-Neutralizing Antibodies.

Working on the Puzzle of Vaccine Induced Protection

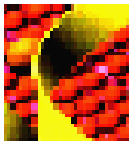






Recombinant protein (gp120)

AIDSVAX B/B’ or B/E



DNA

Live-recombinant vectors

- USING Ad5 Virus –MRKAd5
- Or ALVAC virus (bird pox virus) ALVAC HIV vaccine

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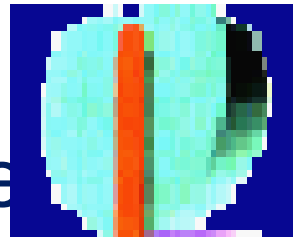
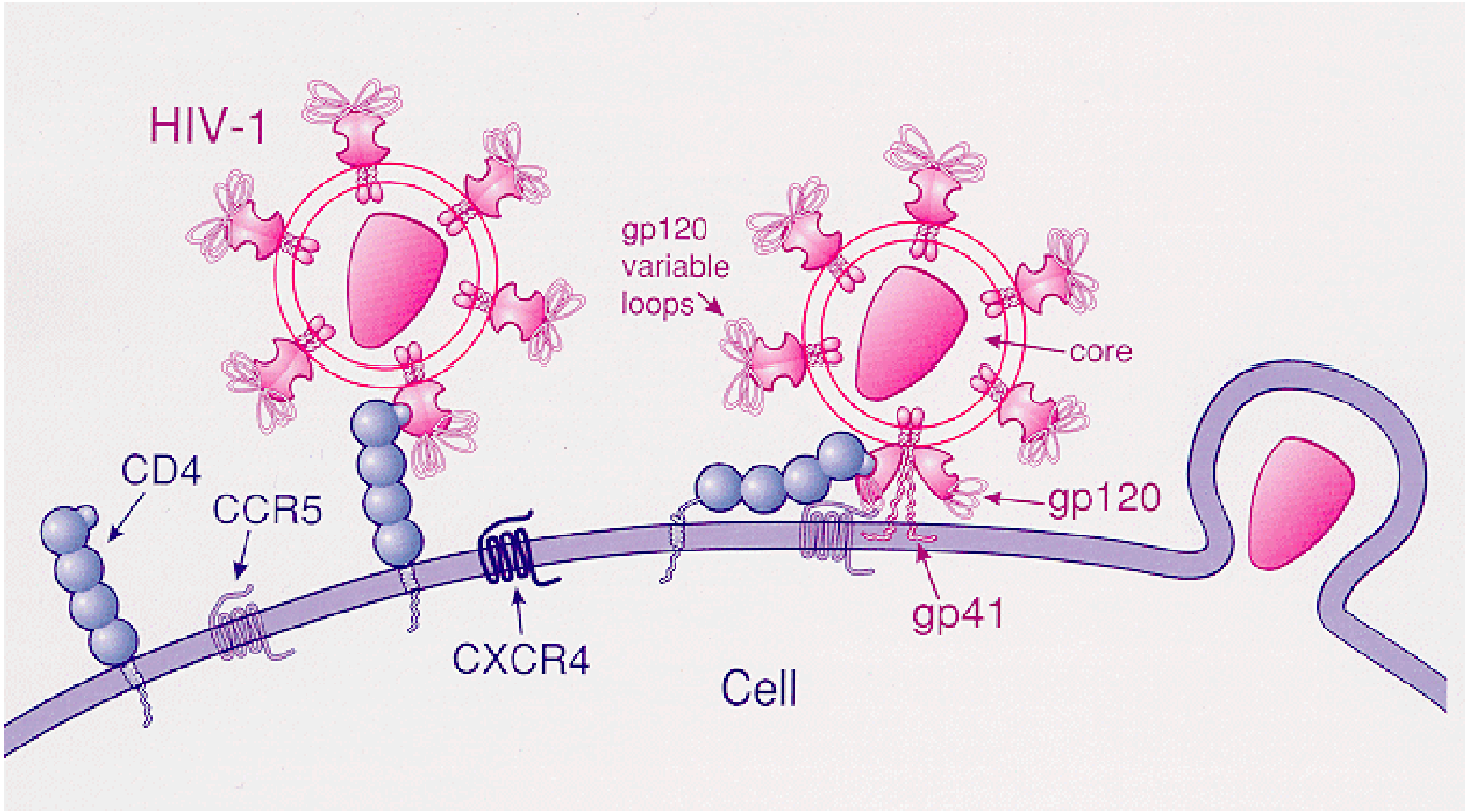
rgp120 vaccine

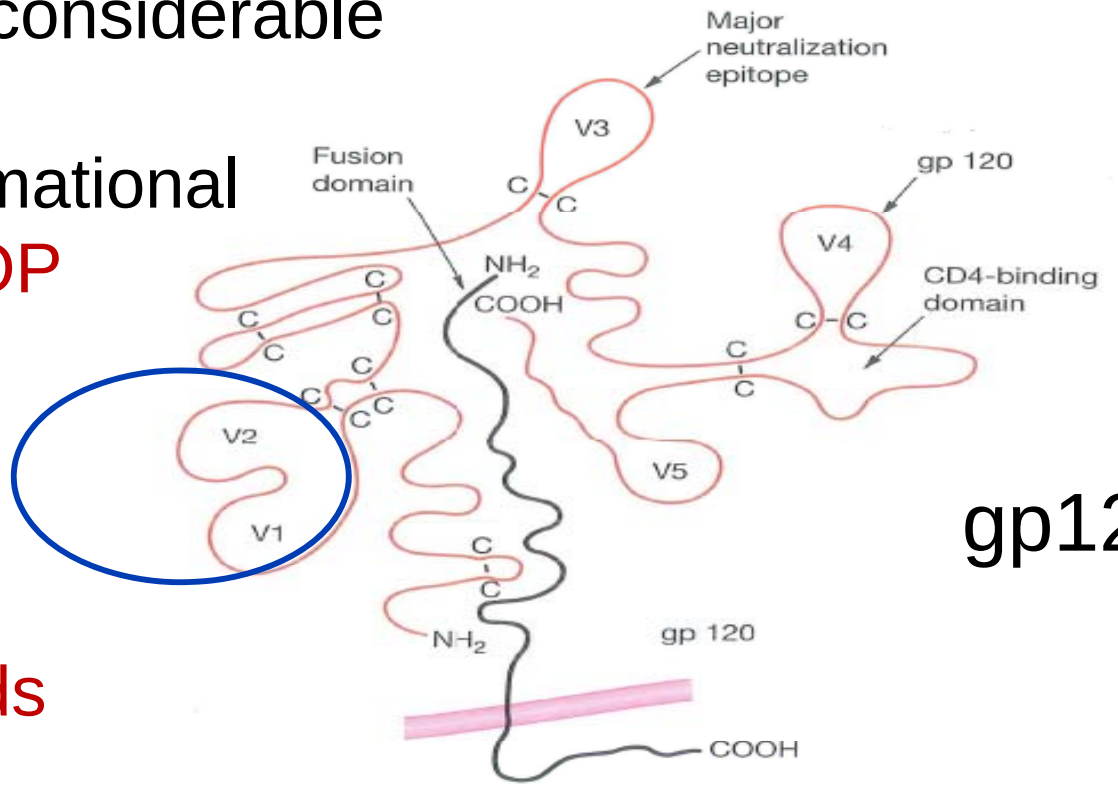


Neutralizing antibody

Cell-mediated immunity



- CD4 binding domain of GP120 is complex conformational motif comprising a recessed pocket flanked by variable regions with considerable glycosylation
- Leading to conformational change of V1-V2 LOOP RESULTING IN THE EXPOSURE OF BINDING SITE
- The choice of co-receptor depends on aa at V3



gp120

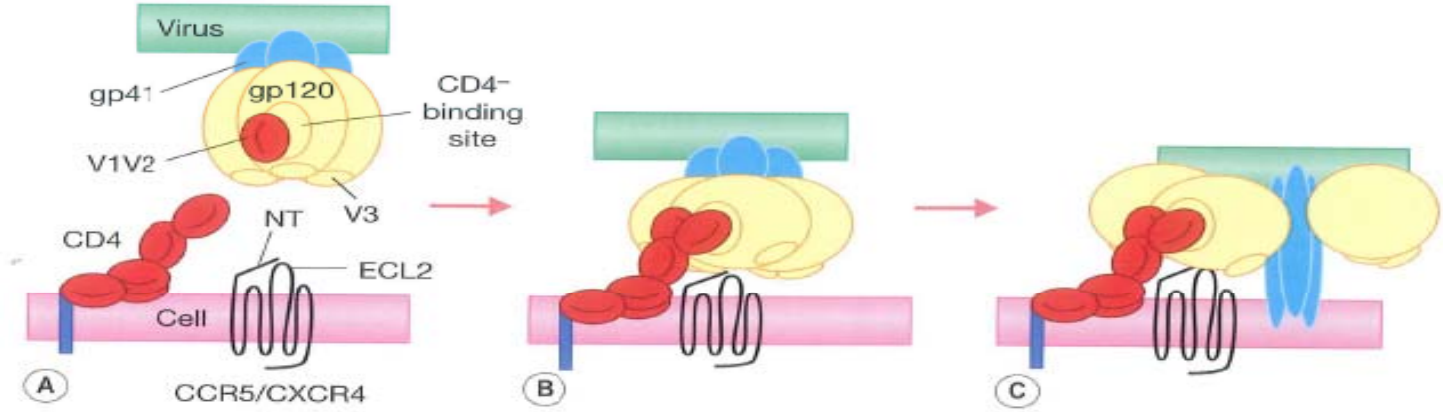


Figure 51-3 Interaction of the Env spike with target cell receptor and coreceptor.

Phase III Trials

Design: randomized, double-blind placebo controlled

	N. America/ Europe AIDSVAX B/B	*Thailand AIDSVAX B/E*
Transmission	Sexual	Blood borne
Volunteers	5,400	2,500
Annual infection rate	1.5%	4%
Clinical sites	59	17
Start date	June 1998	March 1999
Fully enrolled	Oct. 1999	Aug. 2000
Analysis completed	Q1 2003	Q4 2003

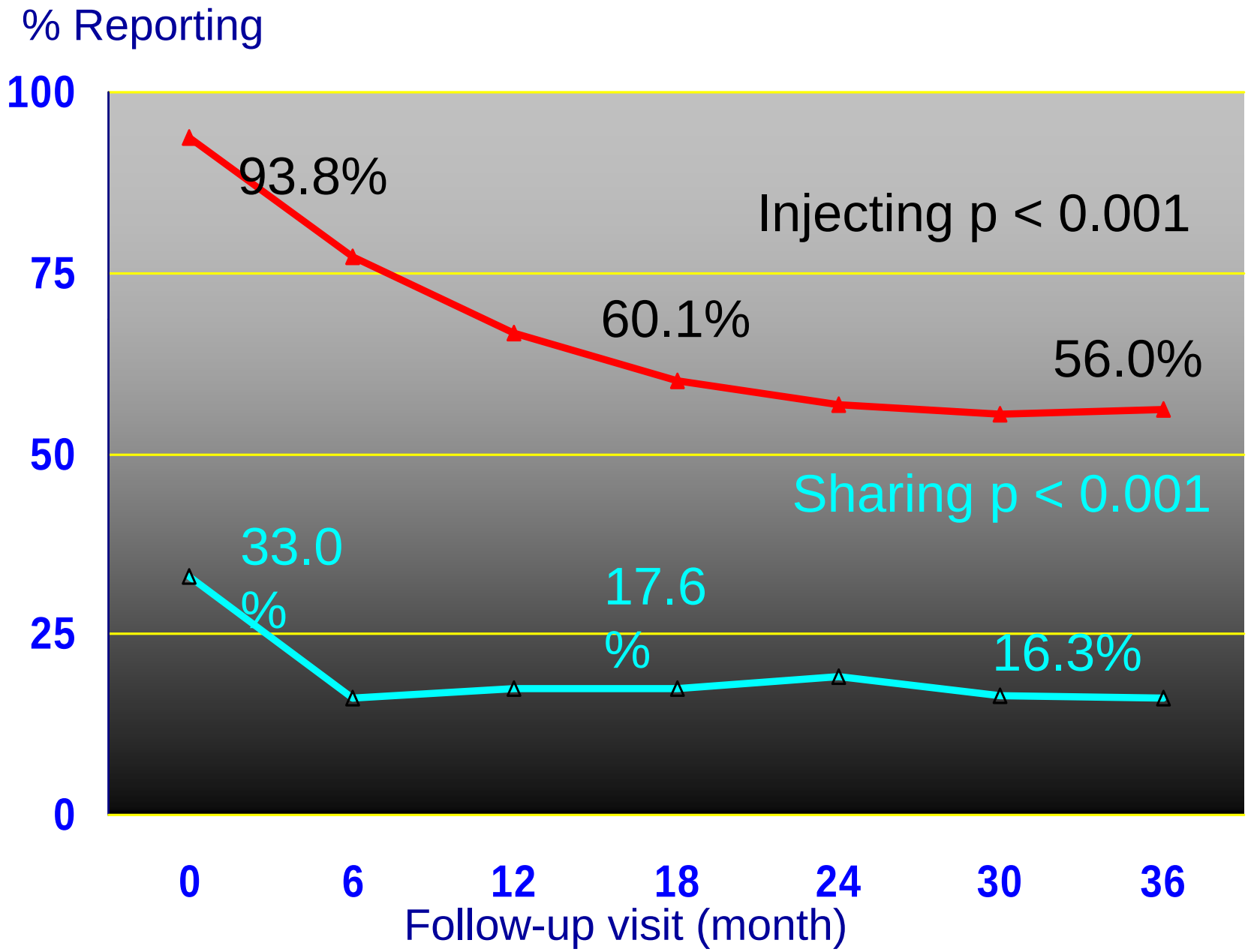
VaxGen

Vaccine Efficacy from North American Trial

	Placebo Inf./total	Vaccine Inf./total	VE (95.12%CI)
All Volunteers	98/1679 (5.8%)	191/3330 (5.7%)	3.8% (-22.9 - 24.7%)
White & Hispanic	81/1508 (5.4%)	179/3003 (6.0%)	-9.7% (-42.8 to 15.7%)
Black /Asian/Other	17/171 (9.9%)	12/327 (3.7%)	66.8% (30.2-84.2 %)*
Black	9/111 (8.1%)	4/203 (2.0%)	78.3% (29.0 - 93.3%)**
Asian	2/20 (10.0%)	2/53 (3.8%)	68.0% (-129.4 - 95.5%)
Other	6/40 (15.0%)	6/71 (8.5%)	46.2% (-67.8 to 82.8%)

* *p <0.01*
** *p <0.02*

Injection and Sharing by Study Visit



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Neutralizing antibody

Cell-mediated immunity

From 2000 onwards

Study	Year	Population	Vaccine	Vaccine Efficacy
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Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial

Susan P Buchbinder, Devan V Mehrotra, Ann Duerr, Daniel W Fitzgerald, Robin Mogg, David Li, Peter B Gilbert, Javier R Lama, Michael Marmor, Carlos del Rio, M Juliana McElrath, Danilo R Casimiro, Keith M Gottesdiener, Jeffrey A Chodakewitz, Lawrence Corey, Michael N Robertson, and the Step Study Protocol Team*

Summary

Background Observational data and non-human primate challenge studies suggest that cell-mediated immune responses might provide control of HIV replication. The Step Study directly assessed the efficacy of a cell-mediated immunity vaccine to protect against HIV-1 infection or change in early plasma HIV-1 levels.

Methods We undertook a double-blind, phase II, test-of-concept study at 34 sites in North America, the Caribbean, South America, and Australia. We randomly assigned 3000 HIV-1-seronegative participants by computer-generated assignments to receive three injections of MRKAd5 HIV-1 gag/pol/nef vaccine (n=1494) or placebo (n=1506). Randomisation was prestratified by sex, adenovirus type 5 (Ad5) antibody titre at baseline, and study site. Primary objective was a reduction in HIV-1 acquisition rates (tested every 6 months) or a decrease in HIV-1 viral-load setpoint (early plasma HIV-1 RNA measured 3 months after HIV-1 diagnosis). Analyses were per protocol and modified intention to treat. The study was stopped early because it unexpectedly met the prespecified futility boundaries at the first interim analysis. This study is registered with ClinicalTrials.gov, number NCT00095576.

Findings In a prespecified interim analysis in participants with baseline Ad5 antibody titre 200 or less, 24 (3%) of 741 vaccine recipients became HIV-1 infected versus 21 (3%) of 762 placebo recipients (hazard ratio [HR] 1·2 [95% CI 0·6–2·2]). All but one infection occurred in men. The corresponding geometric mean plasma HIV-1 RNA was comparable in infected male vaccine and placebo recipients (4·61 *vs* 4·41 $\log_{10}$ copies per mL, one tailed p value for potential benefit 0·66). The vaccine elicited interferon-γ ELISPOT responses in 75% (267) of the 25% random sample of all vaccine recipients (including both low and high Ad5 antibody titres) on whose specimens this testing was done (n=354). In exploratory analyses of all study volunteers, irrespective of baseline Ad5 antibody titre, the HR of HIV-1 infection between vaccine and placebo recipients was higher in Ad5 seropositive men (HR 2·3 [95% CI 1·2–4·3]) and uncircumcised men (3·8 [1·5–9·3]), but was not increased in Ad5 seronegative (1·0 [0·5–1·9]) or circumcised (1·0 [0·6–1·7]) men.

Lancet 2008; 372: 1881–93

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See Comment page 1857

*Members listed at end of paper

HIV Research Section, San Francisco Department of Public Health, San Francisco, CA, USA (S P Buchbinder MD); Merck Research Laboratories, North Wales, PA, USA (D V Mehrotra PhD, R Mogg MS, D Li PhD, D R Casimiro PhD, K M Gottesdiener MD, J A Chodakewitz MD, M N Robertson MD); Fred Hutchinson Cancer Research Center, Seattle, WA, USA (A Duerr MD, Prof P B Gilbert PhD, Prof M J McElrath MD, Prof L Corey MD); GHESKIO, Port-au-Prince, Haiti (D W Fitzgerald MD); Weill Medical College of Cornell University, New York, NY, USA

Case split for infection endpoint
Primary analysis (Ad5 ≤ 200)

	Vaccine	Placebo
Total MITT cases	24	21
Cases included in PP efficacy analysis	19	11

Primary dataset reviewed by DSMB

Source: www.thelancet.com Vol 372 November 29, 2008

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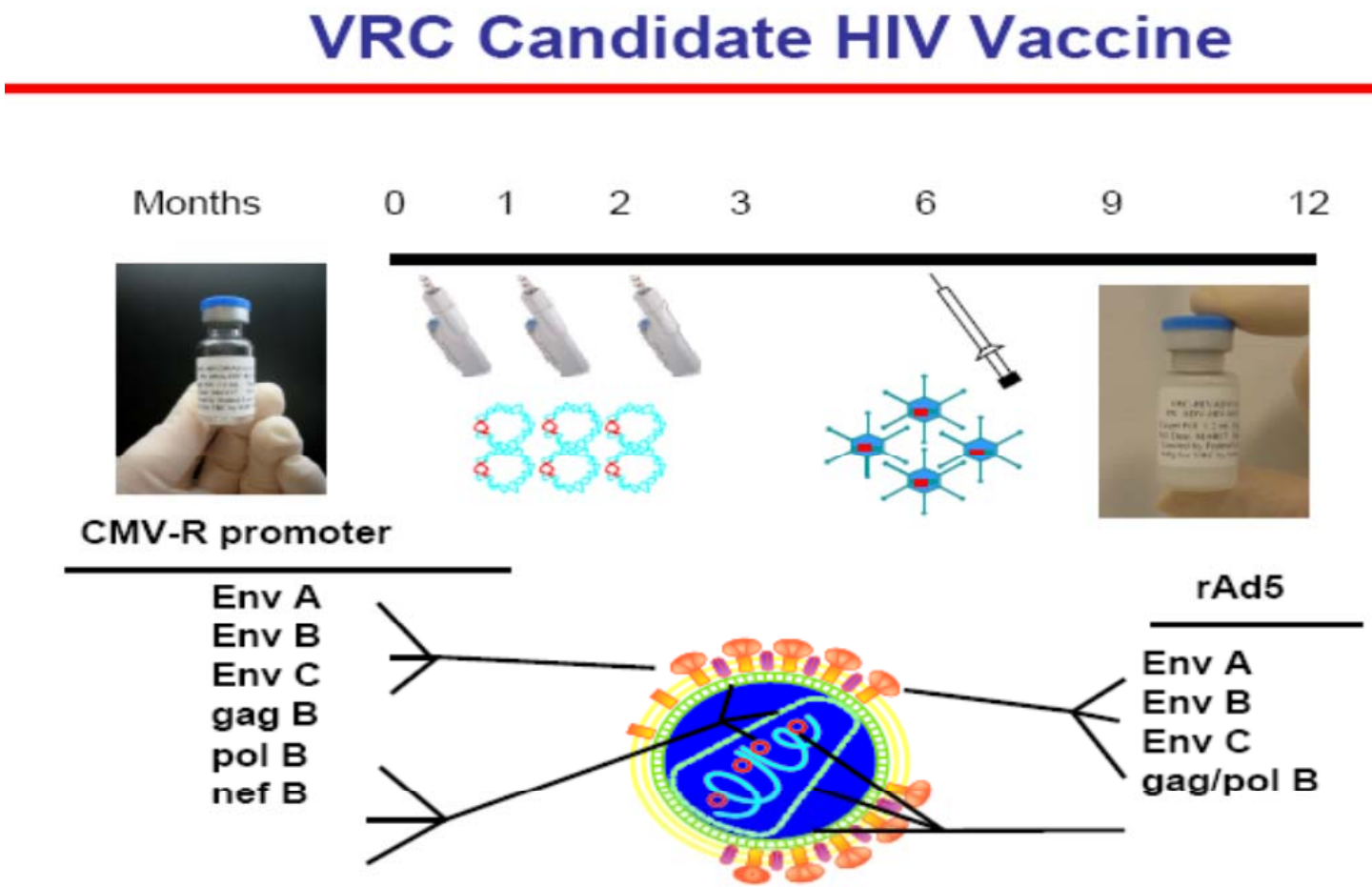
HVTN 505

Phase 2b, using a multiclade HIV-1 DNA plasmid followed by a multi-clade HIV-1 recombinant adenoviral vector in HIV-uninfected, adenovirus type 5 seronegative, circumcised men



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- The HVTN 505 study enrolled 2,504 volunteers at 21 sites in 19 U.S. cities.
- DSMB examined the information gathered from 1,250 volunteers who received the investigational vaccine regimen and 1,244 volunteers who received the placebo vaccine.
- 27 HIV infections occurred among the vaccine recipients, and 21 HIV infections occurred among the placebo vaccine recipients.(Per protocol)

NIH Discontinues Immunizations in HIV Vaccine Study

Source: http://www.hvtn.org

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RV144: *Prime - Boost strategy using two different vaccines:for inducing both humeral and cell mediated immunity*

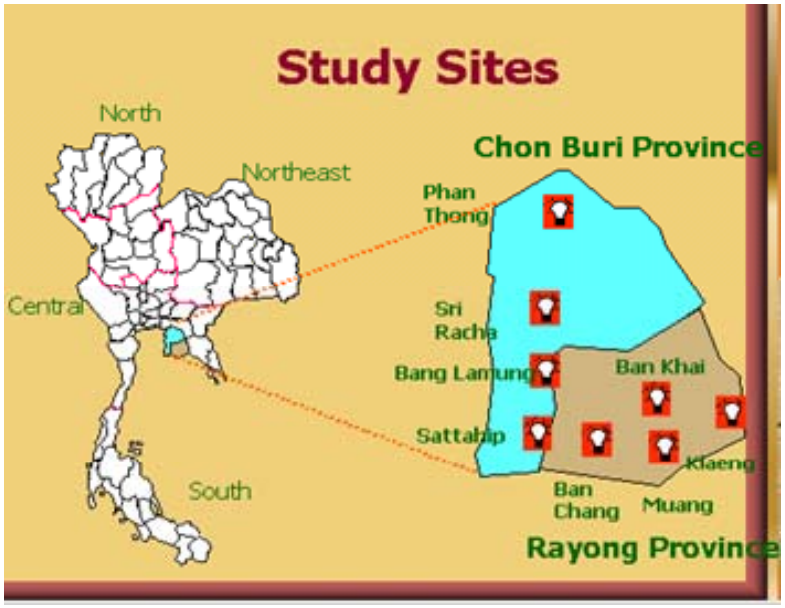
Prime Vaccine: ALVAC-HIV (vCP1521) from Sanofi Pasteur

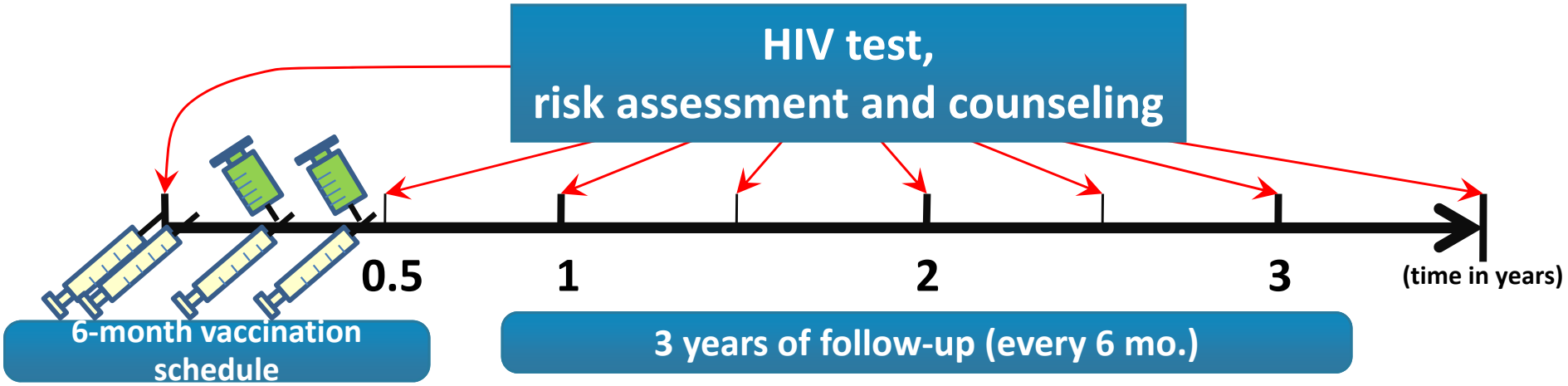
- Recombinant canarypox virus expressing
  the product of HIV-1 env, gag and protease genes
    gp120 env from Thai subtype E (92TH023)
    gp41, gag, and protease from LAI (subtype B)

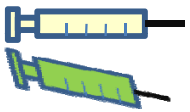
Booster vaccine: AIDSVAX ® B/E from VaxGen Inc.

- Recombinant gp120 from MN(subtype B)and A244 (subtype E)

- 16,402 HIV-negative men and women were enrolled.
- 13,978 participants had completed full series of vaccinations







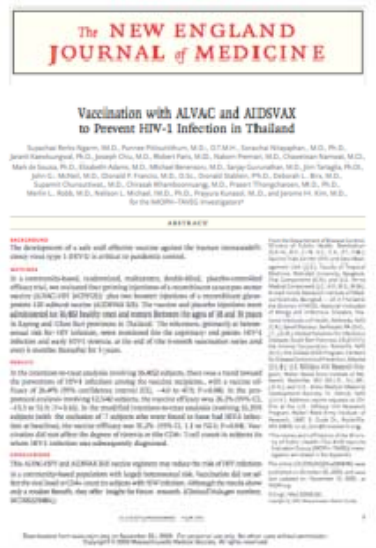
ALVAC®-HIV (vCP1521) priming at week 0, 4, 12, 24

AIDSVAX® B/E gp120 boosting at week 12, 24

First Sign of Success for HIV VAccine R&D:

The Thai HIV Vaccine Study (RV144)

- First HIV vaccine to show modest effectiveness in preventing HIV in humans.
- Demonstrated 31.2% efficacy at end of study (3.5 years)



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GS ID GLOBAL SOLUTIONS FOR INFECTIOUS DISEASES

sanofi pasteur
The vaccines division of sanofi-aventis Group

NIAID

WRAIR

Although protective efficacy was 31.2% 42 months after first vaccination, the highest efficacy was observed at ~12 MO.

Modified ITT Population

	VACCINE			PLACEBO			
Timepoint	Events	KM Rate (%)	SE (%)	Events	KM Rate (%)	SE (%)	Efficacy (%)
6	5	0.06	0.028	11	0.14	0.042	54.46
12	12	0.15	0.044	30	0.38	0.069	59.95
18	24	0.31	0.063	43	0.55	0.083	43.97
24	32	0.41	0.072	50	0.64	0.09	35.7
30	37	0.48	0.078	58	0.74	0.097	35.96
36	45	0.58	0.086	65	0.84	0.103	30.42
42	51	0.68	0.096	74	0.96	0.111	29.15

Proportional Hazard Model Calculations

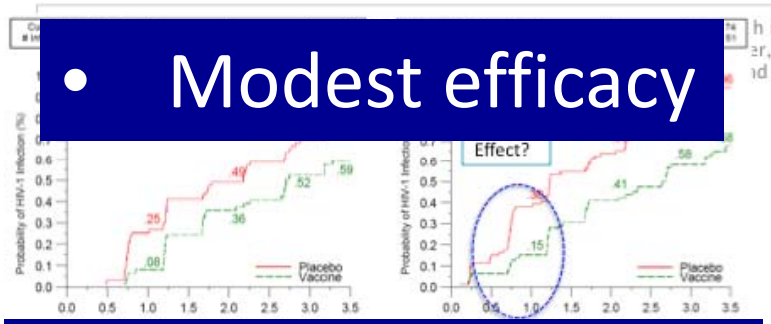
12 months: 60% (Cox PH, 95% CI = 22, 80)

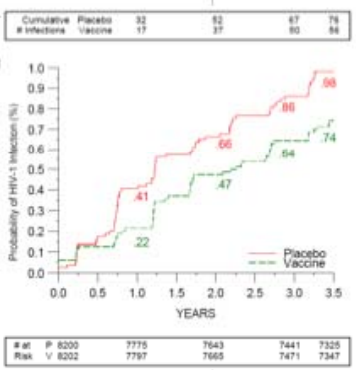
42 months: 31.2% (Cox PH, 95% CI = 1.1, 52.1)

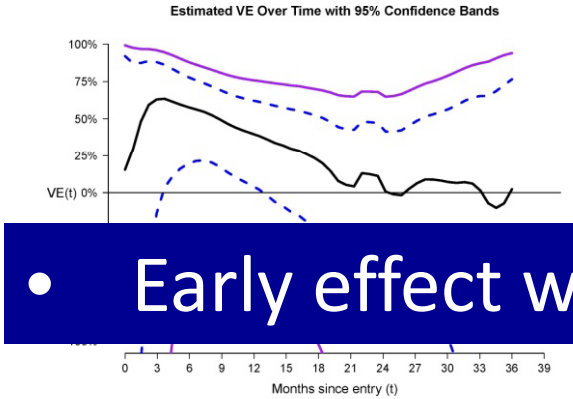
Kaplan Meier (KM) Efficacy Estimate (Vaccine/Placebo) at 6 Month Intervals

RV144 Summary(2009-2011)

- Modest efficacy

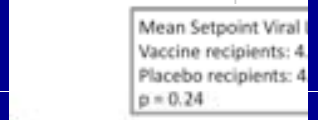




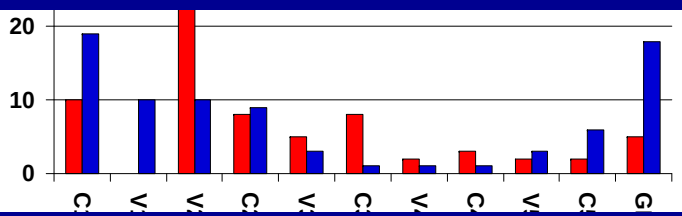


- Early effect wanes

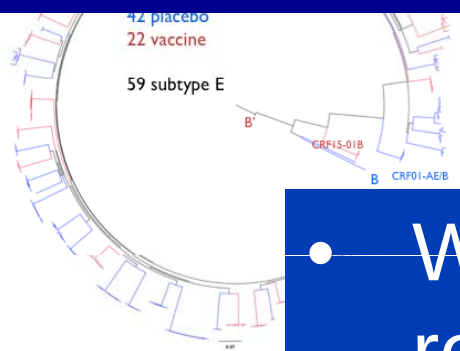
- No impact on post-infection VL or CD4



- 32% -CTL:CD4 > CD8 responses



- 90% of breakthrough viruses CRF01_AE



- 90% -Mainly bAb detected and decreases rapidly
- Binding AB was directed to V2

- Weak neutralizing antibody responses

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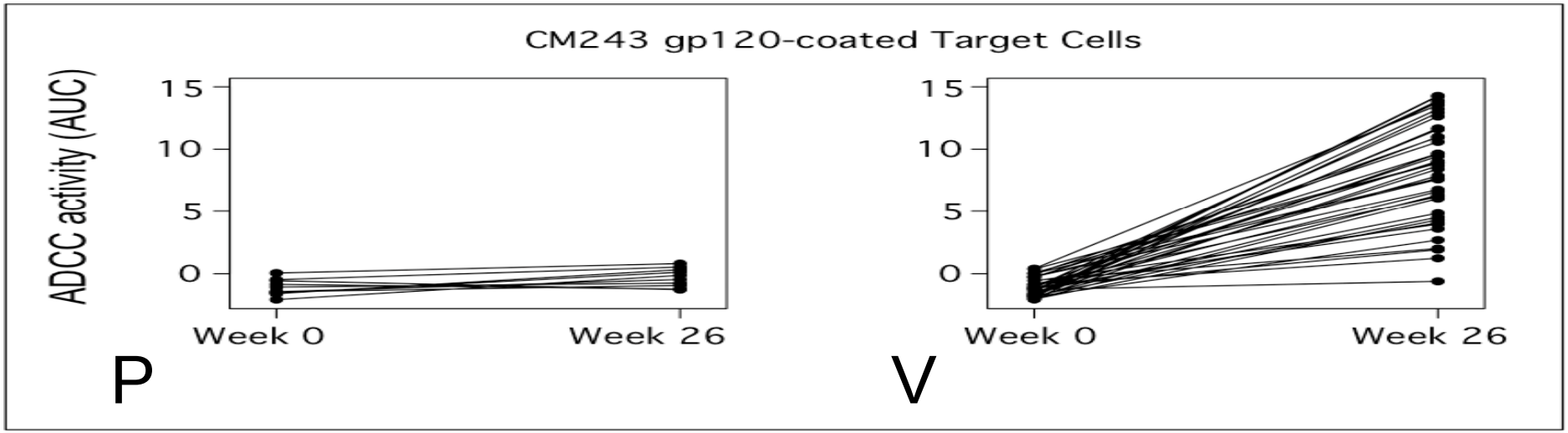
Antibody-Dependent Cell mediated Cytotoxicity

- ADCC may play an important role in the control of SIV and HIV-1 infection.
- Magnitude of ADCC Ab responses correlates inversely with virus set point in acute SIV infection in both unvaccinated macaques and in vaccinated animals after challenge.
- ADCC-mediating Abs have been shown to protect against HIV-1 infection in mother-to-infant transmission to correlate with both control of virus replication and lack of progression to overt disease

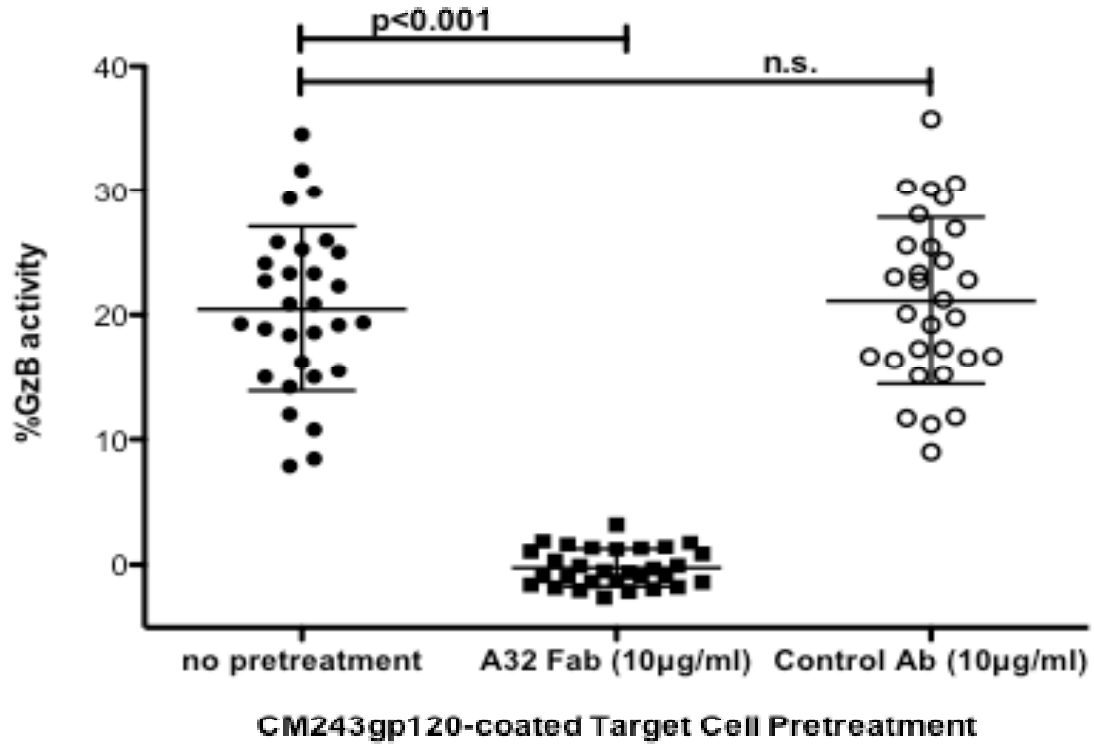
- One of the hypothesis is that the observed protection in RV144 may be partially due to ADCC-mediating antibodies.

		ADCC-CM243 assay N (%, 95% CI)	ADCC-92TH023 assay N (%, 95% CI)
Vaccine Recipients (n=40)	Week 0	0 (0%, 0-31%)	4 (10%, 2.8-23.7%)
	Week 26	36 (90%*, 76-97%)	29 (72.5%, 56.1-85.4%)
Placebo Recipients (n=10)	Week 0	1 (10%, 0-44.5%)	0 (0%, 0-31%)
	week 26	1 (10%, 0-44.5%)	1 (10%, 0.3-44.5%)



Mattia Bonsignori, Bart Haynes et al.J Virol. 2012 Nov;86(21):11521-32..

- As mAb A32 can block p ADCC response during chronic infection,
- 96.2% of ADCC activity generated from the vaccines were blocked by competition with the C1 region-specific A32 Fab fragment



Summary for ADCC

- A32-like ADCC responses are responsible for the majority of the ADCC responses detectable in top 30 responders among the RV144 vaccine recipients using gp120 coated target cells

- Qualitatively similar to anti-HIV-1 responses observed during chronic HIV-1 infections

- May have been partly responsible for the modest degree of protection observed.

Bonsignori M, Pollara J,--, Haynes BF. J Virol. 2012 Nov;86(21):11521-32.

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Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

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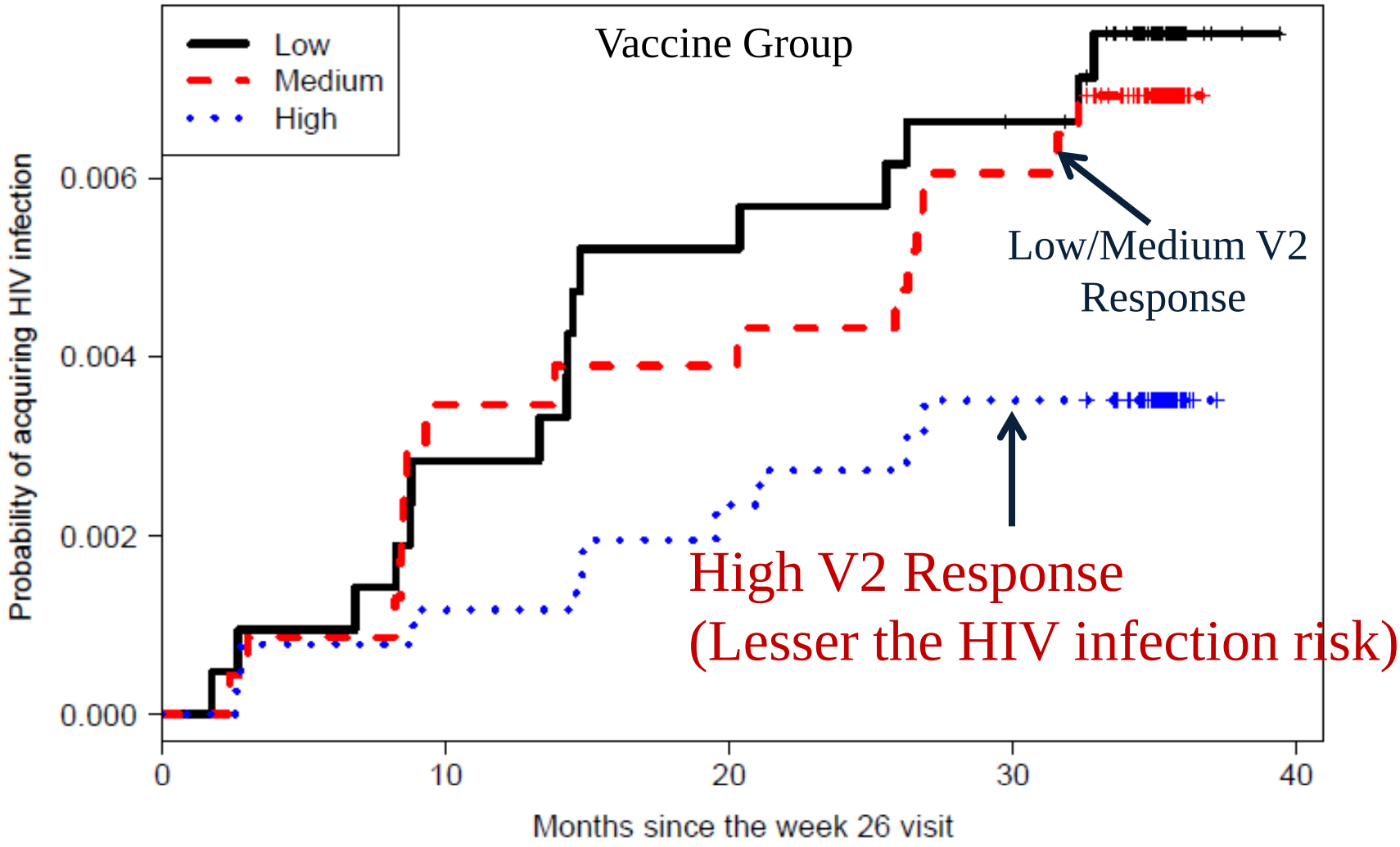
Variable	Relative risk	P-value	Q-value
IgA Binding to Envelope Panel	1.54	0.027	0.08
IgG Avidity A244 gp120	0.81	0.37	0.56
ADCC AE.HIV-1 Infected CD4 Cells	0.92	0.68	0.68
Tier 1 Neutralizing Antibodies	1.37	0.22	0.45
IgG Binding to gp70-V1V2	0.57**	0.015	0.08
CD4+ T Cell Intracellular Cytokines	1.09	0.61	0.68

All 6 variables together in multivariate

2 individual variables were significant:

** Means 43% decrease in the HIV infection rate for every 1sd higher increment in the V2 response level

gp70 V1-V2 Antibody Levels Inversely Correlated with the Rate of HIV Infection



Logistic regression model accounting for the sampling design:
Estimated relative risk = 0.57 per sd increment in V2 response (p=0.015)

43% lower infection rate per sd increase

		Univariate Logistic Regression Interaction			Univariate Cox Regression Interaction		
IgA Binding	20% ADCC	1.11	(0.71, 1.67)	0.60	1.14	(0.75, 1.73)	0.54
	50% ADCC	1.43	(1.01, 2.02)	0.05	1.49	(1.04, 2.15)	0.03
	80% ADCC	1.96	(1.22, 3.14)	0.01	2.11	(1.27, 3.51)	< 0.01
	Interaction	--	--	0.03 (0.10)	--	--	0.03 (0.07)
ADCC	20% IgA Binding	0.55	(0.31, 1.00)	0.05	0.58	(0.34, 0.99)	0.05
	50% IgA Binding	0.74	(0.49, 1.11)	0.14	0.76	(0.52, 1.13)	0.17
	80% IgA Binding	1.06	(0.73, 1.55)	0.75	1.08	(0.73, 1.61)	0.70
	Interaction	--	--	0.03 (0.10)	--	--	0.03 (0.07)

- In secondary immune correlates analyses, low plasma IgA Env antibody levels in association with high levels of ADCC were inversely correlated with infection risk

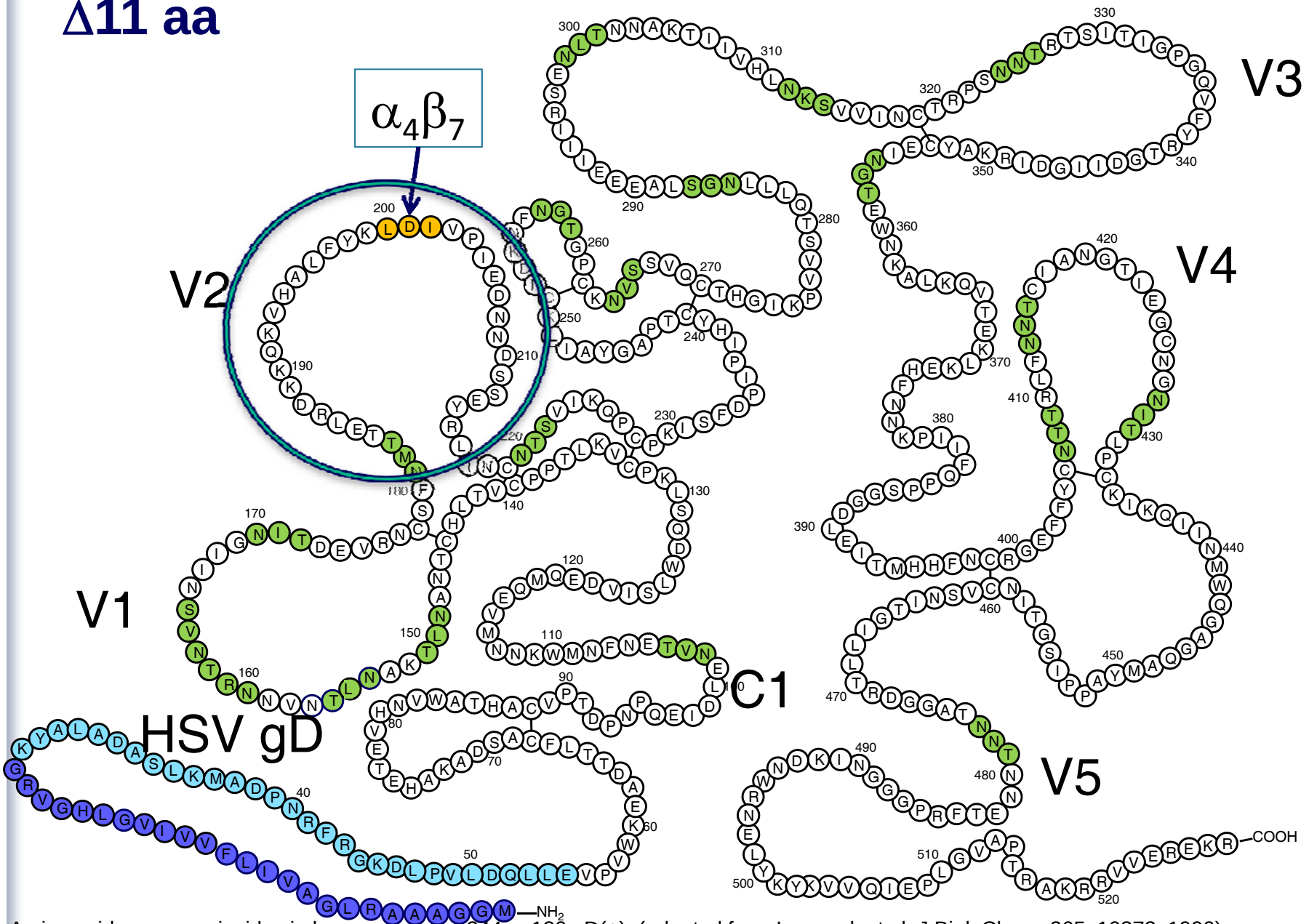
Tomaras GD. Proc Natl Acad Sci USA. 2013 May 28;110(22):9019-24

Summary for Correlates of Risk and Sieve analysis

- IgG to gp70V1V2 (43% decrease in infection risk)
- IgA to Env panel (54% increase in infection risk)

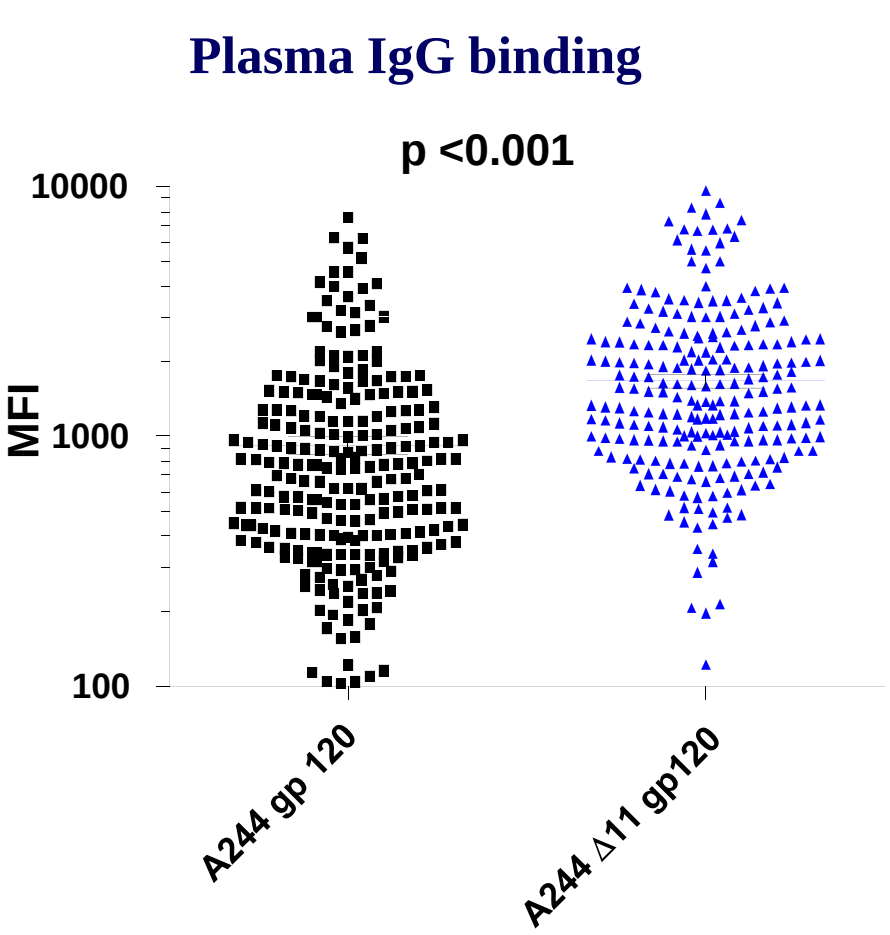
- There is evidence that the RV144 Env IgA correlate involves interactions of antibodies with affinities for different Fc receptors.
- A fraction of RV144 elicited IgA specificities (C1 region specific) are capable of inhibiting IgG and NK mediated ADCC.

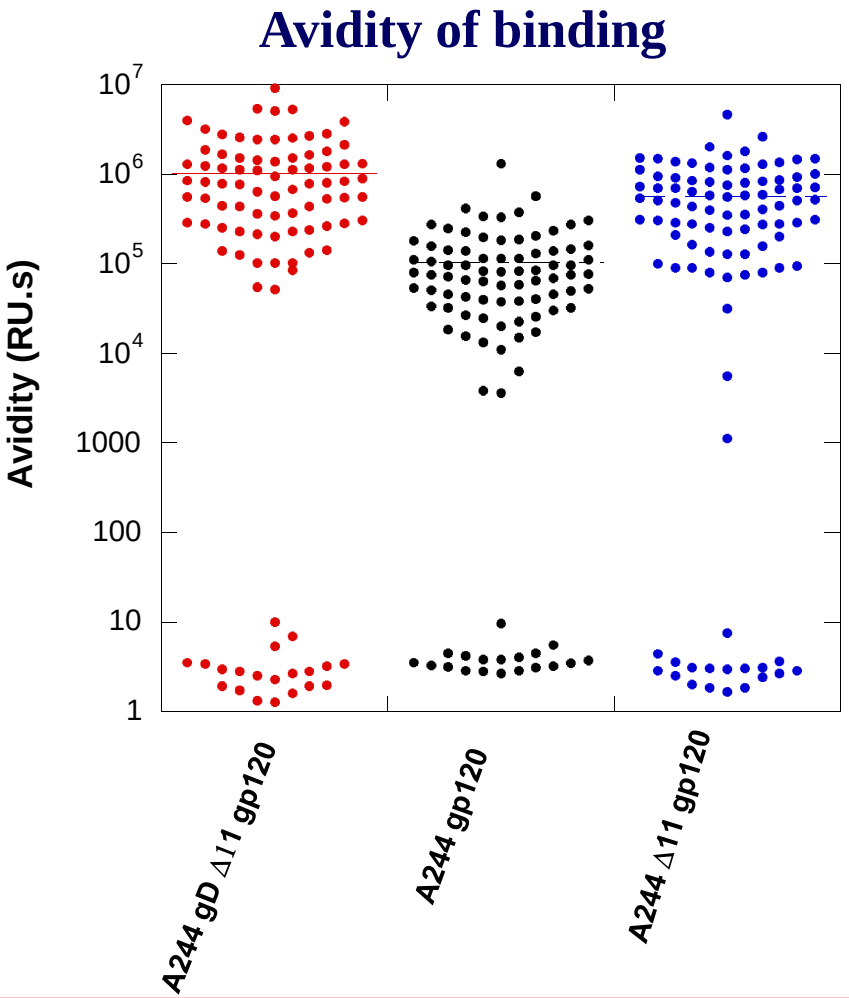
Uniqueness of rgp120 A244 gp120 : gD tag and Δ11 aa



Amino acid sequence inside circles represents A244 gp120 gD(+). (adapted from Leonard, et al.,J.Biol. Chem. 265, 10373, 1990).

Effects of Δ11 and/or gD tag on antibodies responses





Δ11 aa deletion of the rgp120 is important for stimulating binding antibodies

CAVD the collaboration for AIDS vaccine discovery
Global HIV Vaccine Enterprise
BILL & MELINDA GATES foundation

Future HIV VACCINE clinical R&D

MAHIDOL UNIVERSITY
Wisdom of the Land

- Developing vaccines that induce both CD4 and CD8 responses (and different subsets of these responses), together with broad neutralizing antibodies
- Getting a better sense of what's happening at the mucosal sites of exposure—the T-cell responses were measured mainly in the blood, which may or may not be indicative of the quality and magnitude of responses at the mucosal sites of sexual exposure.

Building on RV144: A Regional Vaccine Strategy

RV305:
Secondary Boost

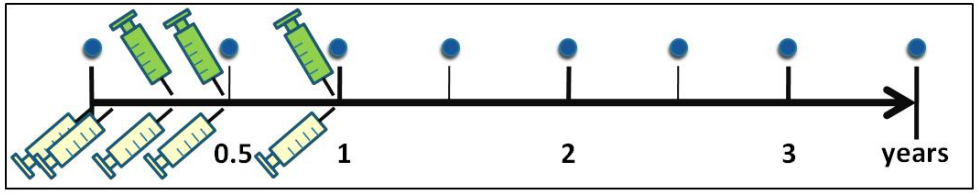
RV306:
1 year boost

Phase IIb/III Efficacy:

- Phase III: Thai community risk or MSM high-risk

Trials are prime-boost regimens with secondary boost

2011	2012	2013	2014	2015	2016	2017



HIV test, risk assessment and counseling

ALVAC prime (0, 4, 12, 24, 52 wk)

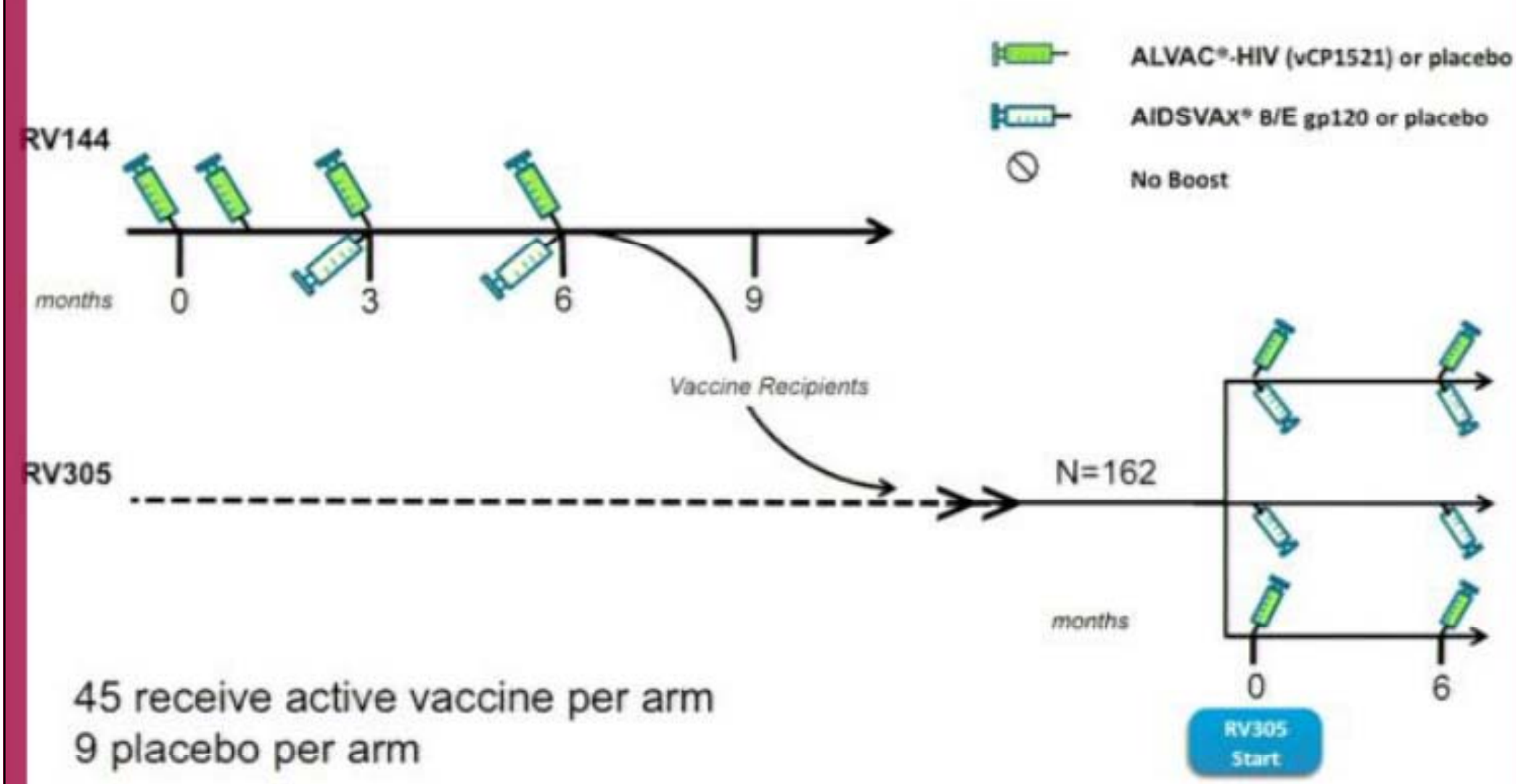
AIDSVAX boost (12, 24, 52 wk)

Global HIV Vaccine Enterprise

The Collaboration for AIDS Vaccine Discovery

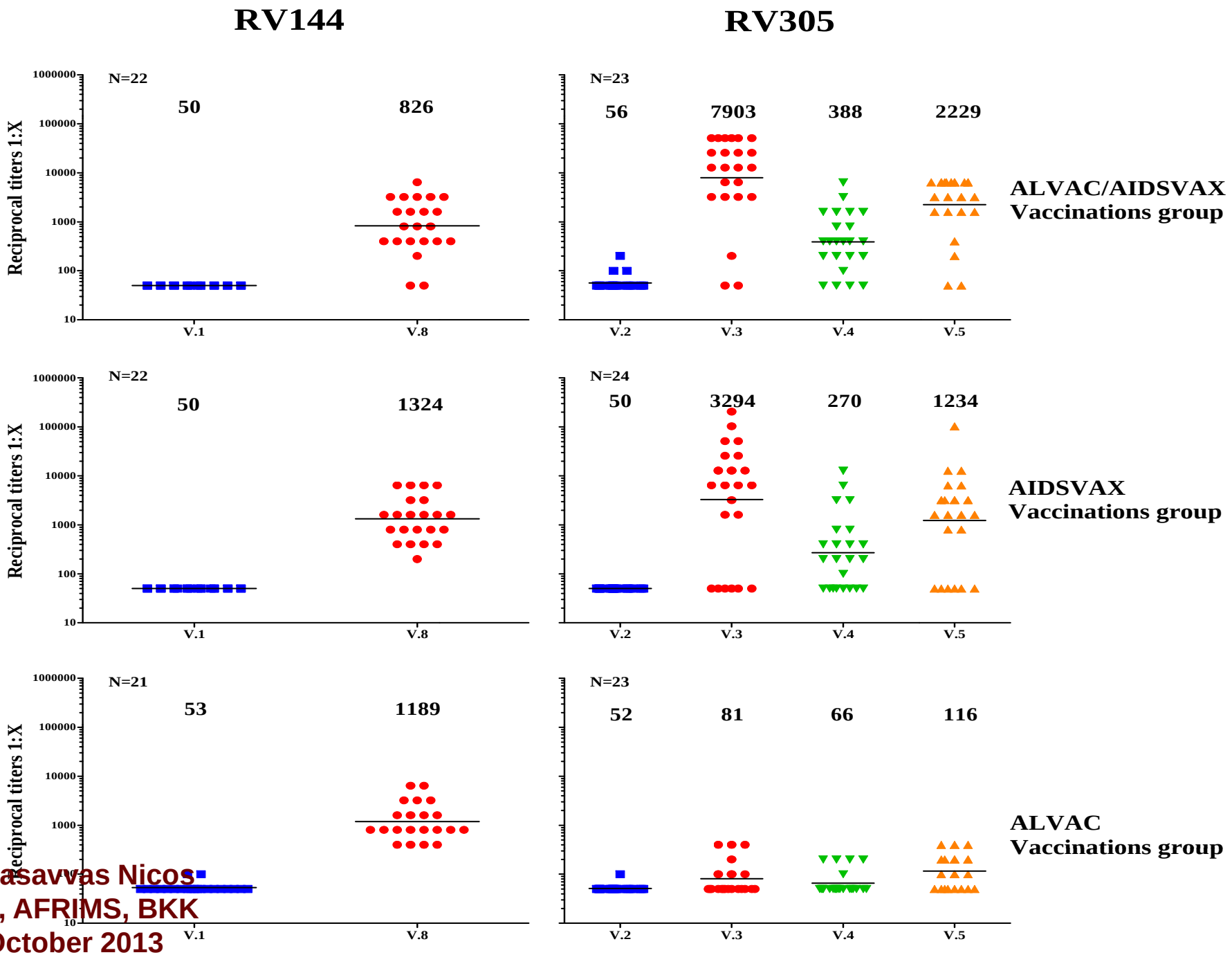
BILL & MELINDA GATES foundation

RV305 Vaccination Schedules



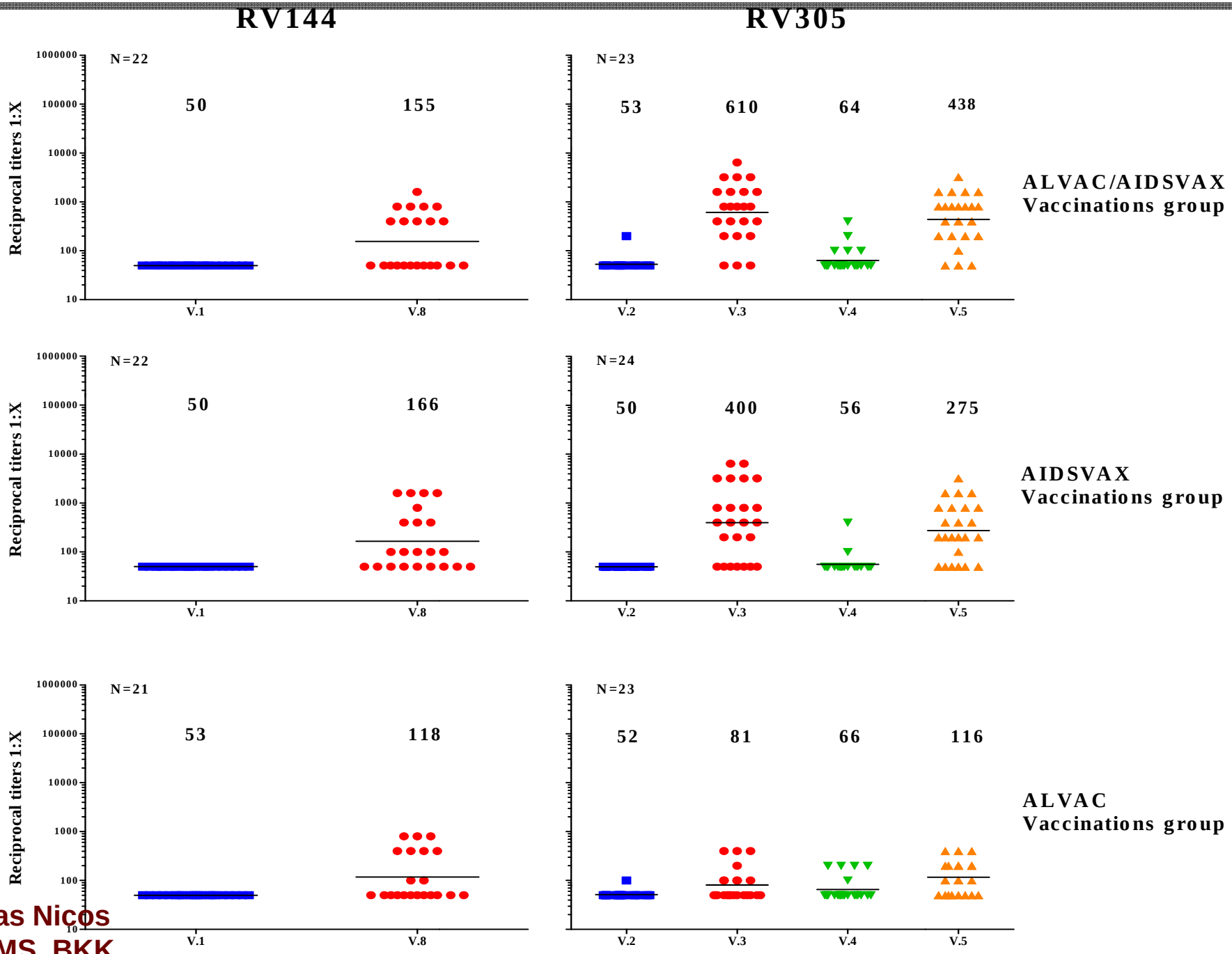
Complete vaccination , FOLLOW up continue

Geometric Mean Titers (GMT) of Antibody Responses (IgG) to gp70 V1V2 E (92TH023) Induced in RV305



Karasavvas Nicos
HIL, AFRIMS, BKK
8 October 2013

Geometric Mean Titers (GMT) of Antibody Responses (IgG) to gp70 V1V2 B (Case A2) Induced in RV305



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8 October 2013

(A)

CD4 T cells	Env	EnvΔV2	V2 loop	Lai Gag
Placebo	0/3	0/3	0/3	0/3
Combination	4/5	3/5	2/5	0/5
AIDSVAX®B/E	0/3	0/3	0/3	0/3
ALVAC-HIV	0/5	0/5	0/5	0/5

(B)

CD8 T cells	Env	EnvΔV2	V2 loop	Lai Gag
Placebo	0/3	0/3	0/3	0/3
Combination	0/5	0/5	0/5	0/5
AIDSVAX®B/E	0/3	0/3	0/3	0/3
ALVAC-HIV	2/5	0/5	0/5	0/5

Alex Schuetz, PhD , J Kim, et al ,AIDSVACCINE 2013

Summary for RV 305

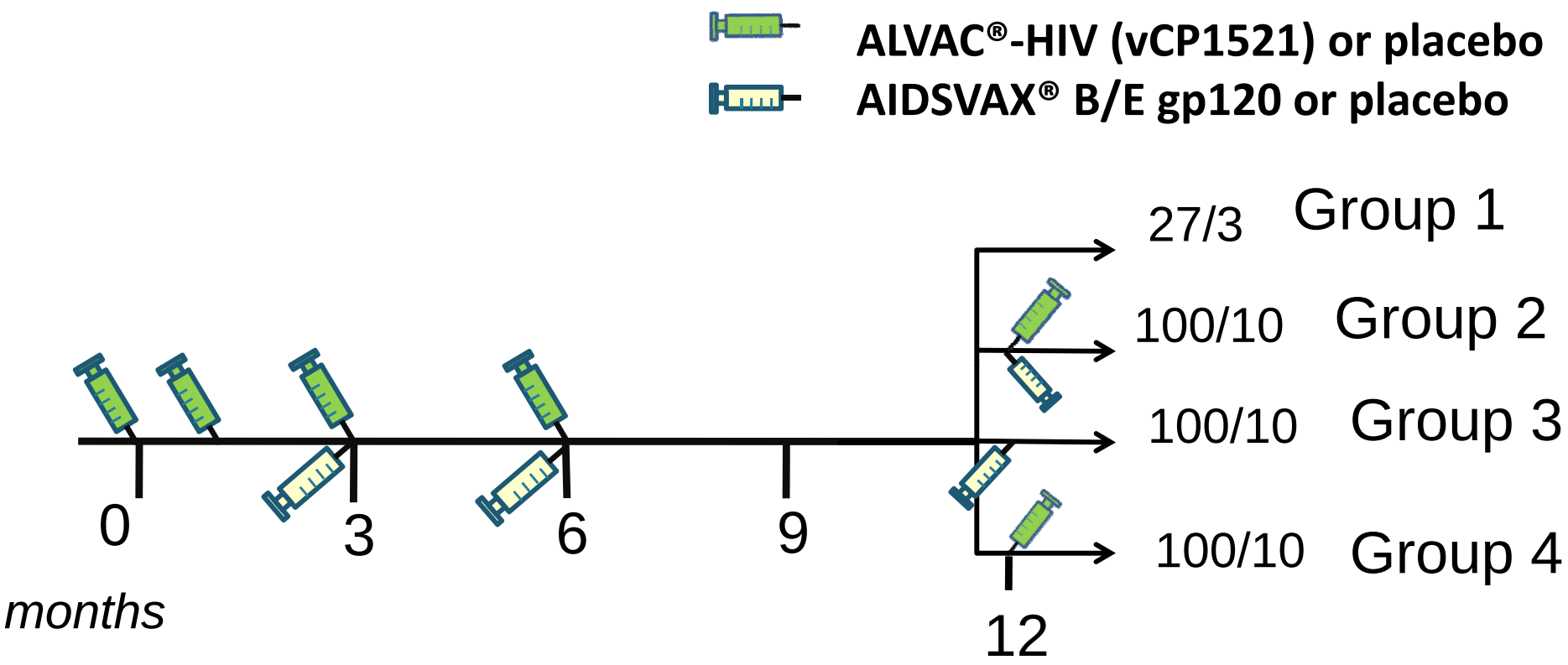
- Plasma bAb and nAb Responses following first boost are higher than RV144 peak immunogenicity :

  Binding to gp120 and V2 scaffold

- The second boost does not achieve same peak binding antibody responses for either gp120 or V2

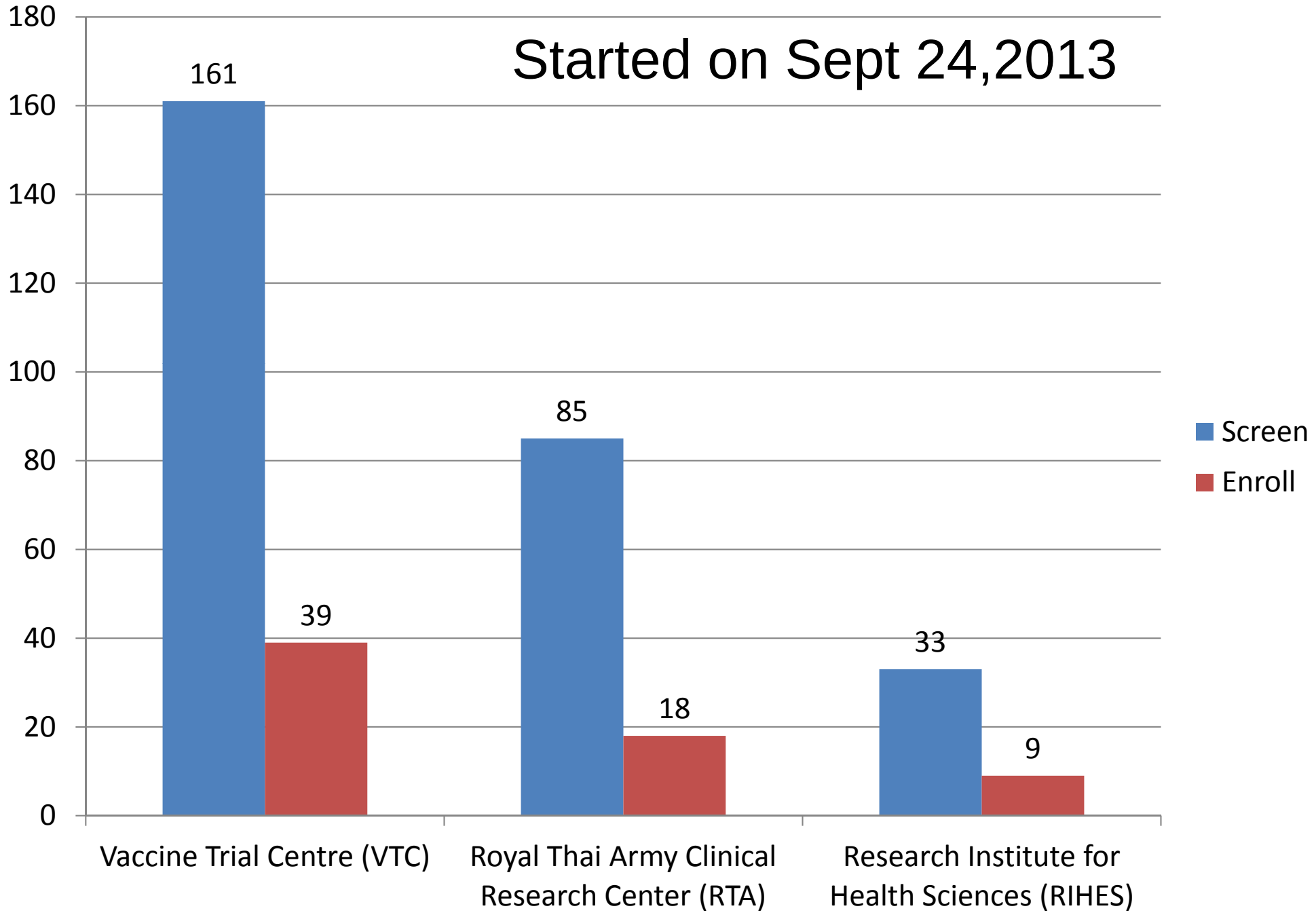
- Cellular data incomplete but unlikely to support ALVAC alone at week 48 as a viable regimen

RV306 Schedules



MHRP

RV306 Screening and enrollment by site (Data as of 26 Nov 2013)



What are the steps from RV144 to a licensed vaccine?

AVEC

Licensure (?)

Two trials: southern Africa (clade C) and Thailand

Higher incidence (risk) hetero-sexual populations and MSM

Better immunogens + new adjuvant + extra “boost” = higher VE

A244 gp120 of AIDSVAX has unique features: V2

Antibody against V1V2 reduces infection risk

RV144: 31% efficacy at 42 months, 60% at 12 months, low risk population

Where is the next vaccine?

- ALVAC-HIV (vCP1521): to be provided by Sanofi-Pasteur
- gp120 B/E
  - VaxGen (AIDSVAX B/E) no longer a company
  - RV144 correlates work has identified improvements in the A244 gp120 protein and a better subtype B protein (6240)
  - Novartis is under contract with Bill & Melinda Gates Foundation to make the cell lines for gp120 B and E

Moving Forward in Thailand

AIDS Vaccine Efficacy Consortium (AVEC) Summit for an AIDS-Free Generation in Thailand

Bangkok, August 2013

U.S. Ambassador to Thailand, Kristie Kenney, Advisor to the Thai Minister of Science and Technology, and the Thai Minister of Public Health address Summit attendees.

- Government of Thailand announced commitment to build on RV144 by supporting:
  - Future HIV vaccine efficacy study
  - Flexible biologics manufacturing capability that could support the production of a efficacious HIV vaccine

- AVEC seeks to develop Thai vaccine production (or biologics) capability in general and HIV vaccine production specifically
- AVEC reduces risk through Thai government support leveraged by other funding support

Challenges for Future Vaccine Trials

- Multiple doses AND COMPLEX regimen / delivery methods-retention , compliance
- Issues of HIV induced positivity- rate and duration of positivity
- Available of diagnostic test kits for true infection in setting of host countries
- Treatment and care: increase demand to provide not only ARV but to include other related cares and preventions

Community education and engagement on social value and scientific validity is very critical

It is going to be a long road to an HIV vaccine

Thanks: To all participants around the world,
To all collaborators globally
To all funders/sponsors
Thanks for your attention

Collaborating Institutions

- MOPH
- AFRIMS – US and Thai Component
- Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH
- Faculty of Tropical Medicine, Mahidol University
- Global Solutions for Infectious Diseases
- Henry M. Jackson Foundation for the Advancement of Military Medicine
- Ministry of Public Health, Thailand
- sanofi pasteur
- The Bill & Melinda Gates Foundation's Collaboration for AIDS Vaccine Discovery (CAVD)
- Center for HIV/AIDS Vaccine Immunology (CHAVI)
- Royal Thai Army
- HIV Vaccine Trials Network (HVTN) Laboratory Program
- Fred Hutchinson Cancer Research Center, SCHARP
- U.S. Military HIV Research Program, Walter Reed Army Institute of Research; U.S. Army Medical Research and Materiel Command
- Ragon Institute
- Pox Protein Public Private Partnership
- Crucell