

Breakthroughs and Big Questions: AIDS vaccine research in 2014

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Future of HIV-1 vaccines is bright

Major breakthroughs in last 5 years converge:

- **First Efficacy signal - RV144**
- **New technology - viral targets, Env structure**
- **Human broadly neutralizing Abs - protect NHP**
- **CD8 T cells - protect NHP, clear infection**

HIV Vaccine Research and Development “breakthroughs”

- RV144 Efficacy Signal

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- Correlates work ongoing
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- Hundreds of new bNabs identified
- 4 viral targets (MPER, CD4bs, glycan V3, V1V2)
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- T cell immunogens

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How long does it take to make a vaccine?

Disease	Years to develop vaccine
Typhoid	105
Haemophilus influenzae B	92
Pertussis	89
Polio	30
Measles	42
Hepatitis B	15
HIV	30 and counting

Source: Modified from H. Markel, NEJM 2005

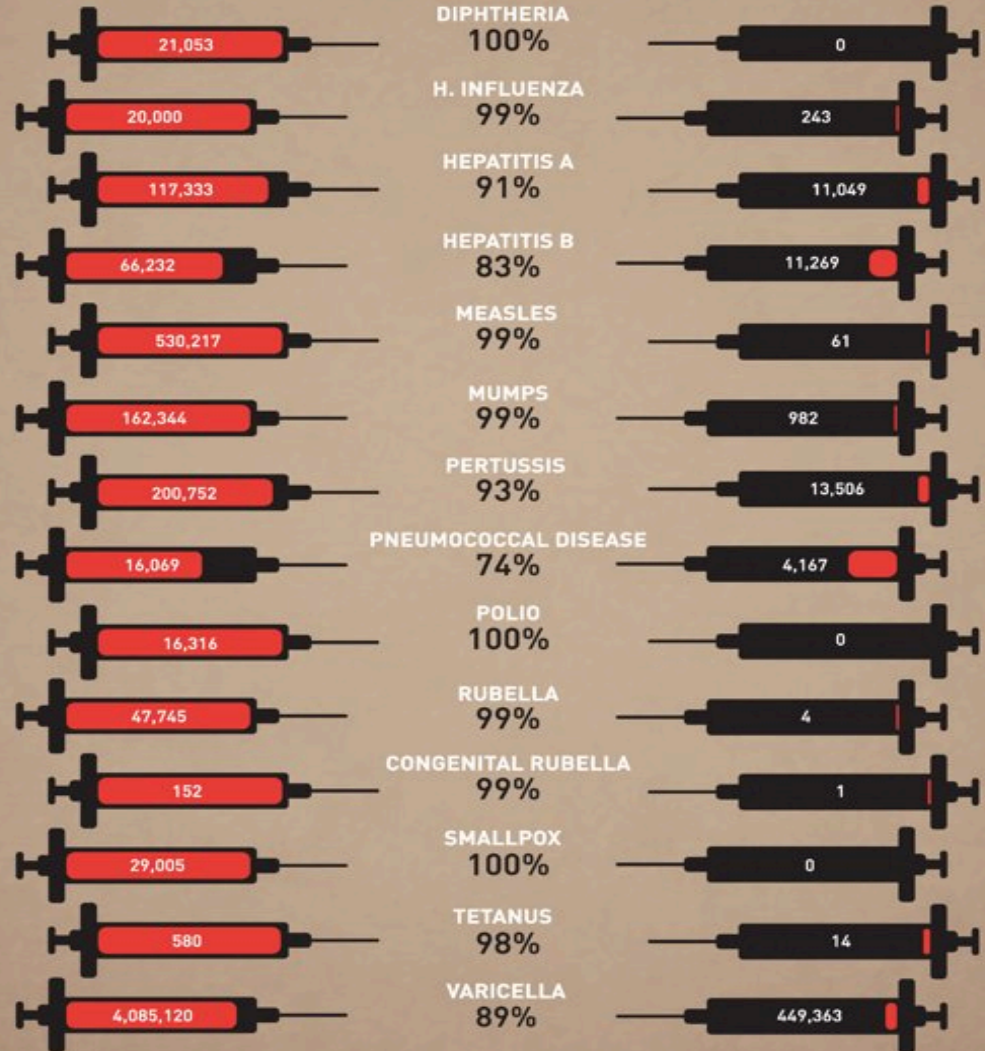
Do they work?

PRE-VACCINE ERA
ESTIMATED ANNUAL
MORBIDITY IN THE U.S.

%

MOST RECENT
REPORTS OF
CASES IN THE U.S.

DECREASE



"How Vaccines Have Changed
Our World in One Graphic"

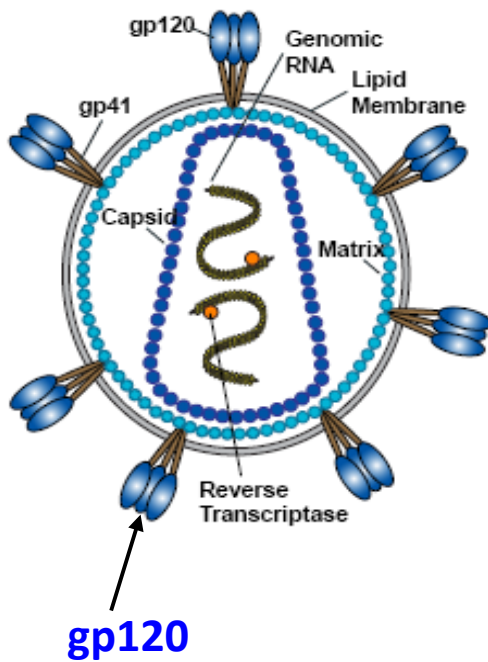
www.forbes.com

Feb. 19, 2013

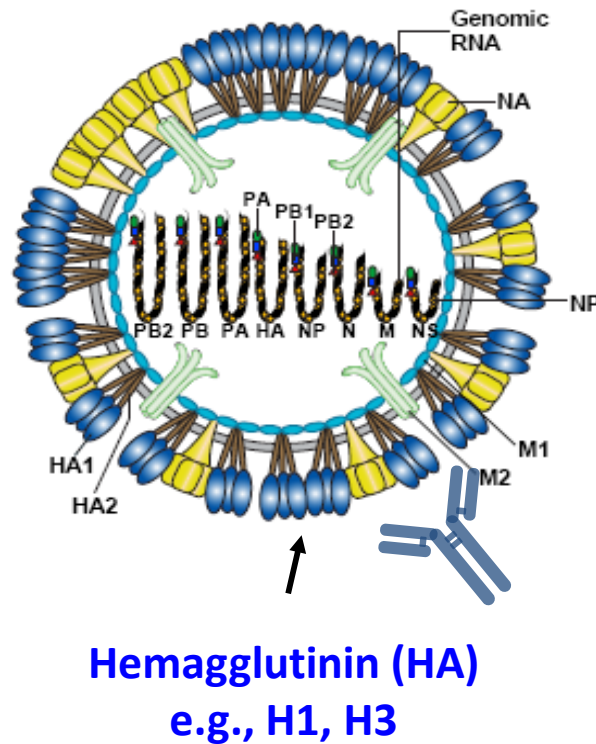
(using data from JAMA 2010)

Most effective vaccines induce Abs to key viral surface protein(s)

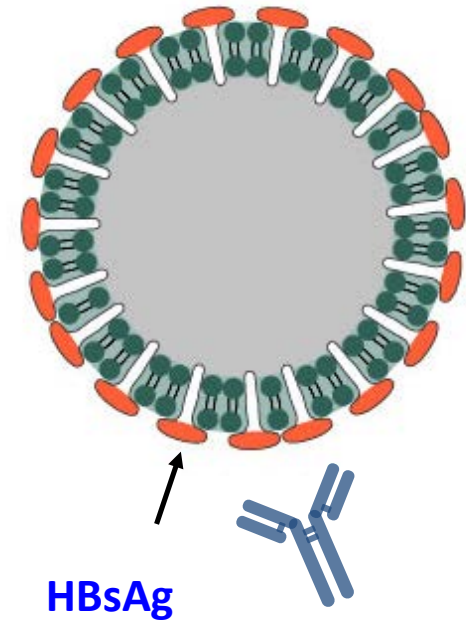
HIV-1



Influenza A



Hepatitis B



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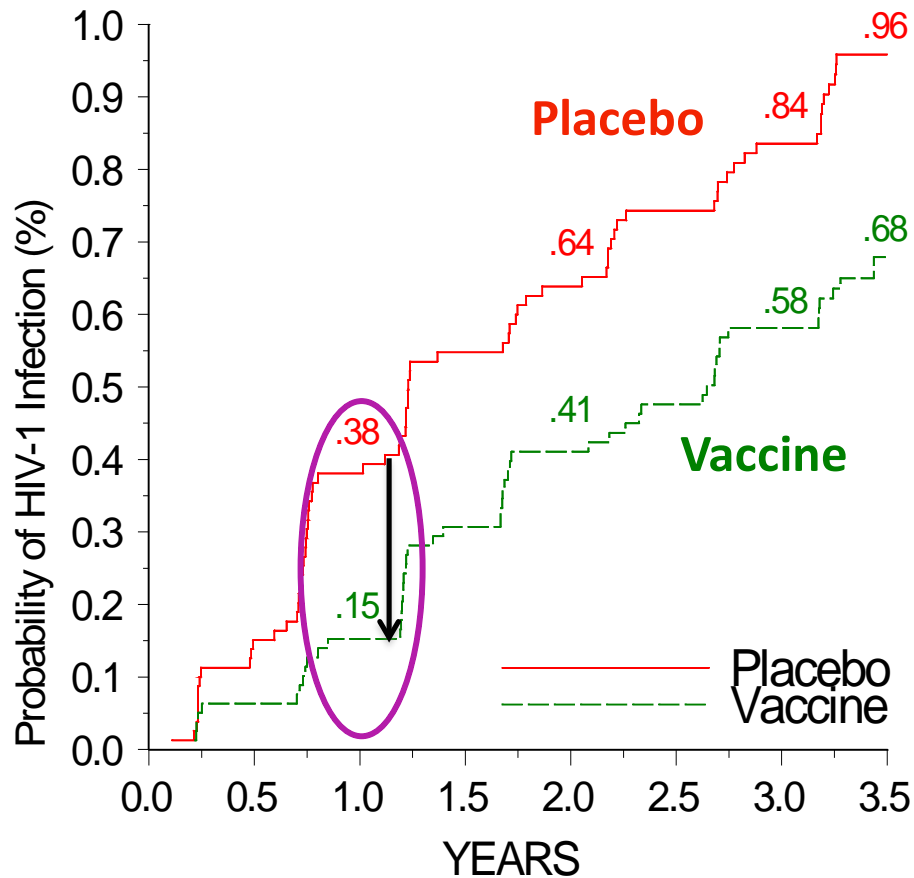
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RV144 – First link to Clinical Efficacy



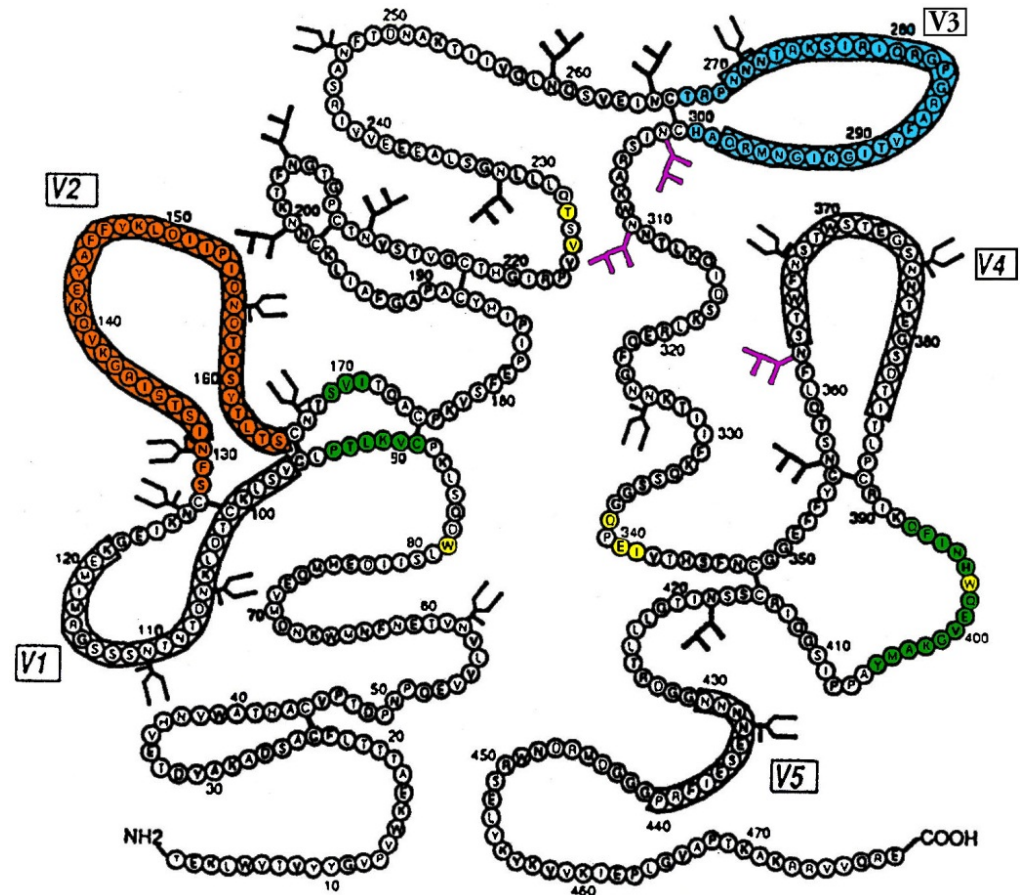
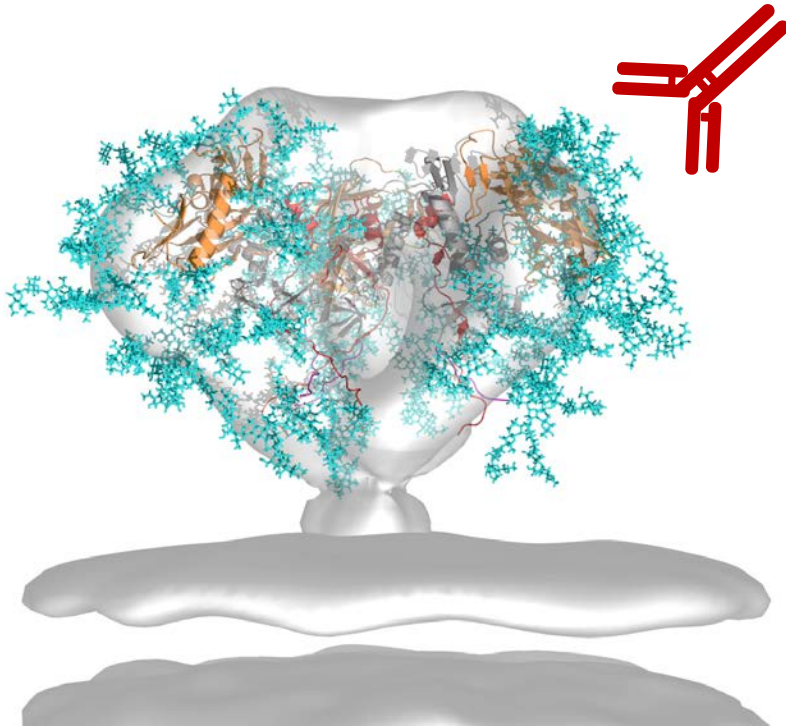
Modified ITT Population

Timepoint	VACCINE			PLACEBO			Efficacy (%)
	Events	KM Rate (%)	SE (%)	Events	KM Rate (%)	SE (%)	
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

Waning durability Ab?

RV144 Antibody Correlates

Antibodies to variable loop regions (V1V2)



V2 IgG Abs correlate with decreased infection risk*

Pox-Protein Public Private Partnership (P5)

- **Goal:** Substantiate and extend the RV144 result in high incidence populations
- **Partnership:** BMGF, NIAID/DAIDS, Novartis, Sanofi-Pasteur and USMHRP with critical linkages to:
 - Medical Research Council of RSA
 - GlaxoSmithKline (provide ASO1B)
- **Implementers:** HIV Vaccine Trials Network

Pox-Protein Public-Private Partnership (P5)

Licensure Track

Products

ALVAC-HIV (vCP2438)

- HIV-1 Clade C (ZM96) gp120 env
- HIV-1 Clade B (LAI) gag, pro and gp41 tm anchor sequence

gp120 Env proteins

- 1086
- TV1

MF59 Adjuvant

Correlates/Discovery Track

Products

DNA-HIV-PT123

- HIV-1 Clade C

NYVAC-HIV-PT1/PT4

- HIV-1 Clade C (ZM96) gp120 env

gp120 Env proteins

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MF59, AS01B Adjuvants

Partners , Geography, and Networks

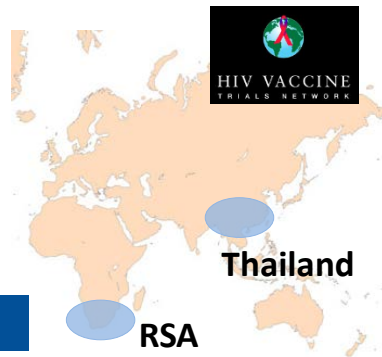
SANOPI PASTEUR

NOVARTIS
VACCINES AND
DIAGNOSTICS

BILL & MELINDA
GATES foundation

MHRP
U.S. MILITARY HIV RESEARCH PROGRAM

NIH National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.



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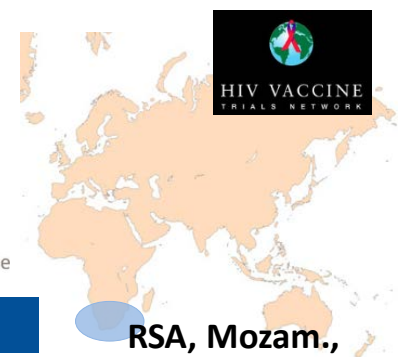
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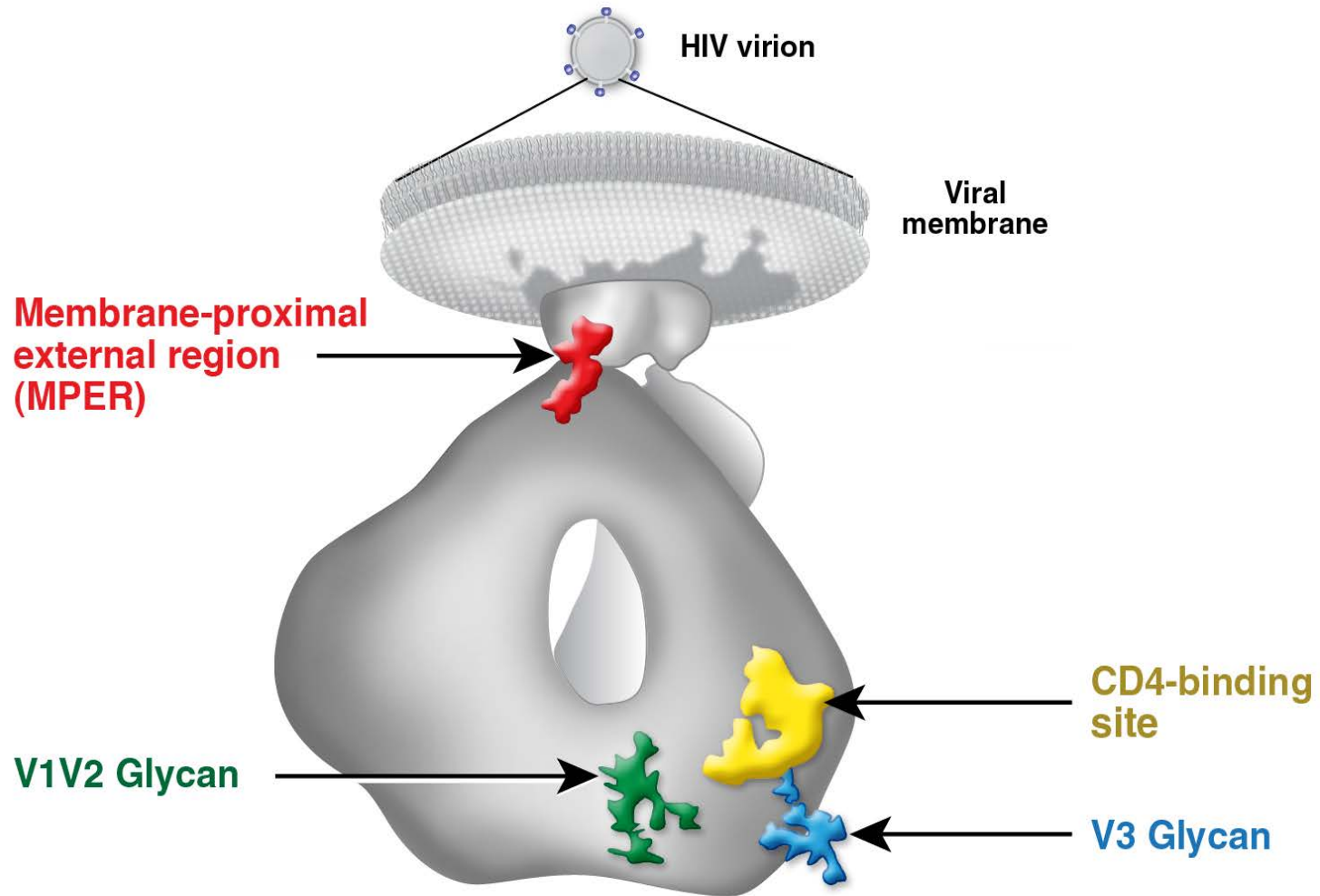
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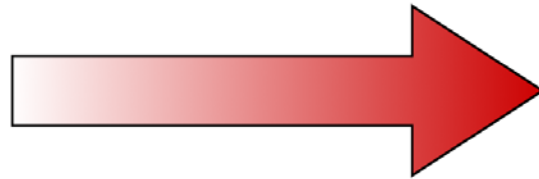
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Sites of vulnerability = targets of BNabs



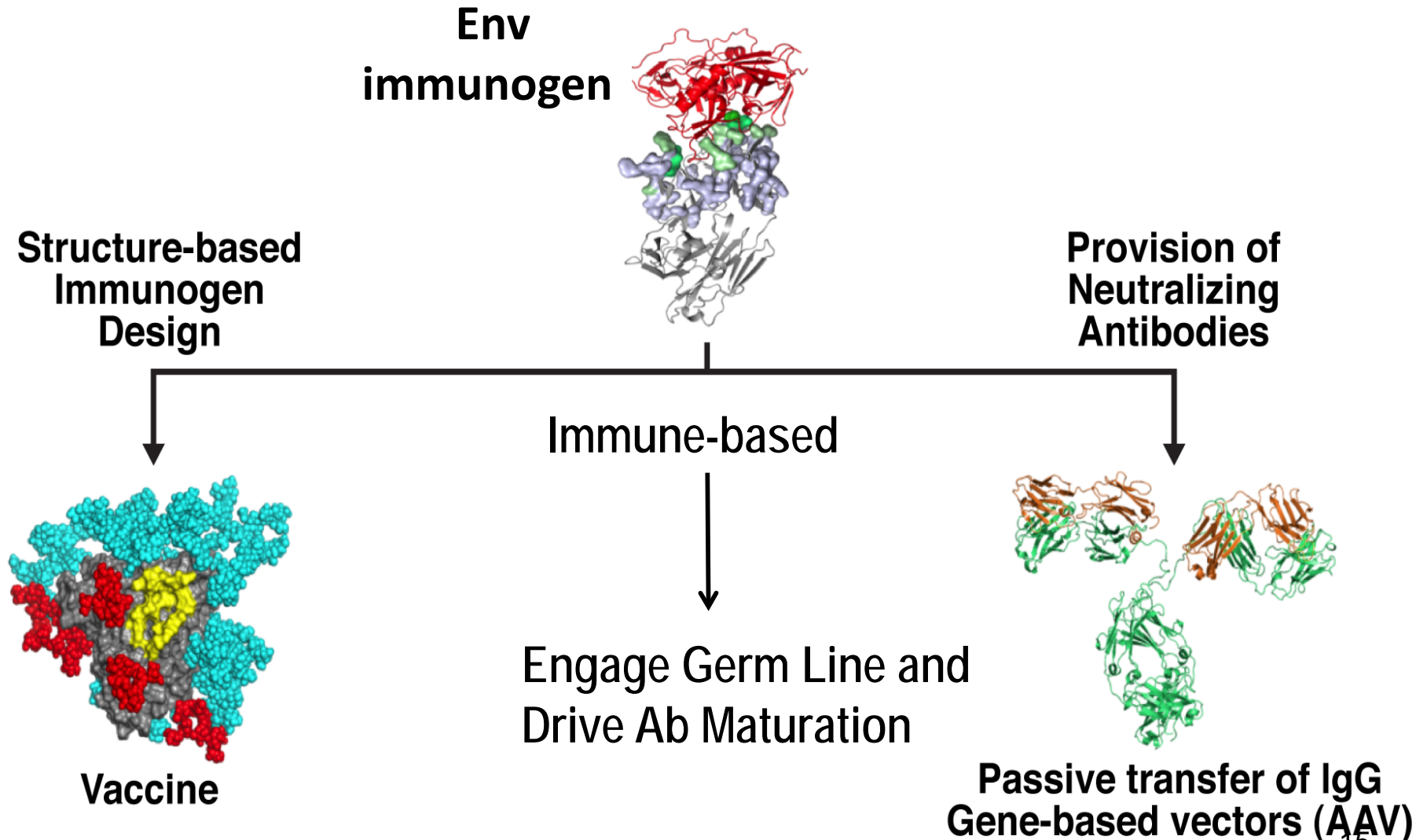
Critical Challenge in the Development of an HIV Vaccine

**Neutralizing
Epitope**



Immunogen

Neutralizing Antibody Approach to HIV Prevention



Neutralizing antibody hurdle

Recent study in AIDS 2014 showed exciting news:

- **Modestly neutralizing Abs may be more common than we think**
 - There is a spectrum of responses
 - Most sera shows some level of cross-neutralization
 - Approx. 50% of sera neutralize 50% of viruses
 - Titers of neutralization (potency) were correlated with breadth
 - Many sera had breadth ~ to several of less potent bNAbs
- **Good news for vaccine induced antibodies**

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nature

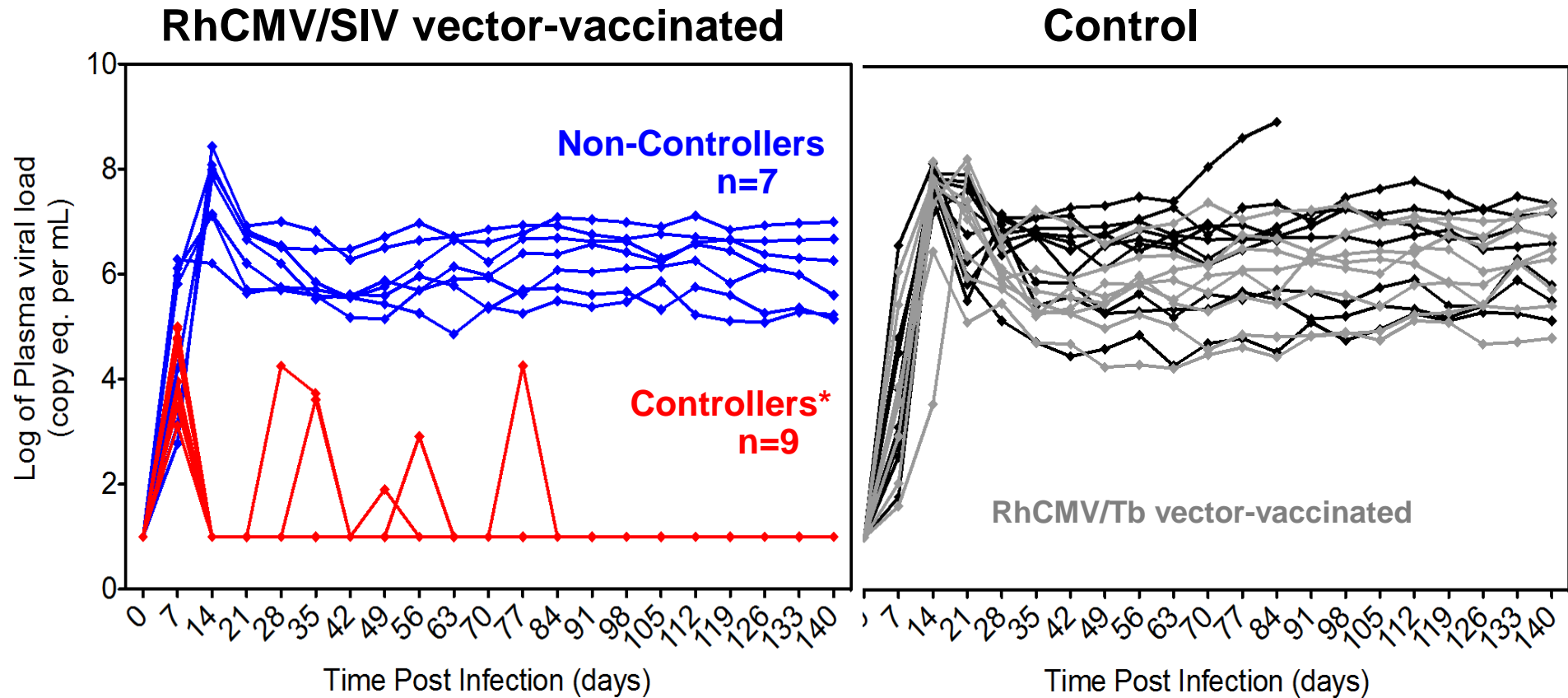
Immune Clearance of Highly Pathogenic SIV Infection

SG Hansen, LJ Picker et al.

- **Live CMV vector vaccine induces potent CD8+ T cell response in monkeys that results in profound early control and progressive immune clearance of highly pathogenic SIV**
- **Implications for preventive and therapeutic HIV vaccines**

RhCMV- SIV Vector controls SIV challenge

Key finding: 50% animals 'cleared' infection; Effector Memory



Vaccine Induced Antibodies: Major Questions to Address Going Forward

1. Antibody Durability
2. Quality of IgG and IgA Binding
3. Mucosal Antibodies
4. Neutralization

Thank you