

# *HIV Vaccines: Marry HIV efficacy studies to science, but take shots on goal*

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*The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.*

# Four concepts, six trials, 30 years....

**Table 1. Clinical HIV-1 Vaccine Efficacy Trials**

Study	Vaccines	Phase	Risk Group	HIV Incidence per 100 Person-Years	Location	Result
Vax003	AIDSVAX B/E gp120 in alum	III	injecting drug users	3.40%	Thailand	no vaccine efficacy
Vax004	AIDSVAX B/B gp120 in alum	III	high-risk women and MSM	2.60%	United States, Europe	no vaccine efficacy
HVTN 502 Step	MRKAd5 HIV-1 gag/pol/nef B	IIb	high-risk women and MSM	3.00%	United States	halted at interim analysis for futility; early transient increased infection in vaccinees
HVTN 503 Phambili	MRKAd5 HIV-1 gag/pol/nef B	IIb	high-risk heterosexual men and women	3.70%	South Africa	no vaccine efficacy; late increased HIV infection in unblinded male vaccinees
RV144	ALVAC-HIV vCP1521, AIDSVAX B/E rgp120 in alum	III	community risk heterosexual men and women	0.28%	Thailand	31.2% efficacy at 42 months as primary endpoint; 60% efficacy at 12 months
HVTN 505	DNA, rAd5 (A, B, C)	IIb	circumcised MSM without pre-existing Ad5 antibodies	1.80%	United States	halted at interim analysis for futility

MSM, men who have sex with men; Ad5, adenovirus serotype 5.

# First Sign of Efficacy: RV144

## The Thai HIV Vaccine Study

- First HIV vaccine to show efficacy
  - Major international collaboration with 16,000 Thai volunteers
  - Showed a preventive vaccine IS possible
- Efficacy of ~60% at 1 year 1; demonstrated 31.2% efficacy at end of study (3.5 years)



# RV144: Follow up



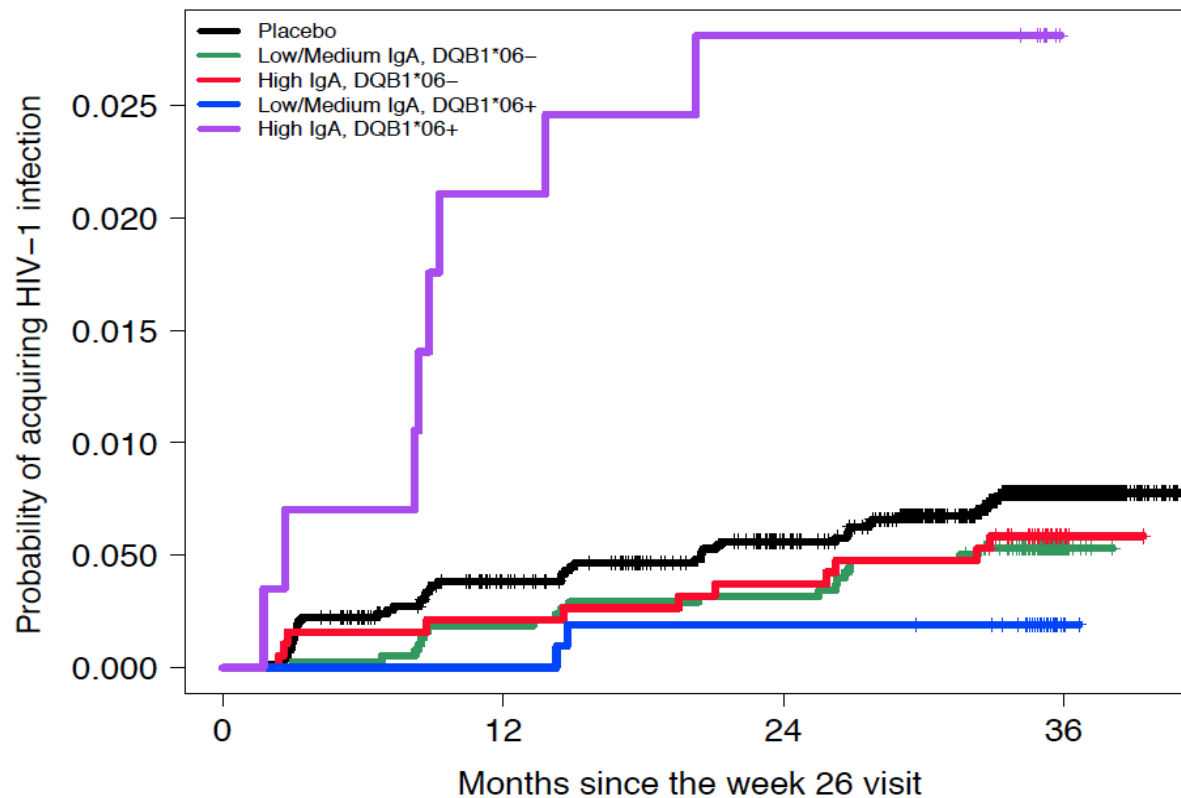
Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

- Intensive Laboratory Studies
  - Provides clues as to why vaccine protected some volunteers
    - Target on the HIV envelope (V2)
  - International collaboration with more than 120 scientists
  - Several subsequent studies and papers in *Lancet*, *Nature* and *Cell* confirm V2 as an important potential target



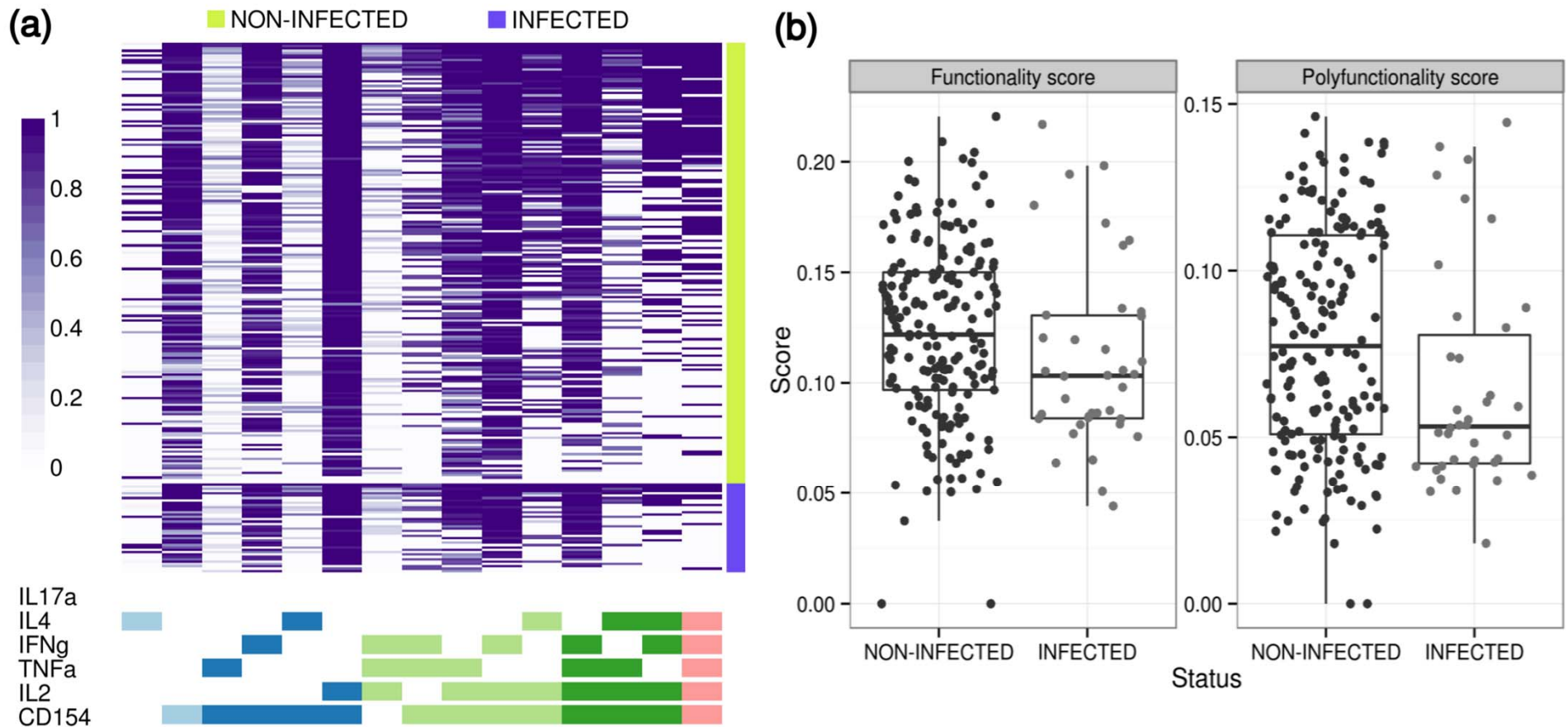
*RV144 continues to inform vaccine development and impact clinical trial design*

# High IgA associates with accelerated time to HIV-1 acquisition in the presence of HLA-DQB1\*06



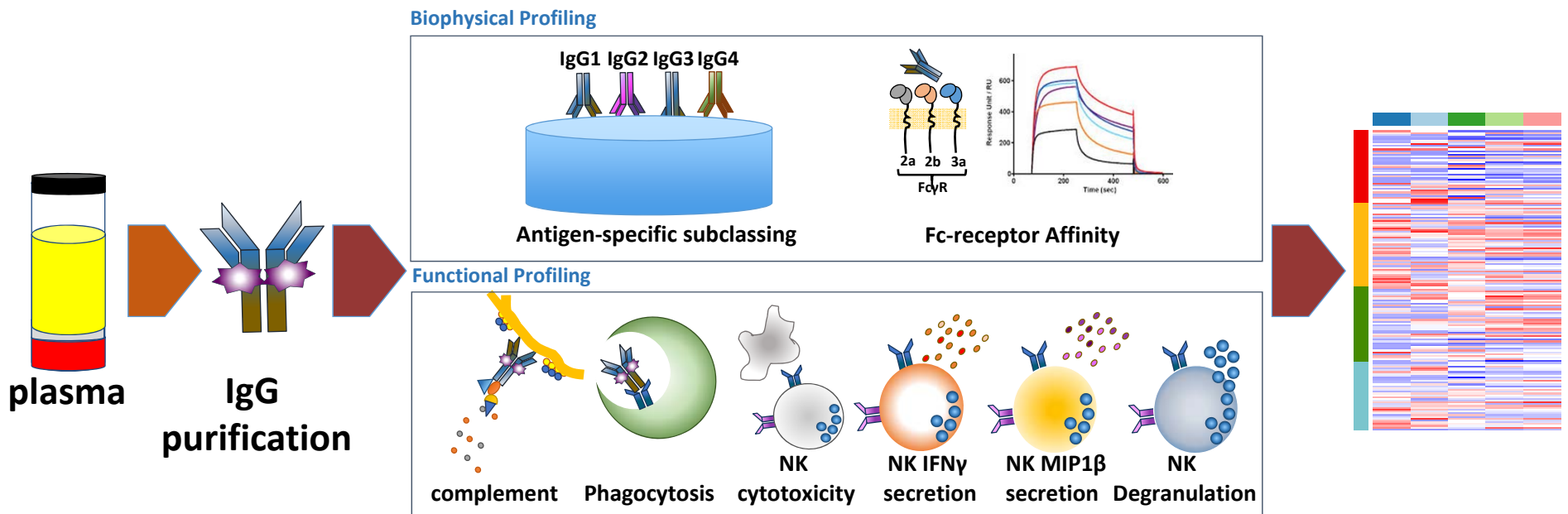
No. at Risk (no. infections)				
	0	12	24	36
Placebo	6267 (0)	6199 (24)	6127 (11)	693 (13)
Low/Medium IgA, DQB1*06-	3770 (0)	3763 (7)	3758 (5)	396 (8)
High IgA, DQB1*06-	1884 (0)	1880 (4)	1877 (3)	174 (4)
Low/Medium IgA, DQB1*06+	1047 (0)	1047 (0)	1045 (2)	95 (0)
High IgA, DQB1*06+	285 (0)	279 (6)	277 (2)	0 (0)

# Computational analysis of CD4 ICS reveals association with infection in RV 144 (Gottardo Nat. Biotech 2015)



Variable	Odds ratio (95% CI)	p value	q value
Functionality score	0.63 (0.43-0.93)	0.019	0.088
Polyfunctionality score	0.58 (0.39-0.85)	0.006	0.059
IL4+IL2+CD154+	0.61 (0.42-0.90)	0.011	0.071
TNF $\alpha$ +IFN $\gamma$ +IL4+IL2+CD154+	0.57 (0.39-0.86)	0.006	0.059

# Systems Serology: A computational method to assess FcR Ig structure and function: IgG3/ADCP = IgG1/ADCP?



*Galit Alter, Margie Ackerman et al. 2015. Cell 163:988.*

Barouch, Michael. 2014. *Cell* 159(5):969.

Leading Edge

## Commentary

Cell

### Accelerating HIV-1 Vaccine Efficacy Trials

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<http://dx.doi.org/10.1016/j.cell.2014.10.046>

Despite major advances in HIV-1 therapeutics and prevention strategies, the development of a safe and effective prophylactic HIV-1 vaccine will likely be critical for ending the global HIV-1 epidemic. Yet only four HIV-1 vaccine concepts have been tested for clinical efficacy over the past 30 years. In this Commentary, we describe key hurdles facing the HIV-1 vaccine development field and outline strategies to accelerate efficacy evaluation of novel HIV-1 vaccine candidates.

**Current State of the HIV-1 Vaccine** ... tested the same vaccine in high-risk ... functional activity. Furthermore, a meta-

- Engage industry in public-private partnerships
- Share risk to advance products to efficacy testing
- Coordinate pre-clinical and clinical testing for cross-validation



# P5 Overview

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- **Who We Are:** The Pox-Protein Public-Private Partnership (P5) is a diverse group of organizations committed to building on the success of RV144, the only HIV vaccine clinical trial to date to show efficacy.
- **Our Goal:** The P5 aims to produce an HIV vaccine that can have significant public health impact in Southern Africa and to deepen our understanding of immune responses associated with HIV prevention.



BILL & MELINDA  
GATES foundation



SANOFI PASTEUR 

Vical



# An HIV Vaccine for Southern Africa

- A series of early-stage trials that started in 2015
  - Aims to prolong and improve the level of protection
- The trials in Southern Africa use a vaccine regimen adapted to subtype C
  - The main circulating HIV subtype in the region.
- The P5 aims to produce a licensable HIV vaccine that can have a significant public health benefit in Southern Africa



*African HVTN clinical trials sites: Cape Town, Durban (2), Harare, Klerksdorp, Kwa Zulu Natal, Lilongwe, Lusaka, Maputo, Mbeya, Soshanguye and Soweto (2)*

# MOSAIC HIV Prophylactic Vaccine

## JnJ/Janssen—Overview Development Program



Current partners

BIDMC  
Harvard

MHRP

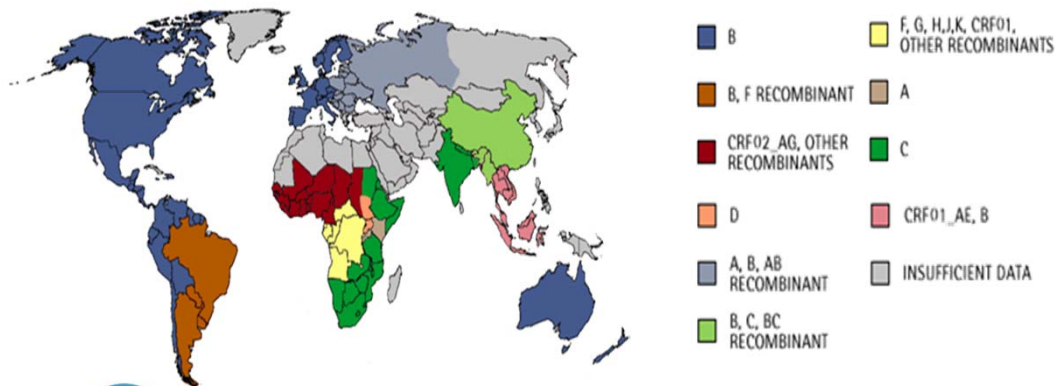
IAVI

Ragon

NIAID/HVTN

# An HIV vaccine designed for protection against all HIV subtypes

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

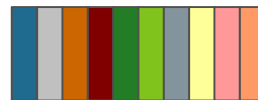
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## Vectors that elicit optimal immune responses

Low seroprevalent Ad26  
Ad26.HIV-Gag-Pol  
Ad26.HIV-Env  
(MVA.HIV-Gag-Pol-Env)

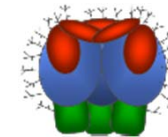
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## Mosaic inserts for global coverage



3

## Trimeric env protein for improved humoral immunity



Protective Efficacy of a Global HIV-1 Mosaic Vaccine against Heterologous SHIV Challenges in Rhesus Monkeys  
Dan H Barouch et al, 2013

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