Polyvalent DNA Prime Protein Boost HIV Vaccine Progress and Next Step

IAS Webinar Series HIV Vaccines
May 19, 2026

www.WHVaccine.com

Focusing on Two Key Technical Challenges

- Low immunogenicity of Env antigens
  Difficulty in generating high level and long lasting immune responses
  Solution: DNA prime + protein boost

- High mutation rate of HIV-1 Env antigens
  Challenging to cover the worldwide variants
  Solution: Polyvalent Env antigens from diverse subtypes

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Immunology
June 2009

Heterologous prime–boost vaccination

Shan Lu[1,2]

An effective vaccine usually requires more than one time immunization in the form of prime–boost. Traditionally the same vaccines are given multiple times as homologous boosts. New findings suggested that prime–boost can be done with different types of vaccines containing the same antigens. In many cases such heterologous prime–boost can be more immunogenic than homologous prime–boost. Heterologous prime–boost represents a new way of immunization and will stimulate better understanding on the immunological basis of vaccines.

Address
[1] China-US Vaccine Research Center and Department of Infectious Diseases, The First Affiliated Hospital, Nanjing Medical University, Nanjing 210029, China
[2] Department of Medicine, University of Massachusetts Medical School, 364 Plantation Street, Worcester 01605, USA

priming immunizations are used for subsequent boost immunizations.

Over the past decade, studies have shown that prime–boost immunizations can be given with unmatched vaccine delivery methods while using the same antigen, in a 'heterologous' prime–boost format. The most interesting and unexpected finding is that, in many cases, heterologous prime–boost is more effective than the 'homologous' prime–boost approach. The rapid progress of novel vaccination approaches, such as DNA vaccines and viral vector-based vaccines, has certainly further expanded the scope of heterologous prime–boost vaccination [1–3] (Table 1).

Curr Opin Immunol. 2009 June ; 21(3): 346–351. doi:10.1016/j.coi.2009.05.016.

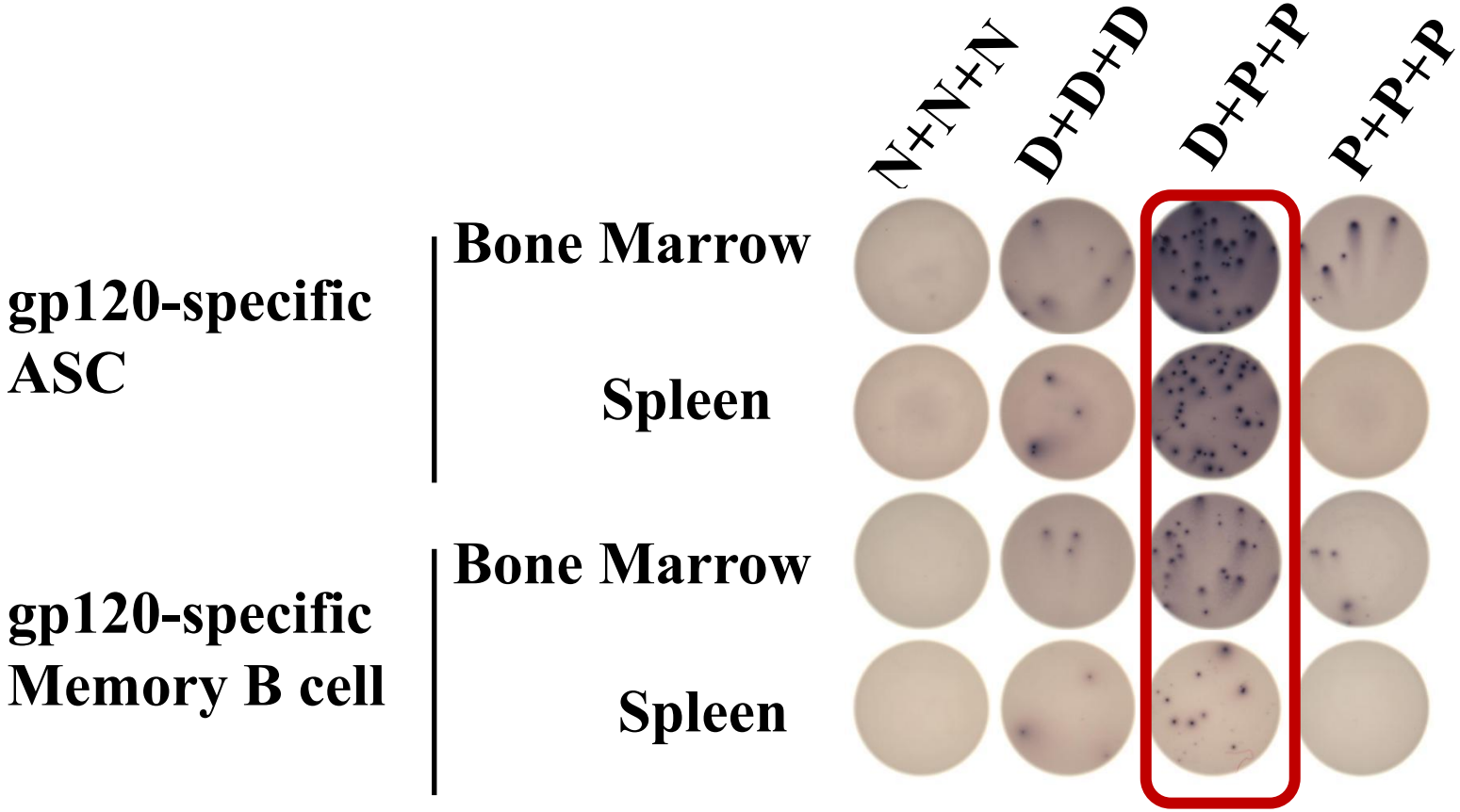
DNA Prime – Protein Boost

Our unique design:

Matched antigens delivered sequentially by different vaccine modalities

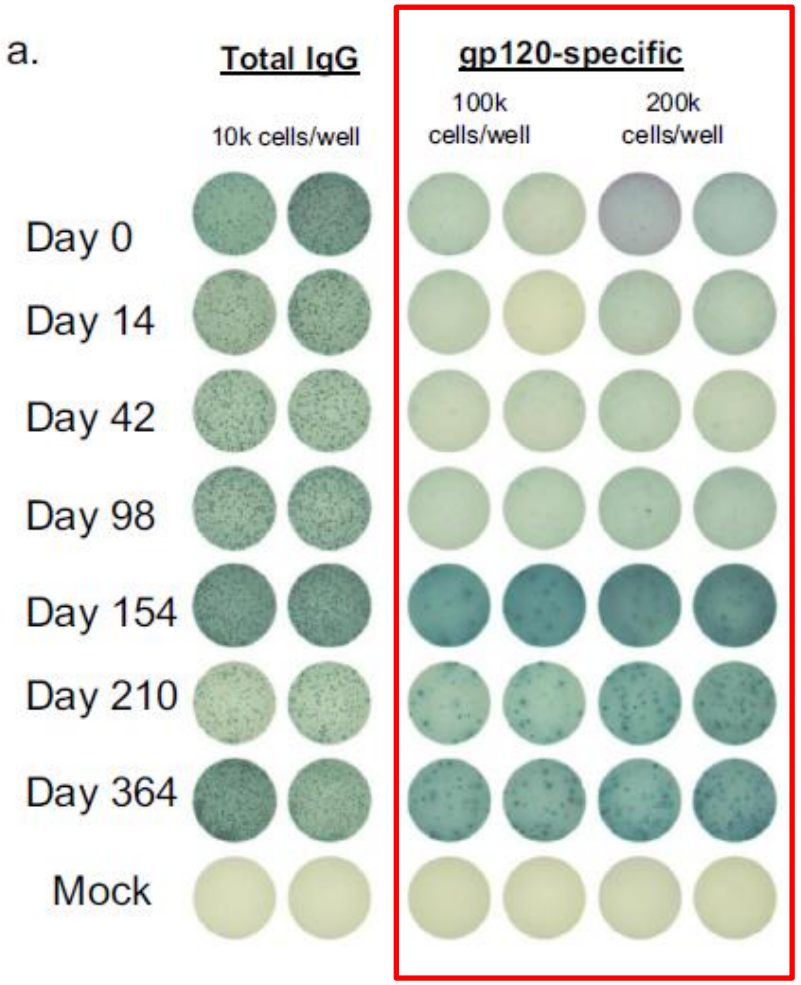
- **Benefits:**
  - ***Prime: DNA***
    - Focusing on chosen vaccine antigens
    - Optimal antigen conformation due to in vivo expression
    - Stimulating antigen specific B cell development (germinal center)
    - Providing T cell help for B cell development (endogenous antigen presentation)
  - ***Boost: protein***
    - To maximize expansion of antigen specific memory B cell population
    - To lead high level and long lasting peripheral antibody productions

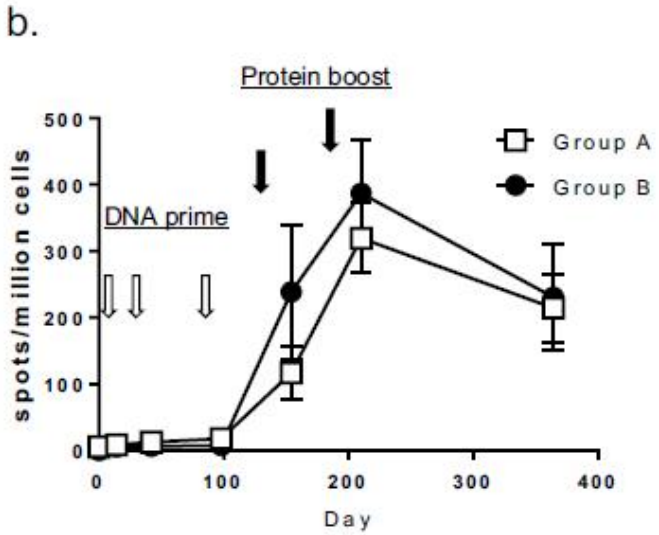
DNA + protein vaccine is more effective than DNA or protein alone in eliciting antigen specific B cell responses



Li et al., Emerging Microbes & Infections, 2021, 10:834

High level and long lasting of gp120-specific memory B cell responses in PDPHV human volunteers





Wang et al. NPj Vaccine, 2022, 7:18

Polyvalent vs. Monovalent

- **Polyvalent (with DNA priming)**
  - Beyond simply mixing different serotypes antigens
  - New understanding: establish more B cell lineages
  - B cell development and antibody affinity maturation – further diversity
  - May minimize antigenic sin when receiving boost
- **Monovalent or “limited” valent**
  - No breadth from the beginning
  - May generate antigenic sin to limit the power of boost
  - Examples: flu vaccines, SARS-CoV 2 vaccines
  - Multiple clade C Env antigens may also lead to narrower responses to the same clade

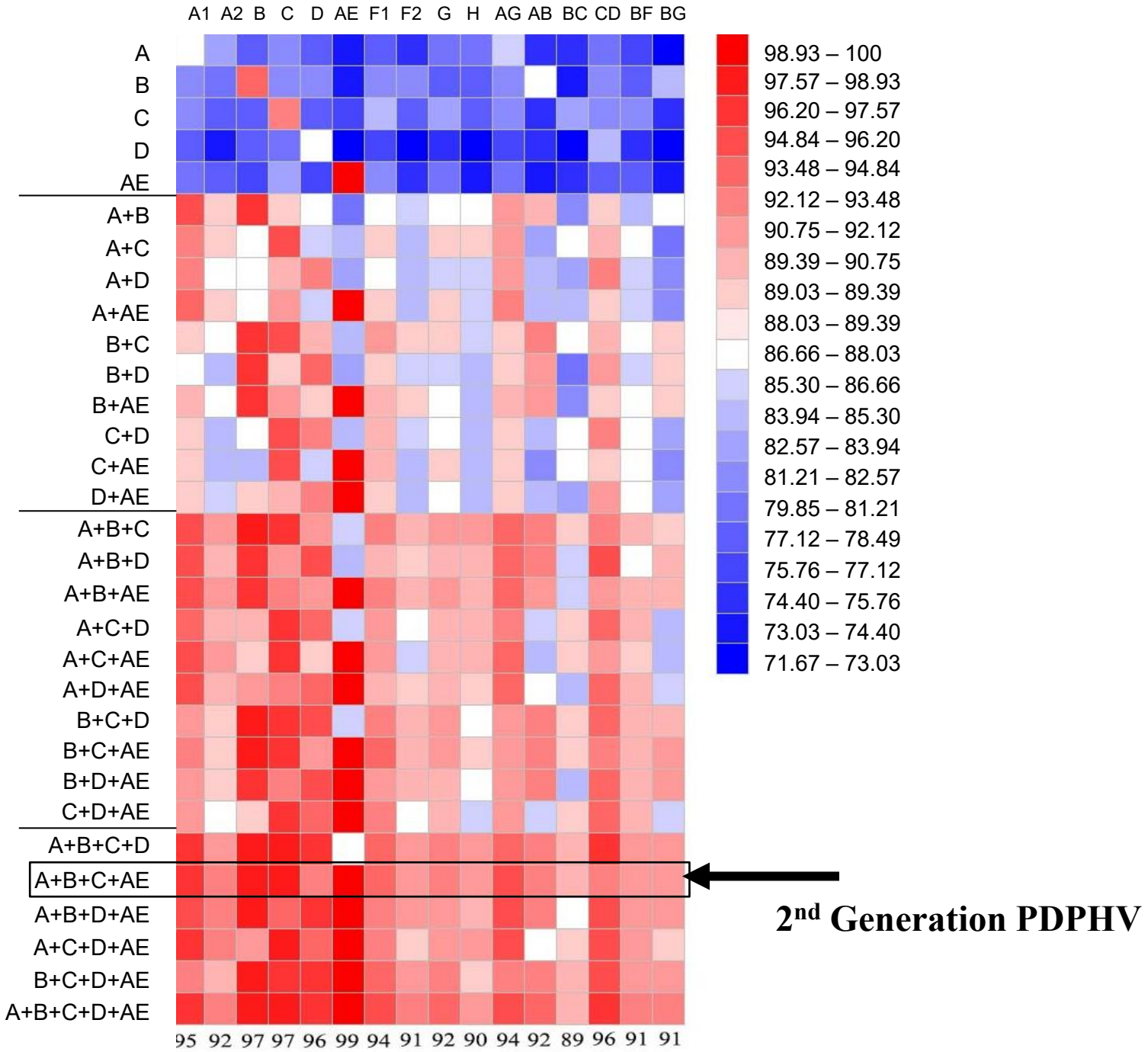
Screening of Env based on NAb breadth (3+13 pseudotyped viruses)

Subtype	Envelope	Tissue of Isolation	Origin	No. of PV neutralized	% of PV neutralized
A	92RW020.5	PBMC	Rwanda	1	6%
A	CA1	PBMC	Cameroon	2	13%
A	92UG037.1	PBMC	Uganda	7	44%
C	92BR025.9	PBMC	Brazil	2	13%
C	96ZM951.2	PBMC	Zambia	2	13%
C	Du123-06	PBMC	S. Africa	2	13%
C	zm153	PBMC	Zambia	2	13%
C	zm233	PBMC	Zambia	2	13%
C	zm53	PBMC	Zambia	2	13%
C	96BW01B22	PBMC	Botswana	3	19%
C	96BW15C02	PBMC	Botswana	3	19%
C	Cap210	Plasma	S. Africa	3	19%
C	Du156-12	PBMC	S. Africa	3	19%
C	DU422	PBMC	S. Africa	3	19%
C	ZM109	PBMC	Zambia	3	19%
C	zm197	PBMC	Zambia	3	19%
C	ZM214	Plasma	Zambia	3	19%
C	zm249	Plasma	Zambia	3	19%
C	CAP45	Plasma	S. Africa	4	25%
C	DU172	PBMC	S. Africa	4	25%
C	93MW965.26	PBMC	Malawi	15	94%
D	92UG021.16	PBMC	Uganda	14	88%
E/A	93TH976.1	PBMC	Thailand	2	13%
F1	93BR020.17	PBMC	Brazil	7	44%
G	92UG975.10	PBMC	Uganda	3	19%

10 Env (16%): >50%
11 Env (18%): 26-49%
41 Env (66%): 6-25%

Subtype	Envelope	Tissue of Isolation	Origin	No. of PV neutralized	% of PV neutralized
B	WITO4561	Brain	USA	1	6%
B	515.01	PBMC	Trinidad	2	13%
B	P6B-42	Lymph Node	UK	2	13%
B	PVO-04	Plasma	USA	2	13%
B	REJ4541	Plasma	USA	2	13%
B	THRO4156	Plasma	USA	2	13%
B	TRJO4551	PBMC	Italy	2	13%
B	TRO.11	Plasma	USA	2	13%
B	692.42	PBMC	Trinidad	3	19%
B	1168.01	PBMC	US	3	19%
B	ADA (AD8)	Brain	USA	3	19%
B	Bal (Bal.opt)	Plasma	USA	3	19%
B	H78639 (H4)	Brain	USA	3	19%
B	P5B-12 (Brain)	Lymph node	UK	3	19%
B	P6B33	Brain	UK	3	19%
B	P6LN-85	PBMC	Italy	3	19%
B	Yu-2	Brain	USA	3	19%
B	AC10.0.29	PBMC	US	4	25%
B	ADA (AD8)	PBMC	USA	4	25%
B	89.6	PBMC	USA	5	31%
B	CAAN5352	PBMC	USA	5	31%
B	RHPA4259	Plasma	Trinidad	5	31%
B	SC422661.8	PBMC	USA	5	31%
B	SF162	Plasma	USA	5	31%
B	1196.01	PBMC	US	6	38%
B	5768.04	PBMC	US	6	38%
B	P6LN40	Lymph node	UK	6	38%
B	92US715.6	PBMC	USA	8	50%
B	AC10.44	PBMC	UK	9	56%
B	P5LN-27	Brain	UK	9	56%
B	6535	PBMC	USA	10	63%
B	93-20#59	Brain	UK	11	69%
B	6101LN	PBMC	USA	12	75%
B	93-176#93	Brain	UK	13	81%
B	92-353#27	Brain	UK	14	88%
B	JR-FL	Brain	UK	14	88%

Bioinformatics analysis on the coverage of 16 HIV-1 subtypes by the valency of gp120 antigens included in the vaccine formulation



2nd Generation PDPHV

Wang et al.
Human Vaccine & Immunotherapeutics, 2017, 13:2996

THE LANCET
HIV

May 2024

Articles

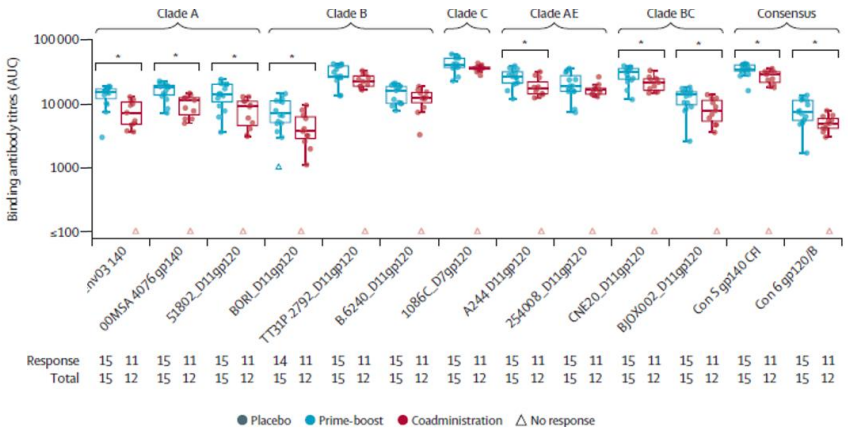
VOLUME 11, ISSUE 5, E285-E299, MAY 2024

Safety and immunogenicity of a polyvalent DNA–protein HIV vaccine with matched Env immunogens delivered as a prime–boost regimen or coadministered in HIV-uninfected adults in the USA (HVTN 124): a phase 1, placebo-controlled, double-blind randomised controlled trial

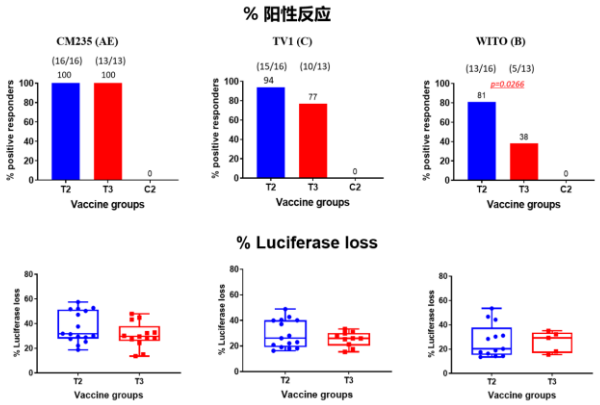
Ian Frank, Shuying S Li, Nicole Grunenberg, Edgar T Overton, Samuel T Robinson, Hua Zheng, Kelly E Seaton, Jack R Heptinstall, Mary A Allen, Kenneth H Mayer, Daniel A Culver, Michael C Keefer, Sri Edupuganti, Michael N Pensiero, Vijay L Mehra, Stephen C De Rosa, Daryl E Morris, Shixia Wang, Michael S Seaman, David C Montefiori, Guido Ferrari, Georgia D Tomaras, James G Kublin, Lawrence Corey, Shan Lu, for the HVTN 124 Study Team

PDPHV induced polyfunctional antibody responses

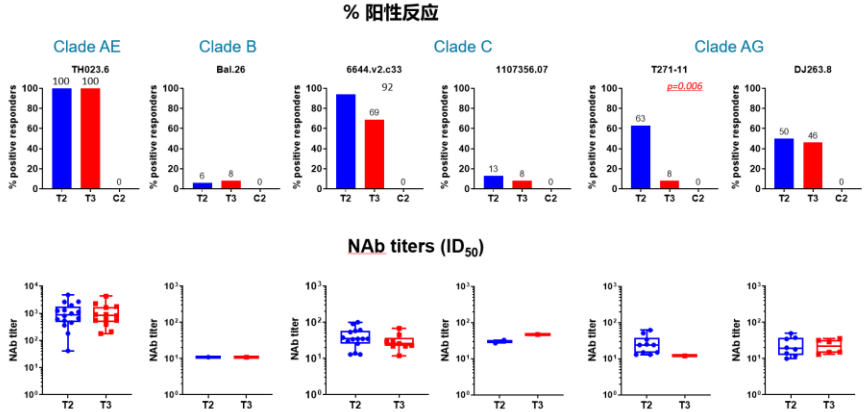
Heterologous IgG



ADCC against IMC infected target cells



Nab against Tier 1B viruses



Serum Env specific IgG responses

- High response rate
- High titers
- Broadly reactive

ADCC responses

- Against different HIV subtypes
- Against IMC infected cells

Neutralizing Ab

- Multiple Tier 1B viruses
- Or by Monogram assay system

IgG against gp70-V1V2

IgG3 against gp70-V1V2

***Figure 3:* gp70-V1V2 antibody response**

IgG (A) and IgG3 (B) responses in the prime–boost (blue) and coadministration (red) groups against gp70-V1V2 panels. Response rates and relevant clades are summarised above each plot. Dots represent individual participants; participants with a non-response are shown as triangles. IgG (C) and IgG3 (D) responses against antigens common across the HVTN 124, RV144, HVTN 702, and HVTN 705 trials are provided to contextualise our results with those of other contemporary HIV vaccine trials; results for the prime–boost group only are presented for the HVTN 124 trial. Net response (MFI–blank) is the IgG or IgG3 response measured by MFI minus a sample-specific background measure (known as blank). Dots represent individual

Env Specific CD4+ T cell Responses

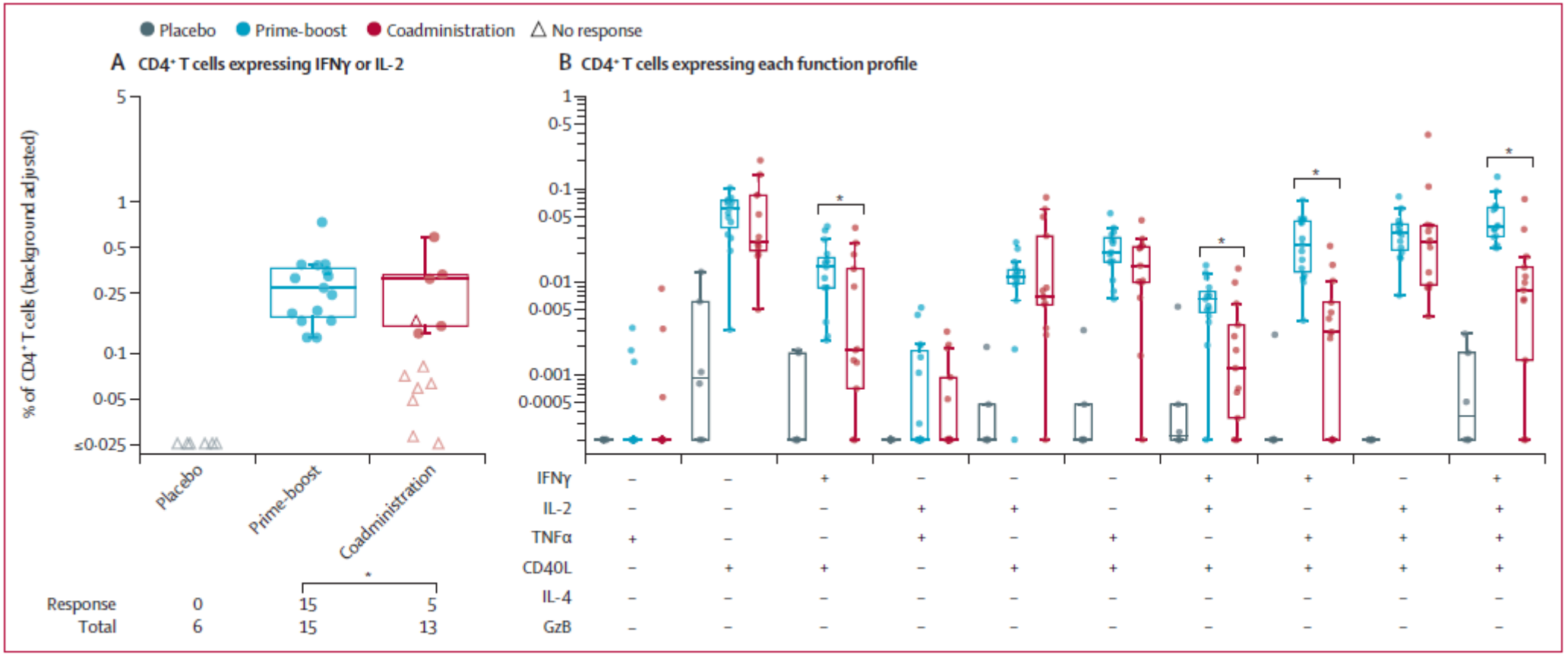


Figure 4: **CD4 cell response**

Response rates and magnitudes of CD4 cells expressing IFNγ or IL-2 (A) and of CD4 cells expressing each function profile (B) from participants receiving prime–boost (blue), coadministration (red), and placebo (grey) in response to Env peptides. There were no measurable CD8 T cell responses (appendix p 4). The line splitting the boxplots in two is the median, the bottom edge of the box is the 25th percentile, the top edge is the 75th percentile, the values at which the horizontal lines stop correspond to the most extreme datapoints that are no more than 1·5 times the IQR away from the median, or if no such datapoints exist, the data extremes. GzB=granzyme B.*p<0·05 (precise p values in the appendix p 20).

nature communications

Article

https://doi.org/10.1038/s41467-024-48514-8

Human CD4-binding site antibody elicited by polyvalent DNA prime-protein boost vaccine neutralizes cross-clade tier-2-HIV strains

Received: 15 September 2023

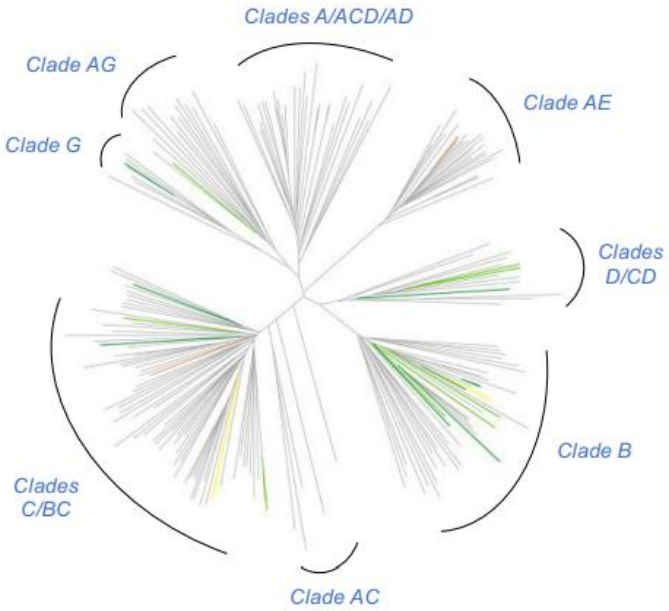
Accepted: 3 May 2024

Published online: 21 May 2024

Check for updates

Shixia Wang[1], Kun-Wei Chan[2], Danlan Wei[3], Xiuwen Ma[1], Shuying Liu[4], Guangnan Hu[1], Saeyoung Park[1], Ruimin Pan[2], Ying Gu[5], Alexandra F. Nazzari[5], Adam S. Olia[5], Kai Xu[5], Bob C. Lin[5], Mark K. Louder[5], Krisha McKee[5], Nicole A. Doria-Rose[5], David Montefiori[6], Michael S. Seaman[7], Tongqing Zhou[5], Peter D. Kwong[5], James Arthos[3], Xiang-Peng Kong[2] & Shan Lu[1]

Neutralizing Activities of HmAb64 (against VRC 208 viruses panel)

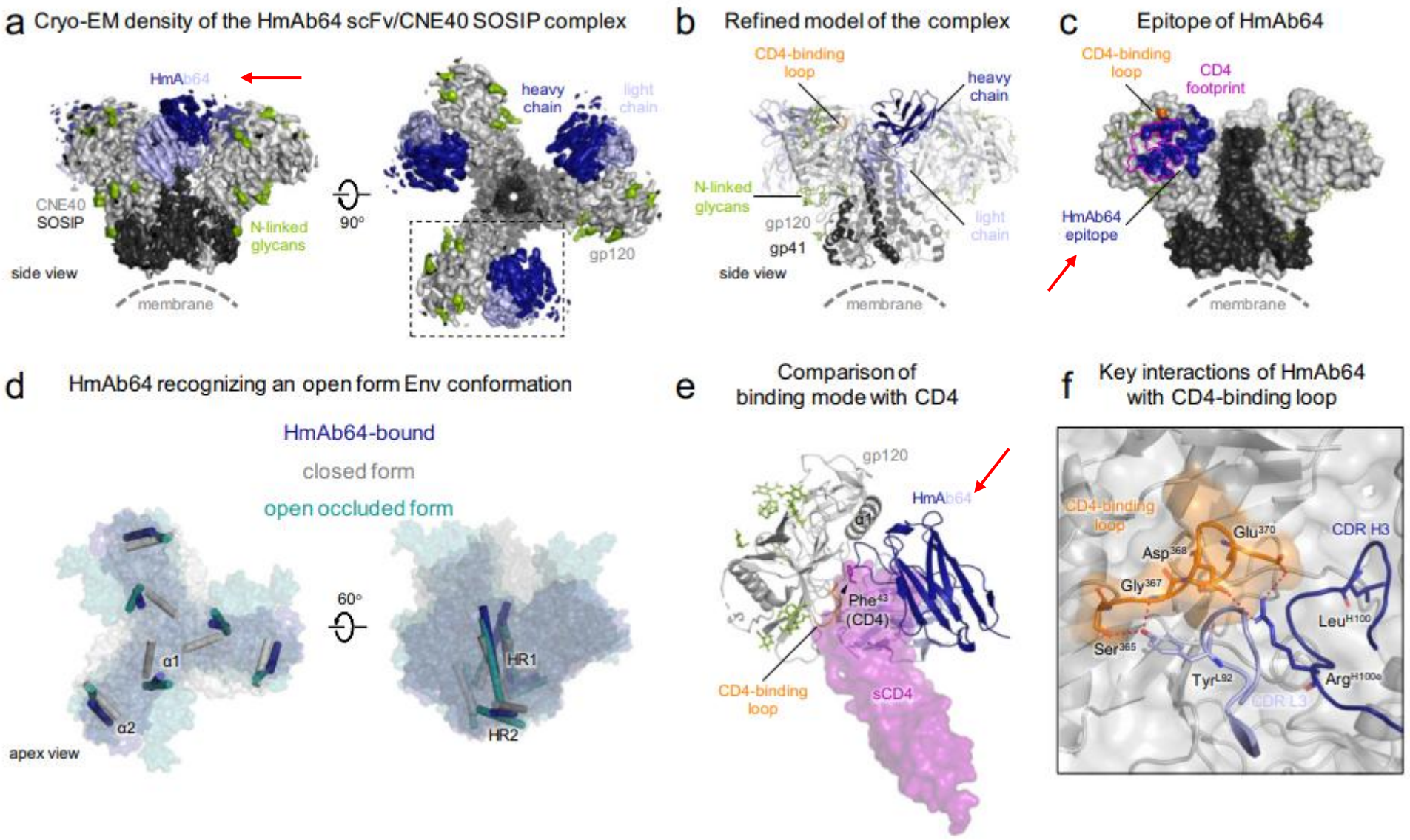


Virus ID	Clade	HmAb64	b12	VRC01	Tier
6095.v1.c10	ACD	39.300	0.3250	0.7990	ND
TH023.6	AE	0.077	ND	0.7710	1A
DJ263.8	AG	1.980	>50	0.0540	1B
6535.3	B	8.4900	0.8740	1.9700	1B/2
ADA.DG	B	17.4000	0.1280	0.4940	ND
Bal.01	B	54.4000	0.0850	0.1400	ND
BaL.26	B	28.2000	0.0640	0.0560	1B
BX08.16	B	14.2000	0.9240	0.4800	1B
CNE4	B	20.3000	>50	0.4390	ND
HXB2.DG	B	0.3130	0.0010	0.0360	1B/2
MN.3	B	7.2500	<0.0006	0.0250	1A
SF162.LS	B	2.0100	0.0320	0.2110	1A
CNE40	BC	0.1210	0.5530	0.2280	2
6644.v2.c33	C	2.3100	0.0310	0.1350	1B
BR025.9	C	15.3000	>50	0.3590	1B/2
MW965.26	C	0.0460	0.0020	0.0330	1A
ZM109.4	C	82.4000	>50	0.1780	1B/2
UG021.16	D	2.9600	0.8380	0.5740	ND
UG024.2	D	4.1900	>50	0.3500	ND
X2131.C1.B5	G	76.3000	ND	0.6550	2

IC_{50} (µg/ml) <0.001 .001-.01 .01-.100 .100-1.00 1.00-10.0 >10.0

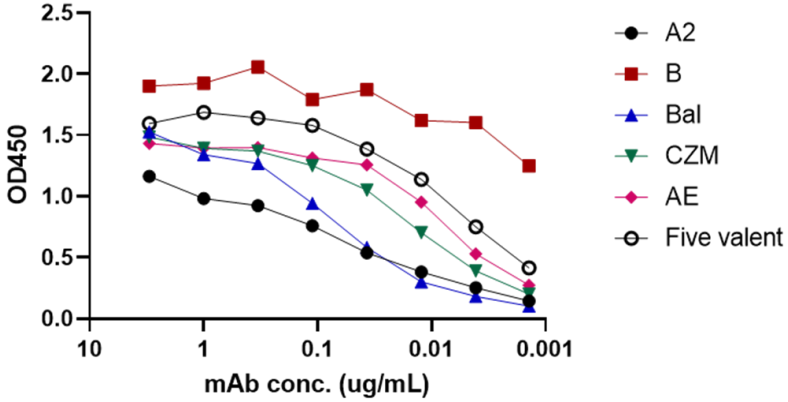
Neutralization resistance tiers	Viruses in VRC Panel	Neutralized by HmAb64	%
Unclassified	57	6	11%
Tier 1A	5	4	80%
Tier 1B	7	4	57%
Tier 1B/Tier 2 or Tier 2	127	6	5%
Tier 3	12	0	0
Total	208	20	10%

EM of HmAb64 binding to CNE40 SOSIP

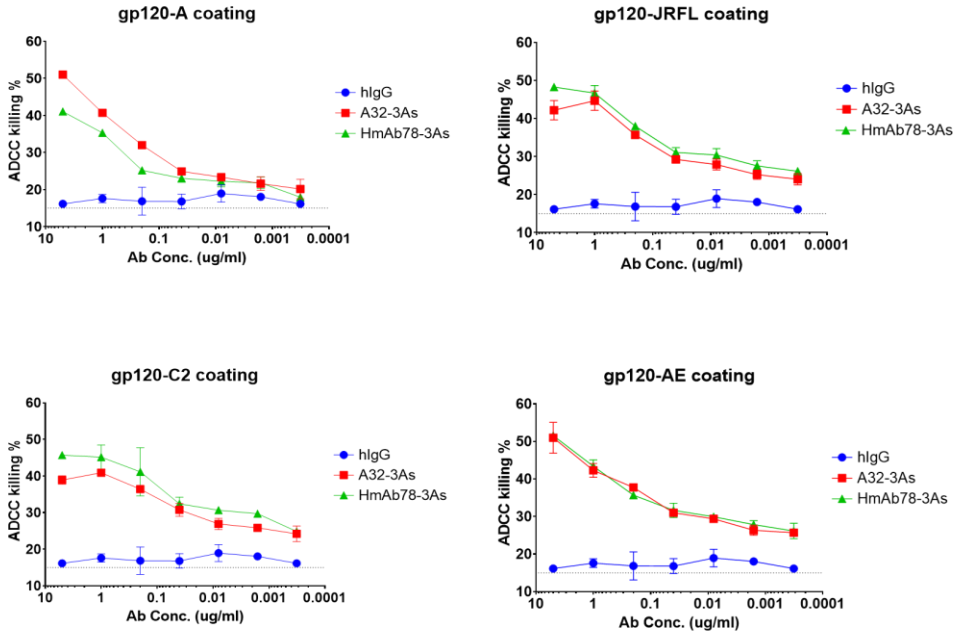


HmAb 78: An mAb Isolated from a PDPHV Vaccinee

HmAb78 binding to diverse gp120

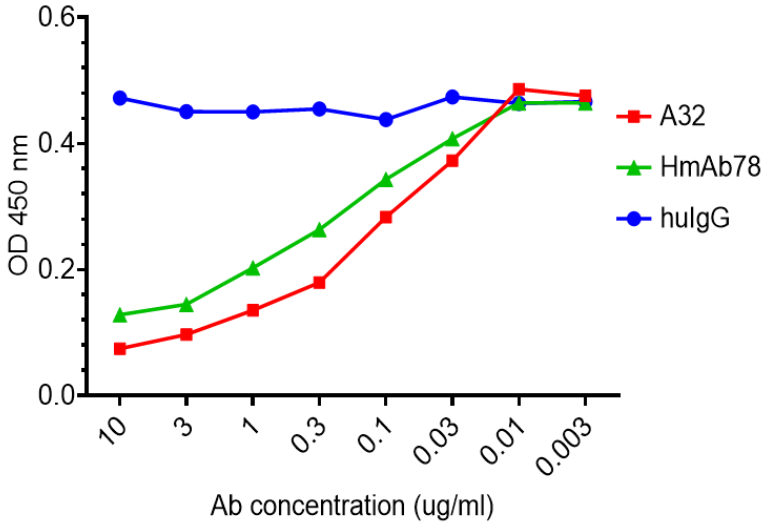


Potent ADCC as A32



HmAb78 shares the same germline with A32

HmAb78 competes with A32



Ig gene sequence comparison

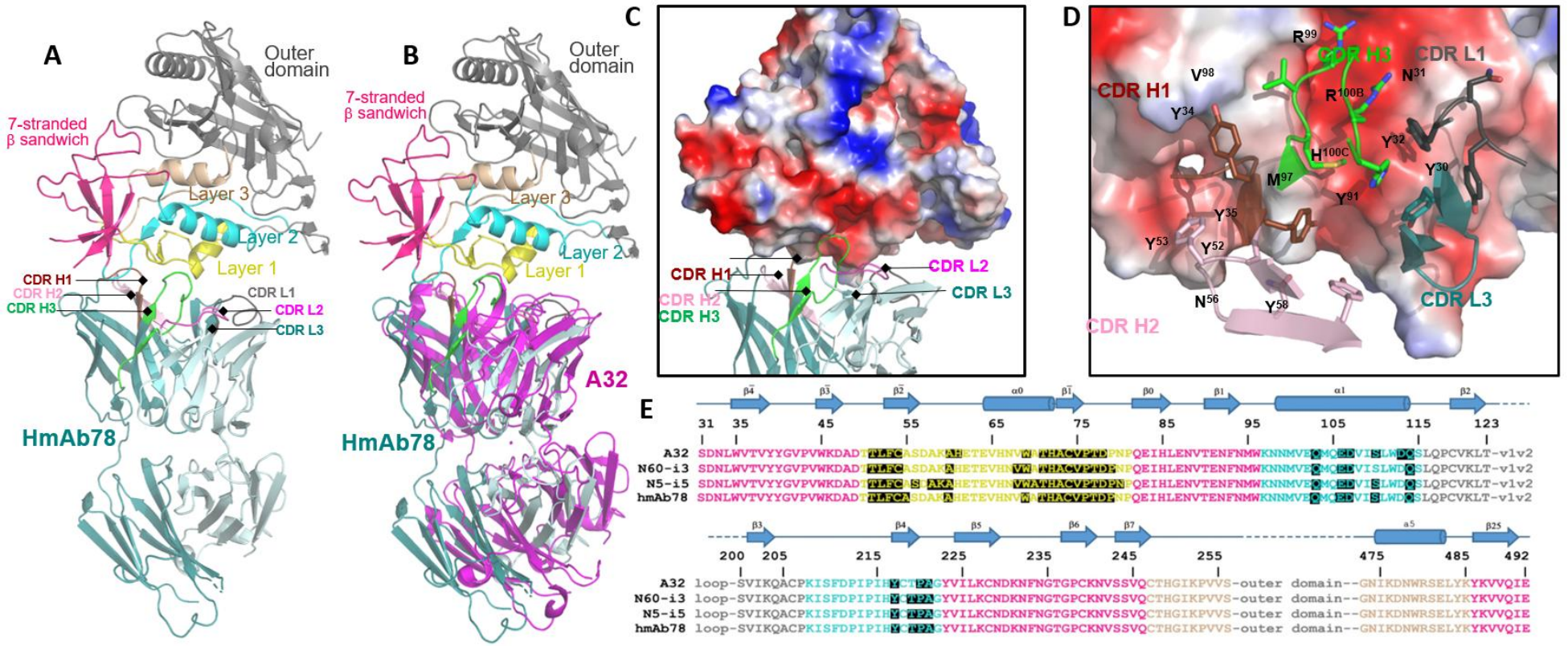
VH sequence alignment for A32, HmAb78 and germline IgGV4-31*02

```
                                        CDR1                                CDR2
A32          QVQLQESGPGLVKPSQTLSLSCTVSGGSSSSGAHYWSWIRQYPGKGLEWIGYIHYSGNTY
IGHV4-31*02  QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEWIGYIYYSGSTY
HmAb78       EVELIESGPGLVQPSQTLSLTCTISGGSISSGGYYWSWIRQHPGKGLEWIGYIYYSGSTY
             :*:* *******:*******:**:*.** ***.:*******:**********:***.**

                                                    CDR3
A32          YNPSLKSRITISQHTSENQFSLKLNSVTVADTAVYYCARGTRLRTLRNAFDIWGQGTMVT
IGHV4-31*02  YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR----------------------
HmAb78       YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVTMVRGVRHAFDIWGQGTMVT
             ********:***  **:********.***.**********

A32          VSS
IGHV4-31*02  ---
HmAb78       VSS
```

VL sequence alignment for A32, HmAb78 and germline IGLV2-14*01

```
                                   CDR1                                CDR2
A32          QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQHHPGKAPKLIISEVNNRPSGV
IGLV2-14*01  QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKAPKLMIYEGSKRPSGV
HmAb78       QSVLTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQHHPGKAPKLMISEVSNRPSGV
             **.****.*.*******:************.** *****:********:* * .:*****

                                        CDR3
A32          PDRFSGSKSGNTASLTVSGLQAEDEAEYYCSSYTDIHNFVFGGGTKLTVL
IGLV2-14*01  SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTL----------
HmAb78       SNRFSGSKSGNTASLTISGLQADDKADYYCSSYTSSSTLVFGGGTKLTVL
             .:***************:*****:*:*:*******.  .:
```

Crystal Structure Confirms the Identical Antigen Binding Site as A32



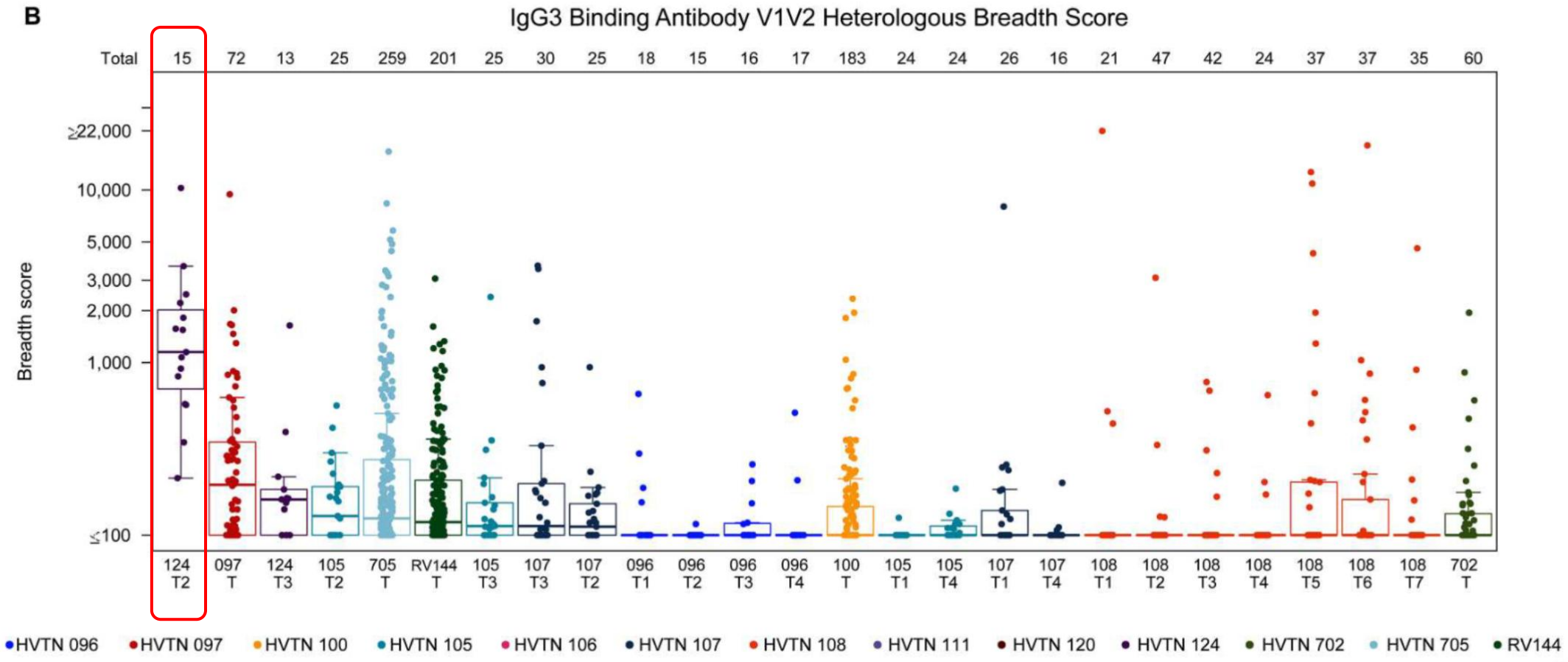
William D. Tolbert, Marzena Pazgier. Uniformed Services University of the Health Sciences, Bethesda, MD

Emerging Microbes & Infections
2025, VOL. 14, 2485317 (20 pages)
https://doi.org/10.1080/22221751.2025.2485317

A polyvalent DNA prime with matched polyvalent protein/GLA-SE boost regimen elicited the most robust and broad IgG and IgG3 V1V2 binding antibody and CD4+ T cell responses among 13 HIV vaccine trials

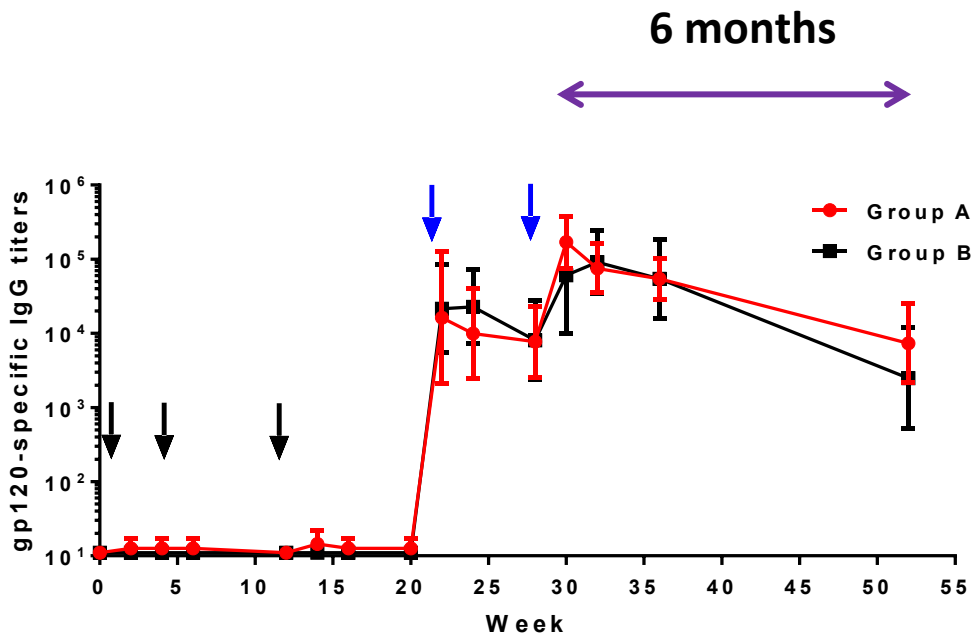
Zoe Moodie[a], Shuying Sue Li[a], Elena E. Giorgi[a], LaTonya D. Williams[b,c,d], One Dintwe[a,e], Lindsay N. Carpp[a], Shiyu Chen[a], Kelly E. Seaton[b,c,d], Sheetal S. Sawant[b,c,d], Lu Zhang[b,c,d], Jack Heptinstall[b,c,d], Shuying Liu[f], Nicole Grunenberg[a*], Frank Tomaka[g], Supachai Rerks-Ngarm[h], Punnee Pitisuttithum[i], Sorachai Nitayaphan[j], Julie A. Ake[k], Sandhya Vasan[k,l], Giuseppe Pantaleo[m], Ian Frank[n], Lindsey R. Baden[o], Paul A. Goepfert[p], Michael Keefer[q], Mike Chirenje[r], Mina C. Hosseinipour[s,t], Kathryn Mngadi[u], Fatima Laher[v], Nigel Garrett[w,x,y], Linda-Gail Bekker[w], Stephen De Rosa[a], Erica Andersen-Nissen[a,e], James G. Kublin[a], Shan Lu[f,z], Peter B. Gilbert[a,aa,bb], Glenda E. Gray[v,cc], Lawrence Corey[a,dd], M. Juliana McElrath[a] and Georgia D. Tomaras[b,c,d]

HVTN124 IgG3 binding antibody against V1V2 heterologous breadth score was better than other 25 HVTN trial arms

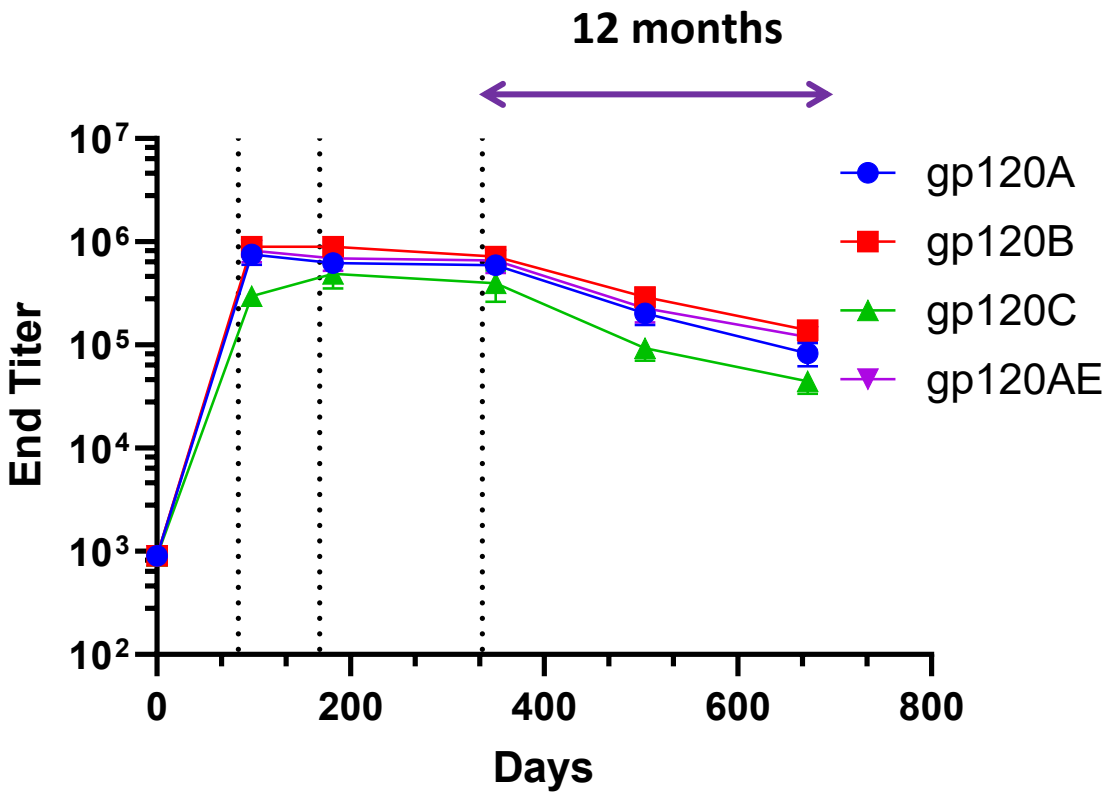


Human Env antibody responses were durable over 6-month or 12-month post last vaccination

DP6-001 (2008)



WHV138 (2023)

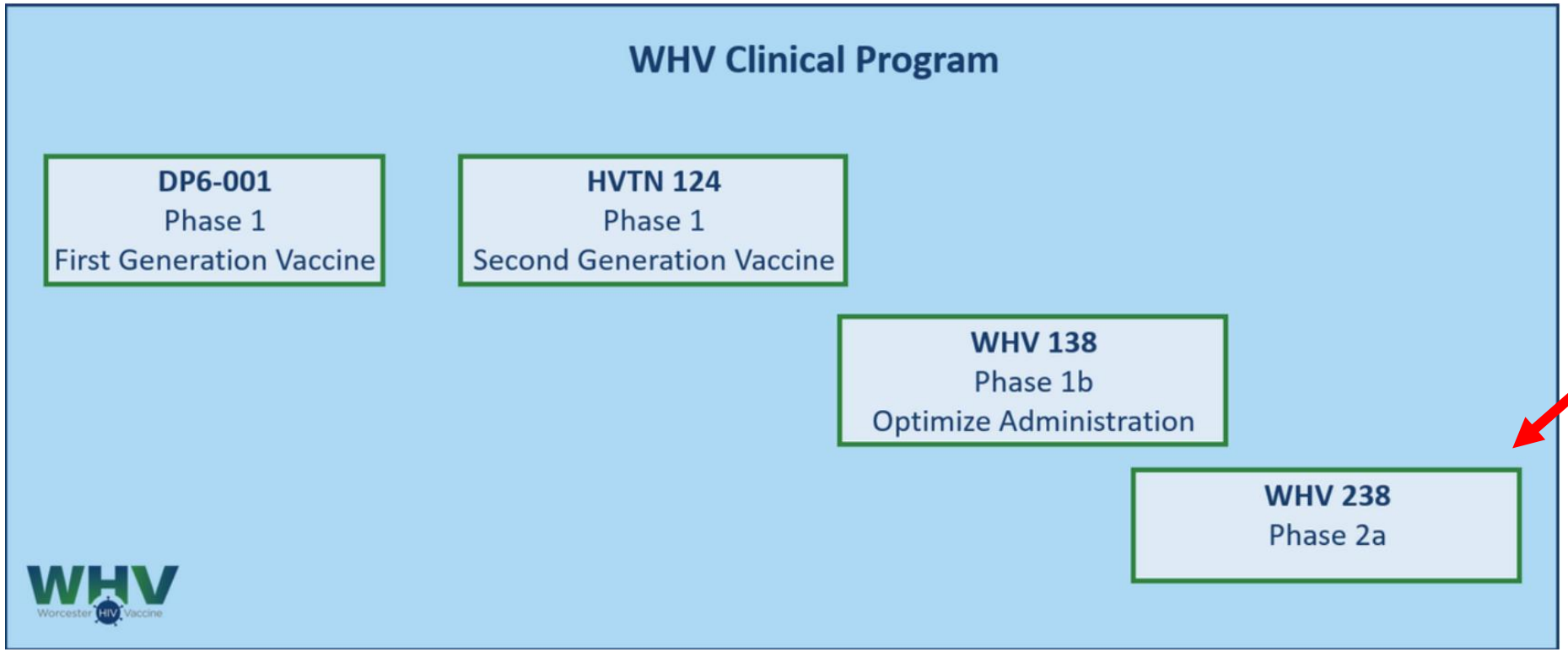


Wang et al. Vaccine, 2008, 26:1098

Summary of PDPHV

- PDPHV has a high safety profile based on HVTN124 and WHV138 studies
- **Polyfunctional antibody activities**
  - High titer (>1:10,000) and broadly cross-reactive binding Ab
  - Anti-V1V2 antibodies: high titer, breadth, IgG3
  - ADCC: against IMC target cells
  - Nab across Tier 1B or Monogram primary viral panels
- 100% CD4+ T cell response rate
- Long lasting human Env specific antibody and B cell responses
- Highest protection correlated breadth score among 13 HVTN trials
  - IgG/IgG3 against V1V2
  - CD4 T cells response rate
- Diverse mAbs isolated from PDPHV vaccinees
  - Proven diverse protective antibodies including CD4bs Tier-2 Nab and A32-like mAb

PDPHV
Next Step: Phase 2a study in South Africa



S Africa &
BWH, Harvard

Outlook for an effective HIV vaccine

- May need to induce diverse types of protective immune responses
- Polyfunctional antibody activities
- Broadly cross reactive against diverse HIV-1 isolates
- Beyond certain “epitopes” but covering entire antigens
- Long lasting human Env specific antibody and B cell responses
- More human efficacy studies to prove the scientific hypothesis

Acknowledgements

THANK YOU to the PARTICIPANTS, SITE STAFF, CAB MEMBERS!!

- University of Pennsylvania - Philadelphia, PA - PI Ian Frank (Chair)
- Rochester Victory Alliance - Rochester, NY – PI Michael Keefer
- Case Western Reserve/University Hospitals AIDS Clinical Trials Unit - Cleveland, OH - PI Jeffrey Jacobson
- Alabama Vaccine Research Clinic at UAB - Birmingham, AL - PI Paul Goepfert
- Fenway Community Health Center, INC - Boston, MA – PI Ken Mayer
- Emory University - The Hope Emory Vaccine Center - Atlanta, GA - PI Srilatha Edupuganti

HVTN124 and Other Acknowledgements

Chair
Ian Frank

Co-chair
Turner Overton

PTL/CMM
Nicole Grunenberg
Marnie Elizaga

Statistician
Sue Li

Medical Officer
Mary Allen

Laboratory Lead
David Montefiori

Lab Representatives
Nicole Frahm

HVTN Leadership
Larry Corey
Jim Kublin

Laboratory
Georgia Tomaras
Guido Ferrari
Julie McElrath
Kristen Cohen
Stephen DeRosa
Kathy Cho
Kelly Seaton
Kristy Long
Sheetal Sawant
Lisa Sanders
Yong Lin
Jack Heptinstall
Lu Zhang
Nichole Yates

SCHARP
Statistical and Data Management Center
Zoe Moodie
Anthony Williams
Yiwen Lu
Hua Zheng
Jin Jia Kee

BIDMC/Harvard Med School
Mike Seaman

WHV138 (BWH)
Stephen Walsh
Lindsey Baden

South Africa sites
Glenda Grey
Linda-Gail Becker
Nigel

Uniformed Service U
William D. Tolbert
Marzena Pazgier

NYU
XP Kong
Kun-Wei Chan

Developer Representatives
Shixia Wang
Yegor Veronin
Iris Benhayoun
Shuying Liu
Zachary Sagawa (AAHI)

NIAID/VRC
Peter Kwong
Tongqing Zhou
Nicole A. Doria-Rose

DAIDS Project Officer
Vijay Mehra
Michael Pensiero