2023 GVIRF

HIV VACCINE UPDATE

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National Medical Center in Infectious Disease/
Fudan University, China

OUTLINE

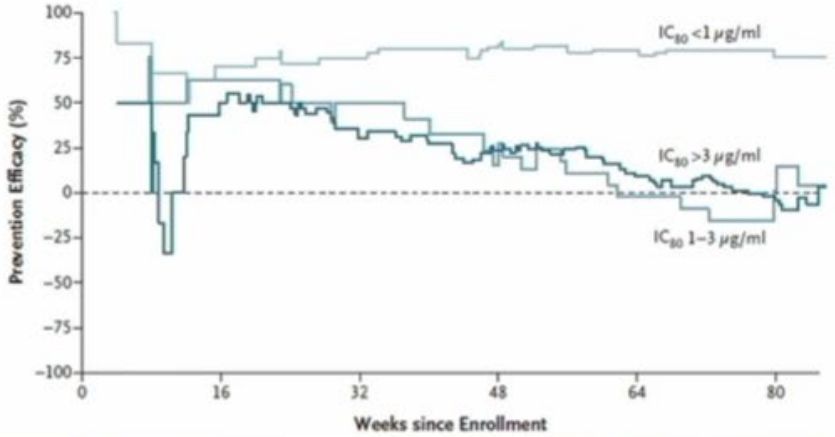
bNAb for HIV prevention

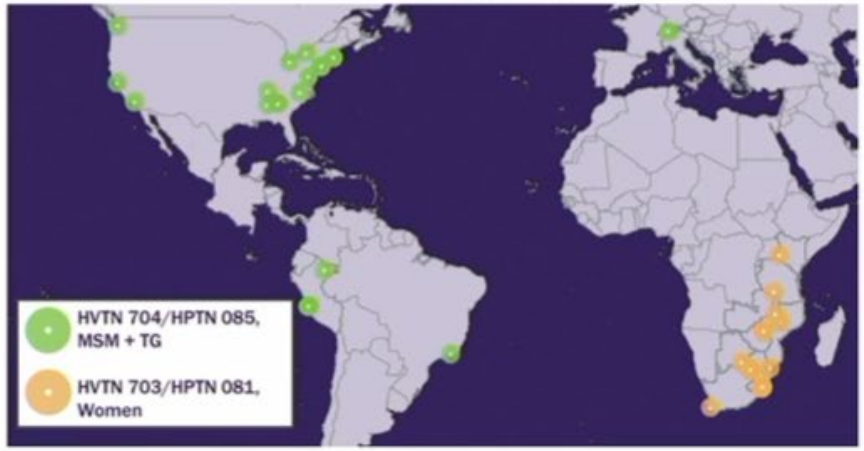
HIV Vaccines

bNAbs for HIV Prevention

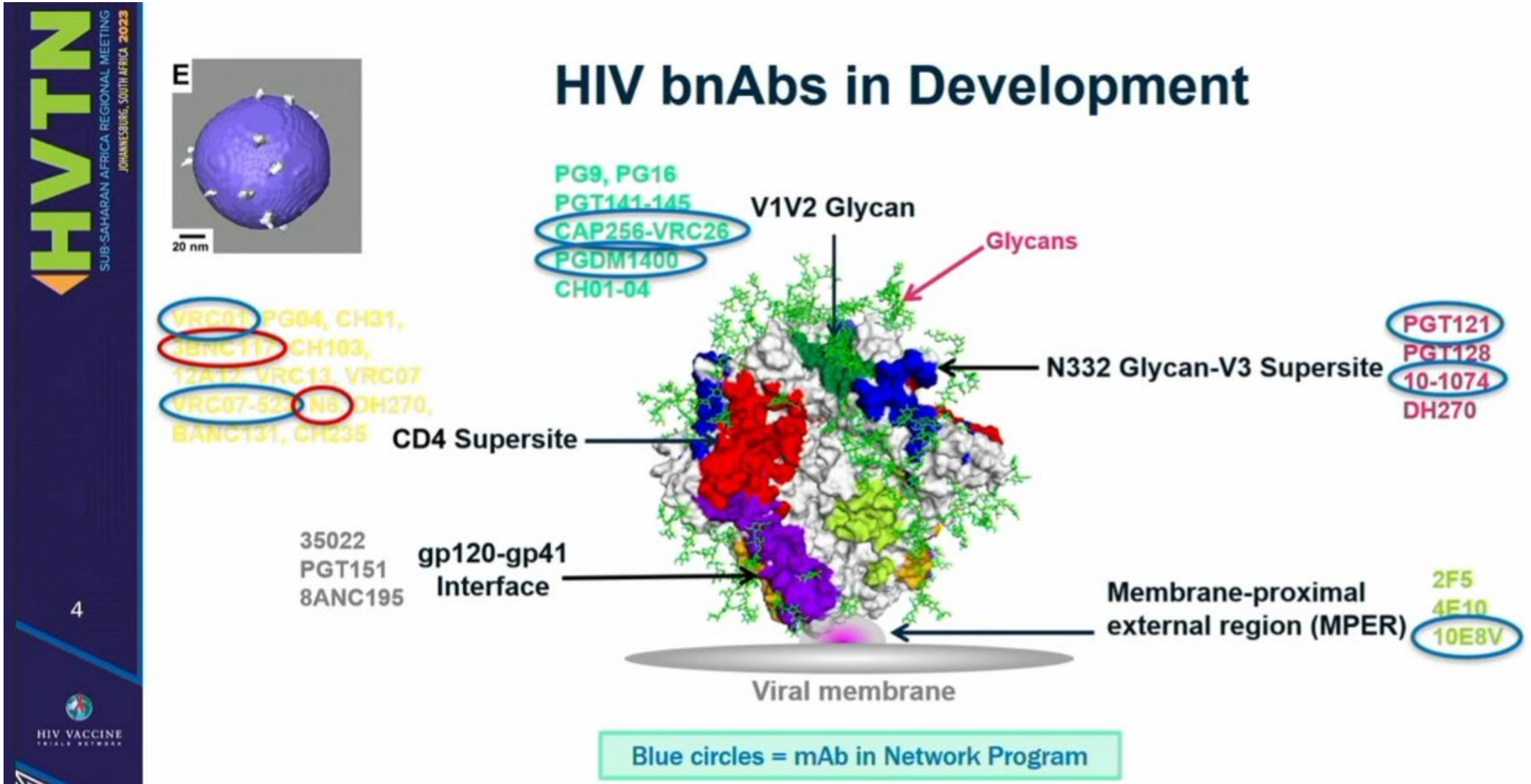
AMP Phase 2b Clinical Trials: HIV bnAb Proof of Concept, Correlate of Protection

- Proof of concept
  - HIV prevention with 1 bnAb is possible – VRC01 protected only against acquisition of highly neutralization-sensitive viruses
  - Correlate of protection
- Large scale IV administration is possible in Africa & elsewhere
  - Enrollment: 4,625
  - Retention: 95% of 97,458 visits
  - Adherence: 99% of 41,116 infusions
- 11 countries
- 46 sites (26 in Americas + 20 in Africa)
- 82.5 KG VRC01 mAb in 144,474 vials





Corey L et al. NEJM 2021;384:1003-14


HVTN
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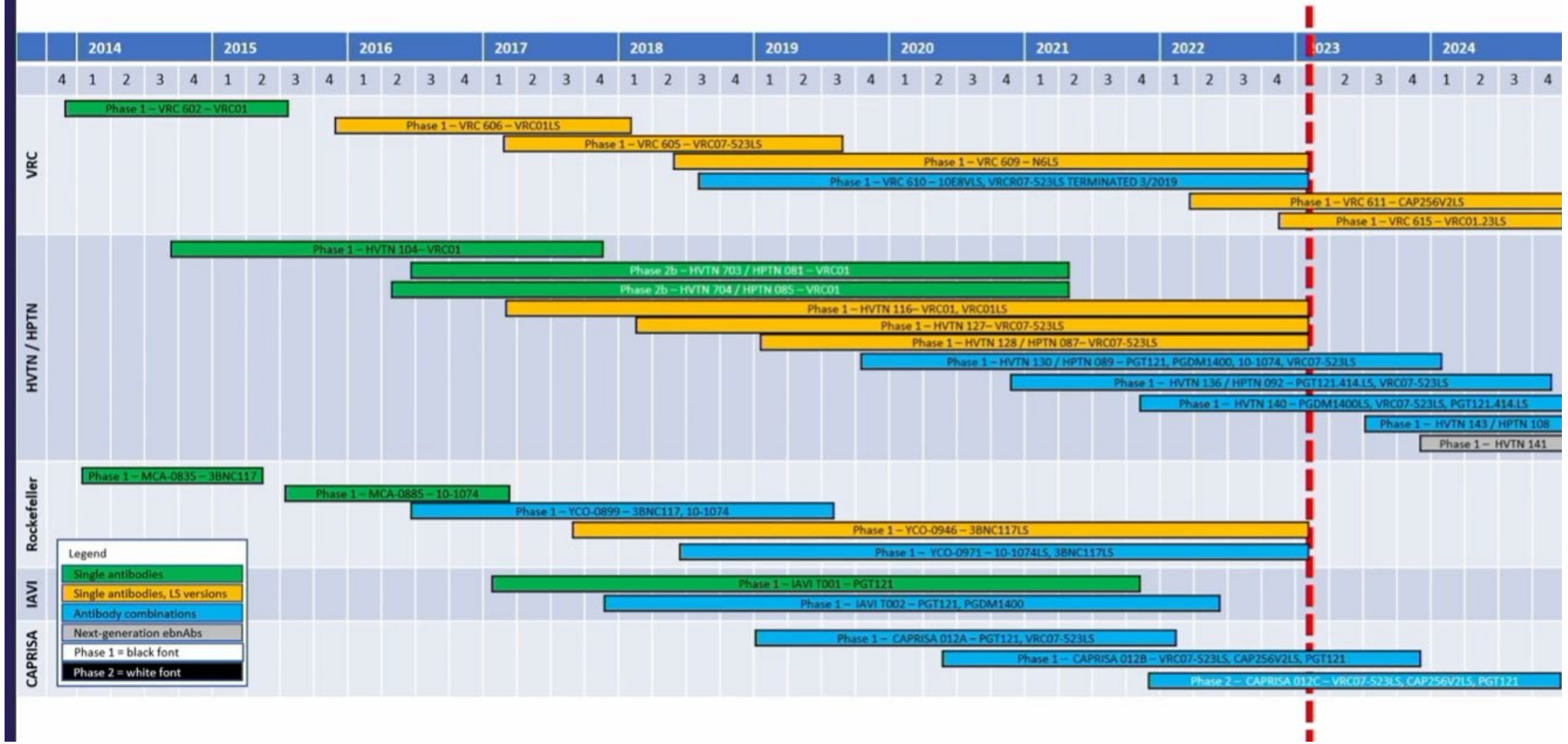
4
HIV VACCINE
E
20 nm
HIV bnAbs in Development
PG9, PG16
PGT141-145
CAP256-VRC26
PGDM1400
CH01-04
V1V2 Glycan
Glycans
VRC01, PG04, CH31,
3BNC117, CH103,
12A12, VRC13, VRC07
VRC07-523, N6, DH270,
BANC131, CH235
CD4 Supersite
N332 Glycan-V3 Supersite
PGT121
PGT128
10-1074
DH270
35022
PGT151
8ANC195
gp120-gp41
Interface
Membrane-proximal
external region (MPER)
2F5
4E10
10E8V
Viral membrane
Blue circles = mAb in Network Program

HIV bnAb clinical trials in HIV-uninfected – 2013-2024



Concept and Steps

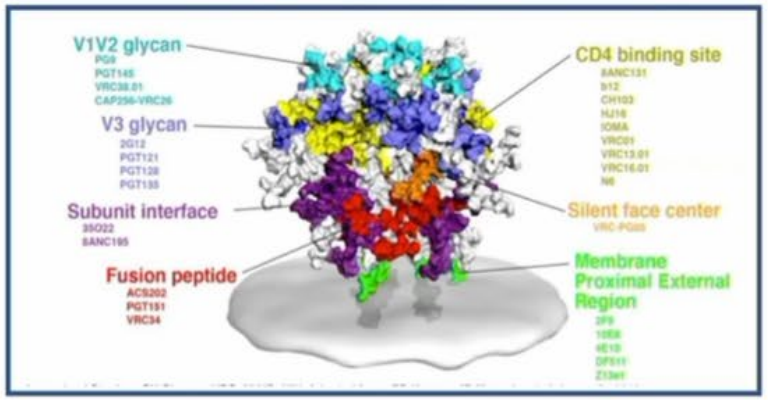
- Passive immunization for prevention of viral infection
- Need to have the pharmacology for twice a year dosing
  - Long acting antivirals are available
- Favorable safety profile for three-antibody cocktail
- Antibody availability: safety and pharmacology trials
- An organization/company for drug supply and leading to licensure

HIV Vaccines

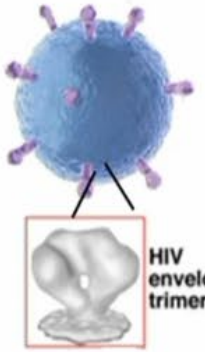
HIV Vaccine Efficacy Trials from the Past 15 Years

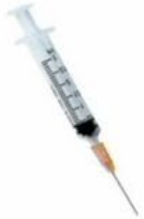
- **STEP** and **Phambili** Trials – Ad5 vector delivered Gag/Pol/Net, stopped in 2007
- **HVTN 505** DNA prime, Ad5 boost in Ad5 seronegative, circumcised men study stopped in April 2013 for lack of efficacy
- **RV144**, ALVAC and AIDSVAX demonstrated statistically significant protection
  - Immune correlates of risk analysis provides clues for a way forward
- **HVTN 702**, trying to improve upon RV144, ALVAC prime and bi-valent clade-C gp120-MF59 stopped February 2020
- Imbokodo (**HVTN 705**) and Mosaico (**HVTN 706**) Ad26 mosaic antigen, followed with HIV Env boost; both stopped for lack of efficacy, Aug 2021 and Jan 2023, respectively

Inducing bNAbs Through Vaccination



Immunogen Design bNAb target



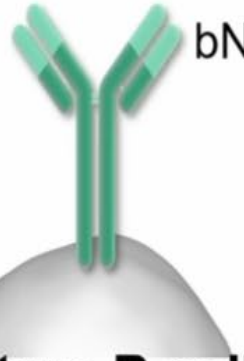


Prime

Naïve B cells

Gym

Germinal center GYM
- Affinity maturation
- Somatic Hypermutation
- T- Follicular Help, TF reg
- Sequential immunization
- **Boosting/Polishing**



bNAbs

Mature B cells

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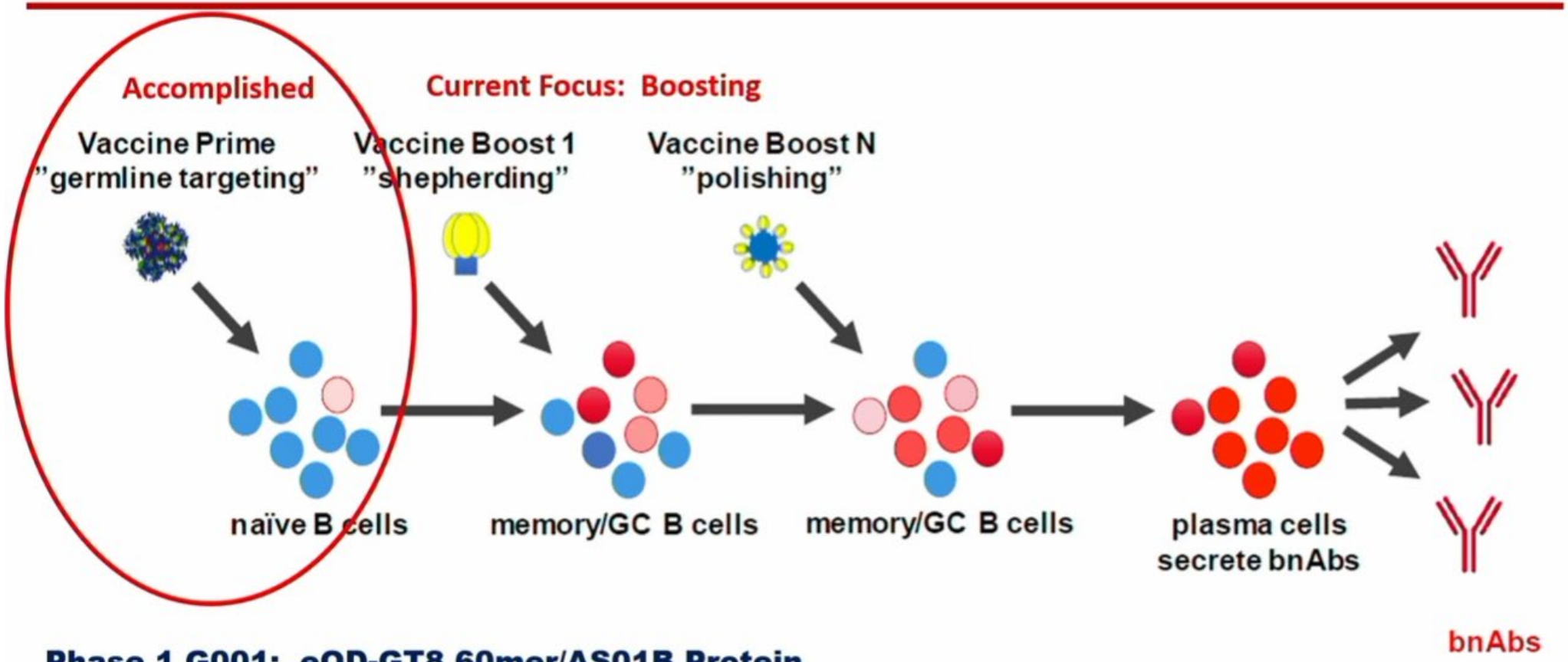
CARL DIEFFENBACH, NIAID/ NIH

Strategy: Sequential Immunization to Induce bNAbs



Phase 1 G001: eOD-GT8 60mer/AS01B Protein

"germline targeting proof-of-concept"

RESEARCH ARTICLE SUMMARY

HIV CLINICAL TRIALS

Vaccination induces HIV broadly neutralizing antibody precursors in humans

David J. Leggat†, Kristen W. Cohen†, Jordan R. Willis†, William J. Fulp†, Allan C. deCamp†, Oleksandr Kalyuzhniy, Christopher A. Cottrell, Sergey Menis, Greg Finak, Lamar Ballweber-Fleming, Abhinaya Srikanth, Jason R. Plyler, Torben Schiffner, Alessia Liguori, Farhad Rahaman, Angela Lombardo, Vincent Philiponis, Rachael E. Whaley, Aaron Seese, Joshua Brand, Alexis M. Ruppel, Wesley Hoyland, Nicole L. Yates, LaTonya D. Williams, Kelli Greene, Hongmei Gao, Celia R. Mahoney, Martin M. Corcoran, Alberto Cagigi, Alison Taylor, David M. Brown, David R. Ambrozak, Troy Sincomb, Xiaozhen Hu, Ryan Tingle, Erik Georgeson, Saman Eskandarzadeh, Nushin Alavi, Danny Lu, Tina-Marie Mullen, Michael Kubitz, Bettina Groschel, Janine Maenza, Orpheus Kolokythas, Nadia Khati, Jeffrey Bethony, Shane Crotty, Mario Roederer, Gunilla B. Karlsson Hedestam, Georgia D. Tomaras, David Montefiori, David Diemert, Richard A. Koup, Dagna S. Laufer, M. Juliana McElrath*, Adrian B. McDermott*, William R. Schief*

Key data

- Immunogen: eOD-GT8 60mer with AS01B ajuvant
- “Induced VRC01-class bnAb precursors in 97% of vaccine recipients with median frequencies reaching 0.1% among immunoglobulin G B cells in blood”
- “bnAb precursors shared properties with bnAbs and gained somatic hypermutation and affinity with the boost”
- “We detected no serum neutralizing activity to any of the several viruses tested…”
- “VRC01-class memory BCRs showed no binding to a native-like trimer and weak binding to core-gp120”

Protein, mRNA and Peptide Liposome Immunogens

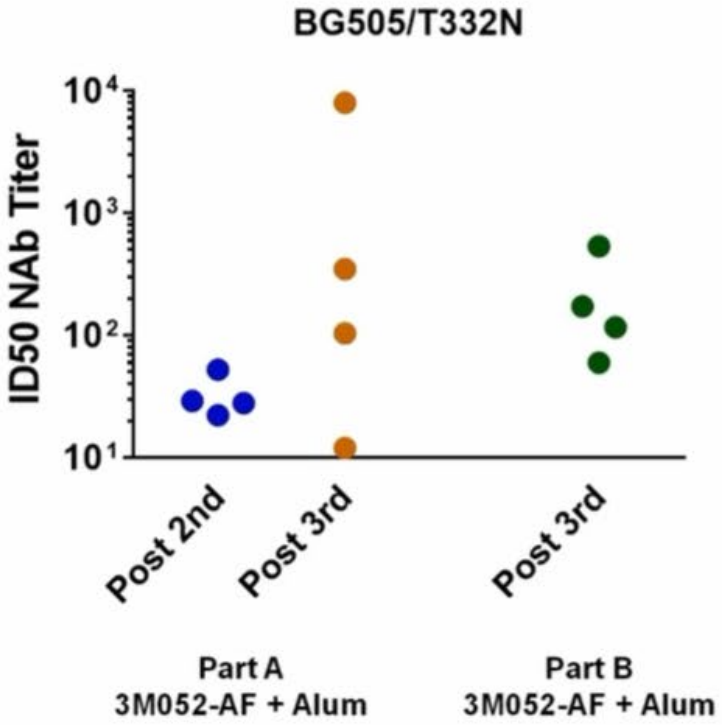
- BG505 SOSIP
  - adjuvanted protein (HVTN 137)
  - mRNA (HVTN 302)
- gp41 MPER-656 liposome (HVTN 133)

HVTN 137

A phase 1 clinical trial to evaluate the safety and immunogenicity of HIV-1 BG505 SOSIP.664 gp140 with TLR agonist and/or alum adjuvants in healthy, HIV-uninfected adults

Adjuvants:

- **3M-052-AF + Alum**
- CpG 1018 + Alum
- GLA-LSQ
- Alum



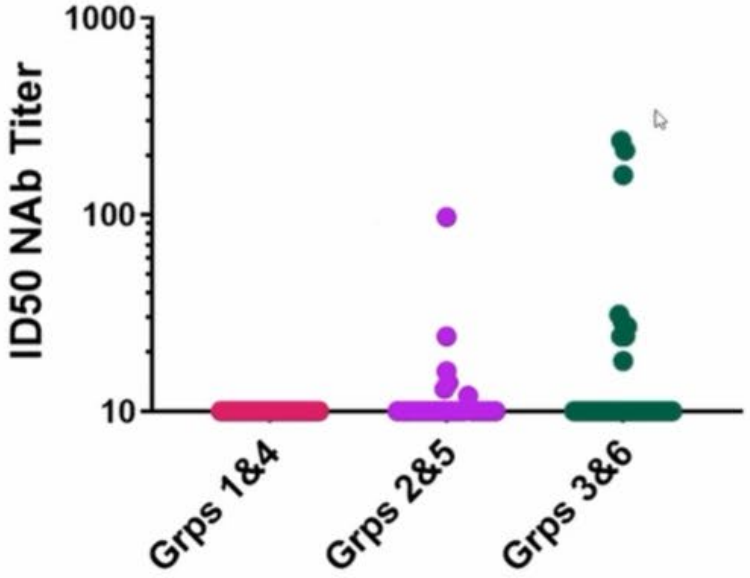
No autologous tier 2 neutralization in the other adjuvant groups.

No heterologous tier 2 neutralization in the 3M-052-AF Alum groups.

HVTN 302

Autologous Tier 2 (BG505/T332N) Neutralization by Group (2 wks post 2nd)

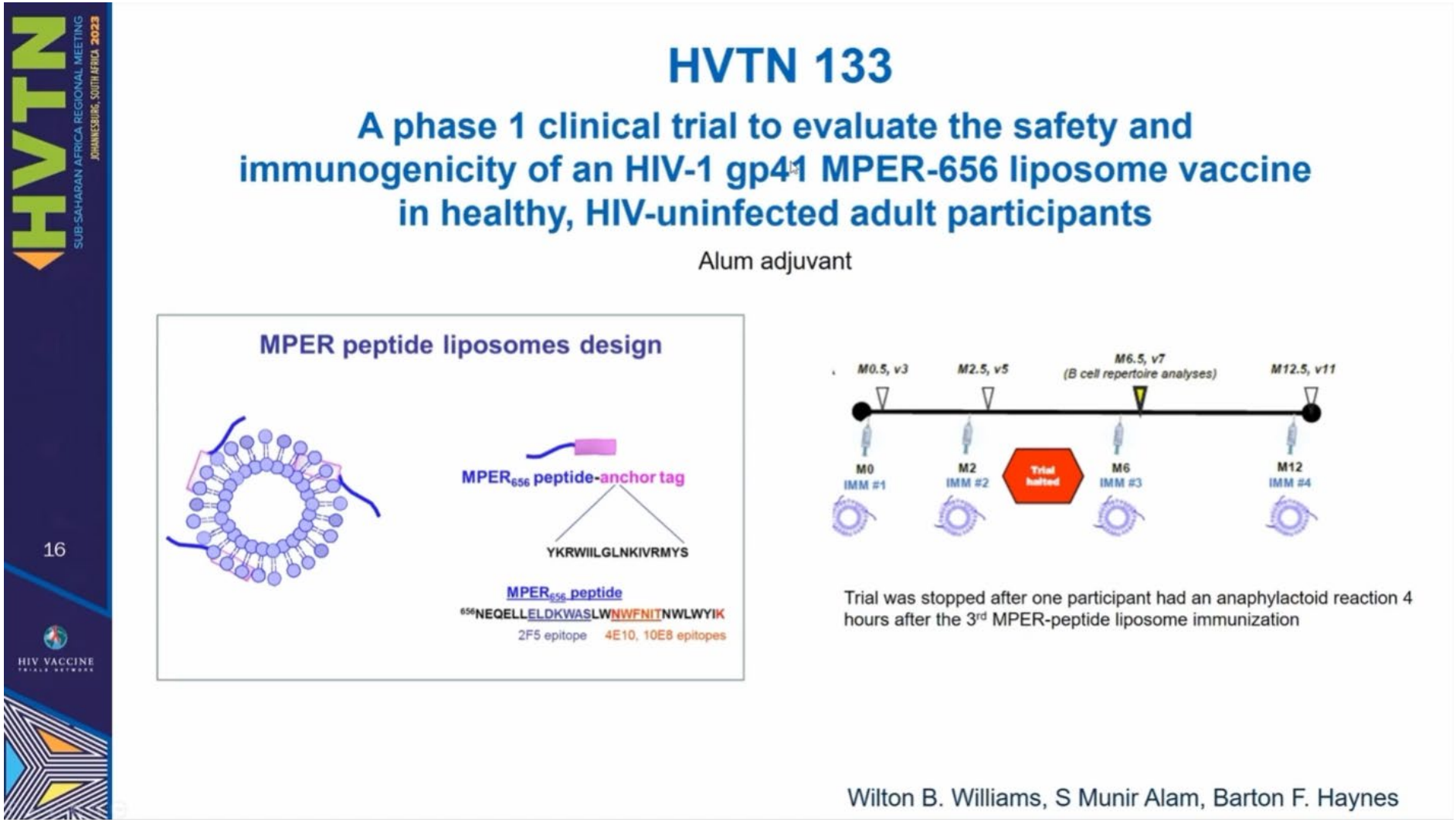
	Grps 1&4	Grps 2&5	Grps 3&6
Pos/Total=	0/28	6/31	9/35
% Pos=	0%	19%	26%



Grps 1&4: BG505 MD39.3 soluble trimer (100 and 250 µg)

Grps 2&5: BG505 MD39.3 membrane-bound trimer (100 and 250 µg)

Grps 3&6: BG505 MD39.3 membrane-bound trimer with CD4bs knock-out (100 and 250 µg)



No heterologous serum neutralization at 1:10 serum dilution but heterologous Nab activities were detected with affinity purified MPER+ IgG in 2 best responders

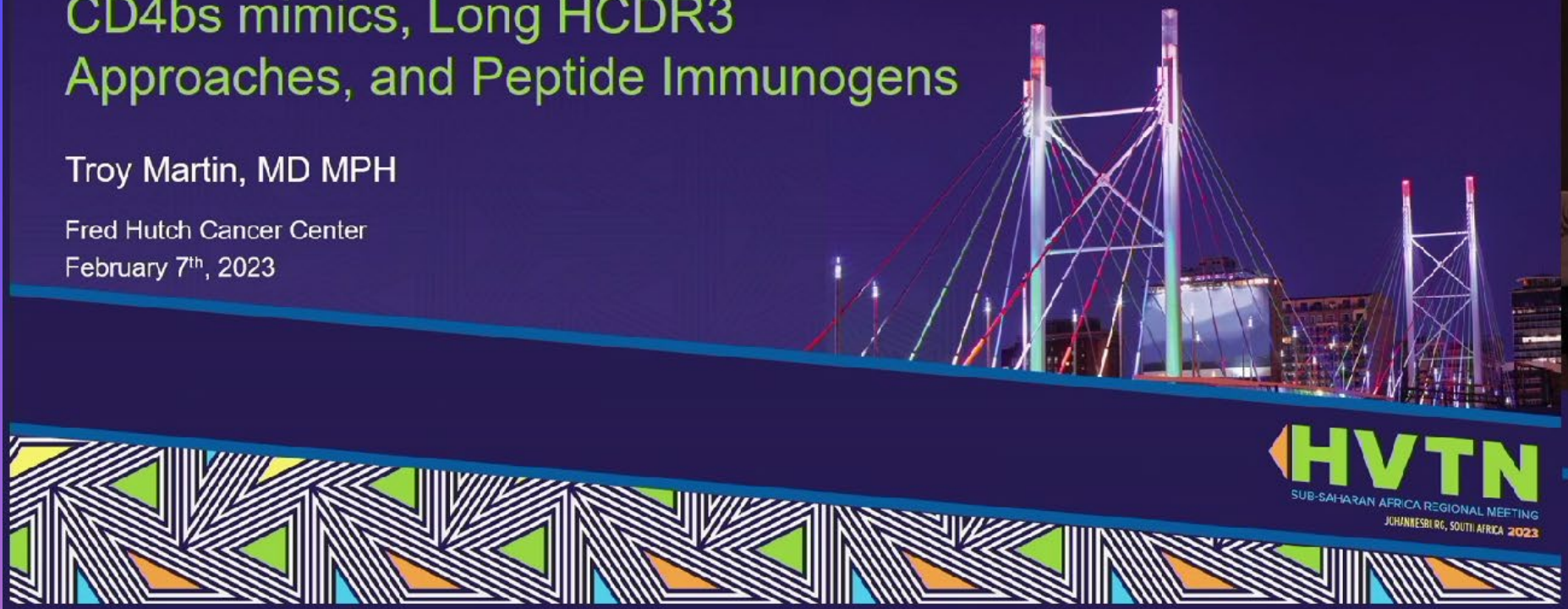
Ex Med Program Overview

CD4bs mimics, Long HCDR3 Approaches, and Peptide Immunogens

Troy Martin, MD MPH

Fred Hutch Cancer Center

February 7th, 2023



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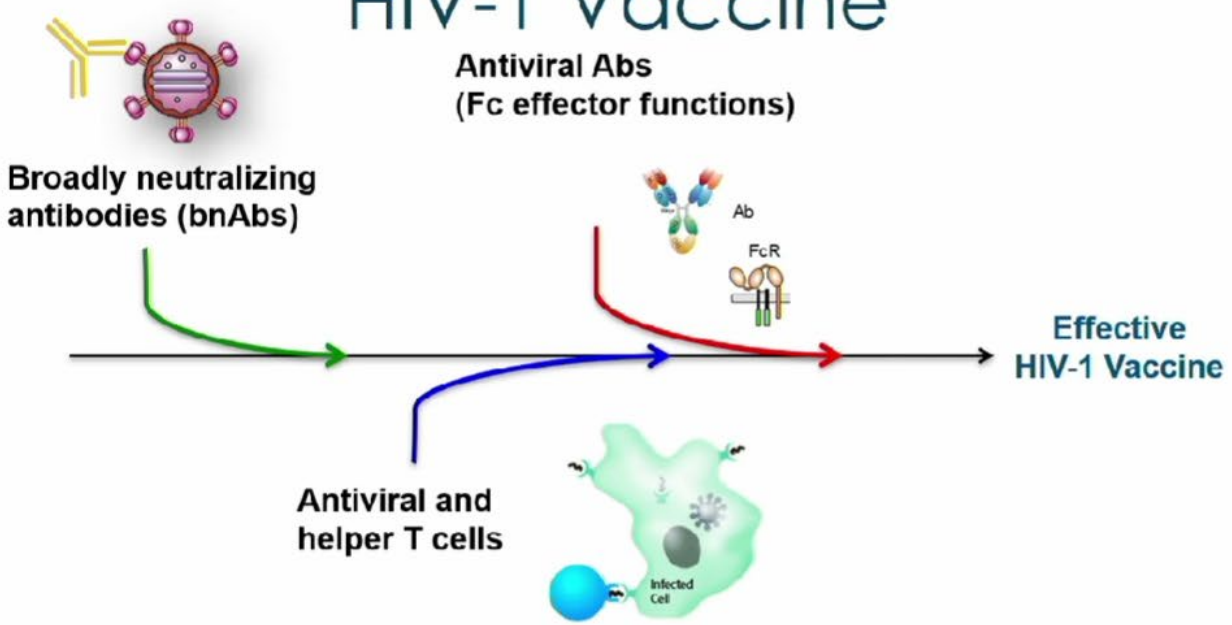
Immunogen structural design concepts

- CD4 mimicking structures
  - Includes the most potent CD4bs bnAbs
    - VRC01, CH235
- Structures that replicate the HCDR3 binding pocket
  - V3 glycan, V2 apex, a minority of CD4bs, MPER, FP
    - BG18, PCT64, CH103, 10E8, PGT151
- Use of epitope specific peptides derived from conserved Env sequences
  - FP, MPER

22 trials anticipated in next two years (n=1,064)
ExMed Protocol Pipeline – 2023-24

#	HVTN Protocol	Short Title	Immunogen(s)	Adjuvant(s)	Developer/ Organization	Manufacturer	bnAb Strategy (immunogen model)	Participants	Trial Opening
1	300	CH505 TF chSOSIP	Clade C CH505 chSOSIP	3M-052-AF/alum & LNP	Bart Haynes & Kevin Saunders/ DHVI	DHVI	CD4bs CH103 lineage (UCA)	12 (Part A) 36 (Part B) 36 (Part C)	11/3/21 (Part A) 11/28/22 (Part B) 3/31/23 (Part C)
2	301	426c Core NP	Clade C 426c Core-C4b (8-mer NP)	3M-052-AF/alum	Leo Stamatatos/ Fred Hutch	DHVI	CD4bs germline (VRC01)	52	7/12/22
3	302	mRNA MD39.3 trimer	Clade C BG505 MD39.3 SOSIP (3 versions: soluble, membrane bound, membrane bound with CD4KO)	LNP	Bill Schief/ Scripps	Moderna	mRNA trimer (epitope agnostic)	108	12/23/21
4	303	Fusion peptide NP	Clade A FP91-rTTHC, Trimer 4571 (modified Clade A BG505), Trimer 6931 (Conc C)	Adjuplex	Peter Kwong/ VRC	VRC	FP germline (VRC34.01)	70	7/27/22
5	304	sD-NLT-AB05 trimer	Clade A BG505 MD39 SOSIP (DNA), Trimer 4571 (modified Clade A BG505)	pIL-12 (INO-9012), 3M-052-AF/alum	David Weiner & Daniel Kulp/ Wistar	Inovio, VRC	Trimer (epitope agnostic)	20	3/23/23
6	305	sD-NP-GT8 NP	eOD-GT8 60-mer (DNA), Trimer 4571 (modified Clade A BG505)	pIL-12 (INO-9012), 3M-052-AF/alum	David Weiner & Daniel Kulp/ Wistar	Inovio, VRC	CD4bs germline (VRC01)	45	3/27/23
7	306	V3G CH848 mRNA prime/mRNA boost	V3 CH848 mRNA-gp160, V3 CH848 mRNA-TR2	LNP	Bart Haynes & Kevin Saunders/ DHVI	DHVI	V3 DH270 lineage (UCA)	34	11/1/23
8	307	V3G CH848 NP protein prime/mRNA boost	V3 CH848 Pr-NP1, V3 CH848 mRNA TR2	3M-052-AF/alum	Bart Haynes & Kevin Saunders/ DHVI	DHVI	V3 DH270 lineage (UCA)	36	4/27/23
9	308	16055 NFL Δgly4 trimer	Clade C 16055 NFL Δgly4 trimer, Ad4 Env145 1086 NFL, Trimer 4571 (modified Clade A BG505)	3M-052-AF/alum	Rich Wyatt & Mark Connors/ Scripps & NIH	ABL/DHVI	CD4bs germline (agnostic)	45	3/9/23
10	309	CH505 M5 (G458Y) trimer NP	Clade C CD4BS CH505M5 Pr-NP1 (G458Y) prime, CH505 TF chTrimer boost	3M-052-AF or LNP	Bart Haynes & Kevin Saunders/ DHVI	DHVI	CD4bs CH235 lineage (UCA)	30	11/1/23
11	310	mRNA 426c trimer VLP	Clade C 426c CD4bs Δgly3 trimer VLP (mRNA), multistep multiclade trimer VLP (mRNA) boosts	LNP	Paolo Lusso/ VRC	Moderna	CD4bs germline (VRC01)	72	2/1/24
12	807	426c Core NP prime/ ATI boost	Clade C 426c Core-C4b (8-mer), ATI boost	3M-052-AF/alum	Leo Stamatatos/ Fred Hutch	DHVI	CD4bs germline (VRC01)	40	8/20/23
13	144	N332 GT5 gp140 trimer	Clade A BG505 MD39 derived N332-GT5 trimer	SMNP	Bill Schief/ Scripps	IAVI	V3 germline (BG18)	84	7/22/23
14	311	Infant CH505 TF chSOSIP	CH505 TF chSOSIP	3M-052-AF +/- alum	Bart Haynes & Kevin Saunders/ DHVI	DHVI	CD4bs CH103 lineage (UCA)	90	7/28/23
15	312	CH505 M5 N197D mRNA-gp160 prime/mRNA boost	Clade C CH505 M5 N197D mRNA-gp160, CH505 TF mRNA-gp160	LNP	Bart Haynes & Kevin Saunders/ DHVI	DHVI	CD4bs CH235 lineage (UCA)	36	11/23/23

Immune responses on the pathway to an HIV-1 Vaccine



- **Context with COVID-19 vaccines:** Effective HIV vaccine MUST prevent infection, while COVID-19 vaccines easily induce nAbs effective at preventing moderate to severe symptoms.
- **Reproducible evidence** from HIV-1 trials that cellular and humoral responses **work together** to decrease HIV-1 risk.
- **All antiviral immune responses may be needed for 'all-hands on deck' strategy for an effective HIV-1 vaccine.**

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Results are consistent with V1V2 Ab being a CoP in both HVTN 702 and RV144

Lower Ab in HVTN 702 potentially explaining VE~0% vs. VE~31%

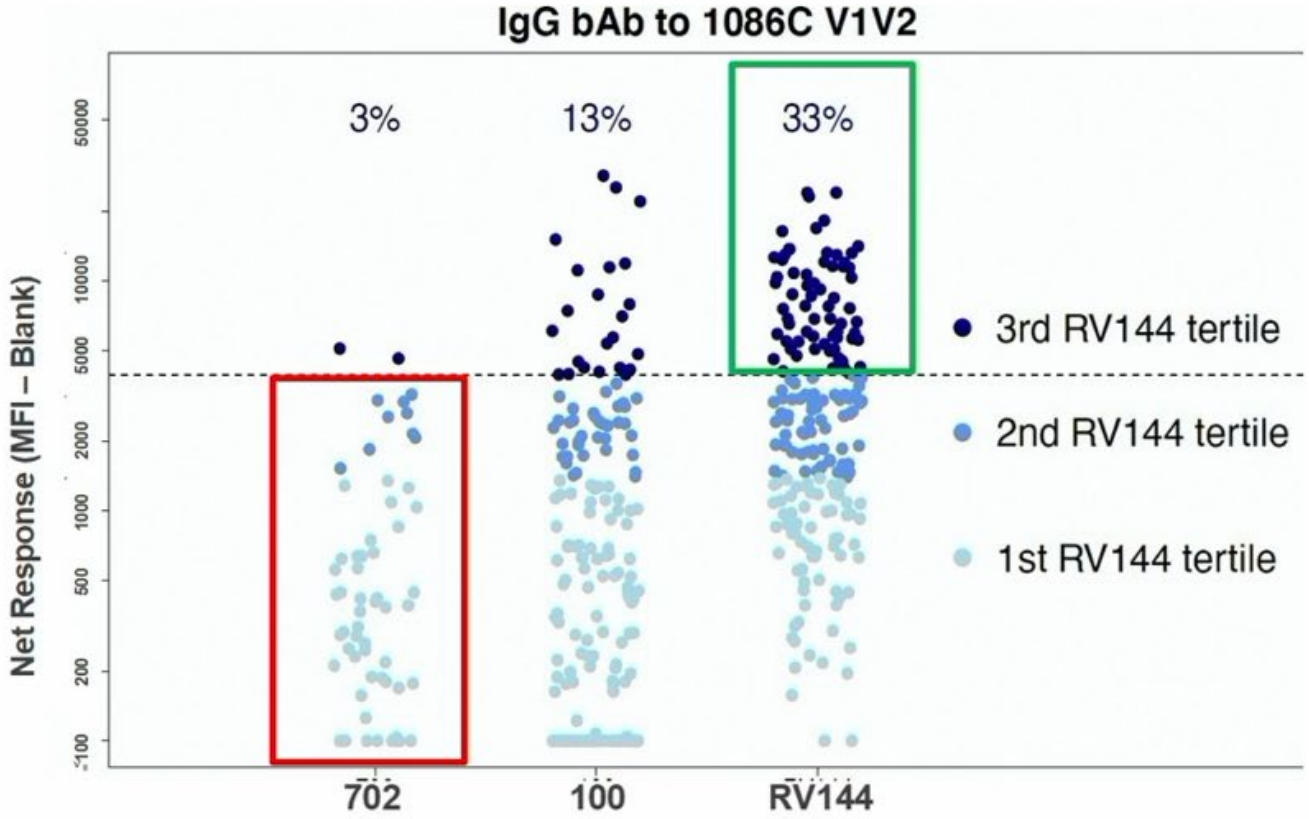
RV144:

- VE ~60% from 6.5 to 24 months for V1V2 Ab in 3rd tertile

- VE ~ 0-20% for Ab in 1st, 2nd tertiles

Uhambo/HVTN 702:

- Almost all vaccinees had V1V2 Ab in RV144 1st, 2nd tertiles



Perspectives from HIV-1 vaccine efficacy trials: Uhambo, Imbokodo, HVTN 505, and RV144

- Results from 4 different vaccine efficacy trials in different populations with different regimens are consistent with a role for V1V2 IgG and/or V1V2 IgG3 in partially protecting against HIV-1 acquisition.

  RV144, HVTN 505, Uhambo/HVTN 702, and Imbokodo /HVTN 705

- 3 vaccine efficacy trials had evidence of an HIV-1 IgG3 immune correlate of decreased risk.

  RV144, HVTN 505, and Imbokodo/HVTN 705

IgG A244 V1V2 and CD4+ T cell interaction correlated with HIV risk in Uhambo/HVTN 702

- **Categorical IgG A244 V1V2** the only primary/secondary marker to meet pre-specified criterion for consideration in interaction analyses
  - Criterion: Unadjusted p-value from univariate model <= 0.10; criterion met with p=0.05
  - Studied interactions of categorical IgG A244 V1V2 with continuous version of all other primary/secondary markers

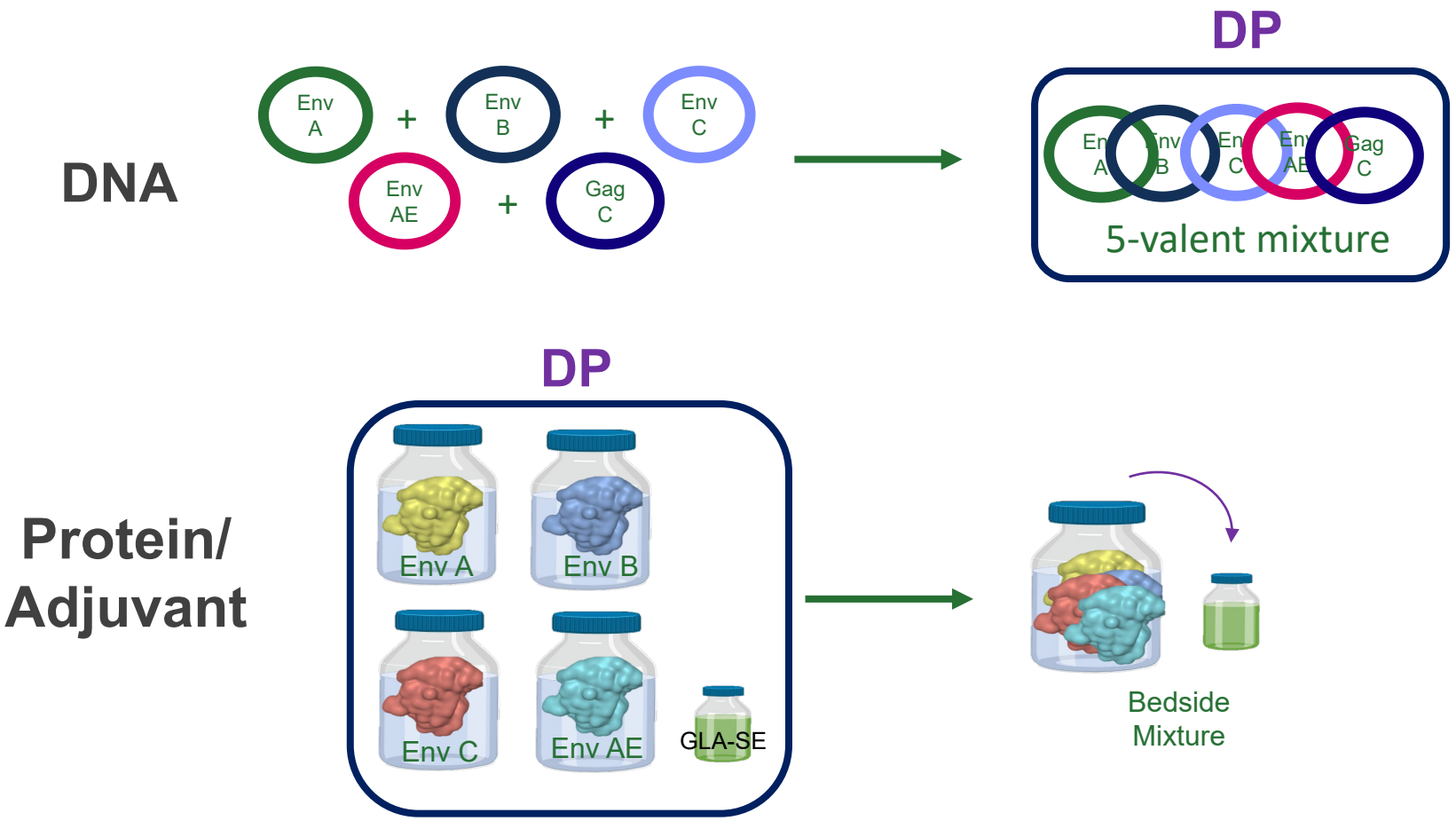
Moodie Z, Dintwe O, Sawant S, *et al*. J. Infectious Diseases 2022 Jul 15;226(2):246-57.

HVTN124: Phase 1 HIV-uninfected adults

Safety and immunogenicity of a polyvalent DNA/polyvalent protein HIV vaccine with matched Env immunogens and delivered as a prime-boost regimen or co-administered in HIV-uninfected adults

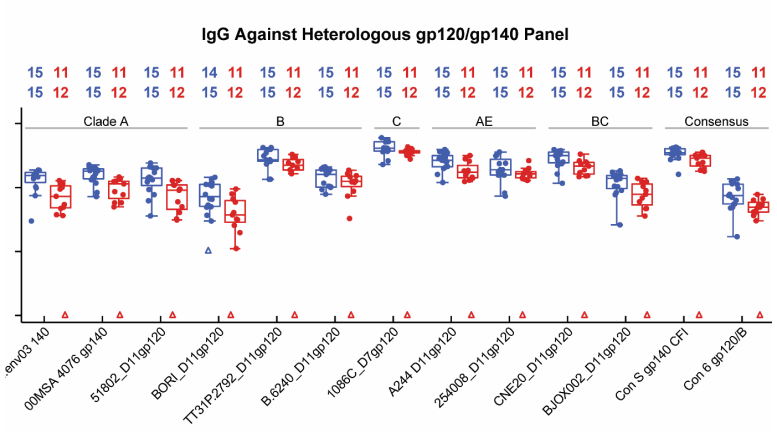
Ian Frank, MD[1*], Shuying S Li, PhD[2], Nicole Grunenberg, MD[2], Edgar T Overton, MD[3], Samuel T Robinson, PhD[2], Hua Zheng, MS[2,a], Kelly E Seaton, PhD[4], Jack R Heptinstall, MS[4], Mary Allen, MSc[5], Kenneth H Mayer, MD[6,7], Daniel A Culver, DO[8], Michael C Keefer, MD[9], Sri Edupuganti, MD[10], Stephen C De Rosa, MD[2], Daryl Morris, MS[2], Shixia Wang, PhD[11], Michael S Seaman, PhD[12], David C Montefiori, PhD[13], Guido Ferrari, MD[13,14], Georgia D Tomaras, PhD[4], James G. Kublin, MD[2], Lawrence Corey, MD[2], Shan Lu, MD, PhD[11*]

Polvalent DNA/Protein Formulation (IM injection)

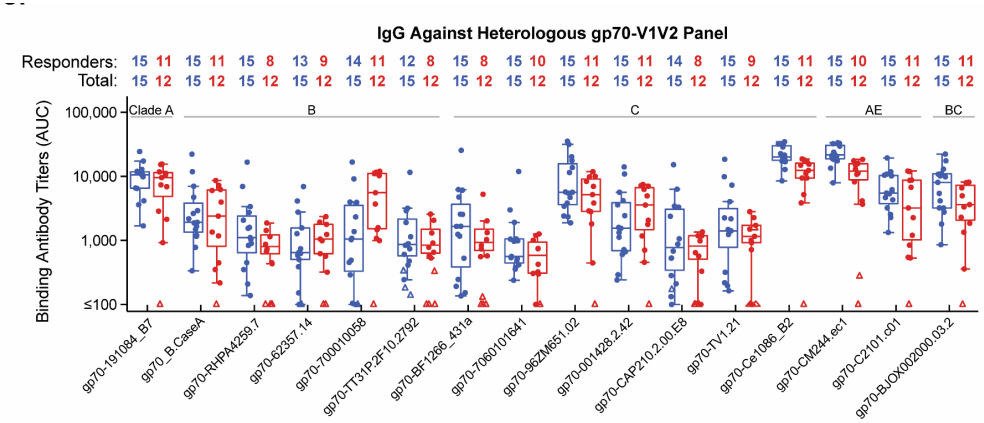


gp120:
A: 92UG037.8 B: JR-FL
C: 93MW965.26 AE: Consensus (UMMS)

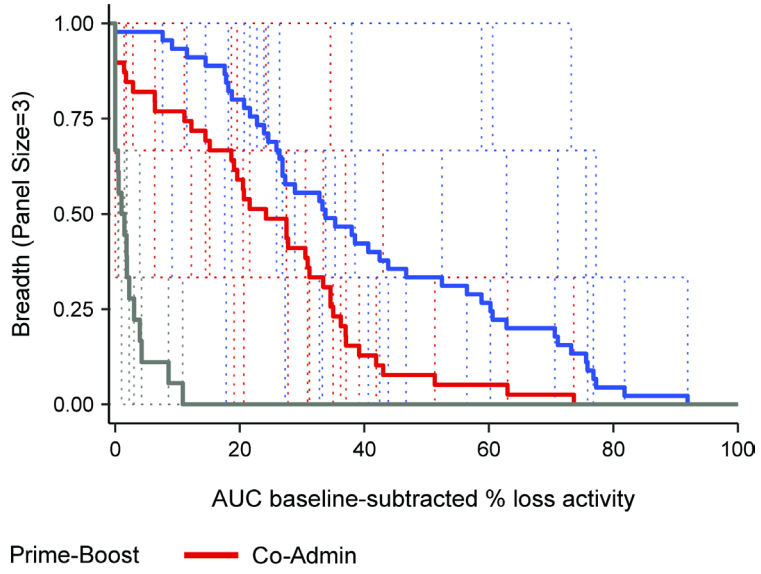
High rate/magnitude and broad IgG against diverse gp120/gp140s



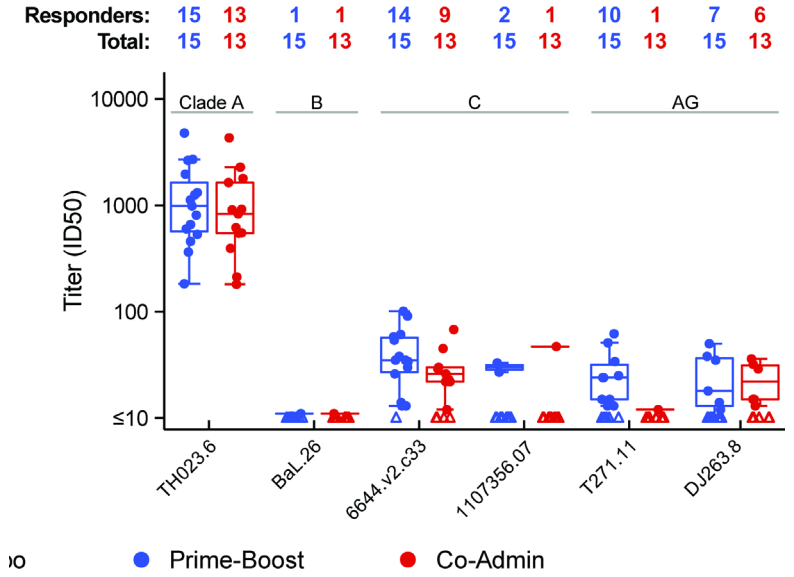
High and broad IgG responses against diverse gp70 V1V2



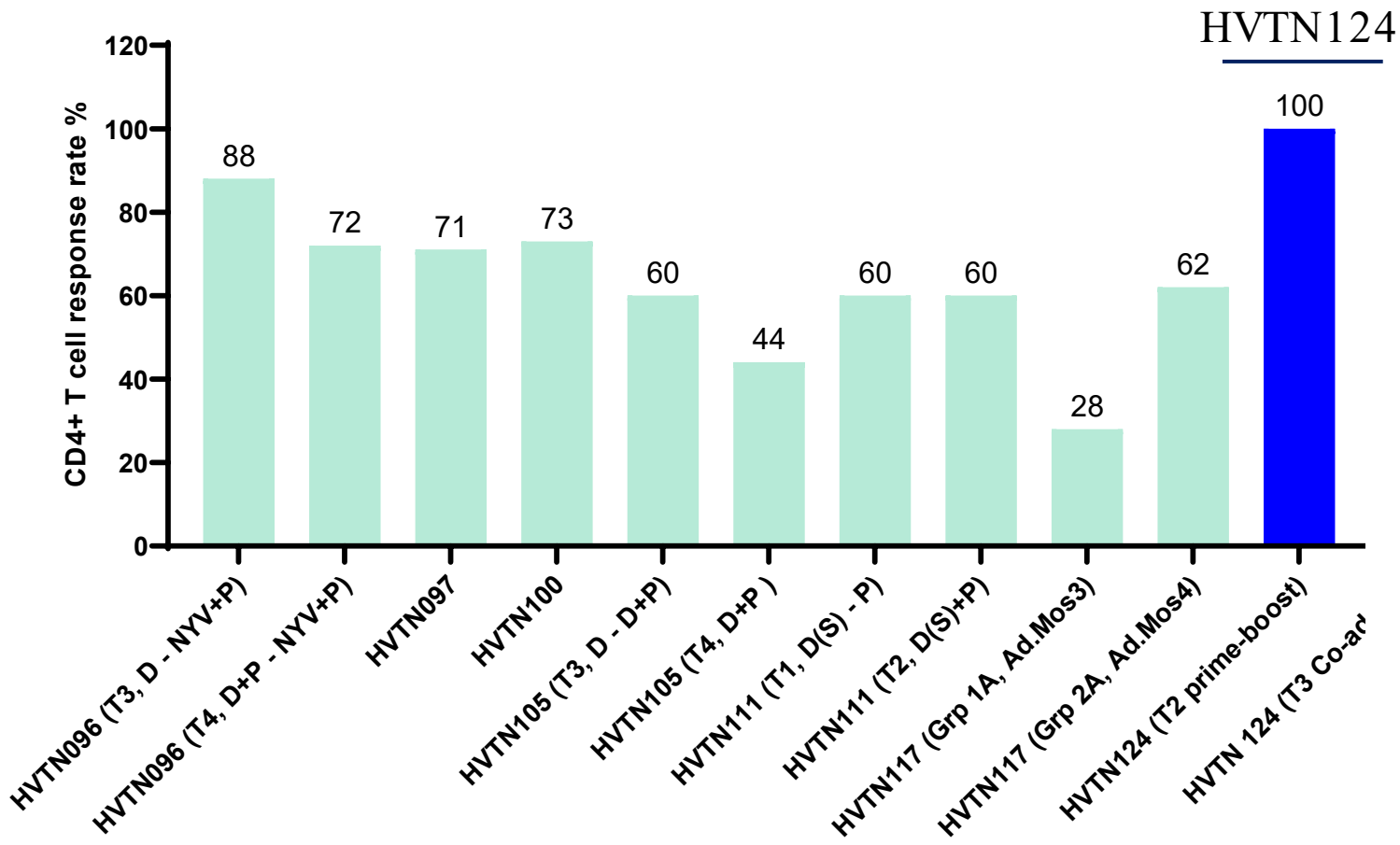
Potent and broad ADCC



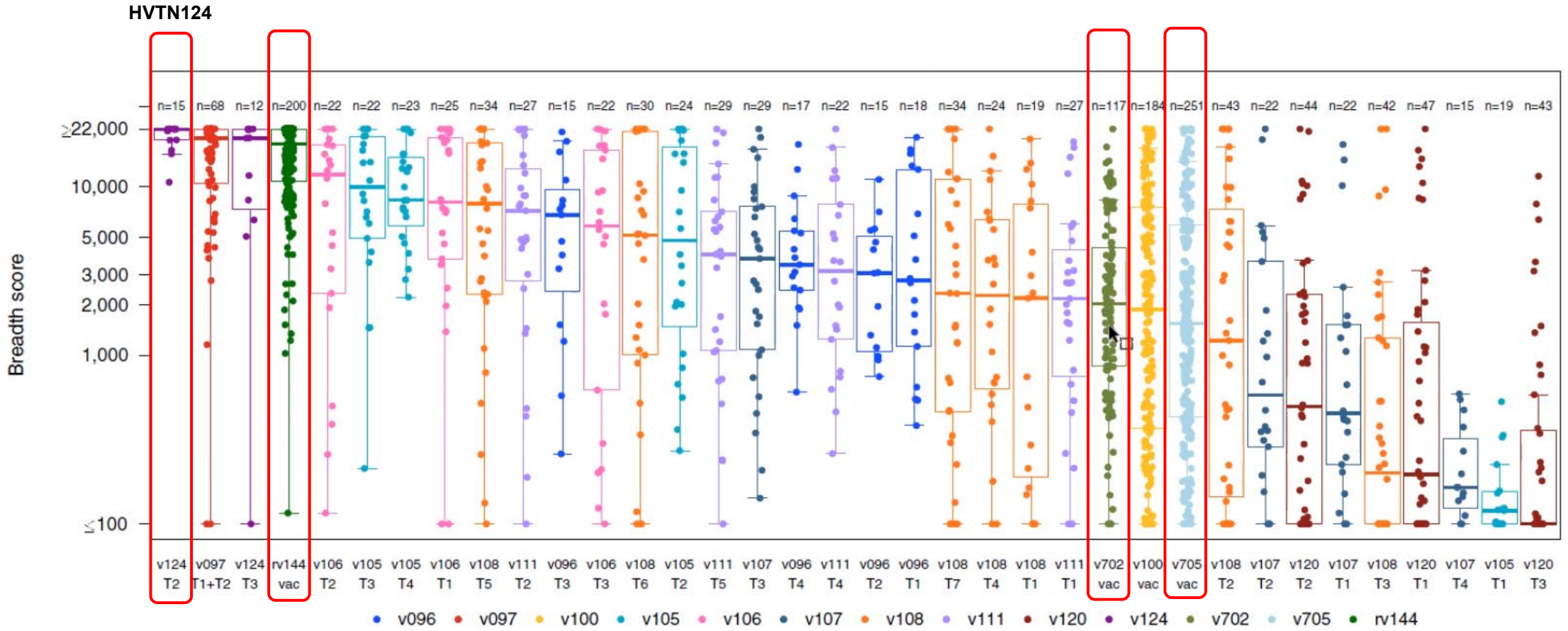
Tier 1B Nab against diverse isolates



CD4+ T cell Response Rates (%)
HVTN124 and Other HVTN Studies (different peptide pools)

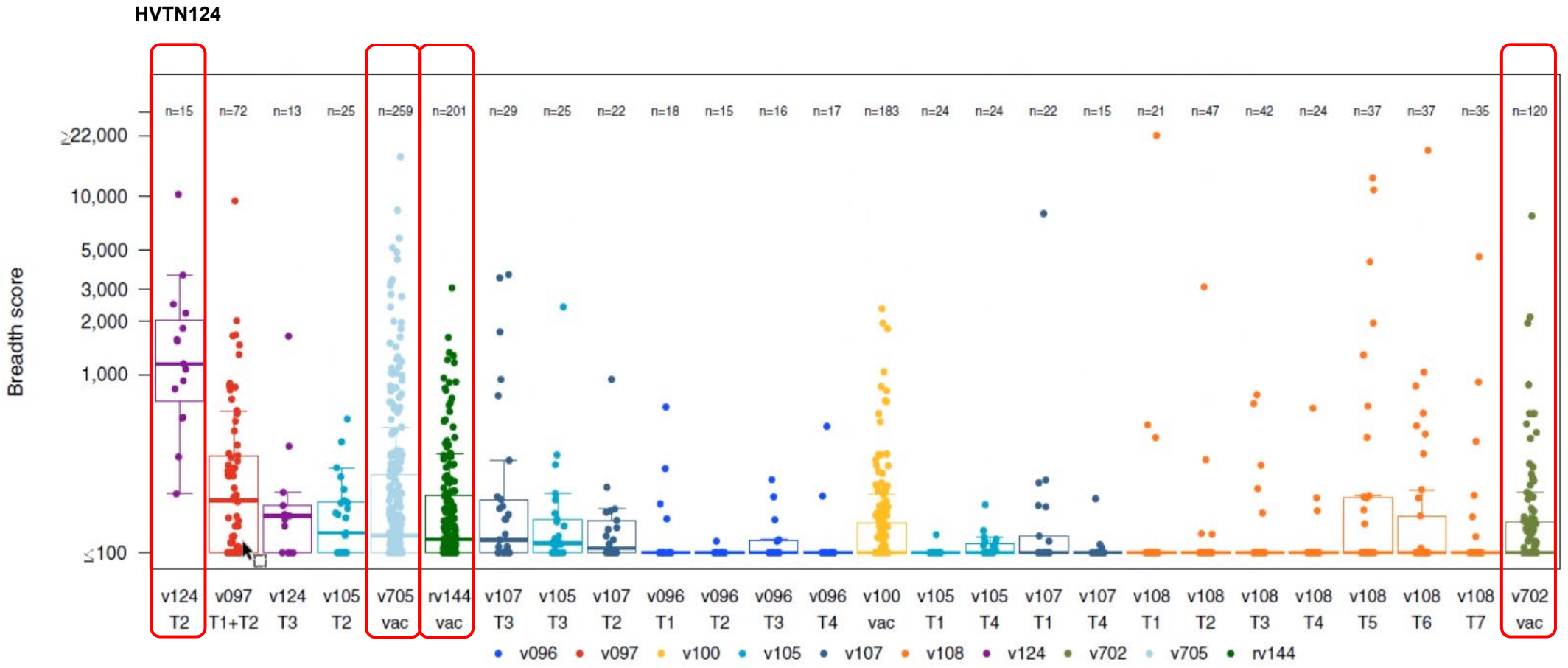


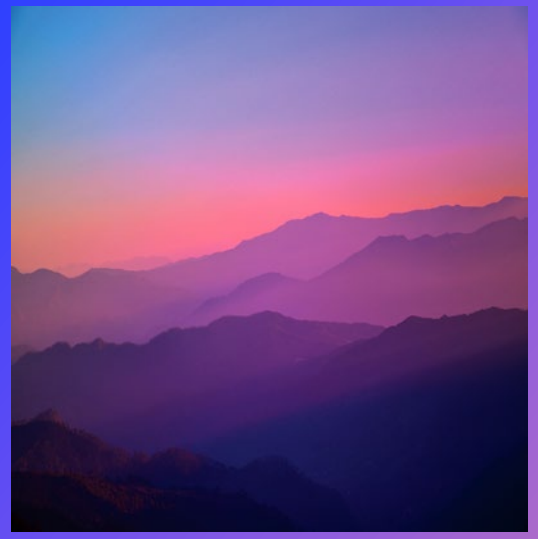
IgG binding antibody against V1V2 heterologous breadth score



Breadth Score:m Geometric mean net response over top 3 antigens responses per arm

IgG3 binding antibody against V1V2 heterologous breadth score





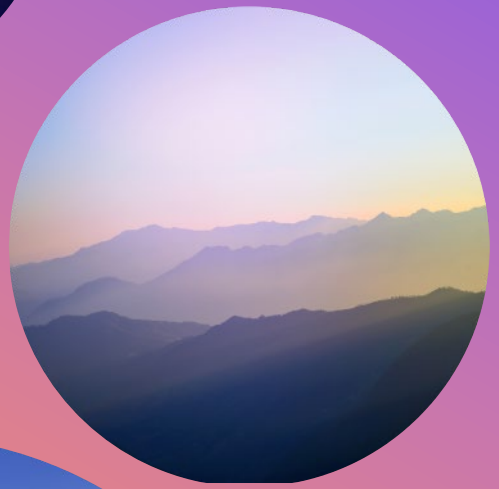
Summary

bNAb as prevention

Information is generated to determine if a concept trial for combination bNAb is feasible

HIV vaccines

- Still early stage for bNAb induction by vaccination;
- Diverse Exp Med trials;
- CoP from RV144 still valid



THANK YOU

To HVTN , other colleagues and volunteers