HIV VACCINE
TRIALS NETWORK

HIV vaccines at the fork in the road: “Just take it” says that great American philosopher, Yogi Berra

Larry Corey, MD

Principal Investigator, NIAID supported HIV Vaccine Trials Network (HVTN)

Past President and Director, Fred Hutchinson Cancer Research Center

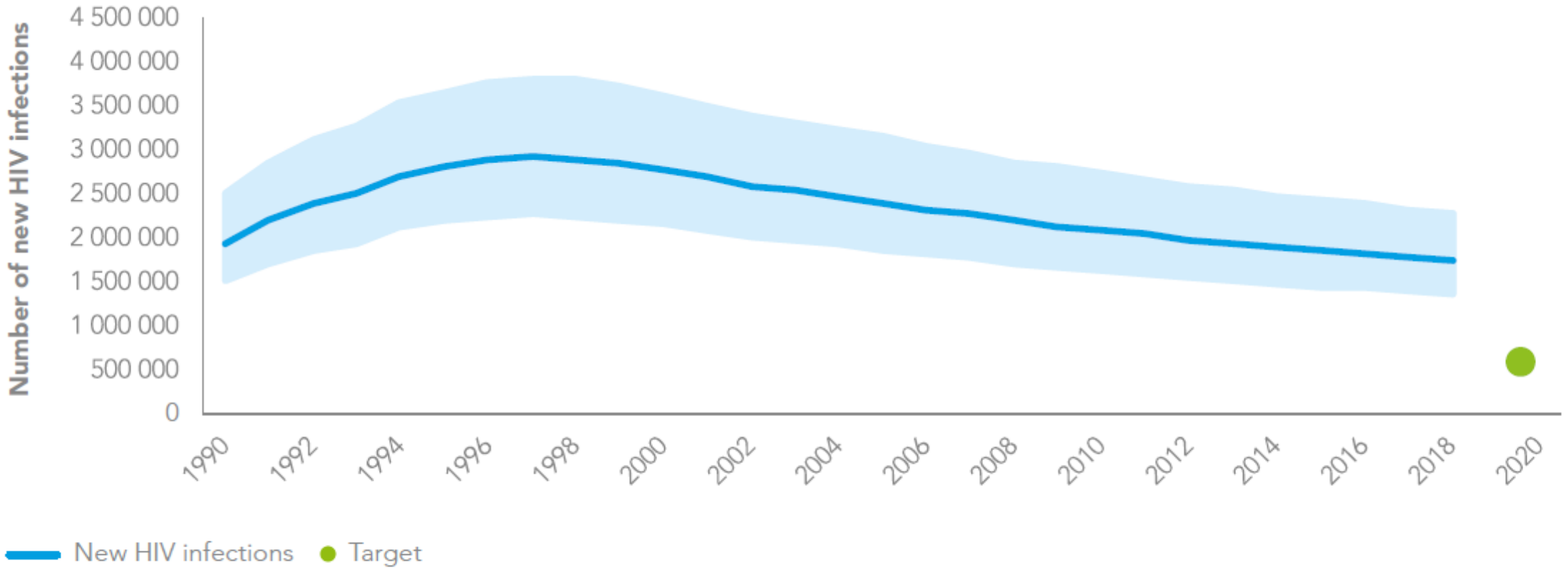
Member, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center

Professor, Laboratory Medicine and Medicine, University of Washington

HIV is Unfortunately Alive and Well Throughout the World

- Globally there are 1.4 million new infections yearly
  - This is 5,000 acquisitions a day
- 180,000 infants a year still infected
- 37 million people living with HIV (76 million since the epidemic started)
- 770,000 HIV related deaths in 2018
- US has “tolerated” 35,000 - 40,000 new infections a year

ADULTS AND CHILDREN NEWLY INFECTED WITH HIV: 1990–2018



Source: UNAIDS 2019 estimates.

Source: UNAIDS 2019

The Need for an HIV Vaccine

- Test and treat is an important strategy for individual health and can have an effect on transmission.
- U=U is correct.
- However, long term adherence and prompt identification of HIV infection is just not translatable and scalable on a large scale.
  - It has not eliminated mother to child transmission, which has a very definable exposure.

ORIGINAL ARTICLE

HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa

D.V. Havlir, L.B. Balzer, E.D. Charlebois, T.D. Clark, D. Kwarisiima, J. Ayieko, J. Kabami, N. Sang, T. Liegler, G. Chamie, C.S. Camlin, V. Jain, K. Kadede, M. Atukunda, T. Ruel, S.B. Shade, E. Ssemmondo, D.M. Byonanebye, F. Mwangwa, A. Owaraganise, W. Olilo, D. Black, K. Snyman, R. Burger, M. Getahun, J. Achando, B. Awuonda, H. Nakato, J. Kironde, S. Okiror, H. Thirumurthy, C. Koss, L. Brown, C. Marquez, J. Schwab, G. Lavoy, A. Plenty, E. Mugoma Wafula, P. Omanya, Y.-H. Chen, J.F. Rooney, M. Bacon, M. van der Laan, C.R. Cohen, E. Bukusi, M.R. Kamya, and M. Petersen

ORIGINAL ARTICLE

Universal Testing, Expanded Treatment, and Incidence of HIV Infection in Botswana

J. Makhema, K.E. Wirth, M. Pretorius Holme, T. Gaolathe, M. Mmalane, E. Kadima, U. Chakalisa, K. Bennett, J. Leidner, K. Manyake, A.M. Mbikiwa, S.V. Simon, R. Letlhogile, K. Mukokomani, E. van Widenfelt, S. Moyo, R. Lebelonyane, M.G. Alwano, K.M. Powis, S.L. Dryden-Peterson, C. Kgathi, V. Novitsky, J. Moore, P. Bachanas, W. Abrams, L. Block, S. El-Halabi, T. Marukutira, L.A. Mills, C. Sexton, E. Raizes, S. Gaseitsiwe, H. Bussmann, L. Okui, O. John, R.L. Shapiro, S. Pals, H. Michael, M. Roland, V. DeGruttola, Q. Lei, R. Wang, E. Tchetgen Tchetgen, M. Essex, and S. Lockman

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2019 VOL. 381 NO. 3

Effect of Universal Testing and Treatment on HIV Incidence — HPTN 071 (PopART)

R.J. Hayes, D. Donnell, S. Floyd, N. Mandla, J. Bwalya, K. Sabapathy, B. Yang, M. Phiri, A. Schaap, S.H. Eshleman, E. Piwowar-Manning, B. Kosloff, A. James, T. Skalland, E. Wilson, L. Emel, D. Macleod, R. Dunbar, M. Simwinga, N. Makola, V. Bond, G. Hoddinott, A. Moore, S. Griffith, N. Deshmane Sista, S.H. Vermund, W. El-Sadr, D.N. Burns, J.R. Hargreaves, K. Hauck, C. Fraser, K. Shanaube, P. Bock, N. Beyers, H. Ayles, and S. Fidler, for the HPTN 071 (PopART) Study Team

Current Phase 2B/3 HIV Vaccine Efficacy Trials

AMP
HVTN 703/704

Uhambo
(Phase 2B/3)
HVTN 702

Imbokodo
(Phase 2B POC)
HVTN 705

MOSAICO
(Phase 3)
HVTN 706

AMP
ANTIBODY · MEDIATED · PREVENTION
STUDY

uhambo

IMBOKODO

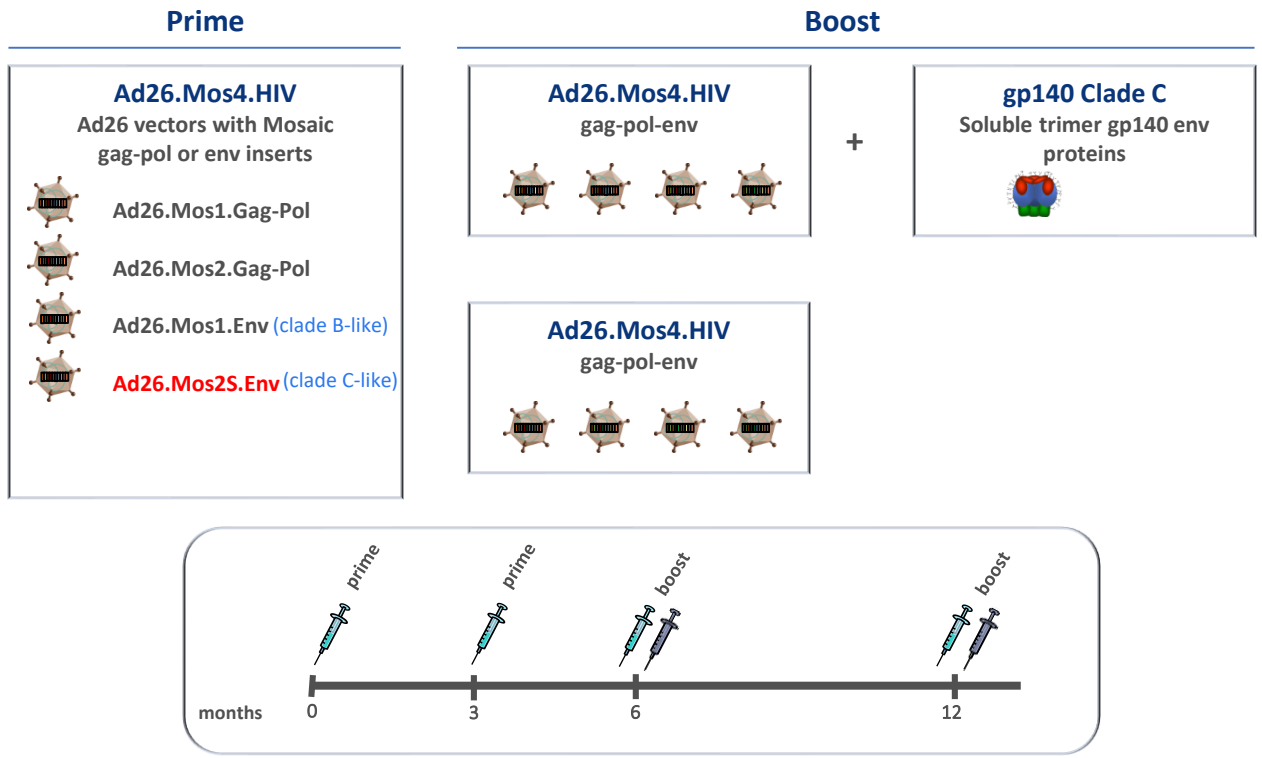
MOSAICO
HVTN 706/HPX3002

HVTN 702 Schema:
5400 South Africans (18-35 yrs)

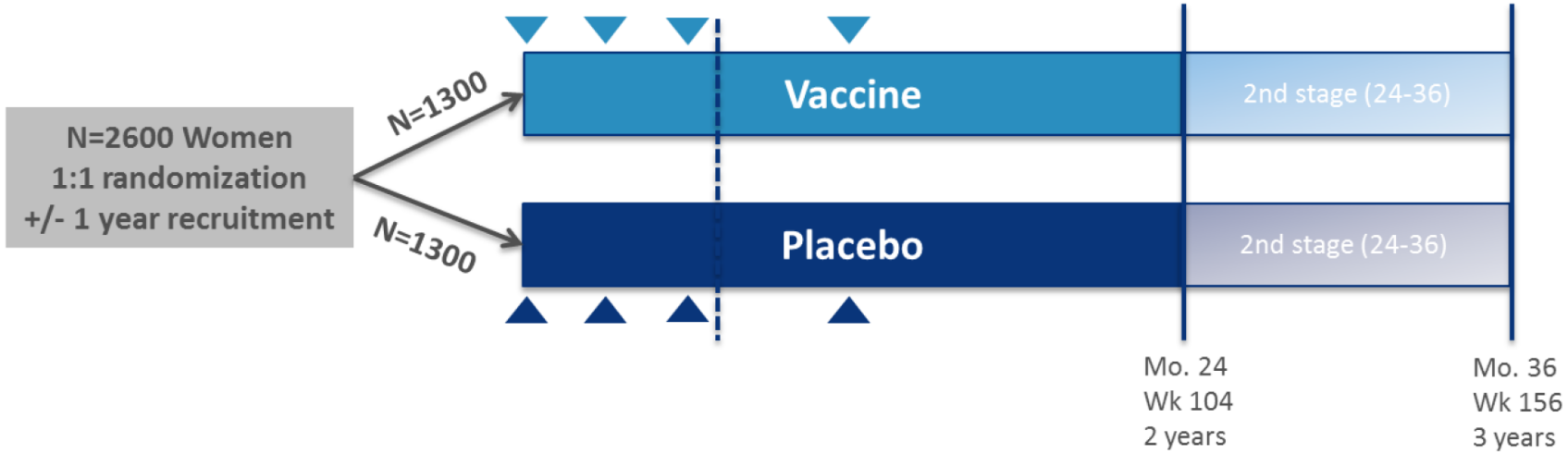
uhambo

Group	N*	Primary vaccine regimen				Boosters	
		Month 0	Month 1	Month 3	Month 6	Month 12	Month 18
1	2700	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59
2	2700	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo
Total	5400						

HVTN 705/HPX2008
Mixture of 4 mosaic Ad26 constructs + gp140 Clade C boost



Study Schema: HVTN 705/HPX2008 Imbokodo



Chairs: Glenda Gray,
Co-chairs: Susan Buchbinder, Kathy Mngadi and Frank Tomaka

HVTN 706/HPX3002 Schema

MOSAICO
HVTN 706/HPX3002

Table: Vaccination Schedule

Group	N	Month 0	Month 3	Month 6	Month 12
1	1,900	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + Clade C gp140, Mosaic gp140, adjuvanted	Ad26.Mos4.HIV + Clade C gp140, Mosaic gp140, adjuvanted
2	1,900	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

Total dose of Ad26.Mos4.HIV is 5x1010 viral particles (vp)/0.5 mL injection.
Clade C gp140, Mosaic gp140, adjuvanted: adjuvanted protein formulation with a dosage strength of 80 mcg Clade C protein, 75 mcg Mosaic protein and 425 mcg aluminum (as aluminum phosphate adjuvant). Note: previously the dose of Clade C gp140 and/or Mosaic gp140 was reported as mcg of glycoprotein: 125 mcg Clade C gp140 and 125 mcg Mosaic gp140 glycoprotein correspond with 80 mcg and 75 mcg of protein, respectively.

Ongoing HVTN Vaccine Efficacy Studies

Trial	Products	N	# of sites	Population	Countries	Public/Private Partnership	Dates for Data
HVTN 702	ALVAC/gp120	5400	14	70:30 split women & men	South Africa	P5	Finishes stage 2 when 50% entrants hit 24 months – April 2020
HVTN 705	Ad26/gp140	2600	24	Women	Malawi, Mozambique, South Africa, Zambia, Zimbabwe	Janssen/J&J and NIAID/HVTN	May 2021
HVTN 706	Ad26/gp140	3800	55	MSM, TG	Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain, US	Janssen/J&J and NIAID/HVTN	**October 2022**

Why separate trials of non-neutralizing vaccine approaches?

- Correlates of protection have some overlap but there are many differences.
  - RV144/HVTN 702 V2 loop, gp120 binding, ADCC and ADCP (recent) and HIV specific CD4+ T cell responses
  - Ad26 regimen: gp140 binding; V2 (+/-) ADCP and ELISPOT

- The magnitude and epitope specific responses and breadth differ.

- This overlap and diversity improve the ability to define what non-neutralizing immune responses are correlated and what areas of the viral envelope are susceptible to clinically effective immune pressure.

Comparison of immune responses between HVTN 702 and HVTN 705 regimens

Overview

HVTN 100 Schema (part A) – Group 1 corresponds to HVTN 702 regimen.

Group	N	Primary vaccine regimen				Booster*
		Week 0	Week 4	Week 12	Week 24	Week 52
1	210	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59®	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59®	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59®
2	42	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo
Total	252					

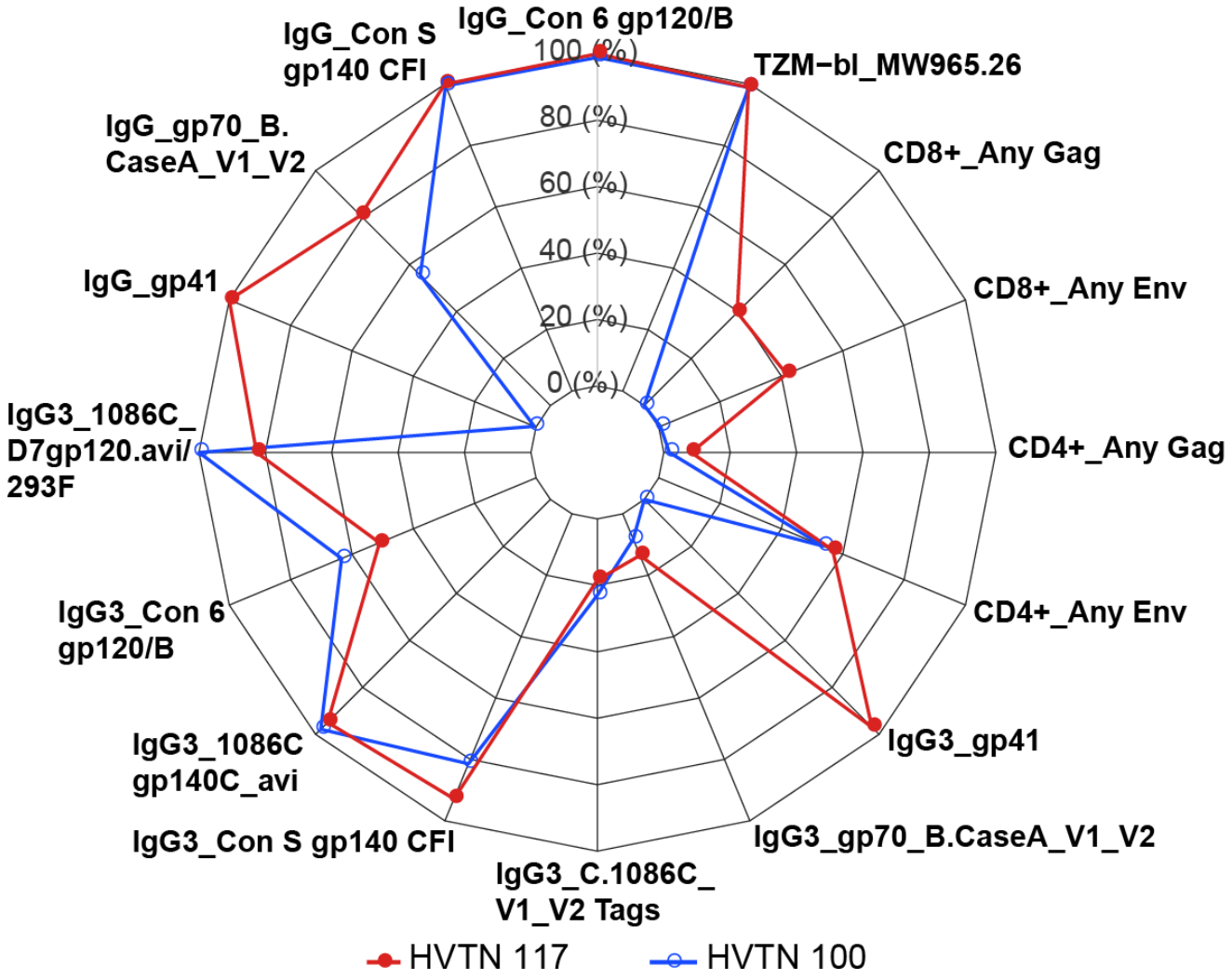
HVTN 117/HPX2004 schema – Group 2A corresponds to HVTN 705 regimen

Study Design VAC89220HPX2004

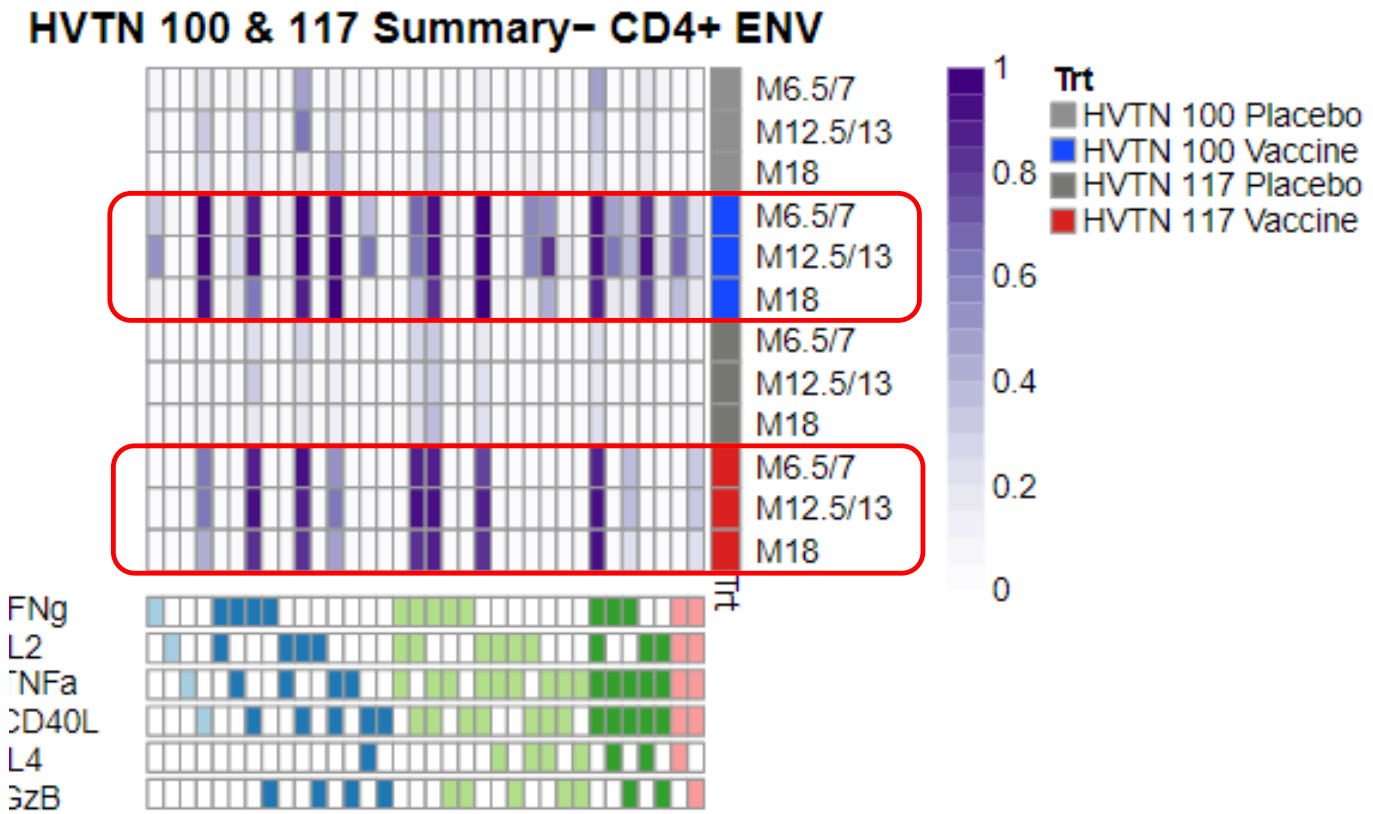
Group	Subgroup	N	Week 0	Week 12	Week 24	Week 48
Group 2	A	110	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + Clade C gp140 (250 mcg + adjuvant)[a]	Ad26.Mos4.HIV + Clade C gp140 (250 mcg + adjuvant)[a]
	B	22	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

[a]250 mcg refers to total protein content; sterile aluminum phosphate suspension will be used as adjuvant. Aluminum content will be 0.425 mg/0.5 mL dose.

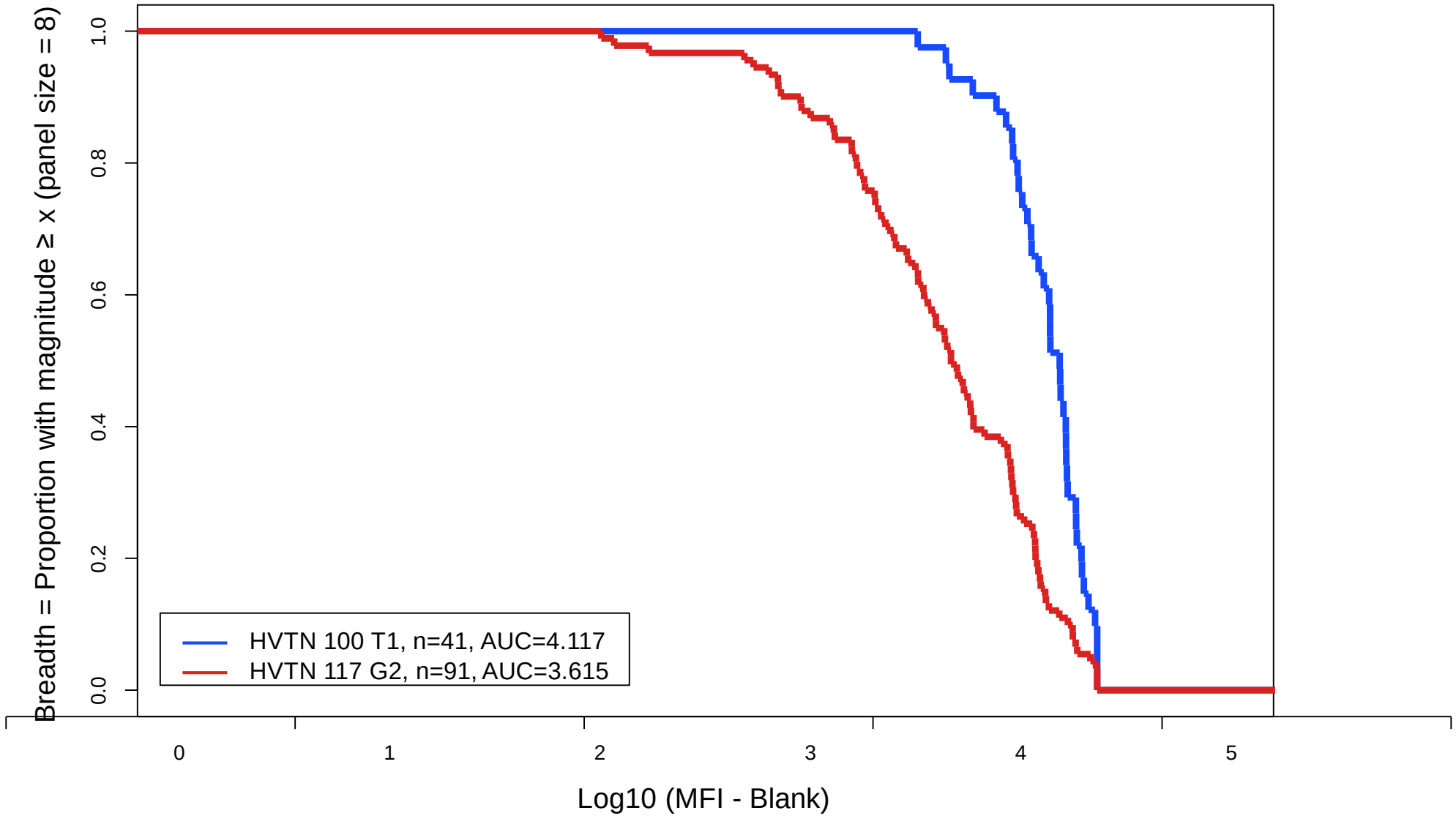
Spider plot comparing prevalence and magnitude of HVTN 702 & 705 regimens based upon the phase 2 go/no-go studies HVTN 100 (702 regimen) & HVTN 117 (705 regimen)



Heatmap summarizing polyfunctionality to vaccine-matched Env



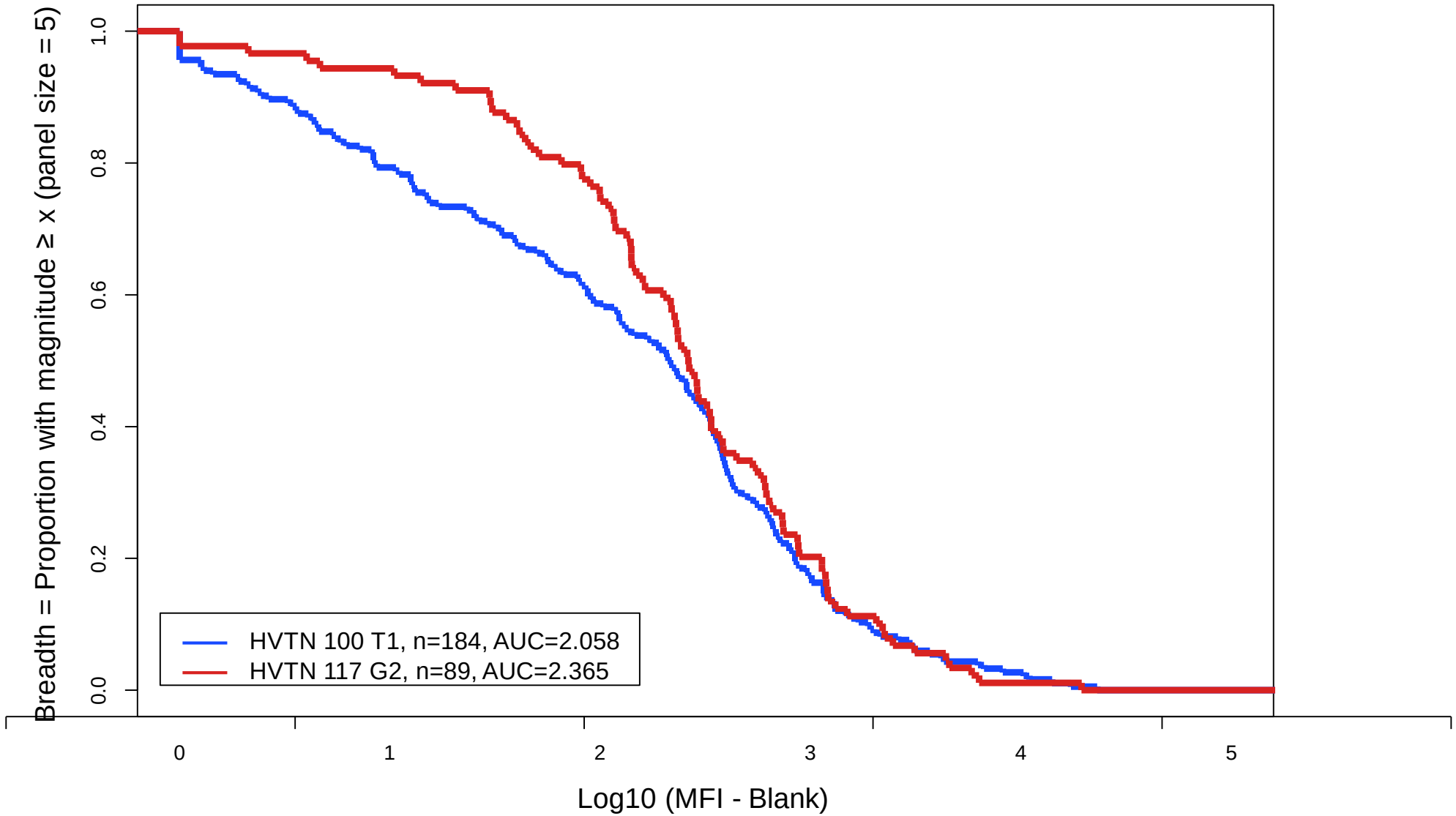
HVTN 100 vs 117 Magnitude-Breadth IgG Binding Antibody Response at Mo6.5/7 to Extended gp120 clade C breadth (mismatched) among Vaccine Arms, Per Protocol Cohort,1:50 diluti



Antigen Panel: 1394C9_G1.D11gp120.avi, 1428_D11gp120.avi/293F, 1641A7_D11gp120.avi/293F, CAP210_D11gp120.avi/293F, CAP45_D11gp120.avi/293F, CH505TF_D7gp120.avi/293F, Ce0042_D11gp120.avi/293F, Du156_D11gp120.avi/293F

SOURCE: SCHARP cyu /trials/vaccine/p100/analysis/lab/117_comparisons/code/figures_mb.r (Sep 25 13:34 2019)

HVTN 100 vs 117 Magnitude-Breadth IgG Binding Antibody Response at Mo6.5/7 to V1V2 clade C breadth (mismatched) among Vaccine Arms, Per Protocol Cohort,1:50 dilution



Antigen Panel: gp70-001428.2.42 V1V2, gp70-7060101641 V1V2, gp70-BF1266_431a_V1V2, gp70-BJOX002000.03.2 V1V2, gp70-CAP210.2.00.E8 V1V2

SOURCE: SCHARP cyu /trials/vaccine/p100/analysis/lab/117_comparisons/code/figures_mb.r (Sep 25 13:34 2019)

Implications of These Timelines on the HIV Vaccine Portfolio

- The two trials are quite harmonized regarding studies of Correlates of Protection.
  - The potential to define a correlate that is associated with partial efficacy is quite high if there is efficacy of at least 25% in either trial.

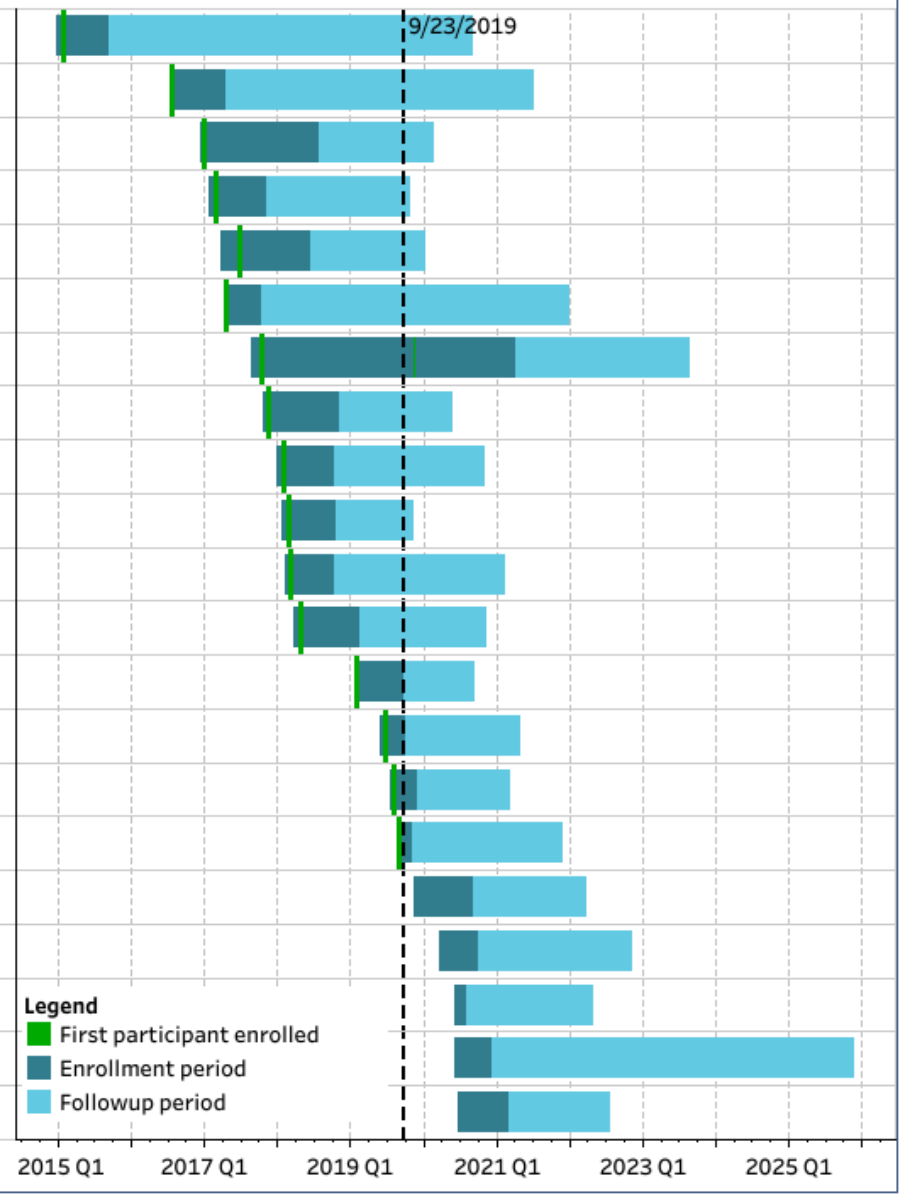
- The HVTN 702 and HVTN 705/706 studies will define the future of the non-neutralizing approach; it will be very hard to muster any more shots on goal for any non-neutralizing regimens until these studies are analyzed and the results understood.
  - In fact, unless NHP studies show some magnificent data from a regimen or that the combination of a neutralizing based regimen trimer is enhanced by a non-neutralizing regimen, advanced clinical development of non neutralizing vaccines will be difficult to muster using NIH funding .
    - The above does not include CMV; Chimp Ad RNA based approaches

HIV VACCINE TRIALS NETWORK

Protocol pipeline: Phase 1 studies

Date data refreshed
September 23, 2019 1:19 PM

Protocol Name	Concept Name	Study N	Protocol Open
HVTN106	CHAVI DNA/MVA-CMDR	105	12/16/2014
HVTN117	Janssen HPX2004 (Traverse)	198	7/19/2016
HVTN108	P5 DNA/Protein + MF59/AS01B	334	12/7/2016
HVTN114	AIDSVAX boost to GeoVax	100	1/17/2017
HVTN107	702 - MF59 vs alum	132	3/23/2017
HVTN118	Janssen HPX2003 (Ascent)	150	4/14/2017
HVTN115	B cell lineage	132	8/22/2017
HVTN119	p24CE DNA	56	10/18/2017
HVTN122	gp145 US phase 1	45	12/27/2017
HVTN120	702 - MF59 vs AS01B	320	1/16/2018
HVTN127/HPTN087	VRC07-523LS	100	2/2/2018
HVTN124	PDPHV	60	3/16/2018
HVTN128	VRC07-523LS mucosal	36	1/18/2019
HVTN123	Transient vs Stable Transfection	30	5/23/2019
HVTN130/HPTN089	Triple mAb combo (2/3 LS)	54	7/17/2019
HVTN133	MPER-656 liposome	24	8/26/2019
HVTN137	SOSIP adjuvants study	105	11/15/2019
HVTN135	Infant B-cell lineage vaccination	38	3/16/2020
CH505TF ch.SOSIP	CH505TF ch.SOSIP	18	6/1/2020
Chimp Ad 6/7 Clad..	Chimp Ad 6/7 Clade C Env+gp140	36	6/1/2020
HVTN129/HPTN088	Trispecific antibody	78	6/17/2020



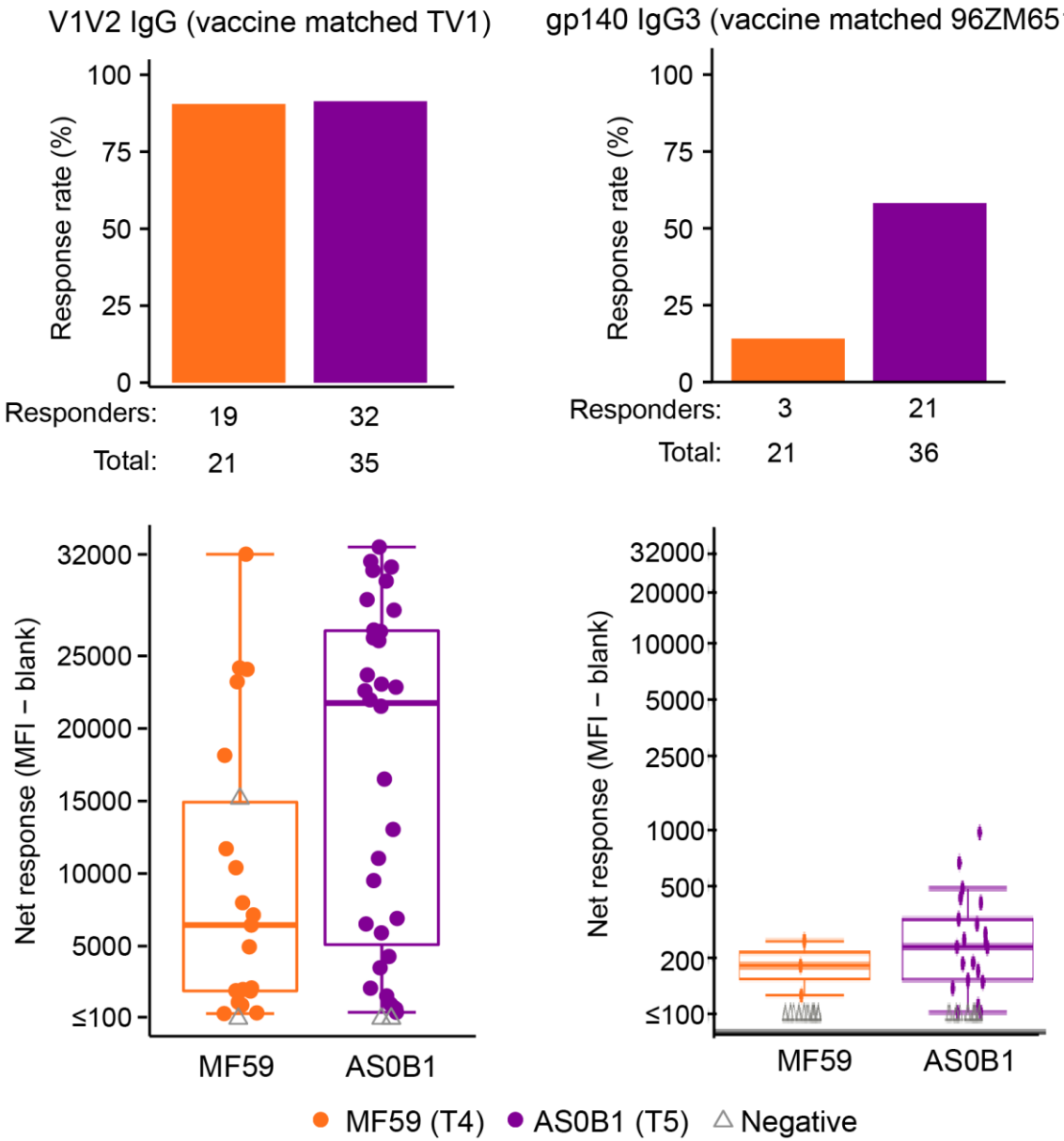
Comment Regarding HVTN 702

- Unlike HVTN 705/706, there is little commitment from Sanofi or GSK to do anything “at risk” to lead to expeditious commercialization if there is success in HVTN 702.
- Looking to bring in outside manufacturer to do the technical development required to bring the manufacturing process up to required standards (years).
- The increased immunogenicity with DNA and AS01B does provide an approach for furthering the development of this regimen during this prolonged manufacturing development timeline.
- Evidence of a correlate would allow bridging to a regimen using AS01B.
- Need some efficacy to make this happen.

HVTN 108 Schema

Group	N	Dose of each protein	Deltoid	Month 0 (Day 0)	Month 1 (Day 28)	Month 3 (Day 84)	Month 6 (Day 168)
1	30	100 mcg	Left	DNA	DNA	DNA	DNA
			Right	Placebo + Placebo*	Placebo + Placebo*	Protein/MF59 + Placebo*	Protein/MF59 + Placebo*
2	50	100 mcg	Left	DNA	DNA	DNA	DNA
			Right	Placebo + Placebo*	Placebo + Placebo*	Protein/AS01$_B$ + Placebo*	Protein/AS01$_B$ + Placebo*
3	50	20 mcg	Left	DNA	DNA	DNA	DNA
			Right	Placebo + Placebo*	Placebo + Placebo*	Protein/AS01$_B$ + Placebo*	Protein/AS01$_B$ + Placebo*
4	30	100 mcg	Left	DNA	DNA	Placebo	DNA
			Right	Protein/MF59 + Placebo*	Protein/MF59 + Placebo*	Placebo + Placebo*	Protein/MF59 + Placebo*
5	50	100 mcg	Left	DNA	DNA	Placebo	DNA
			Right	Protein/AS01$_B$ + Placebo*	Protein/AS01$_B$ + Placebo*	Placebo + Placebo*	Protein/AS01$_B$ + Placebo*
6	50	20 mcg	Left	DNA	DNA	Placebo	DNA
			Right	Protein/AS01$_B$ + Placebo*	Protein/AS01$_B$ + Placebo*	Placebo + Placebo*	Protein/AS01$_B$ + Placebo*
7	50	20 mcg	Left	Placebo	Placebo	Placebo	Placebo
			Right	Protein/AS01$_B$ + Placebo*	Protein/AS01$_B$ + Placebo*	Placebo + Placebo*	Protein/AS01$_B$ + Placebo*
8	24	N/A	Left	Placebo	Placebo	Placebo	Placebo
			Right	Placebo + Placebo*	Placebo + Placebo*	Placebo + Placebo*	Placebo + Placebo*

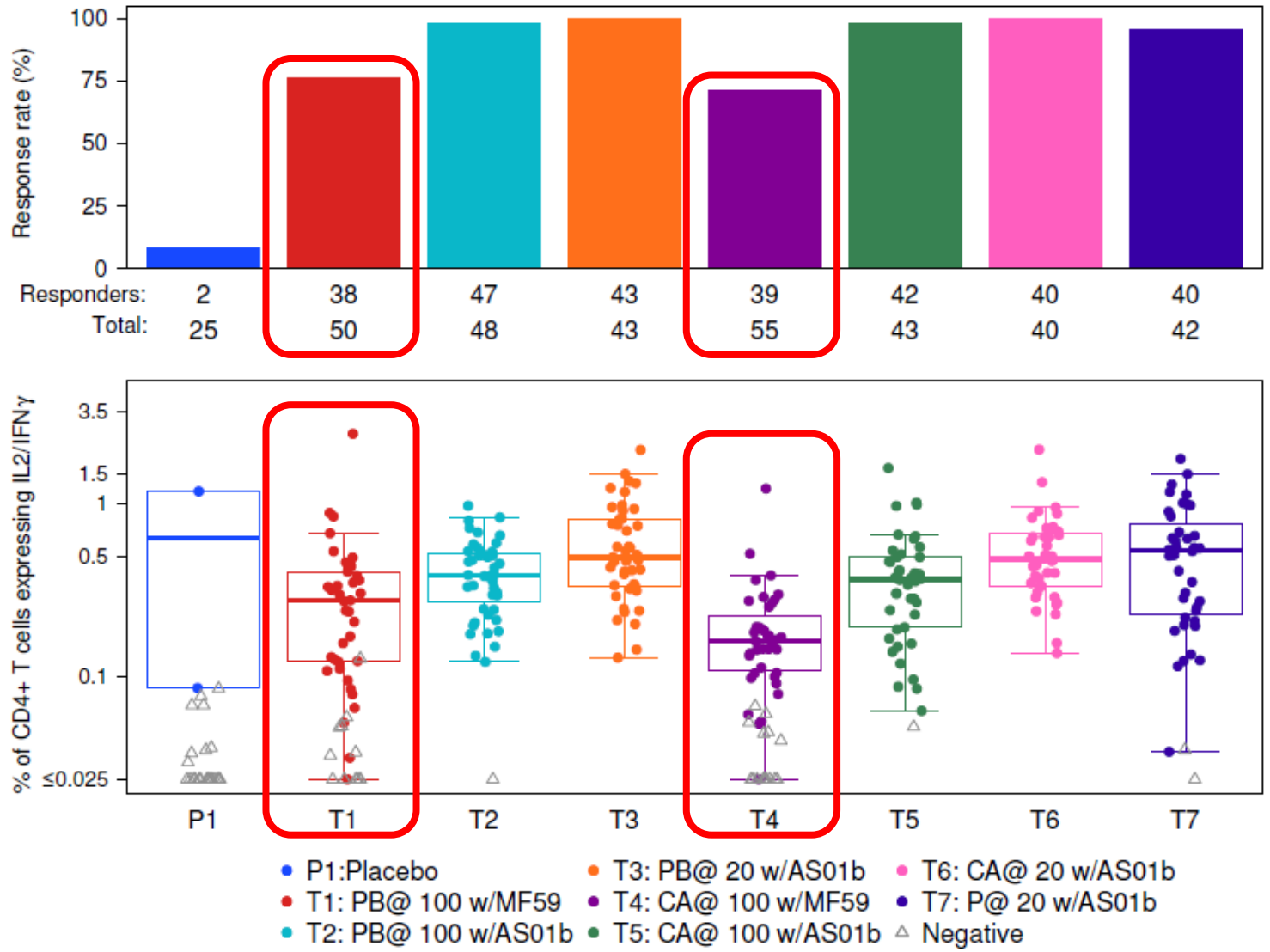
* Two distinct placebo volumes for protein/adjuvant will be needed to maintain the blind since Protein/AS01$_B$ and Protein/MF59 consist of different injection volumes.



HVTN 108 DNA/gp120 clade C antigens (702): AS01B adjuvant increases antibody responses associated with effective immunity

Courtesy G Tomaras and the HVTN 108 Study Team (Nigel Garrett, Chair)

HVTN 108 + 111 ICS CD4+ IL2/IFNγ Expression in Response to ANY HIV at M6.5
DNA Prime – gp120 (clade C TV-1/1086) Boost



PB = Prime Boost
CA = Co-administration

HIV VACCINE
TRIALS NETWORK

Entering the Era of Neutralization

Passive and Active Immunization

Passive Antibody Prevention
Phase IIB Efficacy Studies

AMP = Antibody Mediated Prevention

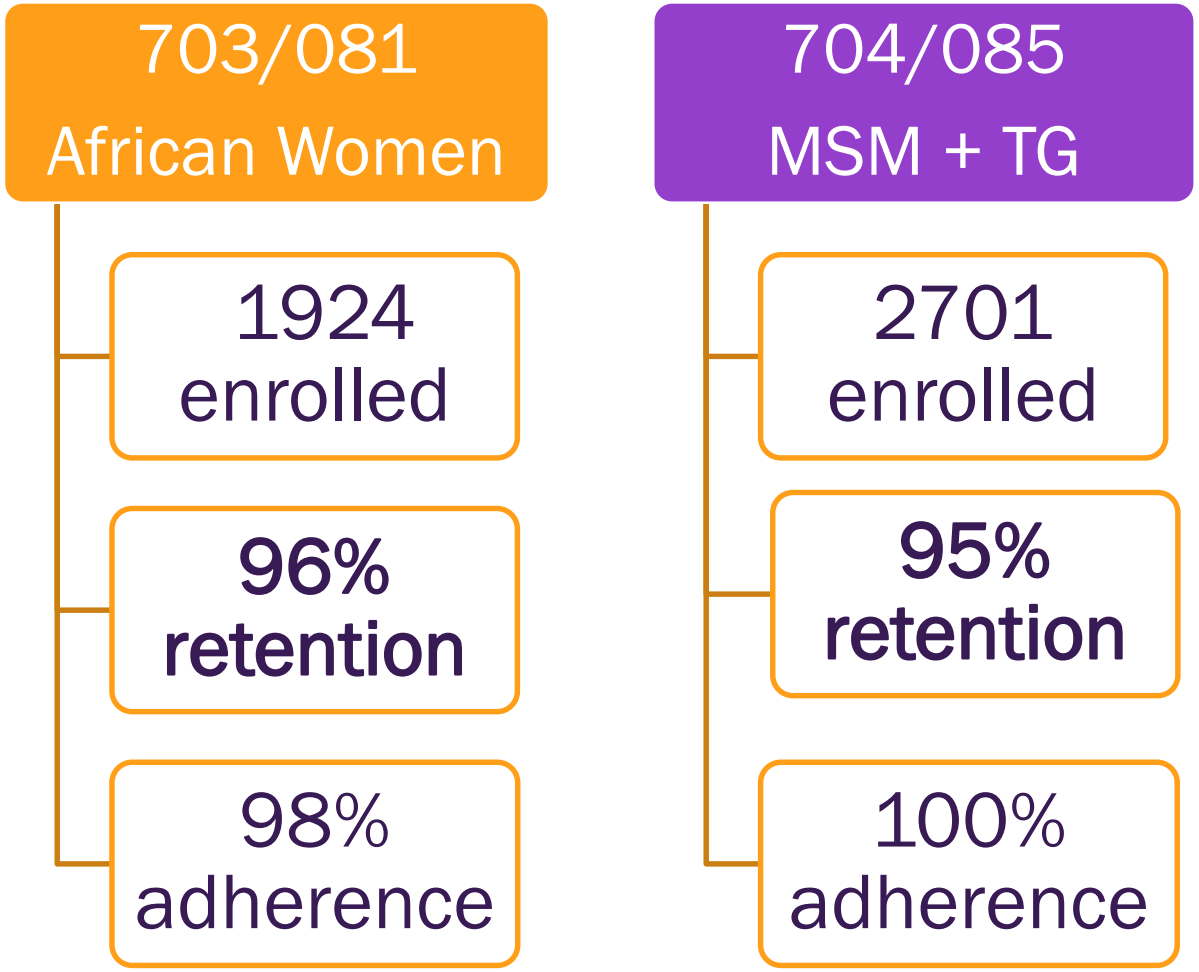
Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults: MSM in Americas & heterosexual women in sub-Saharan Africa

- **Placebo controlled trial of VRC01 mAb (IV), given on 8 weekly schedule**
- **Two cohorts:**
  - **2,400 MSM + TG in North & South America (HVTN 704/HPTN 085)**
  - **1,900 Women in sub-Saharan Africa (HVTN 703/HPTN 081)**

- Both trials opened in April/May 2016
- 703/081 Accrued September 20, 2018 (End July 2020)
- 704/085 Accrued October 5, 2018 (End July 2020)

Chairs: Lawrence Corey, HVTN
Mike Cohen, HPTN
Co-chairs: Srilatha Edupuganti
Nyaradzo Mgodi

Enrollment and Retention Updates



Ongoing HVTN Vaccine Efficacy Studies

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HVTN 706	Ad26/gp140	3800	55	MSM, TG	Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain, US	Janssen/J&J and NIAID/HVTN	**October 2022**
AMP HVTN 703 HPTN083	VRC01	1901	15	Women	Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, Zimbabwe	NIAID	July 2020
HVTN 704	VRC01	2705	25	MSM/TG	Brazil, Peru, US	NIAID	July 2020

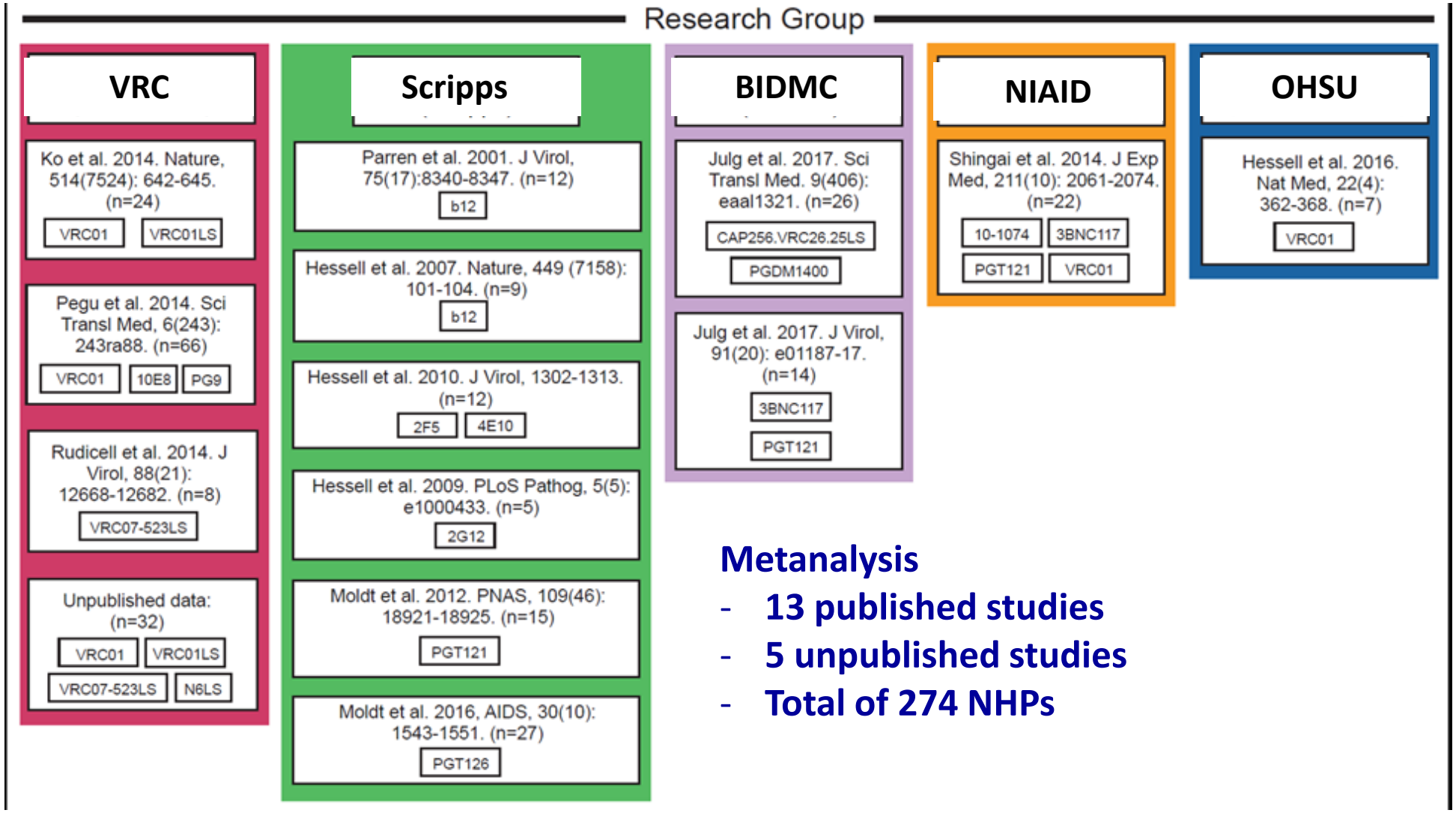
What level of antibody is needed to protect?

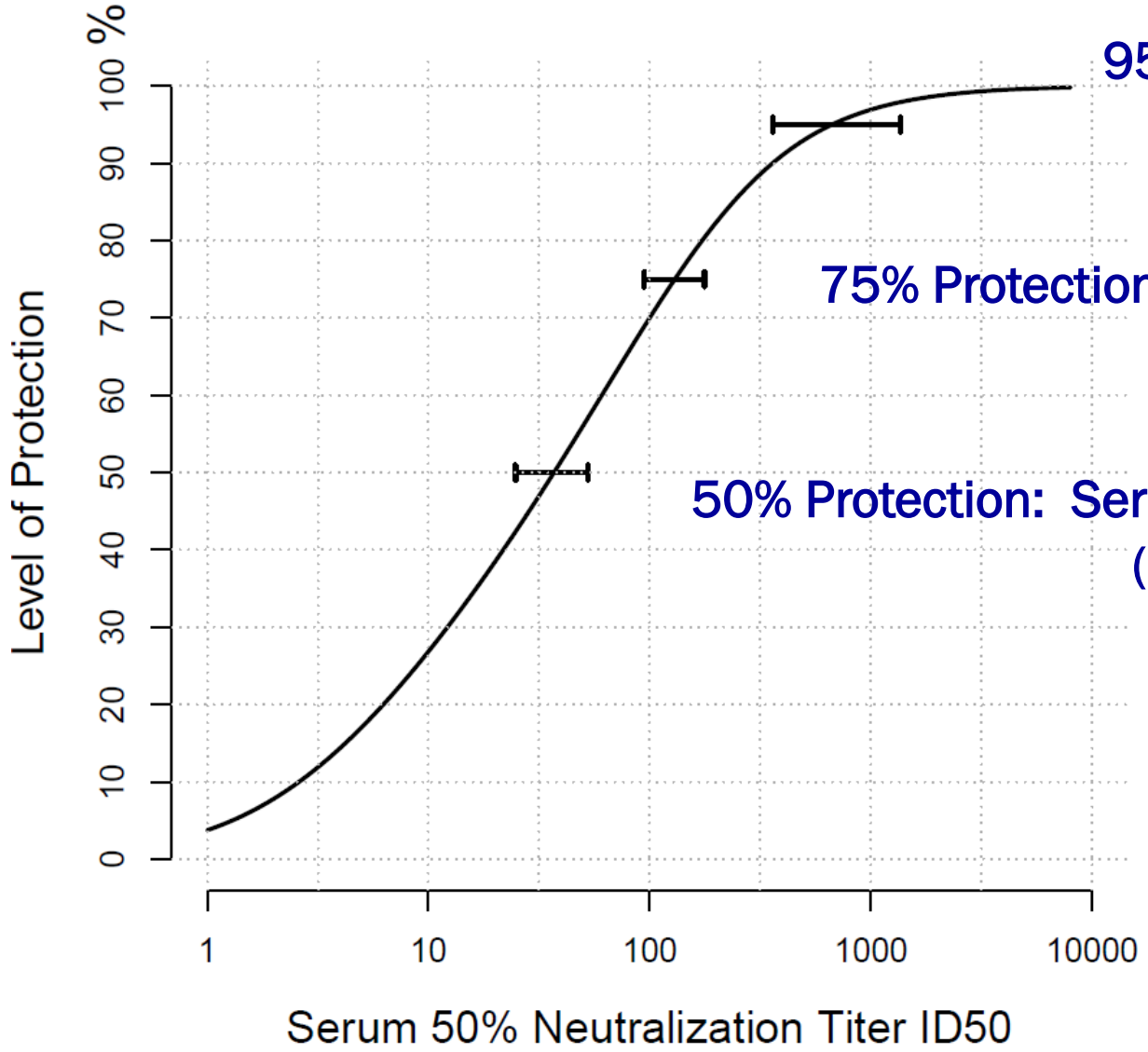
Metanalysis of NHP passive antibody challenge studies:

- **Single infusion of mAb (various mAbs)**
- **SHIV challenge 1-5 days after mAb infusion**

➡ **Serum neutralization level on the day of challenge (vs challenge SHIV) – strongly correlates with protection**

Ying Huang, Yunda Huang, Peter Gilbert (FHCRC)
Larry Corey (FHCRC)
Amar Pegu VRC, NIAID
Devin Sok, Dennis Burton Scripps

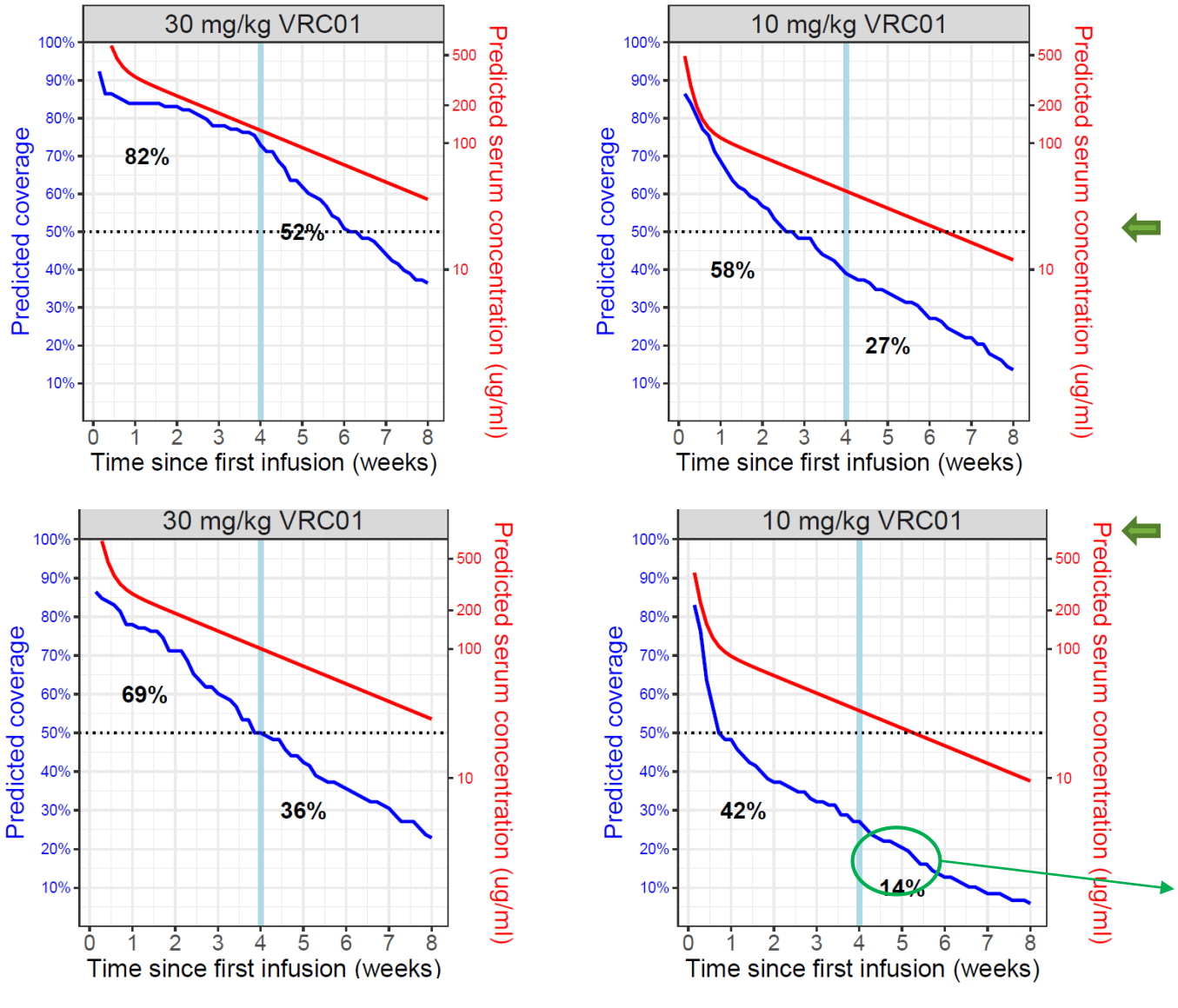

Research Group
VRC
Ko et al. 2014. Nature, 514(7524): 642-645. (n=24)
VRC01
VRC01LS
Pegu et al. 2014. Sci Transl Med, 6(243): 243ra88. (n=66)
VRC01
10E8
PG9
Rudicell et al. 2014. J Virol, 88(21): 12668-12682. (n=8)
VRC07-523LS
Unpublished data: (n=32)
VRC01
VRC01LS
VRC07-523LS
N6LS
Scripps
Parren et al. 2001. J Virol, 75(17):8340-8347. (n=12)
b12
Hessell et al. 2007. Nature, 449 (7158): 101-104. (n=9)
b12
Hessell et al. 2010. J Virol, 1302-1313. (n=12)
2F5
4E10
Hessell et al. 2009. PLoS Pathog, 5(5): e1000433. (n=5)
2G12
Moldt et al. 2012. PNAS, 109(46): 18921-18925. (n=15)
PGT121
Moldt et al. 2016, AIDS, 30(10): 1543-1551. (n=27)
PGT126
BIDMC
Julg et al. 2017. Sci Transl Med. 9(406): eaal1321. (n=26)
CAP256.VRC26.25LS
PGDM1400
Julg et al. 2017. J Virol, 91(20): e01187-17. (n=14)
3BNC117
PGT121
NIAID
Shingai et al. 2014. J Exp Med, 211(10): 2061-2074. (n=22)
10-1074
3BNC117
PGT121
VRC01
OHSU
Hessell et al. 2016. Nat Med, 22(4): 362-368. (n=7)
VRC01
Metanalysis
- 13 published studies
- 5 unpublished studies
- Total of 274 NHPs



95% Protection: Serum ID_{50} = 670
(95% CI: 362-1366)

75% Protection: Serum ID_{50} = 130
(95% CI: 94-177)

50% Protection: Serum ID_{50} = 37
(95% CI: 25-53)



Percent of 118 Clade B isolates (based on their *in vitro* IC50) that would be sensitive to VRC01 at a neutralizing threshold in serum of 1:50 or 1:100 (blue lines)

Serum neut threshold of 1:50

Drop off in coverage occurs:

- **Over time as expected**
- **With lower dose of 10 mg/kg**

Serum neut threshold of 1:100

Drop off in coverage when serum neutralization threshold goes from 1:50 to higher threshold of 1:100

Bolded %'s are average coverage in the first or second 4 weeks

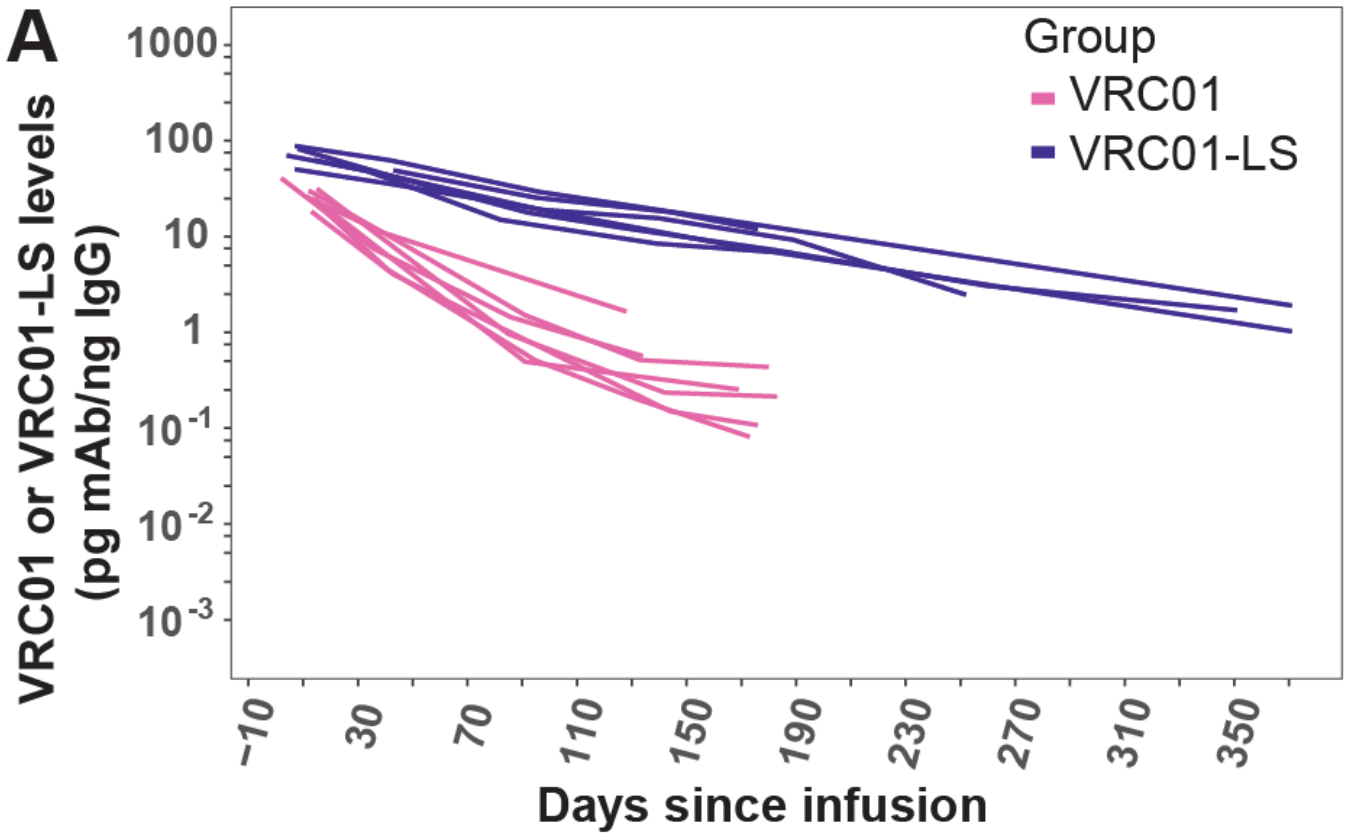
E.g. interpretation: Expect 14% of exposures during the second 4 weeks post-infusions to be with enough VRC01 on board to block HIV-1 transmission

Red lines show predicted geometric mean VRC01 concentration over time based on population PK modeling

Moving to Self Administered Subcutaneous Injections

Extended Half-Life Preparations

Enhanced half-life and augmented antibody levels in cervical biopsies of VRC01-LS vs. VRC01 in HVTN 116



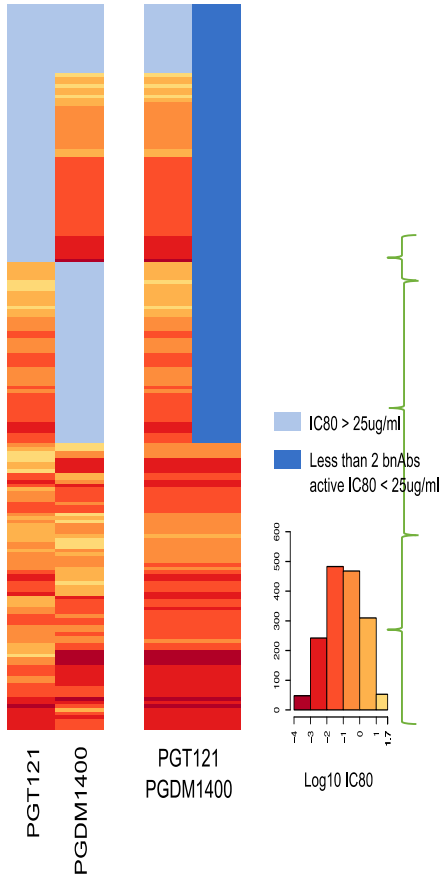
Relative concentrations of antibody extracted from cervical biopsy tissue.
Note the much higher and more stable mAb levels with the LS mutation (purple lines) vs. parental (pink lines).

Increased Coverage by Multiple bnAbs

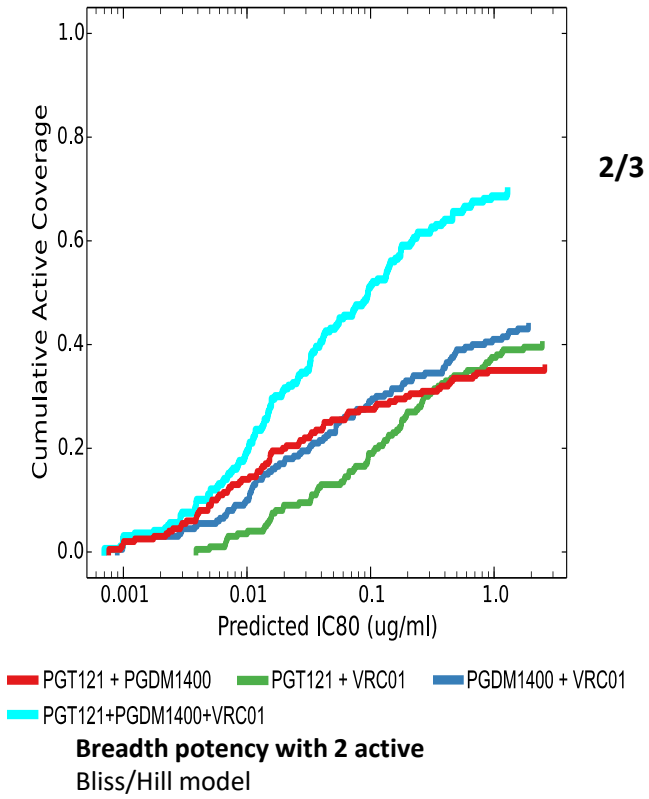
resistant

only a single bnAb
is active, monotherapy

2 bnAbs active



Breadth potency restricted to Envs with 2 active



2/3 active

Breadth potency with 2 active
Bliss/Hill model

- **If virus is targeted by multiple bnAbs, then escape is difficult. For chronic infections, higher coverage with multiple bnAbs active implies higher fraction of viral quasispecies targeted (e.g. patients with V3g-type responses might have V3g resistance).**
- **Most viruses actively neutralized by 1 bnAb in combination for 2 bnAb combinations. Need 3 bnAbs to neutralize most viruses with at least 2 bnAbs active.**

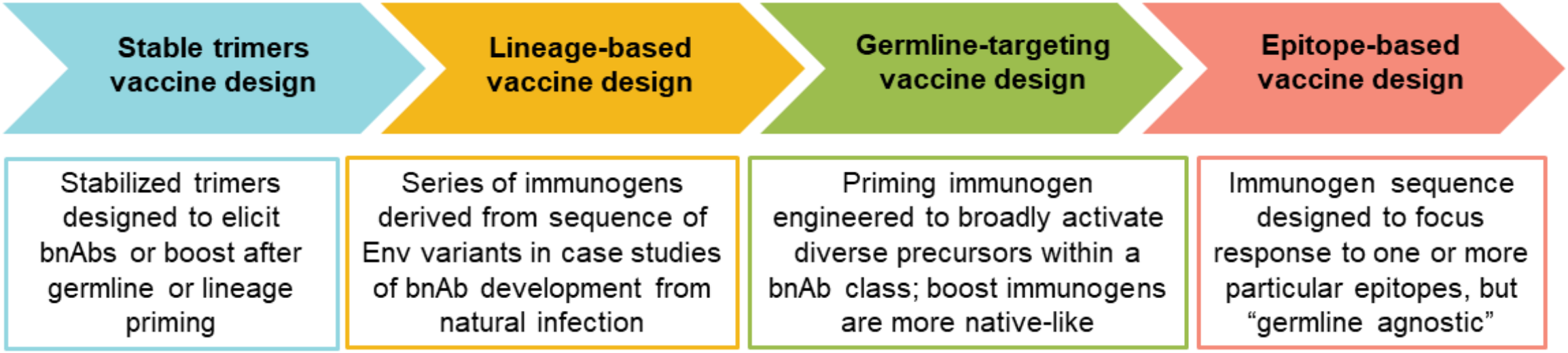
Multiclade Virus Panel

IC80	Triple Combos		Double Combos		Single mAbs				
	VRC07-523-LS +PGT121 +PGDM1400 Theoretical	3BNC117 +10-1074 +PGDM1400 Theoretical	VRC07-523-LS +PGT121 Theoretical	3BNC117 +10-1074 Theoretical	VRC07-523-LS	PGT121	3BNC117	10-1074	PGDM1400
# Viruses	208	208	208	208	208	208	208	208	208
% VS Neutralized									
IC80 <50ug/ml	99	99	97	92	96	58	80	60	74
IC80 <10ug/ml	99	98	96	91	94	55	78	59	72
IC80 <1.0ug/ml	94	96	88	84	83	49	68	52	63
IC80 <0.1ug/ml	67	65	46	35	23	29	14	26	44
For Sensitive Viruses Only:									
Median IC80	0.042	0.047	0.118	0.156	0.238	0.099	0.298	0.126	0.047
Geometric Mean	0.049	0.052	0.133	0.167	0.257	0.157	0.318	0.157	0.069
For All Viruses:									
Median IC80	0.047	0.048	0.123	0.174	0.257	1.57	0.425	0.884	0.209
Geometric Mean	0.055	0.057	0.163	0.259	0.323	1.75	0.861	1.57	0.392

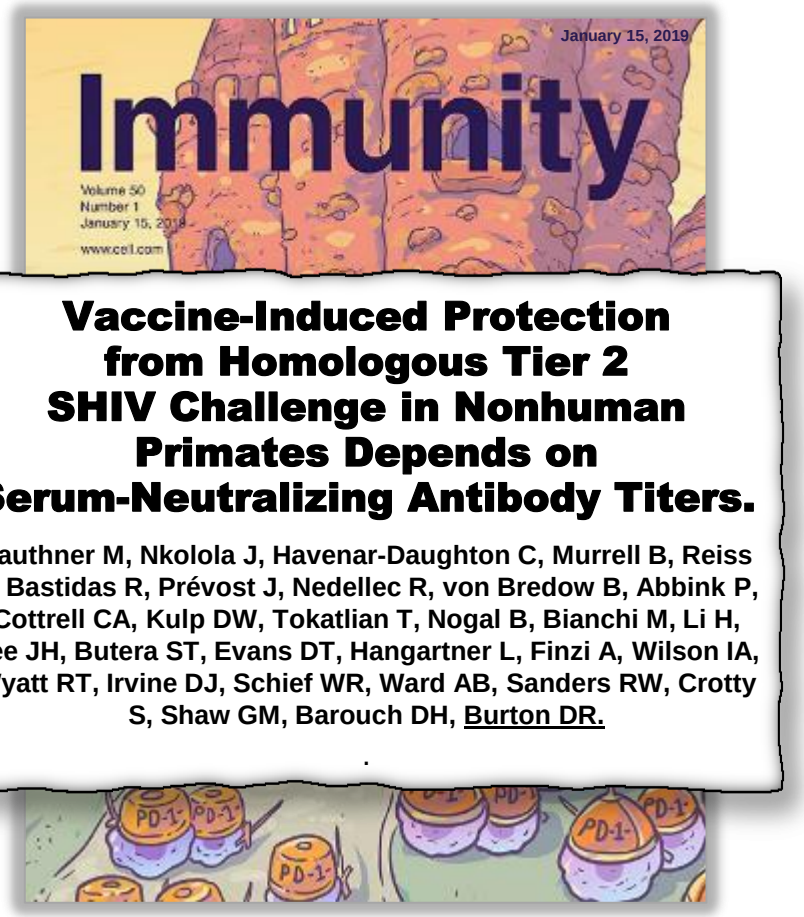
VITL/VRC Multiclade 208 Virus Panel

The bnAb Inducing Immunogen Era

Design approaches to elicit bnAbs



Vaccine – challenge in NHP
(level of serum neutralization needed)



Vaccine-Induced Protection from Homologous Tier 2 SHIV Challenge in Nonhuman Primates Depends on Serum-Neutralizing Antibody Titers.

Pauthner M, Nkolola J, Havenar-Daughton C, Murrell B, Reiss S, Bastidas R, Prévost J, Nedellec R, von Bredow B, Abbink P, Cottrell CA, Kulp DW, Tokatlian T, Nogal B, Bianchi M, Li H, Lee JH, Butera ST, Evans DT, Hangartner L, Finzi A, Wilson IA, Wyatt RT, Irvine DJ, Schief WR, Ward AB, Sanders RW, Crotty S, Shaw GM, Barouch DH, Burton DR.

- Immunized with BG505 trimer
- Intrarectal challenge SHIV BG505
- Serum neutralization titer associated with protection

- 50% protection with serum ID50 neutralization titer of 1:90
- 90% protection, an ID50 titer of 1:476

- Passive Ab studies
  - 50% protection with titer 1:37
  - 95% protection with titer of 1:670

Estimated goal: Vaccine elicited serum neutralization titer of ~ 1:100

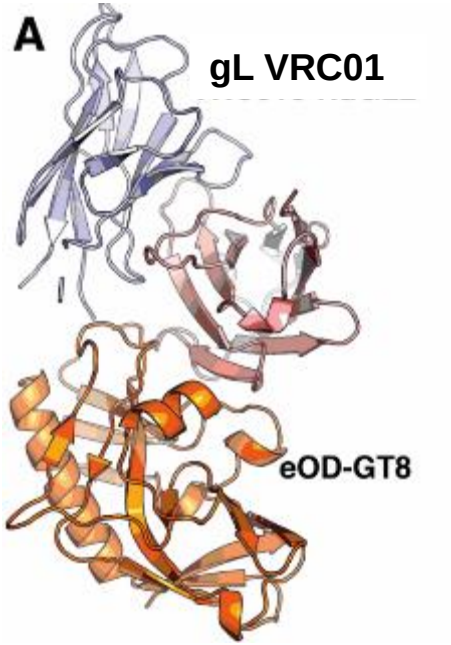
HIV Trimers in GMP or phase 1 trials

Immunogen	Design intent, features	Potential uses	Organization
Trimers			
Cornell BG505.664 SOSIP	Induces autologous nAbs; adjuvant evaluation (NHP, humans) informs model	Trimer boost	Cornell
Cornell BG505.664 DS-SOSIP VRC 4571	Low affinity for CD4, less induction of V3 and CD4i response	Has same FP8 sequence at VRC FP-TT - so can be used as boost	VRC
rAd4 1086C/BG505.664 DS-SOSIP VRC 4571	Uncleaved (non-native) vs native NFL trimer	Trimer prime or boost	Lab of Immunoregulation NIAID
Consensus M, Consensus S SOSIP trimers	Induces nAbs of tier 1 HIV	Heterologous prime-boost	Imperial College
Mosaic SOSIP trimers	Induces nAbs of tier 1 HIV	Heterologous prime-boost	Imperial College
Acute SOSIP trimers		Heterologous prime-boost	
16055 NFL gp140	Soluble cleavage-independent clade C trimer binds V2 apex bnAbs	Boost	IAVI/CHAVD
UFOVax	Uncleaved prefusion-optimized (UFO) stabilized		Scripps

Germline Targeting Immunogens in GMP or phase 1 trials

Germline-targeting Envs			
eODGT8 60-mer nanoparticle	Induces precursors of VRC01-class CD4 binding site bnAbs	Germline targeting prime for sequential prime boost	CHAVD (Scripps)
CH505 TF chimeric stabilized SOSIP	Induces CD4bs, V2 precursors, bnAbs; boost F peptide bnAbs	Trimer prime or boost	CHAVD (Duke)
BG505 GT1.1 SOSIP	Binds to precursor BCR of CD4bs and V3-glycan bnAbs	Germline targeting trimer	R. Sanders
CH505 TF gp120s Env (stable and transient)	Binds low affinity to precursors of CH103 CD4bs bnAb BCRs	Sequential Env lineage concept	CHAVD (Duke)
CH505 M5 gp120	Binds low affinity to precursors of CH235/ANC131-class CD4bs bnAbs	Sequential Env lineage concept	CHAVD (Duke)
CH505 M5 G458Y GNT1- SOSIP nanoparticle	High affinity; induces precursors of CH235/ANC131-class CD4bs bnAbs	Germline targeting trimer/nanoparticle	CHAVD (Duke)
CH848 10.17 DT SOSIP nanoparticle	Induces precursors of DH270 V3-glycan bnAbs	Germline targeting trimer/nanoparticle	
N332 GT 5.2 trimer	Induces precursors of PGT 121 V3-glycan bnAbs	Germline targeting prime for sequential prime boost	CHAVD (Scripps)
MT145K deltaV5 SOSIP trimer	Induces V2 glycan bnAb precursor B cells, immune focusing	Germline targeting/immunefocusing prime or boost	CHAVD (Scripps)

Engineered Outer Domain (eOD-GT8) Self Assembling Nanoparticle to elicit VRC01-class antibodies



gp120 eOD-GT8
lacking glycans 276, 463

Priming a Broadly Neutralizing Antibody Response to HIV-1 Using a Germline-targeting Immunogen

Jardine JG, Burton DR, Schief WR, Nemazee D.

Science (2015)

Immunization for HIV-1 Broadly Neutralizing Antibodies in Human Ig Knockin Mice

Dosenovic P, Stamatatos L, Schief WR, Nussenzweig MC

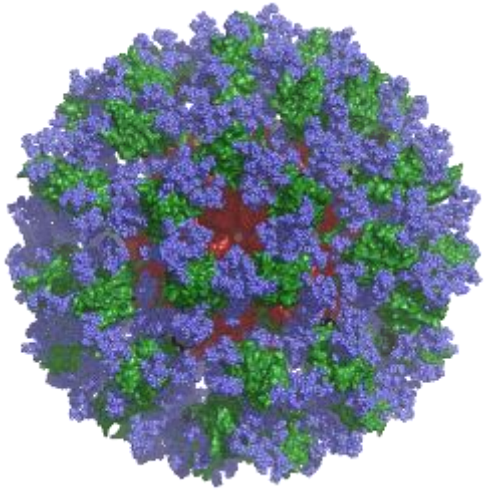
Cell (2015)

Proof of concept, in human gene-KI mouse models, that germline antigens can stimulate naïve B-cell lineages of VRC01 class

Phase 1 started in 2018

Courtesy: Bill Schief

IAVI G001 Phase I Trial: eOD-GT8 60mer/AS01B



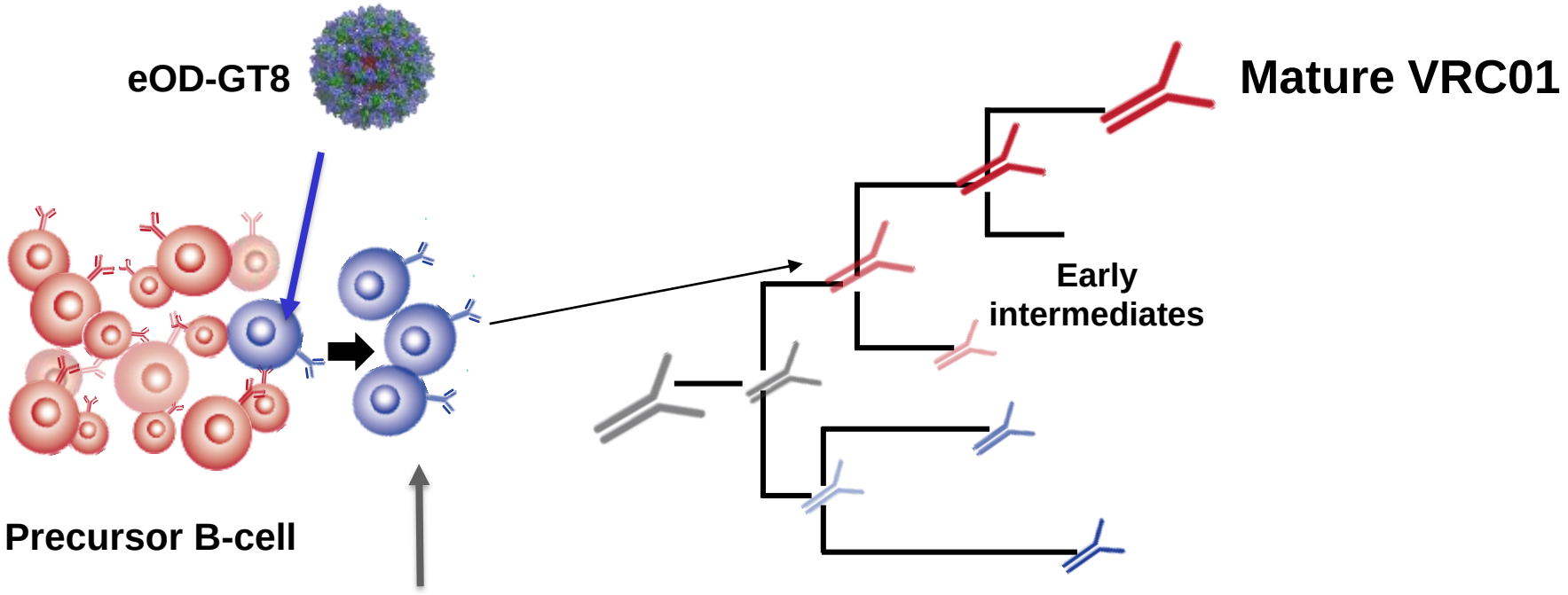
LS-60mer nanoparticle

- Phase 1 start: Sept 2018
- Conducted at FHCRC (Seattle) and GWU (Washington, DC)
- Critical readout by B cell sorting and B-cell sequencing performed at FHCRC and VRC

Study Group	N	eOD-GT8 60mer dose	Week 0	Week 8
1 (low dose)	18	20 µg	eOD-GT8 60mer/ AS01B	eOD-GT8 60mer/ AS01B
	6	-	DPBS	DPBS
2 (high dose)	18	100 µg	eOD-GT8 60mer/ AS01B	eOD-GT8 60mer/ AS01B
	6	-	DPBS	DPBS
Total	48			

Courtesy of Bill Schief, FHCRC and GWU

Phase 1 Immune Analysis
B-cell Genetics



VRC01 class sequences

- Ag-specific cell sorting
- PCR recovery of Ig genes

Success: Vaccine-elicited VRC01-class sequences

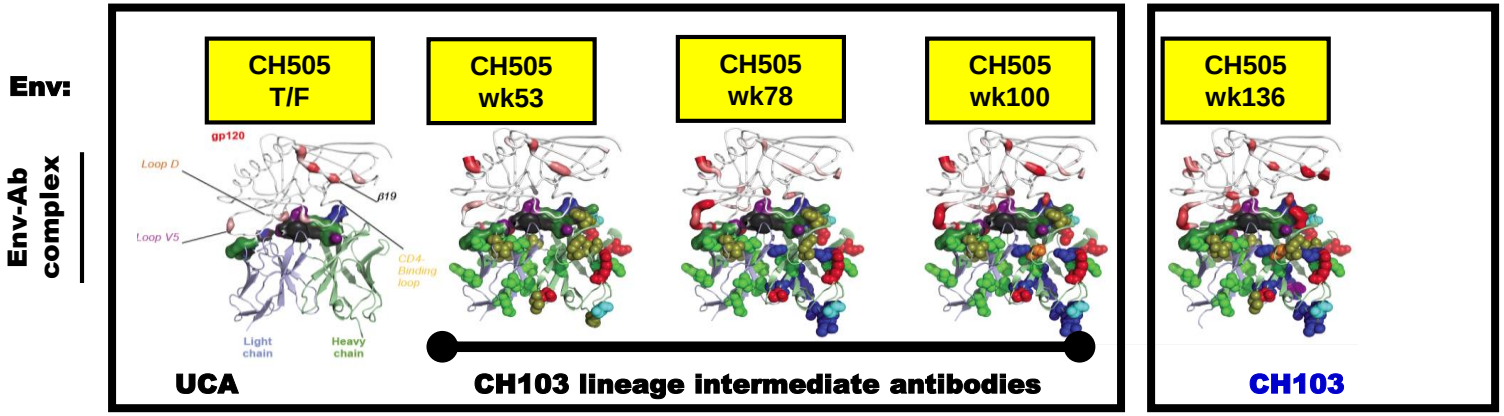
- Relatively low SHM
- Not yet neutralizing

Lineage and epitope based immunogens in GMP or phase 1 trials

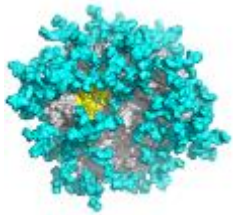
Lineage-based Envs			
EnvSeq-1 CH505 gp120 sequential Envs	Induces precursors of CH103 CD4bs bnAbs	Sequential Env lineage concept	CHAVD (Duke)
426c degly gp120 nanoparticles	Induces precursors of VRC01-class bnAbs after eOD8 prime	Germline targeting prime for sequential boost	Fred Hutch
Epitope-based Envs			
Fusion peptide on carrier protein	Induces nAbs targeting fusion peptide	Prime for a boost with BG505 and/or CH505 TF SOSIP trimers	VRC
MPER peptide liposomes	Binds to, induces precursors of proximal MPER gp41 bnAbs	Germline targeting prime for sequential boost of proximal MPER nAbs	CHAVD (Duke)
Man 9-V3 glycopeptide nanoparticle	Targets V3-glycan and 2G12-like bnAbs	Epitope targeting boost for glycan-reactive antibodies	CHAVD (Duke); Chemitope

Phase 1 ongoing: Lineage Env immunogens

Goal: Elicit the CD4bs (CH103) Ab lineage - leading to broad neutralization



Planned: CH505 TF stabilized SOSIP trimer



Evaluate whether the high affinity germline targeting CH505 lineage TF trimer can expand CD4bs bNAb precursors

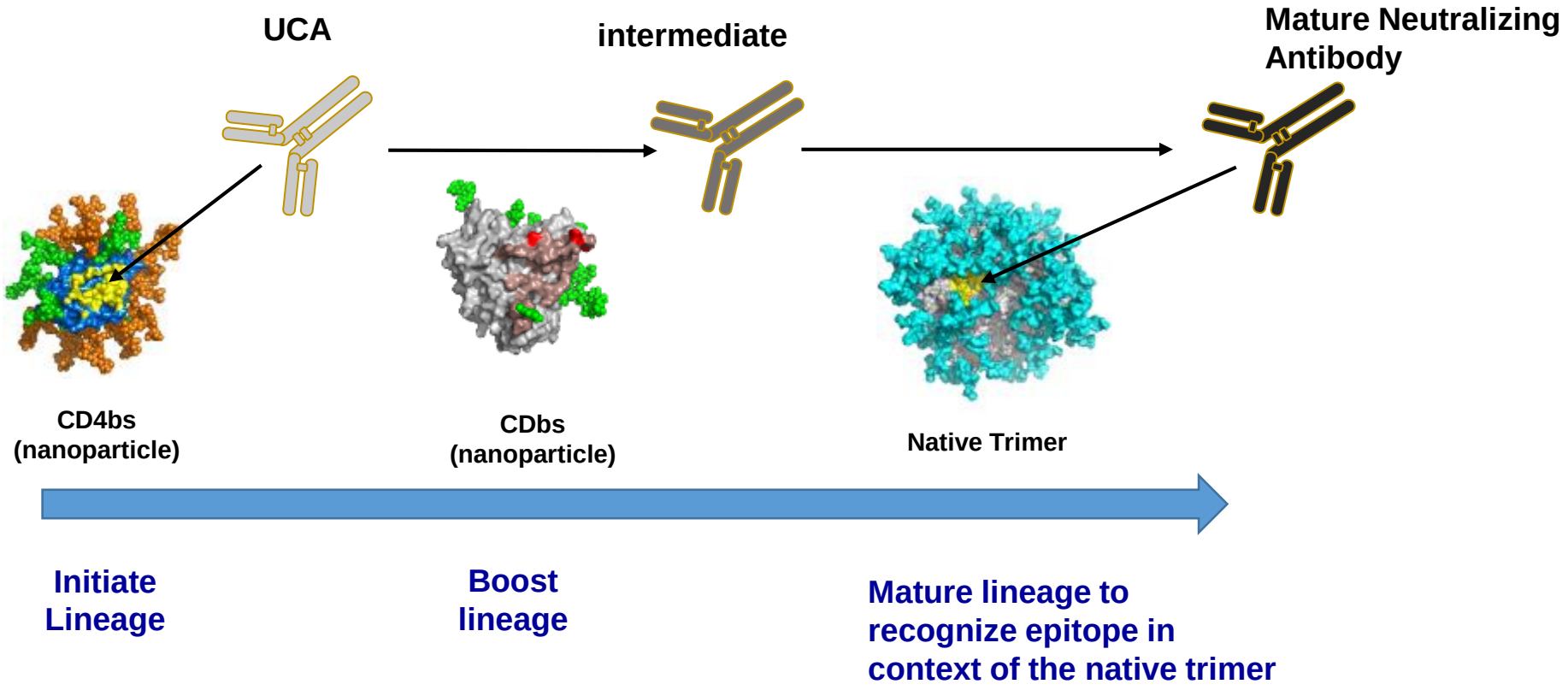
GMP: Q2 2019; Clinical Trial: Q4 2019

Liao, Lynch, Haynes et al. Nature (2013)

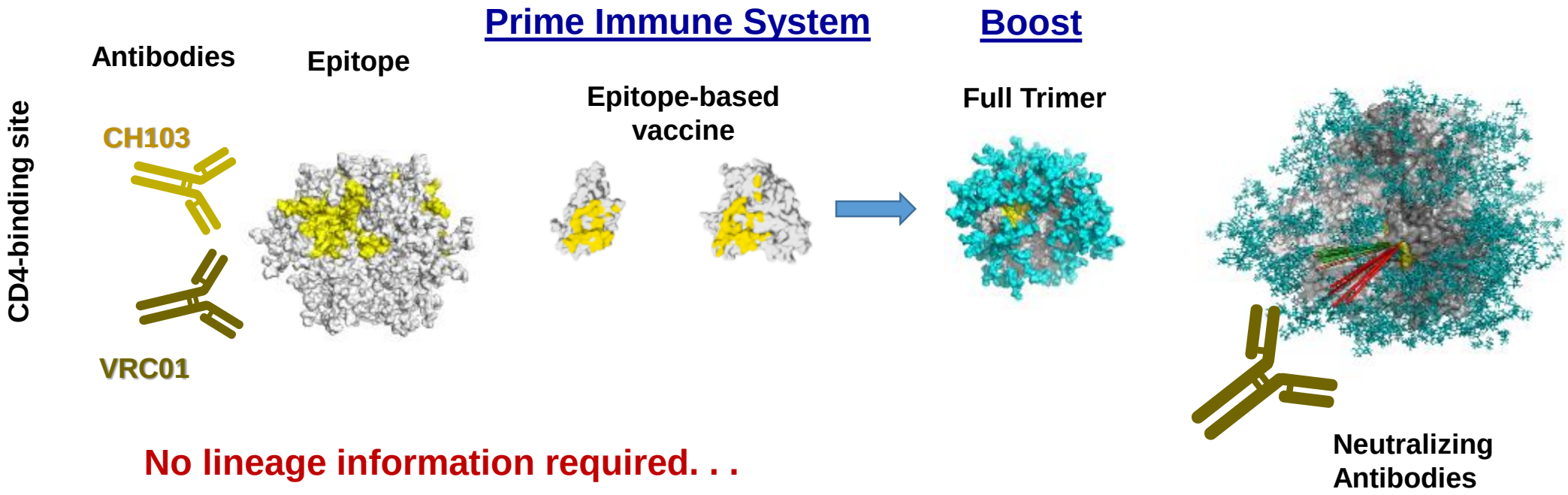
Slide Courtesy: Bart Haynes

CHAVI-ID
Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery

Getting to Tier 2 Neutralization Breadth



Epitope-based Vaccine Design

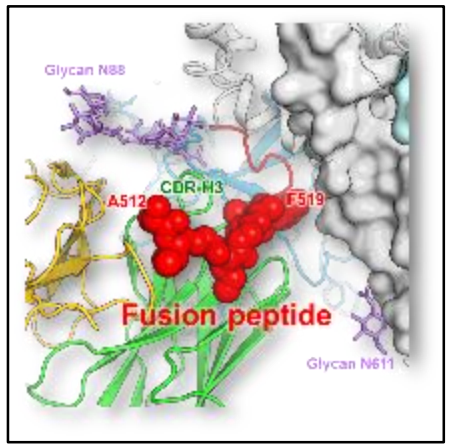


No lineage information required. . .

Use structural knowledge of an epitope, as defined by recognition of a broadly neutralizing antibody, to design the vaccine immunogen; i.e., mimic epitope

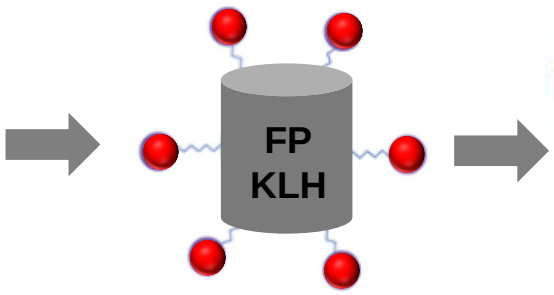
Teach the immune system to recognize the Env trimer

Epitope-based Design: Fusion Peptide



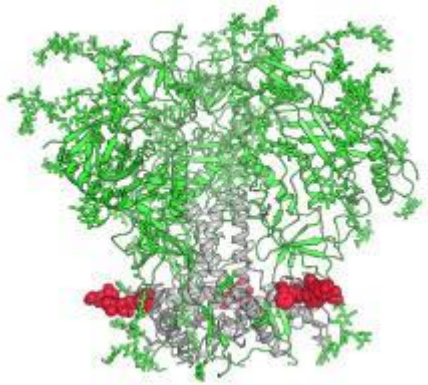
8 AA

Prime

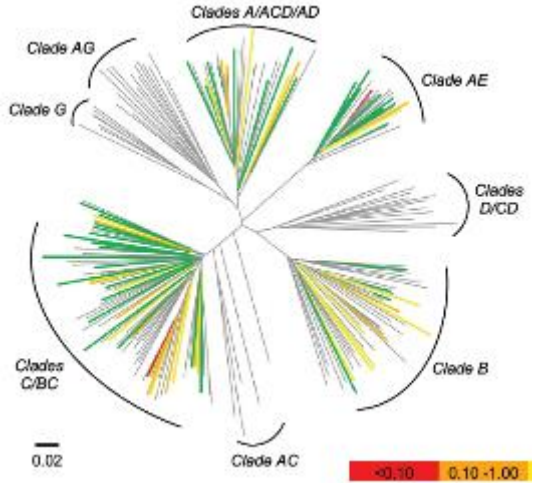


KLH-coupled
fusion peptide (FP8)

Boost
Env trimer



Murine antibody 31% neutralization breadth



Serum – inconsistent, but clear indications of cross-neutralization

K Xu, P Acharya, R Kong, C Cheng, P Kwong et al. Nat Med (2018)

Next 5 years:

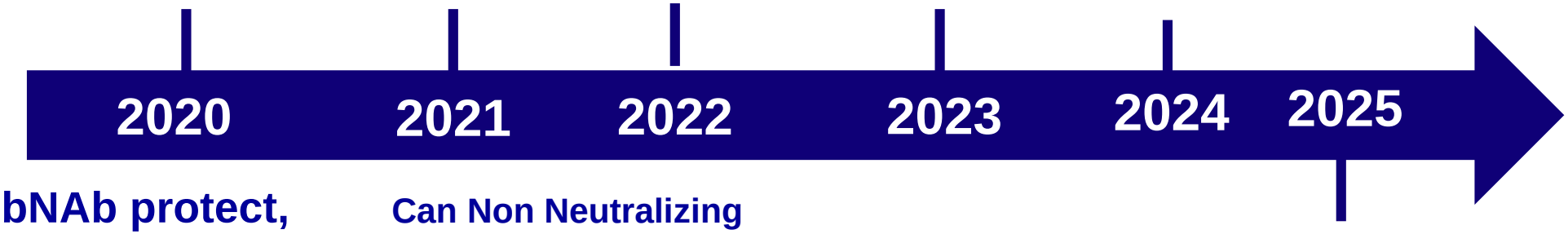
- Phase 2b mAb
- Phase 2b vaccines

Novel vaccine strategies

- Native trimers
- Epitope, lineage-based
- Viral vectors
- Nanoparticles
- Gene-based mRNA

→ Phase 3 combination bNAb prevention

→ Phase 3 vaccine efficacy



Can bNAb protect, how much needed?

Can Non Neutralizing vaccines reproducibly reduce acquisition of HIV ?

Can we induce serum NAbs titers of >1:100 in humans ?

Do we have a vaccine with > 60% efficacy?

Summary

- If any of the HIV vaccines or antibodies in efficacy trial testing are effective, it will unleash an enormous explosion in scientific inquiry to improve, adapt, and most importantly, bring to the world a new form of HIV prevention.

- An HIV vaccine will be the most complex vaccine ever designed:
  - Yes, the regimens will be an implementation challenge.
  - Vaccination may disrupt the way we diagnose HIV.
  - Vaccines will, however, overcome the current barriers to population based control of HIV and provide a tool that could get us to an HIV free generation; a reality that is not present with the current tools.

- And yes, the science behind such a vaccine will have additional spinoffs.

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All the study staff,

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