Fred Hutch Cancer Center

Exploring Susceptible Cutoff Definitions

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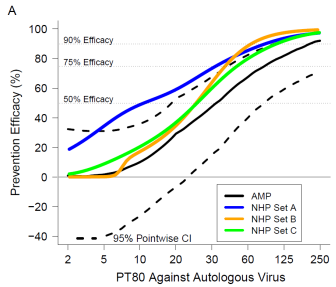
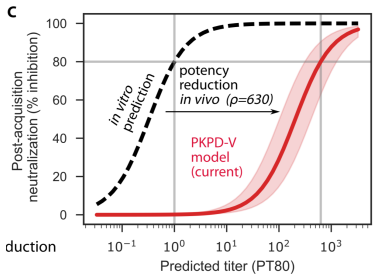
Outline

- Antibody-Mediated-Prevention (AMP) study
- Neutralization biomarkers
  - bnAb-mediated prevention of HIV-1
  - bnAb-mediated suppression of HIV-1 viral load
- Summary



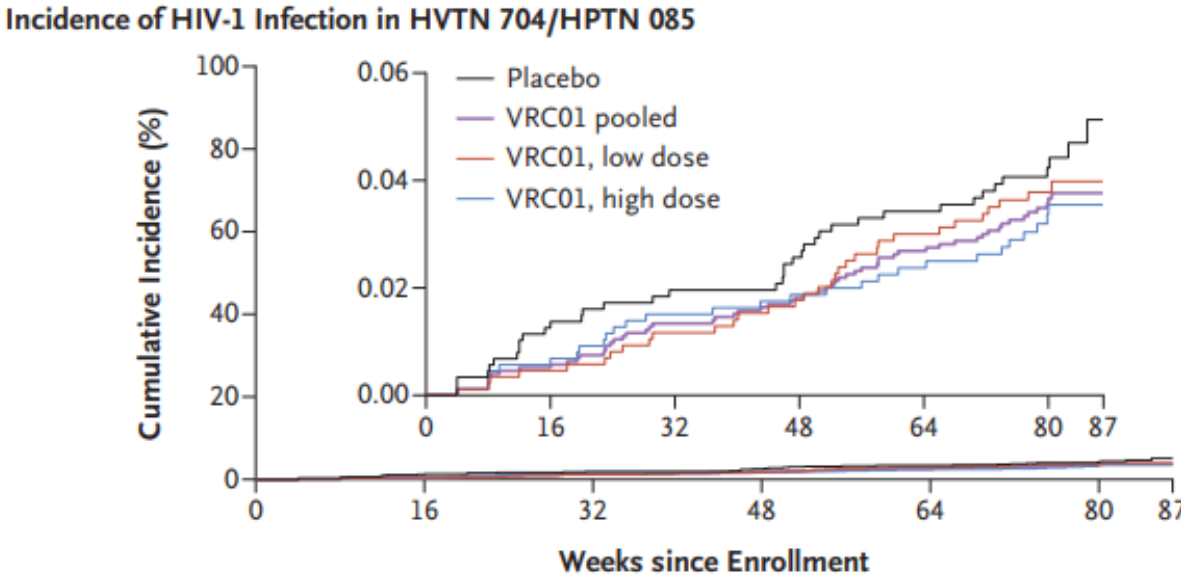


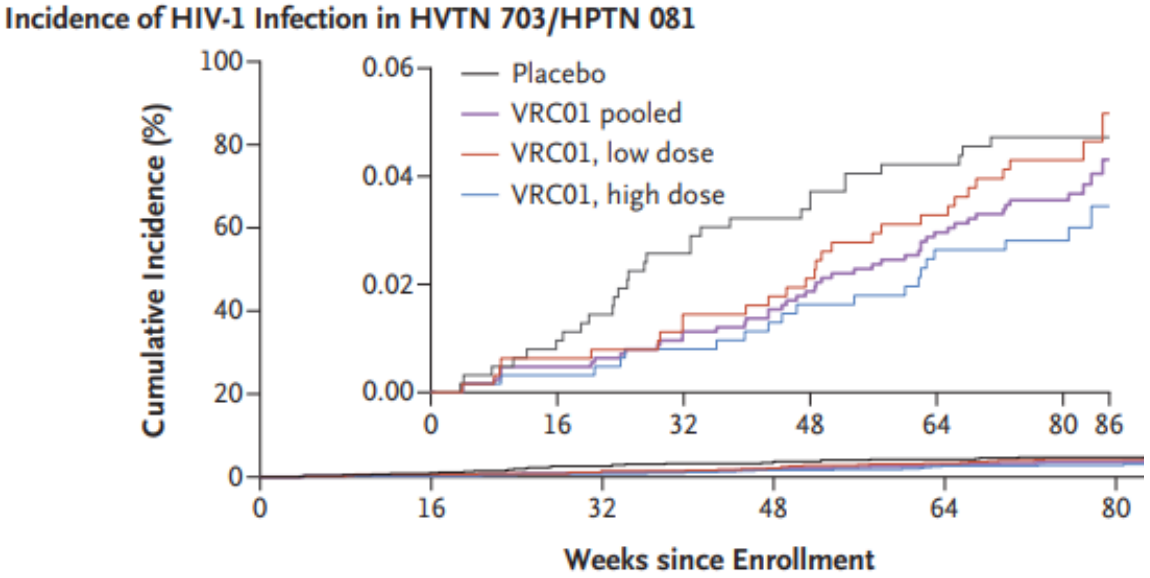
The AMP Trials: Schema

	HVTN704/HPTN085	HVTN703/HPTN081		
REGIMEN	MSM & TG persons in the Americas & Europe	Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	633	1533	10 infusions total & Infusions every 8 weeks Study duration: ~22 months
VRC01 30 mg/kg	900	633	1533	
Control	900	634	1534	
Total	**2700**	**1900**	**4600**	

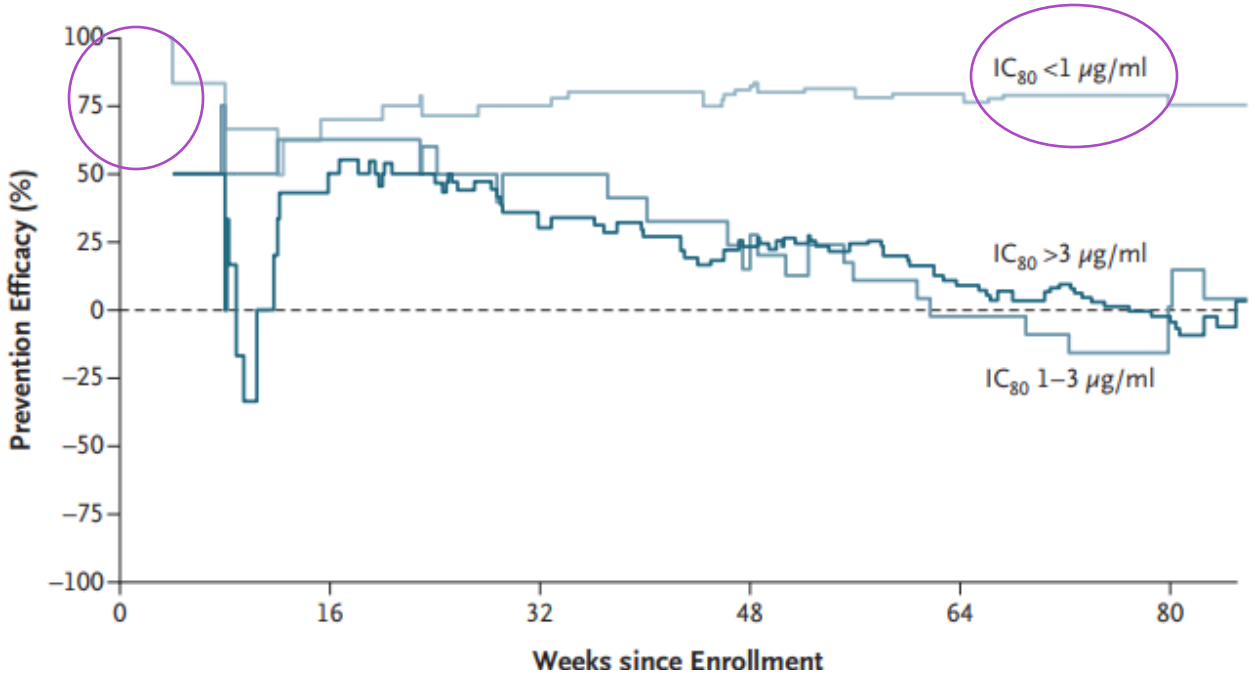
- Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy; Week 104 is the last study visit for assessing safety and tolerability, the tail of VRC01 concentration decline, and a final HIV-1 test
- HIV-1 tests administered every 4 weeks through Week 80, then at Week 88, 96, 104

No Overall Efficacy



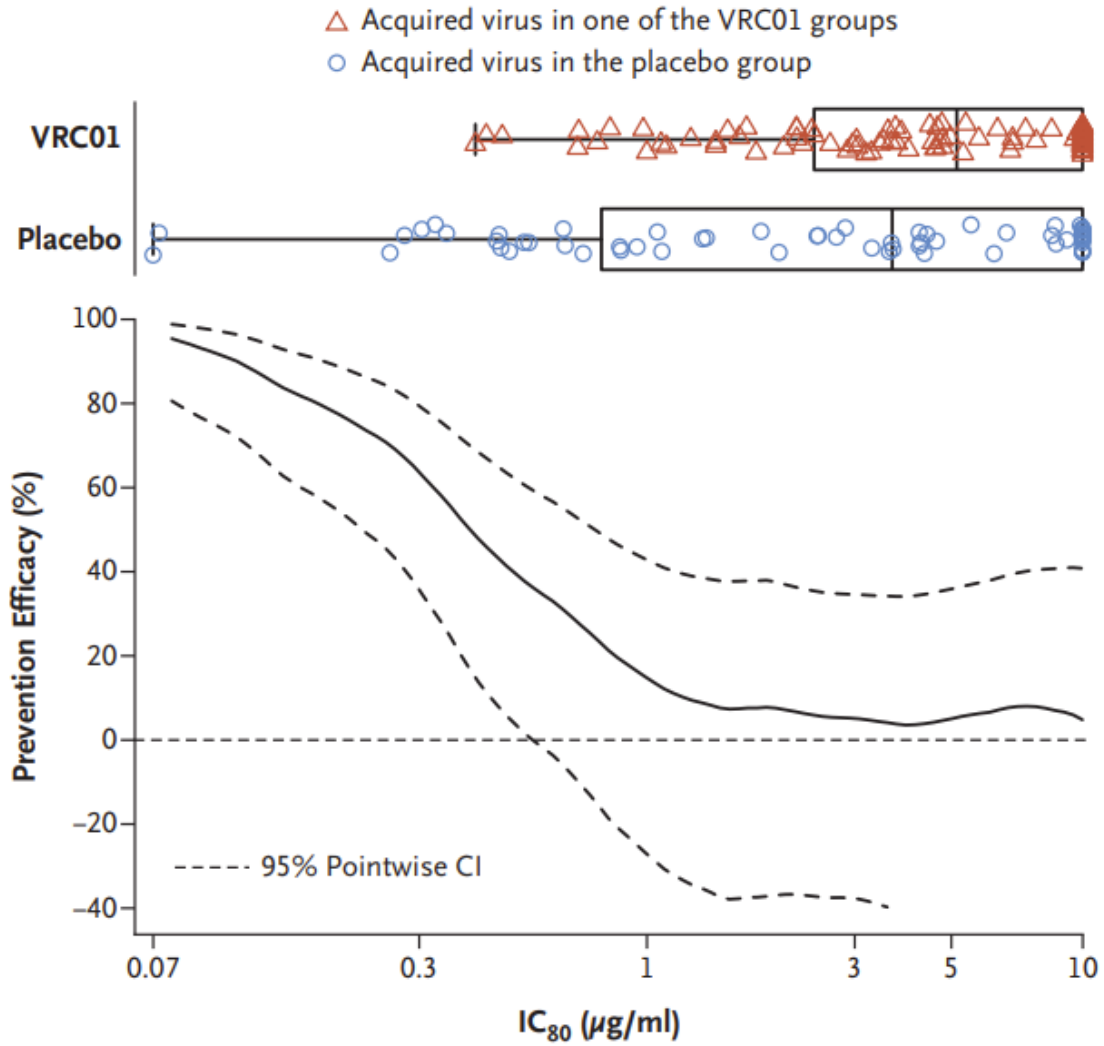


~75% Efficacy of VRC01 Against VRC01-Sensitive Viruses (IC80 < 1 µg/ml)



Corey, Gilbert et al. (2021, *NEJM*)

Prevention Efficacy (PE) Smoothly Decreases with IC80 of VRC01 Against Acquired Virus in AMP



PE was estimated to be 4.5 times higher against viruses 10-fold more sensitive to VRC01 neutralization

- **81.6% against virus with IC80 = 0.2 ug/ml**
- **16.5% against virus with IC80 = 2.0 ug/ml**

However, IC80 is NOT sufficient to quantify the ability of a VRC01 recipient's sera to neutralize an exposing virus at a given time.

Corey, Gilbert et al. (2021, *NEJM*)

Article | Open Access | Published: 22 August 2022

nature medicine

AMP ANTIBODY · MEDIATED · PREVENTION STUDY

PT80

Neutralization titer biomarker for antibody-mediated prevention of HIV-1 acquisition

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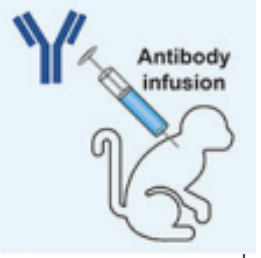
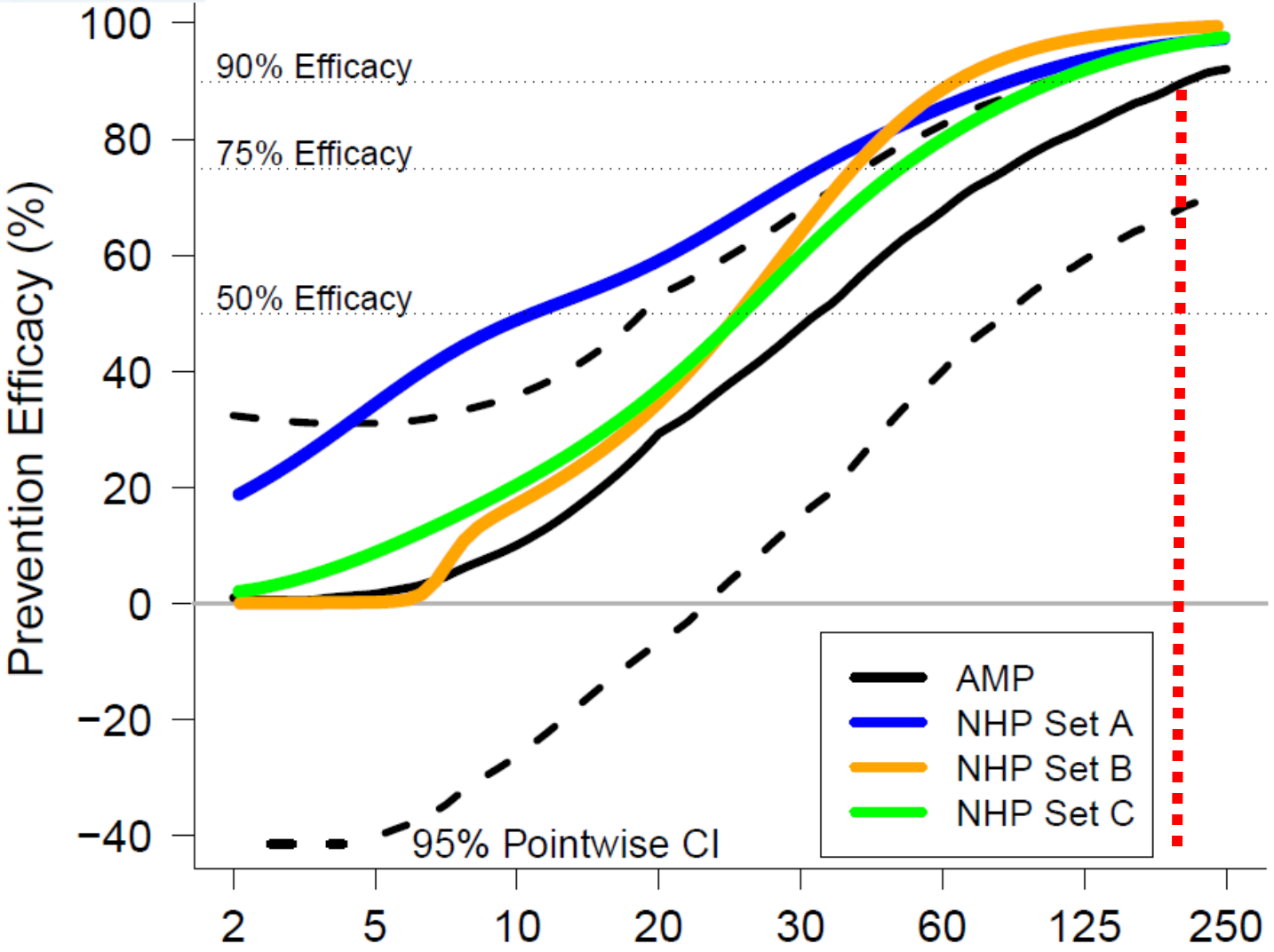


Prevention Efficacy (PE) Smoothly Increases with Predicted ID80 (PT80) Titer in AMP* and in NHP ** studies



PT80 = 80 → ~75% PE

PT80 = 200 → ~90% PE

NHP Set A: all 16 mAbs and 7 challenge viruses

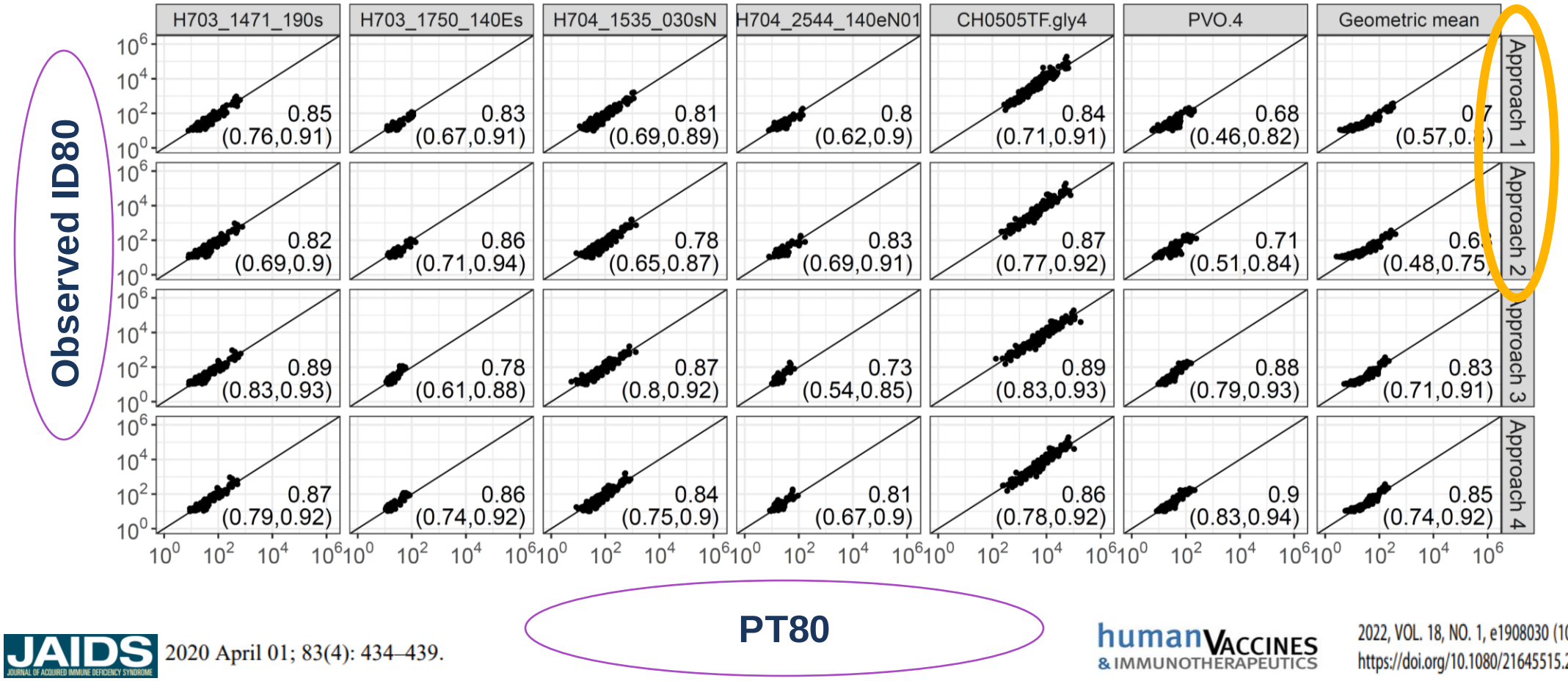
NHP Set B: CD4-bs mAbs, excluding SF162P3

NHP Set C: excluding MPER mAbs and SF162P3

*Gilbert, Huang et al., 2022; **Pegu et al., 2019

VRC01: PT80 is a Proxy of Experimentally Measured ID80

(in a Serum Sample Collected at a Certain Time-point against a Virus)



JAIDS JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROME 2020 April 01; 83(4): 434–439.

Prediction of Serum HIV-1 Neutralization Titers After Passive Administration of VRC01

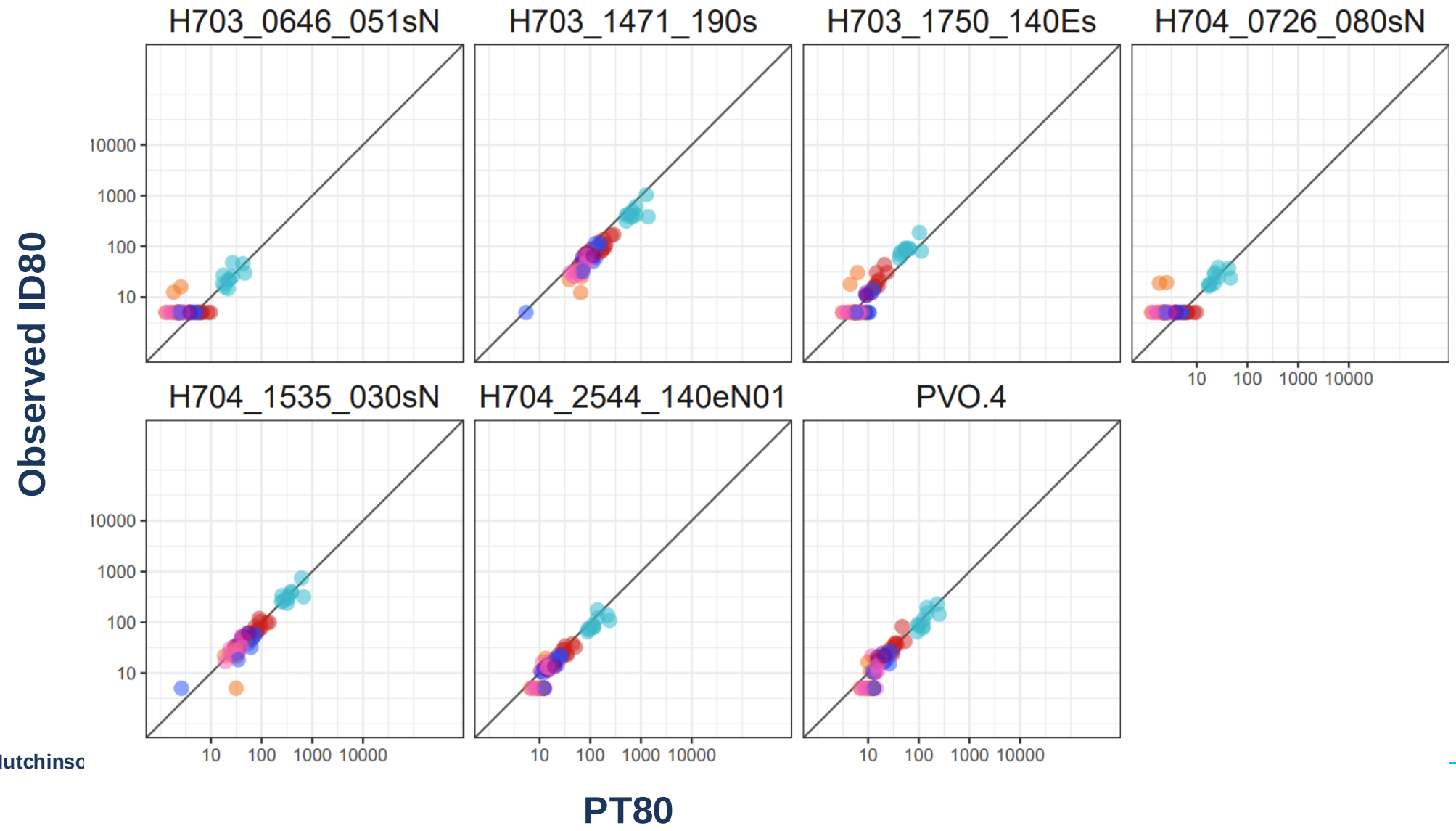
Fre Yunda Huang, PhD[1,2,#], Yuanyuan Zhang, MSc[1], Robert Bailer, PhD[3], Nicole Grunenberg, MD[1], Lindsay N. Carpp, PhD[1], Kelly Seaton, PhD[4], Kenneth H. Mayer, MD[5], Julie Ledgerwood, DO[3], Lawrence Corey, MD[1], John Mascola, MD[3], David Montefiori, PhD[4], Peter B. Gilbert, PhD[1,6]

human VACCINES & IMMUNOTHERAPEUTICS 2022, VOL. 18, NO. 1, e1908030 (10 pages) https://doi.org/10.1080/21645515.2021.1908030

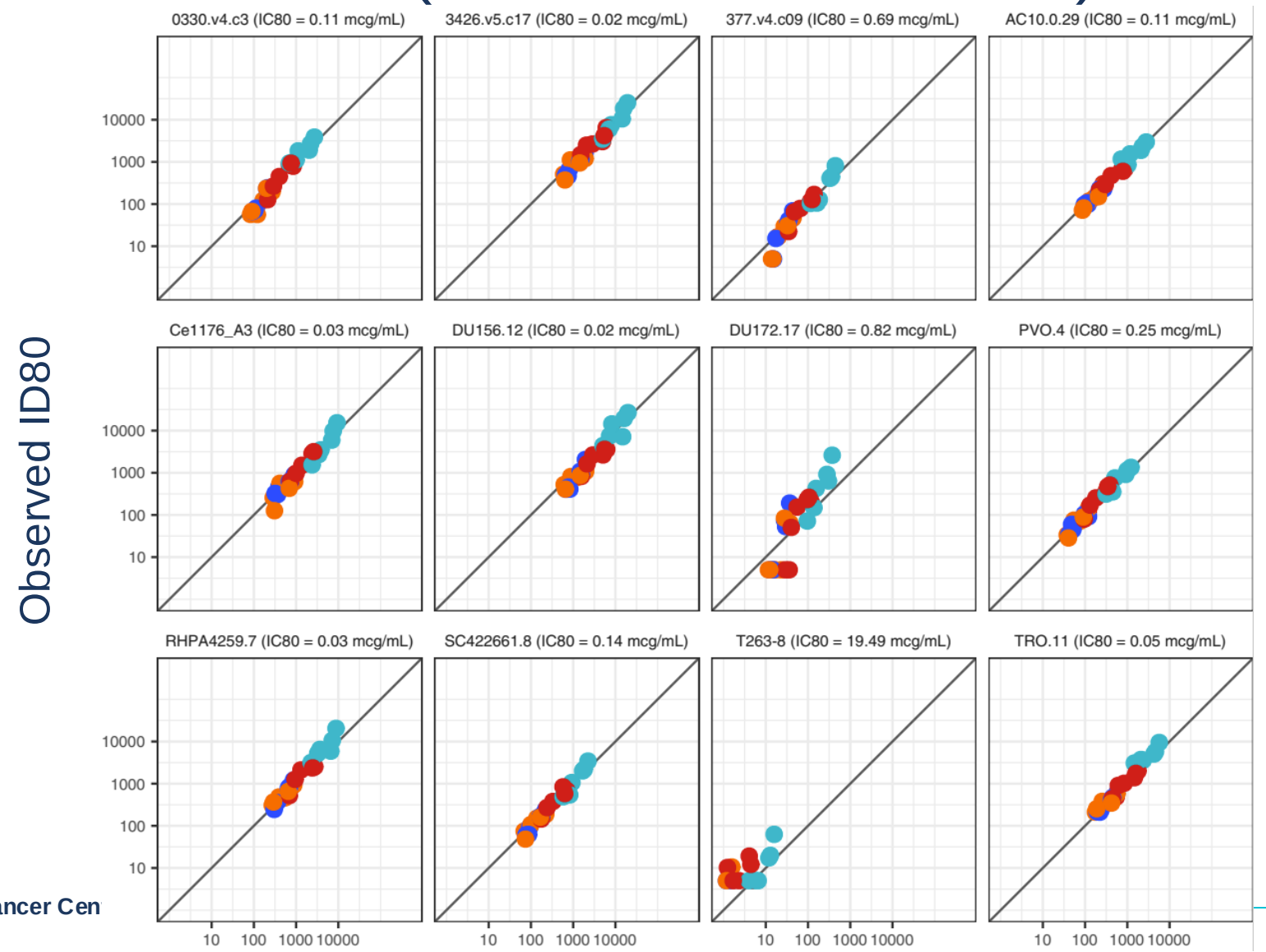
Prediction of Serum HIV-1 Neutralization Titers of VRC01 in HIV-Uninfected Antibody Mediated Prevention (AMP) Trial Participants

Yunda Huang[a,b,c*], Lily Zhang[a], Amanda Eaton[d], Nonhlanhla N. Mkhize[e], Lindsay N. Carpp[a], Erika Rudnicki[a], Allan DeCamp[a], Michal Juraska[a], April Randhawa[a], Adrian McDermott[f], Julie Ledgerwood[f], Philip Andrew[g], Shelly Karuna[a], Srilatha Edupuganti[h], Nyaradzo Mgodi[i], Myron Cohen[j, k], Lawrence Corey[a,l], John Mascola[f], Peter B. Gilbert[a,m], Lynn Morris[e], David C. Montefiori[d]

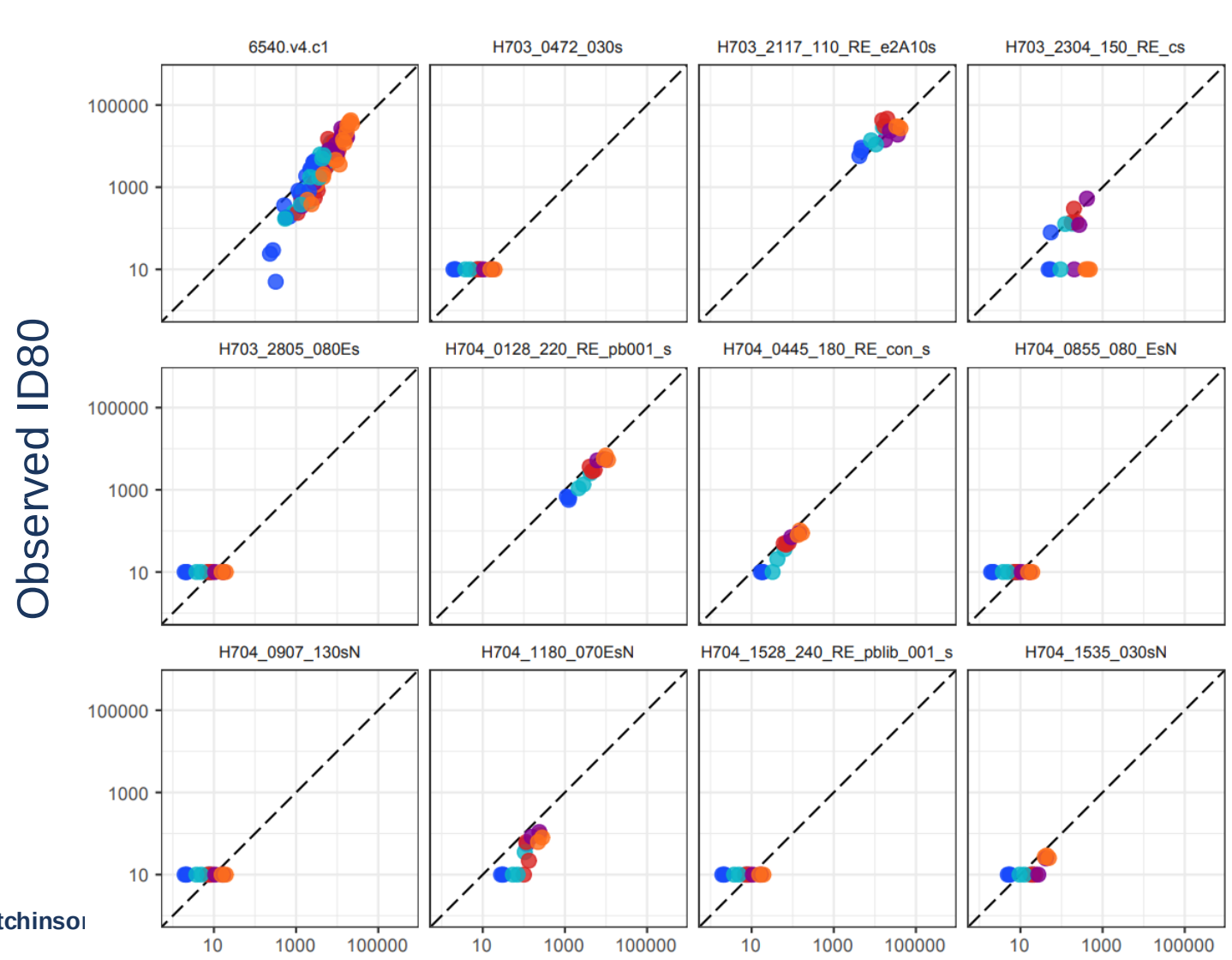
VRC07-523LS: PT80 Predicts Experimentally Measured ID80 (HVTN 127/HPTN 087)



PGT121.414LS: PT80 Predicts Experimentally Measured ID80 (HVTN 136/HPTN 092)



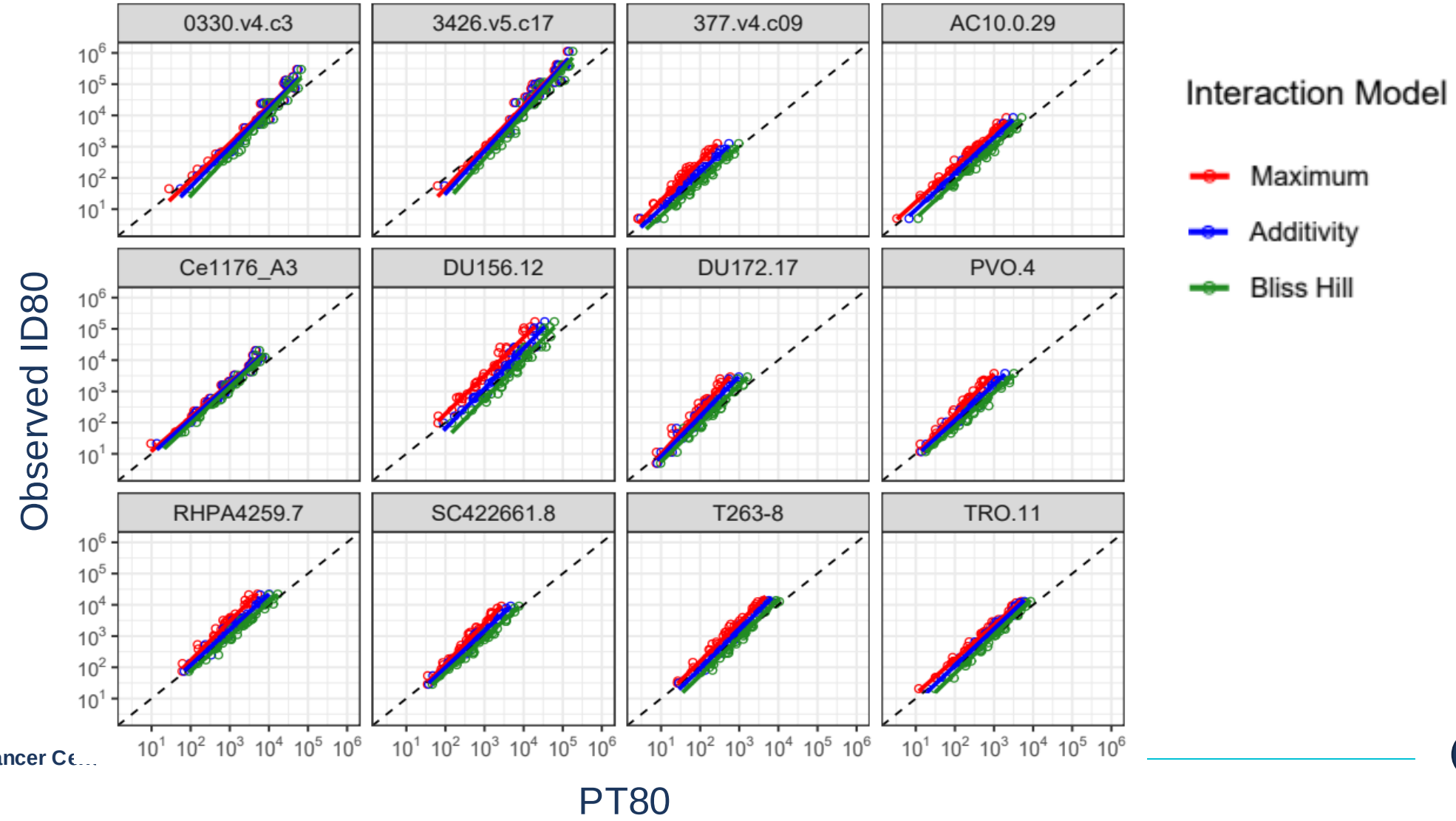
PGDM1400LS: PT80 Predicts Experimentally Measured ID80 (HVTN 140/HPTN 101)



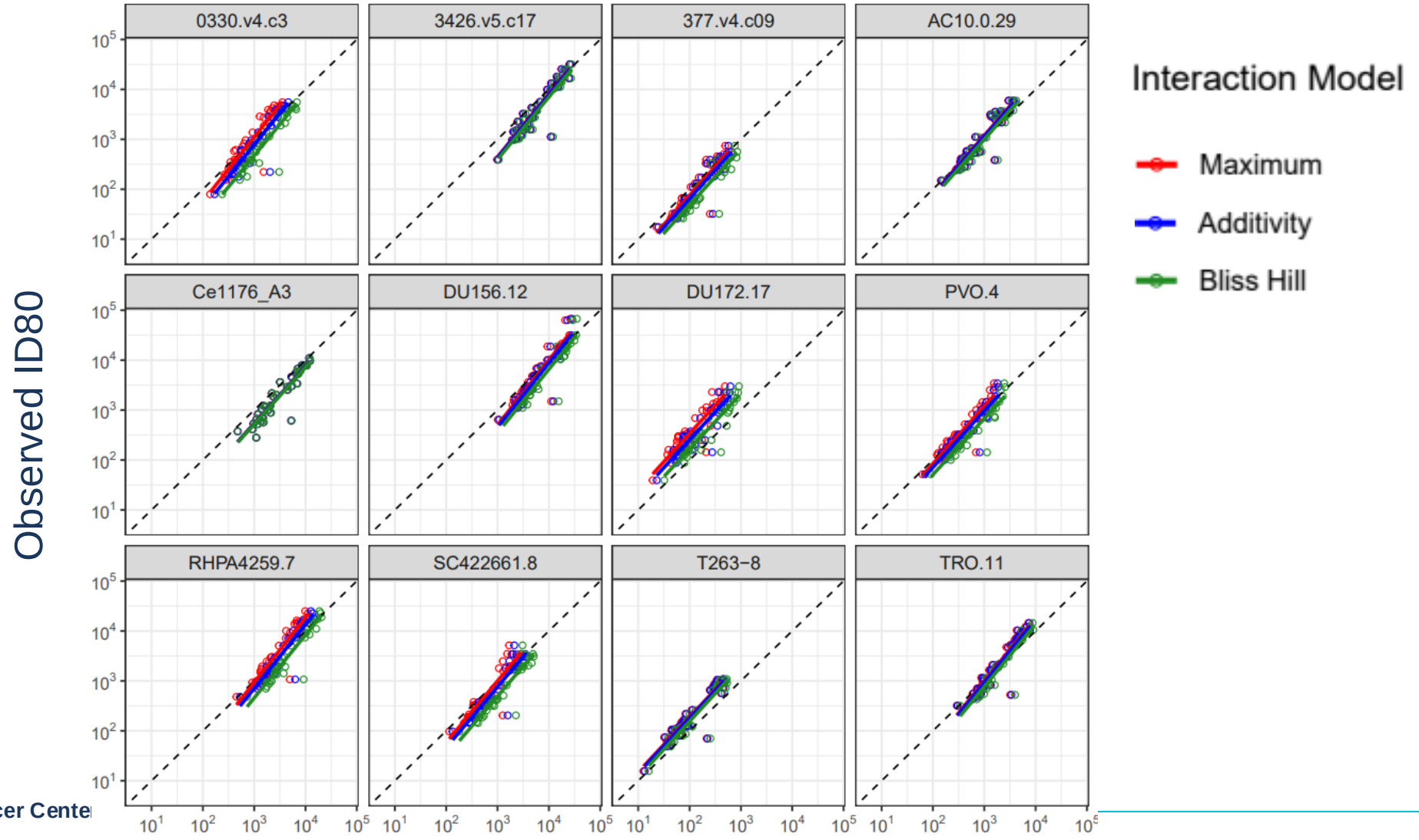
- 6540.v4.c1, IC80 = 0.03
- H703_0472_030s, IC80 = 20
- H703_2117_110_RE_e2A10s, IC80 = 0.01
- H703_2304_150_RE_cs, IC80 = 0.8
- H703_2805_080Es, IC80 = 20
- H704_0128_220_RE_pb001_s, IC80 = 0.03
- H704_0445_180_RE_con_s, IC80 = 2.31
- H704_0855_080_EsN, IC80 = 20
- H704_0907_130sN, IC80 = 20
- H704_1180_070EsN, IC80 = 1.39
- H704_1528_240_RE_pblib_001_s, IC80 = 20
- H704_1535_030sN, IC80 = 7.88

- T1: IV 5 mg/kg PGDM1400LS mo 0
- T2: IV 20 mg/kg PGDM1400LS mo 0
- T3: SC 20 mg/kg PGDM1400LS mo 0
- T4: IV 40 mg/kg PGDM1400LS mo 0
- T5: SC 40 mg/kg PGDM1400LS mo 0

VRC07.523LS + PGT121 + PGDM1400 (HVTN130/HPTN089): PT80 Predicts Experimentally Measured Combination ID80



VRC07.523LS + PGT121.414LS (HVTN136/HPTN092):
PT80 Predicts Experimentally Measured Combination ID80



How Calculate PT80

at **ANY** Time-point (even without specimens collected) against a Virus?

- **Calculation of PT80 for single bnAbs** *(Approaches 1&2, Huang et al. 2020, 2022)*

Observed or PK model-predicted serum bnAb concentration	÷	clinical lot bnAb IC80 against a certain virus	=	PT80
50 µg/ml	÷	2.0 µg/ml	=	25

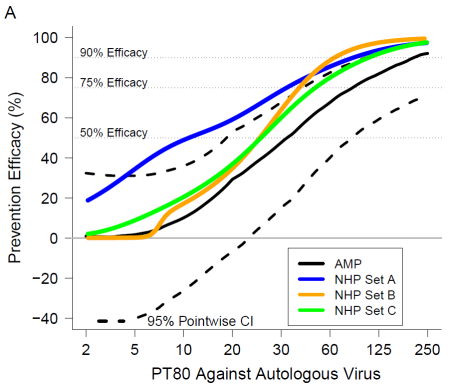
- **Calculation of PT80 for combination bnAbs based on bnAb-specific PT80**
  - **Bliss-Hill, Additive or Maximum model (***Mayer et al., 2022***)**

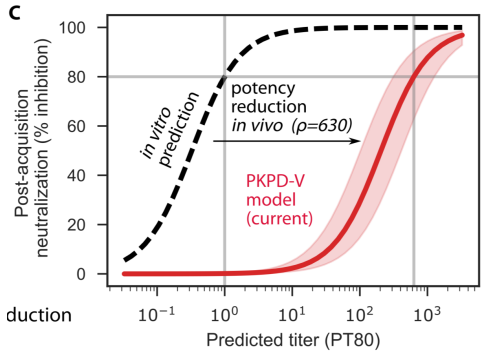
IC80 → PT80

- **IC80:** in vitro neutralization property of the clinical lot of a given bnAb against a given HIV-1 pseudovirus
  - Not a sufficient correlate; has nothing to do with the bnAb concentration in a recipient's serum
- **PT80:** in vivo neutralization property of the serum sample of a bnAb recipient at a given time against a given HIV-1 pseudovirus
  - Could be a sufficient correlate; a property of both bnAb serum concentration and virus

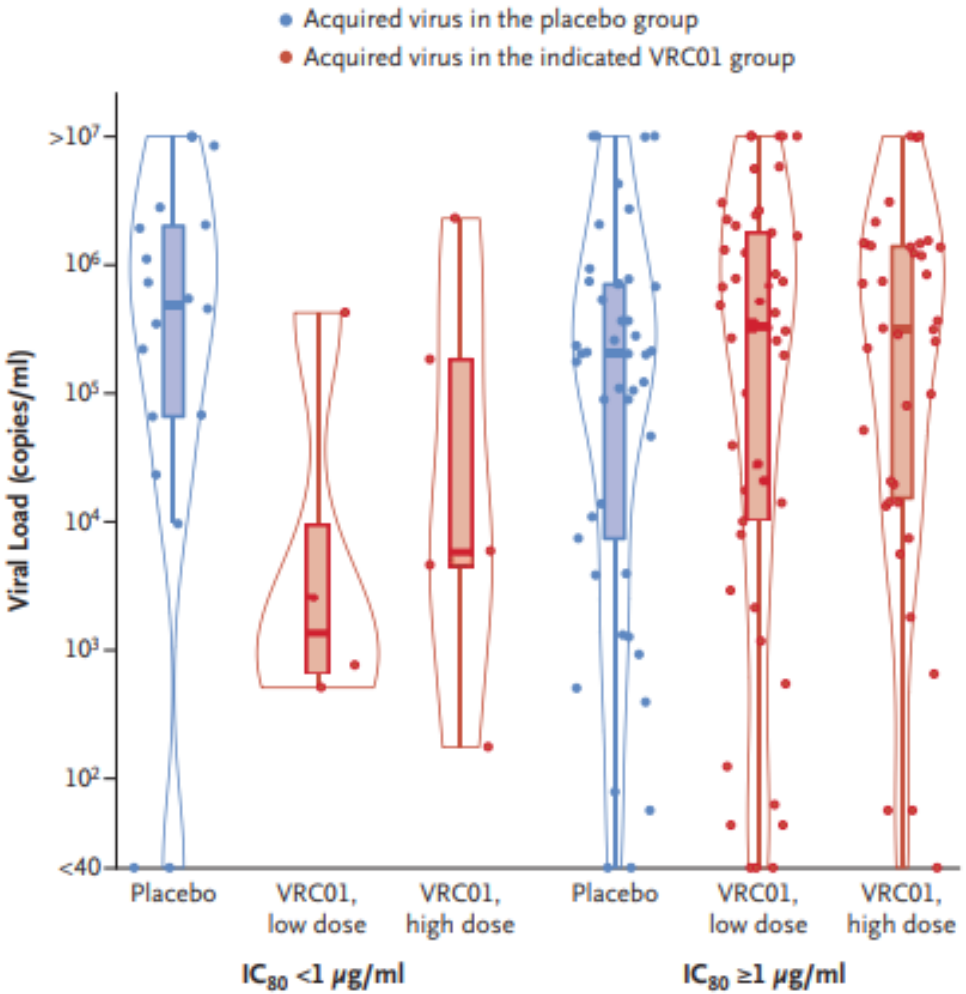
Outline

- Antibody-Mediated-Prevention (AMP)
- Neutralization biomarkers
  - bnAb-mediated prevention of HIV-1
  - **bnAb-mediated suppression of HIV-1 viral load**
- **Summary**





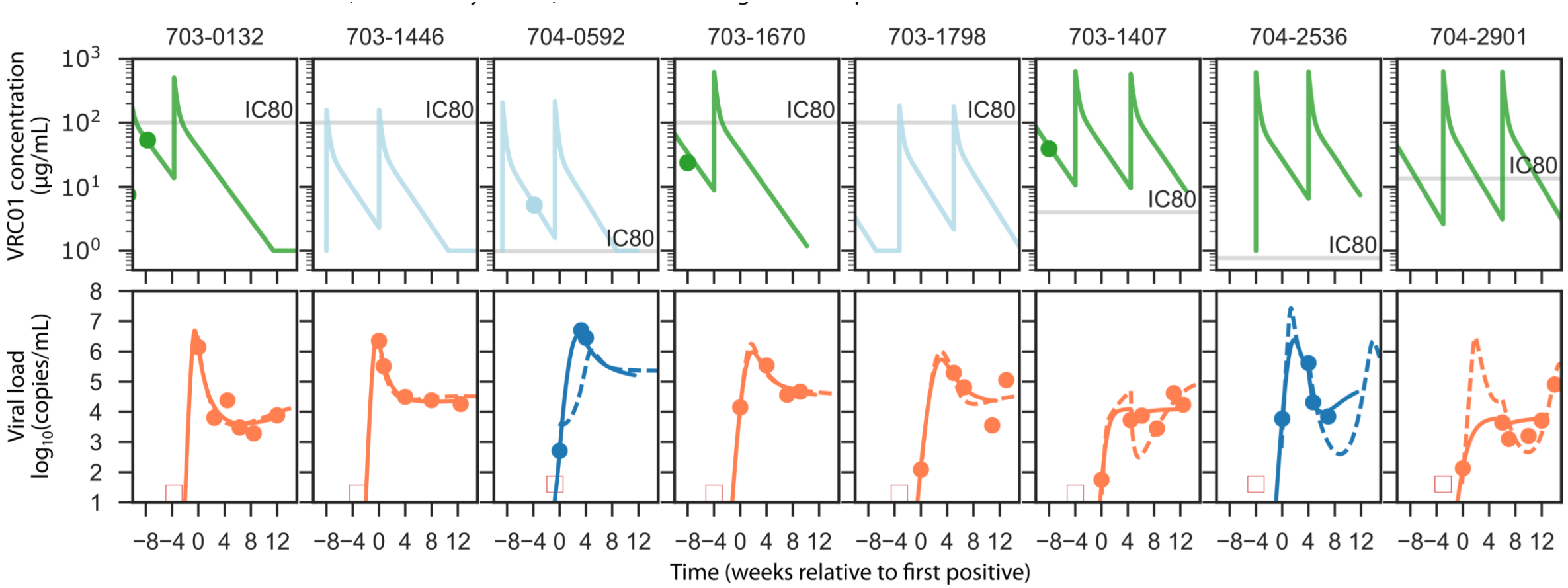
Potential *in vivo* Susceptibility of HIV-1 to VRC01 Varies by *in vitro* Neutralization Sensitivity (IC80) in AMP



- **HIV-1 viral load at the time of first detection was lower in VRC01 vs. placebo among those acquired VRC01-sensitive viruses (i.e., IC80 < 1.0 ug/ml)**
- **However, VRC01 did not influence the initial viral load among participants who acquired more resistant viruses (IC80 ≥ 1.0 ug/ml)**

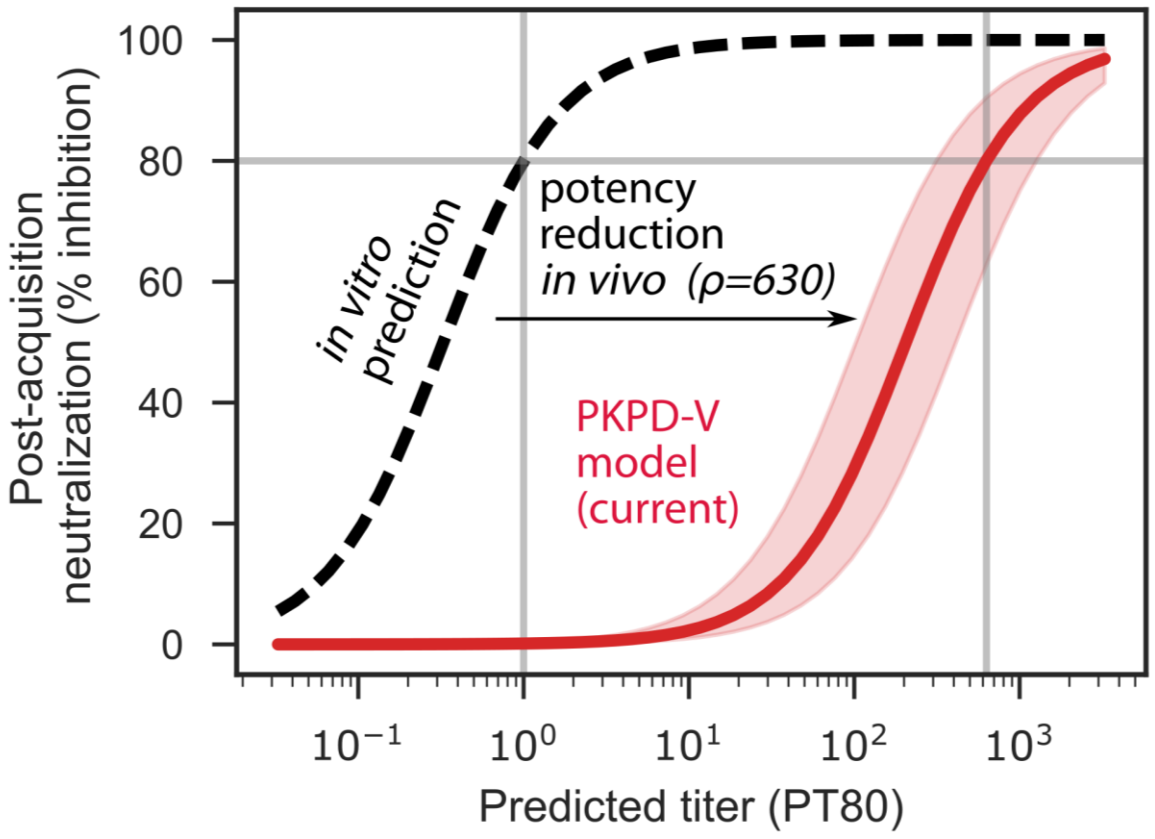
Corey, Gilbert et al. (2021, *NEJM*)

Modeling of HIV-1 Viral Load



Reeves et al. Nat. Commu. In Press.

Estimating *in vivo* Potency Reduction



Neutralization

$$\nu_t = \left\{1 - (\tau/\rho)^{-h}\right\}^{-1}$$

Titer $\quad \tau = C_t/IC50$

Agrees with recent paper that estimated
PT80 titer > 200
would be required to block 90% of acquisition events

[Gilbert et al. Nat Med 2022]

Reeves et al. Nat. Commu. In Press.

Summary

- **PT80 predicts well experimentally measured ID80 for both single and combination bnAbs – an important tool to design future bnAb trials and to evaluate PT80 as a correlate of prevention efficacy.**
- **PT80 can be used to rank bnAb regimens by their potential prevention efficacy because bnAb regimens with greater PT80 levels are predicted to have higher prevention efficacy.**
- **Compared to prevention, higher PT80 is likely needed for viral suppression via HIV-1 nAbs.**

Acknowledgements

Study Teams and Study Participants

- AMP
- HVTN 104
- HVTN 130/HPTN 089
- HVTN 136/HPTN 092
- HVTN 140/HPTN 101

HVTN Statistical and Data Management Center

- Lily Zhang
- Chenchen Yu
- Bryan Mayer
- Dan Reeves
- Peter Gilbert

HVTN Laboratory Center

- David Montefiori Lab
- Nono Mkhize/Lynn Morris Lab
- Kelly Seaton/Georgia Tomaras Lab
- Julie McElrath

HVTN Leadership Operation Center

- Larry Corey
- Jim Kublin
- Dan Barouch
- Glenda Gray

NIH National Institute of Allergy and Infectious Diseases

Dale and Betty Bumpers Vaccine Research Center
National Institute of Allergy and Infectious Diseases
National Institutes of Health

HIV VACCINE TRIALS NETWORK