Broadly neutralizing antibodies (bNAbs) against HIV

DIVISION OF
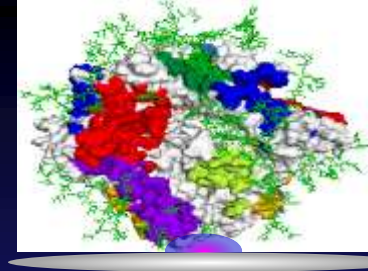**CLINICAL PHARMACOLOGY**

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Dr. Flexner is disclosing the following potential conflicts as required by the organizers:

- Research grants and contracts: NIH
- Consulting: Cipla, Merck, Mylan, ViiV Healthcare
- Expert witness: Gilead
- Stockholder and equity: none to report
- Patents and intellectual property: Two patents related to the development of long-acting formulations for delivery of antiretroviral drugs

Why bNAbs?

Why bNAbs?

- Discovery and development is straightforward.
  - At least 9 anti-HIV bNAbs are in clinical development in 2021.
- They are human B-cell derived antibodies.
  - Low potential for anti-drug antibody (ADA) response
- A simple modification greatly extends their plasma half-life.
  - LS mutation in the Fc binding domain can increase plasma half-life to >3 months.
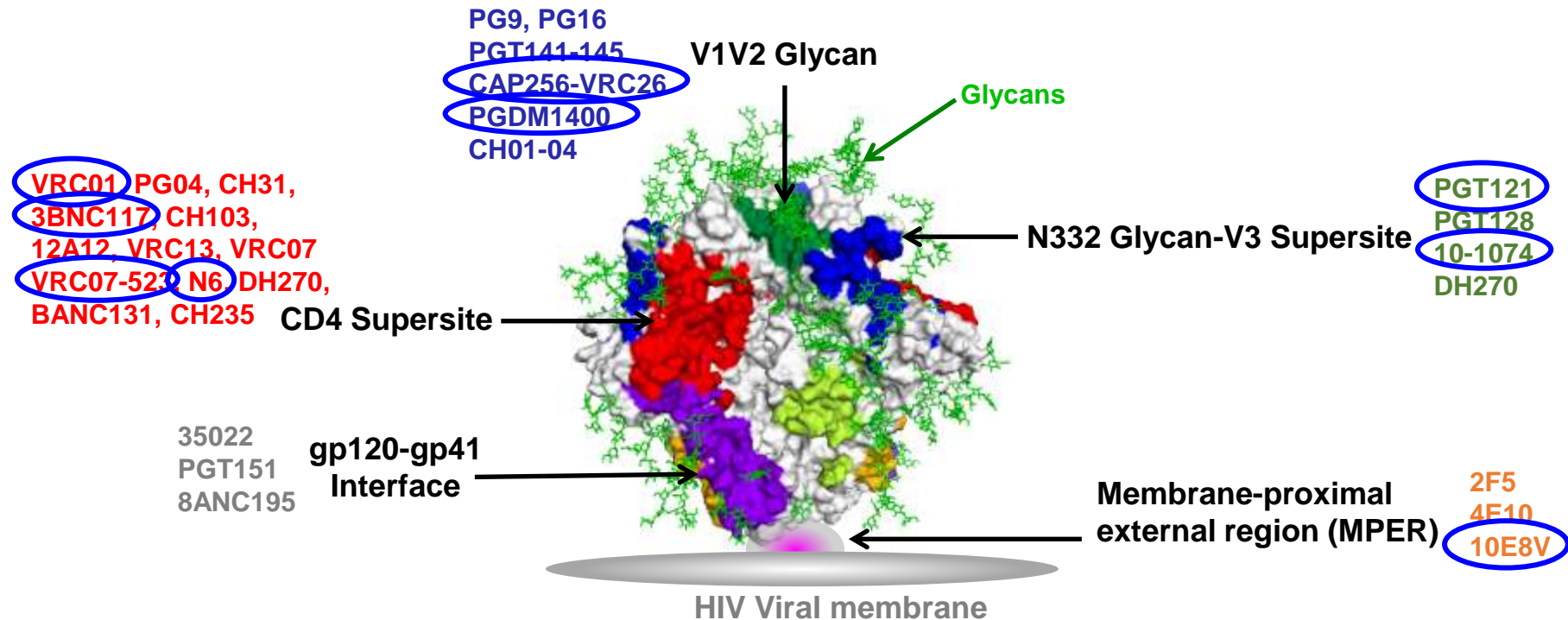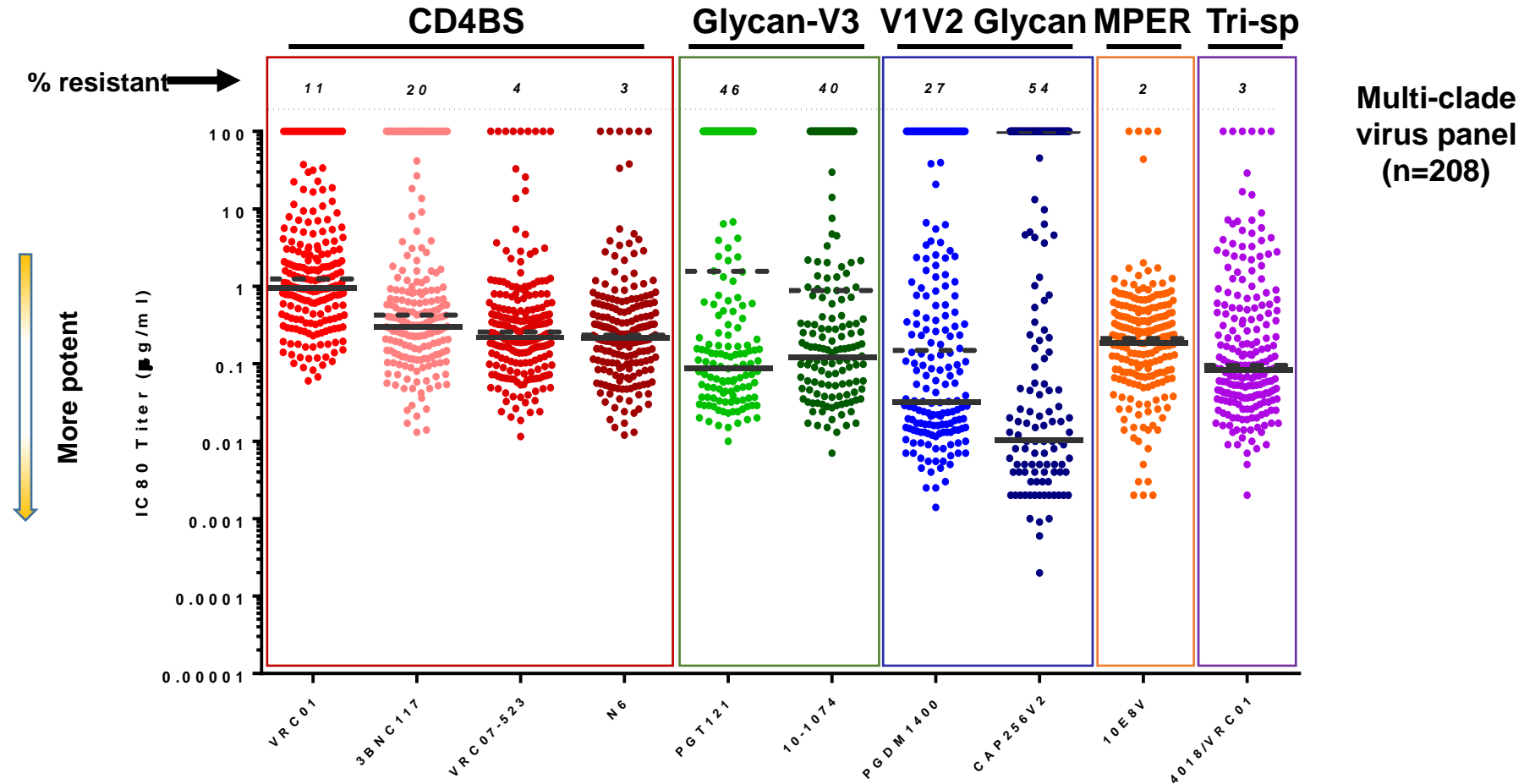 - Does not seem to increase immunogenicity.

- Bonsignori M and Caskey M. *Current Opin HIV/AIDS* 2020; 15 (5)
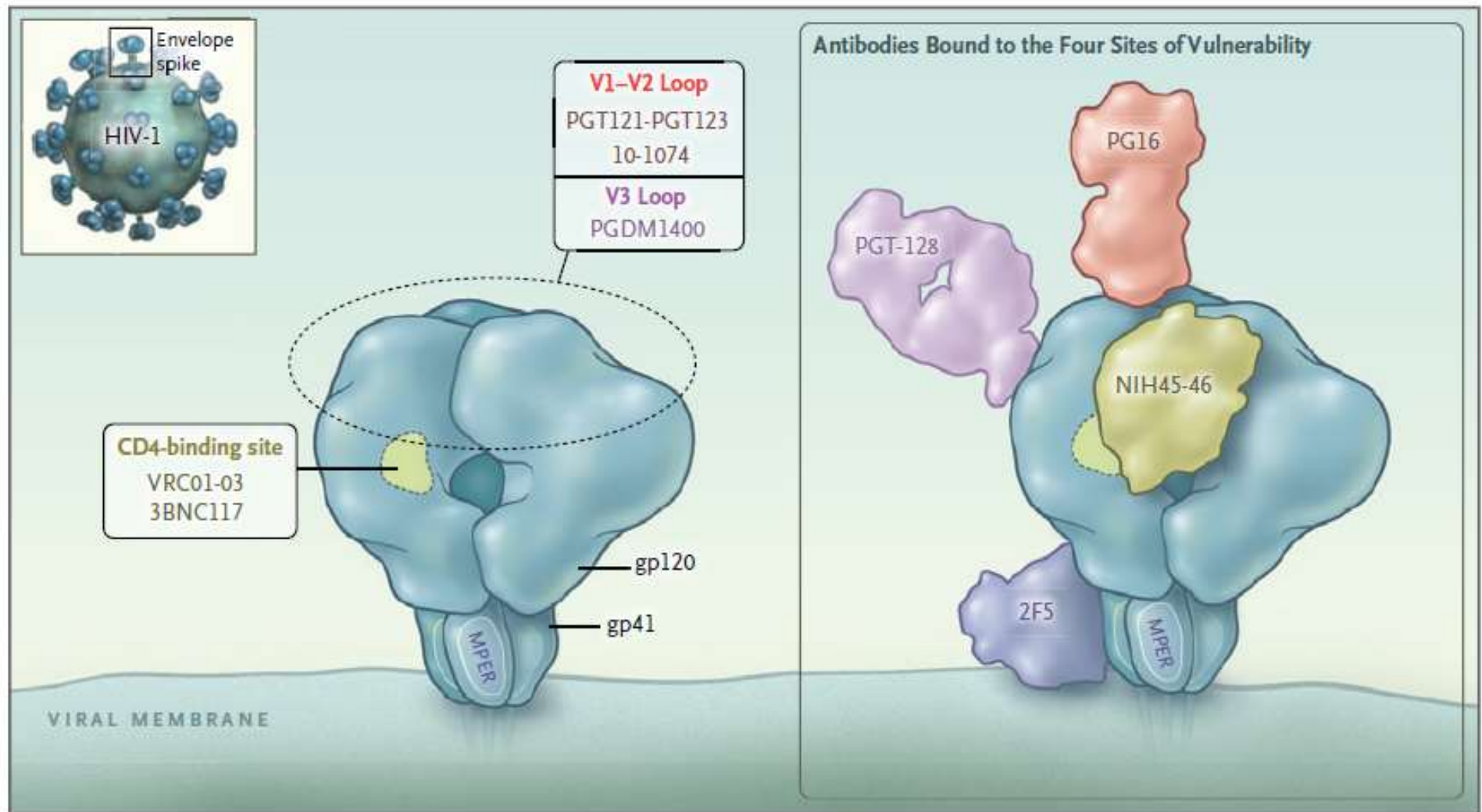
HIV-1 Spike Protein, Showing Sites Targeted by Broadly Neutralizing Monoclonal Antibodies.

The inset shows the virus with its surface spikes. The left panel shows target sites of monoclonal antibodies in clinical development. The right panel illustrates the binding of four different broadly neutralizing antibodies.
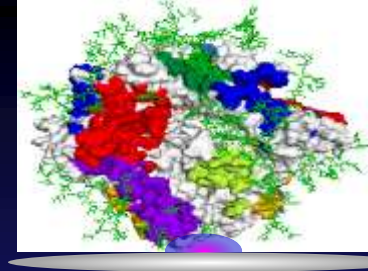
Caskey et al., *New Engl J Med* 2016; 375: 2019

Broadly Neutralizing mAbs in Clinical 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

HIV Viral membrane

Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

Antibody Potency and Breadth

Nicole Doria-Rose, Krisha McKee

Why bNAbs?

- Potency and breadth of activity vary greatly between antibodies.

  - As much as 1000-fold difference in potency, depending on the viral isolate being targeted.

- Combinations of antibodies are needed to cover most circulating HIV isolates in an infected individual.

- Bonsignori M and Caskey M. *Current Opin HIV/AIDS* 2020; 15 (5)

Treatment Interruption inevitably leads to rebound as a consequence of resistance

HIV-1 Antibody 3BNC117 Suppresses Viral Rebound in Humans During Treatment Interruption.

Scheid JF, Horwitz JA, Bar-On Y, Kreider EF, Lu CL, Lorenzi JC, Feldmann A, Braunschweig M, Nogueira L, Oliveira T, Shimeliovich I, Patel R, Burke L, Cohen YZ, Hadrigan S, Settler A, Witmer-Pack M, West AP Jr, Juelg B, Keler T, Hawthorne T, Zingman B, Gulick RM, Pfeifer N, Learn GH, Seaman MS, Bjorkman PJ, Klein F, Schlesinger SJ, Walker BD, Hahn BH, Nussenzweig MC.

Nature July, 2016

Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption.

Bar KJ, Sneller MC, Harrison LJ, Justement JS, Overton ET, Petrone ME, Salantes DB, Seamon CA, Scheinfeld B, Kwan RW, Learn GH, Proschan MA, Kreider EF, Blazkova J, Bardsley M, Refsland EW, Messer M, Clarridge KE, Tustin NB, Madden PJ, Oden K, O'Dell SJ, Jarocki B, Shiakolas AR, Tressler RL, Doria-Rose NA, Bailer RT, Ledgerwood JE, Capparelli EV, Lynch RM, Graham BS, Moir S, Koup RA, Mascola JR, Hoxie JA, Fauci AS, Tebas P, Chun TW.
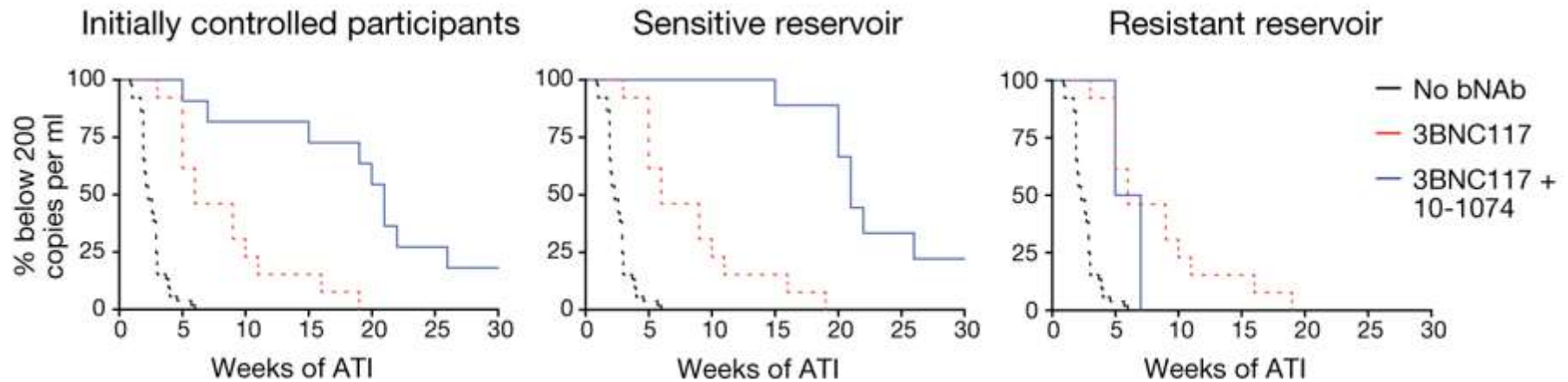
NEJM November 2016

RESISTANCE
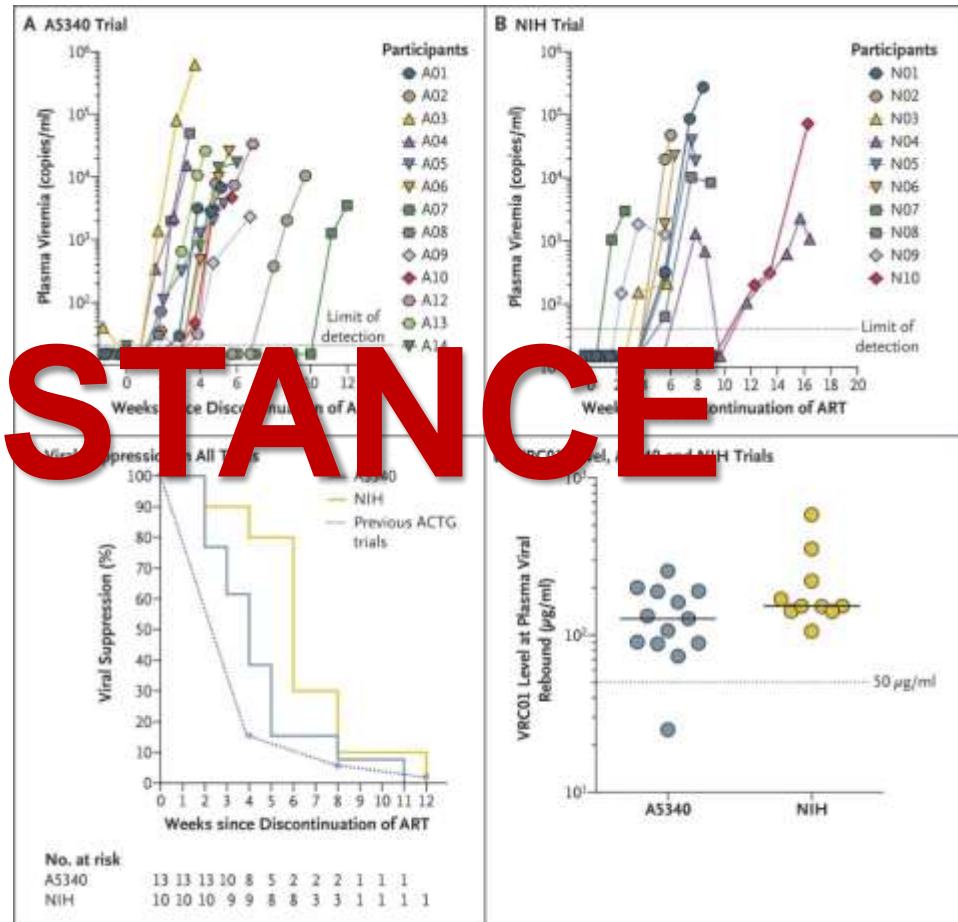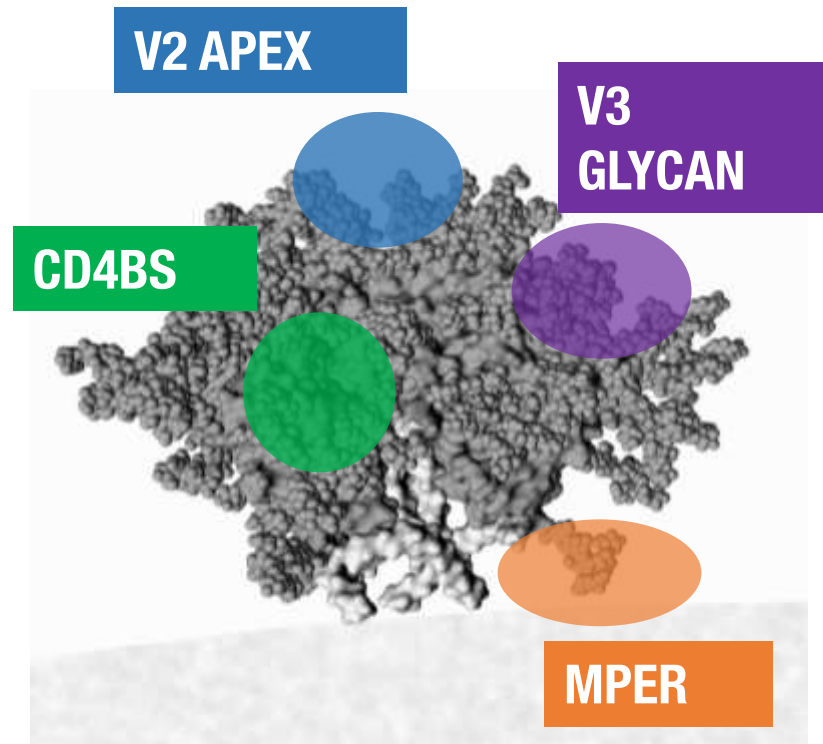
Combination MAbs Delay Rebound Viremia During ATI

Combinations of bnAbs will be needed for therapy, and possibly for prevention

Mendoza et al, Nature 561:479-484, 2018

Optimization of engineered bNabs for HIV prevention

How many antibodies are needed to achieve full coverage?

V2 APEX

V3 GLYCAN

CD4BS

MPER

Most broad and potent combination
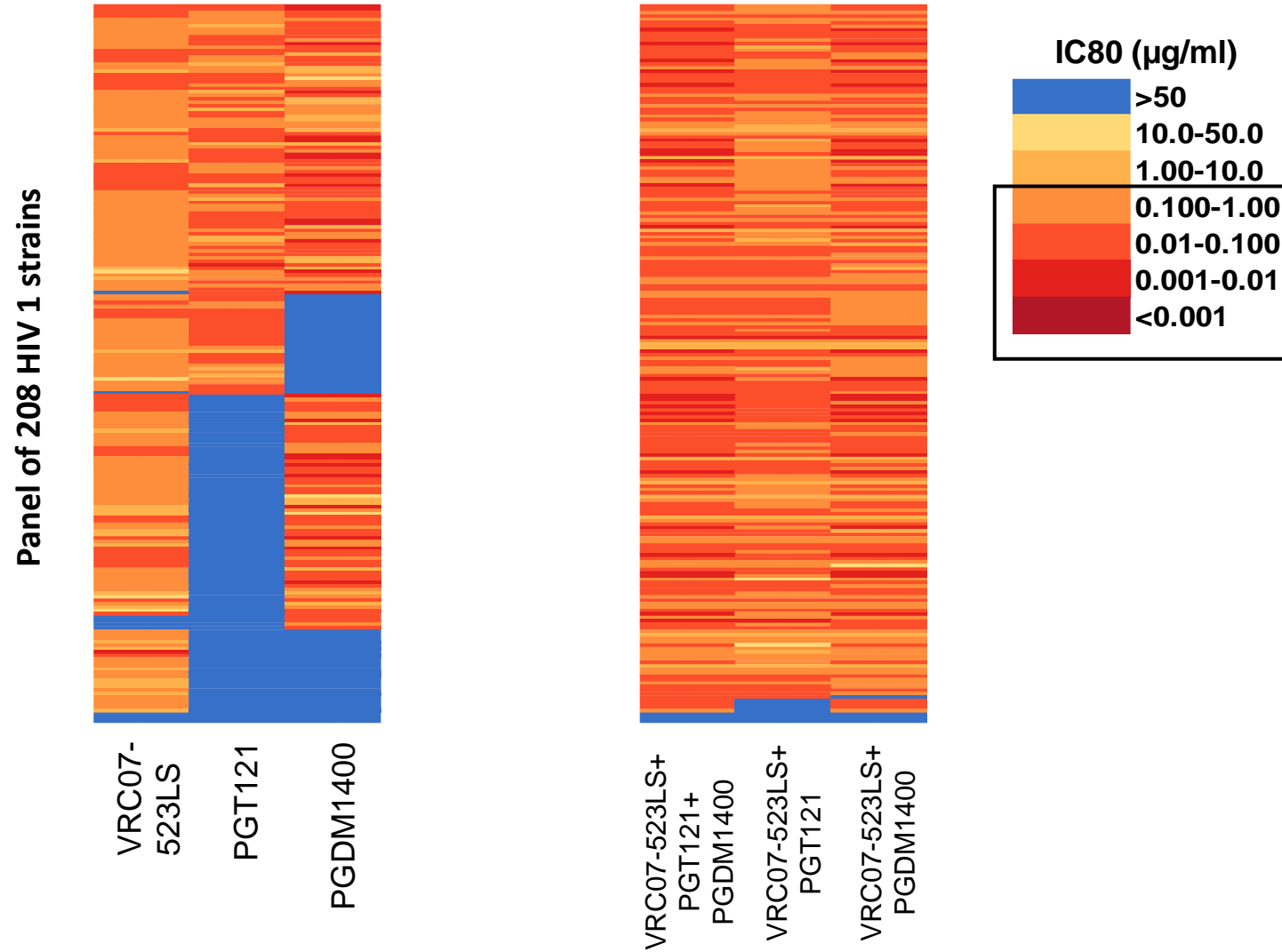
Broad and potent combination with duplicative coverage

IAVI, Scripps, and VRC have been optimizing bNAbs targeting V2-apex, V3-glycan, and CD4bs epitopes
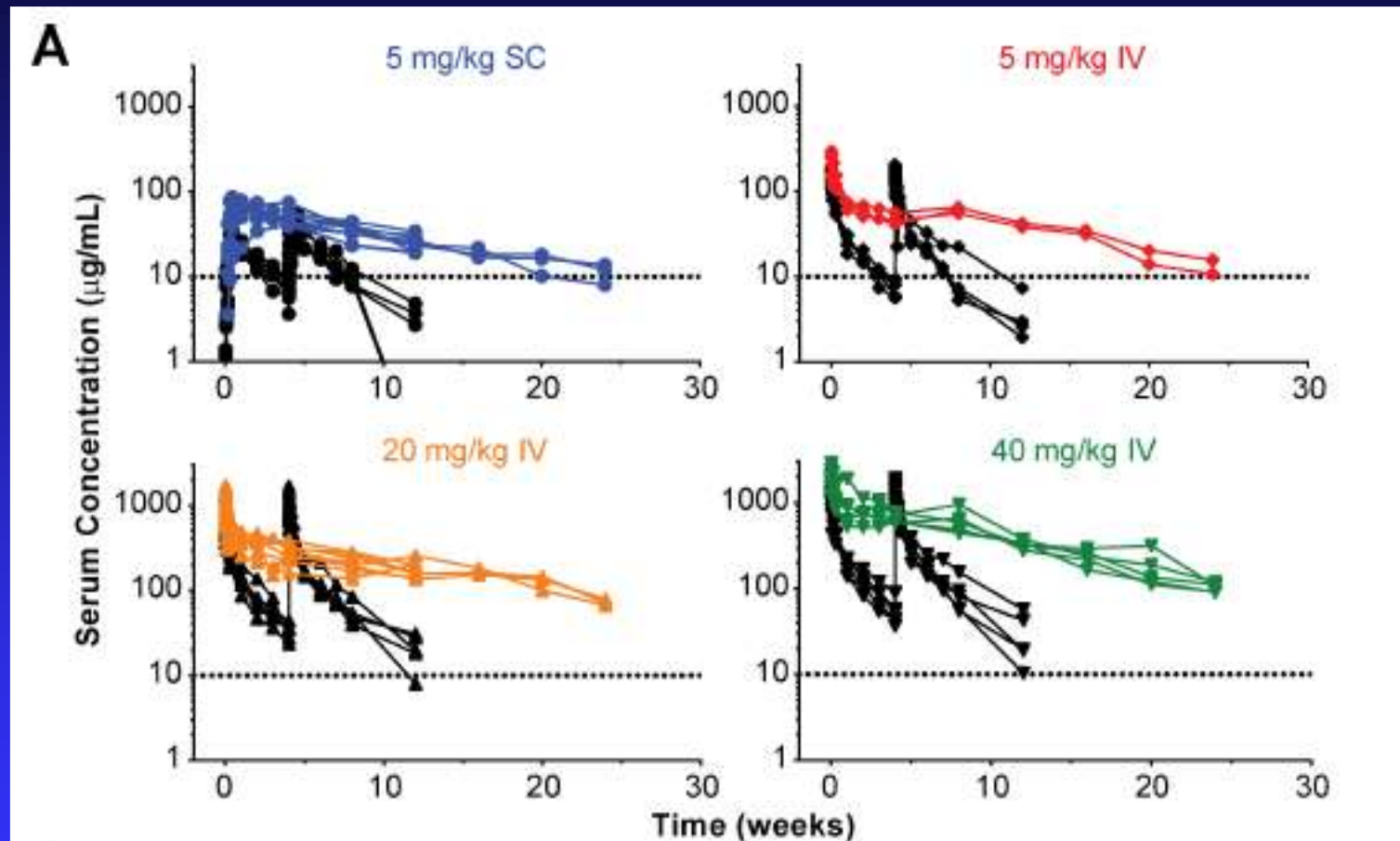
Most broad combination with duplicative coverage

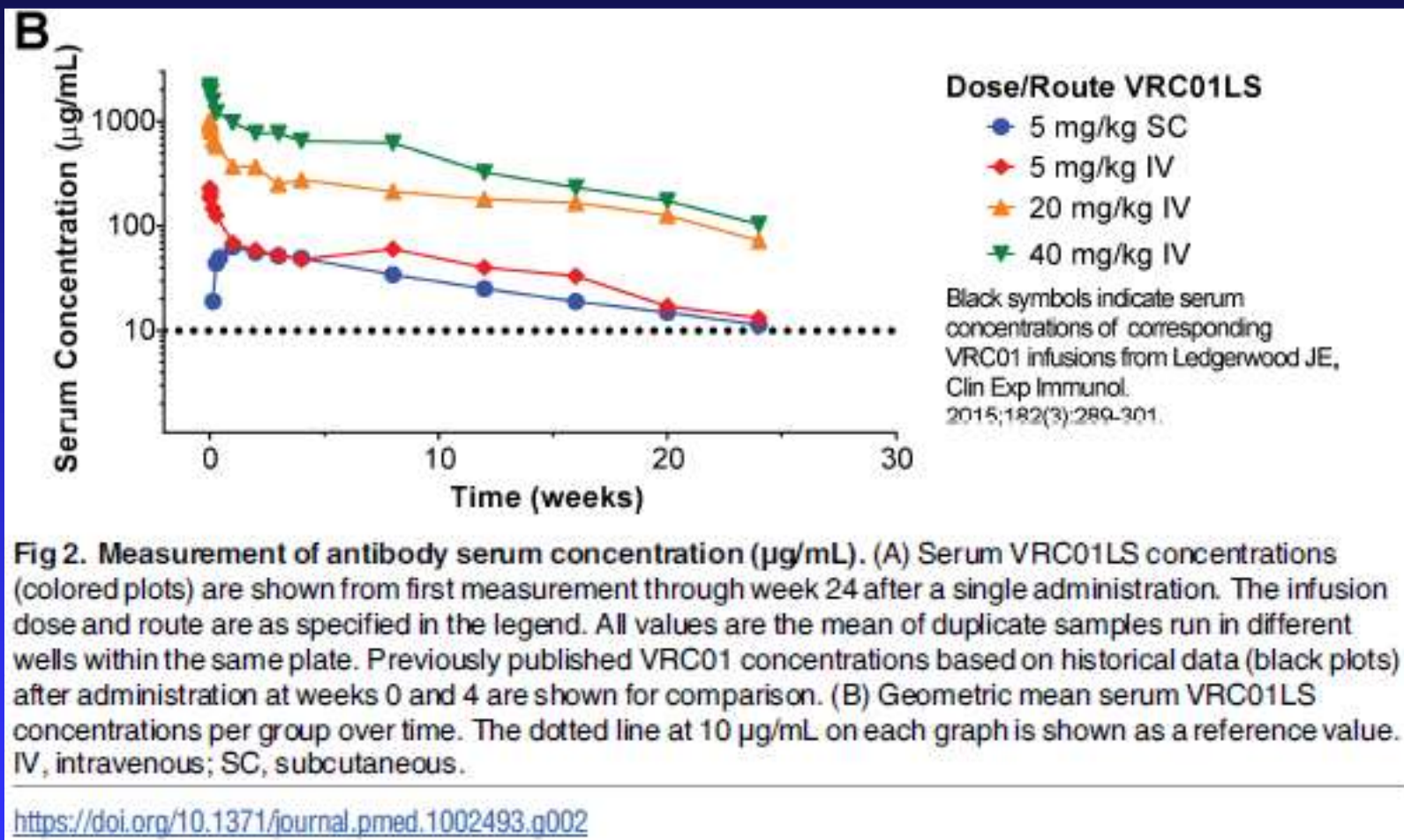# Theoretical Combinations of Antibodies Available in Phase 1

Panel of 208 HIV 1 strains

VRC07-523LS

PGT121

PGDM1400

VRC07-523LS+ PGT121+ PGDM1400

VRC07-523LS+ PGT121

VRC07-523LS+ PGDM1400

IC80 (µg/ml)

- >50
- 10.0-50.0
- 1.00-10.0
- 0.100-1.00
- 0.01-0.100
- 0.001-0.01
- <0.001

Structure-based engineering to improve bNAb pharmacokinetics and pharmacodynamics

PK profile of VRC01-LS

PK profile of VRC01-LS

Fig 2. Measurement of antibody serum concentration (µg/mL). (A) Serum VRC01LS concentrations (colored plots) are shown from first measurement through week 24 after a single administration. The infusion dose and route are as specified in the legend. All values are the mean of duplicate samples run in different wells within the same plate. Previously published VRC01 concentrations based on historical data (black plots) after administration at weeks 0 and 4 are shown for comparison. (B) Geometric mean serum VRC01LS concentrations per group over time. The dotted line at 10 µg/mL on each graph is shown as a reference value. IV, intravenous; SC, subcutaneous.

https://doi.org/10.1371/journal.pmed.1002493.g002

Gaudinski MR et al., *PLoS Med* 2018; January 24

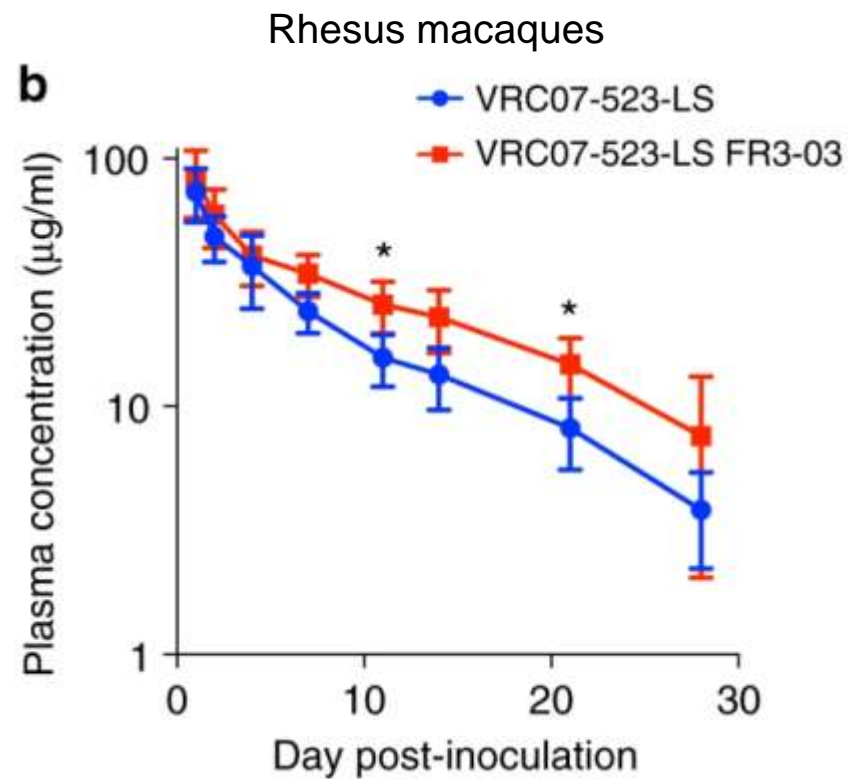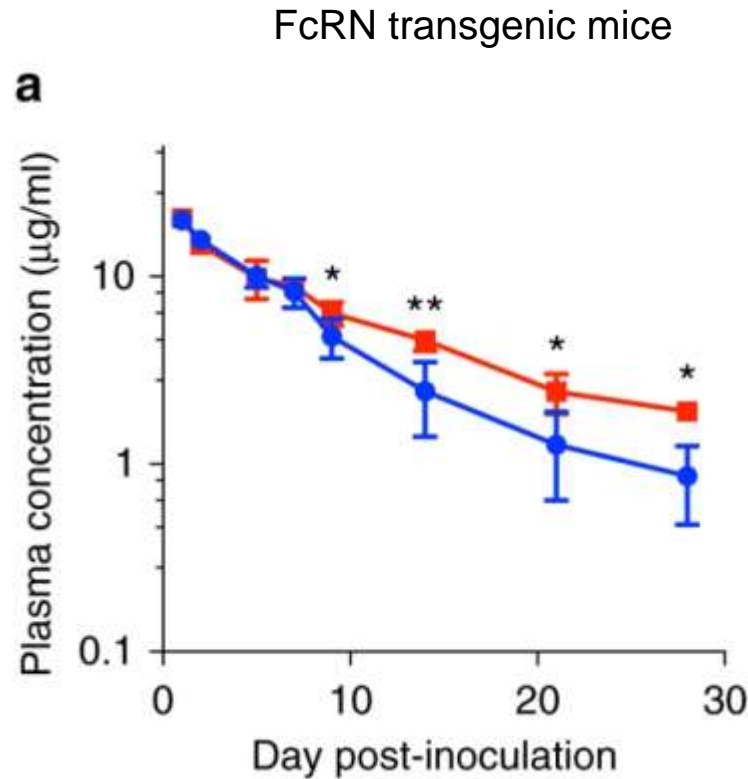# Improved Pharmacokinetic Profile: VRC07-523LS and VRC01LS serum conc.
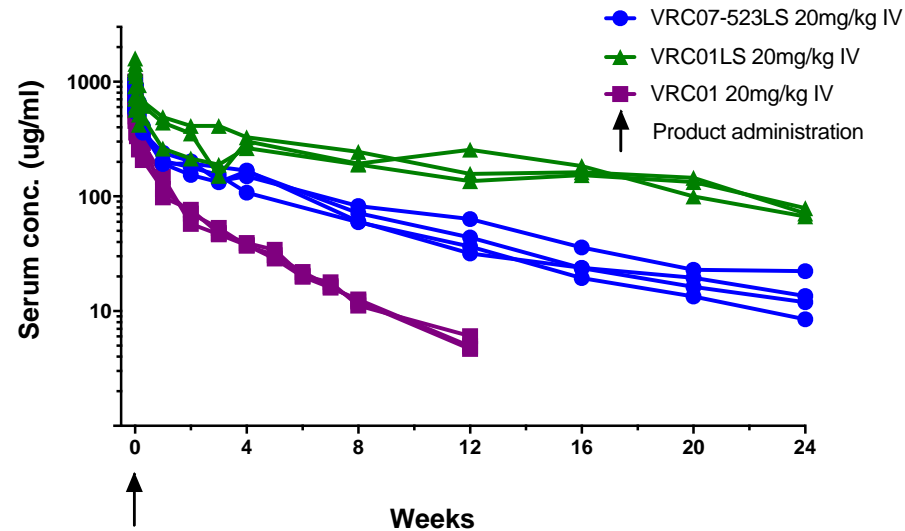
Trough at 12 weeks is 3-fold lower
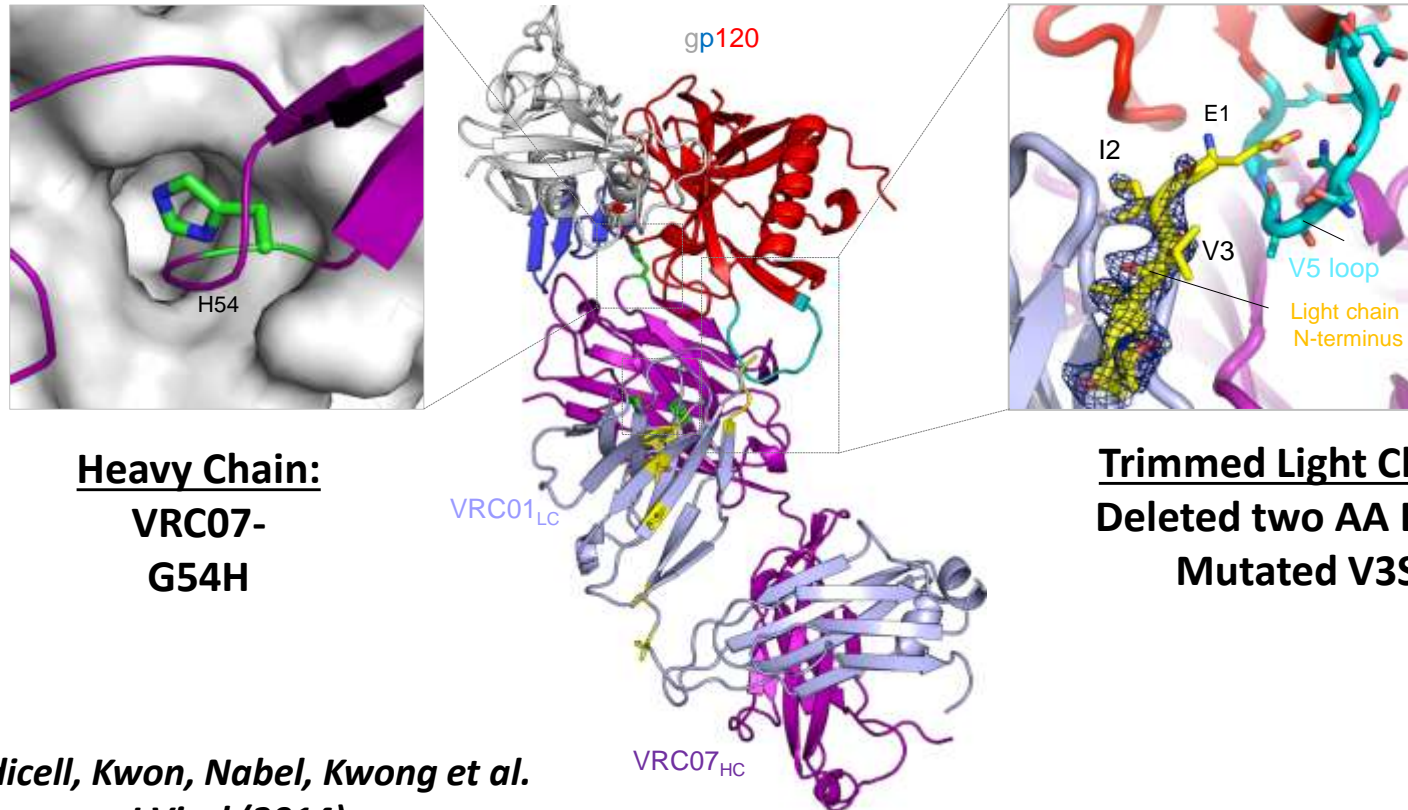**Trough at 16 to 24 weeks is 5-fold lower**

But overall, serum neut is better for VRC07-523LS vs VRC01LS

Gaudinski, Ledgerwood et al. Lancet HIV (2019)

FR-3 insertion improves half-life

FcRN transgenic mice

Rhesus macaques

Structure-based Engineering for Potency (VRC07-523)

gp120

Heavy Chain:
VRC07-
G54H

H54

VRC01_{LC}

VRC07_{HC}

E1
I2
V3
V5 loop
Light chain N-terminus

Trimmed Light Chain:
Deleted two AA E1/I2
Mutated V3S

*Rudicell, Kwon, Nabel, Kwong et al.
J Virol (2014)*

Improved Neutralization Potency
VRC01 ➡ VRC07-523-LS

Breadth ➡ 87 %   96 %

Multiclade Panel
n = 208
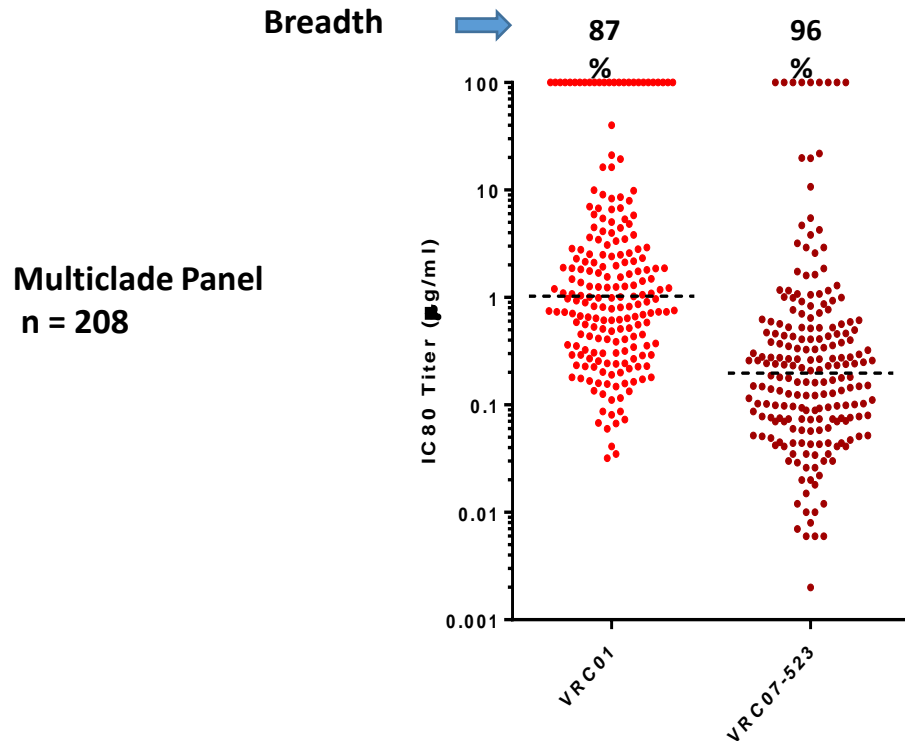
- **5-8 fold more potent**

- **Much lower resistance fraction (<5%)**

- **Substantially better than VRC01 on clade C**

BUT

- **Circulating half-life worse than VRC01LS; trough levels 3-4 fold lower**

Antibody Engineering
Efforts for VRC01/VRC07-523

- ❑ **Extend half-life: part of down selection process**

- ❑ **Improve *in vitro* potency and breadth**

- ❑ **Improve clinical "developability:" expression, solubility, stability**

Next Generation bNAbs: Summary

- ❑ **CD4bs mAbs: 10-fold more potent, greater breadth and as good or better half-life compared to VRC01**

- ❑ **Improved variants of mAbs to other major sites- V1V2, V3-glcan; e.g. PGT121, PGDM1400**

- ❑ **Likely need a cocktail of 3 mAbs to provide > 95% coverage at IC80 <1.0 ug/ml**

Are bNAbs best for HIV treatment or prevention?

Clinical Use of Antibodies
Prevention and Treatment are Different

Prevention

- **Prevent acquisition of infection in high risk individuals**
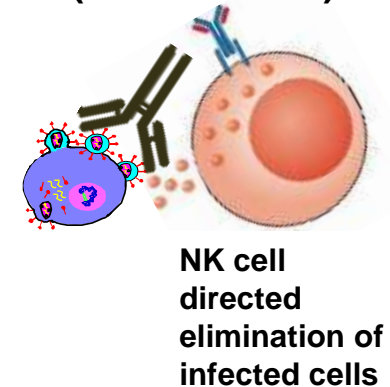- **One bNAb may be enough!**
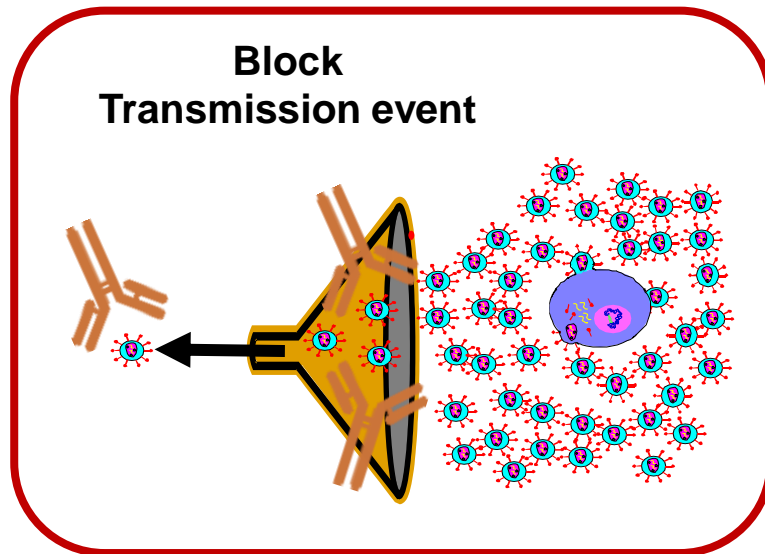
Treatment

- **Kill infected cells; reduce viral reservoir**
- **Maintain viral suppression induced by ARV**
- **Requires more than one bNAb!**

Block Transmission event

Block viral entry

CD4 T-cell
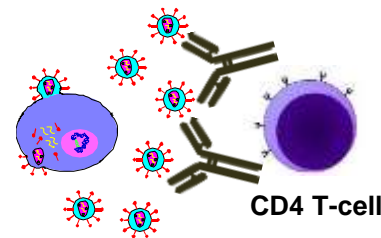
Cell killing (Fc-mediated)

NK cell directed elimination of infected cells

Antibody-Mediated Prevention (AMP)
VRC01 mAb phase 2b

11 Countries
47 Sites
4600 Volunteers

HVTN 704/
HPTN 085
Opened April 2016
Enrolled: 2700

HVTN 703/HPTN 081
Opened July 2016
Enrolled: 1900
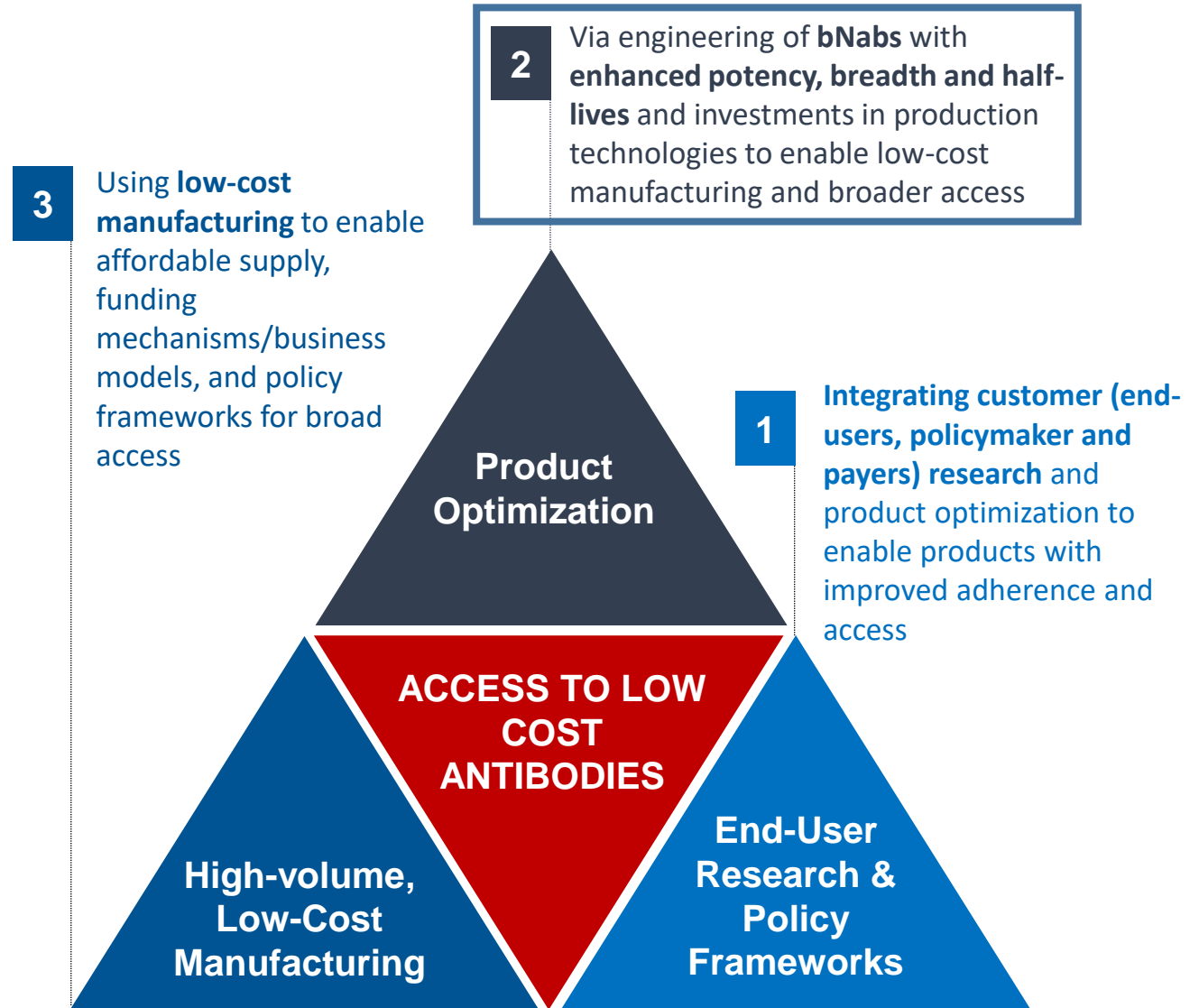
15,300 total mAb infusions
95% retention

DAIDS HVTN and HPTN

Are bNAbs too expensive for LMICs?

IAVI program in partnership with VRC and Scripps

Enabling Global Access of Affordable Antibodies for HIV

2 Via engineering of **bNabs** with **enhanced potency, breadth and half-lives** and investments in production technologies to enable low-cost manufacturing and broader access

3 Using **low-cost manufacturing** to enable affordable supply, funding mechanisms/business models, and policy frameworks for broad access

1 **Integrating customer (end-users, policymaker and payers) research** and product optimization to enable products with improved adherence and access

Product Optimization

ACCESS TO LOW COST ANTIBODIES

High-volume, Low-Cost Manufacturing

End-User Research & Policy Frameworks

Anti-HIV Broadly-neutralizing Monoclonal Antibodies

- Questions for the future:
  - How many bnAbs? For treatment? For prevention?
  - Breadth versus depth?
  - Can bnAbs be given by alternative routes of administration?
    - Subcutaneous
    - Intramuscular
    - Does it matter?
  - Can bnAbs be combined with small molecule LA formulations?
    - ACTG VRC07 plus CBT maintenance study in progress
  - Will bnAbs ever be affordable in LMICs?

Acknowledgements

NIH National Institute of Allergy and Infectious Diseases — Vaccine Research Center

Vaccines for Life®

HIV VACCINE TRIALS NETWORK

HPTN HIV Prevention Trials Network

Scripps Research

iavi International AIDS Vaccine Initiative