From AMP Trials to Emerging Resistance:
Redefining Protective Thresholds for HIV Vaccine Design

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Talk will aim to address two key questions:

Part 1:

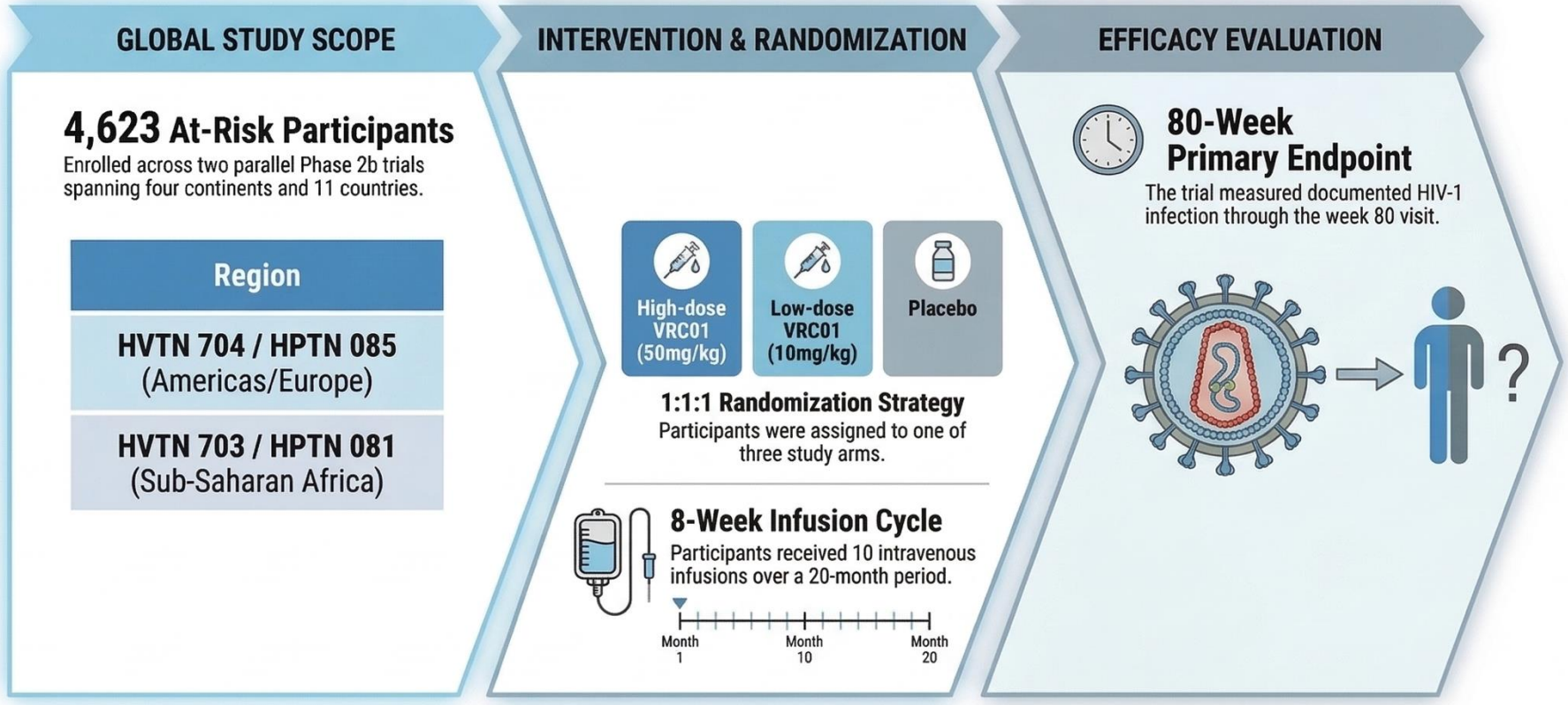
How much antibody is required in the serum to prevent HIV infection (through passive or active immunization)?

Part 2:

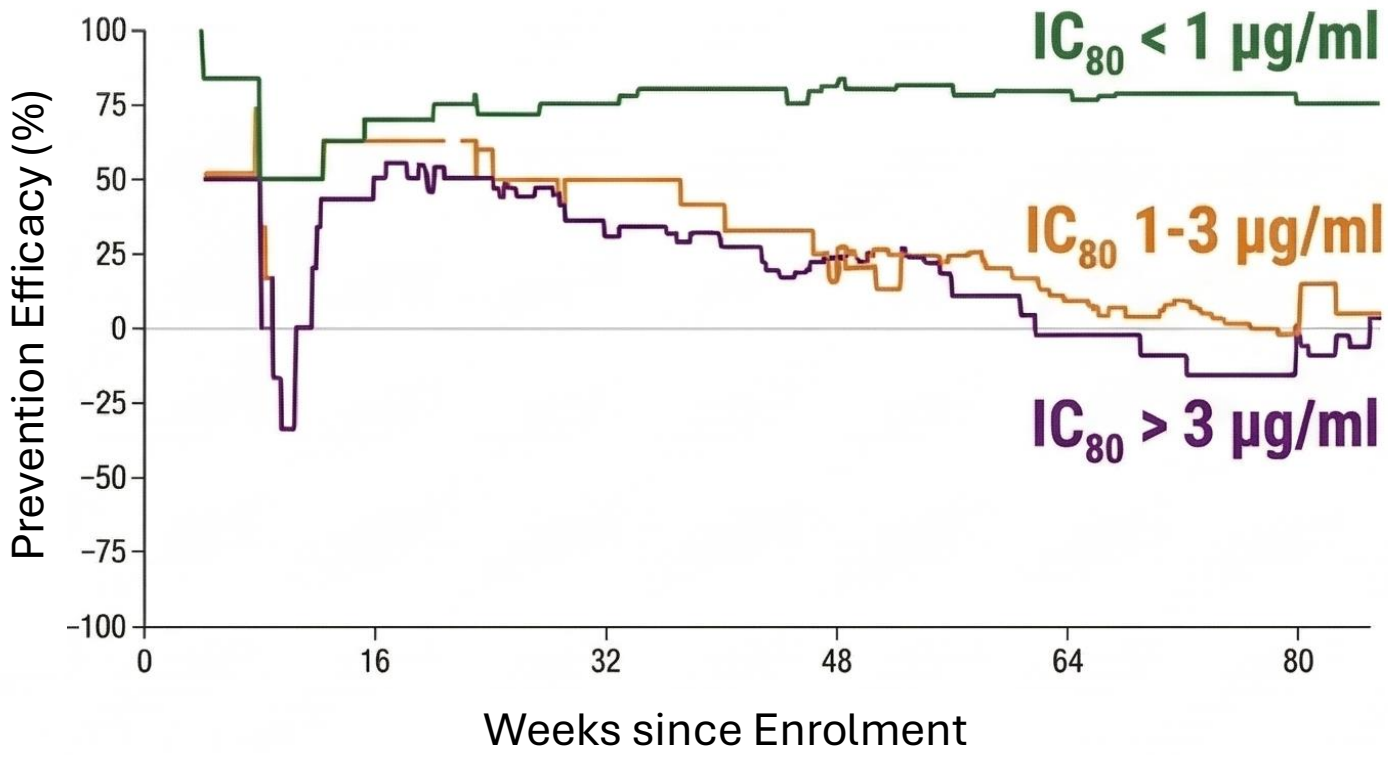
Do we need to worry about HIV evolving to escape antibody neutralization?

Part 1: How much antibody is needed for protection?

The **A**ntibody **M**ediated **P**revention **(AMP)** trial assessed whether passively administered VRC01 could prevent HIV-1 infection



AMP trial showed VRC01 could prevent HIV-1 infection **BUT** limited to highly sensitive viruses



75% Efficacy

Only 31% of placebo viruses

4% Efficacy

3% Efficacy

55% of placebo viruses

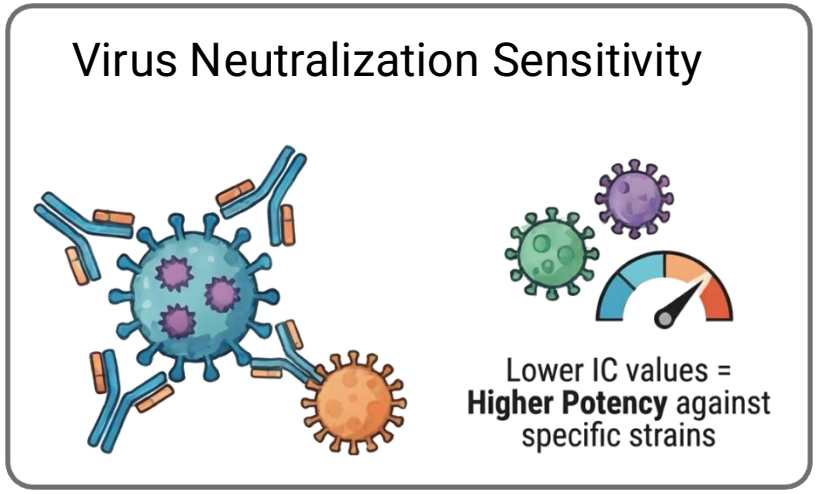
Key findings:

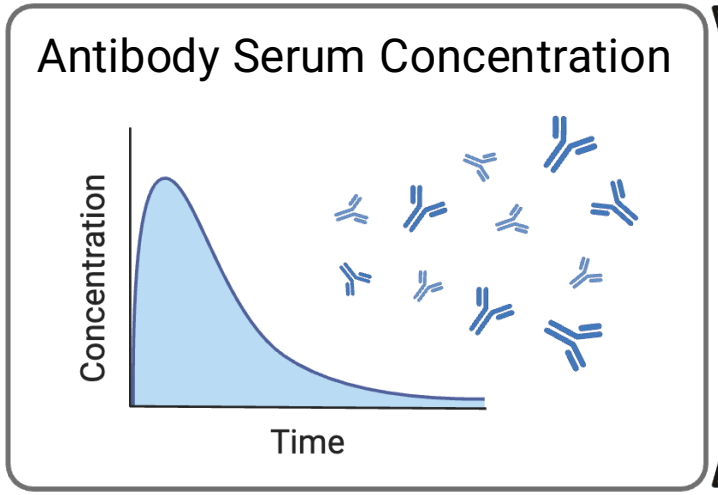
- High efficacy for very sensitive viruses
- These were the minority of viruses circulating in the study populations

Corey *et al*., NEJM, 2021

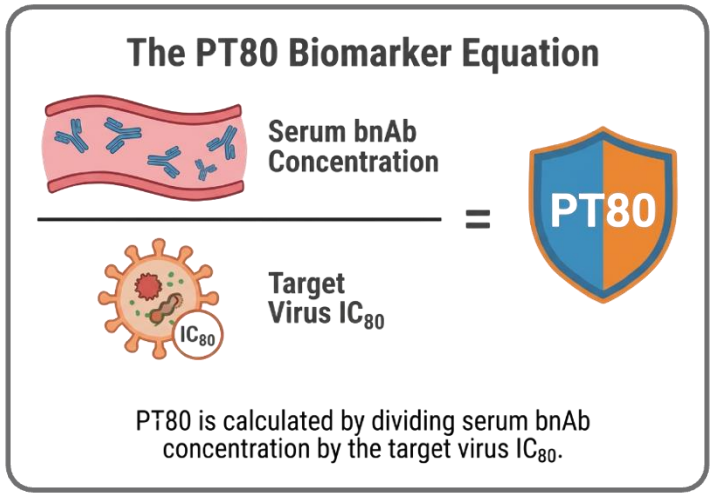
Could a **biomarker** for *in vivo* bNAb protection be determined?

Factors that determine level of protection





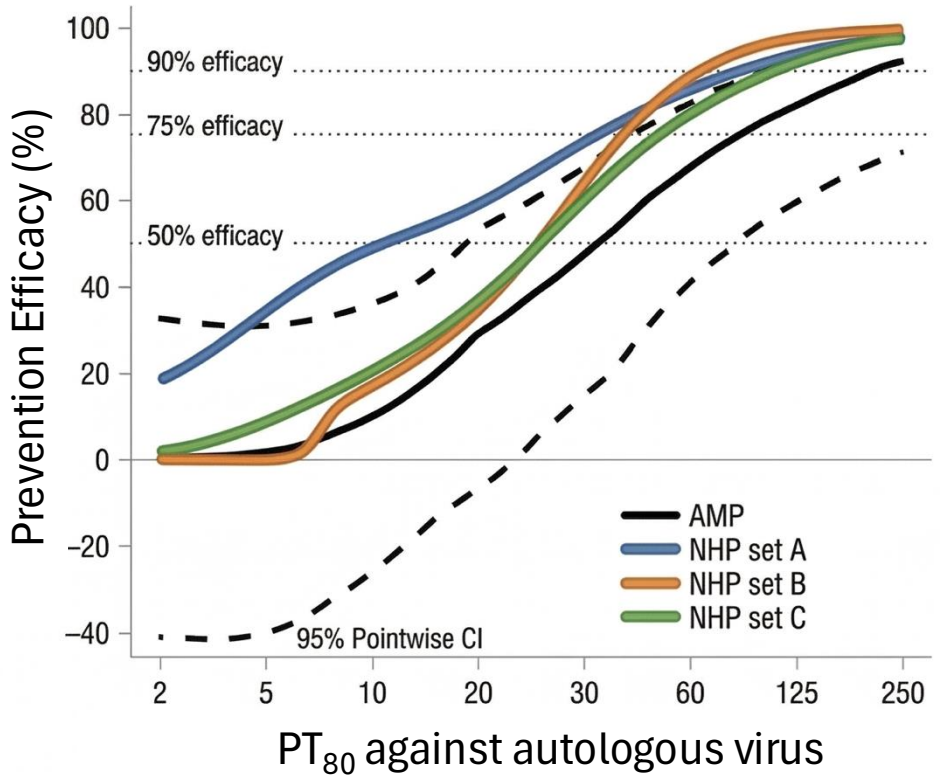
PT_{80}: Biomarker of Protection



What does it mean?

How many times above its IC80 a bNAb's serum concentration needs to be to achieve a defined level of protection

Gilbert *et al.* established the PT_{80} **biomarker** (predicted serum neutralization 80% inhibitory dilution titer) as a validated correlate of protection for HIV-1 prevention



	AMP	NHP set A	NHP set B	NHP set C
50% PE	32	8	22	22
75% PE	82	32	39	48
90% PE	194	83	63	103

- **PT_{80}:** how many times above its IC80 a bNAb's serum concentration needs to be to achieve a defined level of protection
- **PT_{80} as a correlate of protection:** uninfected VRC01 recipients had 2.9× higher PT_{80}
- **PT_{80} of 200 for 90% efficacy** with VRC01 in AMP
- Similar curves seen in NHP studies

Is this generally transferrable? OR VRC01 specific?

bNAbs differ in:

1. Mechanism of neutralization
2. Half-life
3. Biodistribution
4. Fc-mediated effector functions

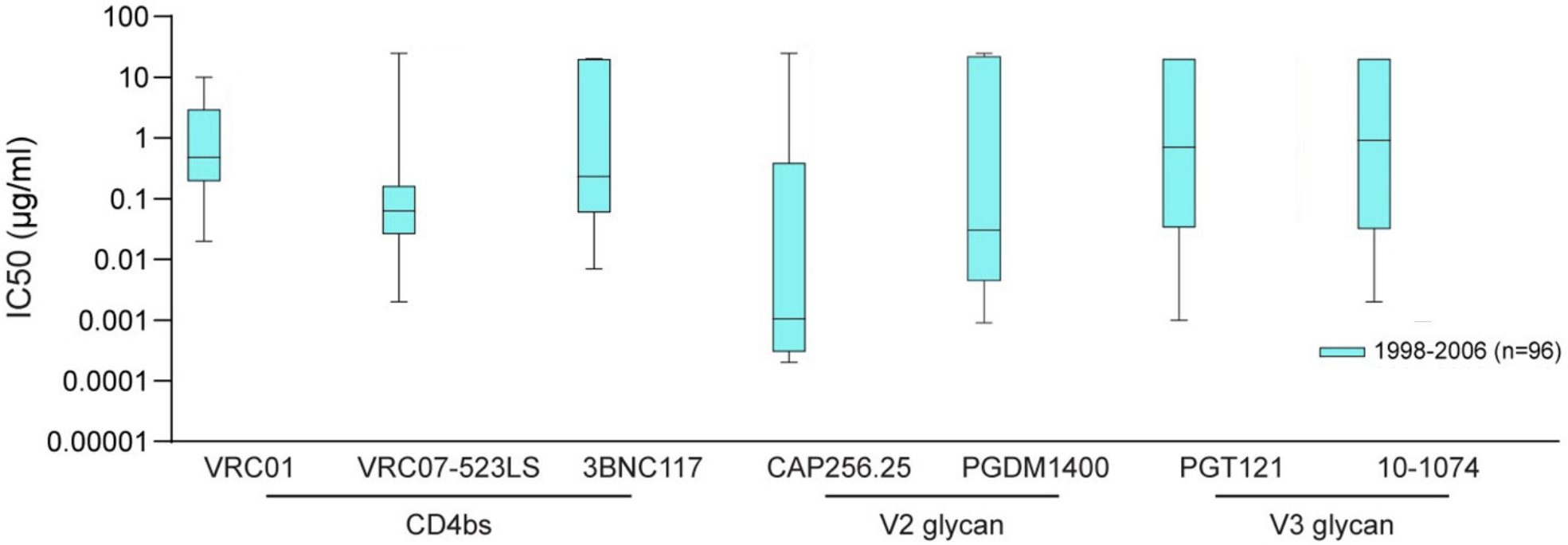
And what about bNAb combinations?

Gilbert *et al.*, Nat Med, 2022

Part 2: Do we need to be concerned by evolving resistance?

HIV-1 is measurably evolving to be less sensitive to neutralization

Increasing bNAb Resistance (more bNAb needed)



Bouvin-Pley *et al.* 2014, Rademeyer *et al.* 2016; Mkhize *et al.*, 2023, Sutar *et al.*, 2025

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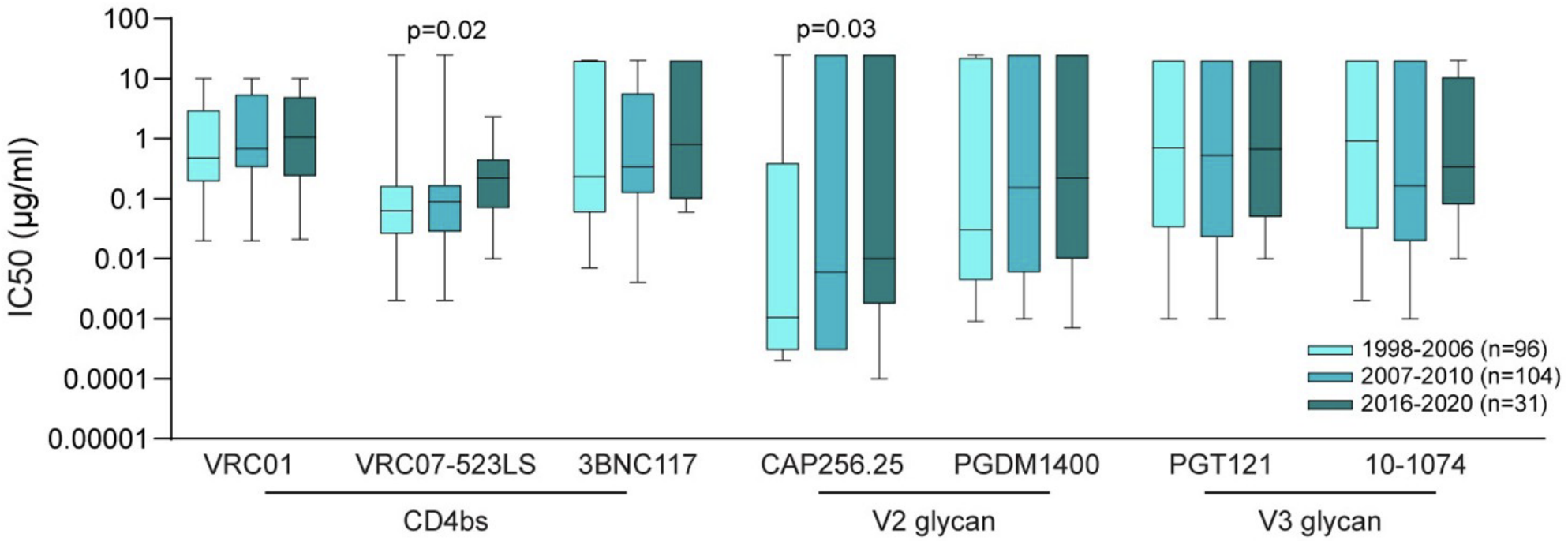
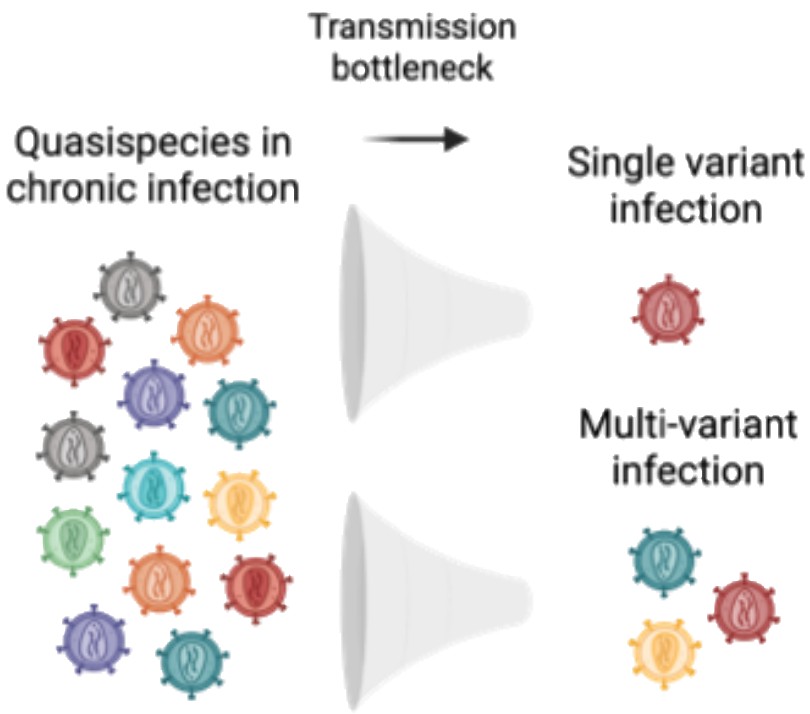


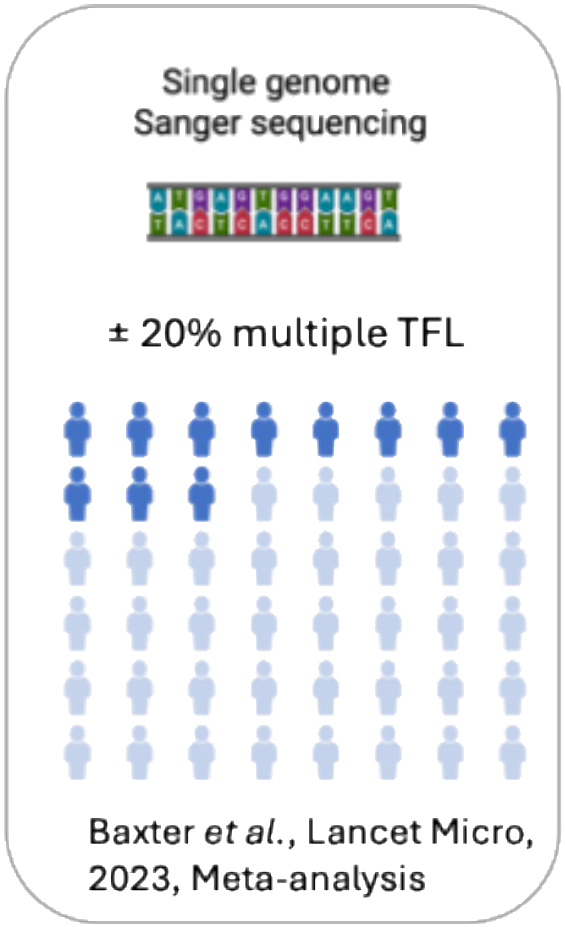
The AMP viruses are getting “old” -
How often will we need to assess this to keep up with the virus?

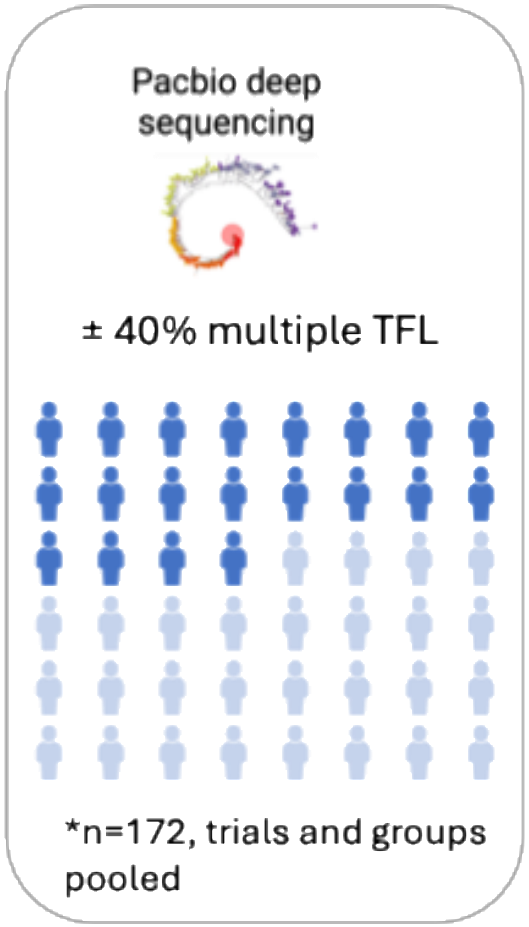
Bouvin-Pley *et al.* 2014, Rademeyer *et al.* 2016; Mkhize *et al.*, 2023, Sutar *et al.*, 2025

Frequency of multi-variant transmission is higher than previously thought



*no difference between VRC01 and placebo groups, or between trials

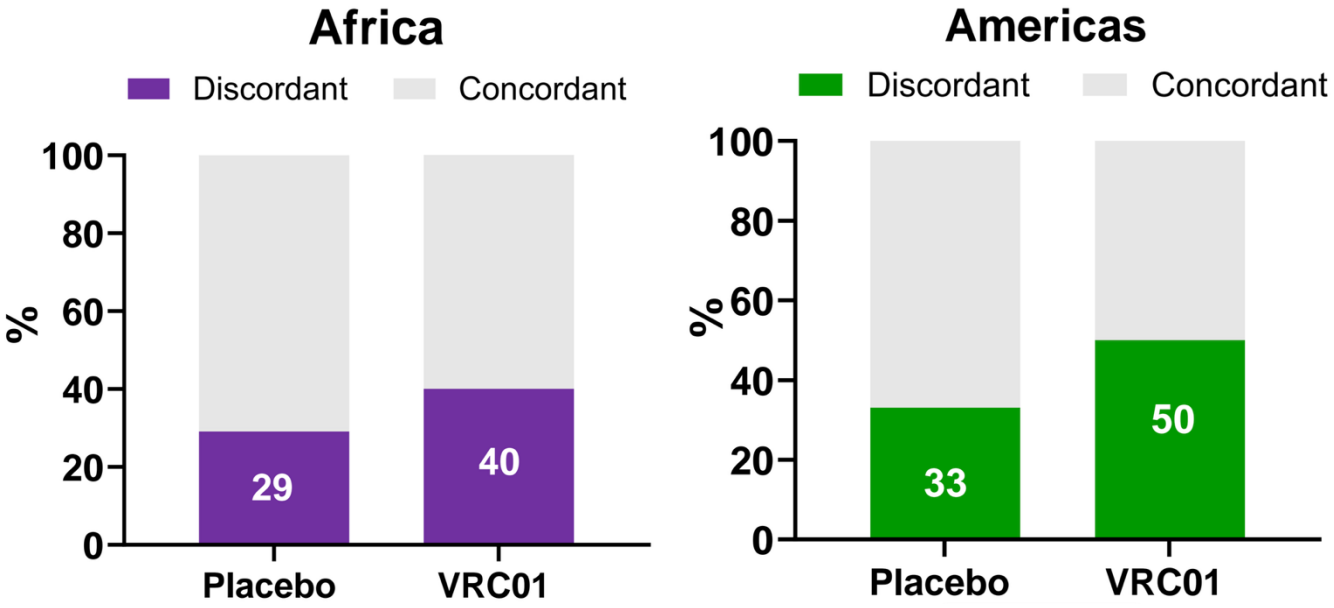




Mullins *et al.*, In press, 2026

Transmitted founder lineages were phenotypically discordant

VRC01 discordant: >3-fold difference in VRC01 IC_{80} titers (up to >100 fold different)



Key findings:

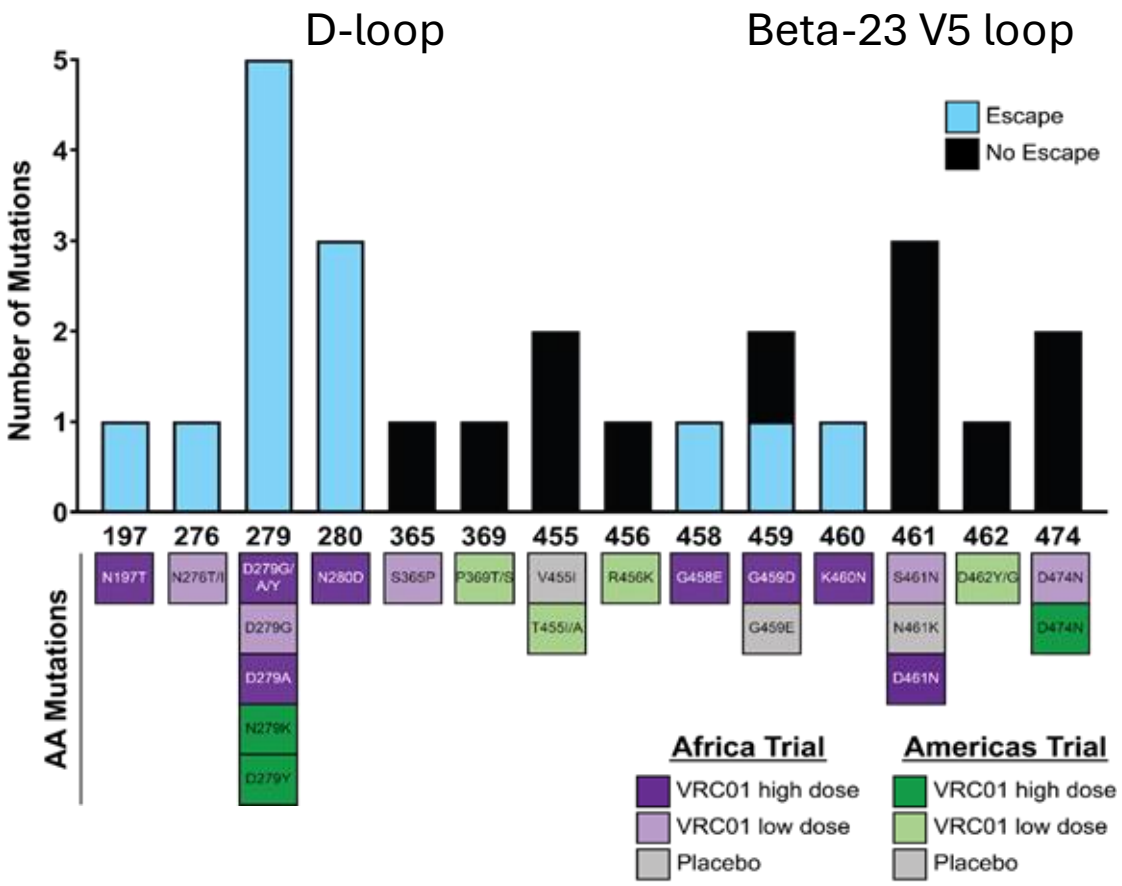
- Overall, 40% of multilineage infections had a VRC01 discordant phenotype
- Greater intra-host neutralization differences with increasing VRC01 dose (Jonckheere-Terpstra test, p=0.072)
- Frequency of VRC01-sensitive lineages decreased over time in treatment group

This expands our understanding of the breadth of viral variants that must be blocked to prevent infection

Williamson *et al.*, BioRXiv, 2025

Sensitive transmitted viruses evolved resistance to VRC01 monotherapy

Escape was identified in 8/26 VRC01 participants but none of 21 placebo participants



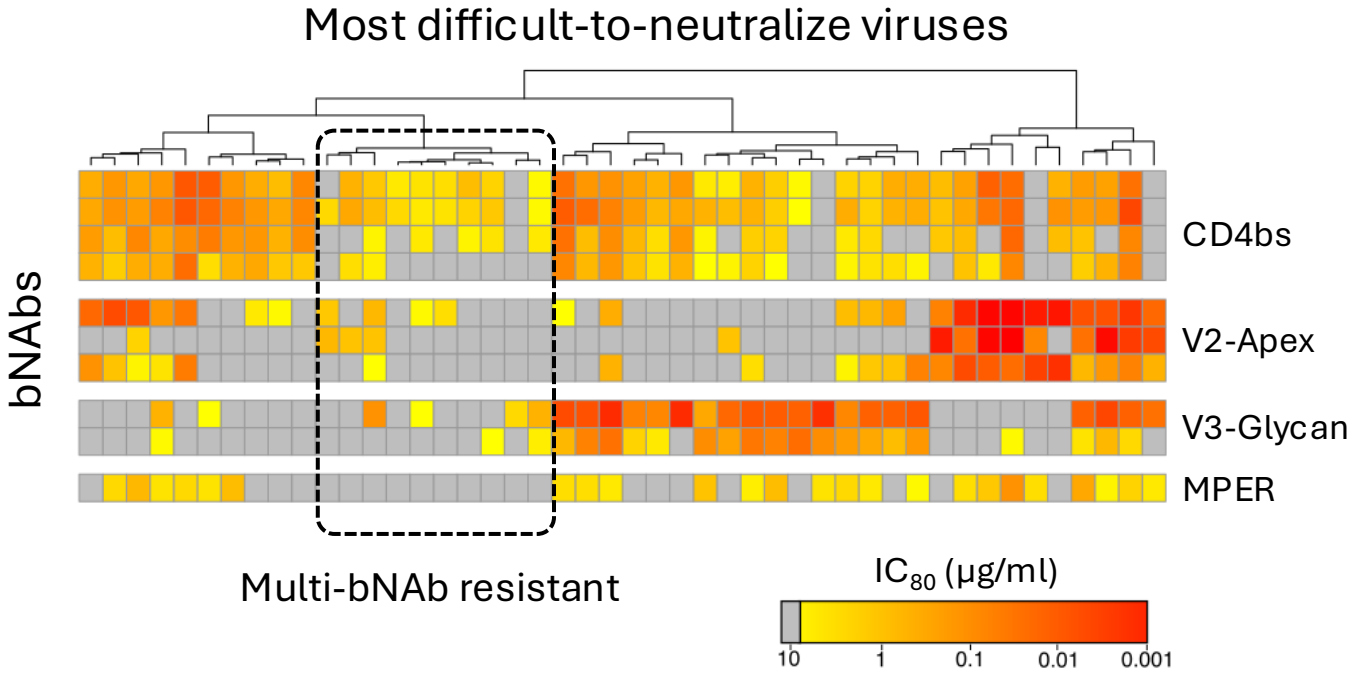
Key findings:

- Subset of participants with VRC01-sensitive single variant transmission
- Evidence for VRC01 resistance selection in treatment arm
- Mutations conferred resistance to other CD4bs-directed bNAbs

Williamson *et al.*, BioRXiv, 2025

Could circulating multi-bNAb resistant viruses pose a challenge to a vaccine?

Multi-bNAb resistant viruses observed in African virus surveillance program



IAVI-ADVANCE Study:

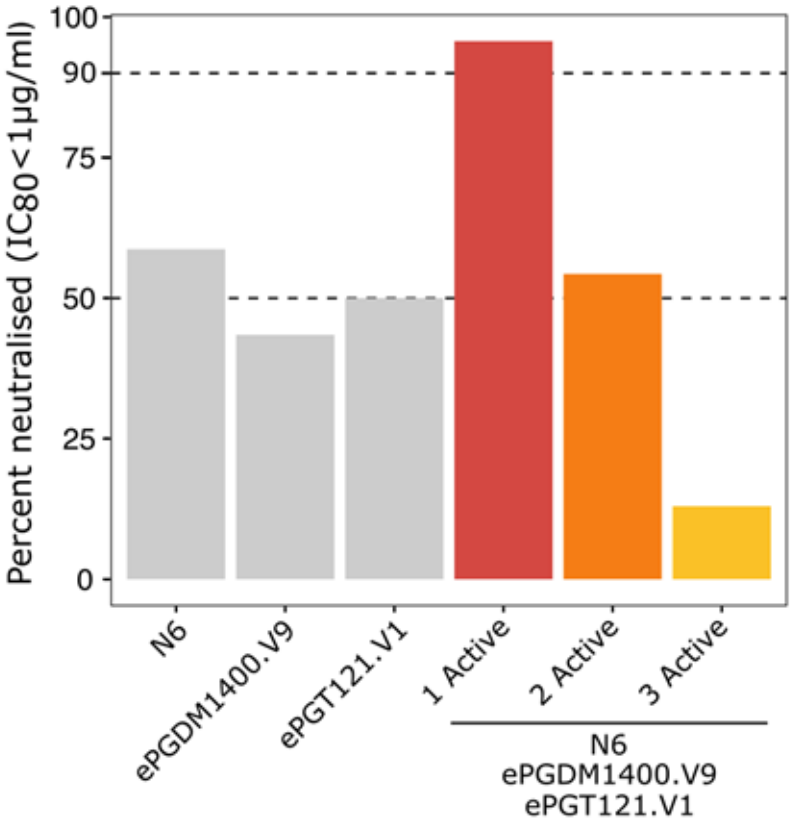
- Viruses from Southern and East Africa (n=192)
- Early infection: sampled within 100 dpi
- Diverse subtypes (A1, A1C, A1D, C & D)

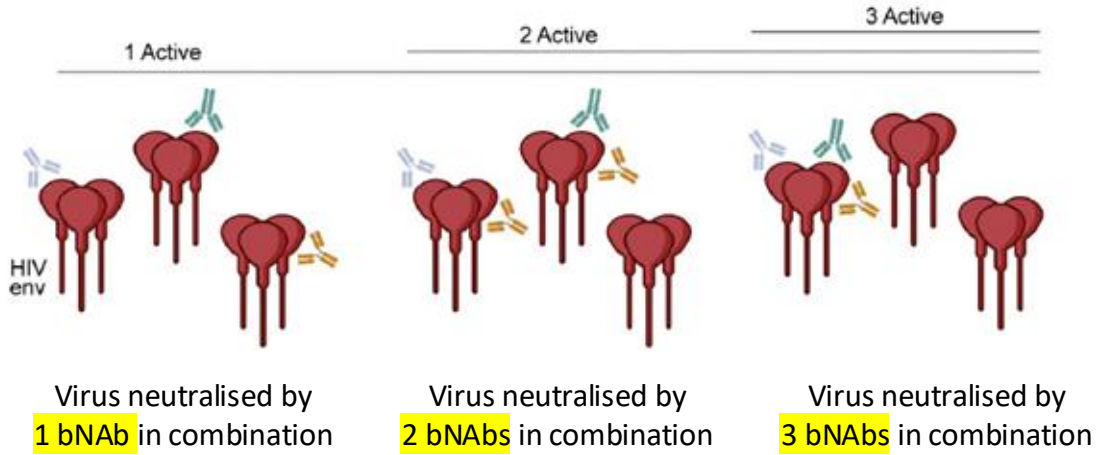
Note: We did not observe any isolates that showed resistance across all bNAb epitope specificities

Kitchin *et al.*, Unpublished

Achieving good coverage challenging for these viruses

All subtypes
(10 most difficult-to-neutralize viruses per subtype)





Virus neutralised by 1 bNAb in combination

Virus neutralised by 2 bNAbs in combination

Virus neutralised by 3 bNAbs in combination

- IC80 < 1 µg/ml as cutoff for neutralisation
- N6, ePGDM1400.V9 & ePGT121.V1 combo predicted to be most efficacious overall
- Will low coverage by >1 bNAb lead to emergence of resistance mutations?

Kitchin *et al.*, Unpublished

Summary:

- PT_{80} established as a correlate of bNAb protection

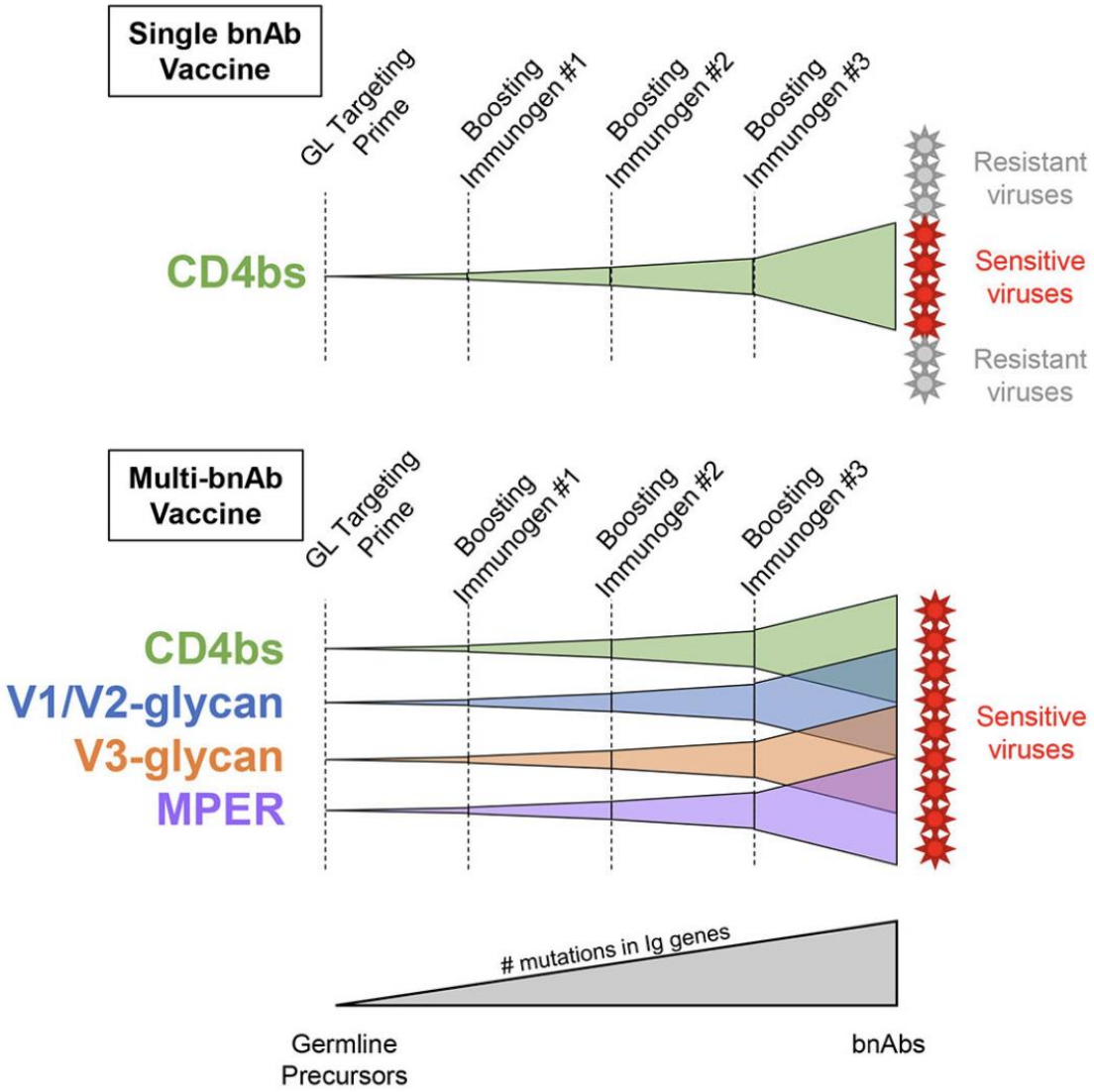
  Vaccine will need to elicit potent, durable responses

- Transmission bottleneck is genetically and phenotypically diverse.

  A vaccine needs to cover the full spectrum of TF populations

- Circulation of multi-bNAb resistant viruses

  Vaccine will need to elicit multiple classes of bNAbs to ensure coverage



Cain *et al.*, Curr. Opin. Virol., 2021

Acknowledgements

SAMRC Antibody Immunity Research Unit

Collaborators, clinical teams and participants

Terminated recently