Broadly neutralizing antibodies for HIV prevention: HPTN/HVTN/VRC/IAVI collaboration

Nirupama Sista, PhD, HPTN Regional Meeting, Lima, Peru

October 5, 2024

Outline

- Additional prevention tools
- Proof of concept for bnAbs
- Long-acting bnAbs and combination
- Status of current and completed HPTN/HVTN studies
- Phase 2 HVTN 206/HPTN 114 study
- Next Steps

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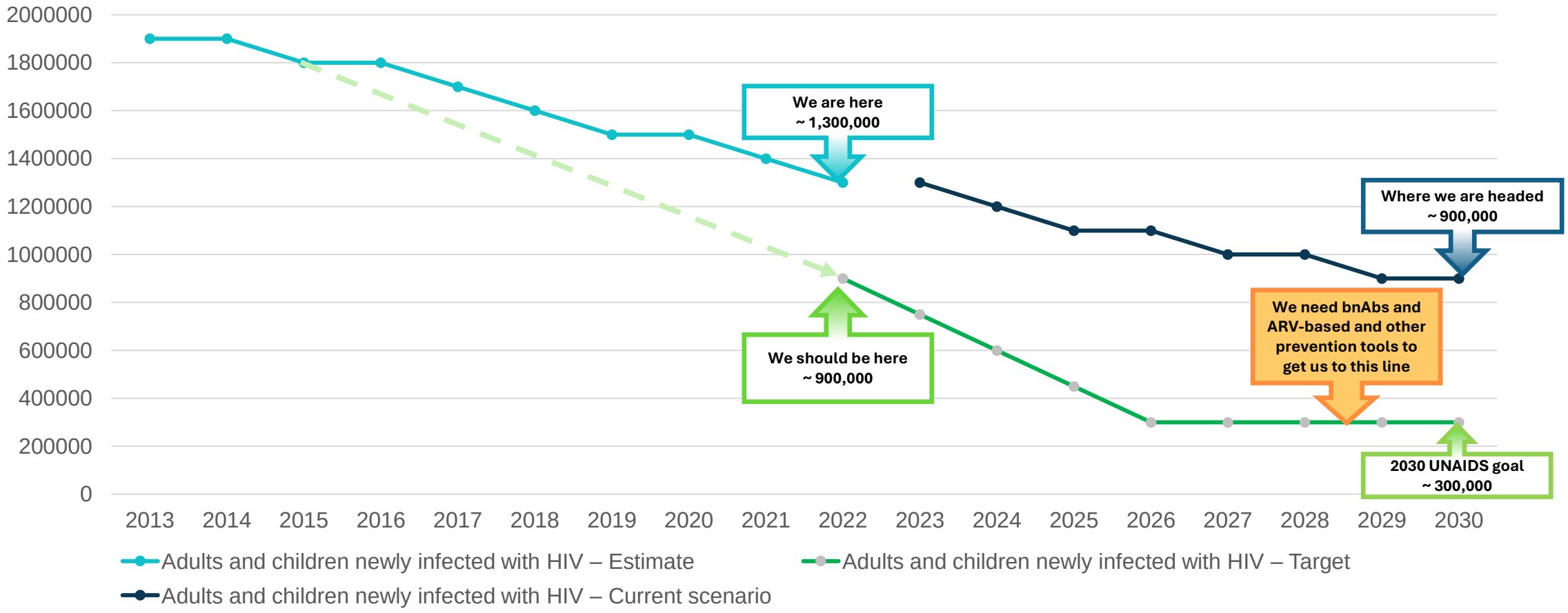
New HIV Diagnoses (Incidence) Not on Track for 2030 UNAIDS Goals



https://www.unaids.org/en/resources/fact-sheet

What is a BROADLY Neutralizing Antibody?

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Monoclonal Antibodies

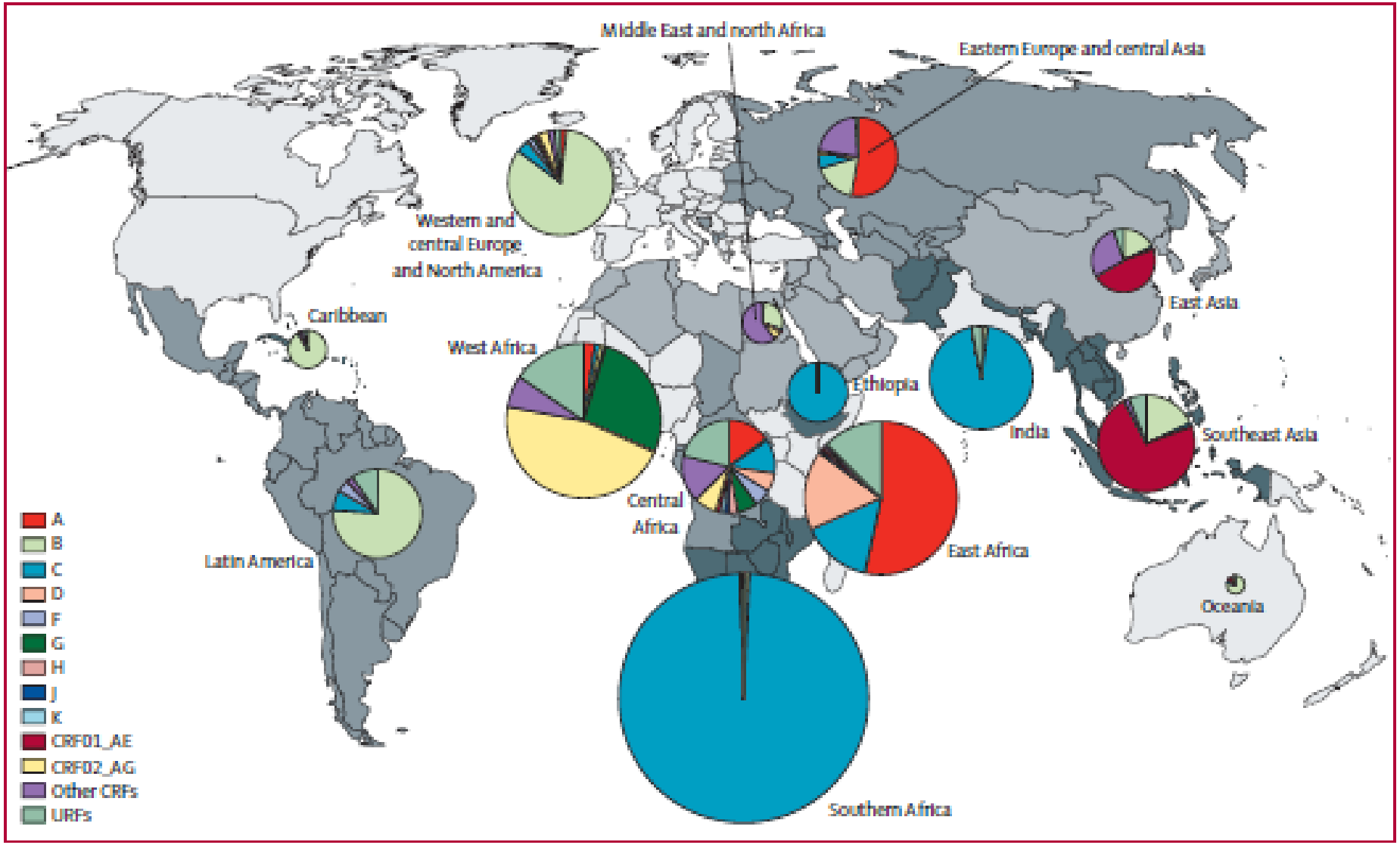
A copy (clone) of 1 (mono) single antibody that has been manufactured in a laboratory

“bnAb”

An antibody whose function is to neutralize (block) a lot of different global strains of HIV (broad/breadth)

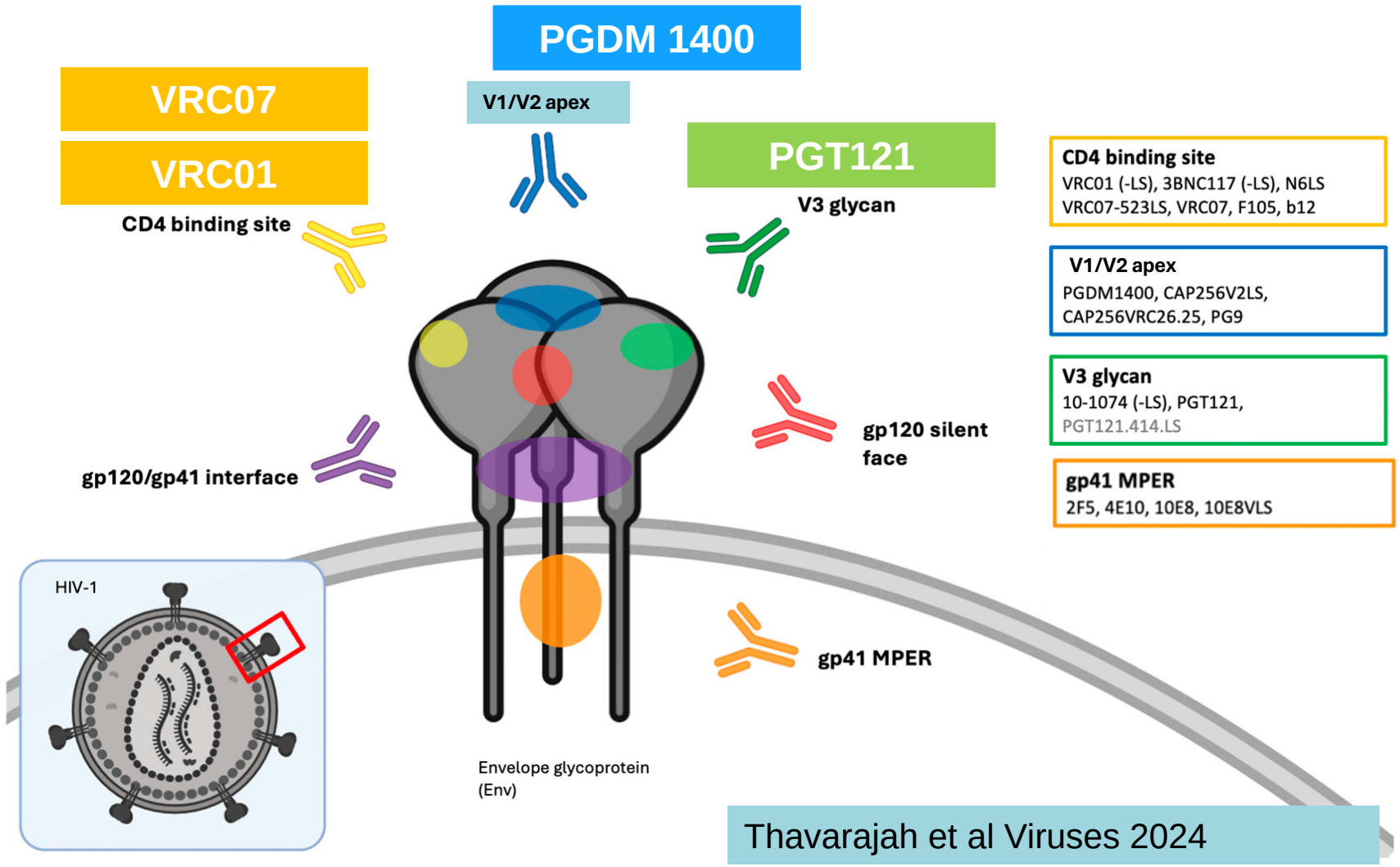
And why is this important for HIV prevention?

HIV-1 Diversity Worldwide



Hemelaar et al. Lancet Infect Dis 2019; 19:143–55

bnAbs in Clinical Development



Thavarajah et al Viruses 2024

AMP: Proof of concept for bnAbs for HIV Prevention

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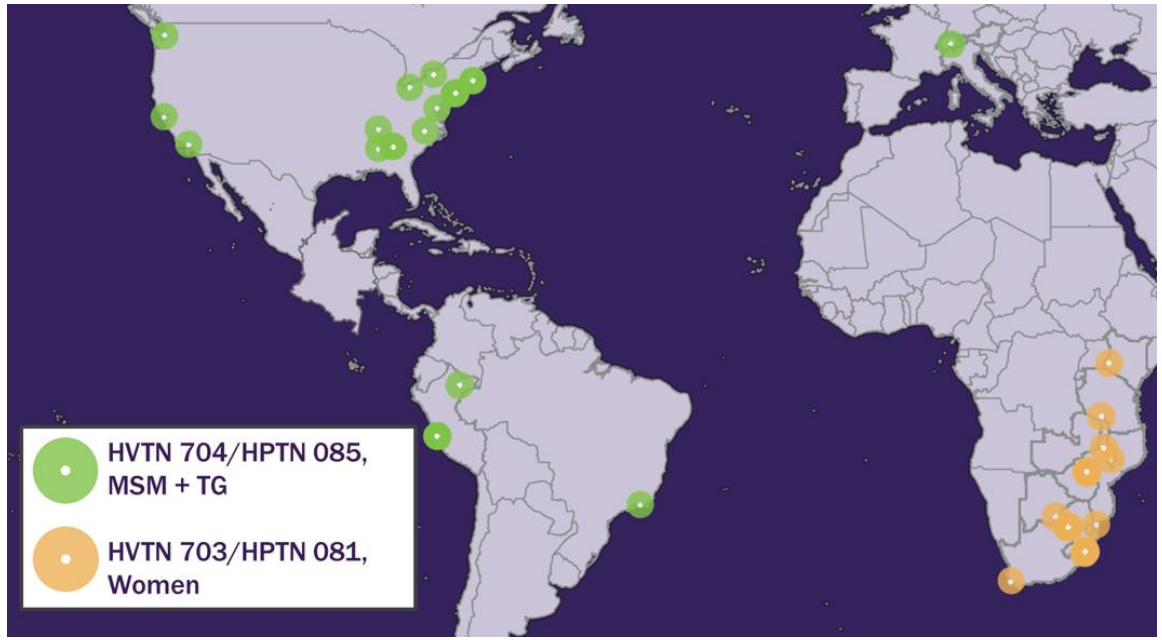
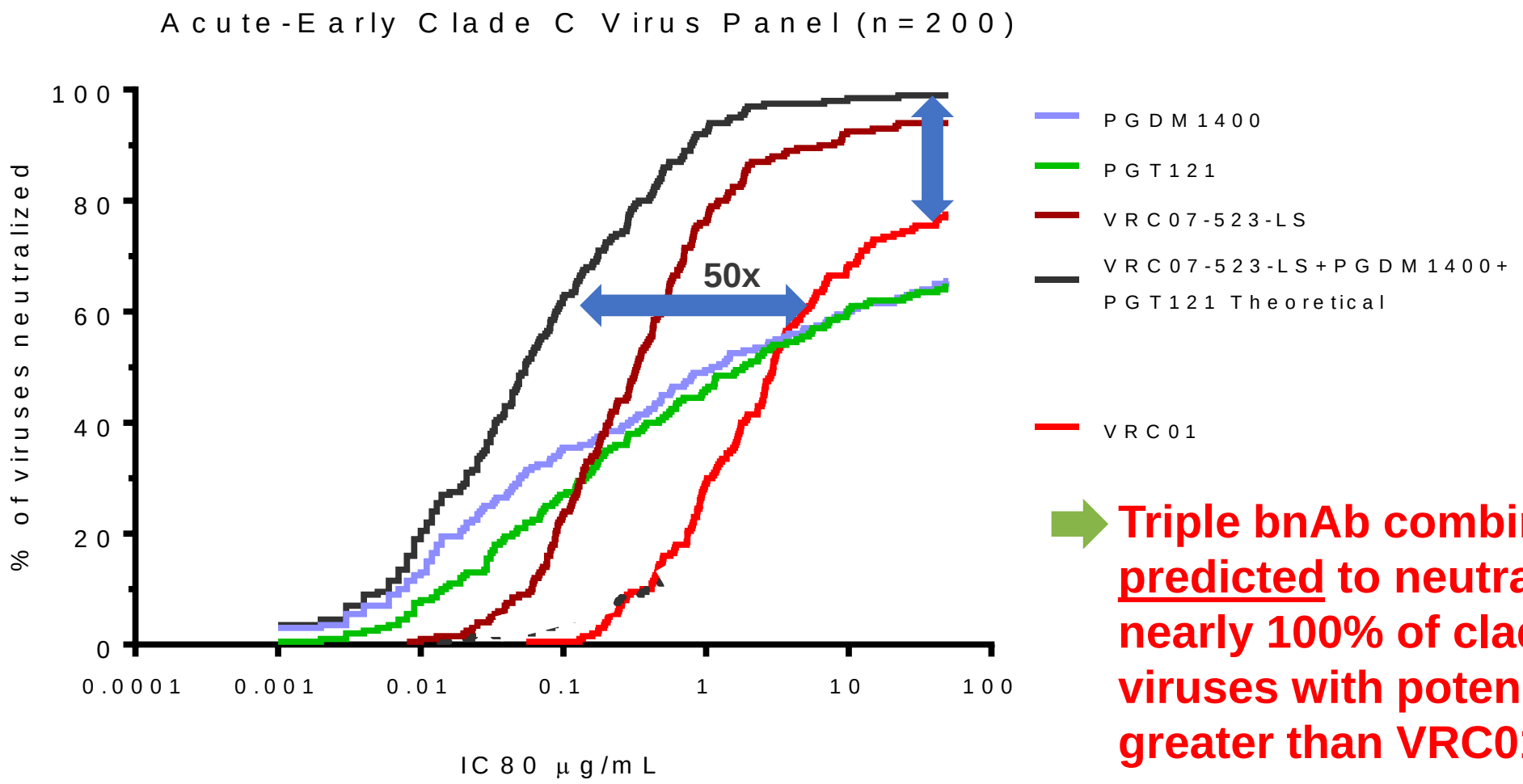
- VRC01 protected only against acquisition of highly neutralization-sensitive viruses
- VRC01 was safe and well tolerated
  - Most participants had no solicited AEs
  - AE rates saline placebo ~ active product
- Large scale IV administration is possible in Africa & Americas
  - Enrollment: 4,625 participants
  - Retention: 95% of 97,458 visits
  - Adherence: 99% of 41,116 infusions



- Neutralization assay is helpful to identify correlates of protection and could be used
- Data and modeling suggested that PK targets along with IC80 (PT80) may predict 90%PE
- A single monoclonal antibody is not sufficient for HIV prevention

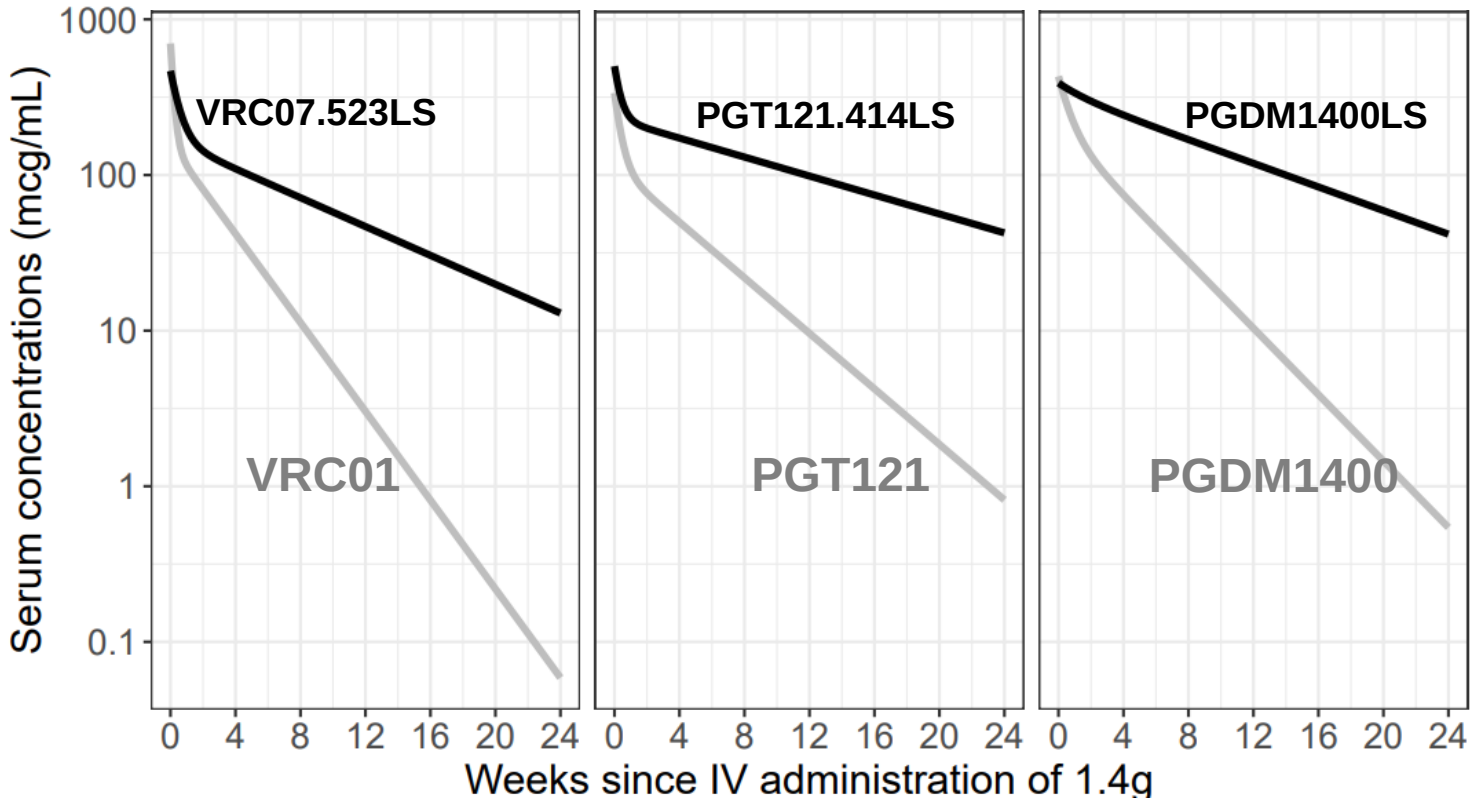
Improved Breadth and Potency of a Triple bnAb Combination



Triple bnAb combination is predicted to neutralize nearly 100% of clade C viruses with potency ~50x greater than VRC01.

LS Mutations Extend bNAb Half-Life

LS mutations in Fc extends serum half-life of bNAbs from ~20 to ~70 days and supports dosing every 6 months for HIV-1 prevention



Mayer et.al. 2024. Pharmaceutics 16, 594

Proposed Combination of 3 bnAbs gives the most potent and broadest in-vitro neutralization

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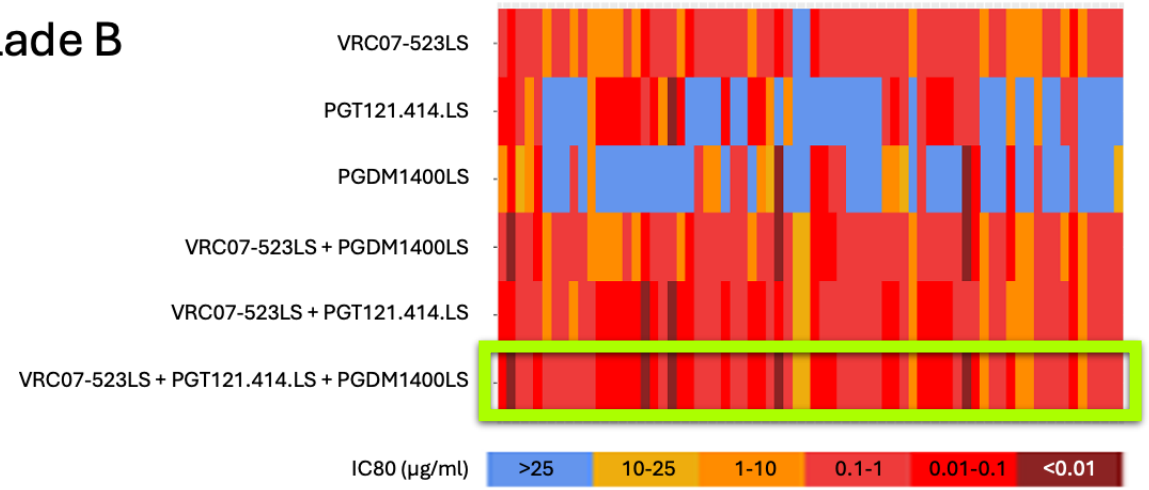
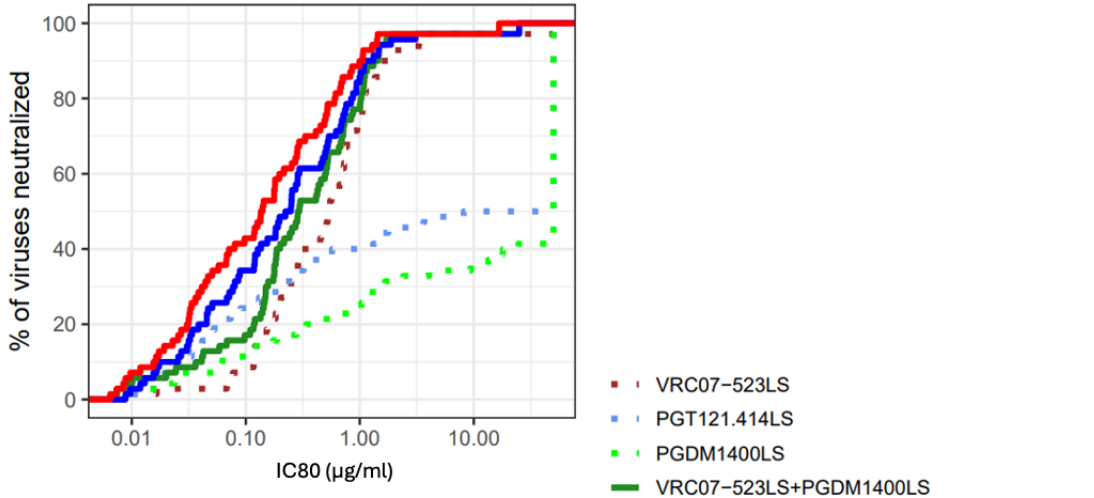
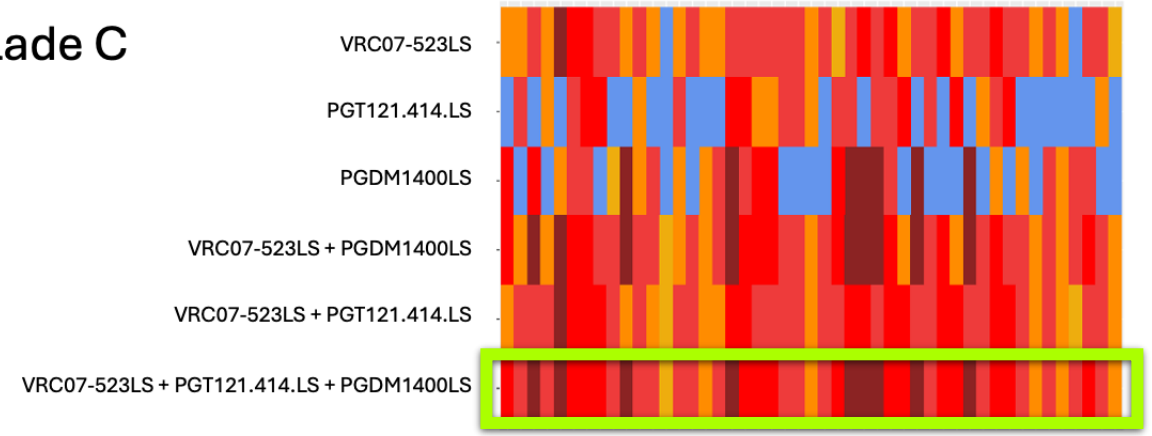
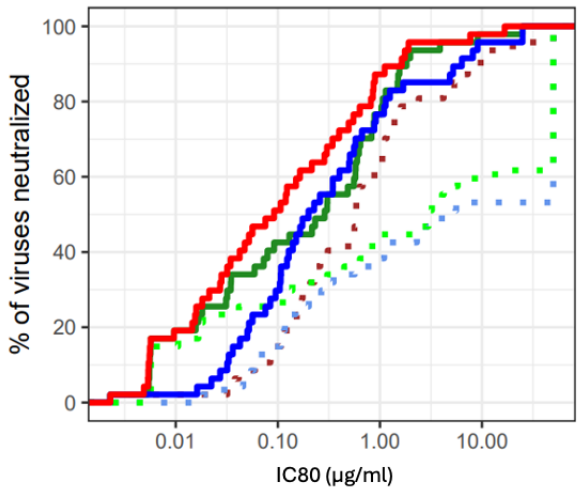
HIV-1 clade B





HIV-1 clade C





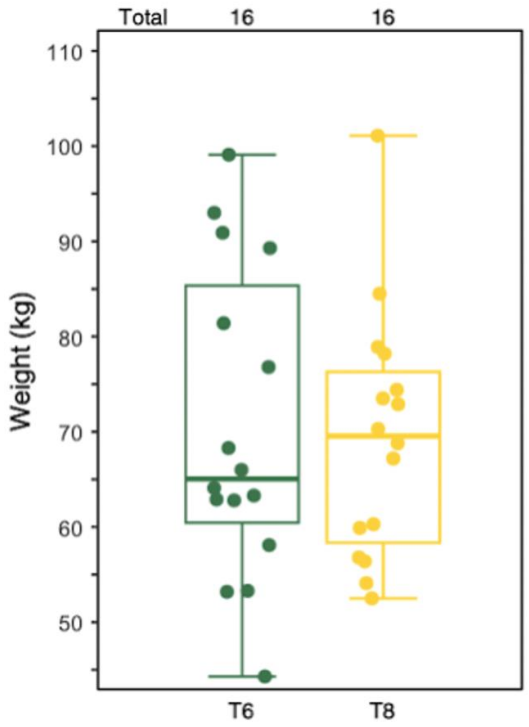
David Montefiori

Safety of Study Products

VRC07-523LS, PGT121.414.LS and PGDM1400LS have had an excellent safety profile for IV infusions

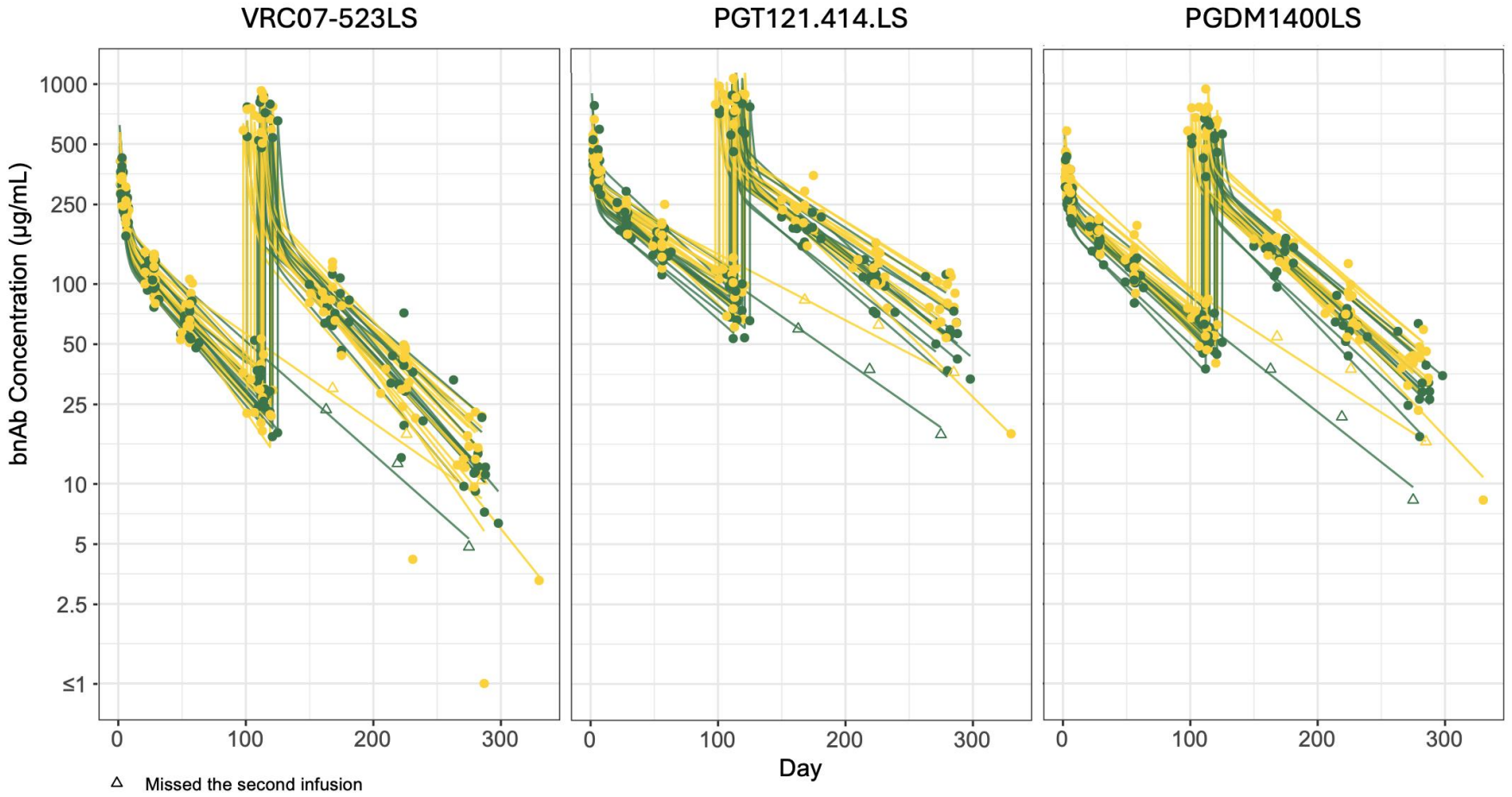
- No related SAEs
- No study safety pauses for AEs
- Product administrations have been relatively well-tolerated

Weight-based and Fixed Dosing PK is Similar



T6: VRC07-523LS + PGT121.414.LS + PGDM1400LS 20 mg/kg each, IV (weight based)

T8: VRC07-523LS + PGT121.414.LS + PGDM1400LS 1400 mg each, IV (fixed dose)



HVTN 140/HPTN 101

HVTN/HPTN completed 6 Phase 1 HIV bnAb trials since start AMP

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	LS versions with extended half-life for dosing Q6M			Combinations of 2 or 3 bnAbs for increased Prevention Efficacy		
Study	**HVTN 116**	**HVTN 127 / HPTN 087**	**HVTN 128**	**HVTN 130 / HPTN 089**	**HVTN 136 / HPTN 092**	**HVTN 140 / HPTN 101**
Products	**VRC01, VRC01LS**	**VRC07-523LS**	**VRC07-523LS**	**VRC07-523LS + PGT121 + PGDM1400**	**VRC07-523LS + PGT121.414.LS**	**VRC07-523LS + PGT121.414.LS + PGDM1400LS**
N = Dose range	**N = 74 10-30 mg/kg**	**N = 120 2.5-20 mg/kg**	**N = 24 10-30 mg/kg**	**N = 27 20 mg/kg**	**N = 33 3-30 mg/kg**	**N = 95 5-40 mg/kg**
Is it **safe**?	Yes	Yes	Yes	Yes	Yes	Yes
Was there **interference** between multiple bnAbs?	NA	NA	NA	No	No	No
Were PK **predictions** accurate?	Yes	Yes	Yes	Yes	Yes	Yes
Do bnAbs retain **neutralizing activity** 6 months after administration?	Yes	Yes	Yes	Yes	Yes	Yes
Do **neutralizing titers** correlate to serum concentrations 6 months after administration?	Yes	Yes	Yes	Yes	Yes	Yes
Where the neutralization **predictions** accurate?	Yes	Yes	Yes	Yes	Yes	Yes
Can we give a **fixed dose**?	NA	NA	NA	NA	NA	Yes
Where there any clinically relevant **ADA**?	No	No	No	No	No	No

HVTN 206 / HPTN 114 phase 2 clinical trial

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Rationale

- More safety data (n=200) for intended combo-AMP combinations VRC07-523LS + PGT121.414.LS + PGDM1400LS 3200 + 1600 + 1600 mg & 400 + 400 + 400 mg before we start combo-AMP efficacy trial

Design

- Multicenter, randomized, double-blind, controlled trial
- Study products are the same as in HVTN 140 / HPTN 101
  - VRC07-523LS (VRC-HIVMAB075-00-AB)
  - PGT121.414.LS
  - PGDM1400LS

- **Study participants**
  - About 200 healthy volunteers without HIV, aged 18 to 65 years
- **Study schema**
  - Both groups will open to enrollment concurrently. Enrollment will be unrestricted
- **Duration per participant**
  - 12 months
- **Study countries**
  - USA, South Africa, Brazil, Peru

HVTN 206/ HPTN 114 study schema

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Study arm	N	Dose*	Route	Month 0	Month 6
Group 1	100	400 mg + 400 mg + 400 mg	IV	VRC07-523LS + PGT121.414.LS + PGDM1400LS	VRC07-523LS + PGT121.414.LS + PGDM1400LS
Group 2	100	3200 mg + 1600 mg + 1600 mg	IV	VRC07-523LS + PGT121.414.LS + PGDM1400LS	VRC07-523LS + PGT121.414.LS + PGDM1400LS
Total	**200**				

IV = intravenous infusion. *Fixed dose regimen based on a mean participant bodyweight of 80kg, comparable in group 1 to 5 mg/kg for each bnAb, and comparable in group 2 to 40 mg/kg for VRC07-523LS, 20 mg/kg for PGT121.414.LS and 20 mg/kg for PGDM1400LS.

Primary objectives and endpoints: Safety

Primary objectives	Primary endpoints
1. To evaluate the **safety** and **tolerability** of VRC07-523LS and PGT121.414.LS and PGDM1400LS when administered via the intravenous (IV) route	• Local and systemic Solicited AEs, laboratory measures of safety, Unsolicited AEs, and SAEs • Early discontinuation of administration and reason(s) for discontinuation and early study termination

Secondary objectives and endpoints

Secondary objectives	Secondary endpoints
1. To evaluate the serum concentrations and **pharmacokinetics** of VRC07-523LS and PGT121.414.LS and PGDM1400LS after each three-mAb administration	• Serum concentrations of VRC07-523LS and PGT121.414.LS and PGDM1400LS at prespecified timepoints among participants who received all scheduled product administrations
2. To evaluate the individual mAb-specific serum **neutralizing activity** of VRC07-523LS and PGT121.414.LS and PGDM1400LS after each three-mAb administration	• Magnitude of serum neutralizing activity measured with mAb-specific Env-pseudotyped viruses in TZM-bl cells at prespecified timepoints among participants who received all scheduled product administrations
3. To determine whether the mAbs maintain their **expected** combined magnitude and breadth of serum neutralizing activity after each 3-mAb administration as **predicted** by the known magnitude and breadth of neutralization of the corresponding mAb combinations	• Magnitude of neutralizing activity against a panel of Env-pseudotyped reference viruses in TZM-bl cells at selected timepoints for all participants in all groups regardless of how many product administrations and how much product they received
4. To determine whether **anti-drug antibodies** (ADA) are present and whether there is a **correlation** among VRC07-523LS and PGT121.414.LS and PGDM1400LS **concentrations** and **ADA titers** in serum samples	• Serum VRC07-523LS and PGT121.414.LS and PGDM1400LS concentrations and ADA titers in each group measured at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

How could bnAbs be a prevention tool?

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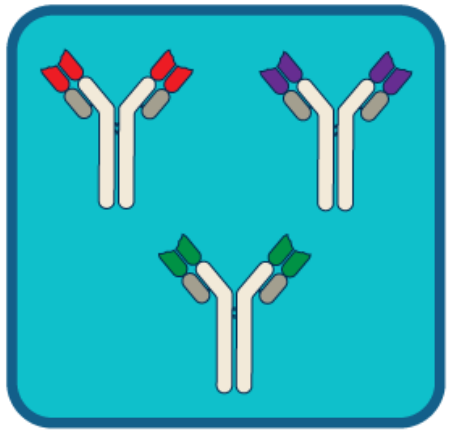
Some <u>possible</u> uses of bnAbs for HIV prevention include:

Protect newborn babies (during & right after birth, during nursing)

Cover the “tail” of long-acting PrEP injections, when the dose of the medication is waning

Cover the ramp-up period of an HIV vaccine that is given in multiple doses over several months to a year

Combine bnAbs + other prevention methods



As an independent prevention tool

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Considerations for the path forward

- Identification of the right combination of bnAbs
  - Breadth
  - Potency
  - Duration
- Greater than 90% efficacy
- Scalability of manufacturing bnAbs
- Affordability and access

Summary

- HPTN/HVTN collaborative studies have identified a potential combination of 3 bnAbs for HIV prevention
- Phase 2 study will evaluate two fixed doses of the combination for safety, tolerability of VRC07-523LS and PGT121.414.LS and PGDM1400LS
- Data from phase 2 study will further inform the bnAb product timeline

Thank you

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- Bonnie Dye

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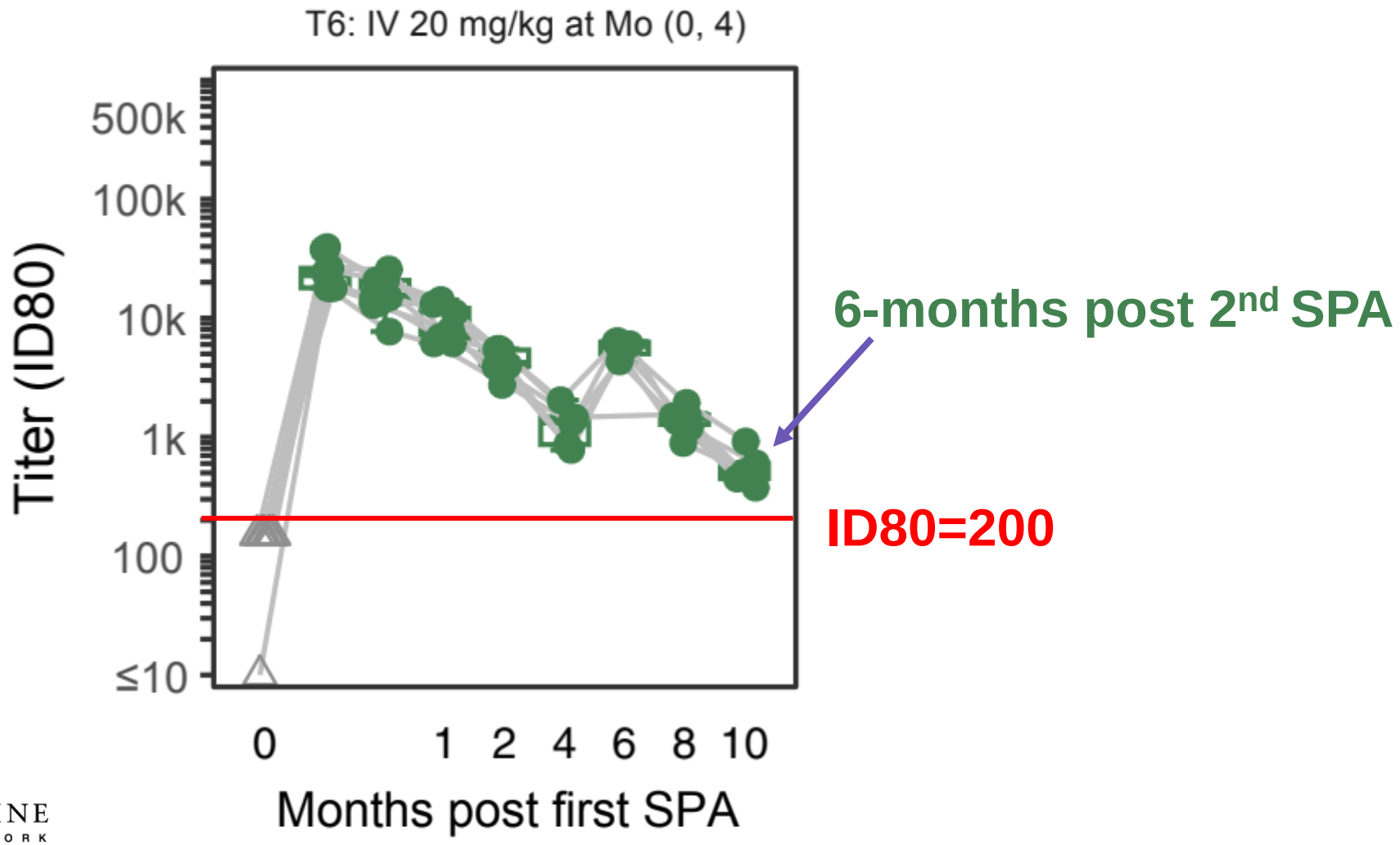
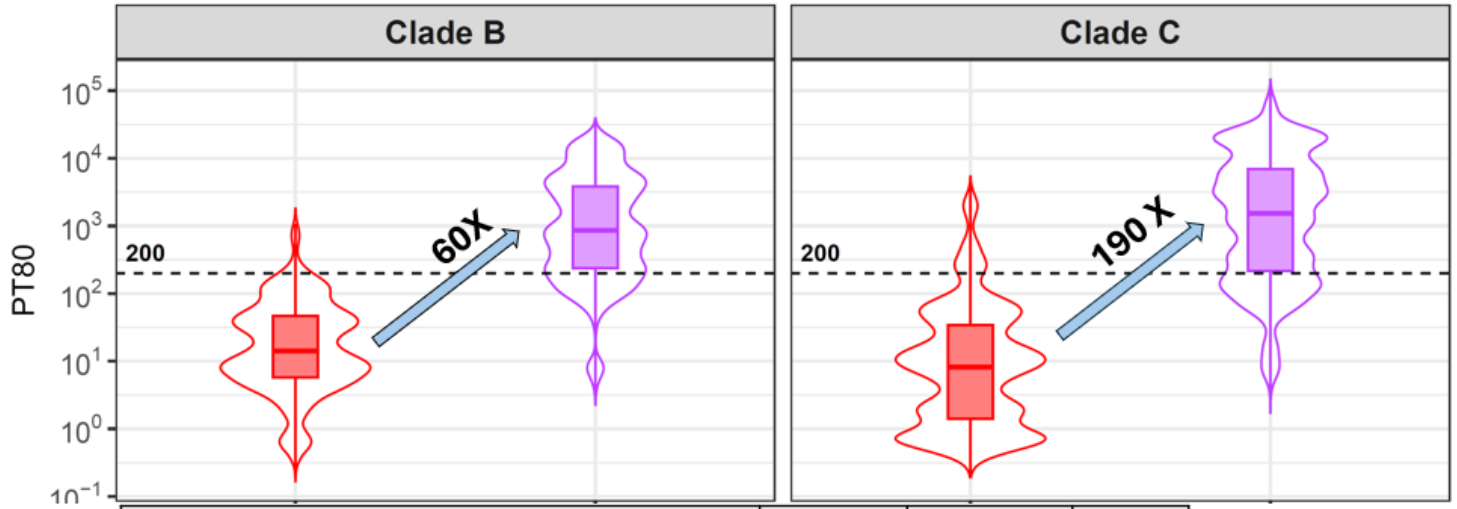
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Observed PGDM1400LS-Specific ID80 Overtime Till 6-months post-2nd Study Product Administration (SPA)



HIV VACCINE TRIALS NETWORK

Time-averaged (median) PT80 across individuals and viruses



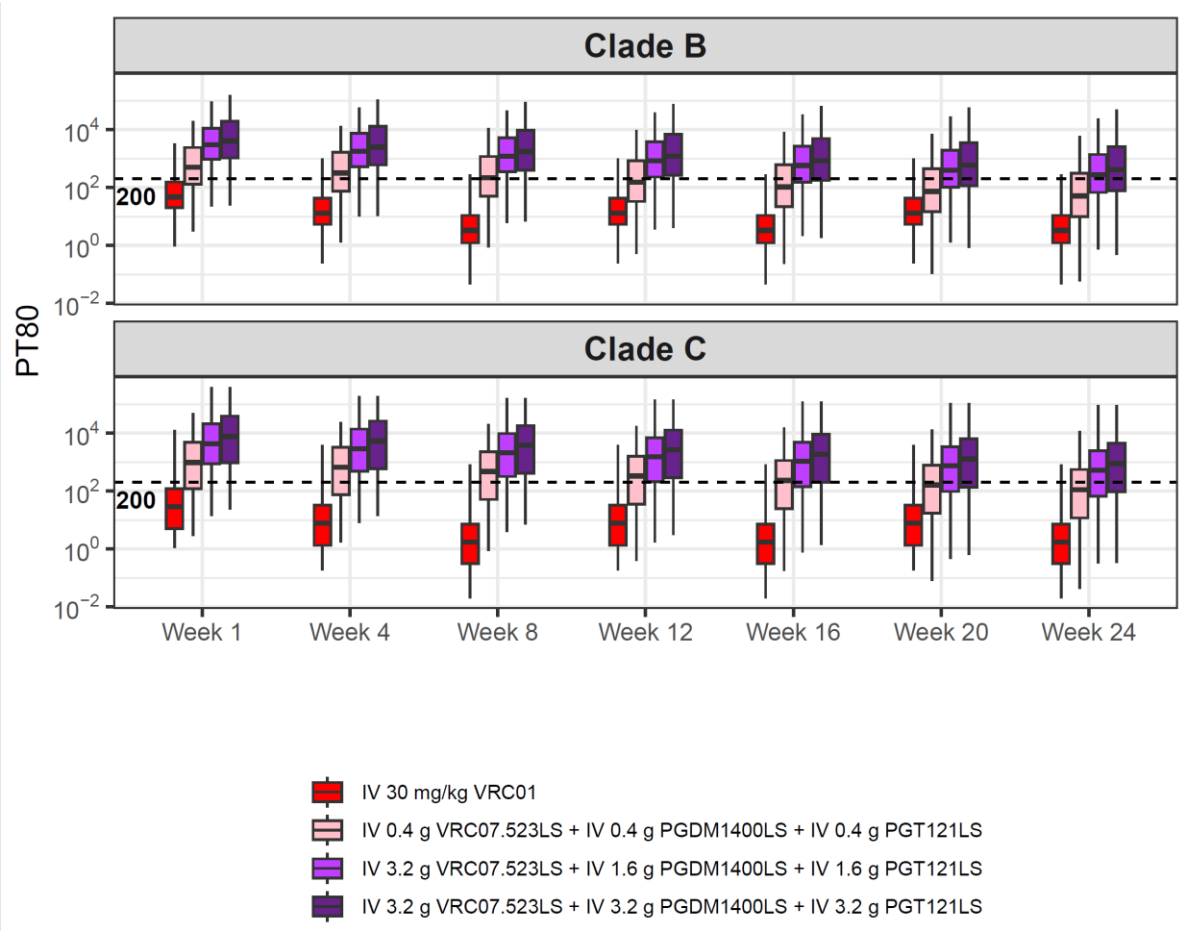
Drug	Clade	% PT80 > 200	Median PT80
IV 30 mg/kg VRC01	Clade B	3%	14
IV 30 mg/kg VRC01	Clade C	7%	8
IV 3.2 g VRC07.523LS + IV 1.6 g PGDM1400LS + IV 1.6 g PGT121LS	Clade B	79%	856
IV 3.2 g VRC07.523LS + IV 1.6 g PGDM1400LS + IV 1.6 g PGT121LS	Clade C	76%	1537

IV 30 mg/kg VRC01

IV 3.2 g VRC07.523LS + IV 1.6 g PGDM1400LS + IV 1.6 g PGT121LS

Data from HVTN 140 / HPTN 101, HVTN 136 / HPTN 092, HVTN 703 / HPTN 081 (AMP) and HVTN 704 / HPTN 085 (A

combination every 6 months vs VRC01 every 2 months against contemporary viruses



Data from HVTN 140 / HPTN 101, HVTN 136 / HPTN 092, HVTN 703 / HPTN 081 (AMP) and HVTN 704 / HPTN 085 (A

Triple-bnAb combination predicted PT80 efficacy compared to single bnAb in AMP