Broadly Neutralizing Antibodies (bNAbs) at the Crossroads: What Lies Ahead?

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Disclosures

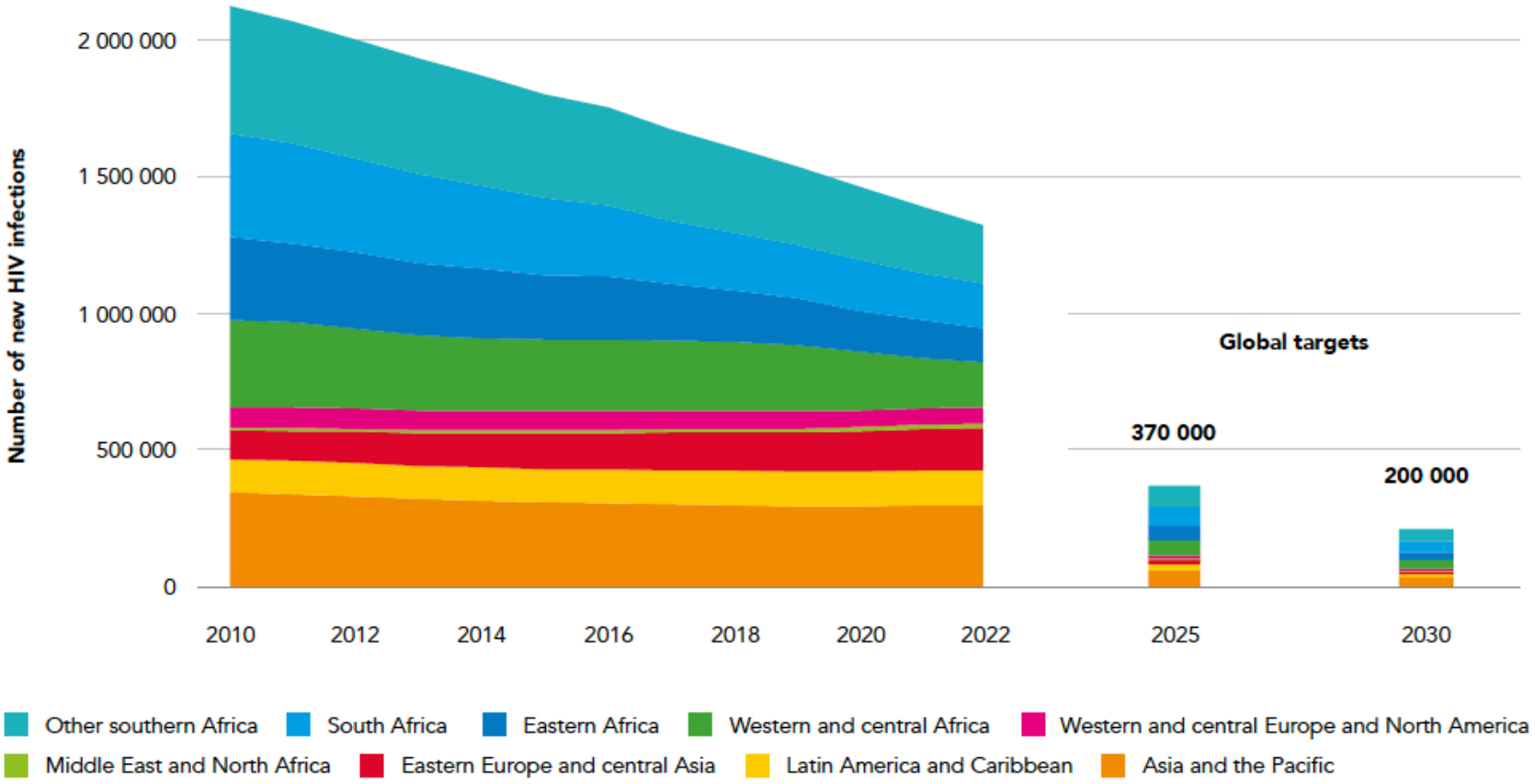
- **Grants to Institution (vaccines, antibodies, virology, immunology, HIV, TB, Zika, COVID-19, yellow fever, influenza):**
  - **BARDA, DARPA, Gates Foundation, Henry Jackson Foundation, MassCPR, NCI, NIAID, Ragon Institute, South Africa MRC, WRAIR**
  - **Alkermes, CureVac, Gilead, Gritstone, GSK, Hookipa, Intima, Janssen, Legend, Leyden Labs, Musk Foundation, Novavax, Pfizer, Pharm-Olam, Sanofi, Zentalis**

- **Consulting (vaccines, virology):**
  - **Avidea, Celsion/Imunon (equity), Laronde, Meissa, SQZ, Sterne Kessler, Vector Sciences (founder/equity)**

Summary

- Antibodies can be combined into a cocktail that covers most global HIV-1 strains
- Long-acting antibodies can be administered every six months
- HVTN, HPTN, and partners are advancing a triple antibody cocktail for HIV-1 prevention

Limited Progress in Global HIV-1 Prevention

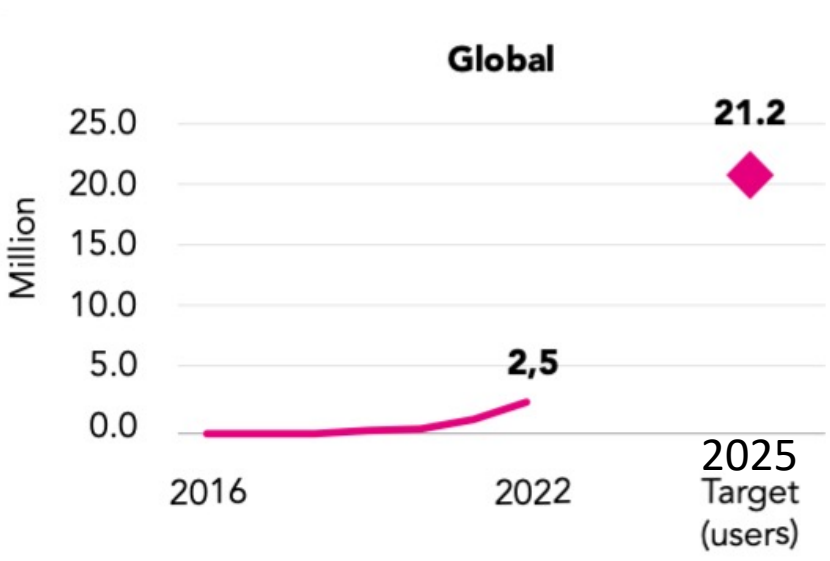


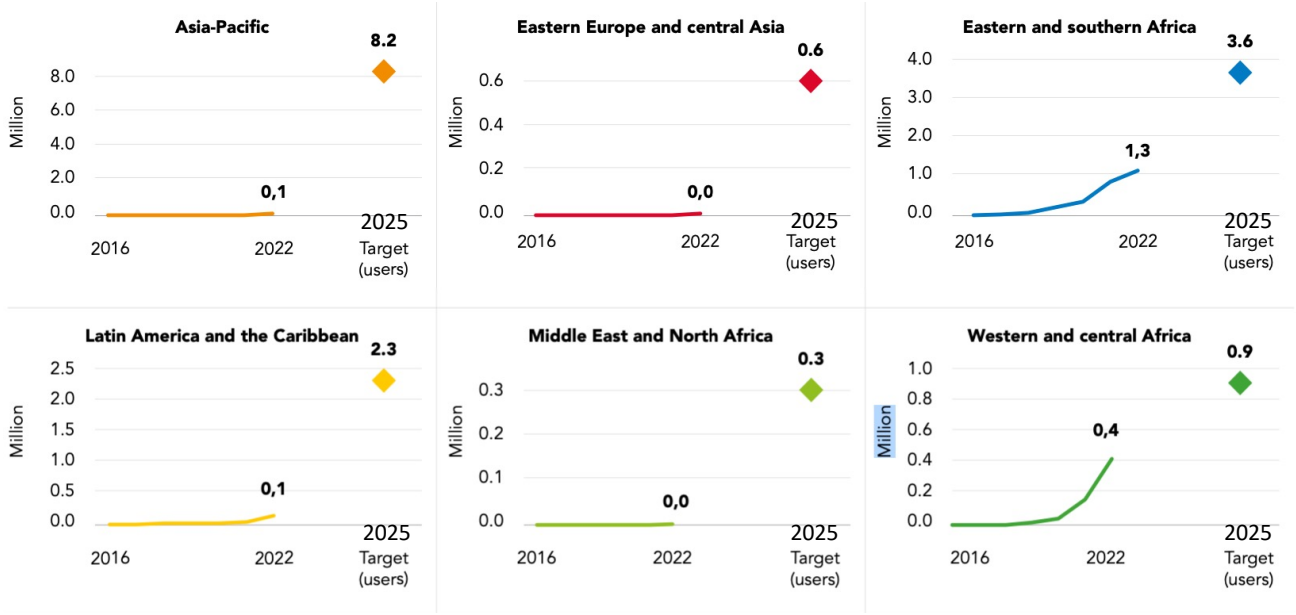
2022 New HIV-1 infections: 1,300,000
2022 HIV-1 deaths: 630,000

UNAIDS

Source: Prepared based on 2023 prevention scorecards and Global AIDS Monitoring https://www.unaids.org/sites/default/files/media_asset/2023-global-hiv-prevention-coalition-scorecards-key-findings_en.pdf

PrEP Use Relative to 2025 UNAIDS Targets: Need for Additional HIV-1 Prevention Options



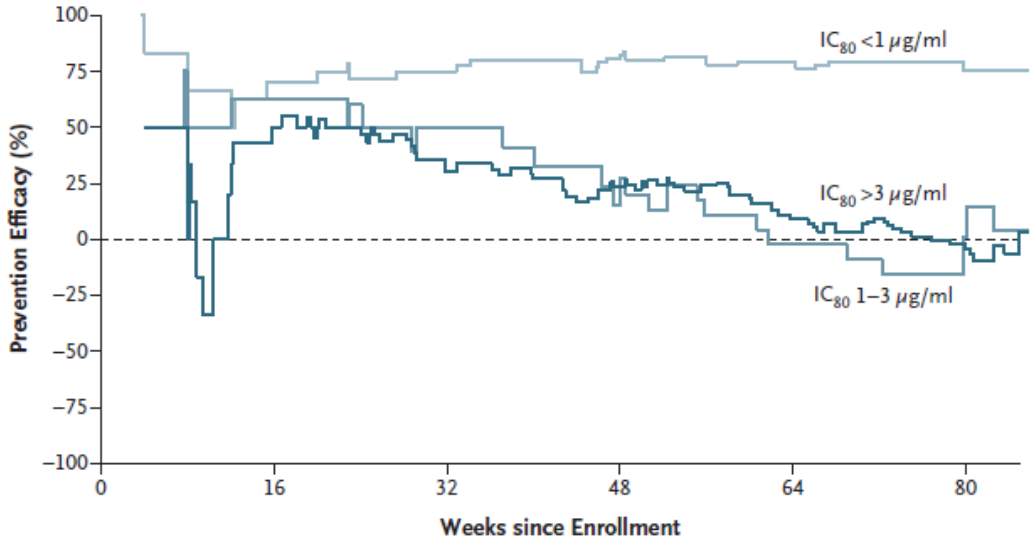


Source: Prepared based on 2023 prevention scorecards and Global AIDS Monitoring https://www.unaids.org/sites/default/files/media_asset/2023-global-hiv-prevention-coalition-scorecards-key-findings_en.pdf

Proof of Concept: VRC01 Antibody HIV-1 Prevention (AMP)

Outstanding Safety, Tolerability, Adherence, Acceptance, Efficacy

A

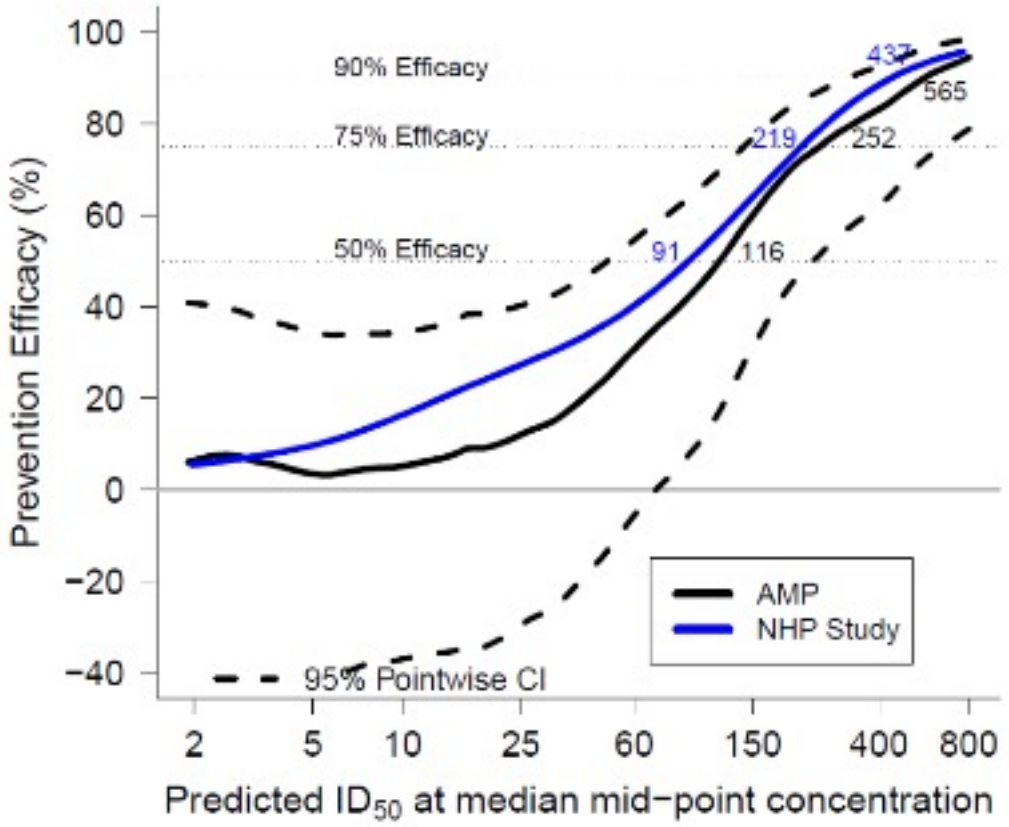


B

Prespecified IC_{80} Category and Treatment Group	No. of HIV-1 Infections	No. of Person-Yr	Rate per 100 Person-Yr	Prevention Efficacy (95% CI)
<1 μg/ml				
Placebo	19	2203	0.86	
VRC01 pooled	9	4427	0.20	75.4 (45.5 to 88.9)
1–3 μg/ml				
Placebo	10	2203	0.45	
VRC01 pooled	19	4427	0.43	4.2 (−108.7 to 56.0)
>3 μg/ml				
Placebo	35	2203	1.59	
VRC01 pooled	70	4427	1.58	3.3 (−48.0 to 36.8)

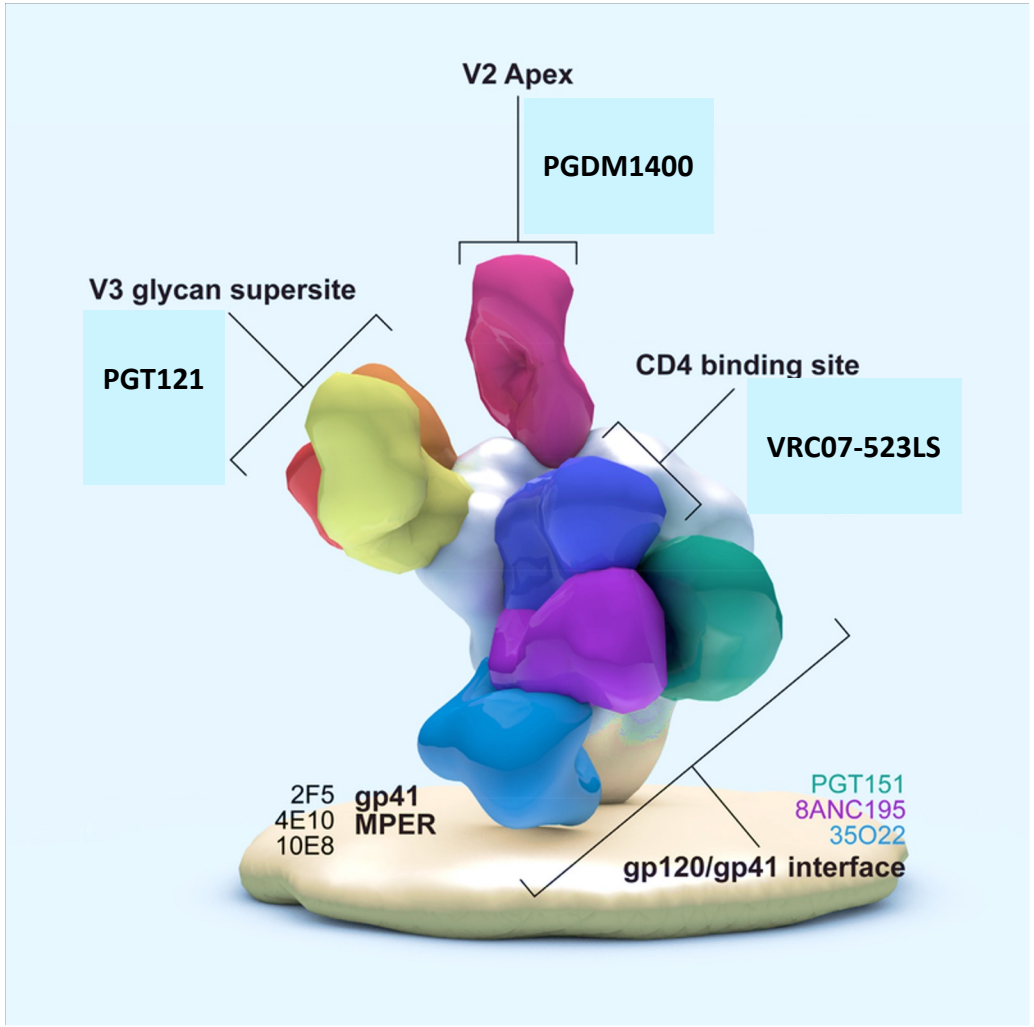
Corey et al. NEJM 2021; 384:1003-1014

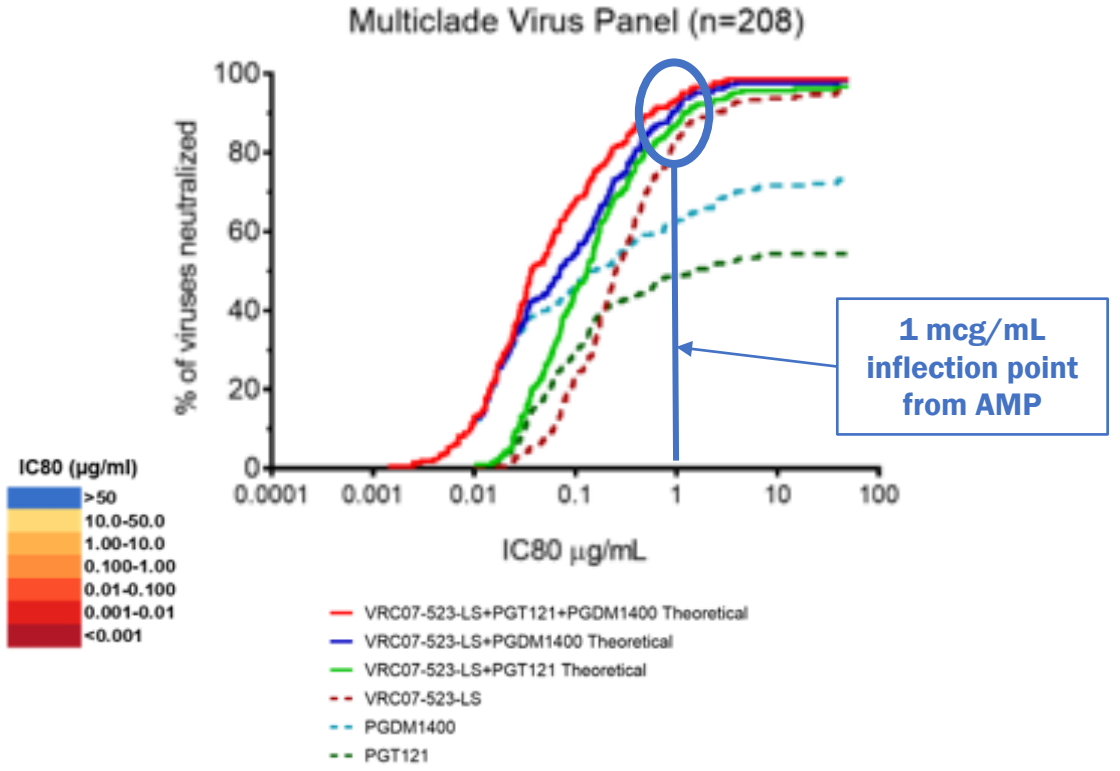
NAb Correlates of Protection in NHPs and Humans (AMP)



Gilbert et al. Nat Med 2022; 28:1924-1932

Long-Acting Triple bNAb Cocktail for Global Coverage: VRC07-523LS, PGT121LS, PGDM1400LS



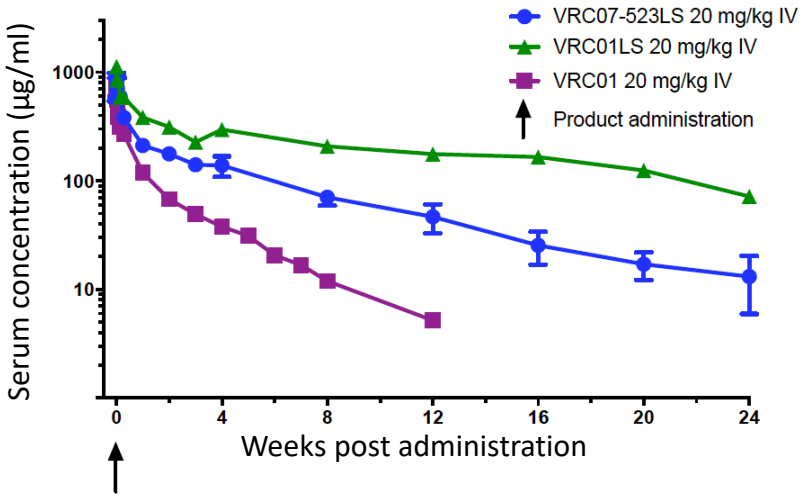


Korber, Barouch, Mascola, Gilbert et al.

LS Mutations Extend bNAb Half-Life

- **LS mutations in Fc extends serum half-life of bNAbs from ~20 to ~70 days and also increases half-life in colorectal tissue**
- **Supports dosing every 6 months for HIV-1 prevention**

HIV bnAb pharmacokinetics in VRC 602, VRC 605, VRC 606 clinical trials



Gaudinski et al. 2019 Lancet HIV https://pubmed.ncbi.nlm.nih.gov/31473167/

HVTN 116 – Extended half-life of VRC01LS in rectum (IHC)

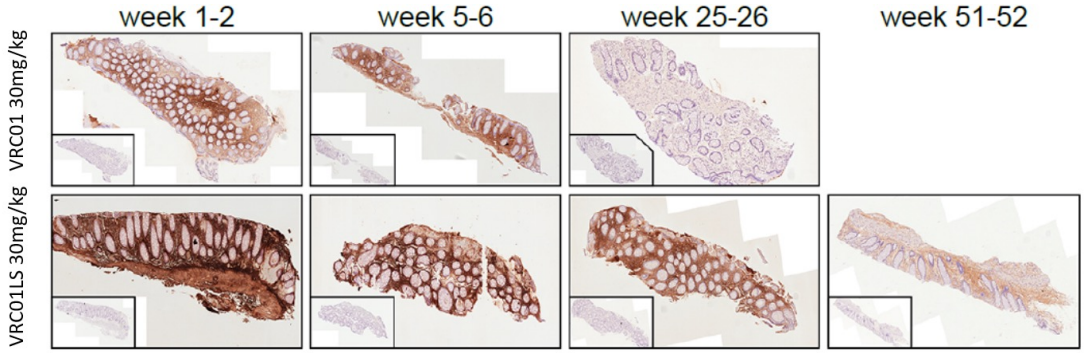
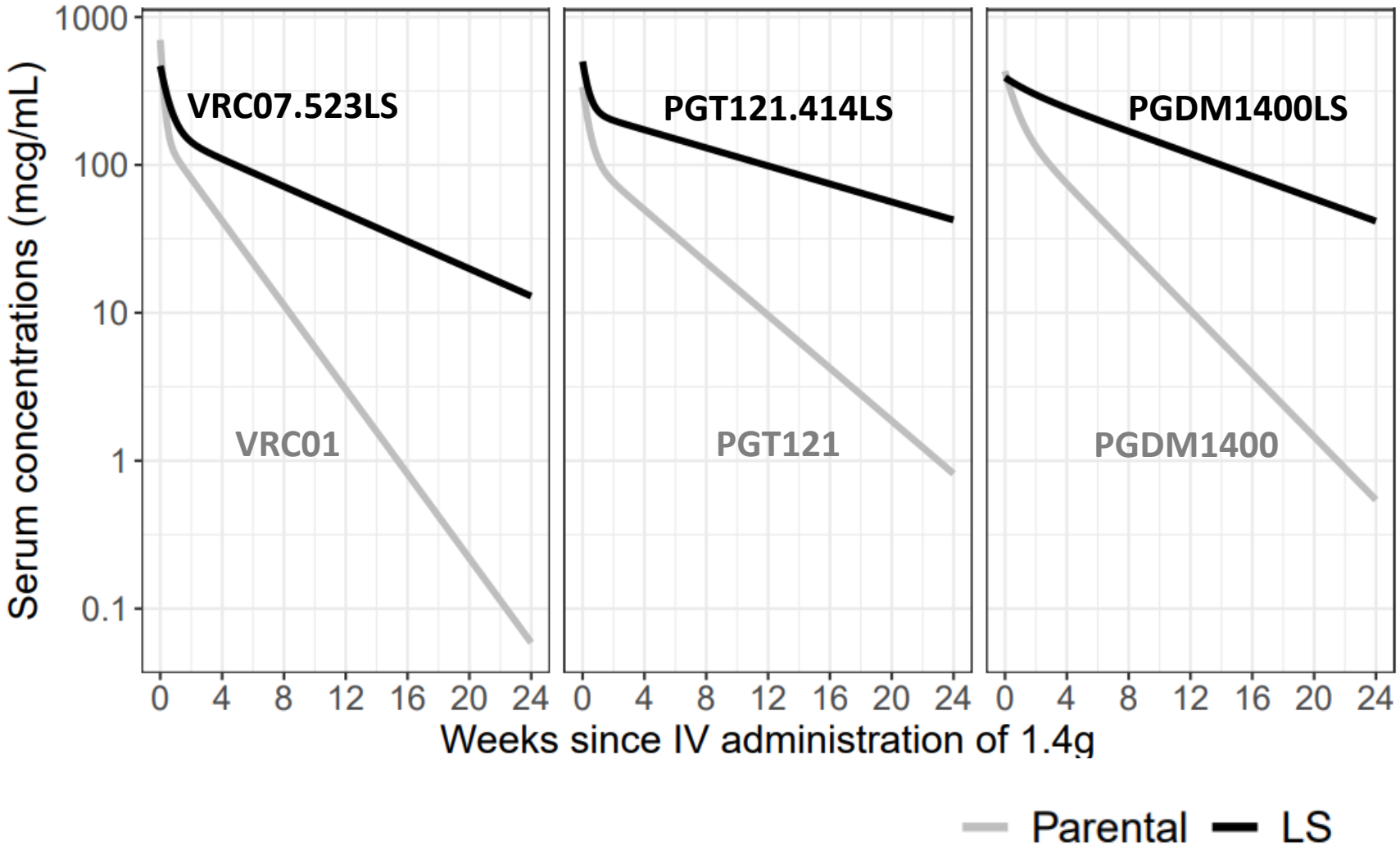


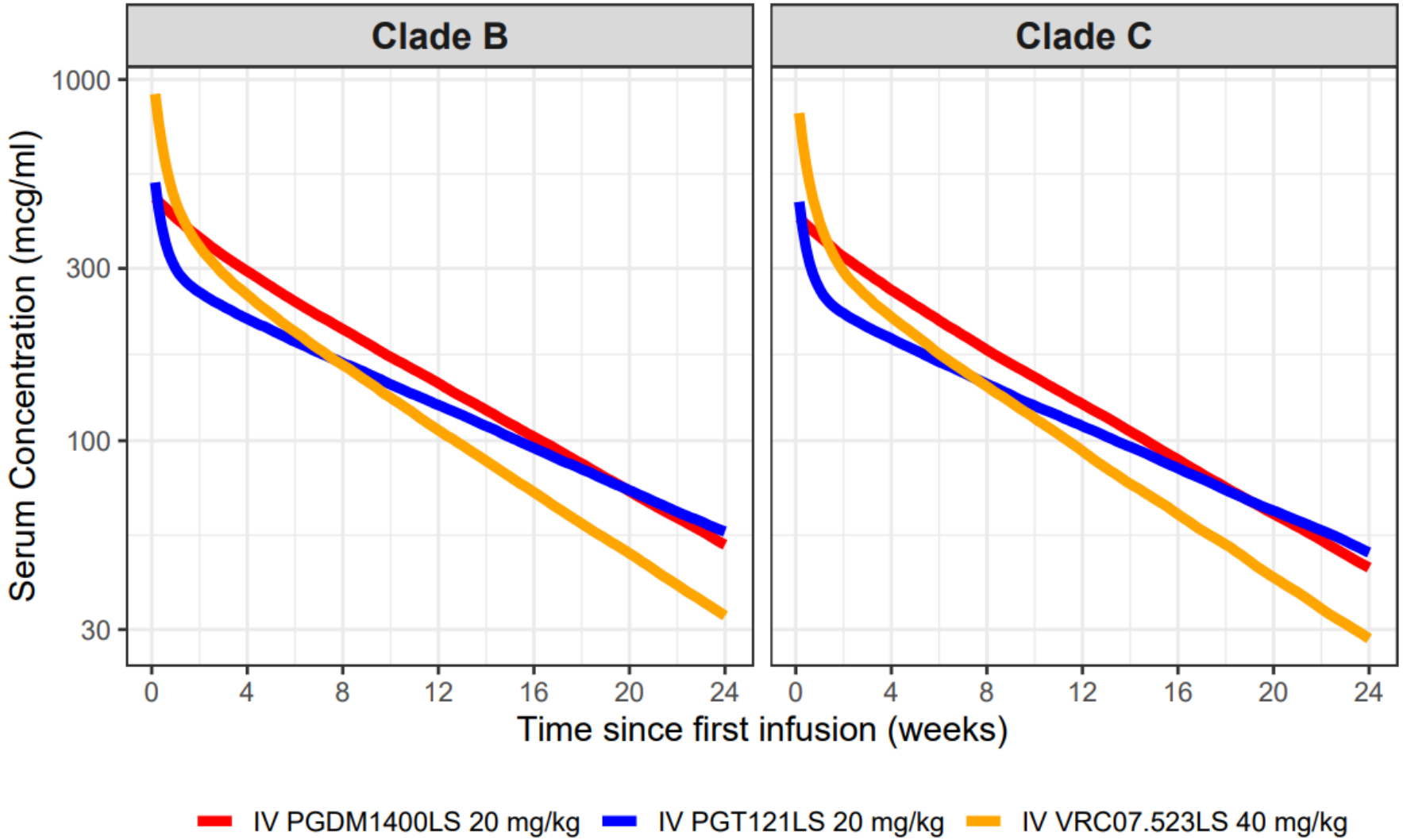
Image: M. Lemos, R. Astronomo, HVTN 116 Study Team.

LS Mutations Extend bNAb Half-Life: VRC07-523LS, PGT121LS, PGDM1400LS



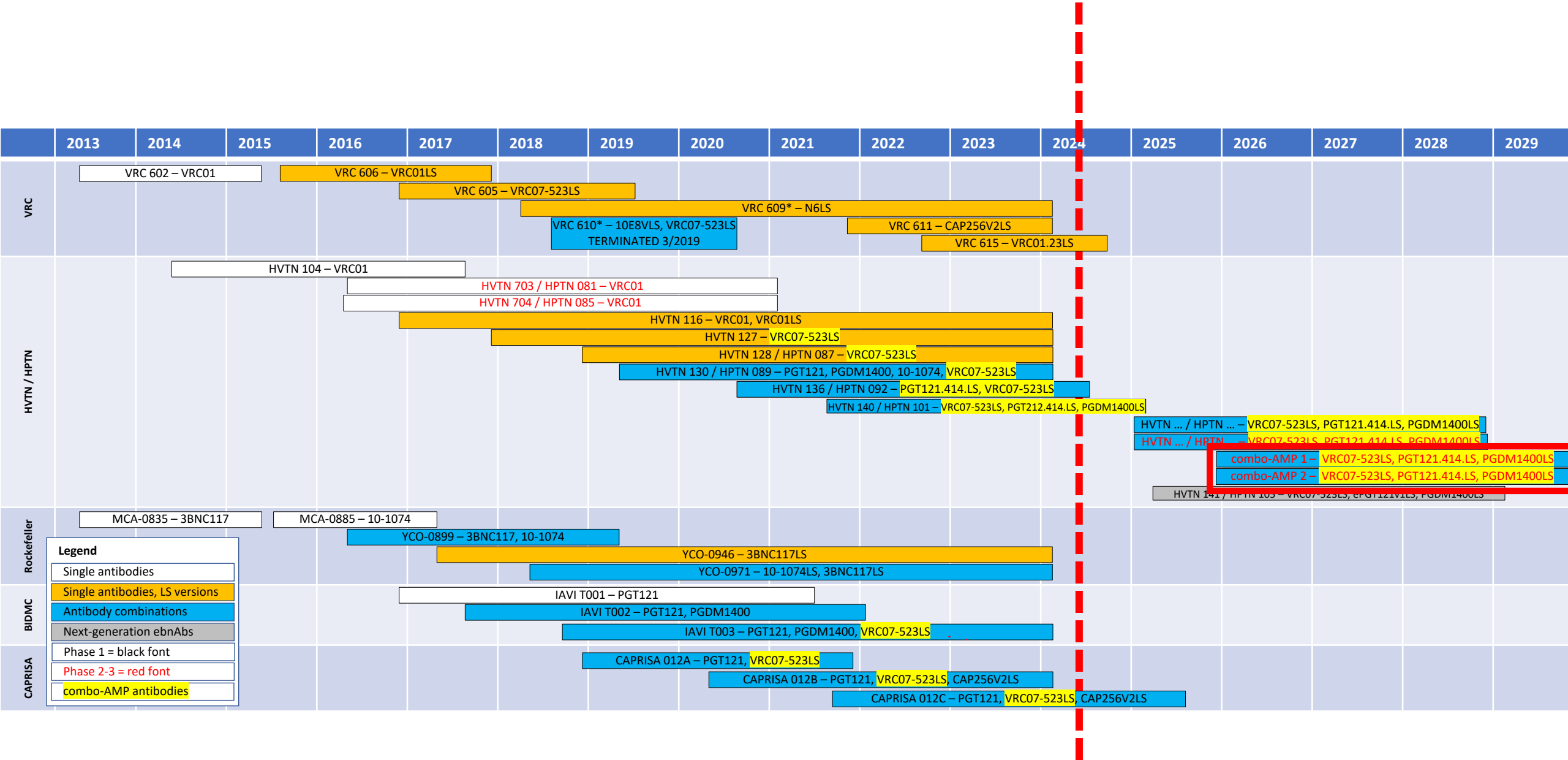
HVTN/HPTN

Similar PK Profiles Support Dosing Every 6 Months: VRC07-523LS, PGT121LS, PGDM1400LS



HVTN/HPTN

Clinical Studies of bNAbs for HIV-1 Prevention



HVTN/HPTN bNAb Program: Strategic Approach and Partnerships

- Proof-of-concept efficacy study (AMP) showed that a single bNAb can protect humans from HIV-1 acquisition against antibody-sensitive virus
- Triple bNAb cocktail achieves outstanding coverage of global HIV-1 and shows substantial therapeutic efficacy in 83% (10 of 12) of PLWH
- It is possible that prevention efficacy will be higher than therapeutic efficacy as a result of limited transmitted/founder variants
- LS mutations extend antibody half-life and support convenient dosing of the bNAb cocktail every 6 months
- Partnership to bring the optimal triple bNAb cocktail into phase 2 efficacy trials: HVTN, HPTN, NIAID, VRC, IAVI

HVTN/HPTN bNAb Program: Goals

2027

- **Initiate 2 harmonized phase 2 trials evaluating efficacy of a bNAb cocktail for prevention of HIV-1 acquisition in populations at risk (Combo AMP)**
- **Define the regimen and efficacy trial design for prevention of HIV-1 in infants**

2030–2032

- **Analyze Combo AMP and determine neutralization correlates for each bNAb to define optimal fixed dose combination regimen (2030–2031)**
- **Perform and analyze efficacy trial of bNAb cocktail in infants (2028–2032)**

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