6 – 10 October · Lima, Peru and virtual hivr4p.org

Monoclonals for Prevention

HVTN 140/HPTN 101:

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, and pharmacokinetics of PGDM1400LS alone and in combination with VRC07-523LS and PGT121.414.LS

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(on behalf of Colleen Kelley, Marc Siegel and the HVTN 140/HPTN 101 team)

HIV R4P conference, Lima, 8 October 2024

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HIV VACCINE TRIALS NETWORK

HPTN HIV Prevention Trials Network

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Summary for Community

What is your main question?

Are these 3 long-acting antibodies safe when given together?

Are these 3 antibodies detectable in blood over time?

Do these 3 antibodies maintain their function in people without HIV?

What did you find?

Safe and remained detectable for at least 6 months

Both ways of giving antibodies (under the skin or into the vein) were well tolerated

Antibodies were detected at levels that have been shown to protect against different strains of HIV (in lab setting)

Why is it important?

These antibodies could be used to protect people from HIV for at least 6 months at a time

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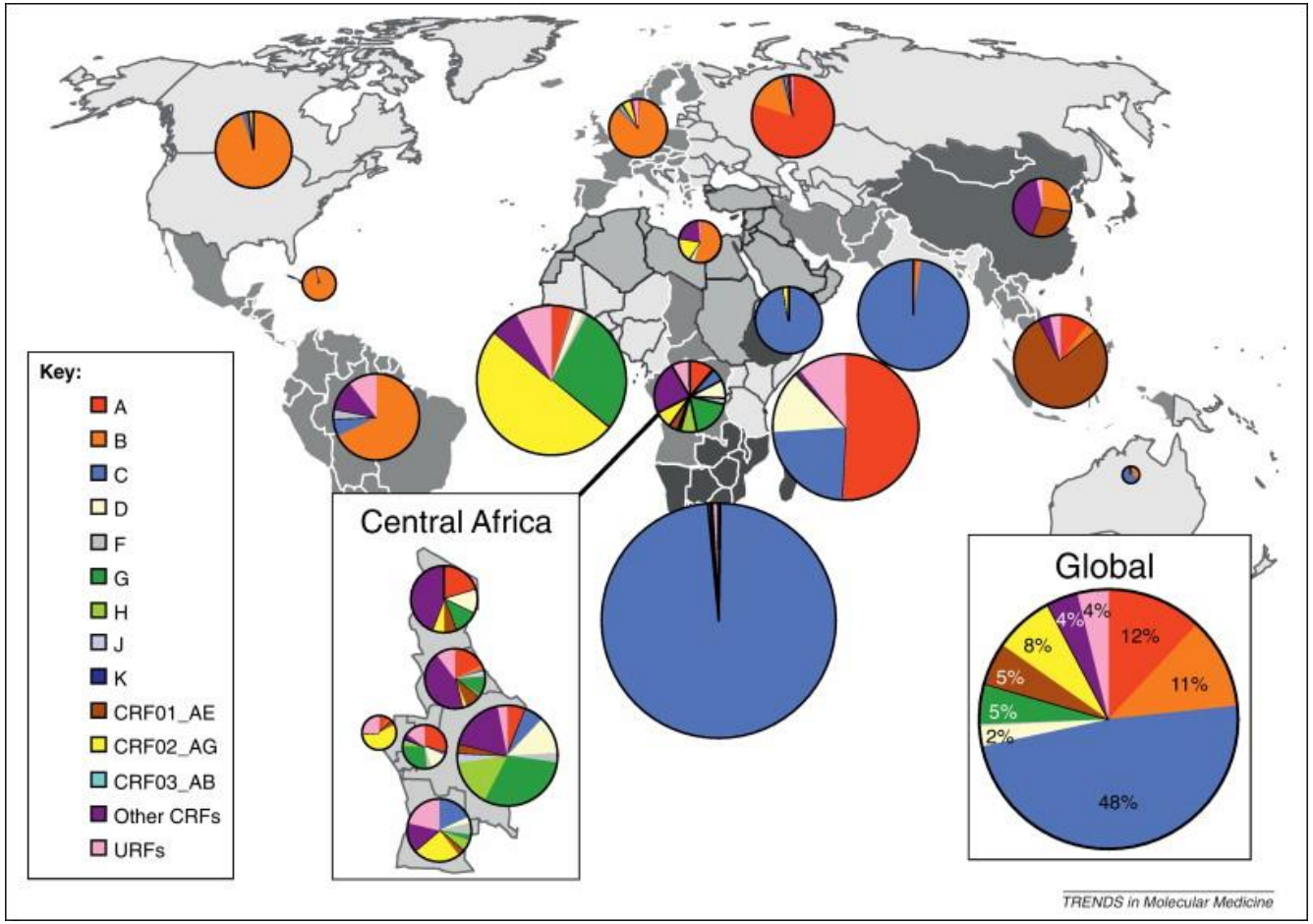
HIV has substantial genetic diversity

HIV has substantial genetic diversity

Combination bNAbs that can neutralise many strains show promise

Early phase trials underway to evaluate safety and pharmacokinetics (PK)



Source: *Hemelaar. Trends Mol Med. 2012*

Prevention efficacy in AMP trials was associated with VRC01 neutralization sensitive viruses

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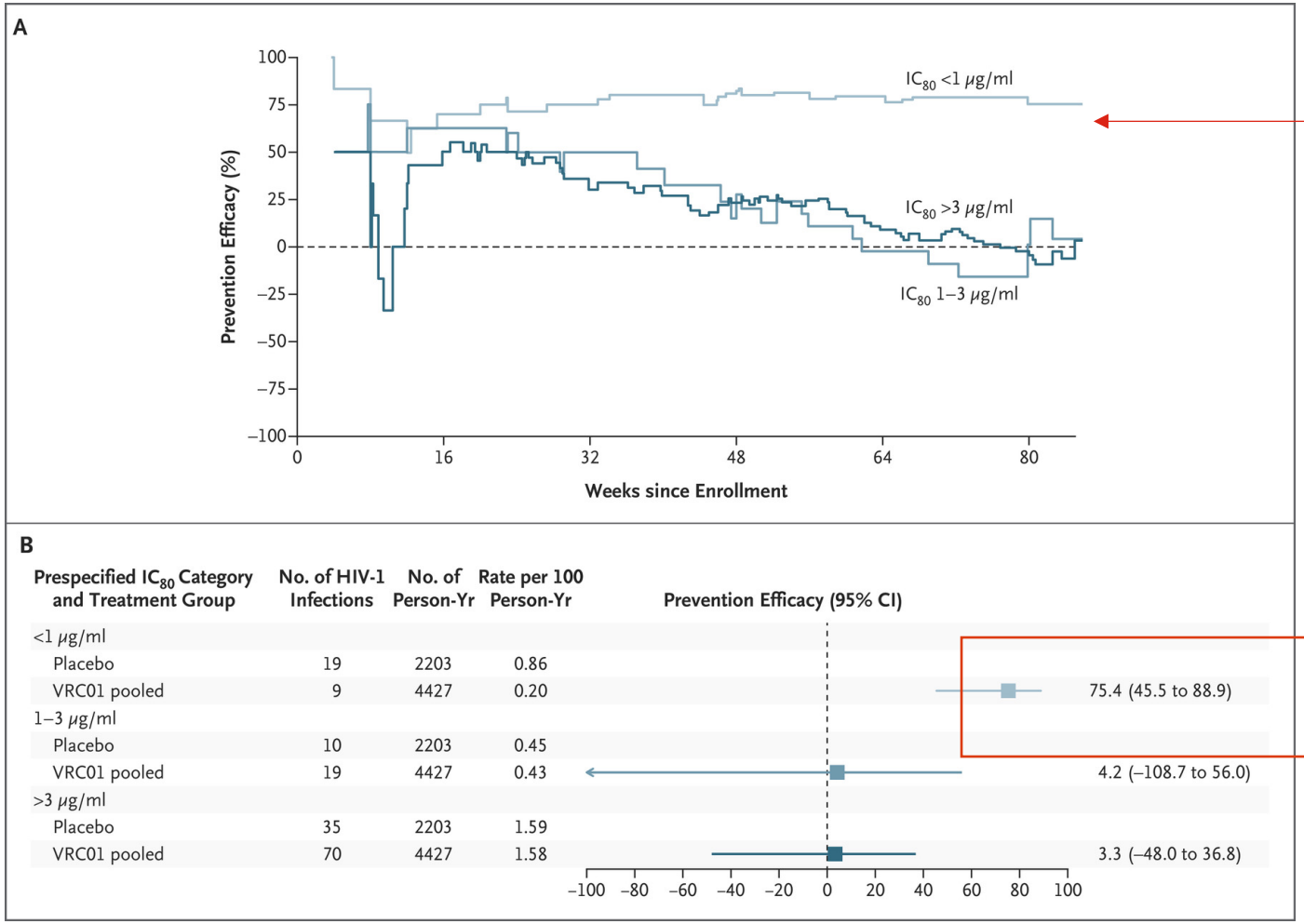

High and sustained Prevention Efficacy for neutralization of sensitive viruses

PE = 75.4%

Source: *Corey, L. et al, New England Journal of Medicine, 384(11), 1003-1014; Gilbert, P. B. et al, Nature Medicine, 28(9), 1924-1932.*

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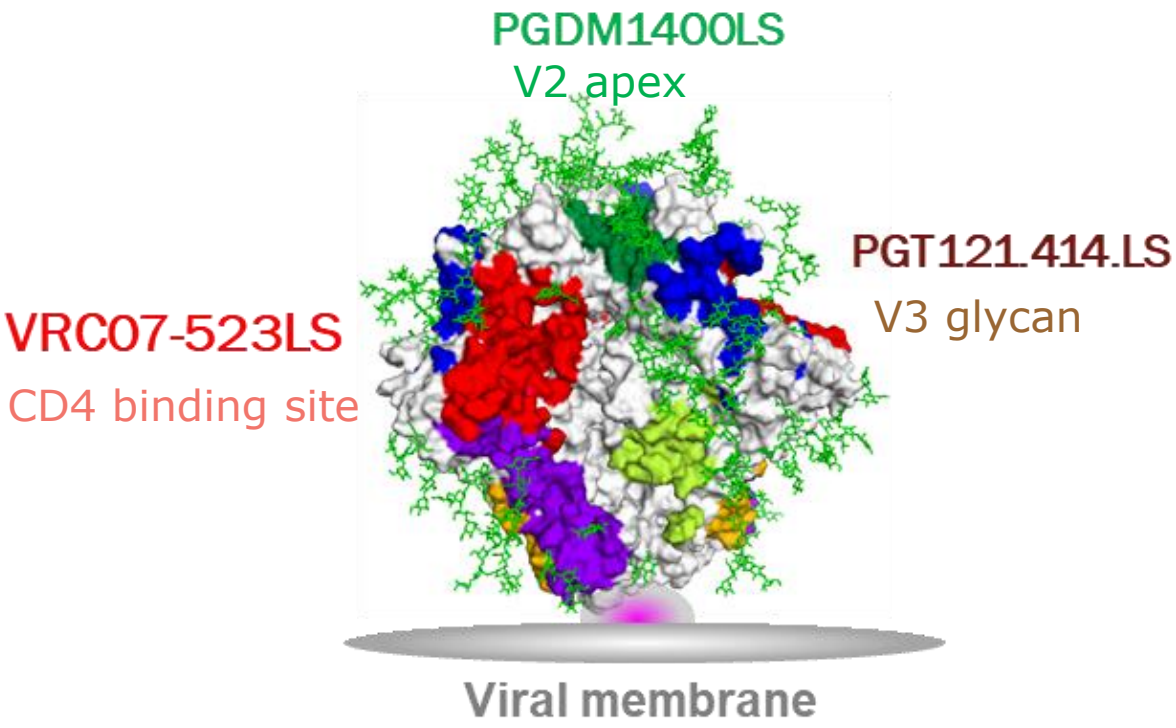
HVTN 140/HPTN 101 assessed a combination of 3 bNAbs



Phase 1 trials of VRC07-523LS and PGT121.414.LS showed safety with favourable PK profiles

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Study overview

Purpose	To evaluate safety, tolerability and PK of PGDM1400LS alone and in combination with VRC07-523LS and PGT121.414.LS
Study design	Phase I, dose-escalation, multi-center, randomized, open-label study
Country of Research	Kenya, South Africa, United States, Zimbabwe
Study participants	Part A (N=15) - PGDM1400LS Part B (N=80) - PGDM1400LS + PGT121.414.LS + VRC07-523LS

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Study design

PART A

PGDM1400LS (5, 20 or 40 mg/kg) intravenously (IV) at month 0

PGDM1400LS (20 or 40 mg/kg) subcutaneously (SC) at month 0

PART B

Body weight dosing - IV (20 mg/kg or 40 mg/kg each mAb at 0, 4 months)

Body weight dosing - SC (20 mg/kg each mAb at 0, 4 months)

Fixed Dosing - IV or SC 1.4 grams* each mAb at 0, 4 months

(*equivalent to 20 mg/kg each, 70 kg ppt)

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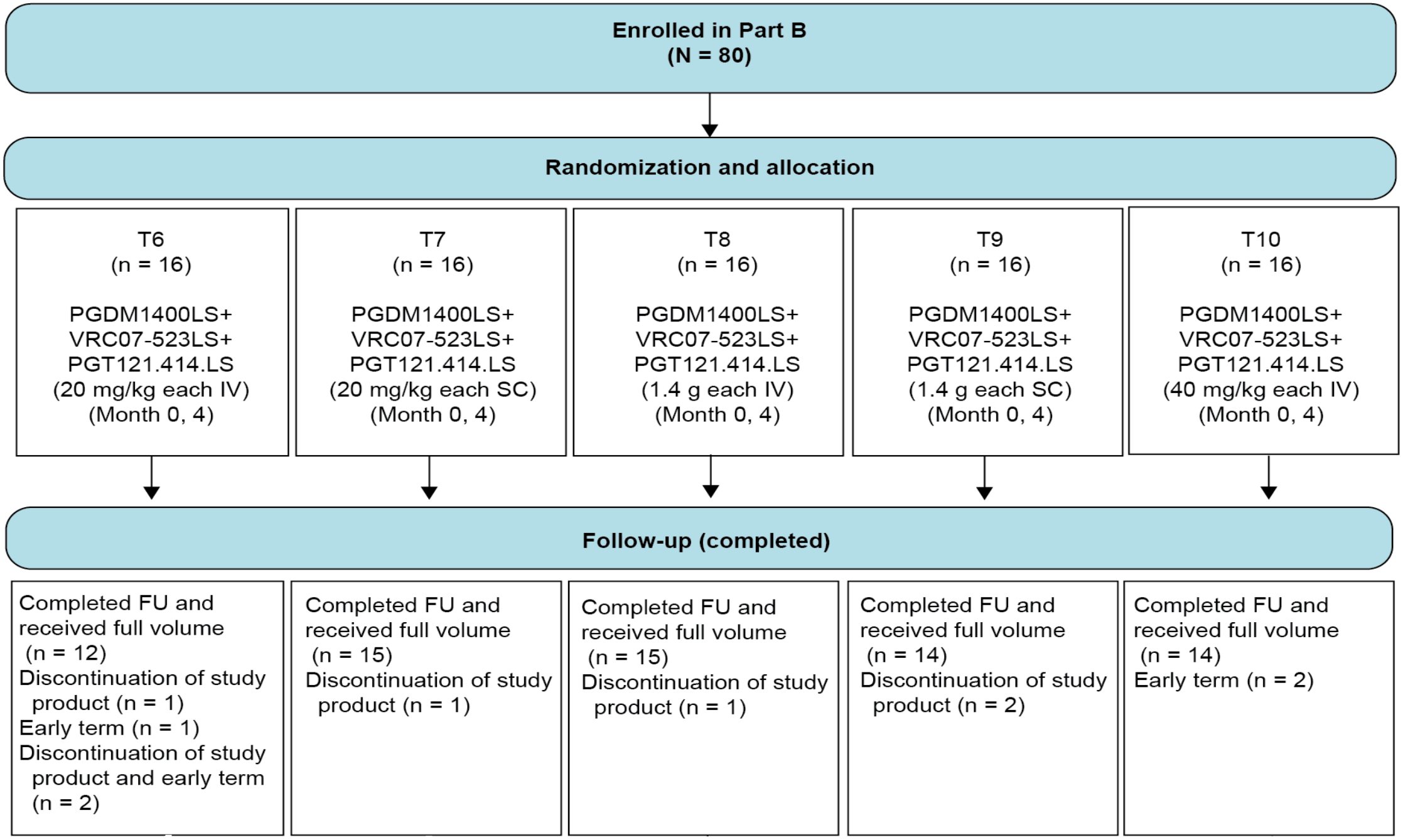
Treatment arms –Part B

Group	Regimen	N	Dose
6	PGDM1400LS + VRC07-523LS + PGT121.414.LS	16	20 mg/kg + 20 mg/kg + 20 mg/kg IV
7	PGDM1400LS + VRC07-523LS + PGT121.414.LS	16	20 mg/kg + 20 mg/kg + 20 mg/kg SC
8	PGDM1400LS + VRC07-523LS + PGT121.414.LS	16	1.4g + 1.4g + 1.4g fixed dose IV
9	PGDM1400LS + VRC07-523LS + PGT121.414.LS	16	1.4g + 1.4g + 1.4g fixed dose SC
10	PGDM1400LS + VRC07-523LS + PGT121.414.LS	16	40 mg/kg + 40 mg/kg + 40 mg/kg IV


Enrolled in Part B
(N = 80)
Randomization and allocation
T6
(n = 16)
PGDM1400LS+
VRC07-523LS+
PGT121.414.LS
(20 mg/kg each IV)
(Month 0, 4)
T7
(n = 16)
PGDM1400LS+
VRC07-523LS+
PGT121.414.LS
(20 mg/kg each SC)
(Month 0, 4)
T8
(n = 16)
PGDM1400LS+
VRC07-523LS+
PGT121.414.LS
(1.4 g each IV)
(Month 0, 4)
T9
(n = 16)
PGDM1400LS+
VRC07-523LS+
PGT121.414.LS
(1.4 g each SC)
(Month 0, 4)
T10
(n = 16)
PGDM1400LS+
VRC07-523LS+
PGT121.414.LS
(40 mg/kg each IV)
(Month 0, 4)
Follow-up (completed)
Completed FU and received full volume (n = 12)
Discontinuation of study product (n = 1)
Early term (n = 1)
Discontinuation of study product and early term (n = 2)
Completed FU and received full volume (n = 15)
Discontinuation of study product (n = 1)
Completed FU and received full volume (n = 15)
Discontinuation of study product (n = 1)
Completed FU and received full volume (n = 14)
Discontinuation of study product (n = 2)
Completed FU and received full volume (n = 14)
Early term (n = 2)

bNAbs were safe and tolerated

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- **Solicited local and systemic adverse events (AEs) - mild to moderate**

- **1 unsolicited related AE**
  - Infusion site erythema Grade 2: T7 (20 mg/kg SC)

- **3 Infusion Related Reactions**
  - Infusion related reaction Grade 2: T6 (20 mg/kg IV)
  - Infusion related reaction Grade 2: T8 (1.4g IV)
  - Infusion site urticaria Grade 2: T9 (1.4g SC)

- **No SAEs, no pregnancies and HIV seroconversions**

Local solicited AEs were > in SC arms

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- **A total of 60 local solicited AEs were reported**
  - 54 reported in SC groups and 6 in IV groups

- **Majority of local solicited AEs - mild to moderate**

- **Six severe local AEs were reported**
  - 2 severe erythema in T7 (20 mg/kg SC)
  - 2 severe induration in T7 (20 mg/kg SC)
  - 2 severe induration in T9 (1.4g SC)

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Related Systemic solicited AEs were > in IV arms

- **A total of 125 related systemic solicited AEs were reported**
  - 87 reported in IV groups and 38 in SC groups
- **Majority of related systemic solicited AEs - mild to moderate**
- **One severe related systemic solicited AE was reported**
  - malaise and fatigue was reported in T10 (40 mg/kg IV)

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bNAbs exhibit expected PK in combo infusions

bNAbs	Half-life (median elimination)	Half-life (range)	SC vs IV bioavailability
PGDM1400LS	54 days	30 - 73 days	75.5%
PGT121.414.LS	66 days	33 - 92 days	77.7%
VRC07-523LS	45 days	24 - 69 days	80.1%

bNAbs exhibit similar PK in fixed vs. body-weight dosing

bnAb concentrations detected over time

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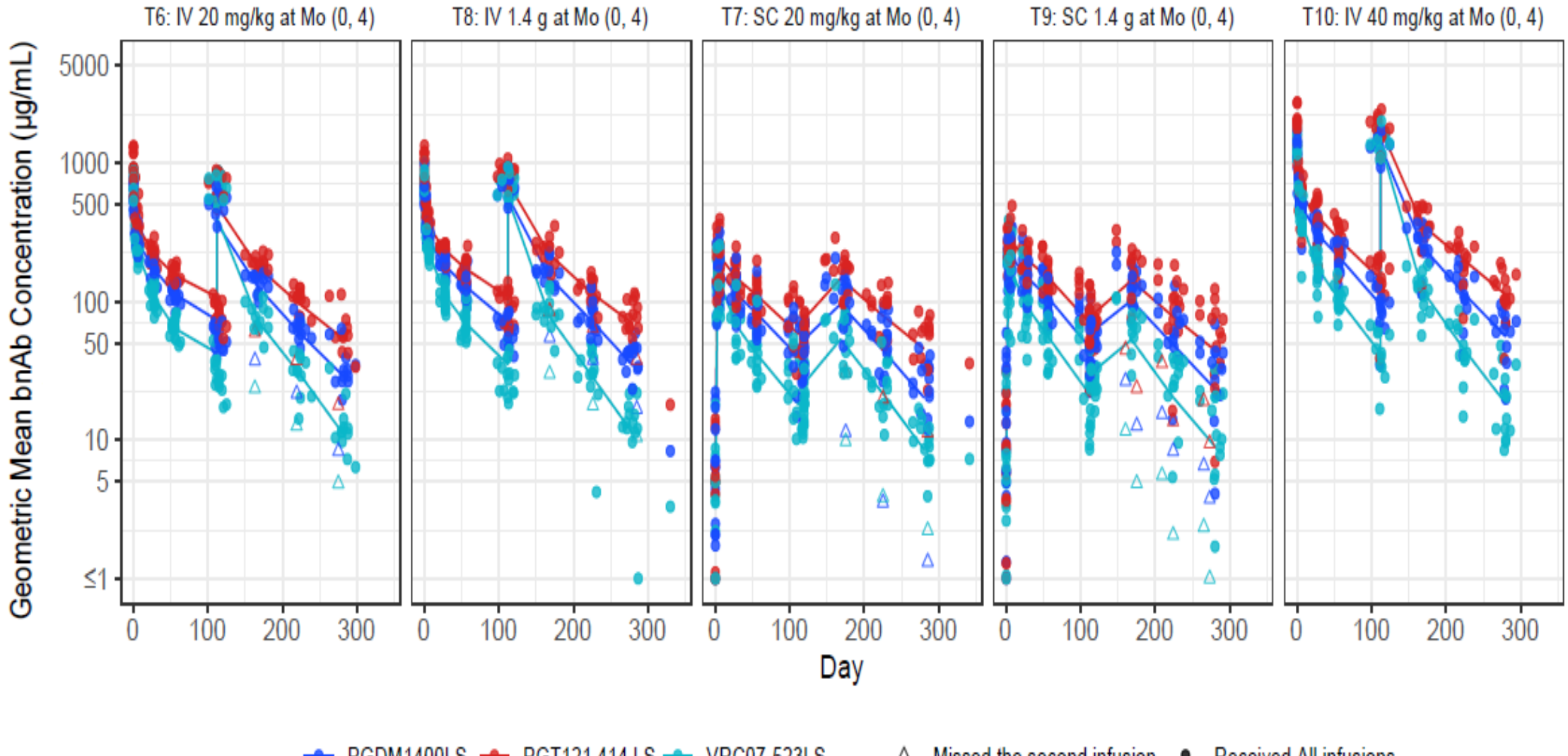

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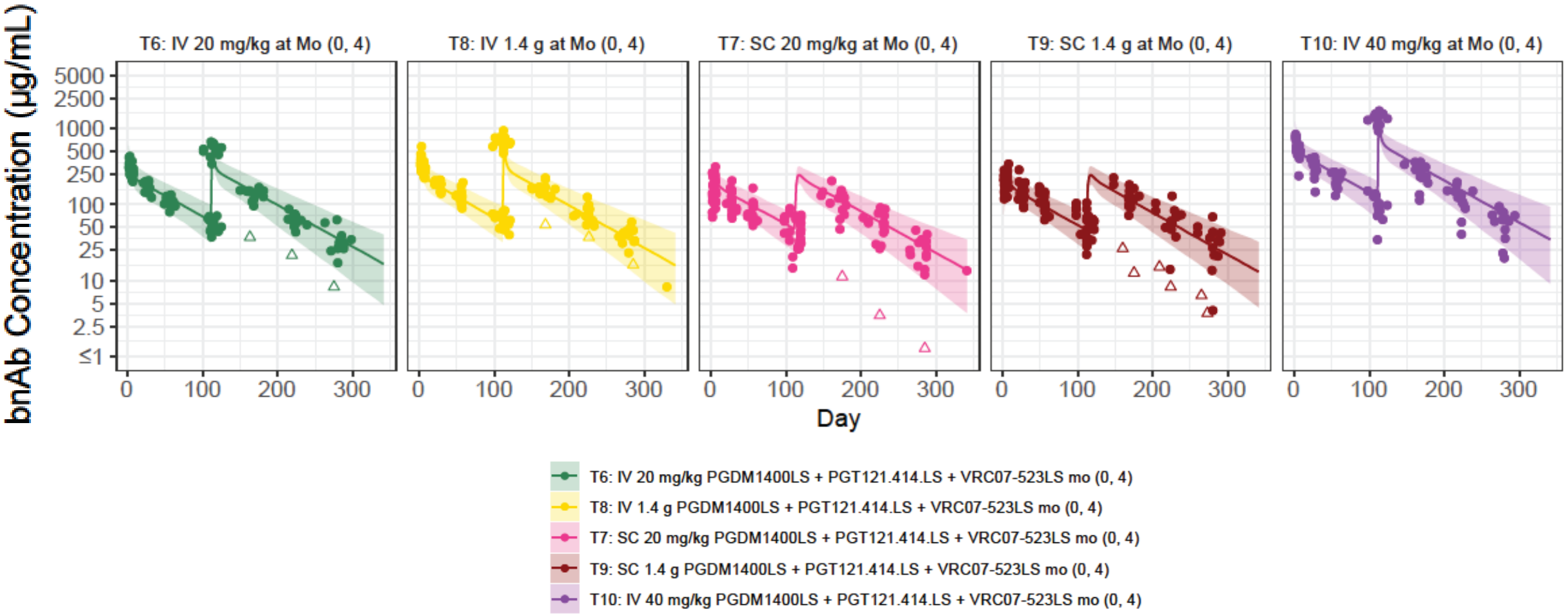
Observed PGDM1400LS Concentrations with 90% Prediction Interval by Treatment



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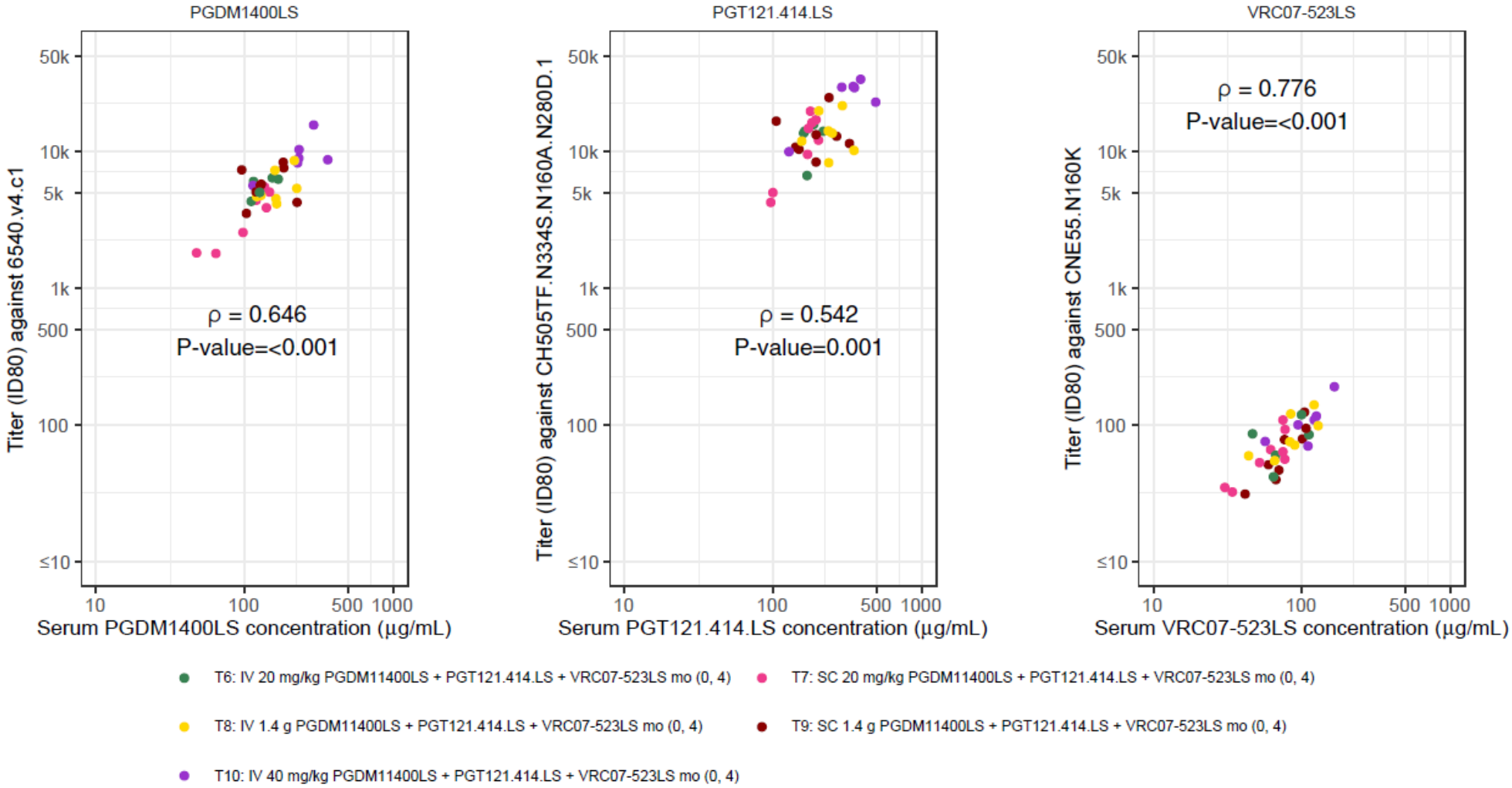
bNAb neutralization activity against the bnAb-specific viruses



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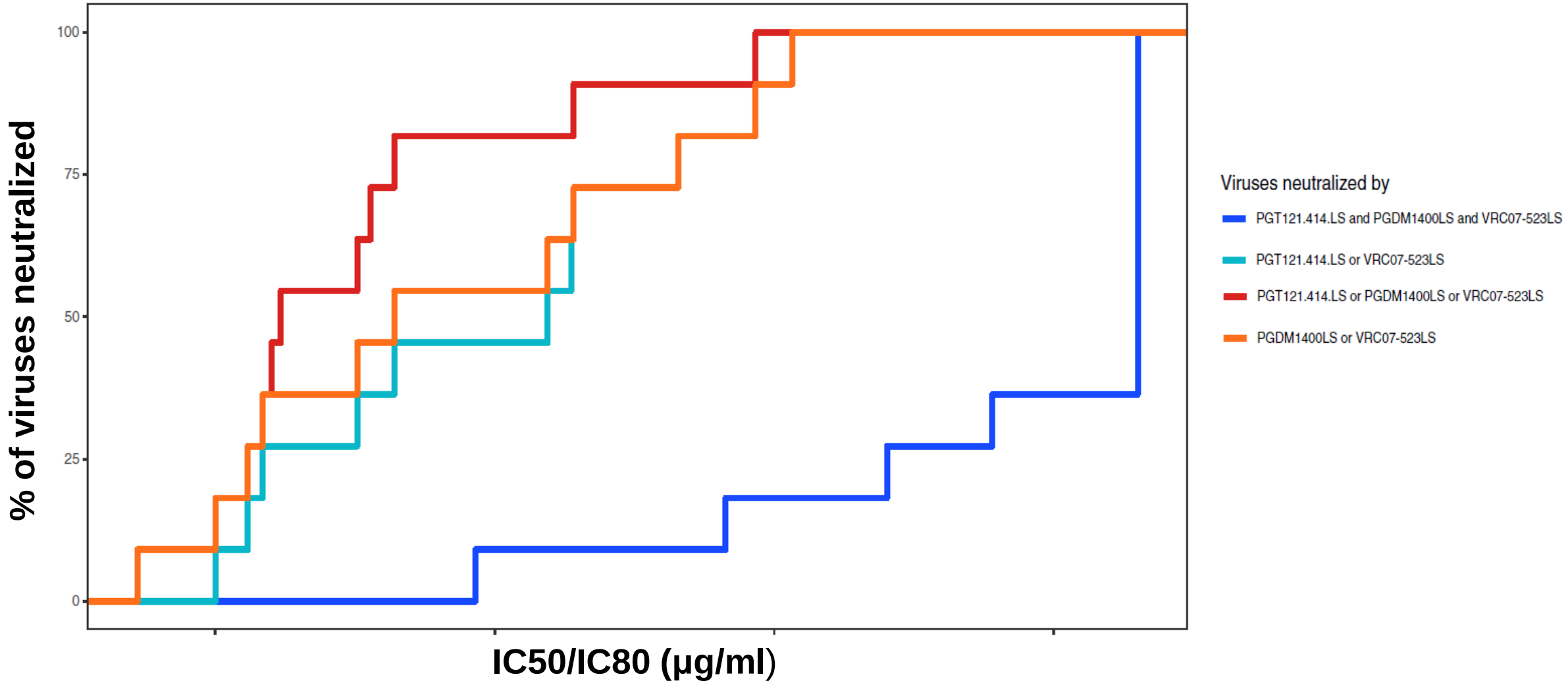
bnAb neutralization activity against the 11 AMP placebo viruses



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Summary & Next steps

- **PGDM1400LS, PGT121.414.LS, VRC07-523LS in combination was safe and well-tolerated**
- **No PK interactions or loss neutralization coverage/breadth**
- **Comparable PK profiles between the weight-based vs. fixed dosing regimens**
- **Findings strongly support the evaluation of this triple combination in future efficacy trials**

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HVTN 140/HPTN 101 Protocol Team Acknowledgements

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- Colleen Kelley
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- Harare – Seke South
- Harare – Spilhaus
- Harare – Milton Park
- Johannesburg – Ward 21
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