Administration of the broadly neutralizing, CD4-binding site targeting antibody VRC07-523LS in dual- and triple-antibody combinations with 10-1074, PGT121 and/or PGDM1400: impact on pharmacokinetics compared to VRC07-523LS administration alone

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Background

Broadly neutralizing antibodies (bnAbs) are a promising approach for HIV-1 prevention. In the only bnAb HIV prevention efficacy studies to date (the AMP studies), intravenous (IV) administration of the CD4-binding site targeting bnAb VRC01 prevented infection only against VRC01-susceptible viruses.

BnAb combinations, particularly using bnAbs engineered for increased potency, breadth, and half-life, may be more efficacious for prevention of HIV-1. Clinical data assessing potential interactions between co-administered antibodies is limited.

We compared pharmacokinetic (PK) parameters of the CD4-binding site targeting bnAb VRC07-523LS administered alone (in HVTN 127/HPTN 087) versus in combination with other bnAbs (in HVTN 130/HPTN 089).

Methods

Both studies enrolled healthy, HIV-uninfected adult volunteers who were between 18 and 50 years of age and were at low risk of HIV acquisition.

From HVTN 127/HPTN 087 (**Table 1**), we analysed the IV groups in which participants received VRC07-523LS administered at four-month intervals at five timepoints. 9 or 10 participants were analysed per group.

In HVTN 130/HPTN 089 (**Table 2**), participants received VRC07-523LS administered IV sequentially in dual combination with 10-1074, PGT121, or PGDM1400 at one timepoint (n=18; 20 mg/kg), or in triple combination with PGDM1400 and PGT121 at two timepoints (n=9; 20 mg/kg).

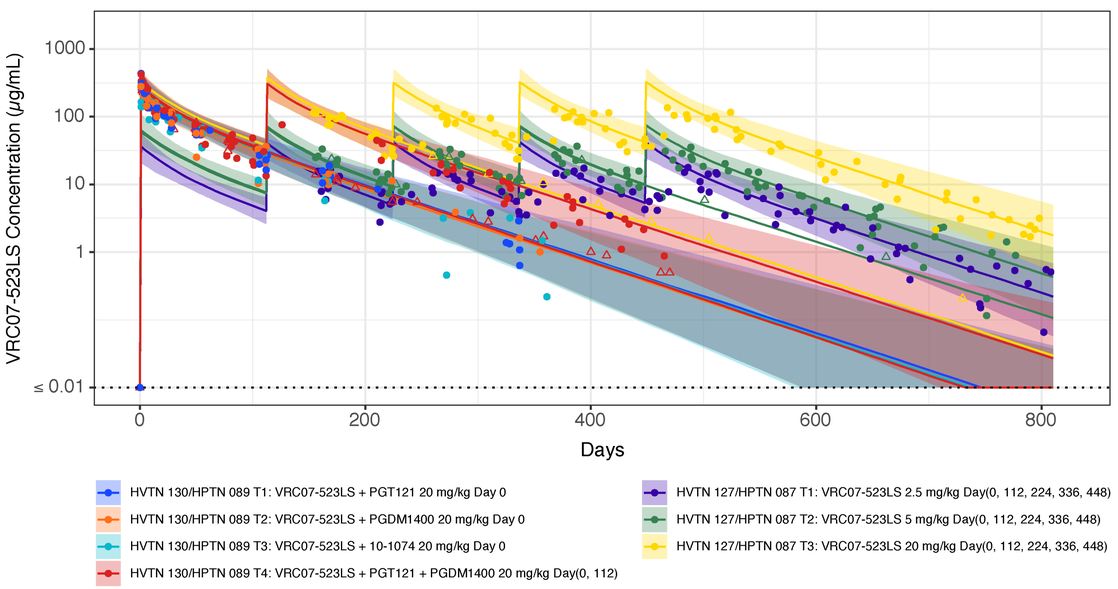
VRC07-523LS serum concentration kinetics were measured by an anti-idiotype Binding Antibody Multiplex Assay (BAMA). From HVTN 127/HPTN 087, VRC07-523LS concentrations measured between the first and second infusions by a different assay were excluded. All available time points were analysed from HVTN 130/HPTN 089.

A two-compartment population PK model (**Table 3**) was fitted to estimate PK parameters and compare PK profiles in participants administered VRC07-523LS alone versus VRC07-523LS used in combination with 1 or 2 other bnAbs.

Table 1. HVTN 127/HPTN 087 study schema.

Group	N	Route	Dose	Product Administration Schedule				
				Month 0	Month 4	Month 8	Month 12	Month 16
1	20	IV	2.5 mg/kg	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS
2	20	IV	5 mg/kg	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS
3	20	IV	20 mg/kg	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS
4	20	SC	2.5 mg/kg	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS
5	20	SC	5 mg/kg	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS
6	20	IM	2.5 mg/kg	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS
	4		Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Figure 1. Observed VRC07-523LS levels with 90% prediction intervals.



Results

Predicted VRC07-523LS levels from the fitted model were in excellent agreement with observed levels (**Figures 1** and **2A**). VRC07-523LS alone has an estimated median half-life of ~54.8 days versus ~52.3 days when co-administered with 10-1074, PGT121, and/or PGDM1400 (p=0.55) (**Figure 2B**). Small changes in clearance, intercompartmental clearance, and peripheral volume PK parameters of VRC07-523LS were observed with co-administration of 10-1074, PGT121, and/or PGDM1400 (**Figure 3**).

Table 4. Participant characteristics.

	HVTN 127/HPTN 087	HVTN 130/HPTN 089
N	29	26
Age – median (range)	30 (18, 50)	26 (19, 50)
Female sex at birth	62%	58%
Weight – median (range)	72 kg (51, 108)	70 kg (51, 86)

Table 3. Pharmacokinetic parameters.

Parameter	Description	Estimate (95% CI)	%RSE
Fixed Effects			
C L (L/day)	Clearance	0.11 (0.10, 0.12)	3.72
Vc (L)	Central volume	5.24 (4.70, 5.77)	5.18
Q (L/day)	Inter-compartmental clearance	0.05 (0.04,0.06)	14.85
Vp (L)	Peripheral volume	1.69 (1.48, 1.91)	6.50
βClcombo	Adjusted fixed effect of Cl for single vs combinations	0.28 (0.20, 0.37)	15.39
βQcombo	Adjusted fixed effect of Q for single vs combinations	1.40 (0.99, 1.80)	14.89
βVpcombo	Adjusted fixed effect of Vp for single vs combinations	0.86 (0.71, 1.02)	9.24
Random Effects			
ωCL	Standard deviation (SD), clearance	0.22 (0.18, 0.27)	10.45
ωVc	SD, central volume	0.32 (0.25, 0.39)	11.40
ωQ	SD, Inter-compartmental clearance	0.42 (0.18, 0.66)	28.86
ωVp	SD, peripheral volume	0.14 (0.04, 0.24)	35.27
Correlations			
ρVc Cl	Correlation between random effects for Vc and CL	0.79 (0.65, 0.93)	8.99
Error Model Parameters			
σ (constant)	SE, additive	0.05 (0.02, 0.07)	27.58
σ (proportional)	SE, proportional	0.13 (0.12, 0.14)	4.67

Table 2. HVTN 130/HPTN 089 study schema.

Group	N	Route	Dose	Product Administration Schedule	
				Month 0	Month 4
1	6	IV	20 mg/kg 20 mg/kg	PGT121 VRC07-523LS	—
2	6	IV	20 mg/kg 20 mg/kg	PDGM1400 VRC07-523LS	—
3	6	IV	20 mg/kg 20 mg/kg	10-1074 VRC07-523LS	—
4	9	IV	20 mg/kg 20 mg/kg 20 mg/kg	PDGM1400 PGT121 VRC07-523LS	PDGM1400 PGT121 VRC07-523LS

Figure 2A. Observed vs predicted VRC07-523LS levels.

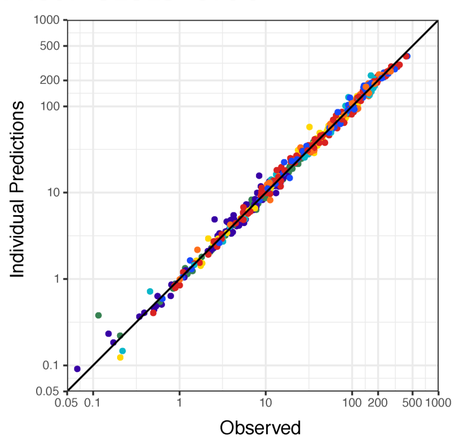


Figure 2B. Elimination half-life.

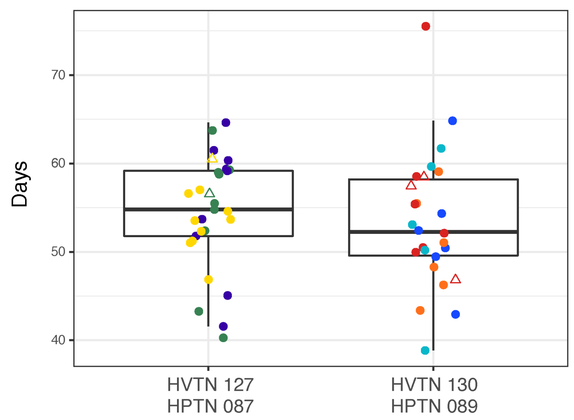
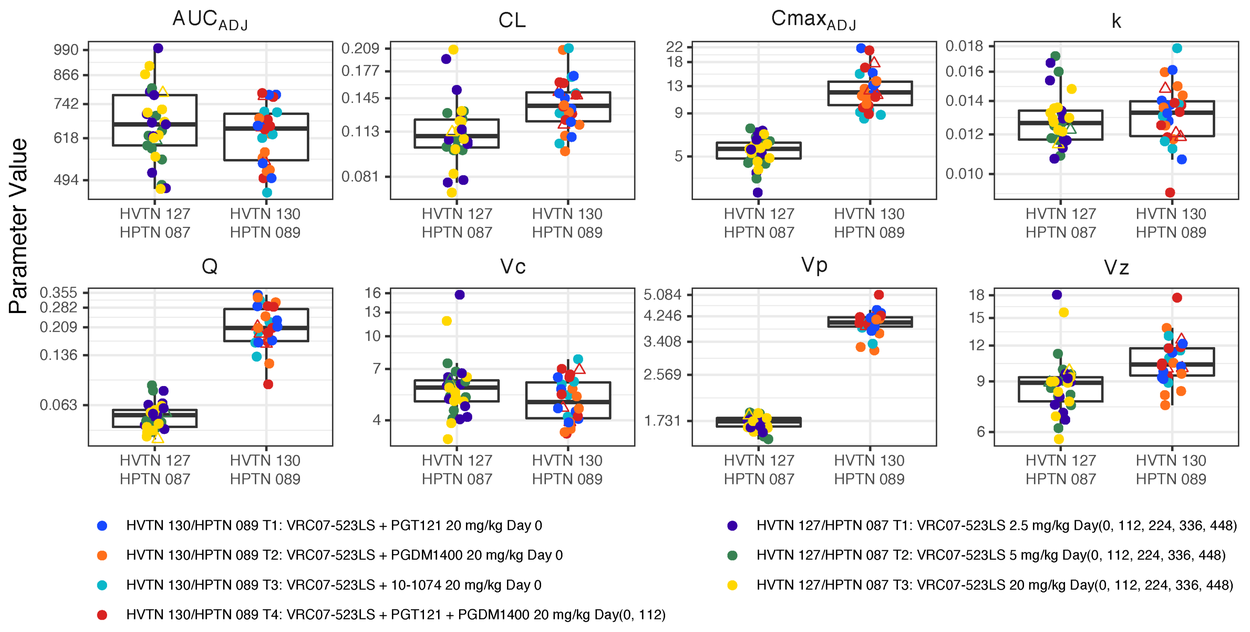


Figure 3. Pharmacokinetic parameters.



Conclusions

VRC07-523LS appears to be cleared more rapidly with a larger peripheral volume when co-administered with 10-1074, PGT121, and/or PGDM1400 than when administered alone, with no significant impact on elimination half-life. These data suggest that the duration of PK coverage observed for single anti-HIV bnAbs, like VRC07-523LS, is preserved in bnAb combinations. Ongoing studies will compare combinations of –LS modified bnAbs administered IV and subcutaneously (SC).

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