Broadly Neutralizing Antibodies to Reduce Vertical HIV Transmission: Safety and PK of VRC01, VRC01LS, and VRC07-523LS

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Presenting on behalf of the IMPAACT P1112 team and collaborators from research sites and VRC

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Passive and active immunization

Passive immunization

- Administration of antibodies
- Immediately active
- Transient activity
- Levels drop over time
- Requires repeated doses for continued efficacy

Active immunization

- Administration of immunogen
- 2-4 week minimum delay till effective protection
- May generate both antibody and cellular immunity
- Long lasting protection after completion of dose series

Passive Immunization is a Potential Strategy to Interrupt Transmission

- Polyclonal antibody previously attempted
  - PACTG 185: HIVIG vs IVIG- stopped for futility[1]
  - HIVIGLOB/NVP Study - no benefit[2]
- Monoclonal antibody
  - Potent
  - Broad
  - Prevent transmission in primates, including neonatal models of transmission

1. Stiehm ER et al. J Infect Dis 1999;179:567-75

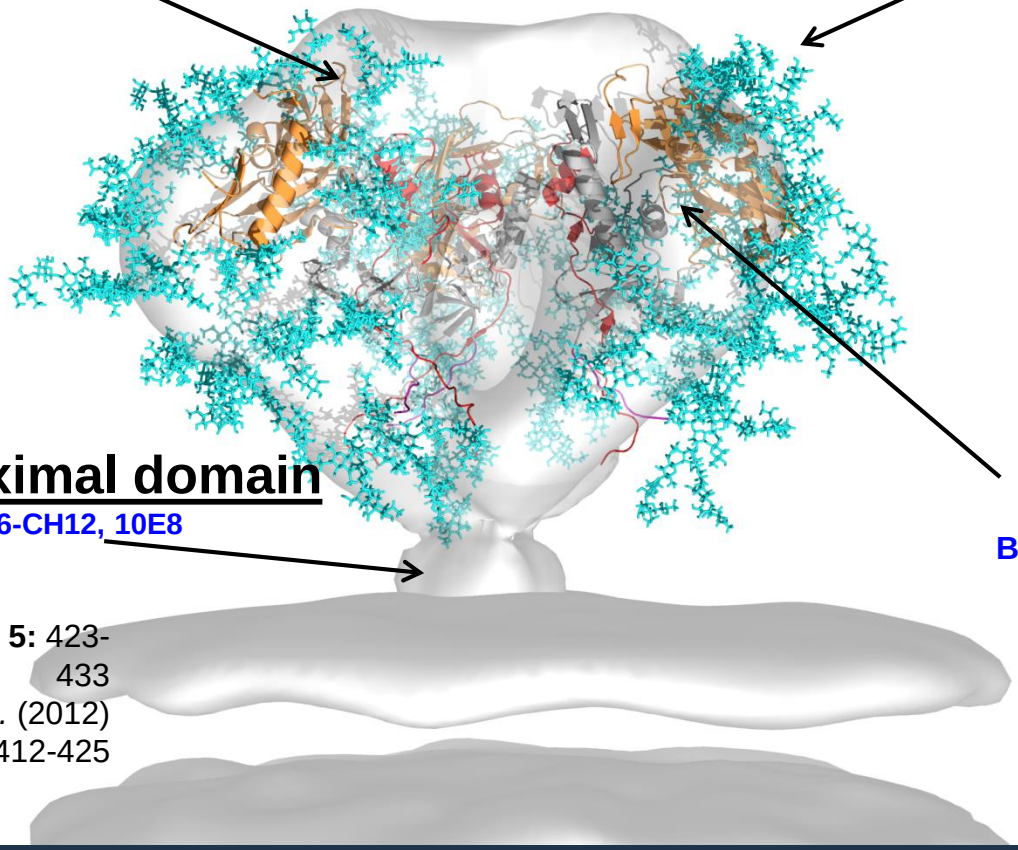
2. Onyango-Makumbi et al. JAIDS 2011:54(4);399-407

Sites of Vulnerability for HIV Neutralization

Antibody Specificity, CDR3 Length, and Somatic Mutation Rates

V1V2
PG9/16, CH01-04, PGT 141-145

V3/glycan
2G12, PGT125-128, PGT131-135, 10-1074



membrane proximal domain
2F5, 4E10, CAP206-CH12, 10E8

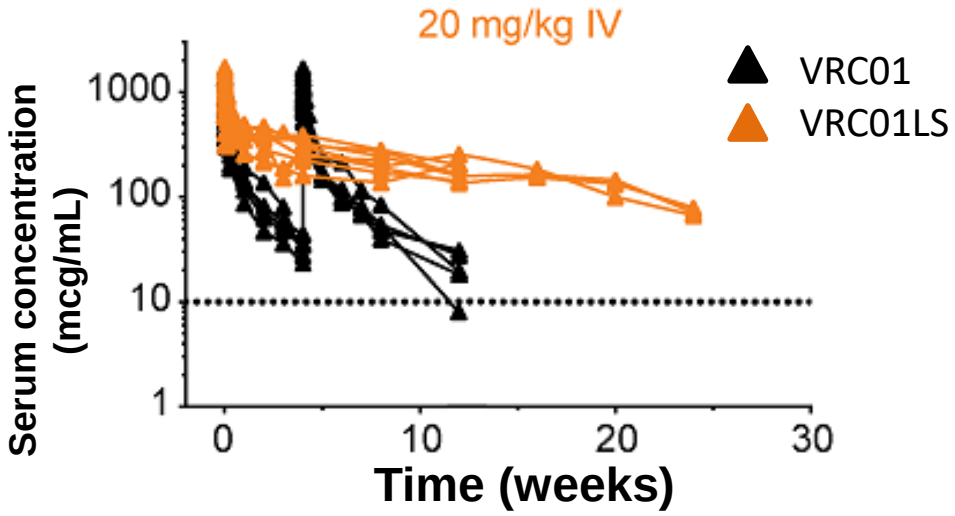
CD4 binding site
B12, VRC01-03, PG04, HJ16
CH30-34, NIH45-46, 12A12,
VRC07-523, 3BNC17

Haynes *et al.* (2012) *Nat.Biot.* **5:** 423-433

Kwong and Mascola *et al.* (2012) *Immunity.* **37:** 412-425

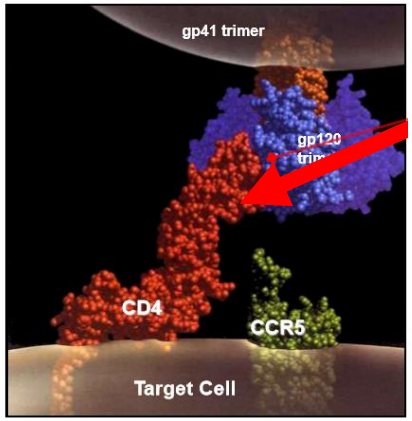
VRC01LS: Increased affinity for neonatal Fc-receptor increases mAb half-life

- Two amino acid substitutions (M428L/N434S) in the Fc domain result in increased affinity for the neonatal Fc-receptor at low pH and recirculation of functional IgG.
- In adults, this results in a dramatic increase in half-life.
- These changes also result in prolonged protection in NHP.



Ko et al, Nature, 514(7524) 2014
Guadinski et al, PLoS Med, 2018

VRC01 and VRC07-523LS: Broadly neutralizing anti-CD4 binding site monoclonal antibodies



CD4 binding site on gp120 is functionally conserved: All viruses must bind CD4

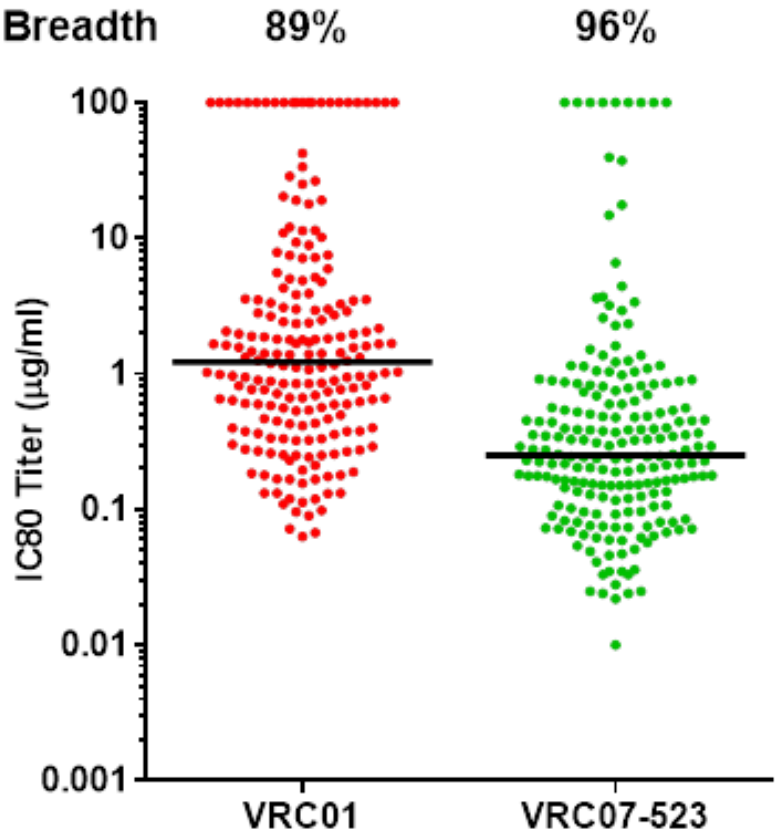
Color shading represents potency as follows:

<.100
.100-1.00
1.00-10.0
>10.0

		IC50 (µg/mL)		IC80 (µg/mL)	
clade	virus	VRC01	VRC07-523LS	VRC01	VRC07-523LS
A	KER2018.11	0.701	0.232	1.920	0.992
A	Q23.17	0.075	0.023	0.257	0.111
A	Q769.h5	0.027	0.003	0.166	0.024
A	RW020.2	0.159	0.024	0.535	0.125
AC	6540.v4.c1	>50	>50	>50	>50
AD	Q168.a2	0.108	0.026	0.385	0.175
AE	C1080.c3	1.360	0.050	7.010	0.539
AE	CNE59	0.567	0.036	2.260	0.205
AE	TH966.8	0.062	0.006	0.675	0.045
AG	DJ263.8	0.042	0.001	0.392	0.010
B	6101.10	0.066	0.005	0.205	0.042
B	Bal.01	0.034	0.0007	0.165	0.008
B	BG1168.01	0.647	0.097	2.970	0.351
B	CAAN.A2	1.410	0.213	4.460	0.719
B	JRCSF.JB	0.246	0.019	0.939	0.131
B	JRFL.JB	0.014	0.0006	0.074	0.002
B	PVO.04	0.418	0.041	1.380	0.233
B	THRO.18	1.700	0.330	13.100	4.920
B	TRJO.58	0.080	0.017	0.258	0.090
B	TRO.11	0.455	0.069	1.430	0.223
B	YU2.DG	0.057	0.003	0.203	0.032
C	CNE58	0.154	0.017	0.527	0.069
C	DU156.12	0.087	0.004	0.271	0.031
C	DU172.17	>50	0.071	>50	0.565
C	DU422.01	>50	6.990	>50	>50
C	ZA012.29	0.491	0.103	2.370	0.495
C	ZM106.9	0.285	0.017	0.876	0.145
C	ZM55.28a	0.306	0.020	1.090	0.109
D	57128.vrc.15	>50	0.193	>50	2.470
G	X1632.S2.B10	0.033	0.0008	0.287	0.013

VRC07-523LS

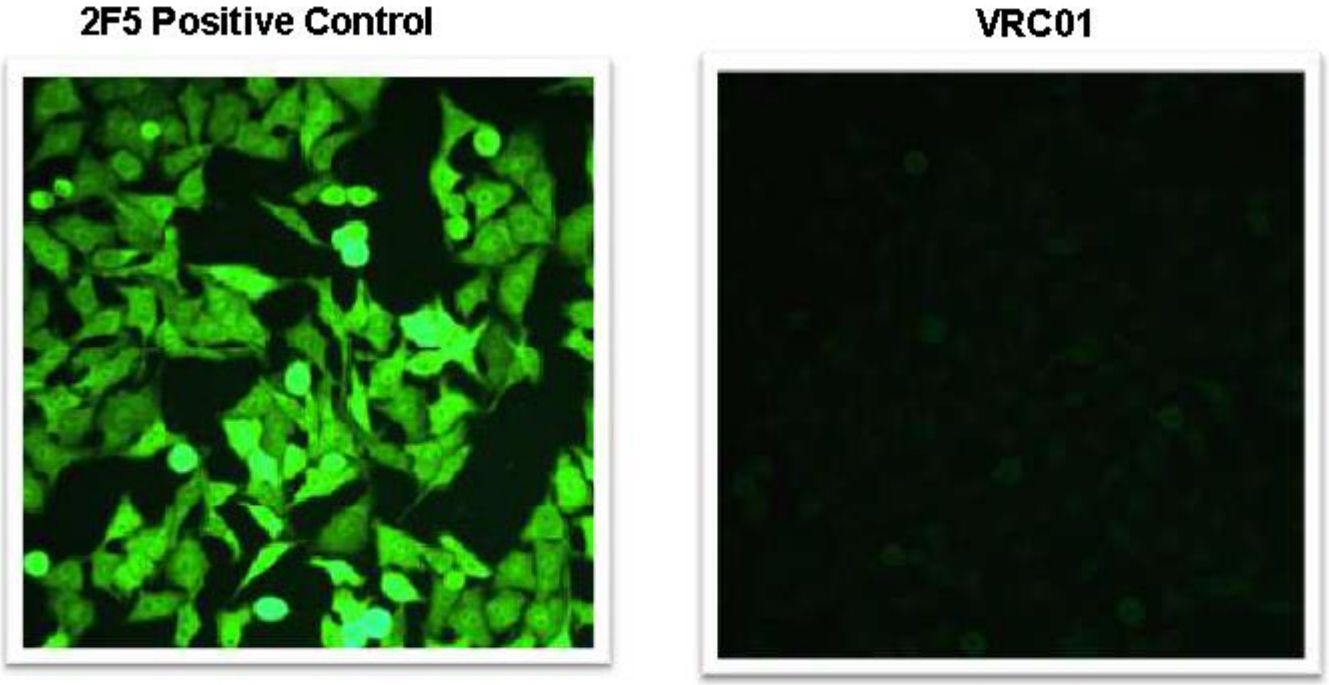
- VRC07-523LS has greater breadth and increased potency compared to VRC01LS, although t1/2 is not as long



Panel of 208 Env-pseudoviruses: Doria-Rose, Louder, McKee, Bailer et al.

No Auto-Reactivity

- No evidence of auto- or poly-reactivity with human tissue (absent ANA, anticardiolipin, or anti-PTT)
- 38 types of issue for adults and 21 for neonates—no cross-reactivity



Barton Haynes
Julie Ledgerwood

IMPAACT P1112: *Study Overview*

Open label, dose-escalating, phase I study of safety and pharmacokinetics of single and multiple subcutaneous (SC) doses starting at birth

VRC01 (VRC-HIVMAB-060-00-AB)

- Dose group 1 (N=13, non-breastfed)
  - Birth dose 20mg/kg
- Dose group 2 (N=14, non-breastfed)
  - Birth dose 40mg/kg
- Dose group 3 (N=13, breastfed)
  - Birth dose 40mg/kg
  - Monthly dose 20mg/kg

VRC01LS (VRC-HIVMAB-080-00-AB)

- Dose group 4
- Cohort 1 (non-breastfed, N=10)
  - **Birth dose** weight bands

    Wt <4.5 kg: 80mg

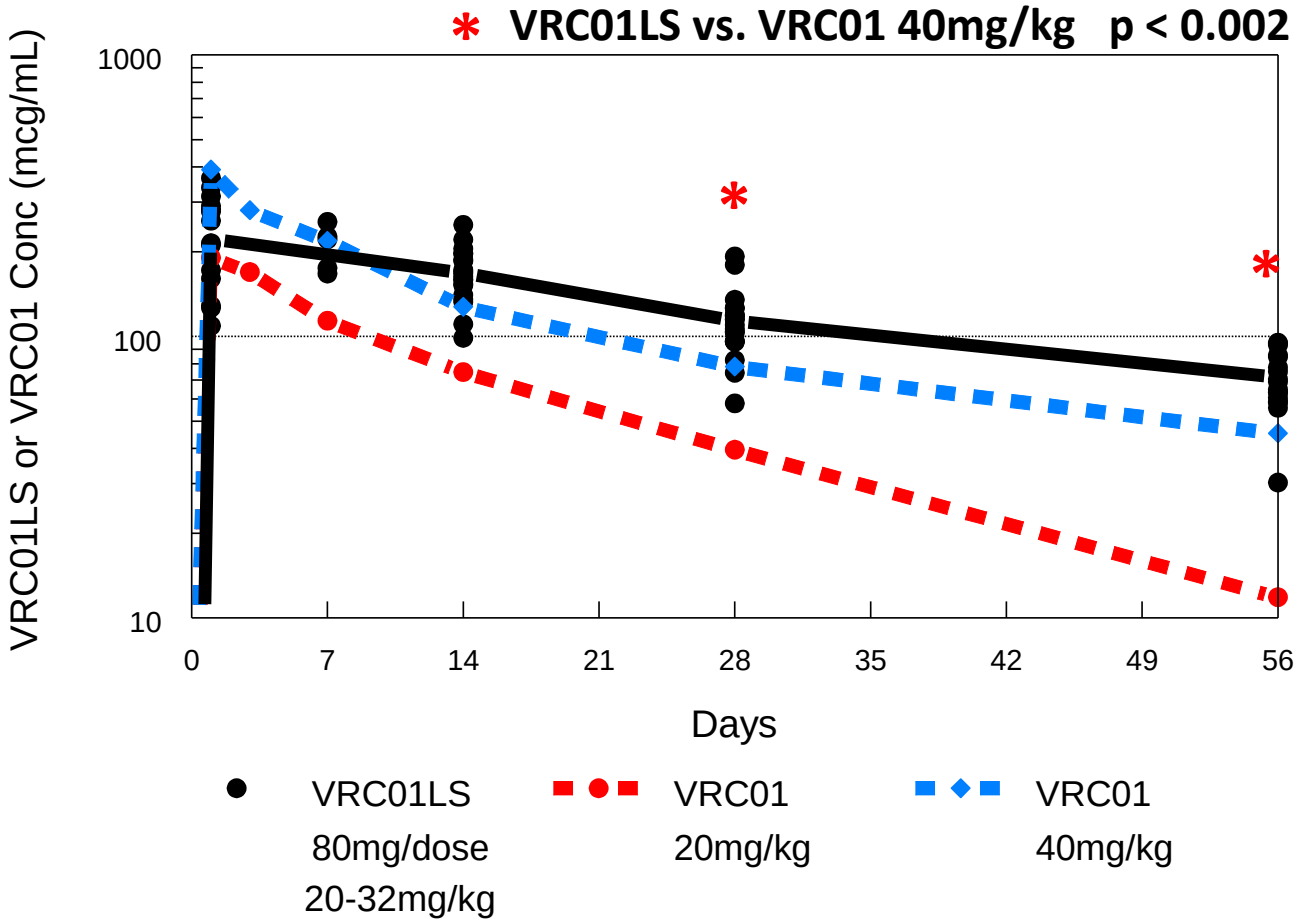
    Wt ≥ 4.5 kg: 100mg
- Cohort 2 (breastfed, N=11)
  - **Birth dose** weight bands

    Wt <4.5 kg: 80mg

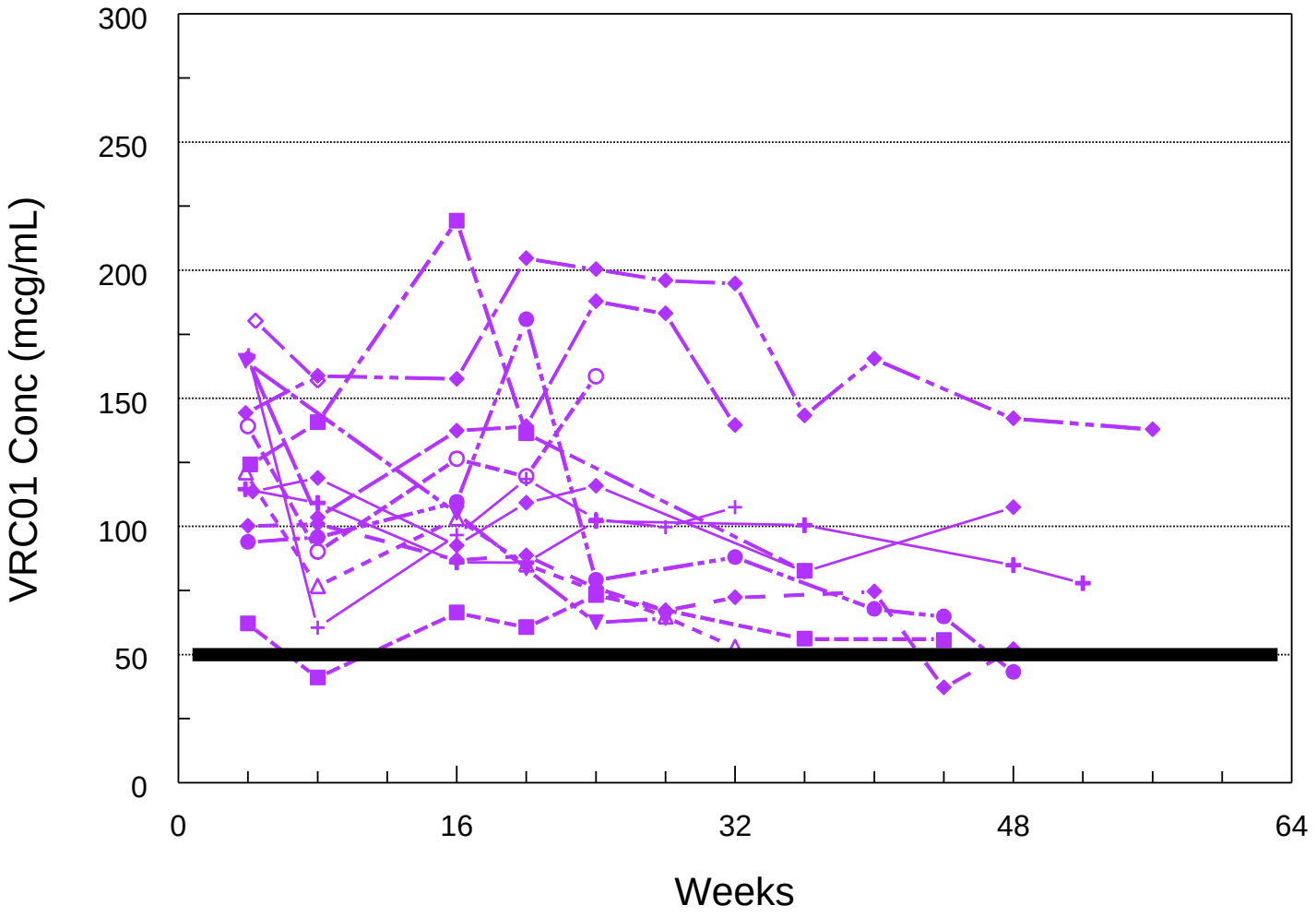
    Wt ≥ 4.5 kg: 100mg
  - **Week 12 dose** : 100mg

Characteristic		Dose Group 1 (20mg/kg) (N=13)	Dose Group 2 (40mg/kg) (N=14)	Dose Group 3 (40/20 monthly) (N=13)	Dose Group 4 Cohort 1 (N=10)	Dose Group 4 Cohort 2 (N=11)
Gender	M	8 (62%)	6 (43%)	8 (62%)	6 (60%)	5 (45%)
Race	Black	6 (46%)	11 (79%)	13 (100%)	8 (80%)	11 (100%)
	White	6 (46%)	2 (14%)	0	1 (10%)	0
Infant ART	3TC, ZDV	1 (8%)	0 (0%)	0	0	0
	3TC, ZDV, NFV	1 (8%)	0 (0%)	0	0	0
	3TC, ZDV, NVP	2 (15%)	5 (36%)	0	2 (20%)	0
	NVP	0	1 (7%)	12 (92%)	2 (20%)	11 (100%)
	ZDV	4 (31%)	4 (29%)	0	5 (50%)	0
	ZDV, NVP	5 (38%)	4 (29%)	1 (8%)	1 (10%)	0
Age (days) at Administration	Mean (s.d.)	1.5 (1.1)	1.9 (0.9)	2.7 (1.4)	2.0 (0.9)	2.4 (0.8)
	Median	2	2	2	2	2
	Min, Max	0, 3	0, 3	1, 5	0, 3	1, 4
Birth Weight (grams)	Mean	3,185	3,134	3,055	3123	2948
	Median	3,045	3,160	2,860	2,865	2,920
	Min, Max	2,330, 4,675	2,609, 3,580	2,330, 4,320	2,535, 4,045	2,500, 3,545
Enrollment site	S. Africa and Zimbabwe	1 (8%)	5 (36%)	13 (100%)	3 (30%)	11 (100%)
	United States	12 (92%)	9 (64%)	0	7 (70%)	0

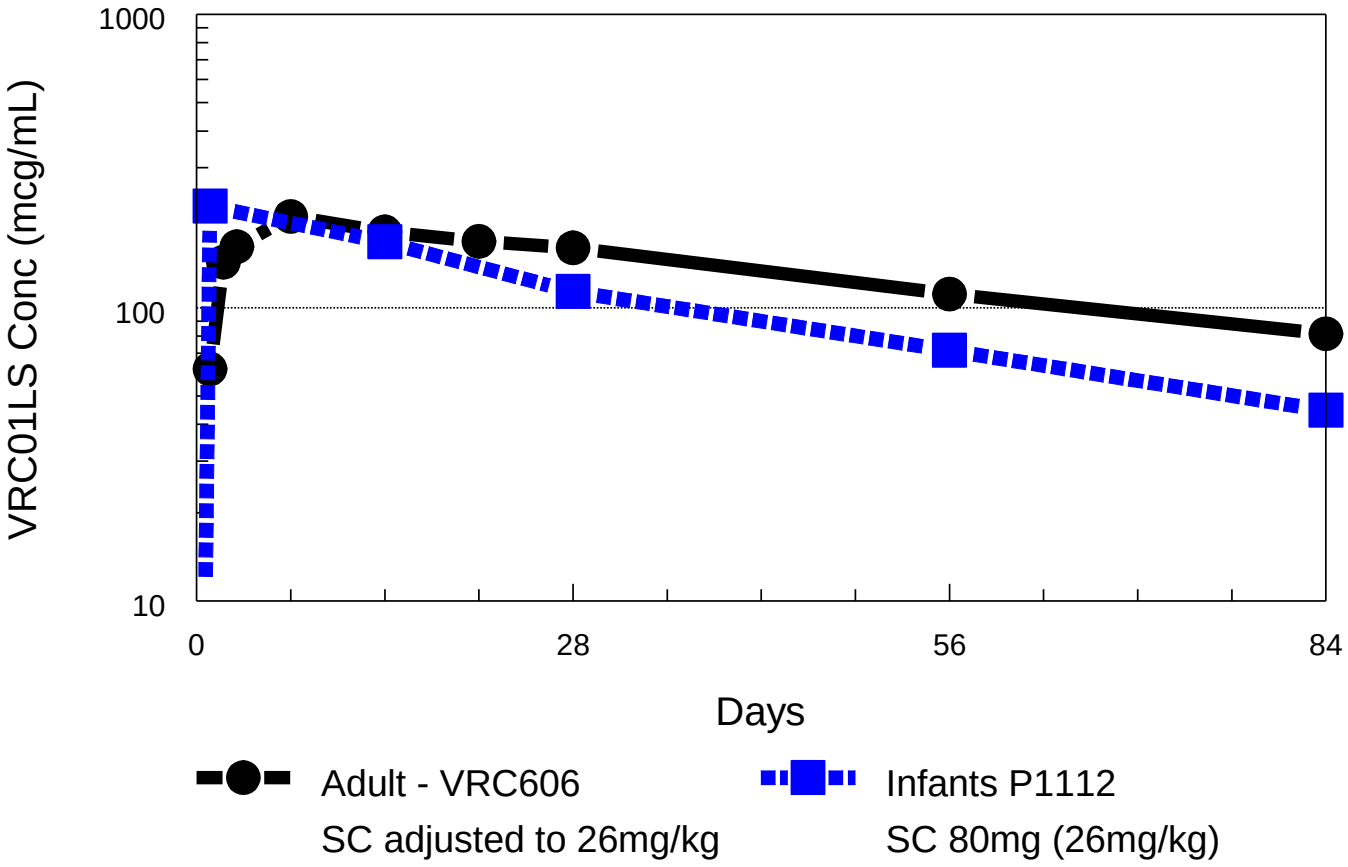
Infants receiving VRC01LS (Dose Group 4) achieved significantly higher levels at day 28 and later time points.



Infants receiving multiple doses (dose group 3) remained over 50 mcg/mL almost all the time.



Infants receiving VRC01LS (Dose Group 4) maintain lower levels at later time points compared to the modeled adult values.



VRC01 and VRC01LS Safety

- Frequent local reactions, generally mild and resolved rapidly
- No serious adverse events attributed to study drug
- No infants HIV-infected

Dose Group 4: Local Reactions

Local reactions were common, especially with the first dose; almost all mild and resolved within hours

	Cohort 1: dose 1 (n=10)	Cohort 2: dose 1 (n=11)	Cohort 2: dose 2 (n=10)
Volume per site, mean (min/max)	**0.8 mL (0.8/0.8)**	**0.6 mL (0.4/0.8)***	**0.6 mL (0.3/1.0)***
% of children with any reaction^	**50%**	**82%**	**20%**
Grade mean (min/max)&	**1 (1/1)**	**1 (1/1)**	**2 (2/2)**
Resolution by 1 hr	**60%**	**89%**	**0%**
Resolution by 24 hr	**100%**	**100%**	**100%**

* Some infants received dose split across two injection sites

^ Erythema 9-55%; edema 10-45%, induration 0-20%, bruising: 1 infant

& Reaction size: most 1-2 cm; maximum 3.5 cm

In conclusion

- VRC01 and VRC01LS are well tolerated.
- VRC01 and VRC01LS can be administered at birth and subsequent time points to achieve desired levels.
- Broadly neutralizing antibodies are feasible as an additional strategy to prevent perinatal transmission of HIV in infants at increased risk.
- **Next steps:**
  - VRC07-523LS enrolling- increased potency & breadth (*IMPAACT P1112)*
  - Studies of bNAb as adjunct to ART for neonatal HIV prevention and early treatment *(IMPAACT 2008; IMPAACT P1115)*

Next Steps

- What data would be needed to bring one of these products into the clinic?
- Who is the target population?
- Which product(s)?
- Single agent or combination?
- Passive only or active/passive together?

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Sites

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