The development of broadly neutralizing antibodies in HIV-infected infants

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FRED HUTCH
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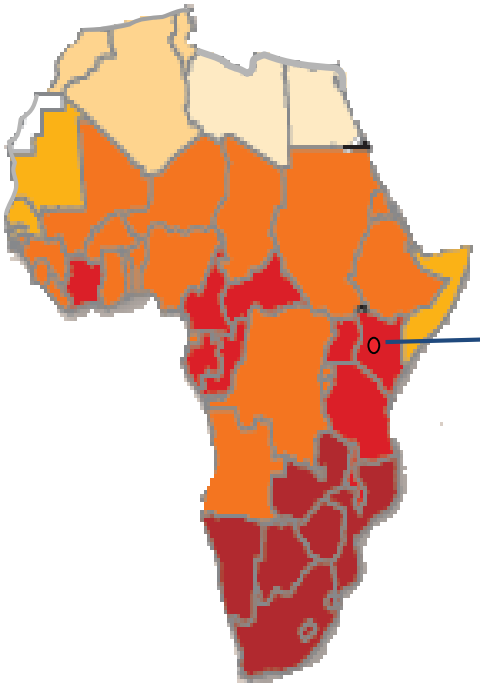
Studies of infant nAb responses to HIV

Seattle/Kenya Collaboration

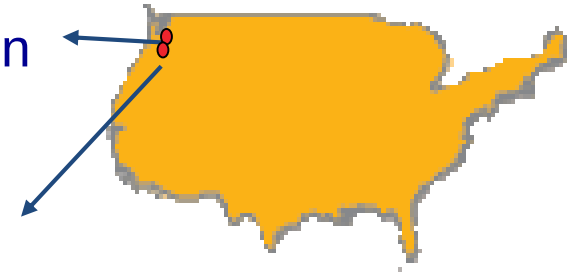


Collaborating Institutions:

University of Nairobi

Fred Hutchinson

University of Washington

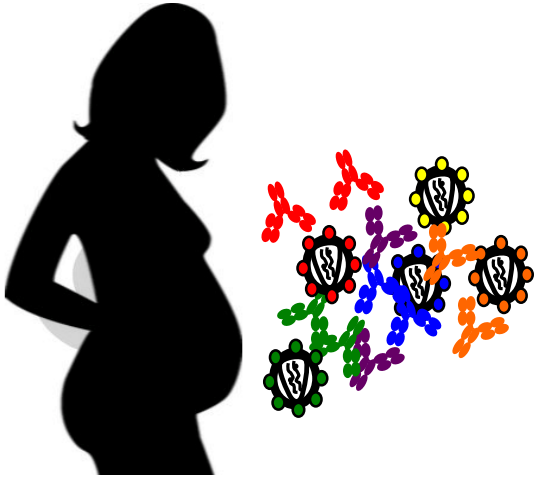


What is the nAb response to HIV infection in infants?

There are many unique aspects of MTCT

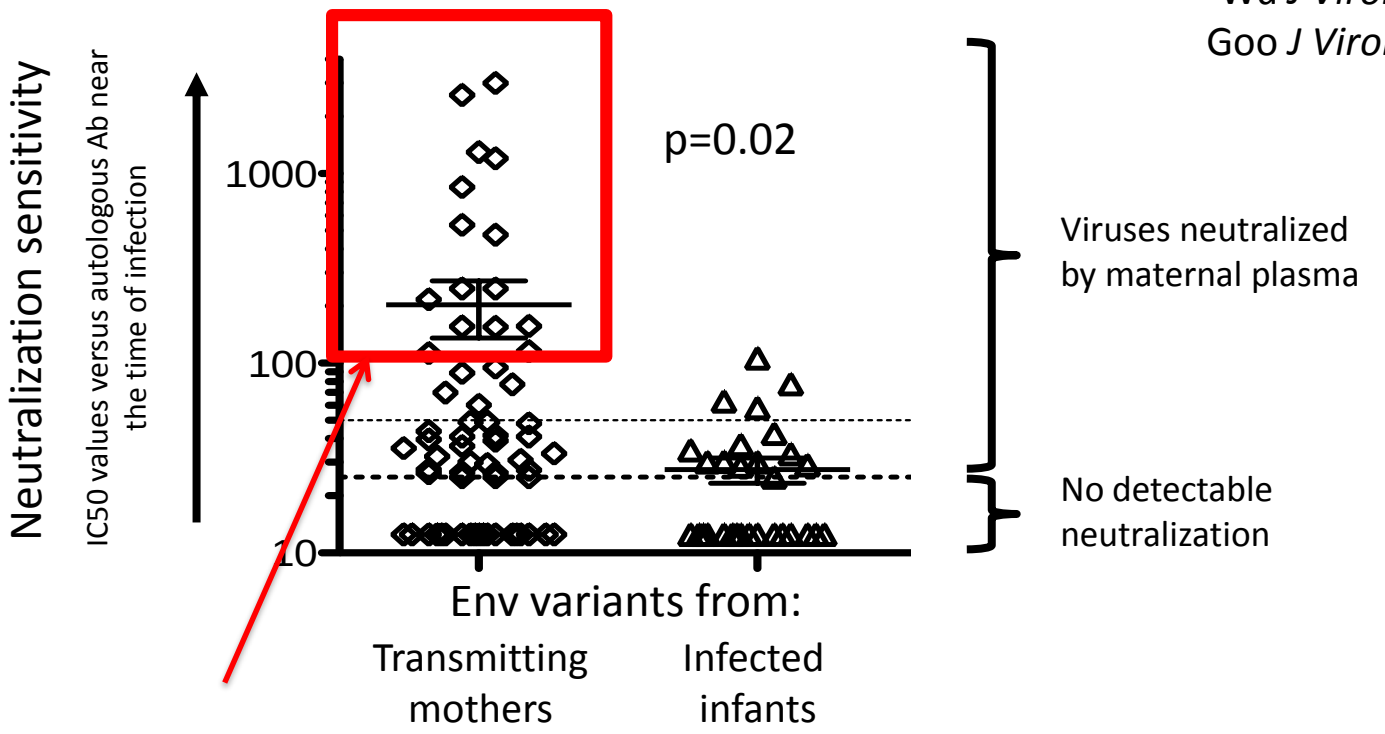
In the case of intrapartum and breastfeeding transmission, infection occurs and infant antibody responses develop in the face of **passively acquired HIV-specific antibodies from the mother**

- These maternal HIV-specific Abs could create immune complexes that enhance the developing Ab responses in infants
- Studies from the Haigwood lab in NHP suggest passive abs can augment de novo responses (Haigwood *JV* 2004, Ng *Nat Med* 2010)



The viruses that establish infection in infants are generally neutralization escape variants

Wu *J Virol* 2006
Goo *J Virol* 2012

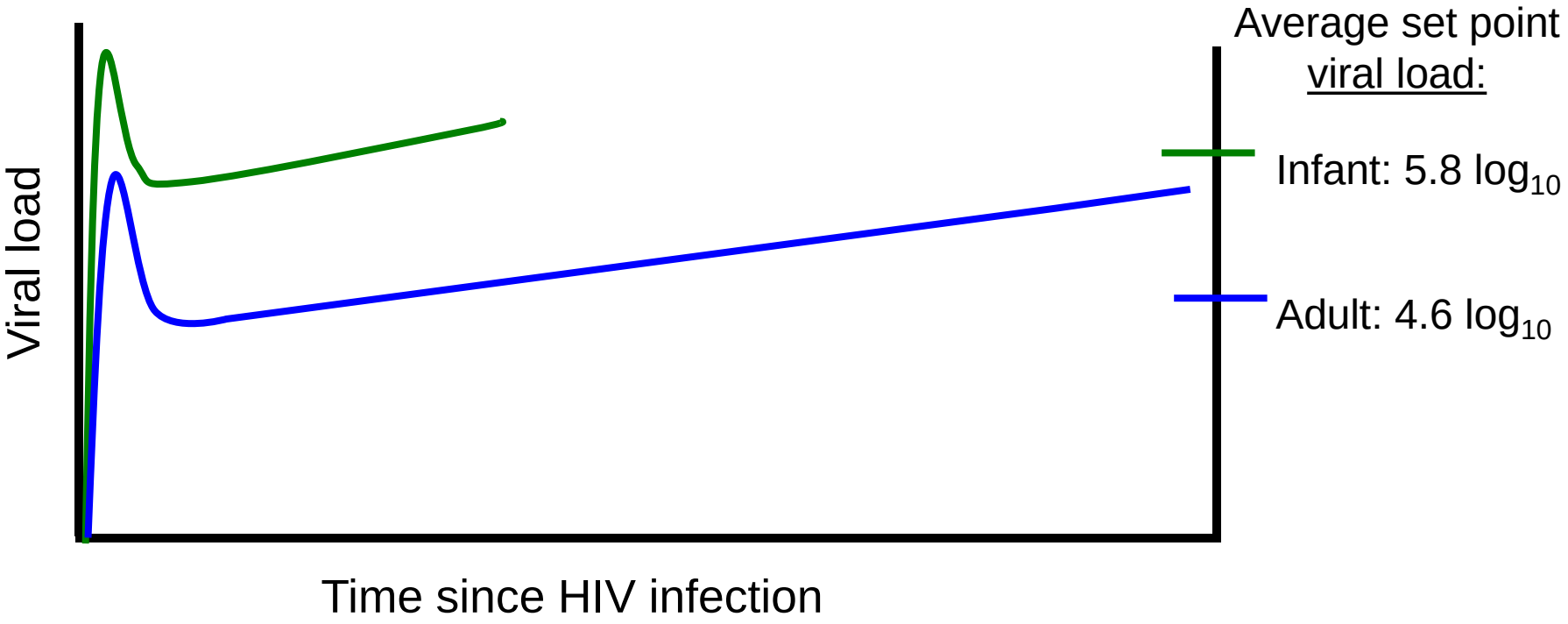


- Escape occurs through conformational masking not by mutation in the epitope itself
- **Perhaps the Env protein of viruses transmitted to infants have unique properties**

Infants have higher viral loads than adults

Viral load is correlated with development of bnAbs

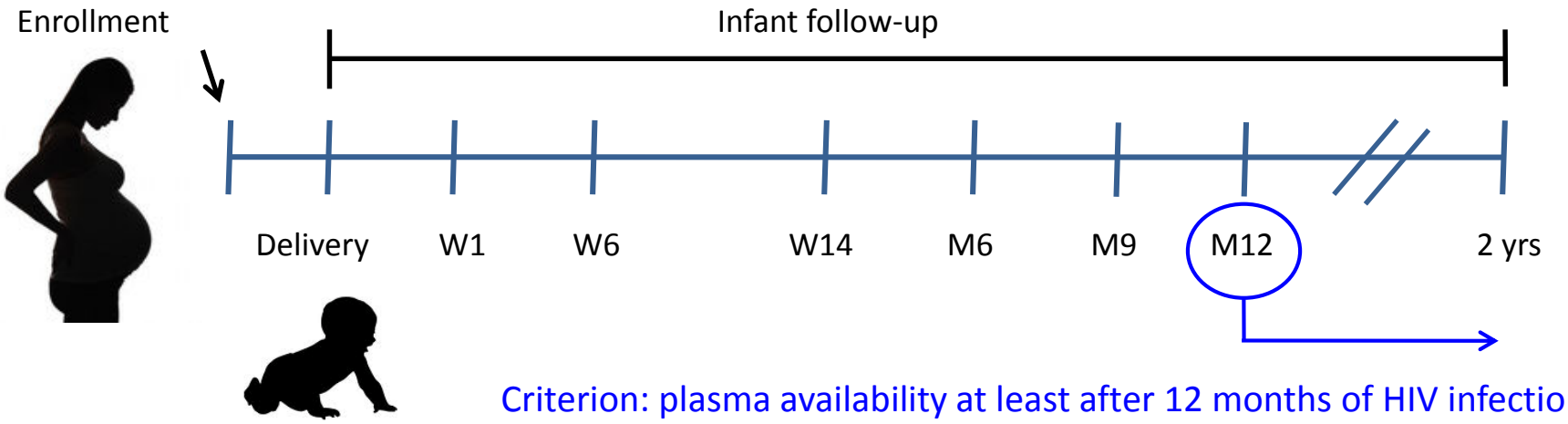
Piantadosi *JV* 2009; Sather *JV* 2009; Euler *JID* 2010; Gray *JV* 2011; Rusert *Nat Med* 2016



Richardson *J Virol* 2003

Do infants develop bnAbs?

Nairobi Breastfeeding Clinical Trial: conducted 1992-1997 (pre PMTCT)



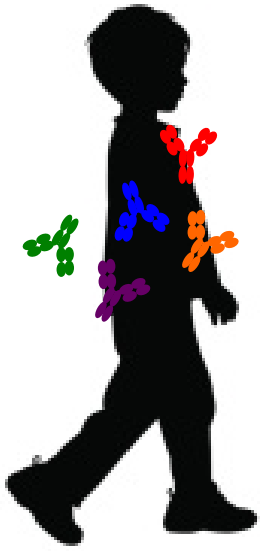
Criterion: plasma availability at least after 12 months of HIV infection
N = 28; median of 22 months PI

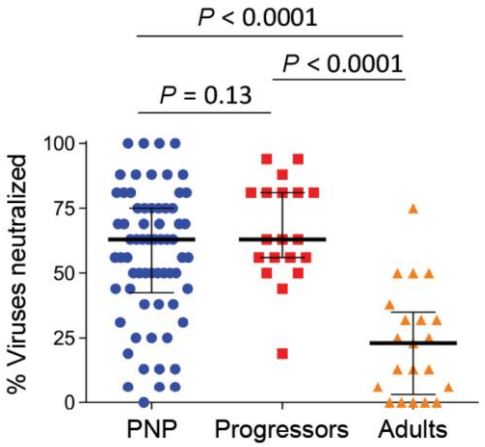
Leslie Goo

Goo *Nature Medicine* 2014

Pediatric broadly neutralizing antibody responses

Goo *Nature Medicine* 2014





Muenchhoff *Science Translational Medicine* 2016

12-30 months of age

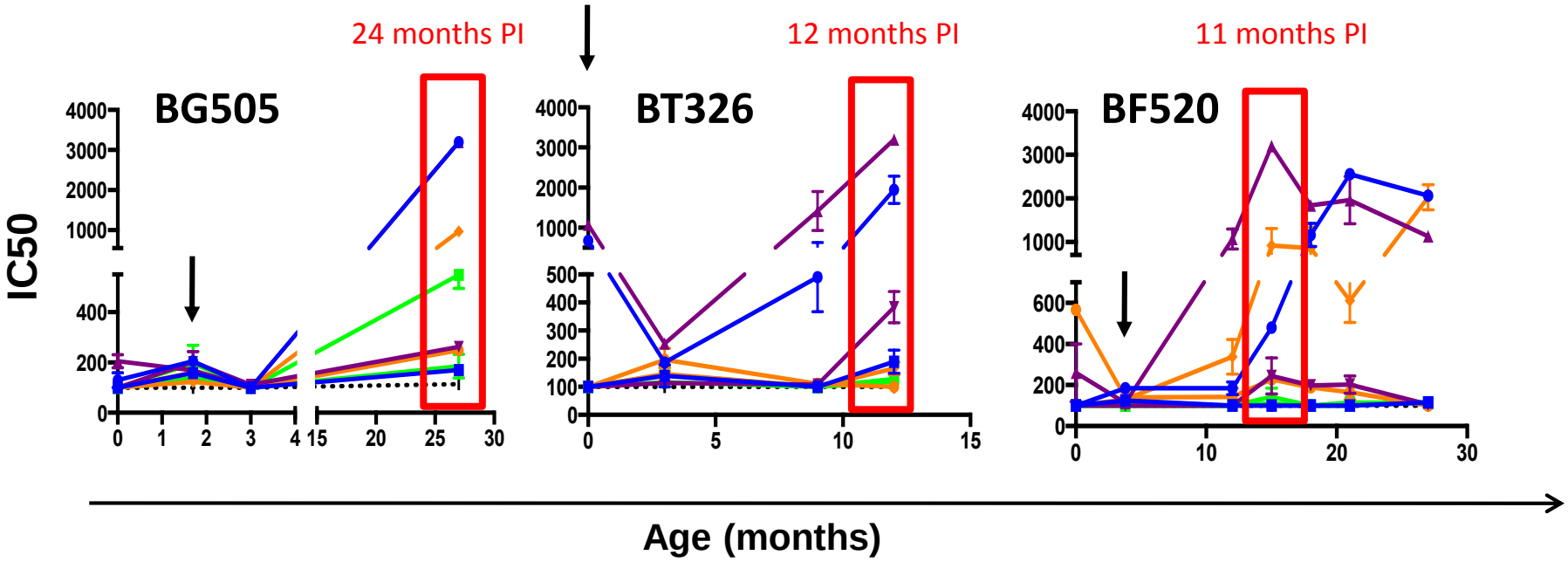
- **71%** (20/28) tier-2, cross-clade neutralization
- **29%** (8/28) neutralized viruses from 4 different clades

Median age of 6.6 years

- **75%** (64/85) neutralized >50% of a cross-clade panel of viruses

Viral load associated with neutralization breadth

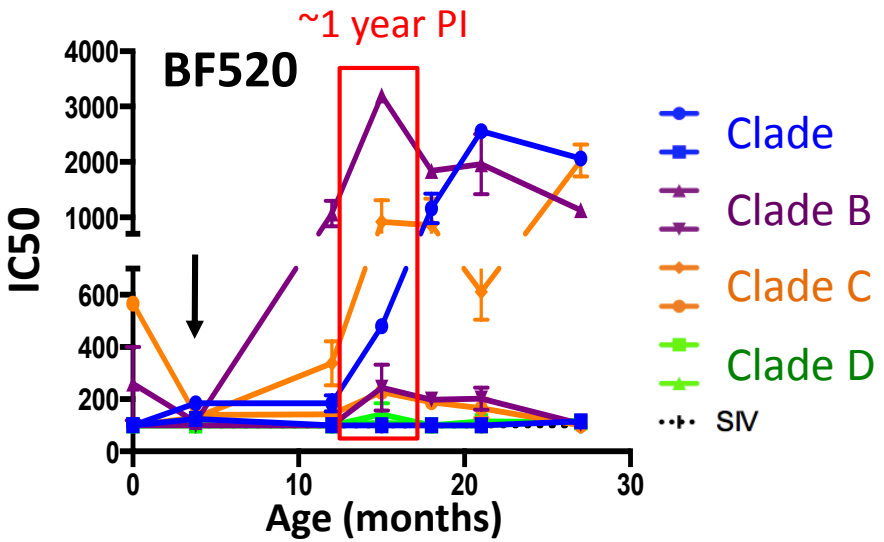
Some infants develop bnAbs with rapid kinetics



- 20/28 infants developed cross clade nAbs at a median of 22 months post-infection
- Some developed bnAbs within the first year of infection
- Unable to detect dominant plasma responses targeting known bnAb epitopes, suggesting the responses may be polyclonal and/or directed to novel epitopes

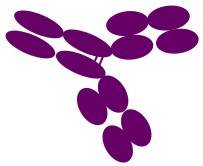
Goo *Nature Medicine* 2014

First case of infant-derived HIV antibodies



- Clade A infected infant; first positive at 4 months (HIV RNA and DNA negative at 1.5 months of life)
- Cross-clade neutralization detected at ~1 year post-infection
- Stored sample from Nov 1995

- **Screened individual IgG$^+$ memory B cell culture supernatants for neutralizing activity**
- Ten HIV-specific nAbs were isolated
- 6 show some ability to neutralize a Tier 2 virus
- One showed cross-clade breadth: BF520.1
- All were unique B cell lineages



A combination of mAbs contribute to breadth, one of which has cross-clade breadth

			BF520 Plasma	BF520.1	BF520.2	BF520.3	BF520.4	BF520.5	BF520.6	BF520.7	BF520.8	BF520.9	BF520.10
		SIV	<100	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20
Tier 1	Clade B	SF162	>3200	0.22	0.65	1.47	6.96	2.67	1.32	0.75	1.07	3.41	1.08
Tier 2	Clade A	Q461.d1	480	>20	1.72	1.76	6.23	>20	0.69	1.97	2.23	>20	>20
		Q23.17	339	0.29	>20	>20	>20	>20	>20	>20	>20	>20	>20
		Q842.d16	306	>50	25.7	19.5	26.7	11.4	>50	23	>50	42.1	>50
		Q769.B9	<100	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20
		Q259.d2.26	121	>50	>50	>50	>40	>50	>50	>50	>50	>50	>50
		BJ613.E1	188	>50	>50	>50	>40	>50	>50	>50	>50	>50	>50
		Q168.a2	<100	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20
		Q842.d12	115	>50	>50	>50	>40	>50	>50	>50	>50	>50	>50
	Clade A/D	BF535.A1	128	>50	>50	>50	>40	>50	>50	>50	>50	>50	>50
	Clade B	TRO.11	244	5.26	>20	>20	>20	>20	>20	>20	>20	>20	>20
		THRO4156.18	<100	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20
		CAAN.A2	124	42.2	>50	>50	>20	>50	>50	>50	>50	>50	>50
Tier 3		TRJO4551.58	124	>20	>20	>20	>40	>20	>20	>20	>20	>20	>20
		PVO.4	119	38.1	>50	>50	>20	>50	>50	>50	>50	>50	>50
Tier 2	Clade C	ZMN109F.PB4	108	>20	>50	>50	>40	>50	>50	>50	>50	>50	>50
		QC406.F3	922	0.2	>20	>20	>20	>20	>20	>20	>20	>20	>20
		DU156.12	228	5.33	>20	>20	>20	>20	>20	>20	>20	>20	>20
		DU422.1	159	6.81	>50	>50	>20	>50	>50	>50	>50	>50	>50
		DU172.17	159	20.6	>50	>50	>20	>50	>50	>50	>50	>50	>50
		CAP210.E8	186	>20	>50	>50	>40	>50	>50	>50	>50	>50	>50
	Clade D	QB857.B3	142	>20	>50	>50	>40	>50	>50	>50	>50	>50	>50
		QD435.A4	110	>20	>50	>50	>40	>50	>50	>50	>50	>50	>50

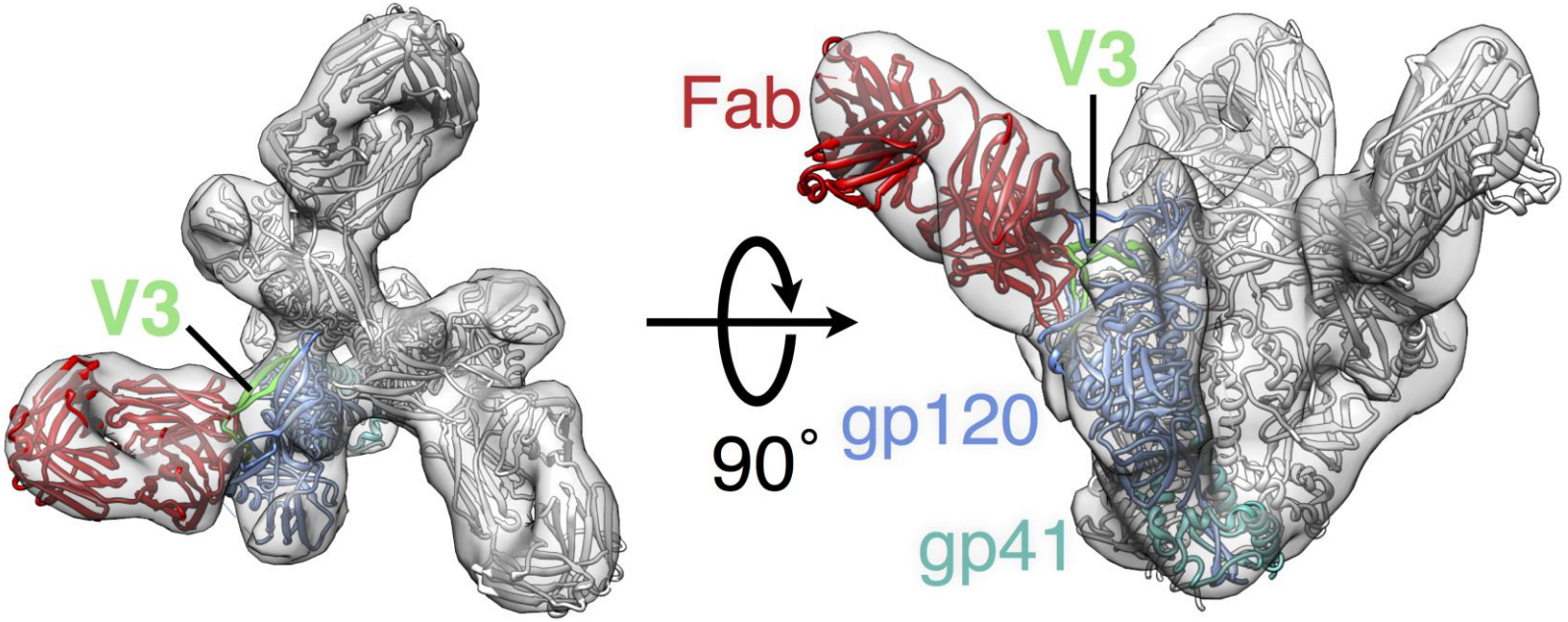
Plasma IC_{50}

- IC_{50} > 1000
- 500 < IC_{50} < 1000
- 200 < IC_{50} < 500
- 100 < IC_{50} < 200
- IC_{50} < 100

mAb IC_{50} (μg ml^{-1})

- IC_{50} < 0.2
- 0.2 < IC_{50} < 2
- 2 < IC_{50} < 10
- 10 < IC_{50} < 20-50
- IC_{50} > 20-50

Negative stain EM reconstruction of Env:Ab

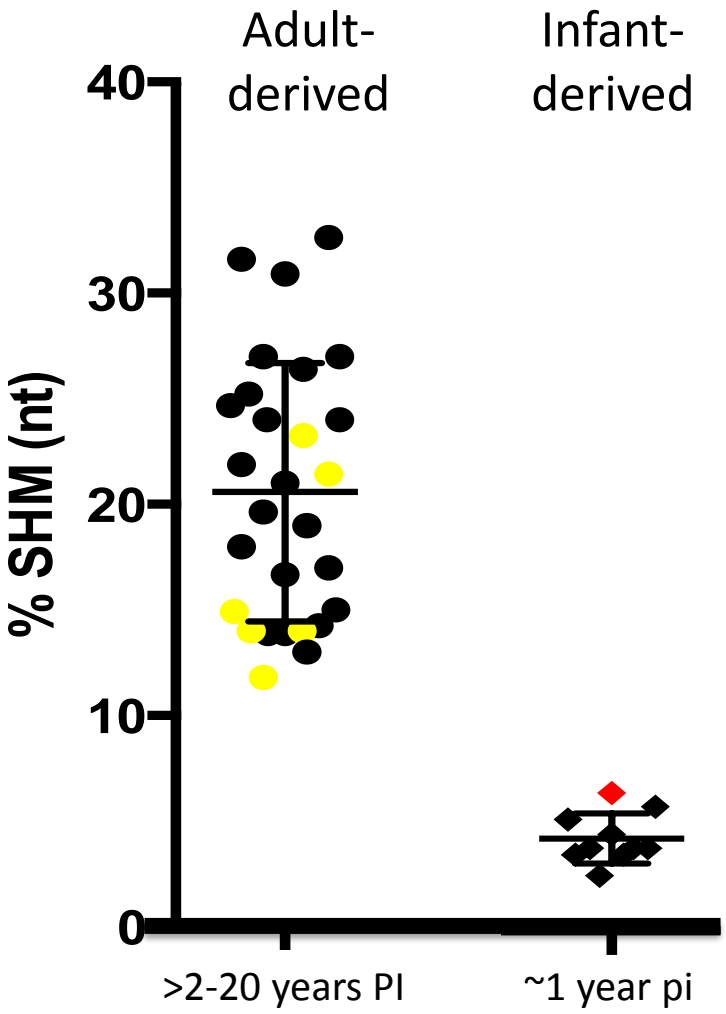


BG505 T332N- an infant derived clade A SOSIP trimer - with bnAb BF520.1 Fab

- BF520.1 targets the N332 supersite in V3
- BF520.1 utilizes distinct germline genes, has less SHM and lacks rare indels compared to adult mAbs targeting the N332 supersite

Hans Verkerke, James Williams, Kelly Lee

Infant nAbs exhibit low levels of somatic hypermutation



Data from bnAber.org and Corti (2013) *Annual Rev Immuno,* Li (2015) *Molecular Immunology,* Scheid (2009) *Nature,* Mouquet (2001) PLoS ONE

BF520

- This infant had a polyclonal response that led to breadth at ~ 1 year PI
- There was one N332 bnAb, BF520.1, that contributed to breadth along with other more clade specific nAbs
- BF520.1 binds, but does not neutralize autologous transmitted virus; nor did any of the other 9 nabs from BF520
    - binding may have initiated the response
- BF520.1 does neutralize later autologous variants (2 months later)

Simonich *Cell* 2016

Julie Overbaugh

Participants and Staff of the Nairobi Breastfeeding Clinical Trial

National Institutes of Health
Turning Discovery Into Health

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Current and former members of the Overbaugh lab

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Former Postdoc

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PhD 2013

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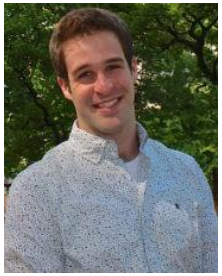
Fellow

Ted Gobillot
MSTP student



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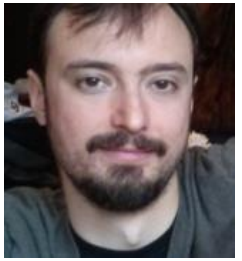

Vladimir Vigdorovich