Babies and bNAbs
Peds Pharmacology and Lessons from Adults

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AIDS Clinical Trials Network

Overview

- Anti-HIV mAbs (bNAbs) uses in infants, children and adults
- Important issues that affect bNAb PK/PD variability and differs from small molecules
- Use of PK/PD modeling and simulation to optimize mAb studies and dosing

bNAbs for HIV Prevention and Treatment

- **Prophylaxis**
  - PrEP – works for sensitive virus (AMP studies)
  - Perinatal
  - Breast Feeding – limited ARV options in infants
- **Treatment**
  - Limit initial viremia and HIV reservoir seeding in acute infection (infants)
  - Enhance adherence and reduce toxicity
  - Substitution for ARVs
  - Promote adaptive immunity - alone and in combination with vaccines
- **PK/PD considerations and targets different based on setting**

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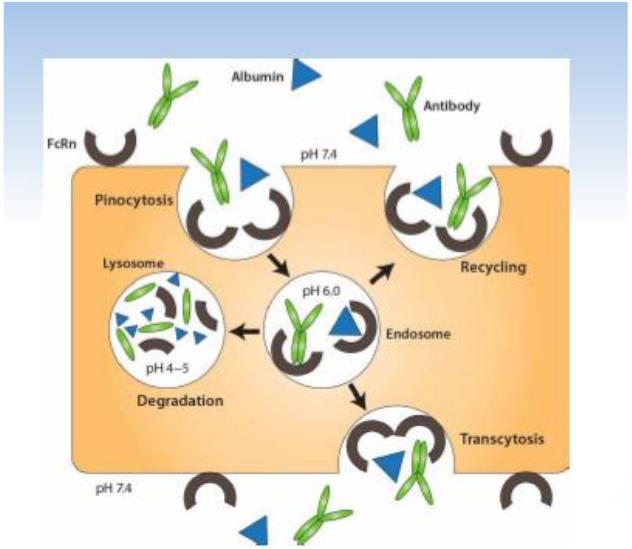
Antibody Distribution and Clearance

- Volume of distribution (Vd) is typically small ~3-8 L
- Nonspecific Clearance (CL) – Proteolysis with lysosomal recycling
  - CL 90-500 mL/d
  - $t_{1/2}$ 10-30 d
- Standard drug metabolizing enzymes – DME (CYPs, UGTs) are NOT involved in mAb elimination
- PK “Boosting” through stabilization of FcRn binding in at low pH
- Additional Clearance Mechanisms
  - Immunogenicity and ADA Formation
  - Target Mediated Drug Disposition
    - Often non-linear



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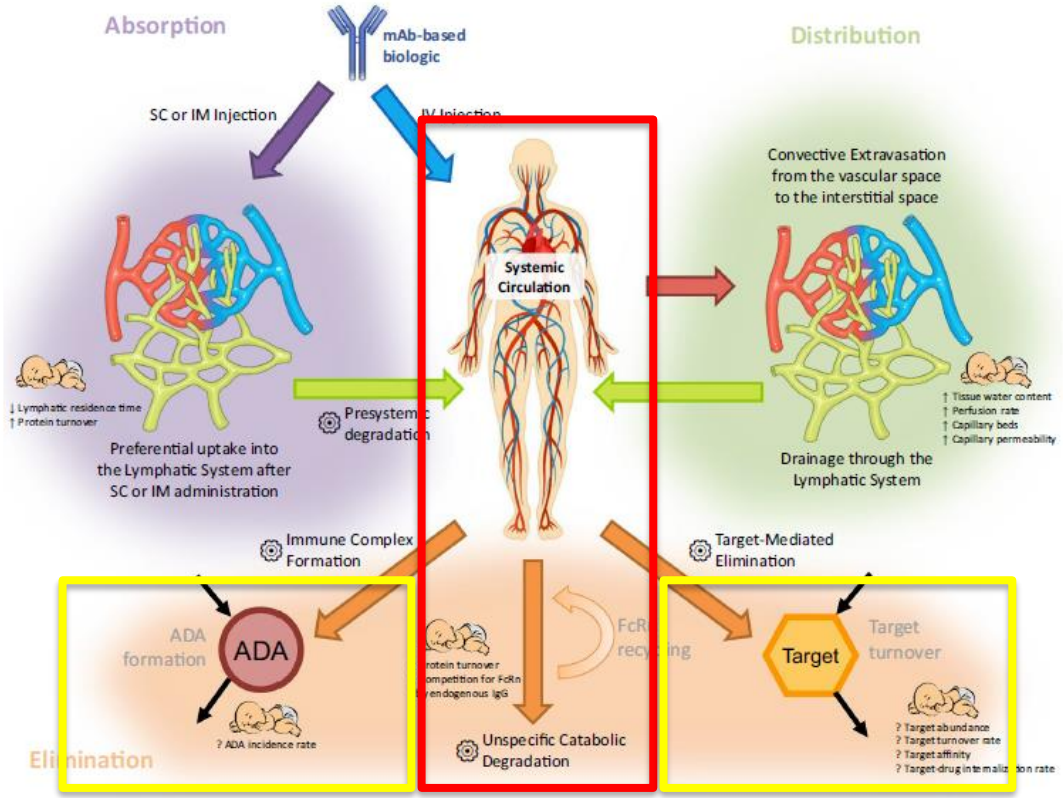
Antibody Disposition and Clearance Pathways



Z Temrikar Ped Drugs 2020

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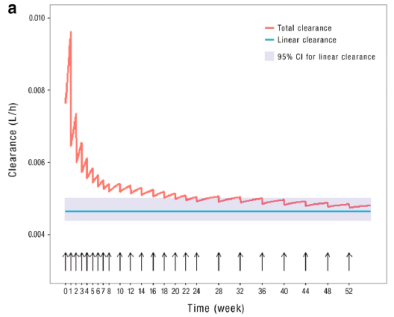
Characterizing mAb Elimination

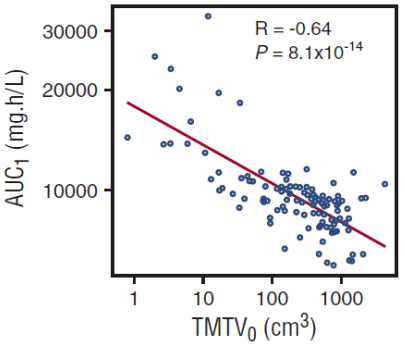
Clearance (CL) , Half-life, and Target Mediated Drug Disposition (TMDD)

- CL – PK parameter used to characterize elimination
  - Dictates the AUC / average concentration of a dosing regimen
- $T_{1/2}$ – "Hybrid" PK parameter : A Function of Distribution (Vd) and Elimination (CL):
  - $T_{1/2} = 0.693 * Vd / CL$
  - Dictates the peak/trough fluctuation during dose interval
  - Various ways to estimate and sensitive to study design
- Target Mediated Drug Disposition (TMDD)
  - mAb Binding to Antigen influence mAb elimination (CL) and/or distribution (Vd)
  - Commonly seen with mAbs for oncology
  - May encounter with bNAb combinations and with HIV viremia
- Study design and analysis complexities with slow bNAb elimination

Daratumumab*



Rituximab**



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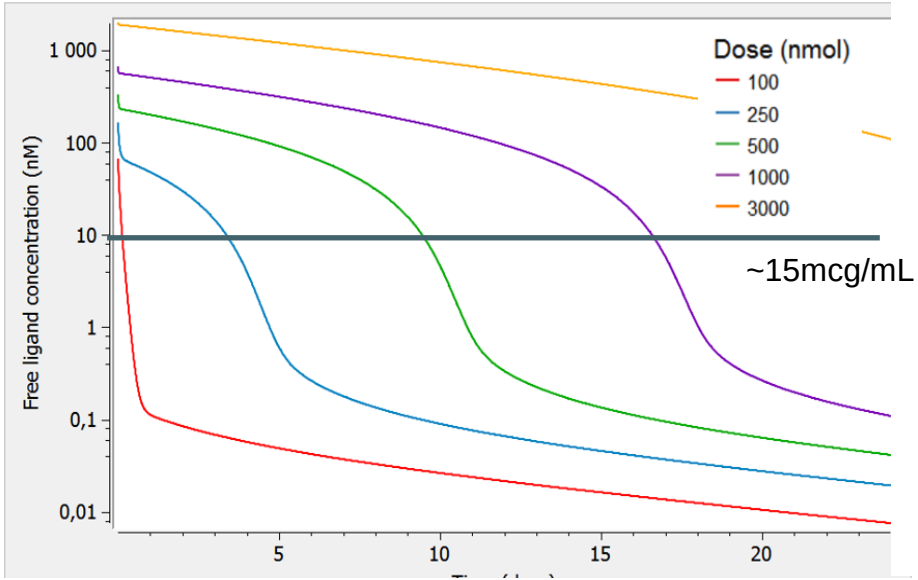
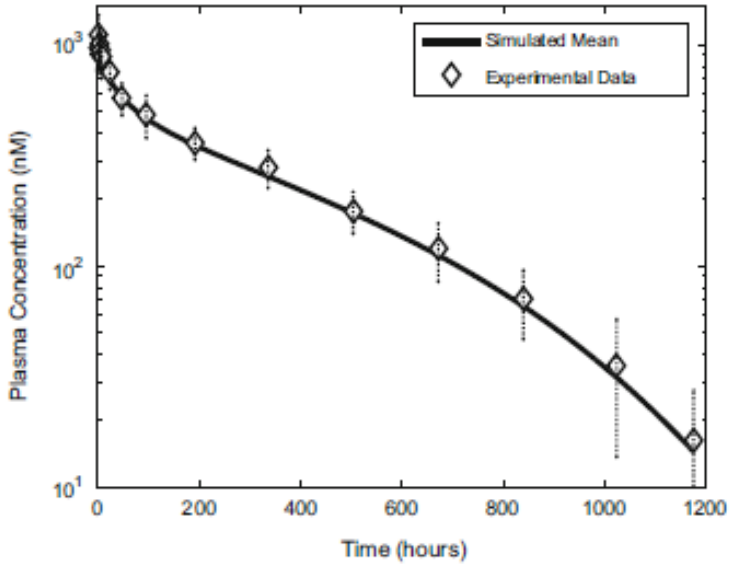
Target Mediated Drug Disposition of mAbs

Binding effects PK at low dose/conc



Trastuzumab



Maulik et al J PKPB 2016

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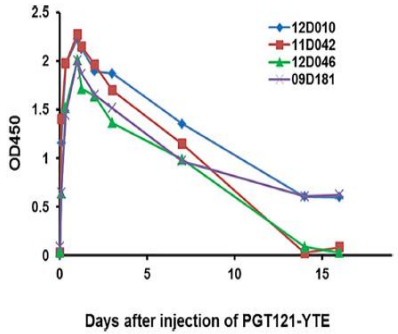
Immunogenicity Can Impact mAB PK

Primate Study of PGT121-YTE



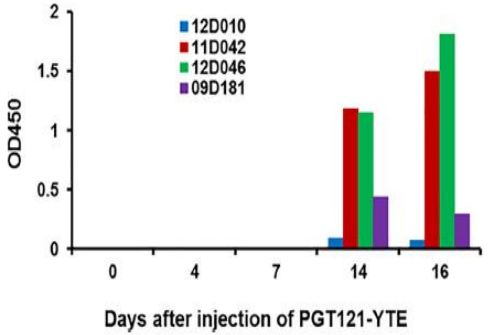


Table 1. Pharmacokinetic parameters in four macaques following a single SC injection with 5mg/kg PGT121-YTE.

PK parameter	12D010	09D181	12D046	11D042
T1/2 (hr)	139	177	55	35
Cmax (µg/ml)	131	108	112	133
AUC (µg-hr/ml)	27,443	18,570	13,493	18,499
MRT (hr)	169	211	92	90

https://doi.org/10.1371/journal.pone.0212649.t001

Clinical development of PGT121.414LS does **NOT** have the YTE Fc-modification

Rosenberg PLOSOne 2019

Why PK / PD Modeling of bNAbs?

- Builds on PK knowledge of bNAb - best approach to assess dose with predictions and simulations for future studies.
- Single dose PK studies very long in duration due to washout.
- Non-compartmental PK evaluation of terminal slope overly depended on very late conc and can give imprecise terminal $t_{1/2}$ and AUC calculations.
- Studies often rely on small dose cohorts n=3-4. Modeling allows overall analysis across dose cohorts and test of PK linearity.
- Better suited to evaluate dynamic and multiple covariates
  - HIV status, viral load, dose, weight/age

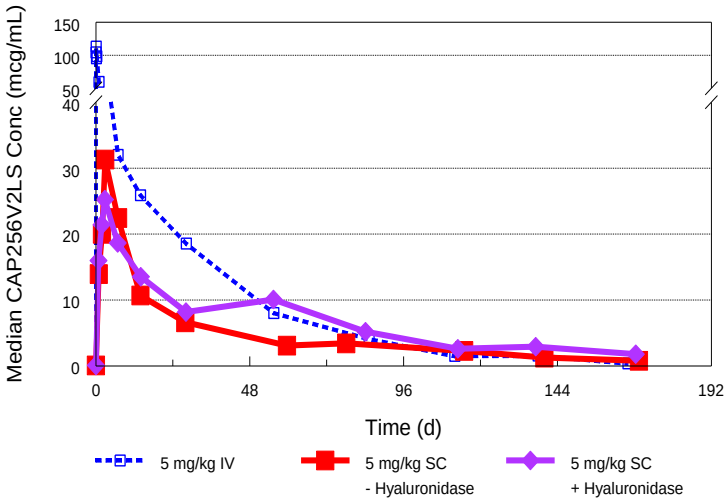
Absorption of bNAbs with SC Administration

- Absorption and distribution driven by lymphatic flow (100 mL/h) not blood flow (300-400 L/h)
- Adult PK studies focus on IV administration with some low dose SC assessments
- Infant PK studies focus on SC administration
- Dose can impact SC bioavailability and rate of absorption
- Rate of SC absorption
  - Rapid in neonates compared to adults – t_{max} at 24-48h
- Bioavailability (F)
  - SC bioavailability is less than complete often ~40-90%.
  - May be different between adults and infants
  - May be different between native Fc and LS modified Fc

bNAb PK with SC Administration -
Larger Doses Can be Administered SC with Hyaluronidase

SC bNAb PK with Hyaluronidase

SC (+Hyaluronidase) vs. SC (-Hyaluronidase) vs. IV



SC mAbs Examples in Oncology

Name	Antibody
Abagovomab	murine monoclonal antibody against CA125
Veltuzumab	humanised monoclonal antibody against CD20
Alemtuzumab (MabCampath®)	humanised antibody against CD52
Rituximab (MabThera®)	chimeric (murine/human) monoclonal antibody against CD20
Trastuzumab (Herceptin®)	humanised monoclonal antibody against HER2
Denosumab (Xgeva®)	human monoclonal antibody against RANK ligand

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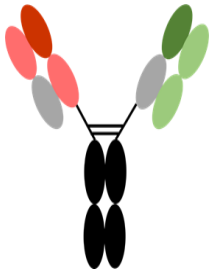
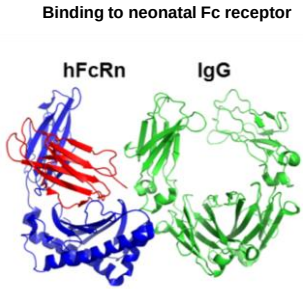
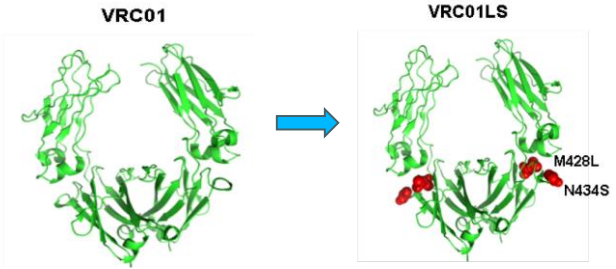
Extending the bNAb Half-life

- Fc region binds with high affinity to FcRn at acidic pH (<6.5) in endosome
- Protects antibody from endosomal degradation
- IgG released back into circulation at physiological pH (7.4)
- <u>Results in prolonged circulating half-life</u>

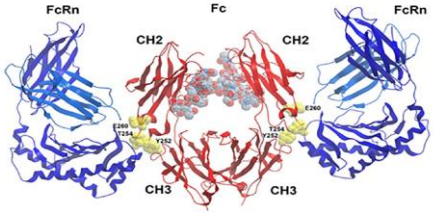




Zalevsky et al.
Nat. Biotechnol, 2010



LS



YTE

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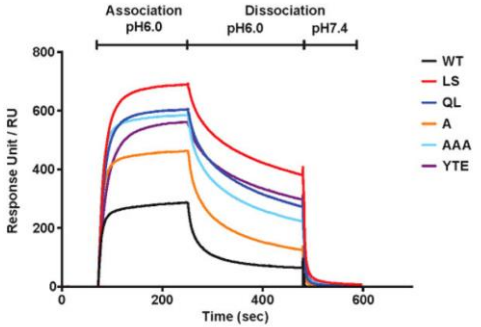
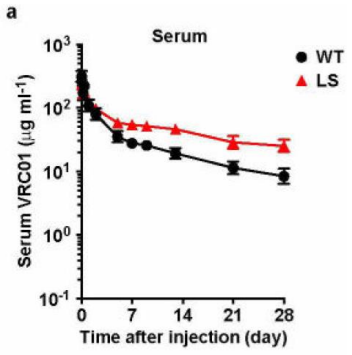
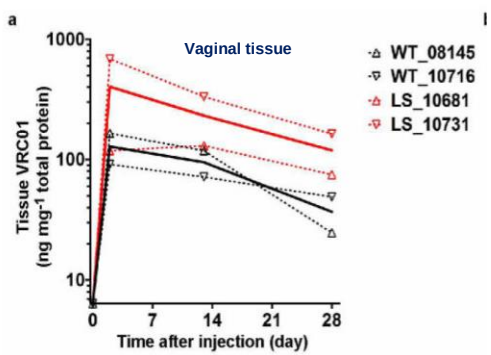
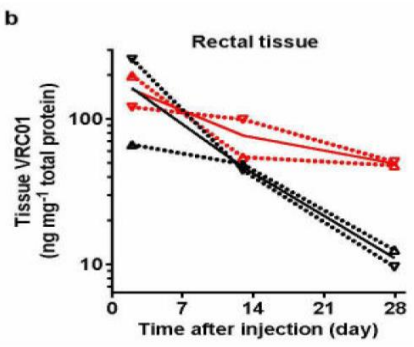
Reduced mAb CL with Fc Modifications

- Enhanced bNAb - FcRN binding under acidic pH (<6.5) in endosome protects bNAb from endosomal degradation
- Pre-clinical studies suggest effect seen in serum, vaginal and rectal tissues
- Impact of FC modification not the same for all bNAb









Ko Nature 2014

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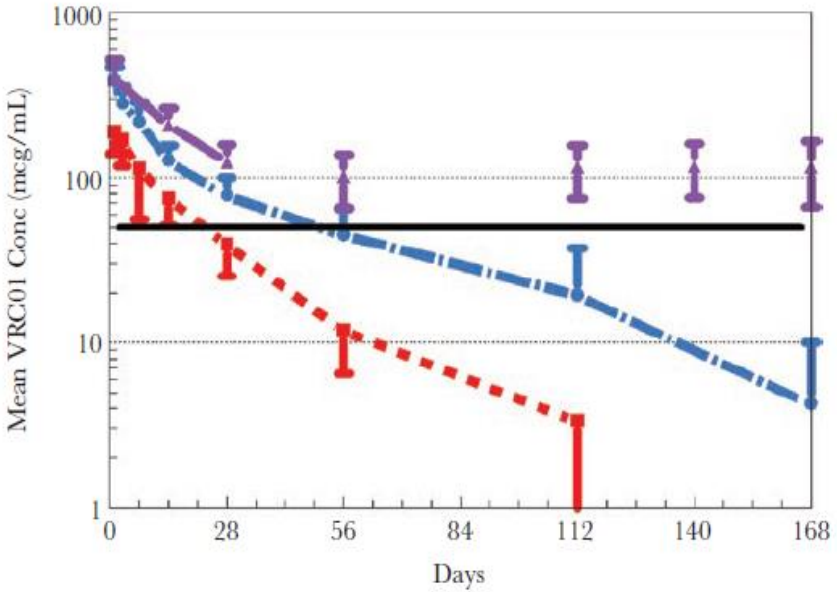
Important Factors to Consider to Explore in Clinical Pharmacology of bNAbs

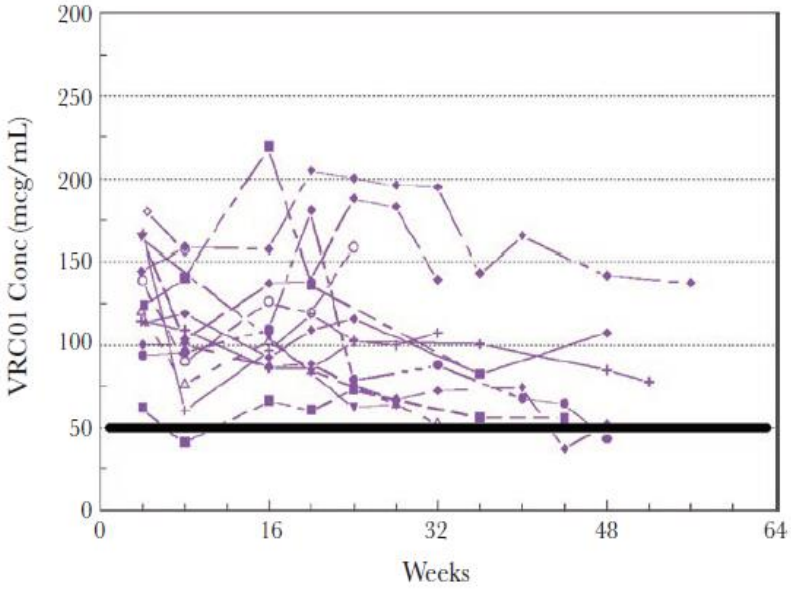
- Age / Weight
- bNAb/bNAb combinations
- HIV Status on PK
- Target bNAb concentrations
- SC dosing +/- hyalurondise

VRC01 in HIV Exposed Infants
IMPAACT P1112 – Arms 1-3

20-40mg/kg +/- 20mg/kg q 4WK



40mg/kg then 20mg/kg q 4WK



C Cunningham JID 2020

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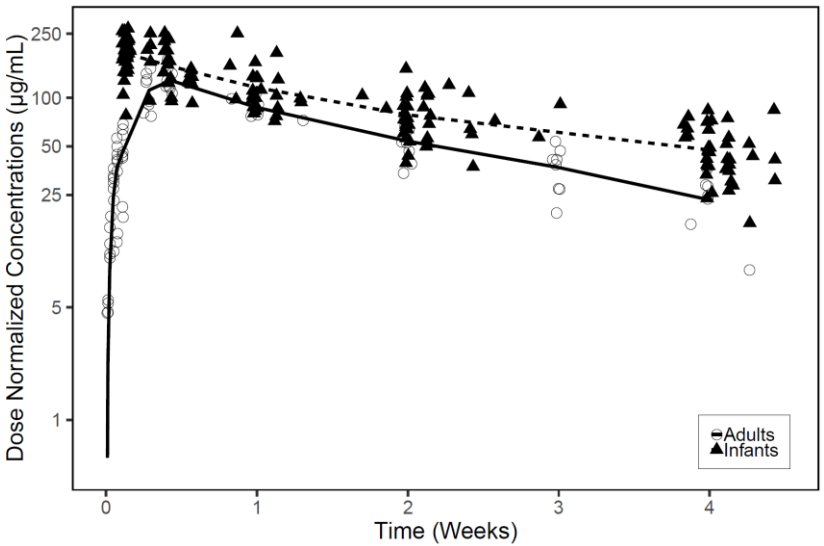
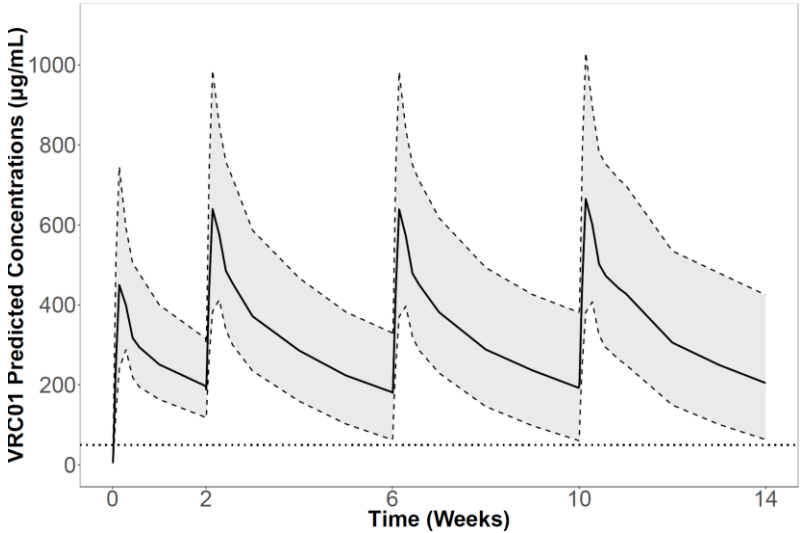
Model Informed Infant VRC01 Study Design -
PopPK to Simulate VRC01 for Treatment (IMPAACT 2008)





J Li et al CPT 2021

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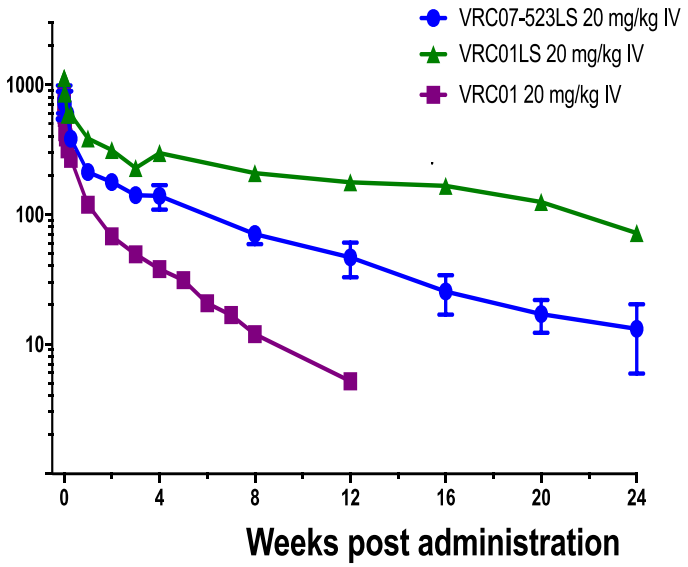
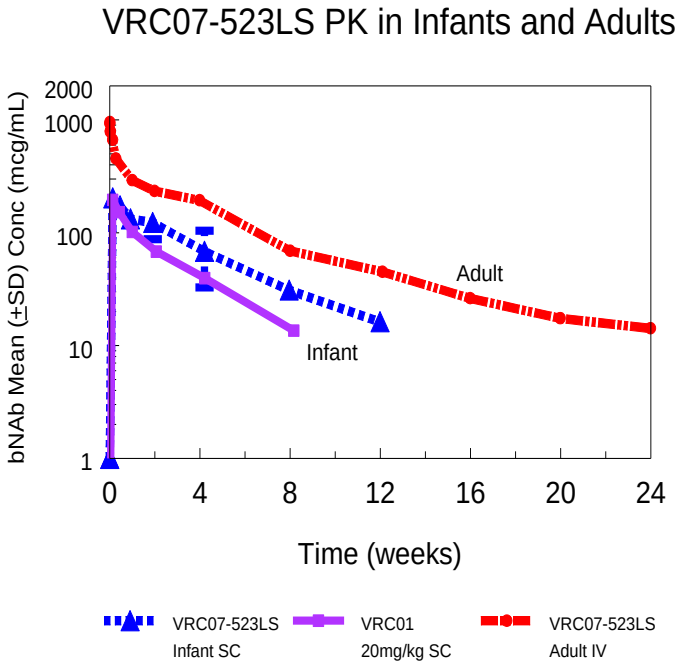
PK of VRC07-523LS vs VRC01 and VRC01LS





Ledgerwood Clin Exper Immunol 2015, M Gaudinski PLOS Med 2018, Gaudinski Lancet HIV 2019, Cunningham HIVR4P 2021, Cunningham CROI 2022

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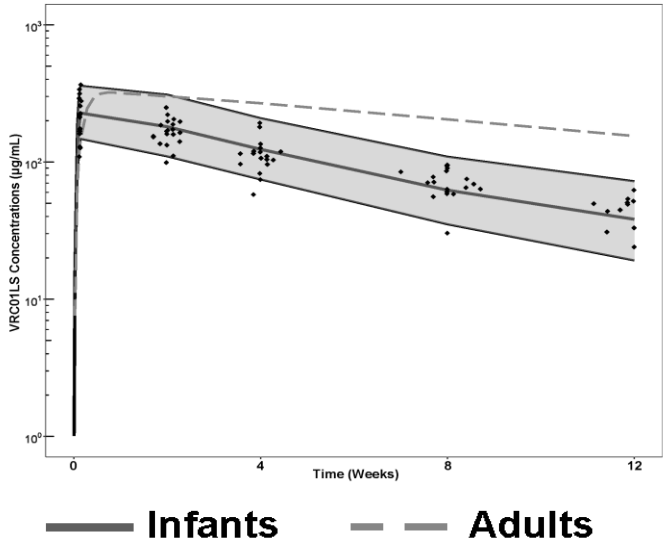
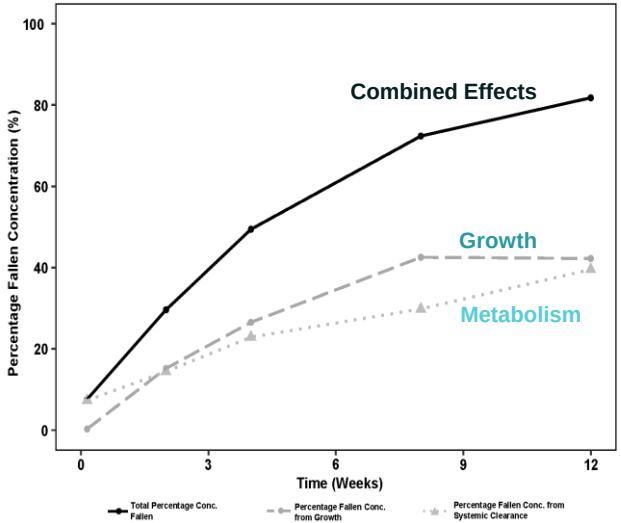
VRC01LS Pharmacokinetics – Newborn vs. Adult





Weight
3.0 kg

Weight
5.7 kg

Yang J, HIV Pcgy Workshop 2020

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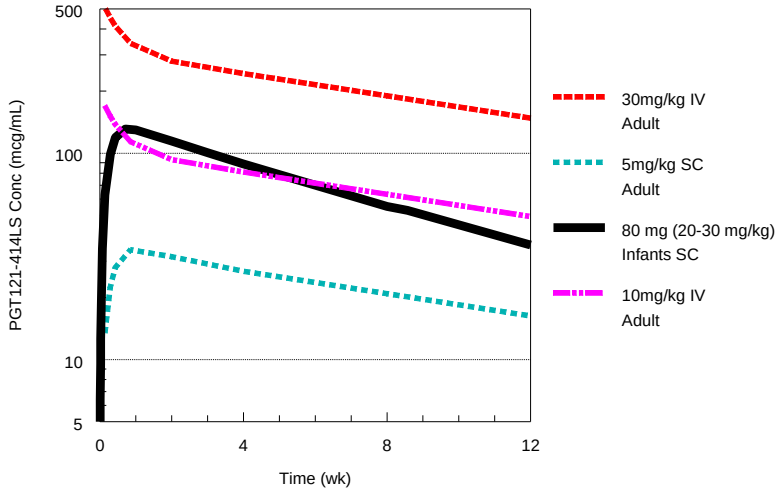
Initial PK Modeling and Simulation of PGT121.414LS for 2037
Infant Effects Extrapolated from P1112 (VRC01LS and VRC07-523LS PK)

- Working with Qing Ma (Buffalo) on modeling and simulation to design adult/infant studies
- Updating with PK data from HVTN 136 (Y Huang/C Yu 258-EXS_Ma_Capparelli_136)

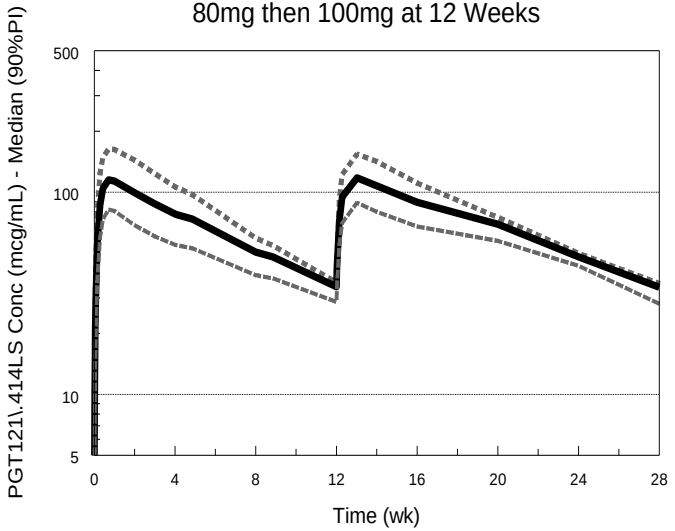
Preliminary bNAb PK Model and Simulation

Includes Expected Infant Effect on Metabolism (CL) and Absorption (F/KA)



Predicted PGT121.414LS in Infants

80mg then 100mg at 12 Weeks



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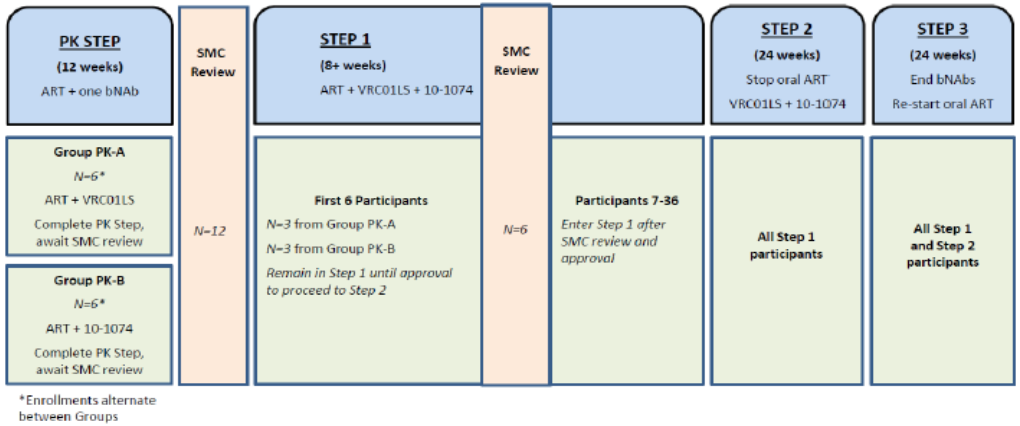
Tatelo Study – VRC01LS and 10-1074 for Maintenance of HIV Suppression in Toddlers Treated with ARVs from Birth



Median age = 3.6 years (range 2.4, 5.6)
Median CD4 count 1198 cells/mm^3
All were receiving lopinavir/ritonavir-based ART

40 Children in EIT Cohort

12 ineligible
(VL detectable >24 wks)

28 Children entered Tatelo Study

ART + bNAbs

32 week ART-bNAb overlap (N=6)

8 week ART-bNAb overlap (N=22)

3 with viral rebound
-- 2 prior to starting bNAbs
-- 1 while on ART/bNAbs

25 had ART held and continued bNAbs alone (Step 2)

R Shapiro CROI 2022

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Tatelo Study – VRC01LS and 10-1074 for Maintenance of HIV Suppression in Toddlers Treated with ARVs from Birth

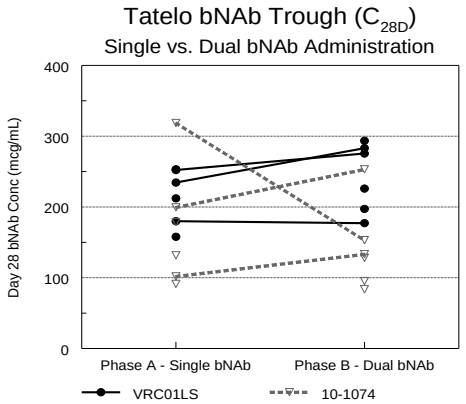
Results:

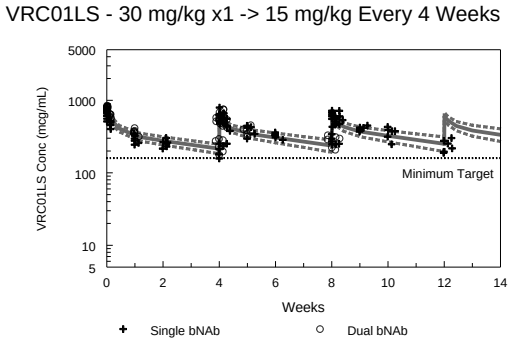
PK Step and Step 1

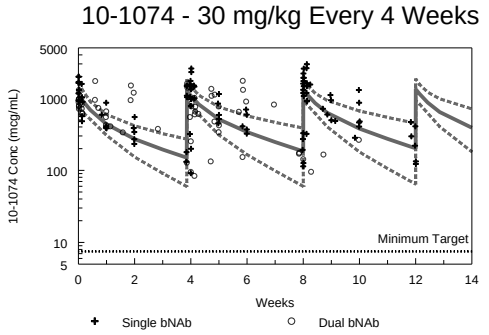
- VRC01LS troughs were lower than expected based on adult PopPK model and simulations– Dose increased in Step 2
- No difference in CL or troughs when given in combination
- Vd 46% larger 10-1074 / 15% smaller VRC01LS in combination

Step 2 (ATI)

- 11 (44%) maintained HIV RNA <40 copies/mL through 24 wks of bNAb-only treatment 95% CI: 24%-65% success
- 1 (4%) had a single viral load of 234 copies/mL at week 16, then returned to < 40 copies/mL
- 13 (52%) had viral rebound to >400 copies/mL, median time to failure = 4 weeks (range 1, 20 weeks)







E Capparelli JAIDS 2022, R Shapiro CROI 2022

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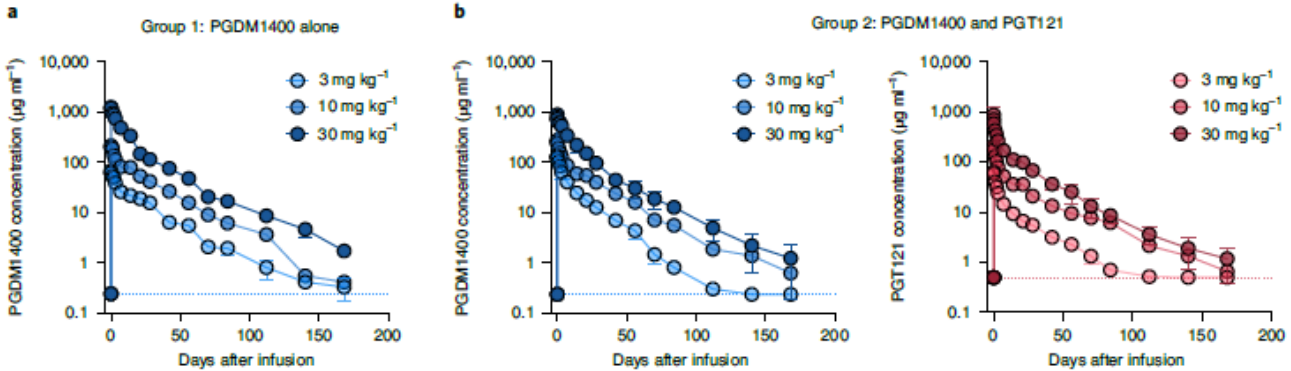
Combo bNAb PK in Healthy Adults – PGDM1400 alone and with PGT121



Parameter	Median [Min, Max] Group 1 (n = 9)	Group 2 (n = 9)	P-value
CL	0.19 [0.17, 0.21]	0.20 [0.14, 0.27]	0.6048
Vz	5.72 [4.79, 6.35]	5.62 [3.42, 8.04]	0.6665
AUC_{ADJ}	398.07 [263.76, 507.73]	362.40 [301.49, 476.98]	0.7304
Elimination half-life	20.77 [17.76, 24.74]	17.43 [15.29, 24.09]	0.0503

Note:
ADJ: dose- and weight-adjusted.

B Julg Nature Med 2022

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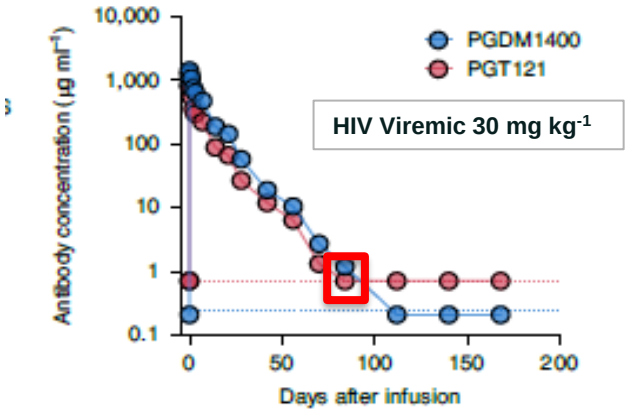
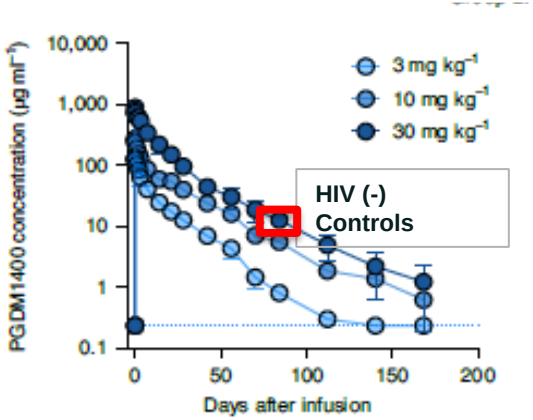
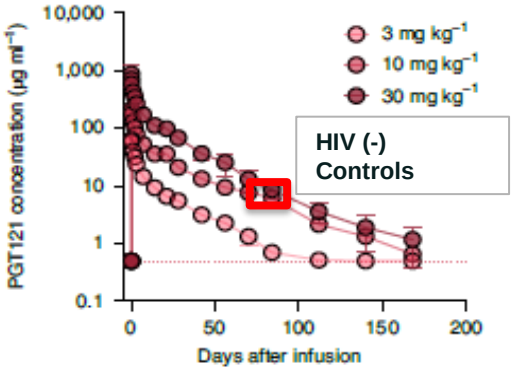
PK of Combined PGDM1400 with PGT121

More Rapid Elimination in HIV Viremic Adults – Wk12 Conc reduced by ~90%







	Elimination half-life		
	Median (days)	Min	Max
HIV uninfected			
PGDM1400	19.4	15.3	24.7
PGT121	20.2	15.8	27.8
HIV infected			
PGDM1400	11.0	10.1	18.7
PGT121	11.8	10.4	20.5
VRC07-523LS	29.3	27.4	37.9

B Julg Nature Med 2022

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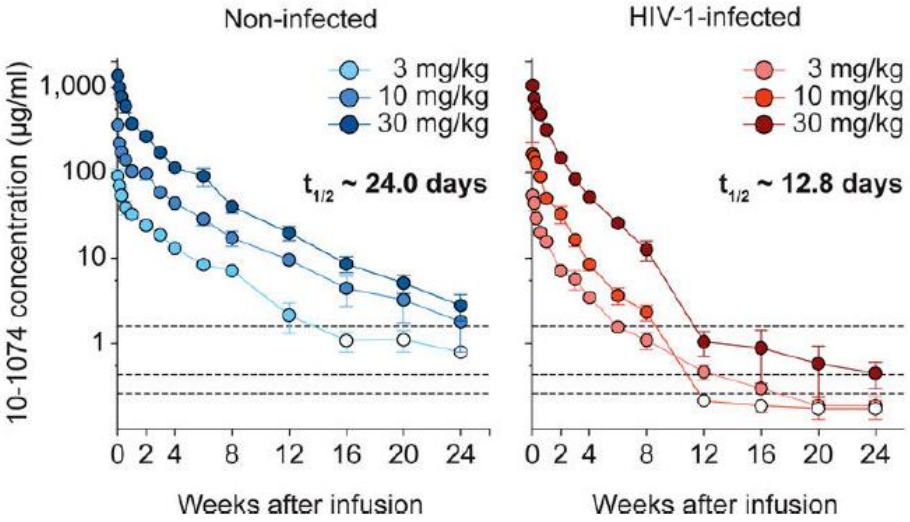
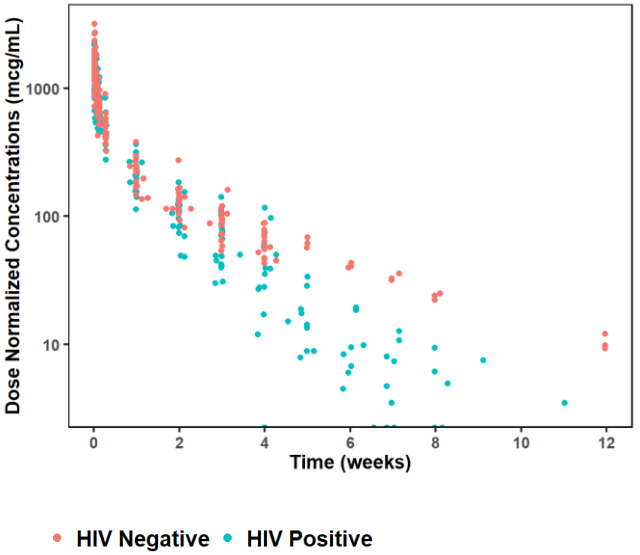
HIV Status Affects bNAb PK

10-1074



M Caskey Nat Med 2017

VRC01



J Li CPT 2020

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bNAbs for PreP – the AMP Studies

Resistance Limits Value of Single bNAbs

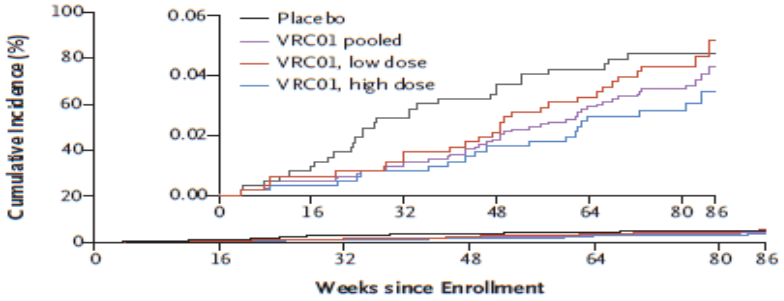
AMP VRC01 Dosing

10 mg/kg q 8 WK for target conc = 5 mcg/mL

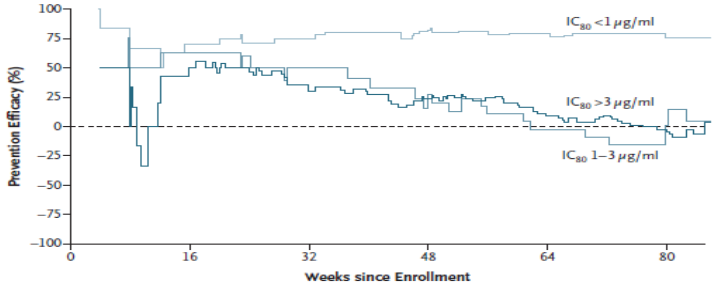
30 mg/kg q 8 WK for target conc = 15 mcg/mL

(Y Huang et al mABs 2017)

Overall 18% Reduction - NS



IC80 <1: 75% Reduction



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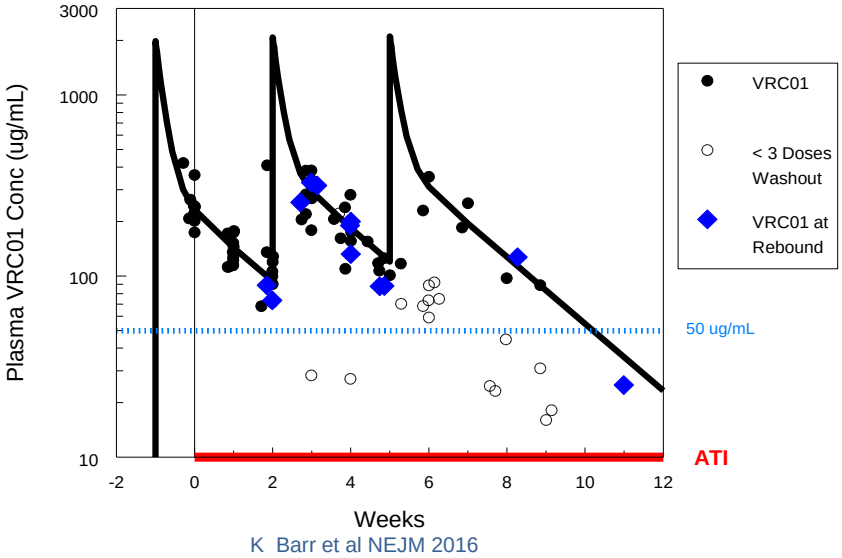
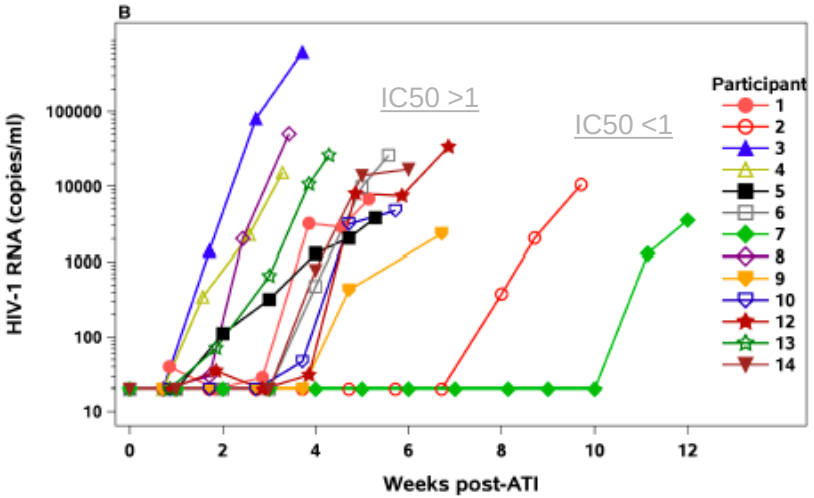
ACTG 5340 - VRC01 Observed and Predicted Following 40mg/kg IV q 3 Weeks



K Barr et al NEJM 2016



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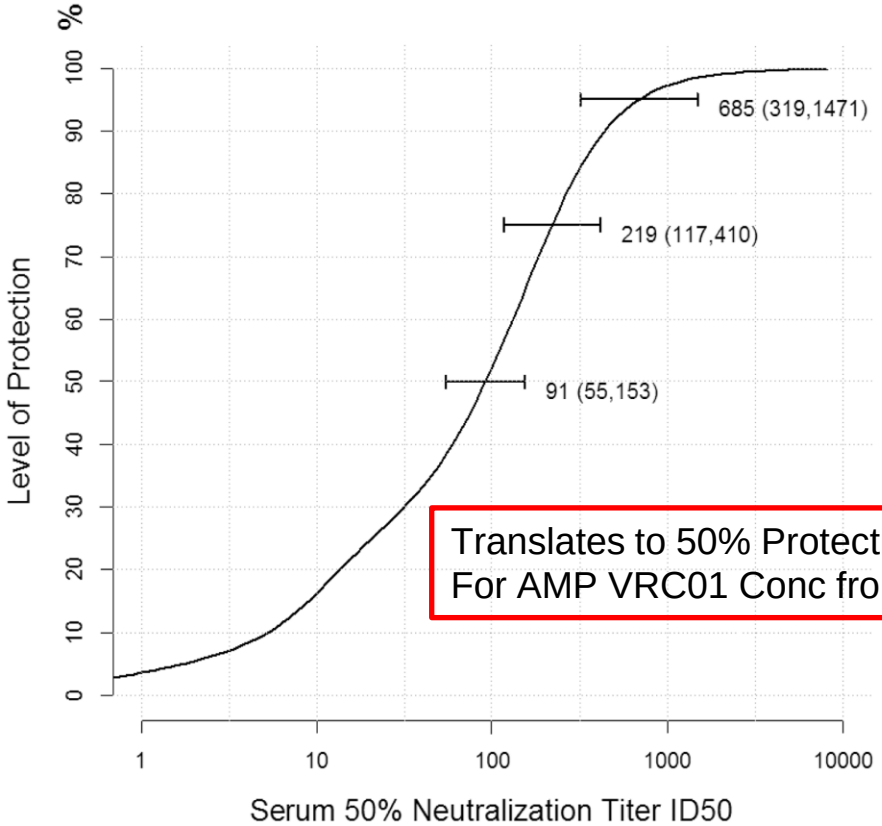
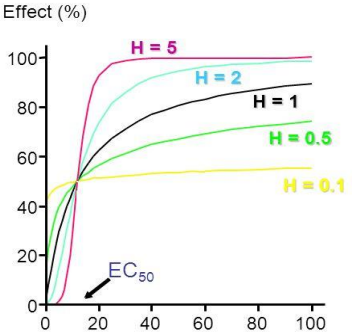
PD Target for Prevention of HIV Infection

Meta-Analysis SIV Preventions with Various bNAbs (N=274)
Challenge Route: 76% rectal, 22% vaginal, 3% oral



Continuous Variable	Median	Range
Ab Dose (mg/kg)	5	(0.05,50)
Ab Conc at day of challenge (ug/ml)	25.02	(0.11,1122.33)
ID50 titers *	113.67	(2.17,8010.58)
ID80 titers *	29.05	(0.003, 4005.29)
IIP **	2.42	(0.34, 8.46)

$$\tau_{ij}(t) = \frac{C_i(t)}{\mathrm{IC50}_{ij}},$$



Translates to 50% Protection with ID80 <0.2 - 0.6
For AMP VRC01 Conc from 10-30mg/kg q8WK

A Pegu et al Cell Host Microbe 2019

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bNAb PK/PD Knowledge Gaps to Inform Infant Dosing

- bNAb PK studies in patient populations are needed to understand impact of HIV infection and other factors for models to predict exposure of dosing strategies.
- Changes in PK parameters (CL, Vd and $t_{1/2}$) with bNAb combinations and repeat dosing are likely modest but still require precise characterization as these effects are magnified with extended dosing intervals.
- Better understanding of PD targets based on purpose.
- Distribution and PK at the target tissue level.
- Translating PK following SC administration in adults, using hyaluronidase, to infants

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Sites

Cape Town, S. Africa
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