Clinical development of bnAbs for HIV prevention, treatment and cure

IMPAACT Annual Meeting
June 2022

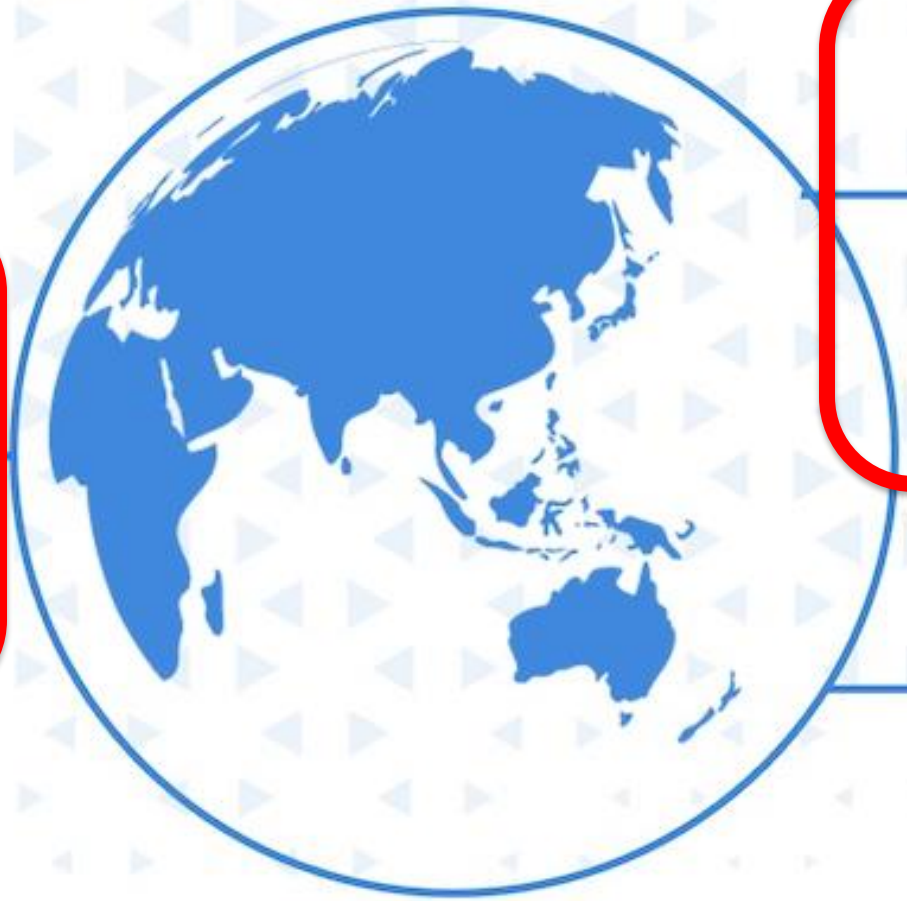
Katharine J. Bar, MD
University of Pennsylvania

Continued burden of the HIV Pandemic

2020
Globally

37.7 million
People living with HIV

+19%
Relative to 2010



1.5 million
People newly infected

- 31%
New infections/year
relative to 2010

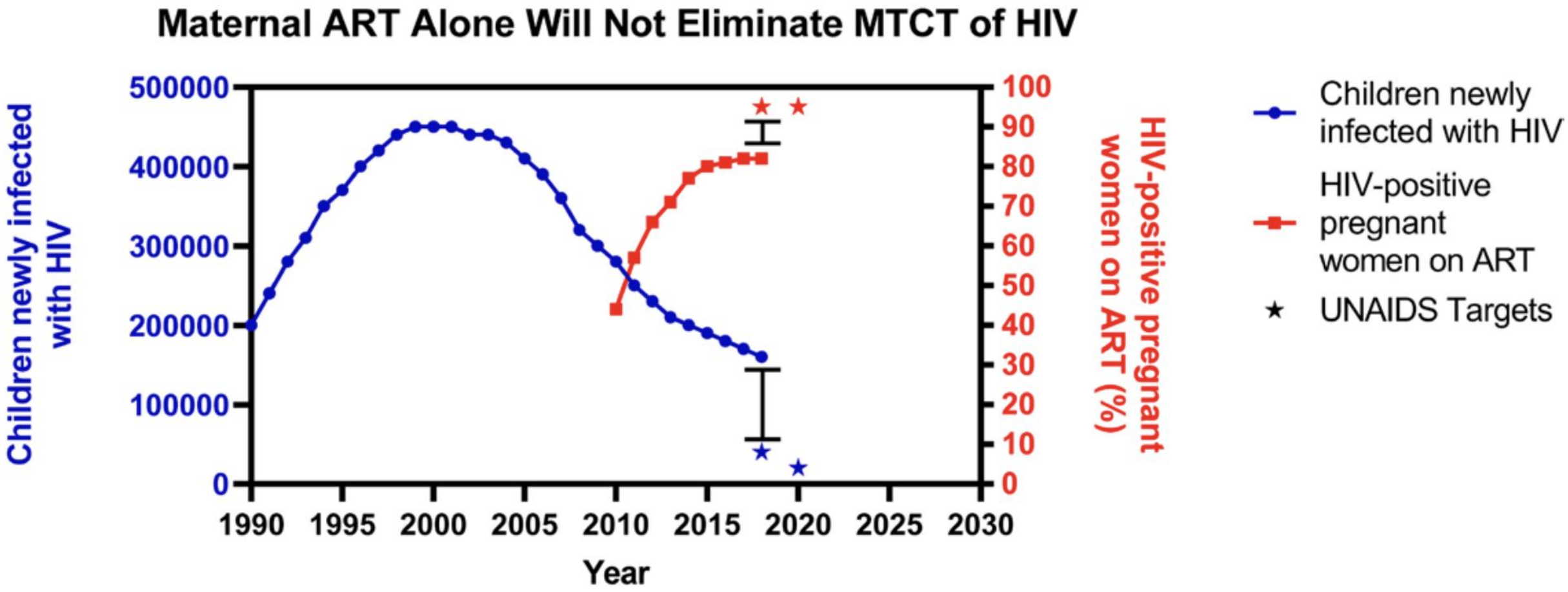
0.68 million
HIV-related deaths

- 47%
Deaths/year
relative to 2010

Source: UNAIDS/WHO and HIV.gov

Need novel approaches to Prevention and Treatment

Continued burden of HIV Pandemic

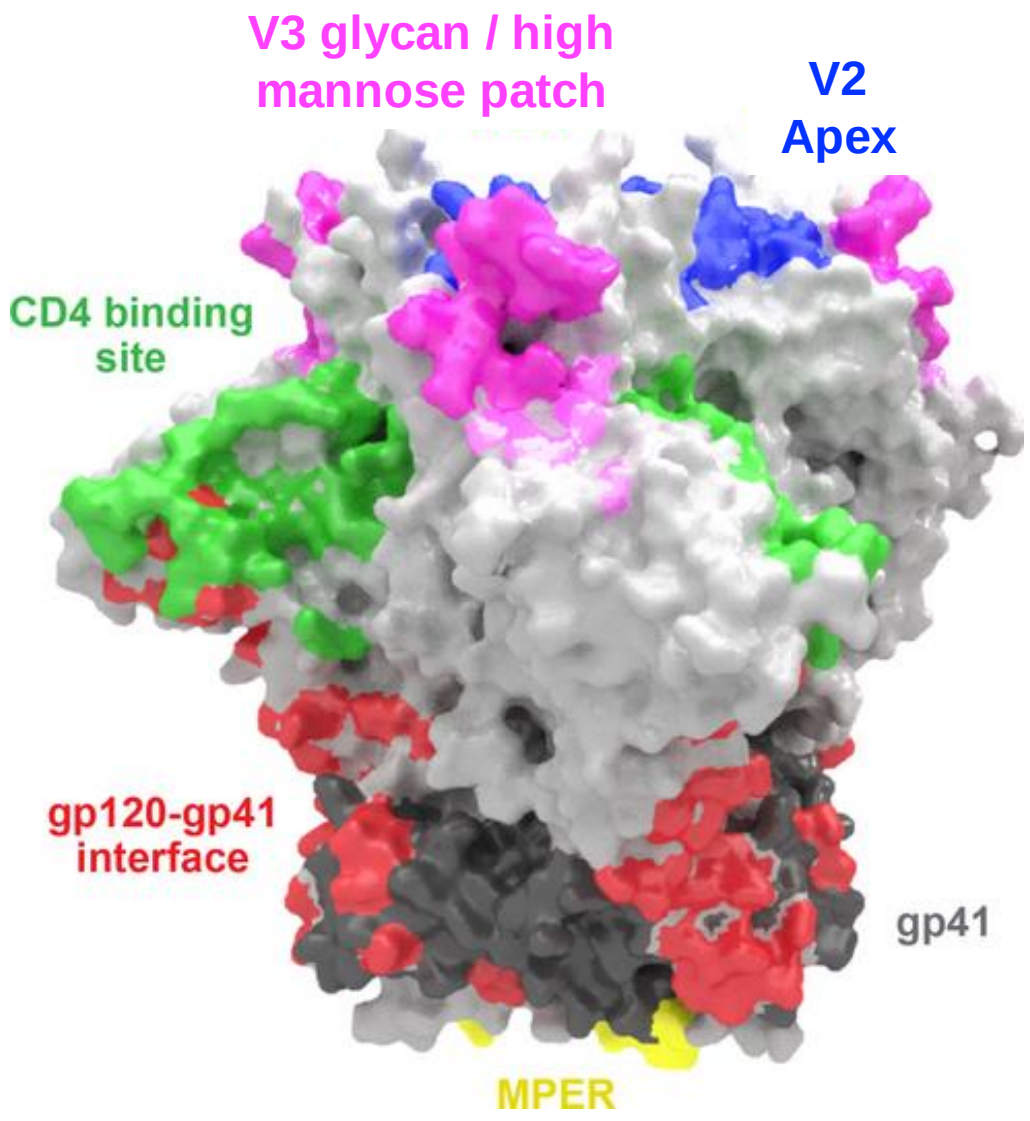


Need novel approaches to Prevention and Treatment

Mangold et al., *PIDJ* 2021

BnAbs can contribute to novel approaches to treatment and prevention of HIV-1

Brief History of bnAb Discovery



HIV-1 Trimer

1993-4:

- First generation bnAbs: modest breadth, potency
- ***Proof of principle that human immune system could generate bnAbs***

2009:

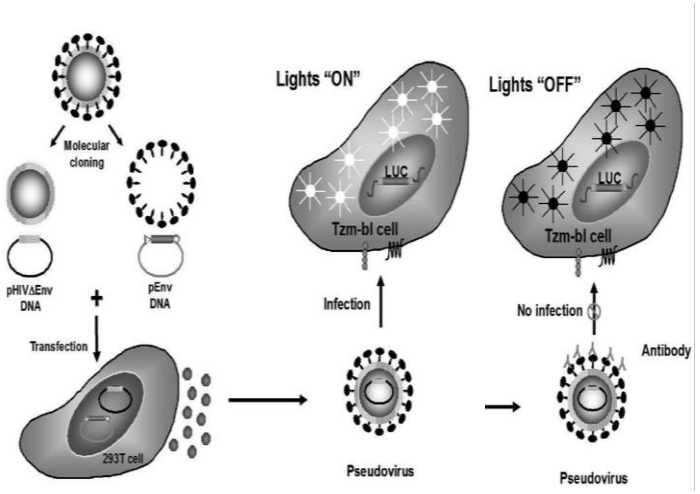
- Enabling technologies→ **broad, potent mAbs**
- ***Passive immunization hypothesis: administration of bnAbs could provide highly effective HIV prevention, treatment, cure***

Today:

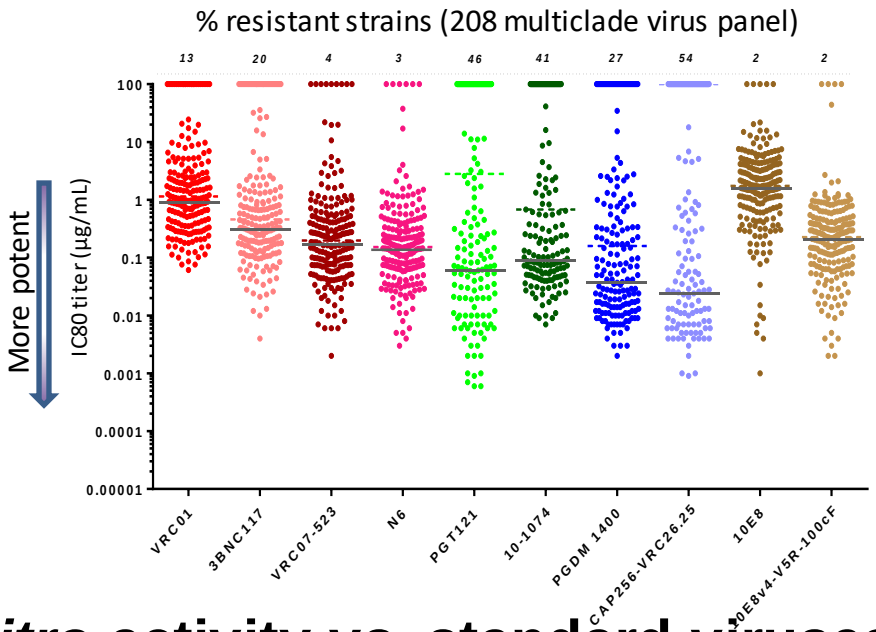
- >7 classes of bnAbs targeting conserved epitopes
- 4 in advanced clinical development for prevention, treatment
  - **CD4bs, V3 glycan, MPER, V2 Apex**
  - **Engineered mAbs: multispecific, immunoadhesins**
- ***Clinical testing for prevention, treatment, SVR/cure***

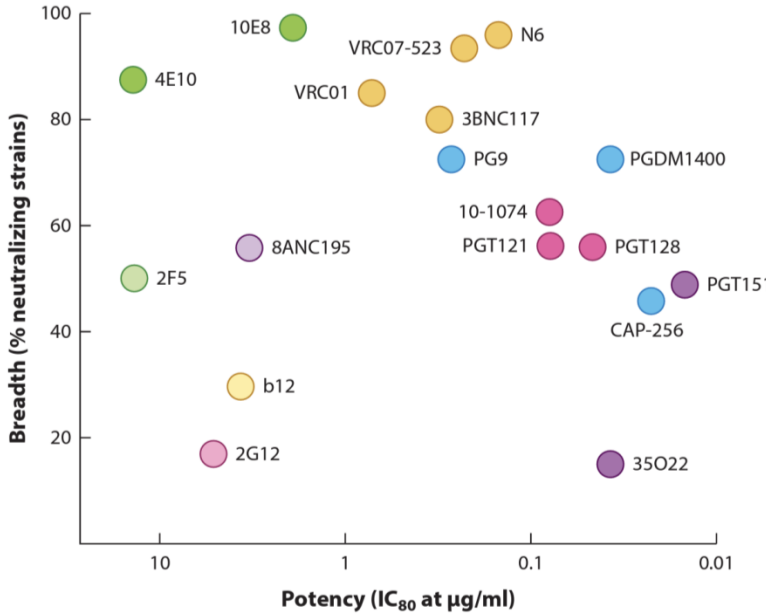
McCoy and Burton, Immunological Reviews 2017

In vitro activity →//→ Clinical efficacy



TZM.bl Neutralization Assay





- **BnAbs defined by *in vitro* activity vs. standard viruses**
  - Assay provides a concentration of bnAb that partially neutralizes a specific virus Env *in vitro.*
    - Need to study target viruses: community (prevention), reservoir (treatment)
    - Where do we need bnAb to be present, at what level? (biodistribution, PK)
- **What is the correlate of clinical efficacy**:
  - *What titer is required for Prevention? Suppression in PLWH? Effector or immune activity?*
  - *Other relevant functions beside neutralization?*

Biomedical HIV Prevention

- **Pre-Exposure Prophylaxis**
  - Oral PrEP has demonstrated effectiveness when used
  - Long Acting Injectables have striking efficacy in trials
  - *PMTCT via antenatal screening and ART for all PLWH*
- **Vaccine** research is ongoing
- ***How might bnAbs have a role in HIV prevention?***

NIAID/NIH; HIV.gov

Rationale for bnAbs in HIV Prevention

- **Advantages vs. current ART**
  - Distinct mechanisms, precludes resistance to cART
  - Long-acting
  - Non-toxic, with high therapeutic index, reliable PK across populations
  - Immunomodulatory *(potentially)*
  - Provides additional option

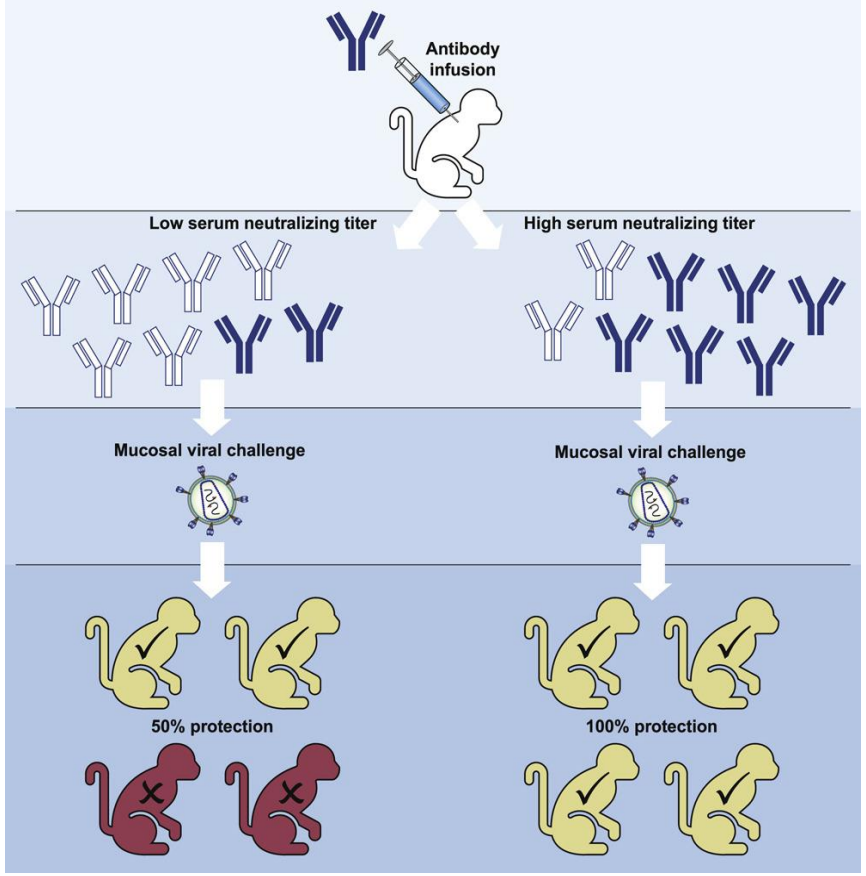
Rationale for bnAbs in Prevention: Pediatrics

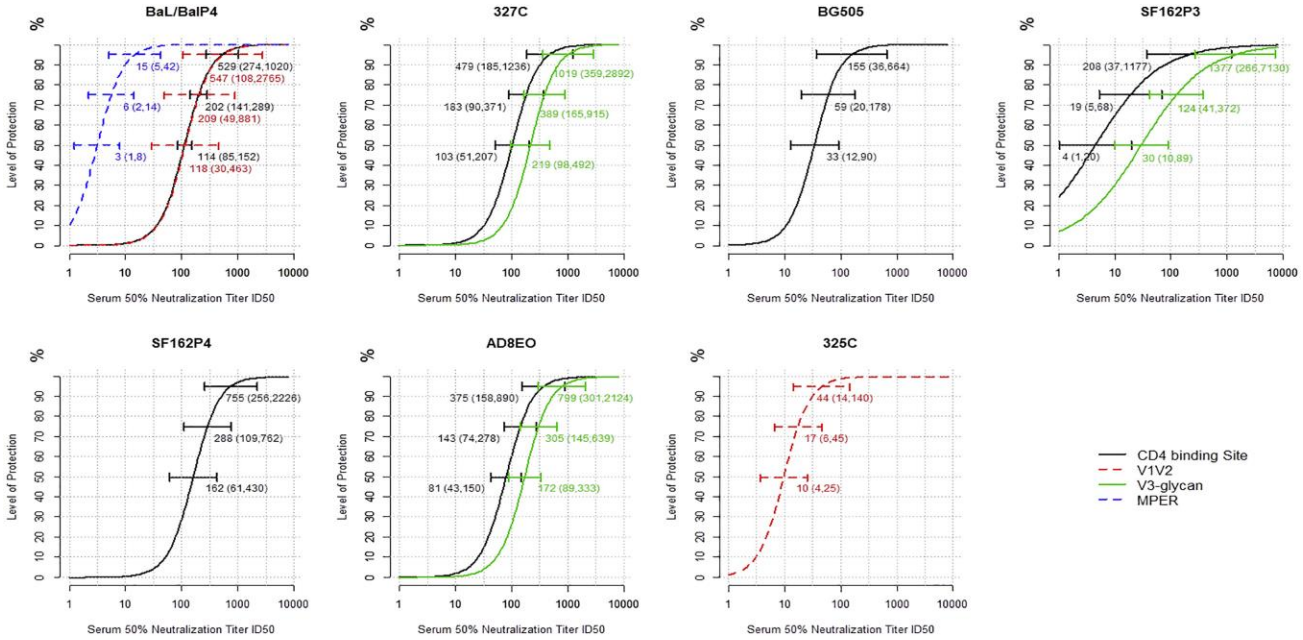
- **Pregnancy and breastfeeding infants**
  - Known time-limited period of risk
  - predictable PK, high therapeutic index
    - Precedent of HBIg, RSV mAb
  - Use in both PLWH, those at high risk for acquisition
- **Adolescents**
  - Long-acting, consistent PK
  - Poor adherence would not threaten standard ART

Thanks to Betsy McFarland

HIV Prevention: NHP data

- NHP challenge studies consistently show bnAbs confer protection vs. SHIV challenge



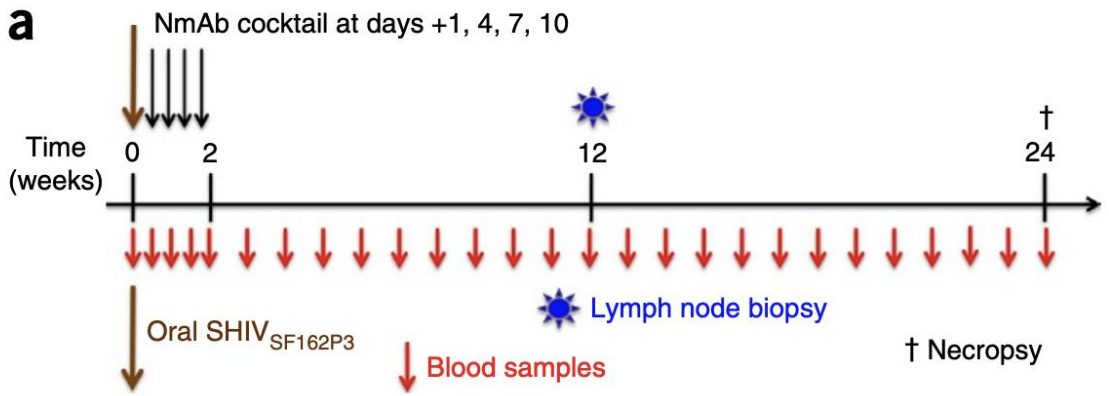


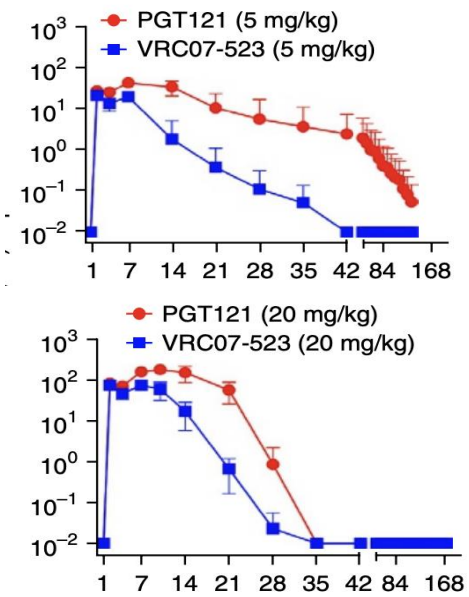
- Meta-analysis of single bnAbs vs. mucosal SHIV challenge in 274 RM, 16 bnAbs, 18 studies *(Pegu)*
  - Serum-Neutralizing Antibody Titer (ID50) correlates with protection
  - Higher titers required for efficacious protection (~1:685).

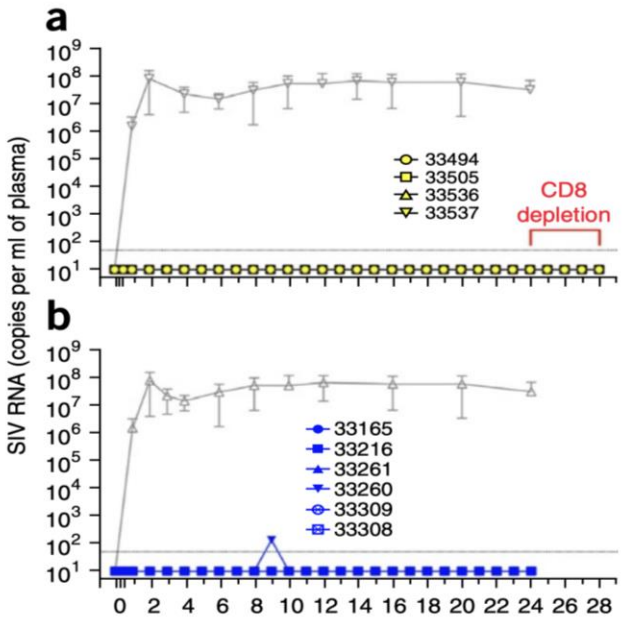
Pegu CHM 2019

HIV Prevention MTCT: NHP data

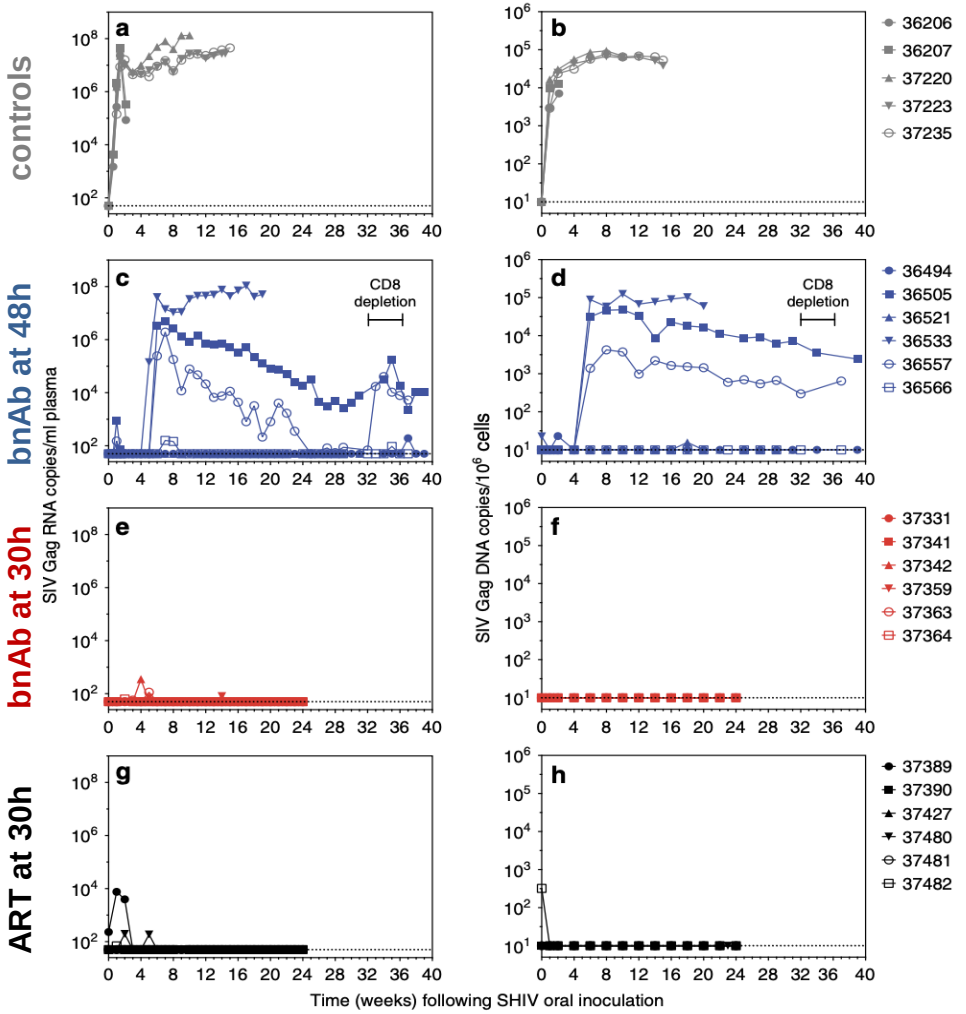
Pre-Exposure Prophylaxis







Post-Exposure Prophylaxis



Hessel Nat Med 2016; Shapiro Nat Comm 2020

NHP challenge study → Clinical trial

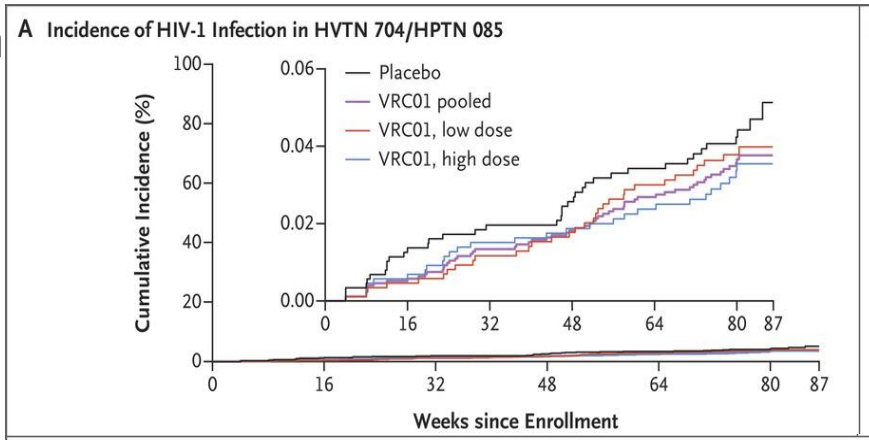
- **NHP study:**
  - Defined virus challenge
    - Extensively characterize SHIVs
  - Defined number, conditions of mucosal challenge
  - Controlled adherence to study treatments
  - Frequent sampling to identify time of acquisition

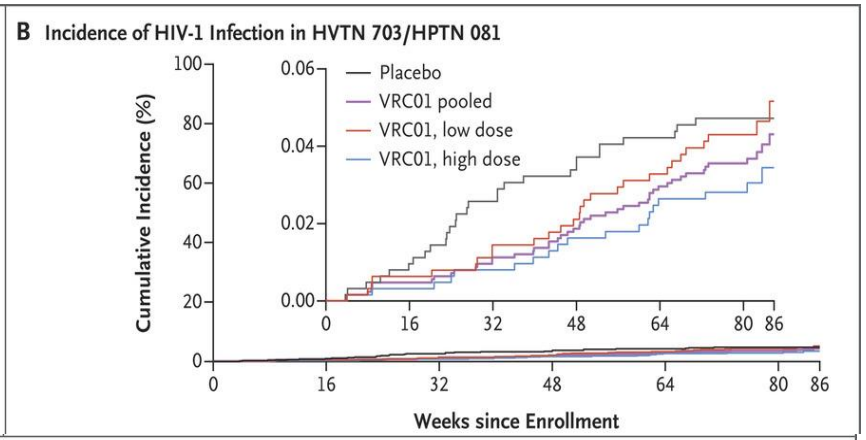
- **Clinical trial & real world:**
  - Unknown virus challenge
    - Estimate from community viruses?
  - Variable number and type of exposures
  - Variable adherence to study visits
  - Delayed sampling post-acquisition

HIV Prevention: AMP Trial

Antibody Mediated Protection

- 2 phase 2b studies, 11 countries, 4623 participants
  - MSM/TGSM in Americas; Women in Africa
- VRC01 @10 mg/kg, 30 mg/kg, vs. placebo; q4 weeks x 10, over 20 months
  - HIV testing q4 weeks
  - *>80 kg VRC01 used*
- **No significant overall protection**:
  - 2.35 (VRC01) vs. 2.98 (placebo) annual incidence
  - Prevention efficacy: 26.6 (95% CI: -11.7 to 51.8), p=0.15



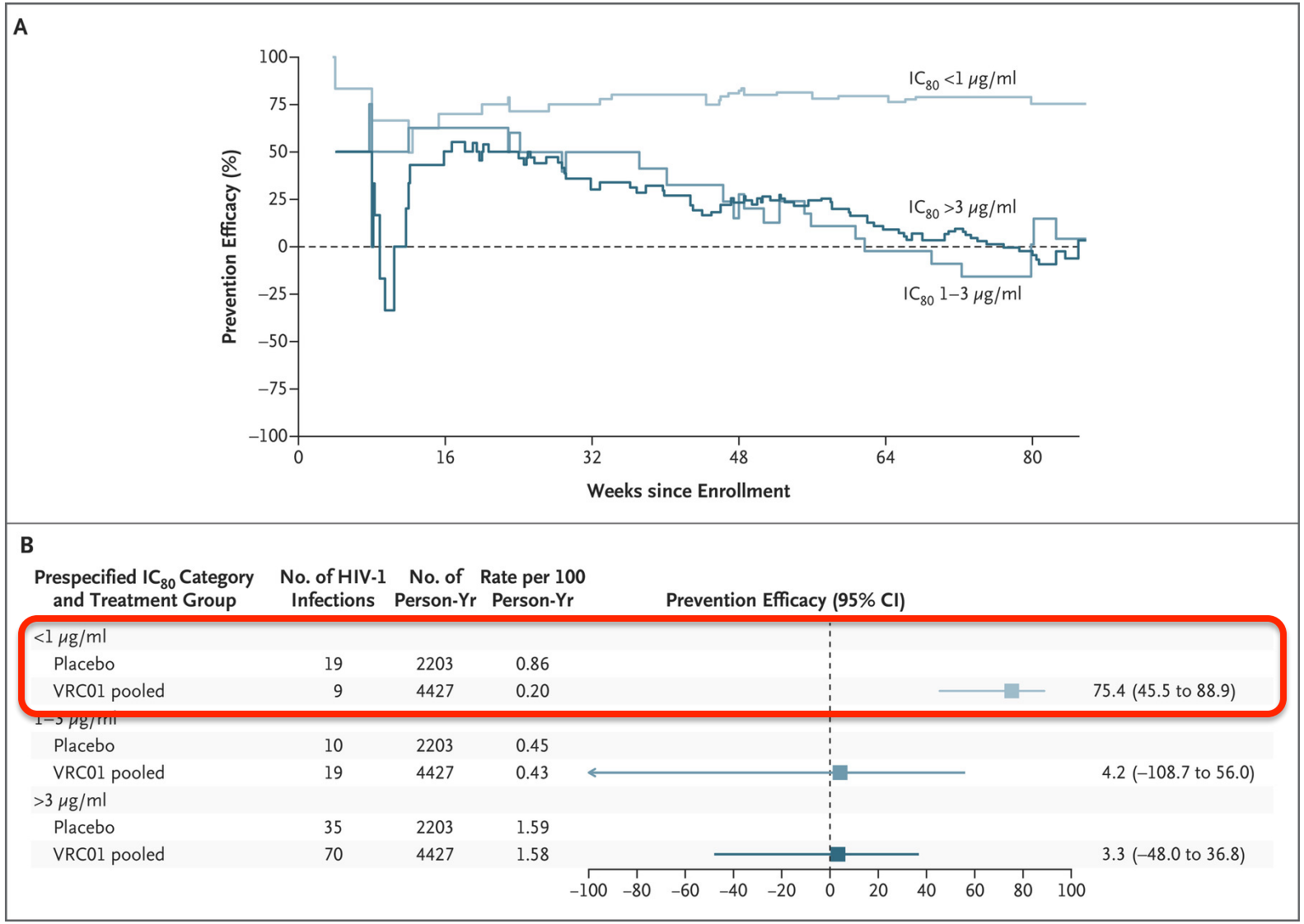


C Annualized Incidence and Prevention Efficacy

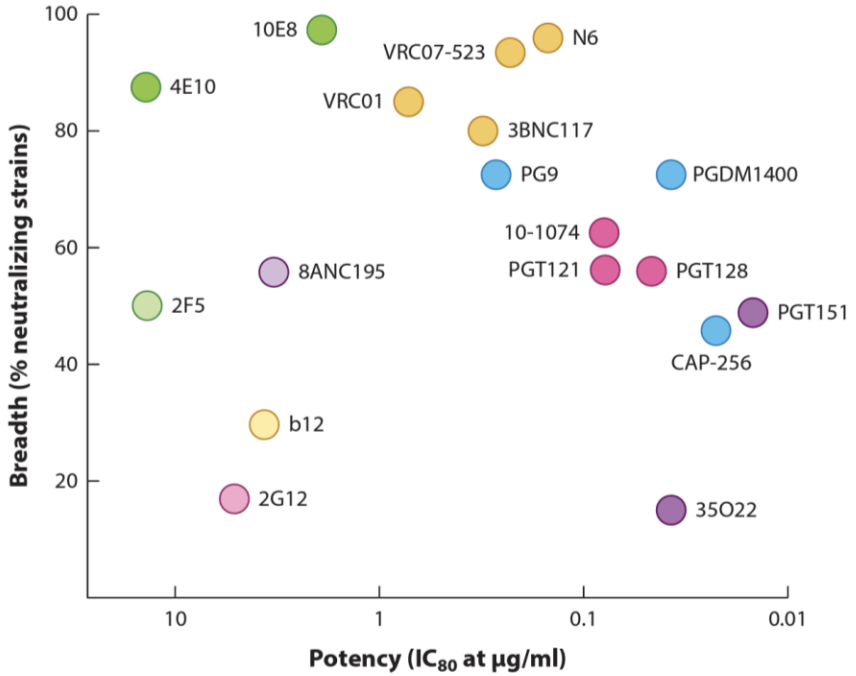
Trial and Treatment Group	No. of HIV Infections	No. of Person-Yr	Rate per Person-Yr	Prevention Efficacy (95% CI)	P Value
HVTN 704/HPTN 085					
Placebo	38	1275	2.98		
VRC01 pooled	60	2555	2.35	26.6 (–11.7 to 51.8)	0.15
VRC01, low dose	32	1281	2.50	22.4 (–25.5 to 52.0)	
VRC01, high dose	28	1274	2.20	30.9 (–13.9 to 58.0)	
HVTN 703/HPTN 081					
Placebo	29	935	3.10		
VRC01 pooled	47	1889	2.49	8.8 (–45.1 to 42.6)	0.70
VRC01, low dose	28	941	2.98	–9.3 (–85.3 to 35.5)	
VRC01, high dose	19	948	2.00	27.0 (–30.7 to 59.3)	
Pooled trials					
Placebo	67	2207	3.04		
VRC01 pooled	107	4436	2.41	18.1 (–12.2 to 40.2)	0.21
VRC01, low dose	60	2217	2.71	7.2 (–33.3 to 35.3)	
VRC01, high dose	47	2219	2.12	29.0 (–4.0 to 51.6)	

HIV Prevention: AMP Trial

- Prespecified secondary analyses of inferred sensitive viruses (IC_{80} <1 µg/mL):
- 0.2 (VRC01) vs. 0.86 (placebo) annual incidence
- 75.4% estimated prevention efficacy, (95% CI, 45.5 to 88.9)
- ***Provides optimism that more broad, potent bnAbs could provide strong protective efficacy vs. "sensitive" viruses***



Ongoing studies of safety, delivery, distribution



First in humans, PK, Safety Studies *(partial list!)*

HVTN	HVTN 116	**VRC01** & **VRC01-LS** in HIV- adults serum & mucosa
HVTN	HVTN 127/HPTN 087	**VRC07-523LS** in HIV- adults
HVTN	HVTN 128	**VRC07-523LS** in HIV- adults (mucosal analysis)
HVTN	HVTN 129/HPTN 088	**SAR441236** in HIV- adults
HVTN	HVTN 130/HPTN 089	**VRC07-523LS** + PGT121 + PGDM1400 + 10-1074 in HIV- adults
HVTN	HVTN 136 / HPTN 092	**VRC07-523LS** + PGT121BIJ414LS in HIV- adults
HVTN	No number yet	**CAP256V2LS** and VRC07-523LS in HIV- adults
IMPAACT	P1112	**VRC01** & **VRC01-LS** & **VRC07-523LS** in at-risk infants
NIAID	19-I-0069 WINGS	AD4-HIV & **Trimer-4571** in HIV- adults
MRC-SA	Goga	**VRC07-523LS** + **CAP256V2LS** in at-risk infants
MRC-SA	Scarlatti	**VRC07-523LS** in at-risk infants
CAPRISA	CAP 012a	**VRC07-523LS** + PGT121 in HIV- adults
CAPRISA	CAP 012b	**VRC07-523LS** + **CAP256V2LS** in HIV- adults

- Many ongoing studies of far more potent bnAbs, bnAb combinations, engineered bnAbs
- Studies of vectored, DNA, RNA delivery

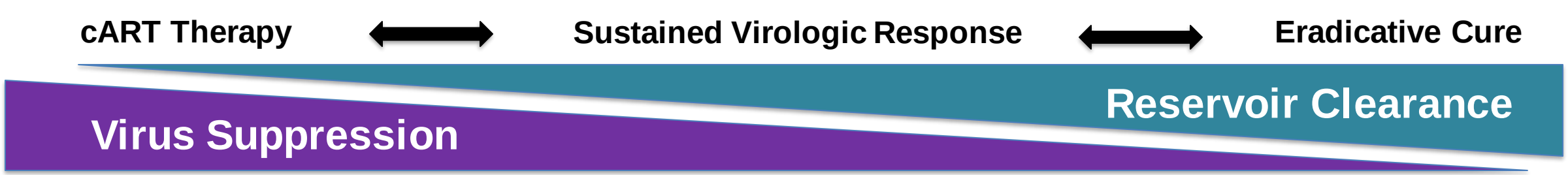
Key Questions for Prevention

- **Protection vs. "sensitive" viruses**
  - Should ~IC80 <1 ug/mL via TZM.bl be presumed correlate?
  - Should other Ab properties be considered—*effector functions*?
  - How to survey circulating viruses across regions, globally?
  - Which bnAbs and bnAb combinations to study?
- **Clinical trial strategy**
  - Attempt another large prevention efficacy study in adults?
    - Costly, challenged by effective PrEP
  - ***Prioritize studies in key populations***
    - ***PMTCT? Adolescents? In regions most impacted by HIV?***

HIV Treatment

- **cART**
  - Daily oral ART is highly effective, well-tolerated
  - Long-acting ART has increasing use, potential
- ***What roles are there for bnAbs in treatment?***

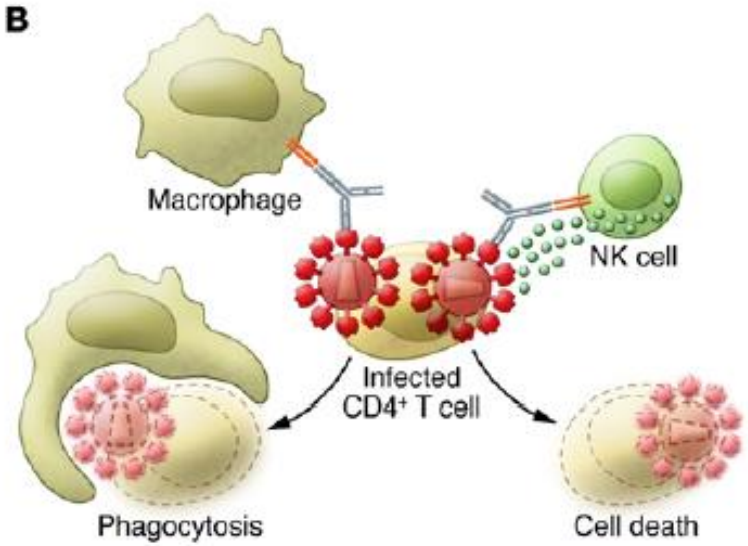
HIV treatment: Virus Suppression and SVR/Cure



- Goals for bnAbs in PLWH
  - Durable virus suppression
    - Long-activity, low toxicity, high therapeutic margin, predictable PK
  - ***Reservoir reduction*** and ***immune enhancement***
    - Effector functions to clear HIV-infected reservoir cells
    - Enhancement of immune responses via vaccinal effect

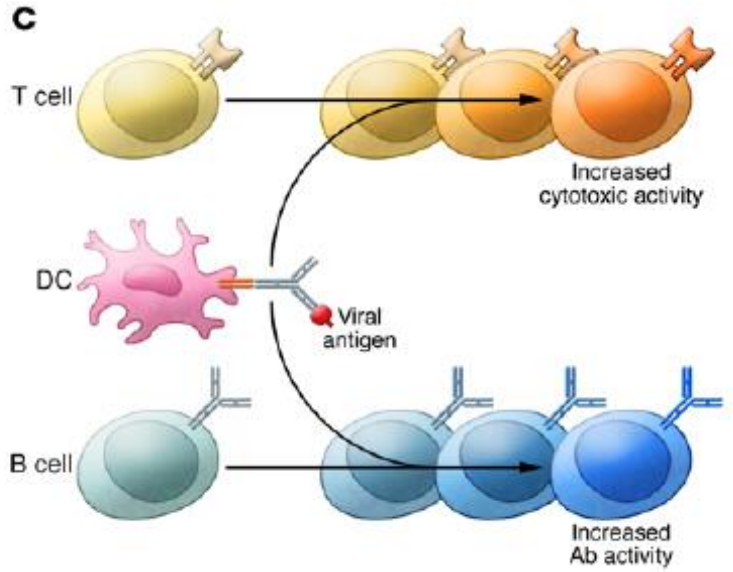
Additional Rationale for Treatment and SVR/Cure

Reservoir Reduction via Effector Function



Binding and clearance of virus-infected cells: ADCC via NK cells or phagocytosis via macrophages

Immunomodulation via Vaccinal Effect

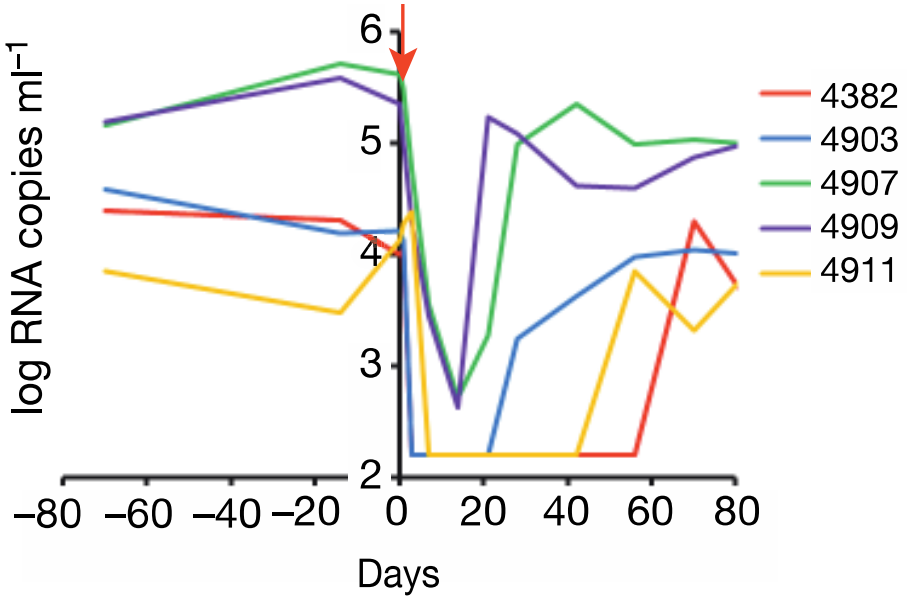


Virus-bnAb immune complexes taken up by APCs can stimulate host immune system and improve T and B cell responses

Demonstration and Optimization of these functions in PLWH is a priority for HIV Cure.

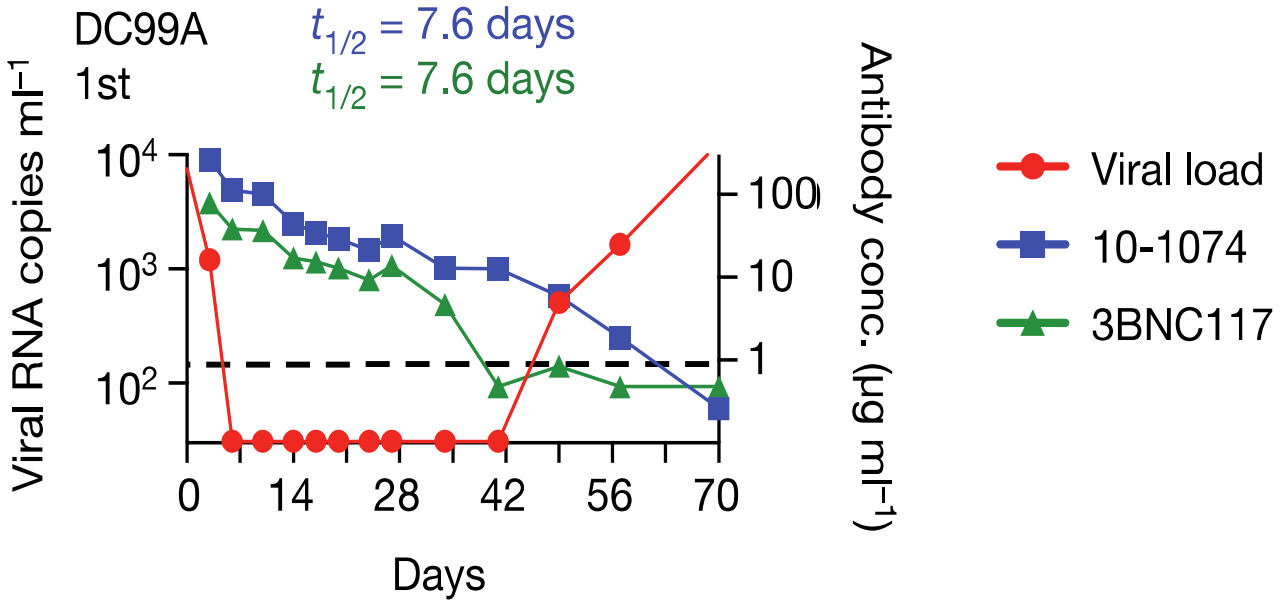
HIV Treatment: Antiviral activity in NHP

PGT121



- Single dose of V3 glycan bNAb suppressed virus for weeks or longer in viremic macaques

3BNC117 + 10-1074

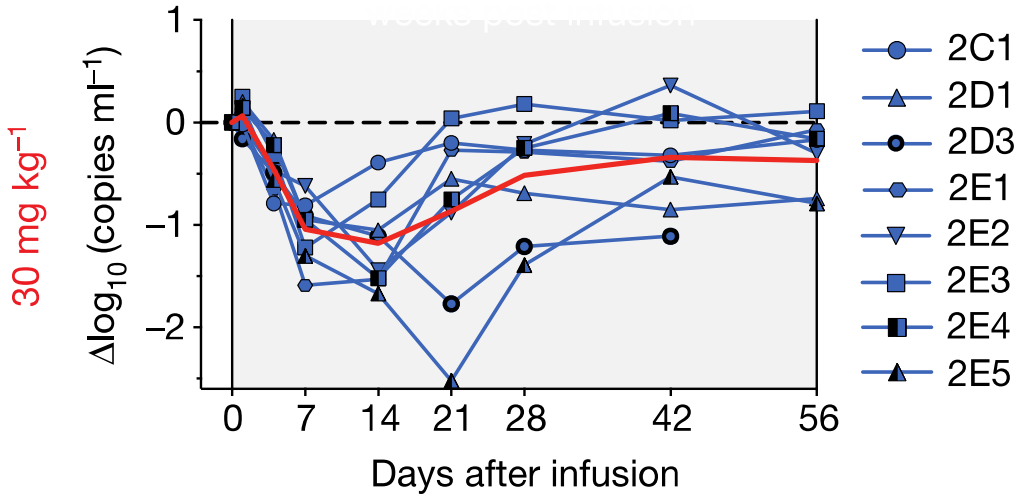


- Single dose combo CD4bs + V3 glycan bnAbs suppressed virus for days to weeks in viremic macaques

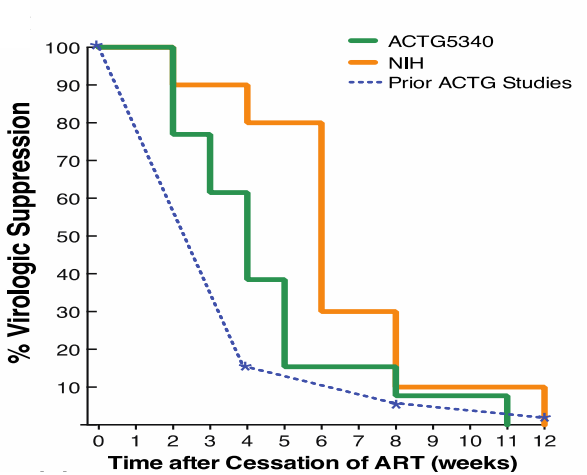
Shingai et al., Nature 2013; Barouch et al., Nature 2013

Clinical data: single bNAb

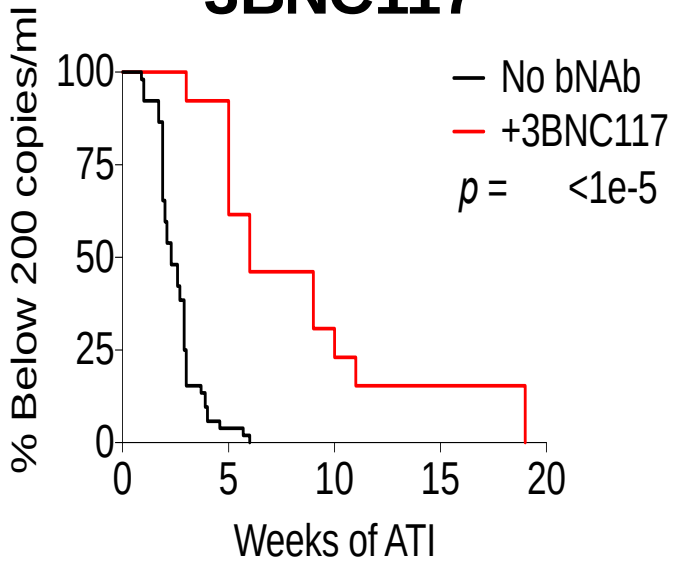
3BNC117



VRC01



3BNC117

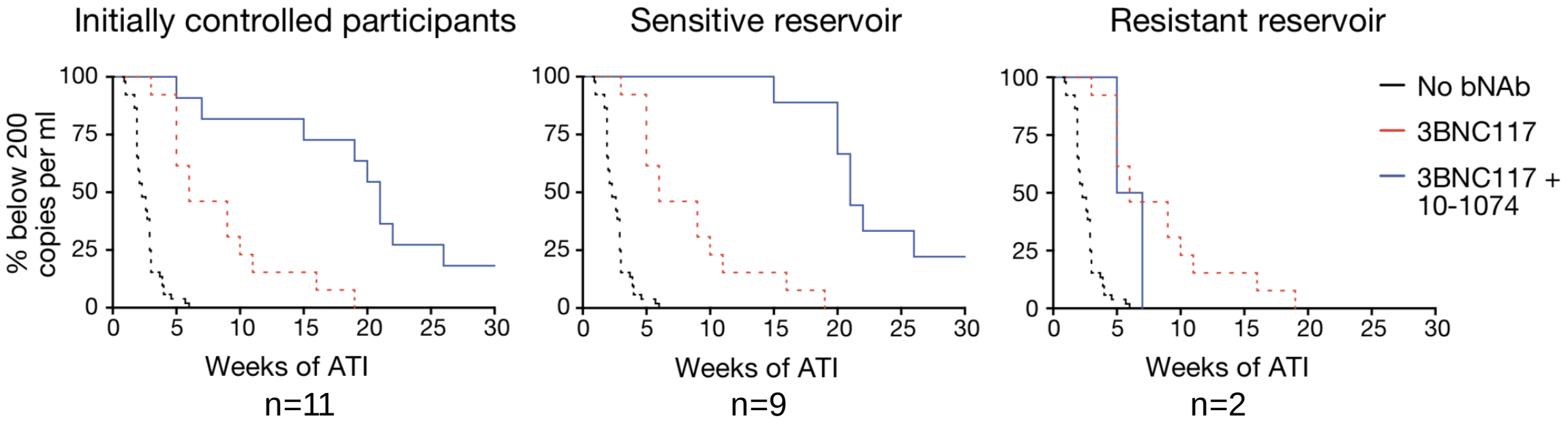


- **Single bnAb in viremia**
  - Transient reduction in plasma viremia
  - Resistant virus emerged rapidly

- **Single bNAb at ATI**
  - Time to rebound modestly delayed
    - median of 4-6 wks (VRC01), 6-10 wks (3BNC117).
  - Baseline resistance was common

Caskey et al., *Nature* 2015; Bar et al., *NEJM* 2016; Scheid et al., *Nature* 2016

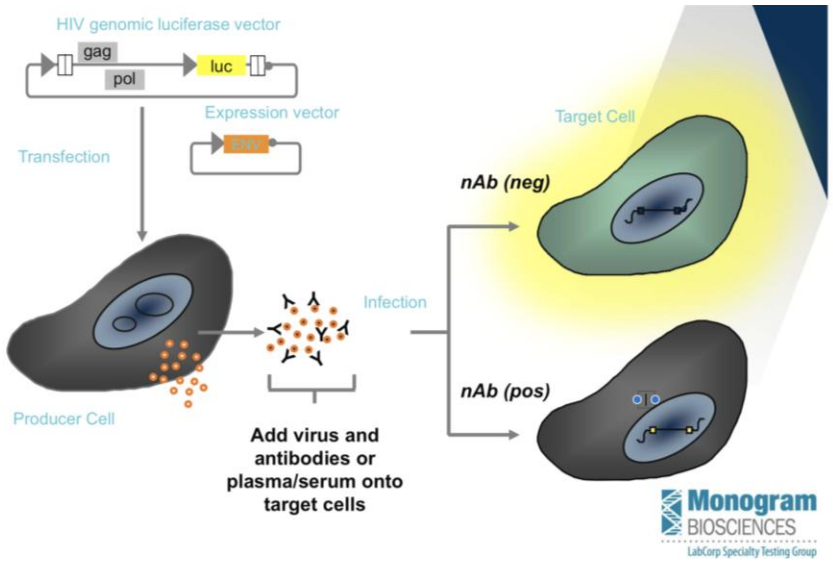
Combo bNAbs suppress sensitive virus



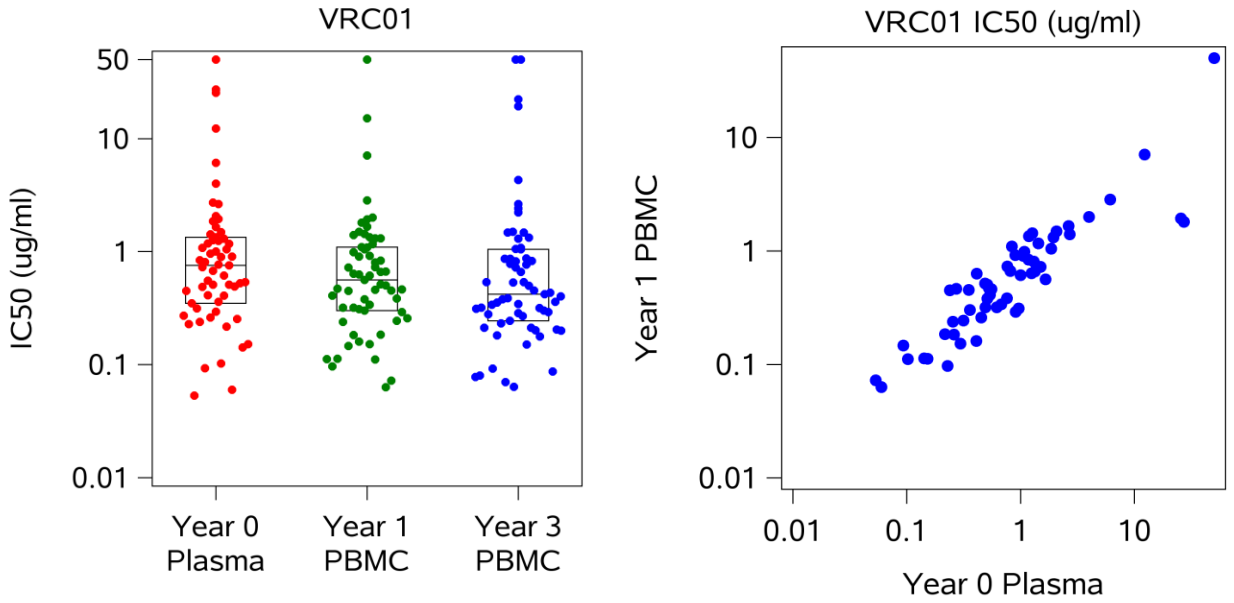
- **3BNC117 + 10-1074 in ART-suppressed PLWH**
- Sensitive reservoir: median 23 weeks suppression
- Resistant reservoir: median 5 weeks suppression

Mendoza et al., Nature 2018

Screening for resistance to bNAbs



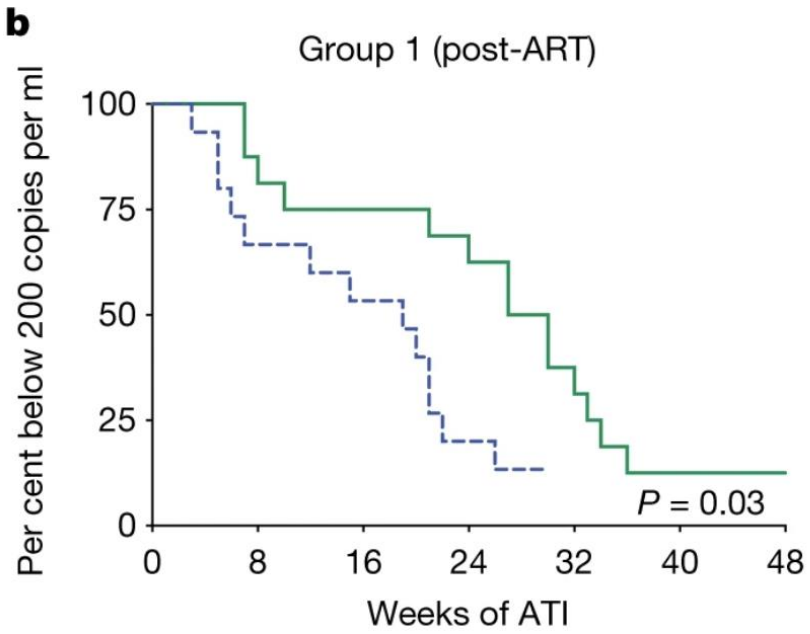
Monogram Phenosense Assay

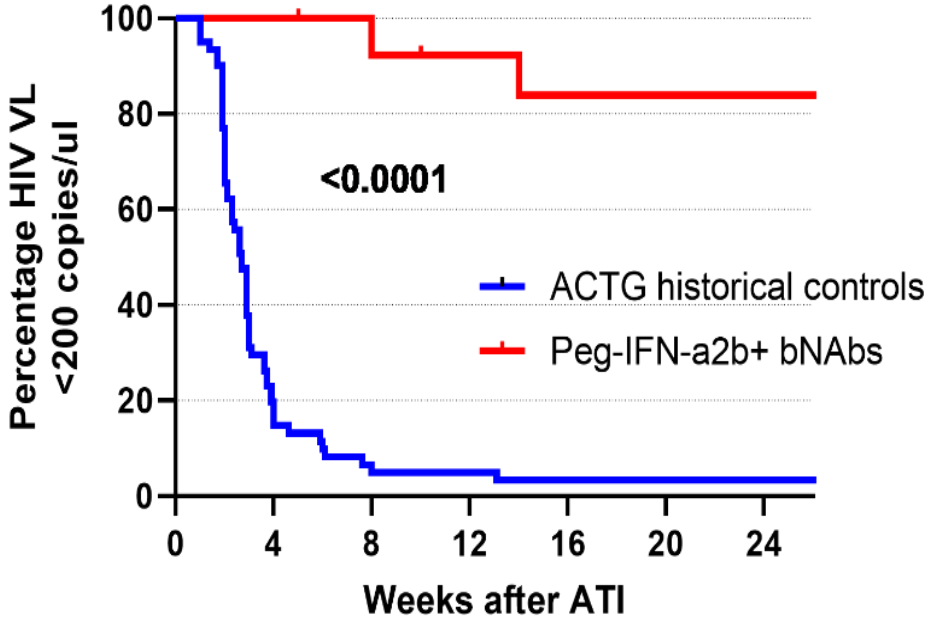


ACTG NWC413

- Rebound-competent reservoir is diverse, challenging to sample.
  - Laboratory methods are laborious, expensive, or insensitive.
- **Monogram Phenosense** is CLIA/CAP certified; currently in studies where predictive capacity can be assessed
- Validation and new assays are a priority

Combination bnAbs: Durable suppression





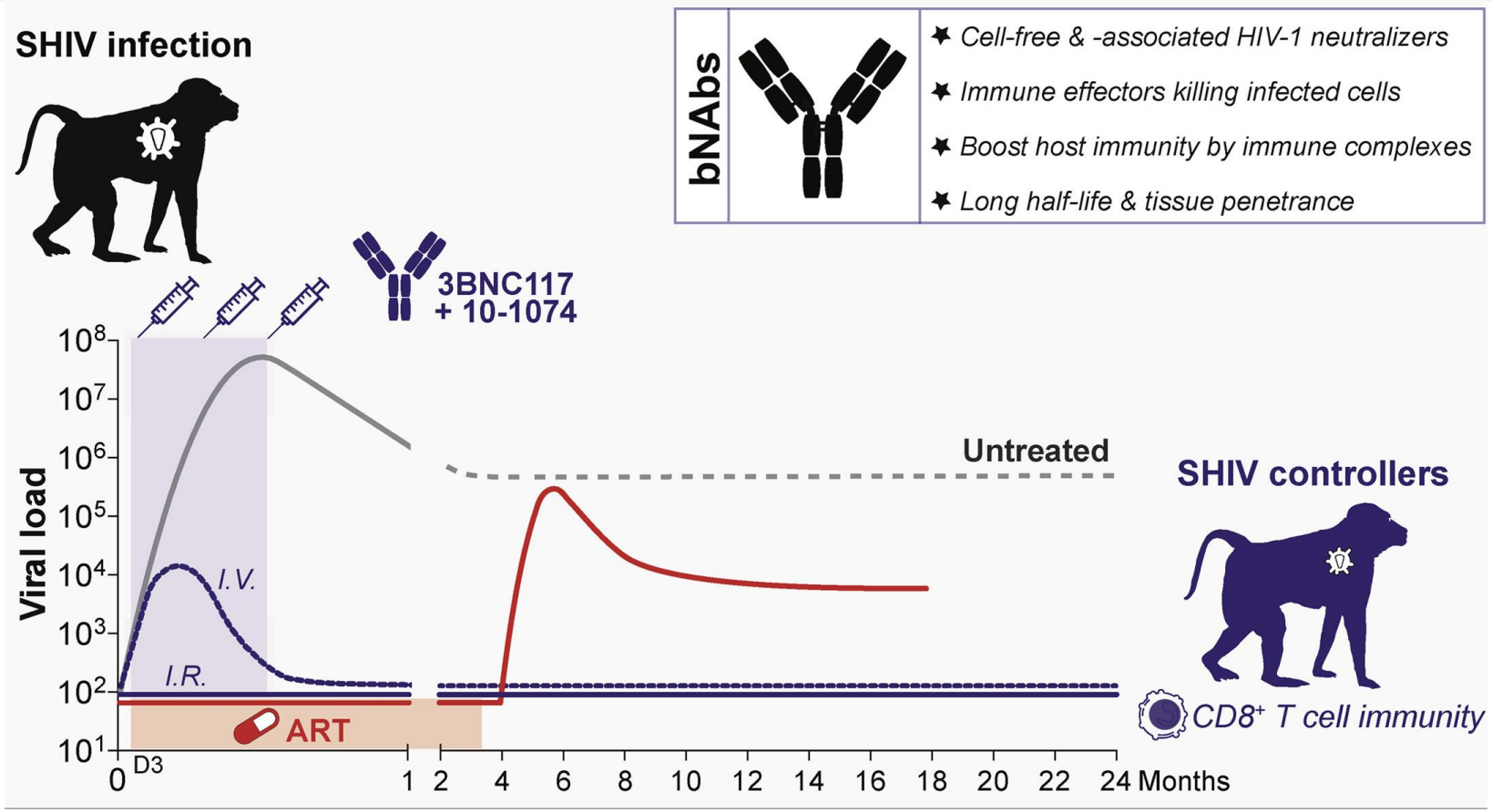
- **3BNC117 + 10-1074**
  - 7 doses
  - No screening; post-hoc not predictive
- 76% efficacy (13/17)

- **3BNC117 + 10-1074 +IFNa2b**
  - 7 doses
  - Prescreening w Phenosense
- 83% efficacy (10/12)

Gaebler et al., Nature 2022; BEAT-HIV Team, CROI 2022

NHP: Evidence for Reservoir Reduction or Immunomodulation

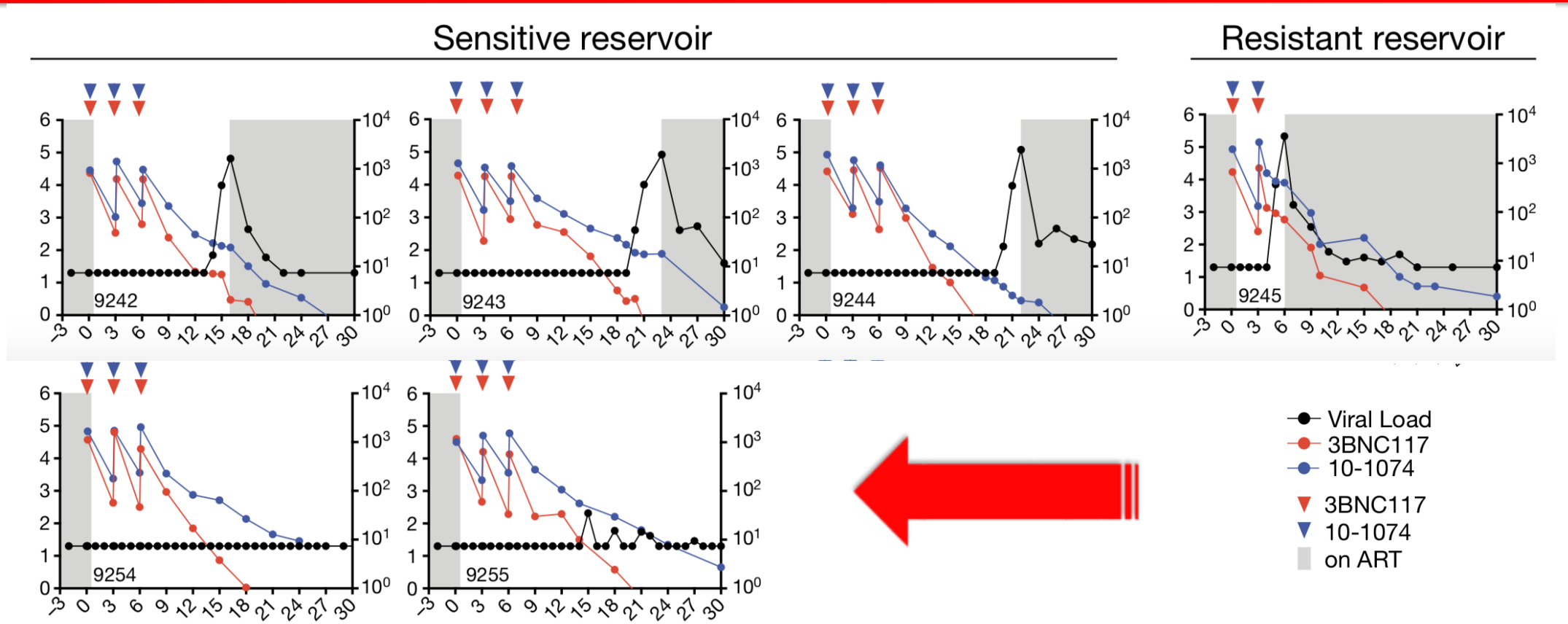
bnAbs + ART during Acute Infection



- Passive infusion of bNAbs + ART in acute infection led to immune (CD8 T cell) mediated virus control at ART interruption.

Nishimura et al., Nature 2017; Moquet et al., Immunity 2017; Borducchi Nature 2018

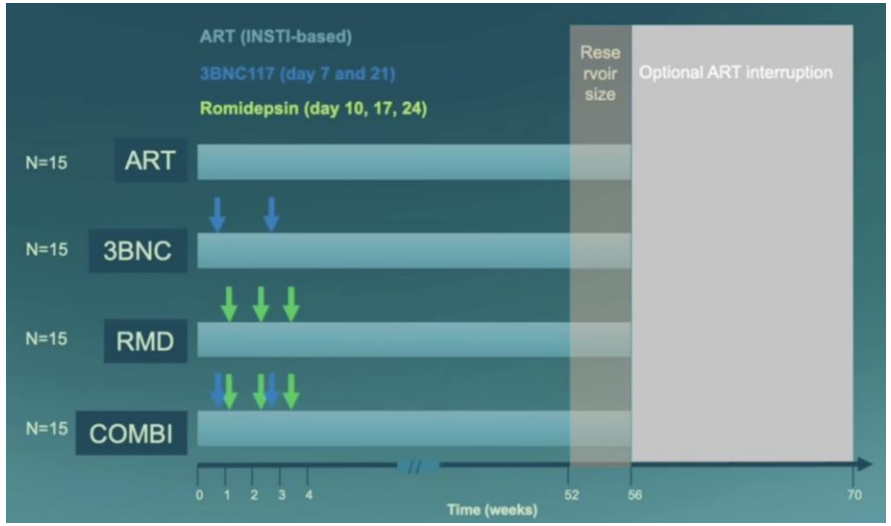
Post-Intervention Control w bnAbs

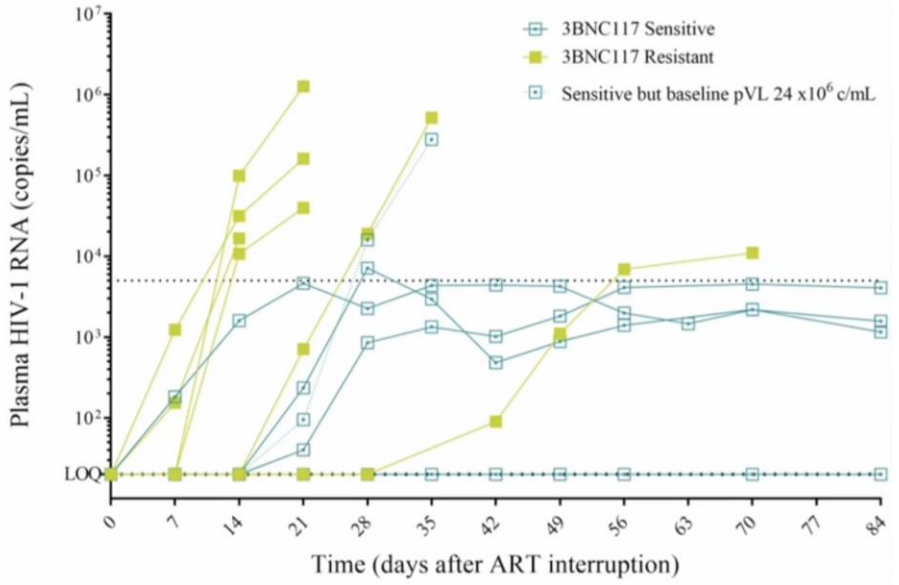


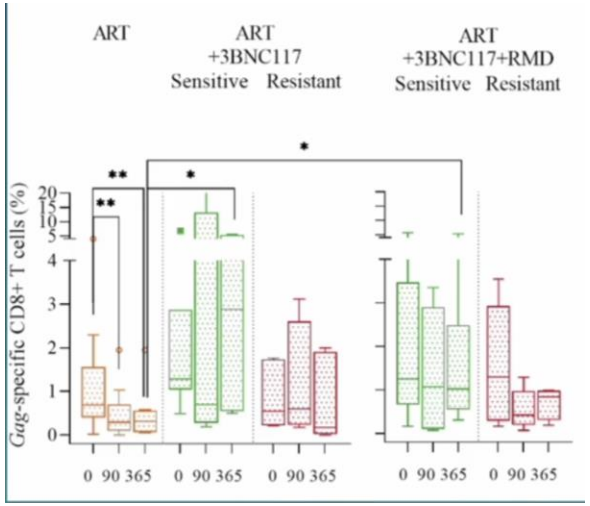
- Across bnAb studies, small fraction of recipients demonstrate durable **Post-Intervention Control**
  - *Unclear if this is more frequent than with ART alone*.

Mendoza et al., Nature 2018

eCLEAR: bnAb + LRA at ART initiation







- Open label RCT of +/- bnAb/LRA at ART initiation
- 3BNC117 w baseline sensitive virus at ART initiation
  - Faster phase 2 virus decline
  - Enhanced virus control, delay ART re-initiation
  - Enhanced HIV-specific T cell responses

Sogaard et al. CROI 2022

Key Questions: bnAbs for Treatment + SVR/cure

bnAbs can durably suppress sensitive viruses

- Extend population with "*sensitive*" virus
  - bnAbs of greater potency, breadth
  - predictive screening for baseline resistance in the reservoir?
- Demonstrate reservoir reduction and immunomodulation
  - ***Do eCLEAR results translate to pediatrics?***
- Build on advantages of bnAbs
  - ***Prioritize bnAb therapy trials for key populations***
    - LA bnAbs for infants, children, adolescents living with HIV
- Enhance equity of clinical testing, access for bnAbs

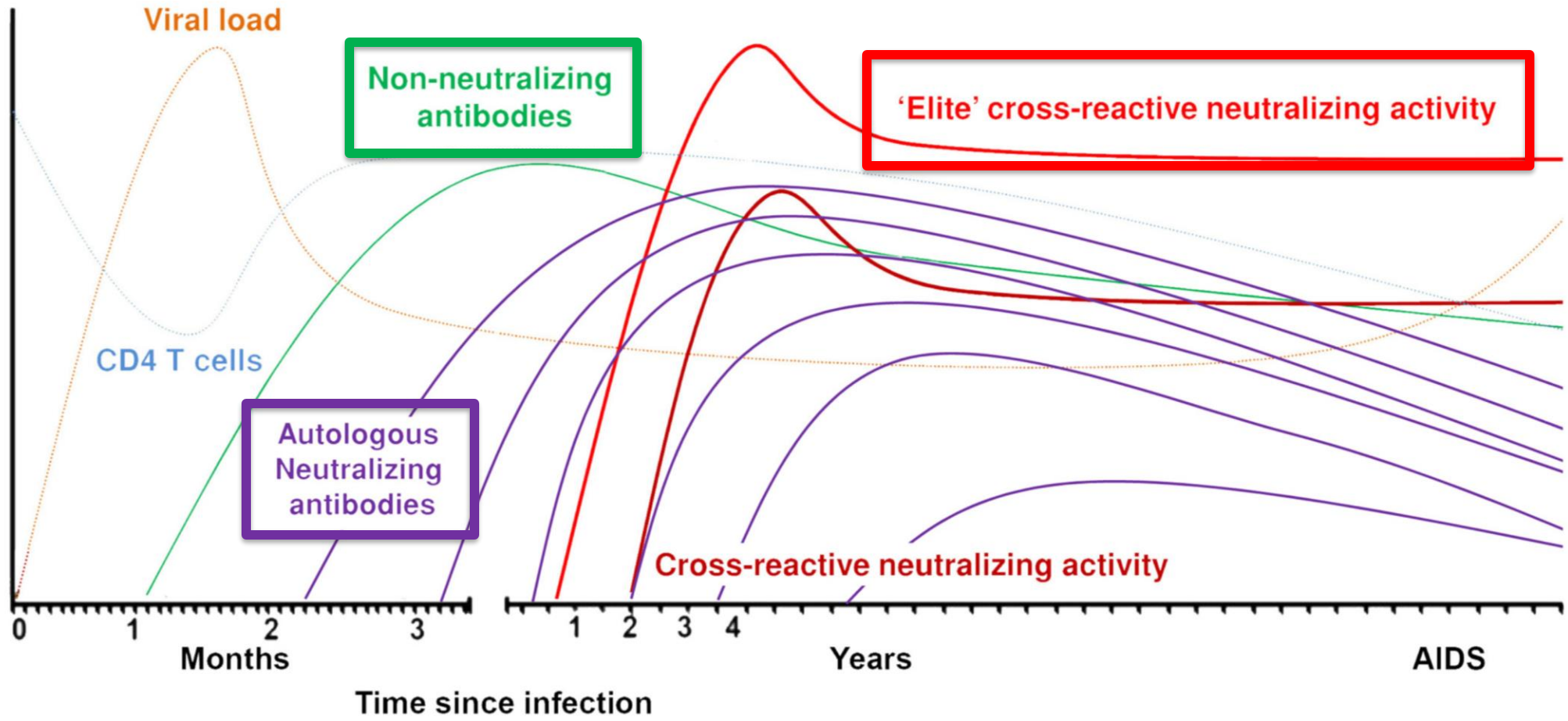
Equity

- **Development**
  - Are we developing the bnAbs with activity against entire HIV-1 Pandemic (non-clade B viruses)?
  - Are we allowing science to proceed with “products”
- **Clinical Testing**
  - Are we conducting clinical trials in populations who are most in need and/or can most benefit?
    - Highest prevalence regions? Women? Pregnant and breastfeeding? Infants? Adolescents?
- **Access**
  - How can we make bnAbs cost-effective and accessible?
    - Manufacturing, licensing
    - Delivery methods, longer acting agents

Summary and Comments

- **Continued development of potent, broad, complementary bnAbs**
  - Mechanistic & experimental medicine studies
  - Continued innovation in PK, delivery, Ab engineering, bnAb combinations
- **Thoughtful design of clinical trials**
  - Trials in pregnancy/infancy, women, global communities, diverse subtypes and modes of acquisition
  - **Prevention**: build on AMP, consider current prevention landscape
  - **Treatment/SVR**: tackle resistance, test bnAbs at ART initiation, experimental medicine of combination cure strategies
- ***Thank you!***

Autologous nAb response to HIV-1 infection



- Strain specific neutralizing Abs arise within 2-3 months
- **Broad neutralization arises after 2-3 years, in 5-30% of patients**
  - *bnAbs develop faster, differently in infants*

Euler and Schuitemaker, Frontiers in Immunology 2012