Autologous nAb responses in bnAb-treated SHIV.D-infected macaques

Katharine J. Bar, MD

University of Pennsylvania

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NIH National Institute of Allergy and Infectious Diseases

CFAR Center for AIDS Research University of Pennsylvania Children's Hospital of Philadelphia Wistar Institute

ACTG AIDS CLINICAL TRIALS GROUP

UAB Center for AIDS Research

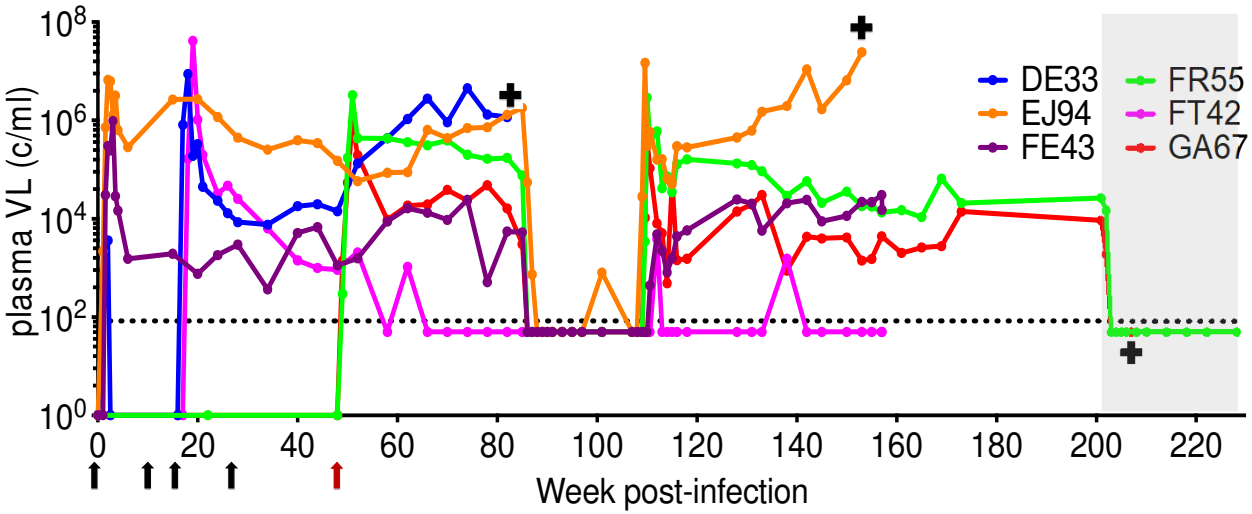
BEAT-HIV DELANEY COLLABORATORY

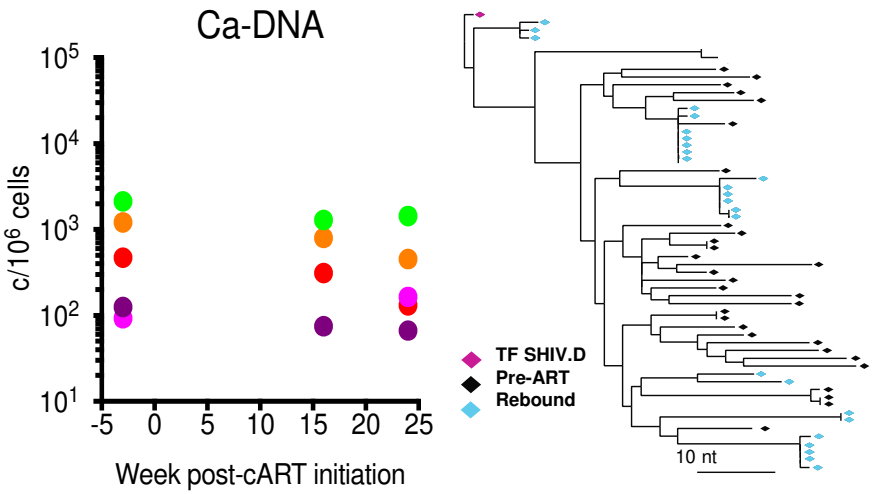
HIV CARE Collaboratory of AIDS Researchers for Eradication

NHP studies of bnAb activity and mechanism

- **Human studies of bnAbs have shown promise**
  - prevention, virus suppression, reservoir reduction, and immunomodulation
- Key determinates of bnAb activity remain unclear, may be better characterized in a **validated NHP model**, which:
  - mirrors key features of HIV-1 viral and immune dynamics
  - allows experimental control of virus diversity and phenotype, co-morbidities, interventions, and tissue sampling
- NHP study of bnAb monotherapy at ATI to characterize bnAb activity and engagement with host immunity

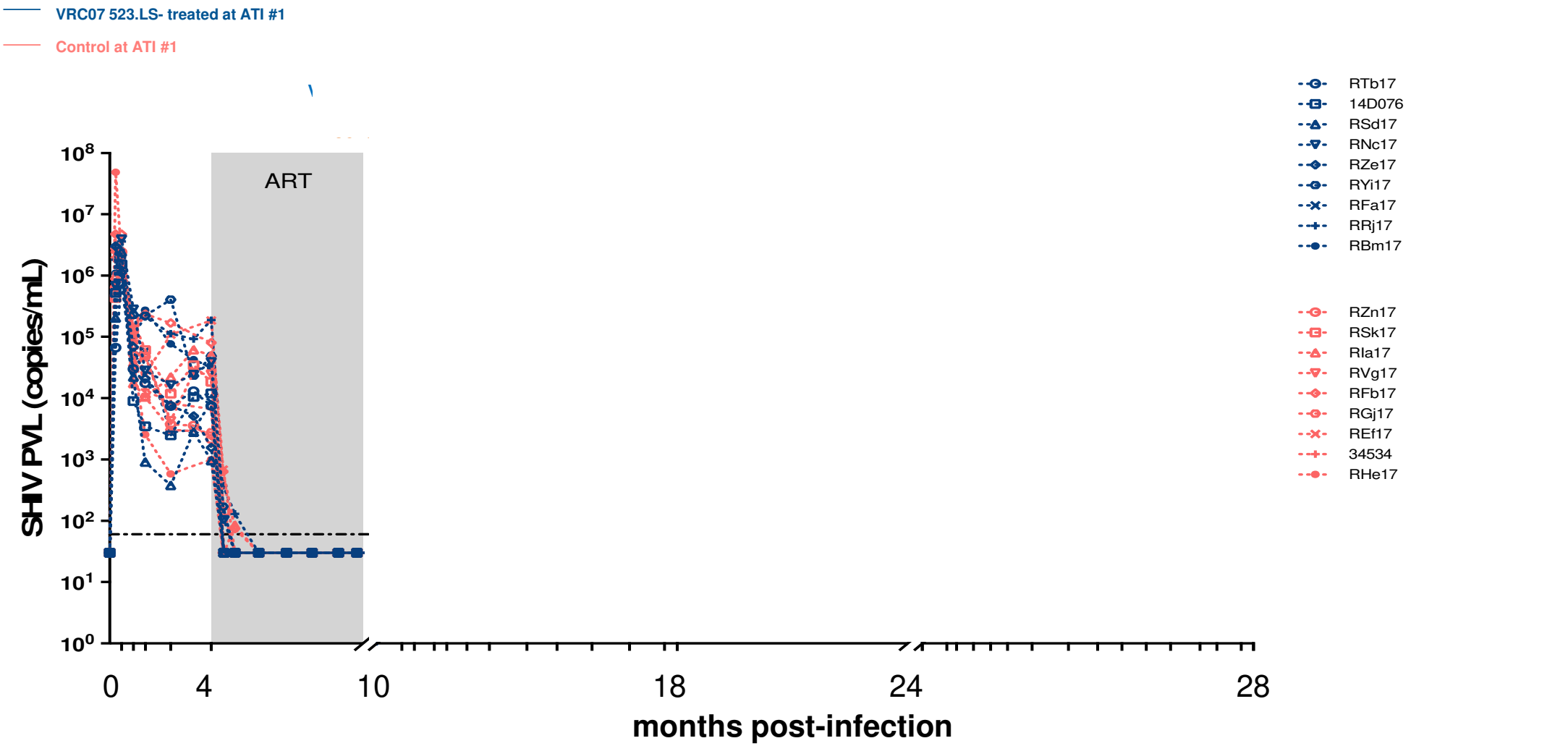
SHIV.D – Rhesus Macaque model



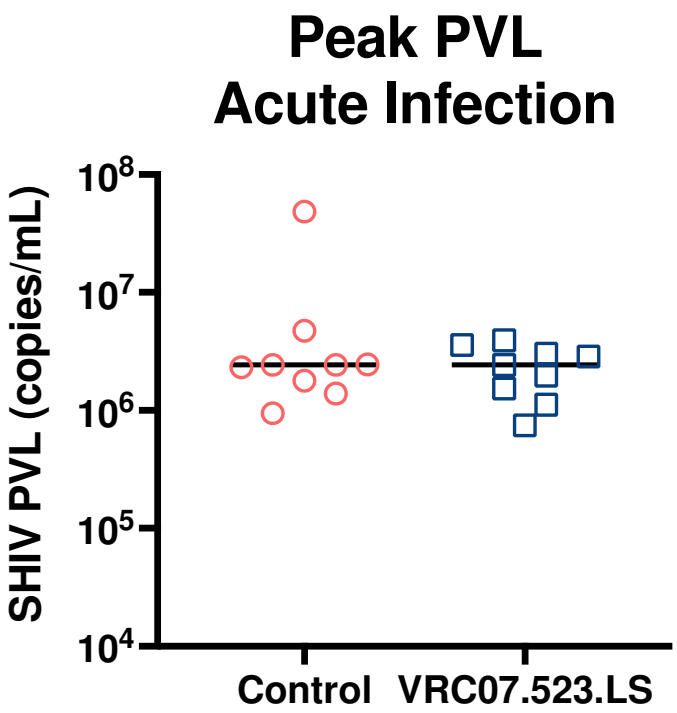


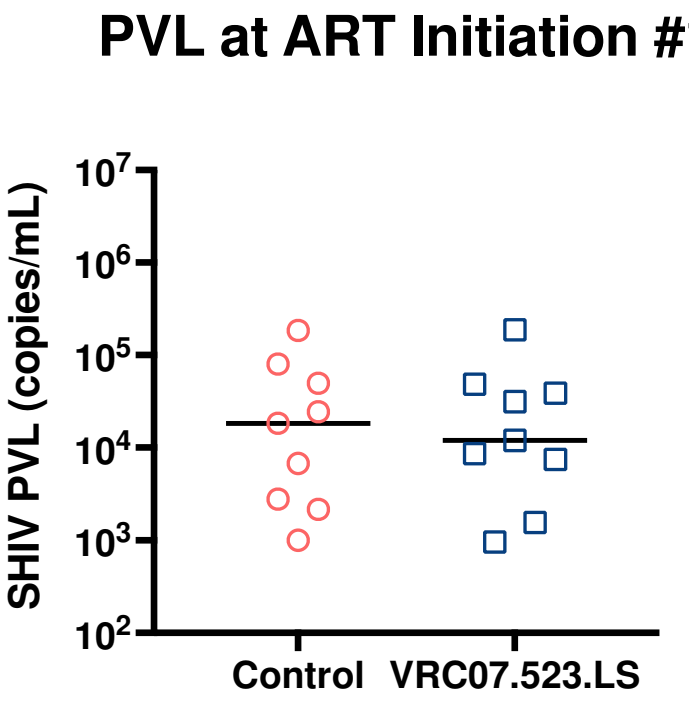
- TF Env: Clade D, R5 tropic, T-cell and Macrophage-tropic
- Validated to replicate consistently over time, persist on ART
- Moderately sensitive to CD4bs bnAbs: VRC07523.LS IC50 ~0.8 ug/ml

CD4bs bnAb monotherapy at ATI

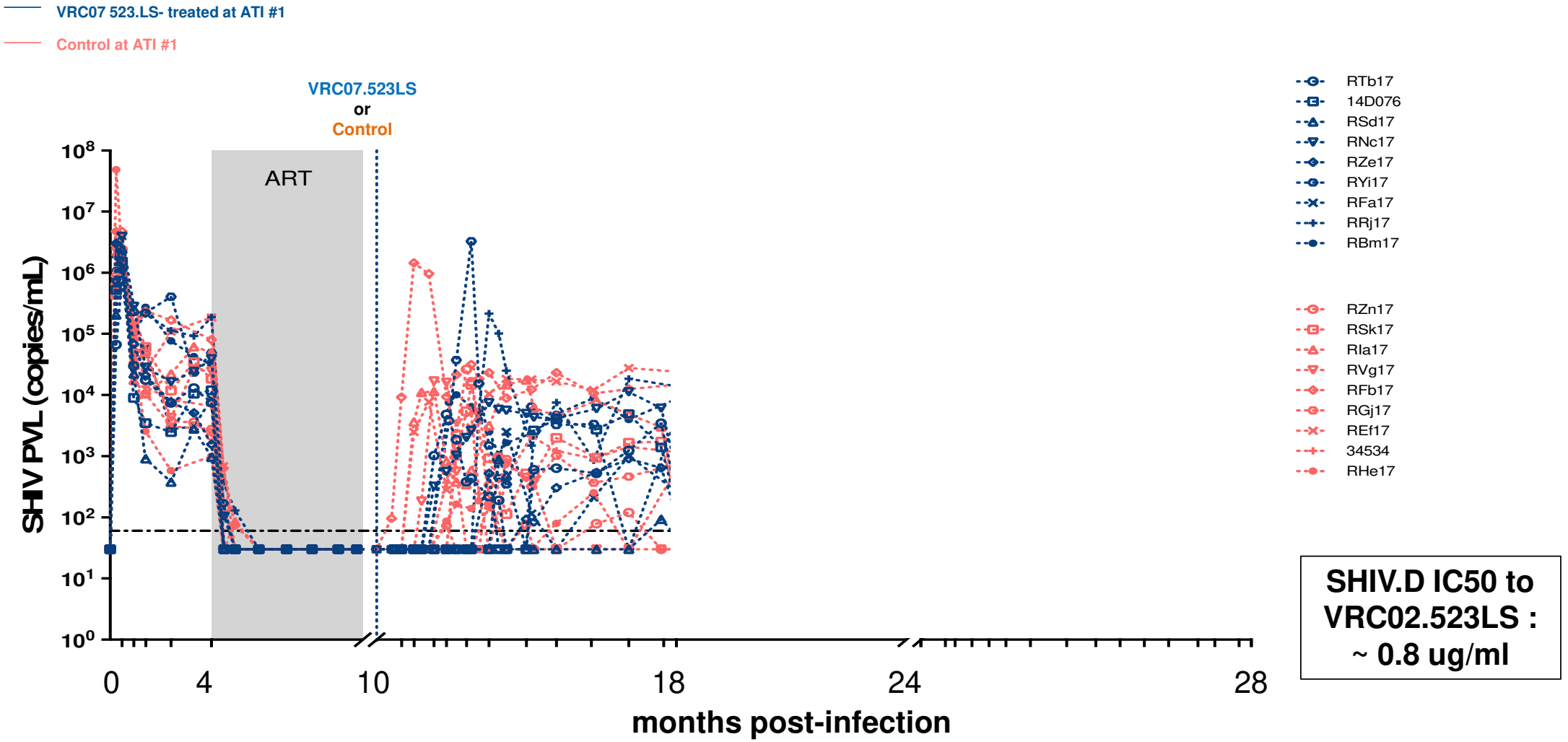


Desirable Viral Kinetics



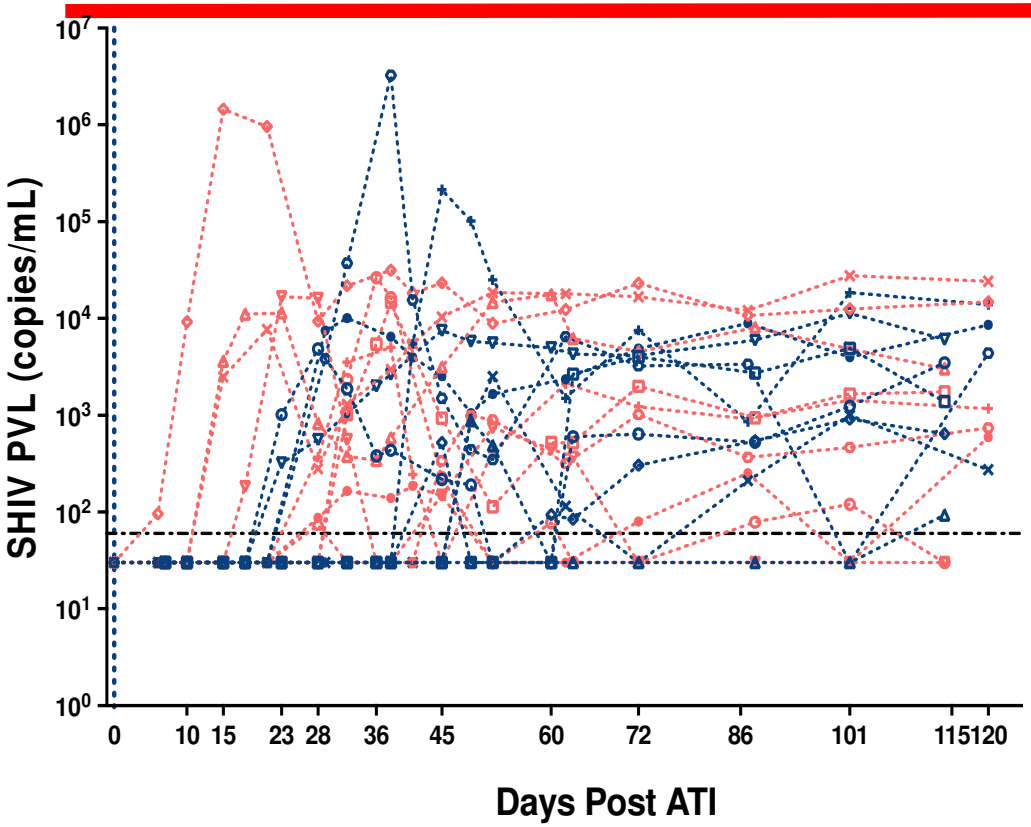


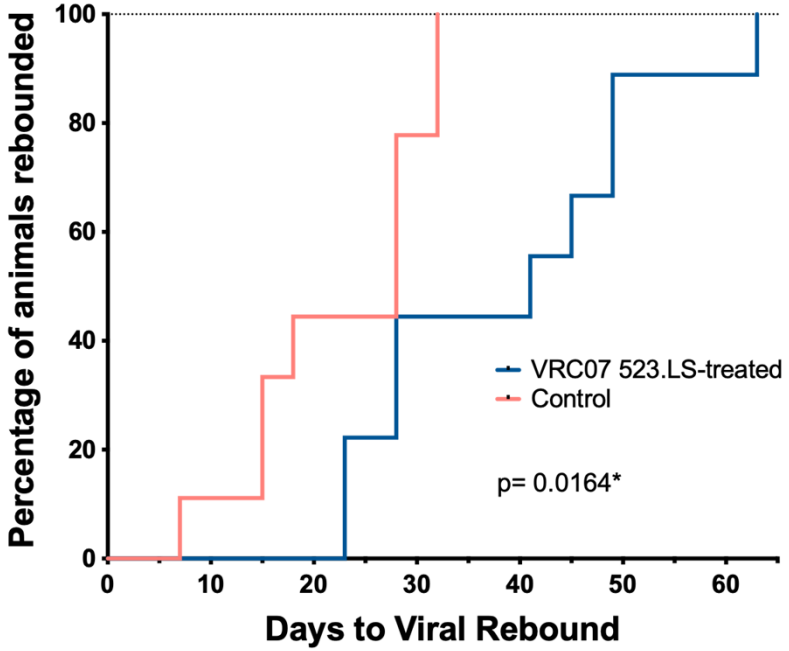
CD4bs bnAb monotherapy at ATI



SHIV.D IC50 to VRC02.523LS : ~ 0.8 ug/ml

VRC07.523LS-treated with modest delay in time to rebound

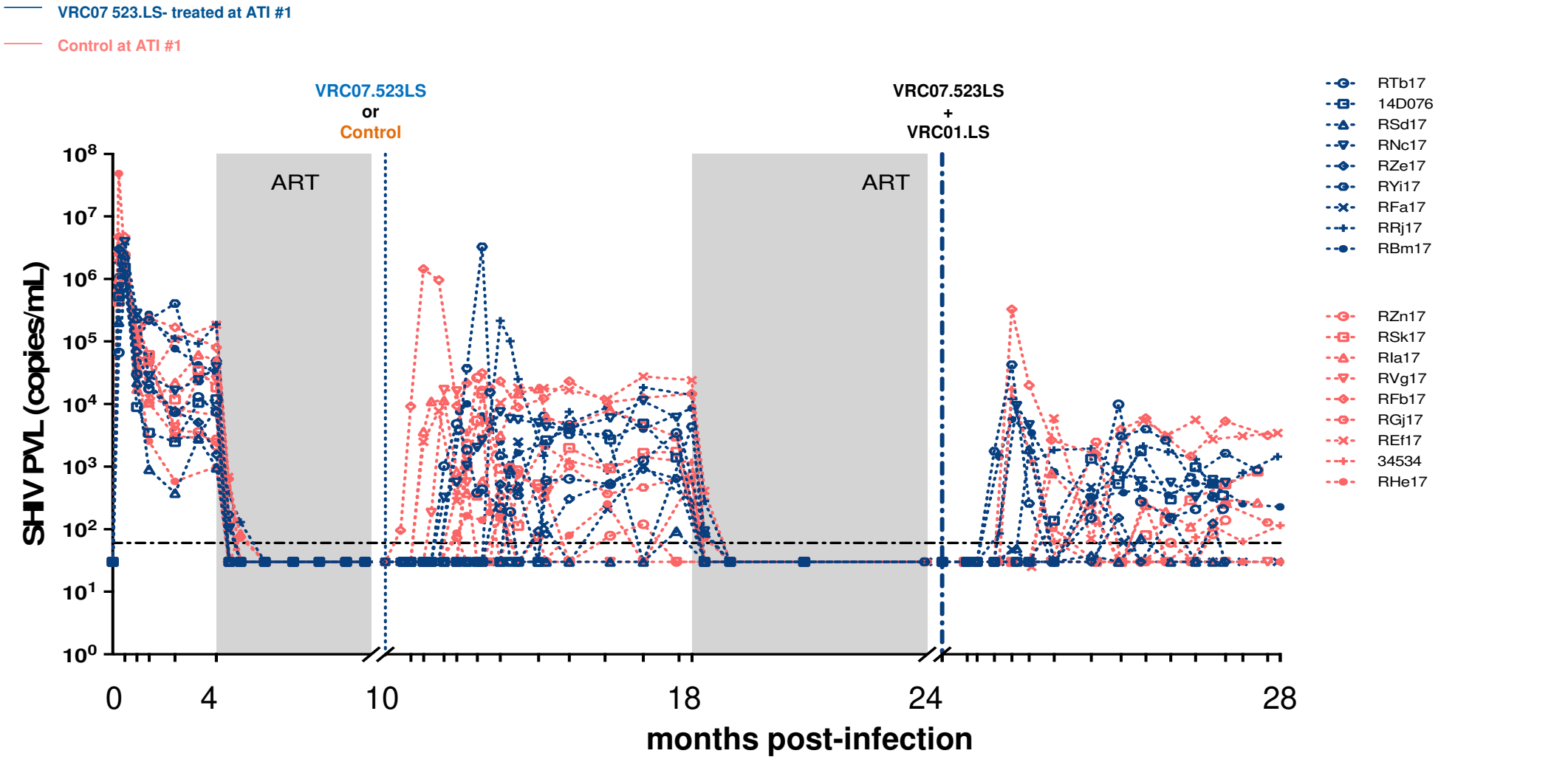




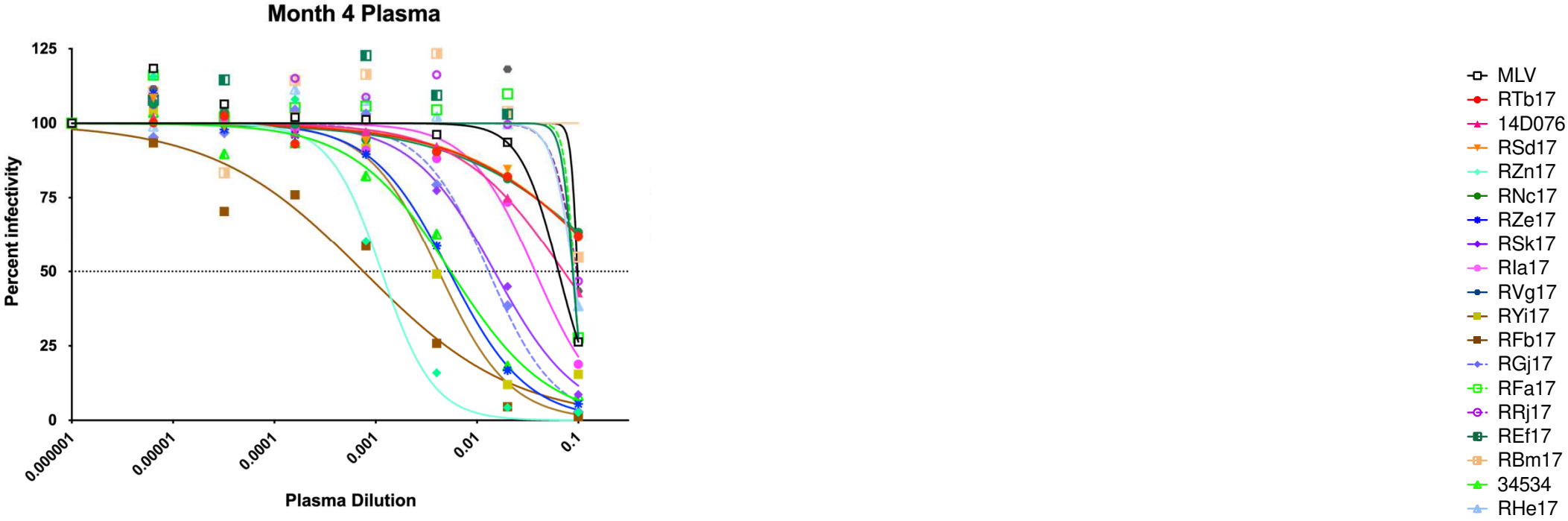
Median time to rebound: VRC07-treated: 41 days vs. Control: 28 days; p=0.0164

- akin to human clinical trials with modest potency vs. virus at ATI
- highlights role of virus:bnAb sensitivity as ***one factor*** in time to rebound

CD4bs bnAb monotherapy at ATI

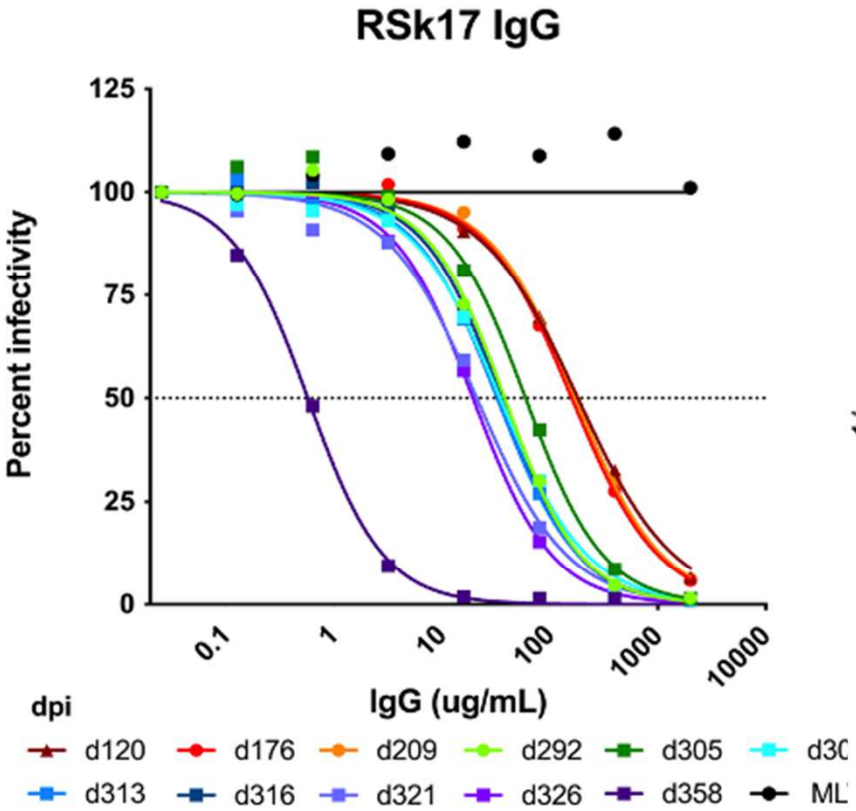


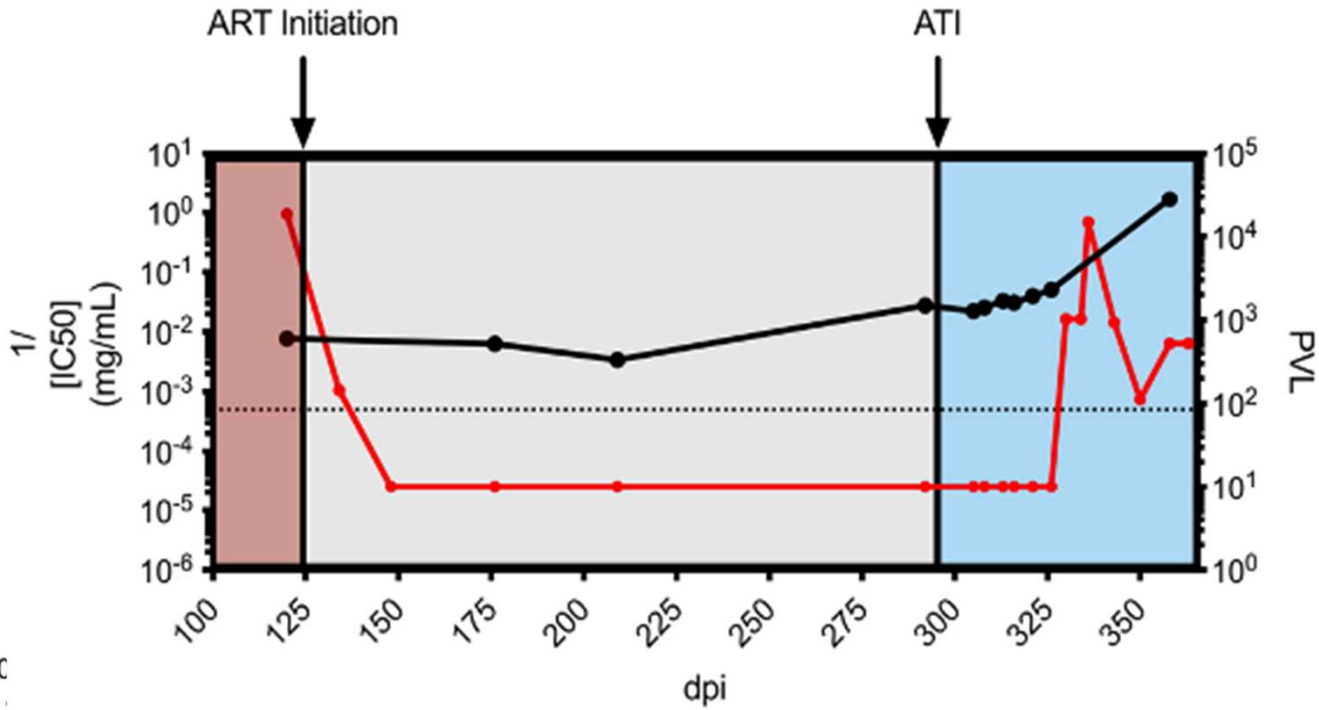
Autologous nAb Responses at 4 months



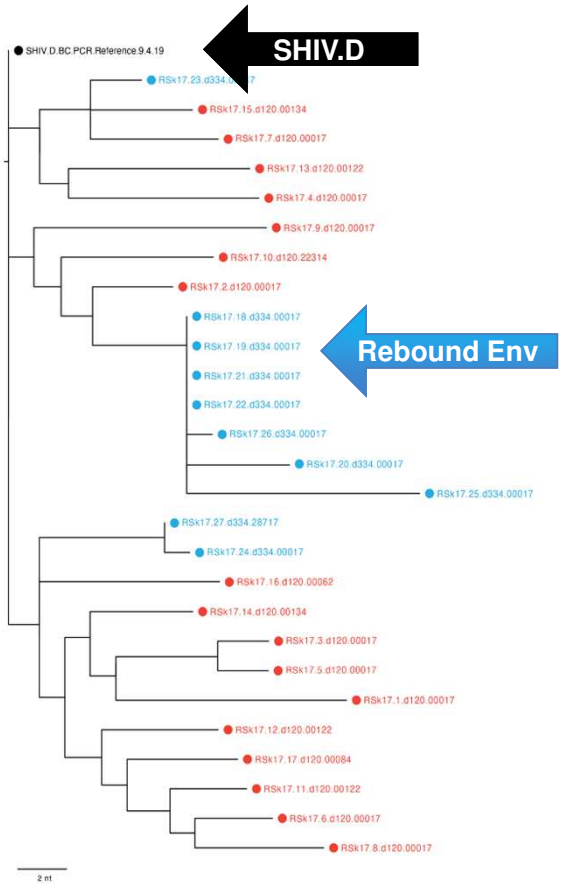
- **56% (10/18) RM developed anAb at 4 months**
  - IC50 > 1:50 plasma dilution by TZM.bl
- Spearman rho: 0.85, p=1E-5 between plasma and IgG

Longitudinal anAbs: Control RM RSk17



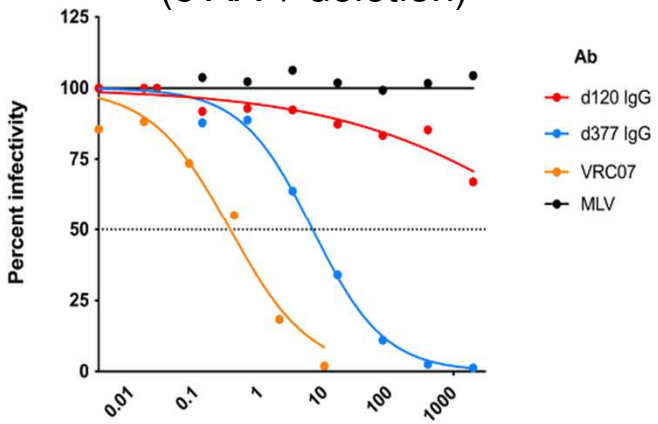


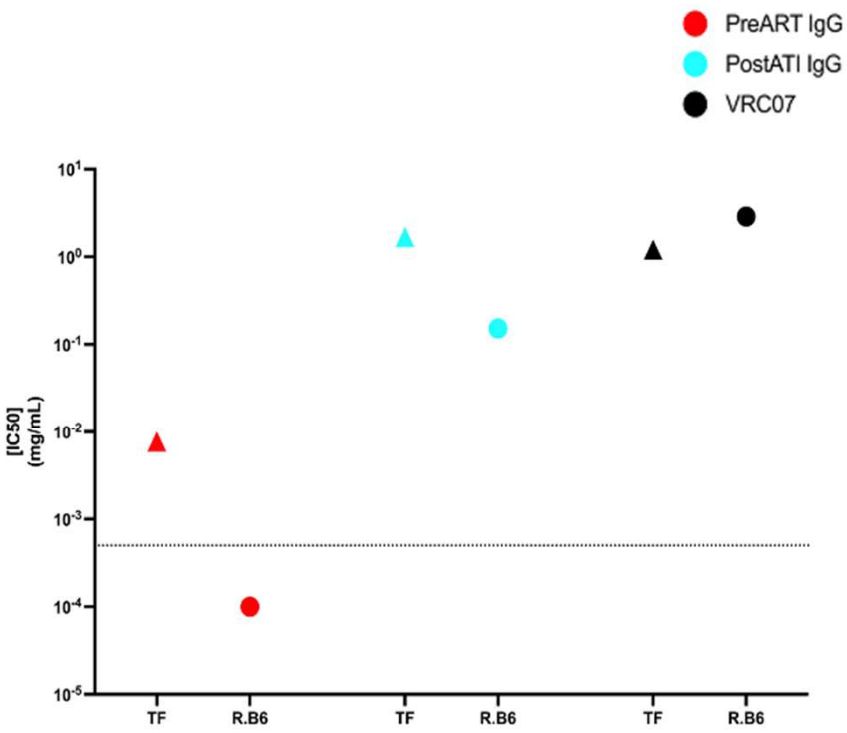
Longitudinal anAbs: Control RM RSk17



SHIV.D
Pre-ART (d120)
Rebound (d334)

Rebound Env
(5 AA + deletion)





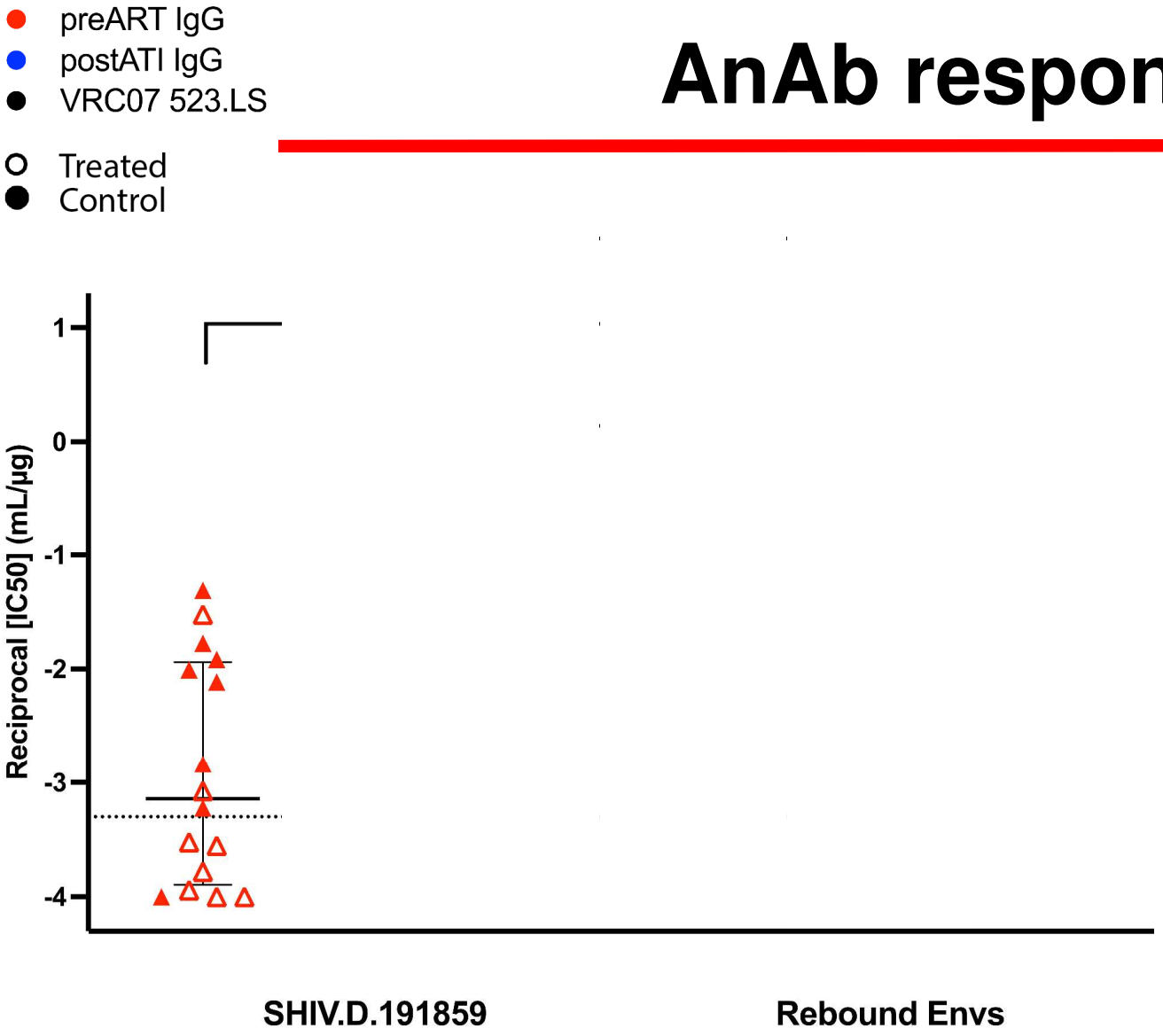
Pre-ART day 120

Post-ATI day 334

VRC07

Neutralization (1/IC50)

AnAb responses



- Detectable anAbs to TF SHIV.D at 4 months in 56%
  - similar to kinetics in PLWH
- Rebound Envs resistant to baseline nAb
  - suggests humoral immune pressure
- AnAbs boosted post-rebound, preferentially vs. TF
  - antibody imprinting
- Modest increase in VRC07-resistance in treated RM p=0.03.

Summary

- **Validated NHP model:** SHIV.D infected RM mirror key features of human clinical trials with control of experimental variables (*eg*, virus diversity & phenotype).
- **BnAbs delay rebound:** Virus sensitivity to bnAb (by TZM.bl assay) is ***one factor*** determining time to rebound
- **Autologous nAbs**: Arise in ~50% animals with early ART, generally remain stable over ART, are boosted with viral rebound.
  - Rebound virus is universally resistant to anAbs, suggesting humoral selective pressure at ATI.
- **Ongoing**: mapping determinants of anAb response, anAb resistance, and overlap between anAb and bnAb epitopes; measuring reseeding of virus with ATI; assessing for immunomodulation; determinants of viral rebound.

Key question(s): What is the role of macaques' own antibody responses when receiving bnAb therapy?

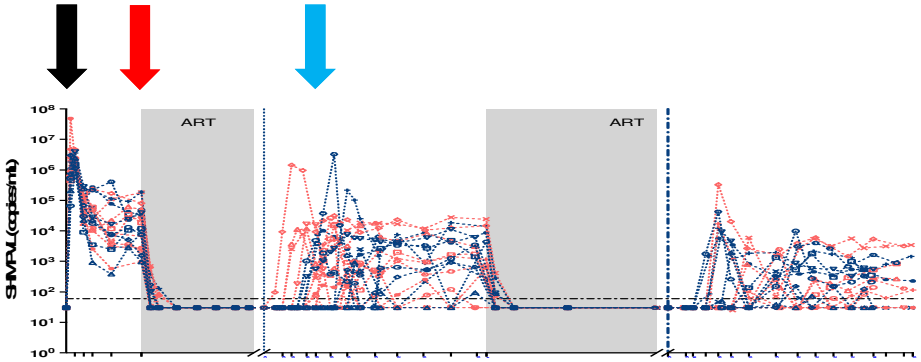
Key findings and take home message: Antibody responses arise within the first months of viremia, persist through ART, and may prevent some viruses from rebounding.

Next steps: Determine what drives these antibody responses and if and how these antibodies may help or hinder bnAb therapy.

Env sequence evolution

Rebound 1.1: first plasma virus > 500 c/ml

- median 2 lineages (range 1-5)
- no difference treatment vs. controls



Env evolution

Rebound 1.9: *increased diversity in treated?*

- No. similar diversity, divergence per day of viremia in treatment vs. controls

Rebound 2.1: *virus aligns?*

- 2nd rebound aligns with Rebound 1.9
  - reservoir stabilized w ART vs. phenotypic advantage