

MHRP Studies in Early Treatment and The Journey towards HIV Remission

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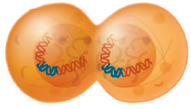
WRAIR

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Institute of Research

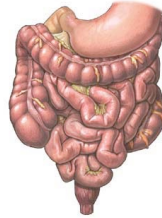
The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.



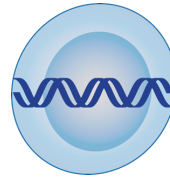
Why is Acute HIV Infection Important?



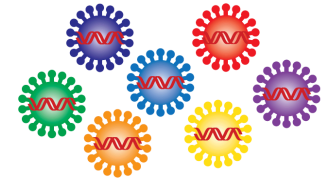
More cells
are infected



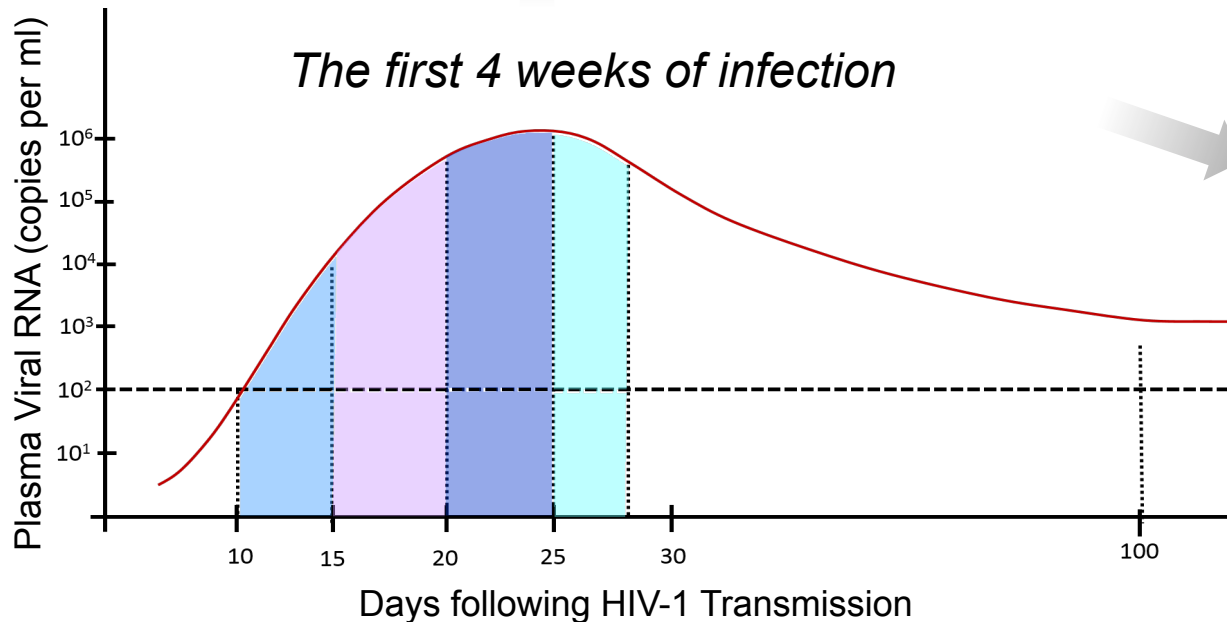
CD4 depletion
Tissue infection



Exhausted
immune system



Mutated HIV
evades immunity



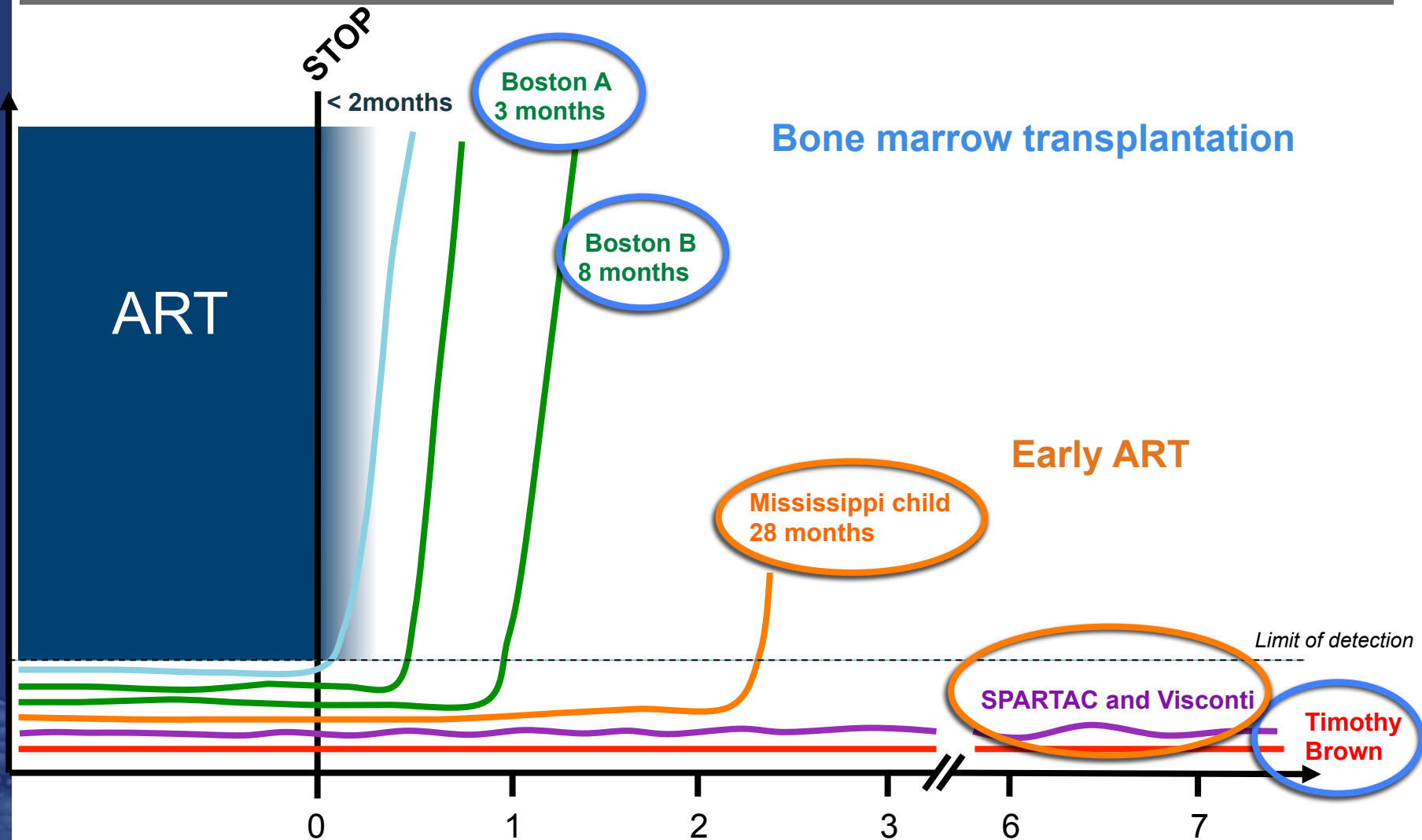
Transmission
of HIV

Two Ways to Achieve HIV Remission

(Undetectable Viral load in Blood without ART)

MHRP

Circulating virus



From Nicolas Chomont, 2015 IAS Plenary, Vancouver

Hütter, NEJM 2009; Persaud, NEJM 2013; Luzuriaga NEJM 2015; Henrich, JID 2013; Henrich, Ann Intern Med 201; Stöhr, Plos One 2013; Hocqueloux, AIDS 2010; Saez-Cirion, Plos Path 2013; Adapted from Cohen, Science 2015

MHRP/Thai Red Cross Acute Infection Studies

RV217

Prospective acute infection study
in high risk individuals

Twice weekly testing in E. Africa/
Thailand of **2555** uninfected persons



Acute HIV infection
(**n=124**)

Robb ML, NEJM 2016

SEARCH010/RV254

Acute infection cohort with early ART

Real-time screening of **200,000**
samples in Thailand



Acute HIV infection
(**n=430**)

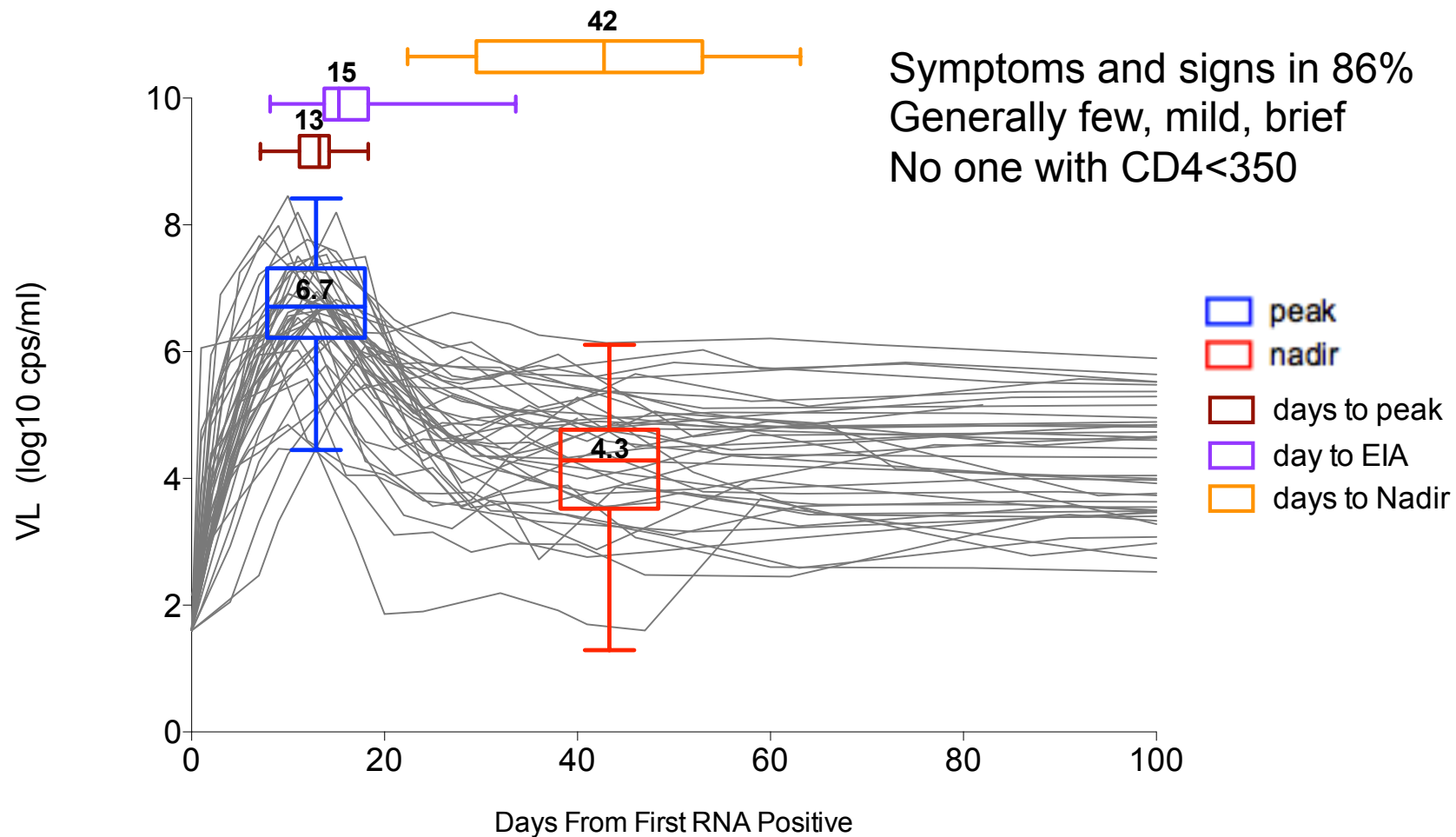
de Souza M, Ananworanich J, AIDS 2015

RV217 Population

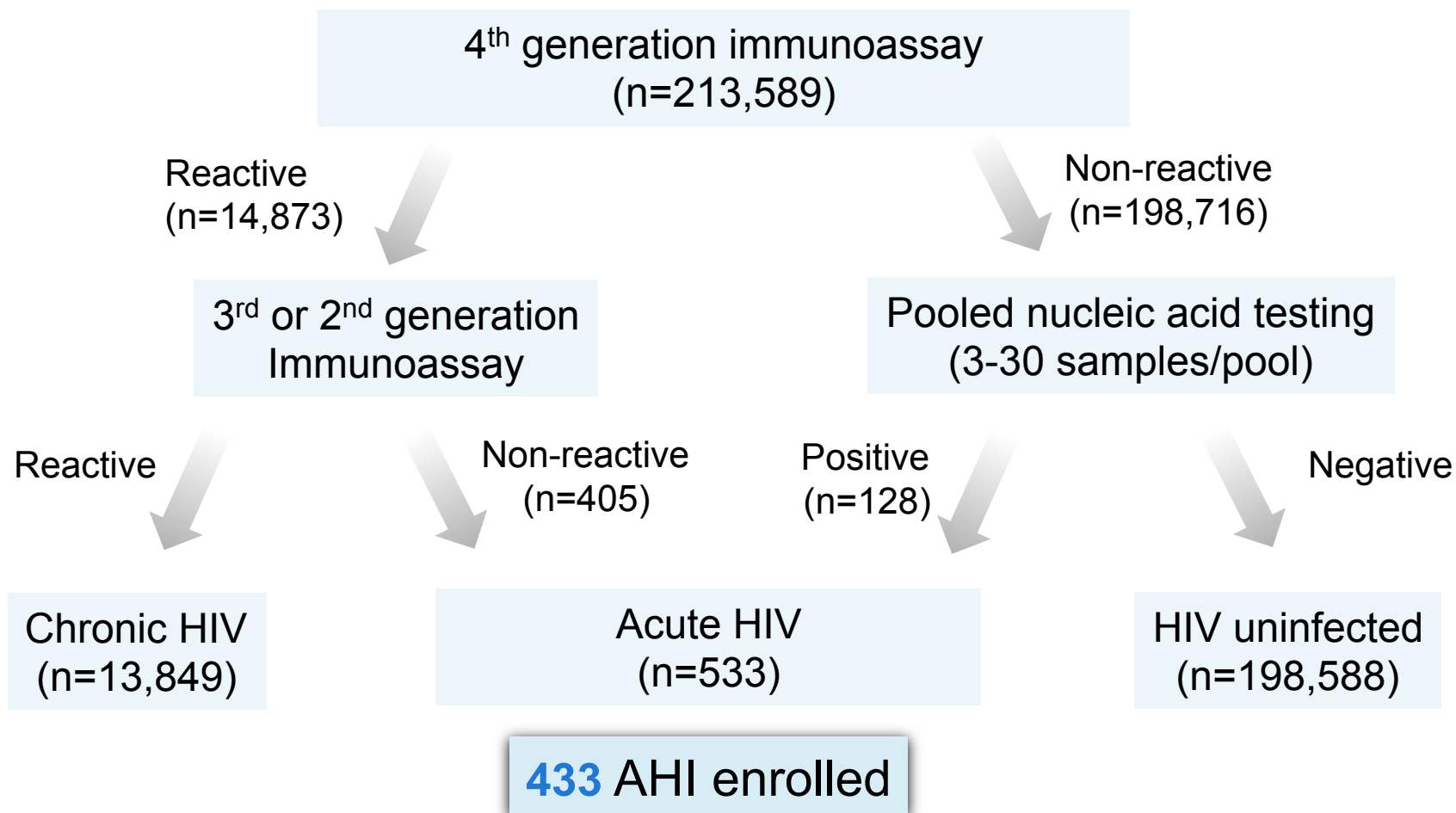
- Participants from East Africa, Thailand
- High risk behavior determined by an audio-computer assisted self interview
- Twice weekly finger sticks performed to identify HIV RNA
- Regular risk reduction counseling
- All receive HAART since 2014-2015



Viral Load during Acute HIV Infection (RV217)



Acute HIV Diagnosis Algorithm in RV254 Study



- HIV prevalence: 11%
- incidence of AHI: 2.2 per 100 person-years.

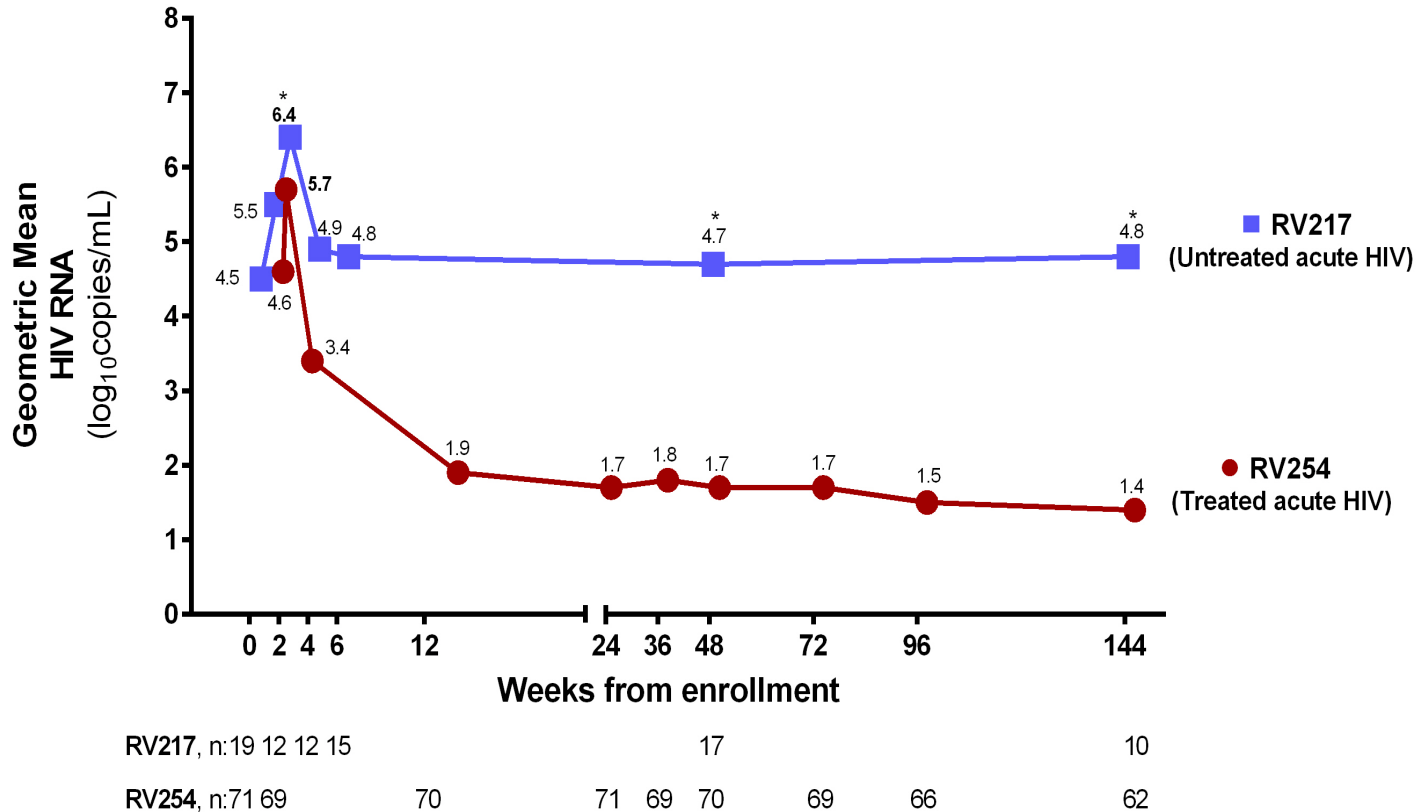
What can early treatment do and not do to help reach HIV remission?



Key Questions

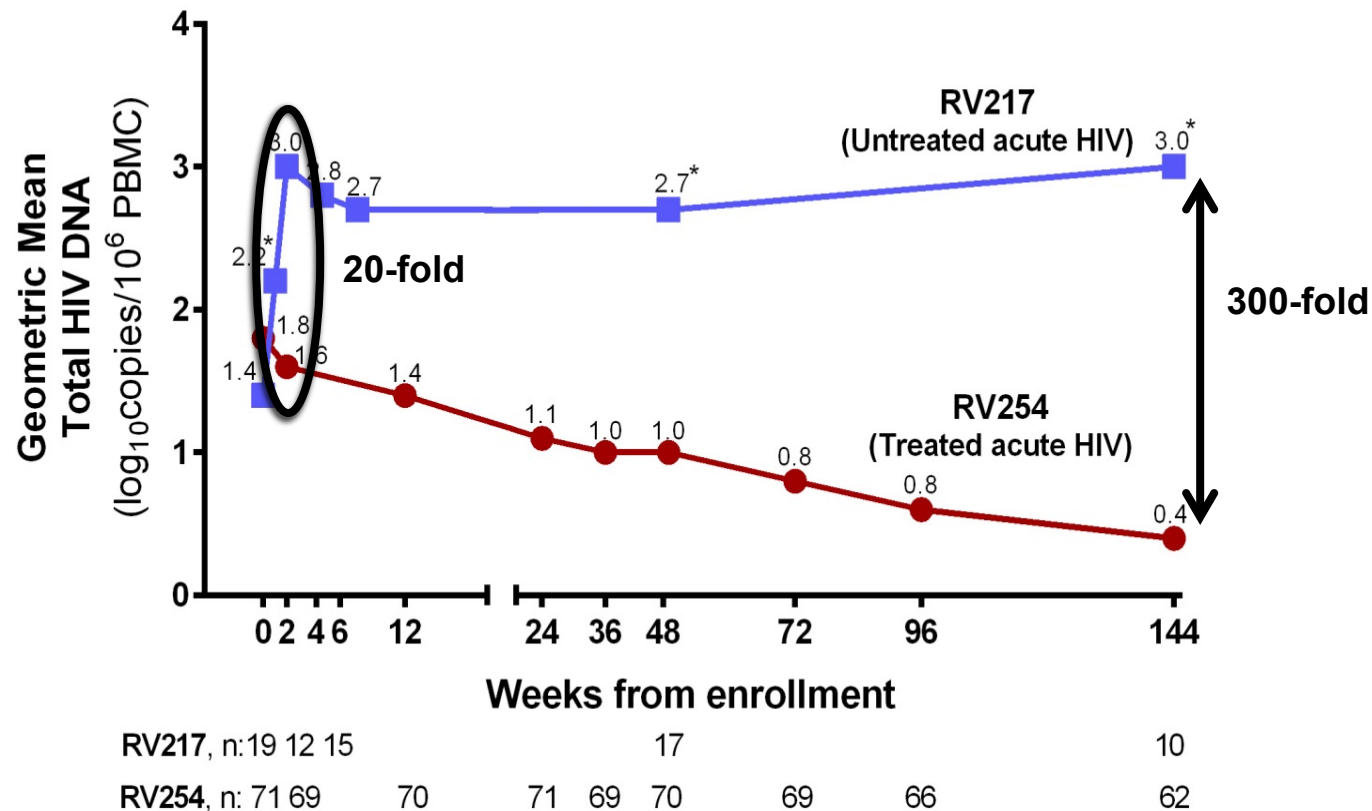
- What can **early treatment** do and not do to help reach HIV remission?
 - Data from RV217 and RV254 acute HIV infection studies
- Does **early treatment** in RV254 delay time to viral load rebound after treatment interruption?
- What might HIV remission treatment look like?

Plasma HIV RNA in RV217 untreated and RV254 treated acute HIV infection participants



- In RV217 untreated group: peak viremia is at week 2 and set-point is at week 4
- In RV254 treated group: 97% with HIV RNA < 50 at week 144

Stark Differences in HIV Reservoir in Untreated vs. Treated Acutely HIV-Infected Thai Adults

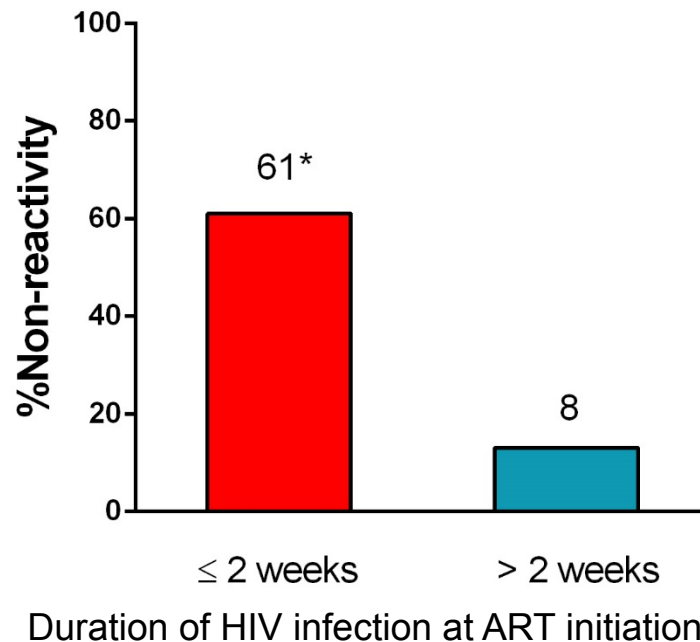


Reservoir “set-point” is established early in acute infection and determines reservoir size in chronic infection

Window of opportunity to significantly alter reservoir size is with early ART

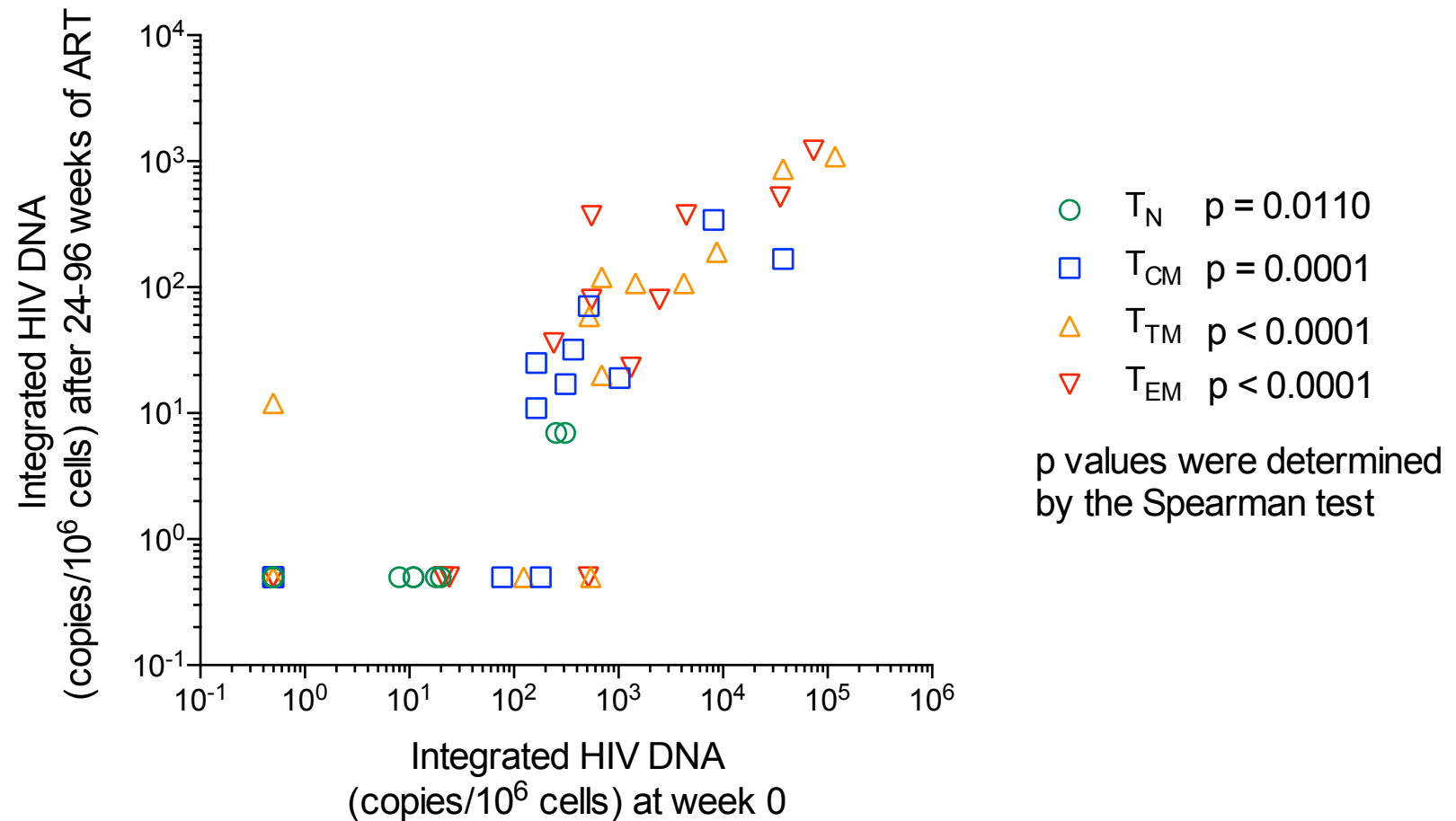
High Seronegativity in Very Early Treated Thais

4th generation antigen-antibody combo immunoassay 6 months after ART



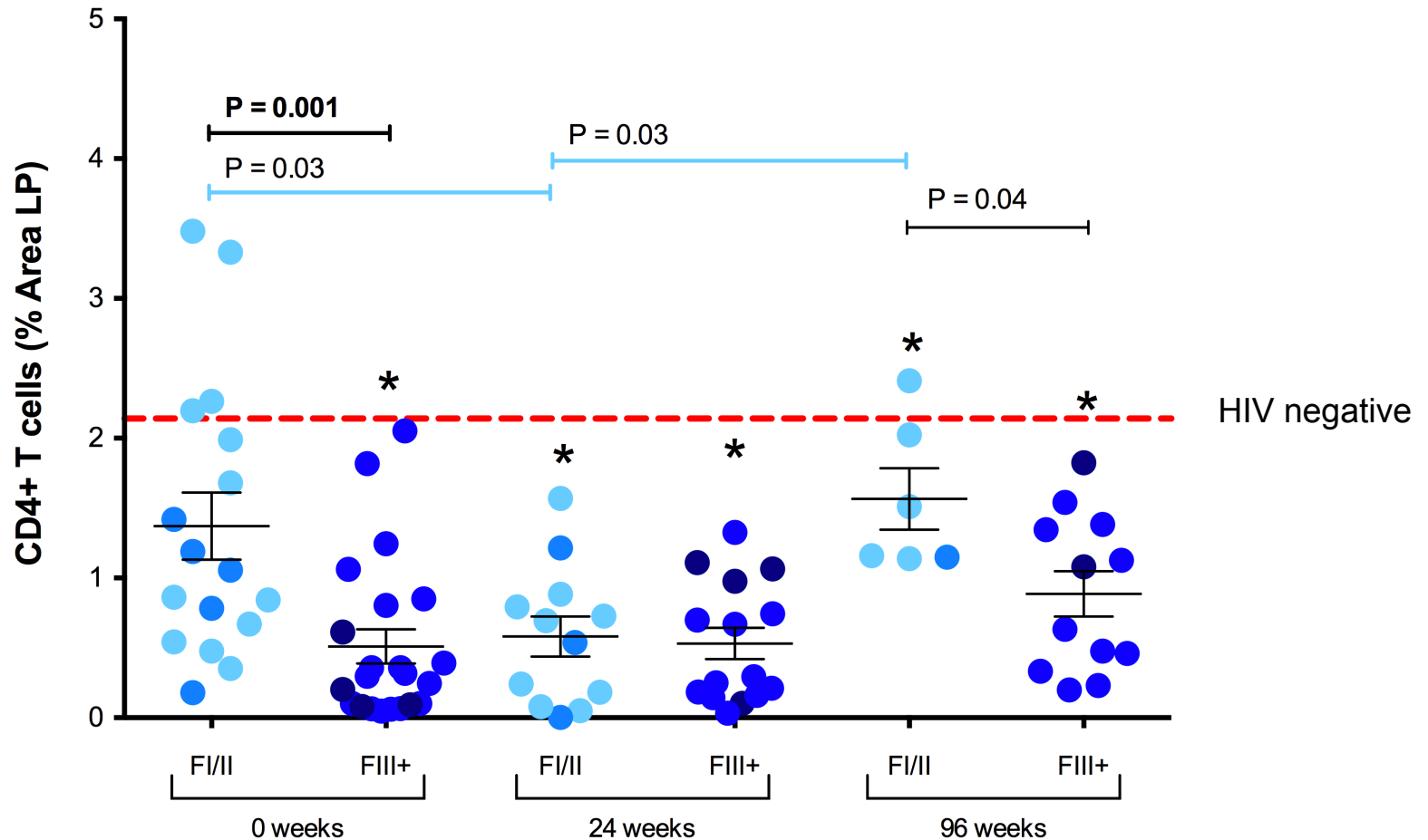
Very early treated individuals can remain HIV antibody negative more than 6 months from onset of infection

What You Start With is What You End Up With

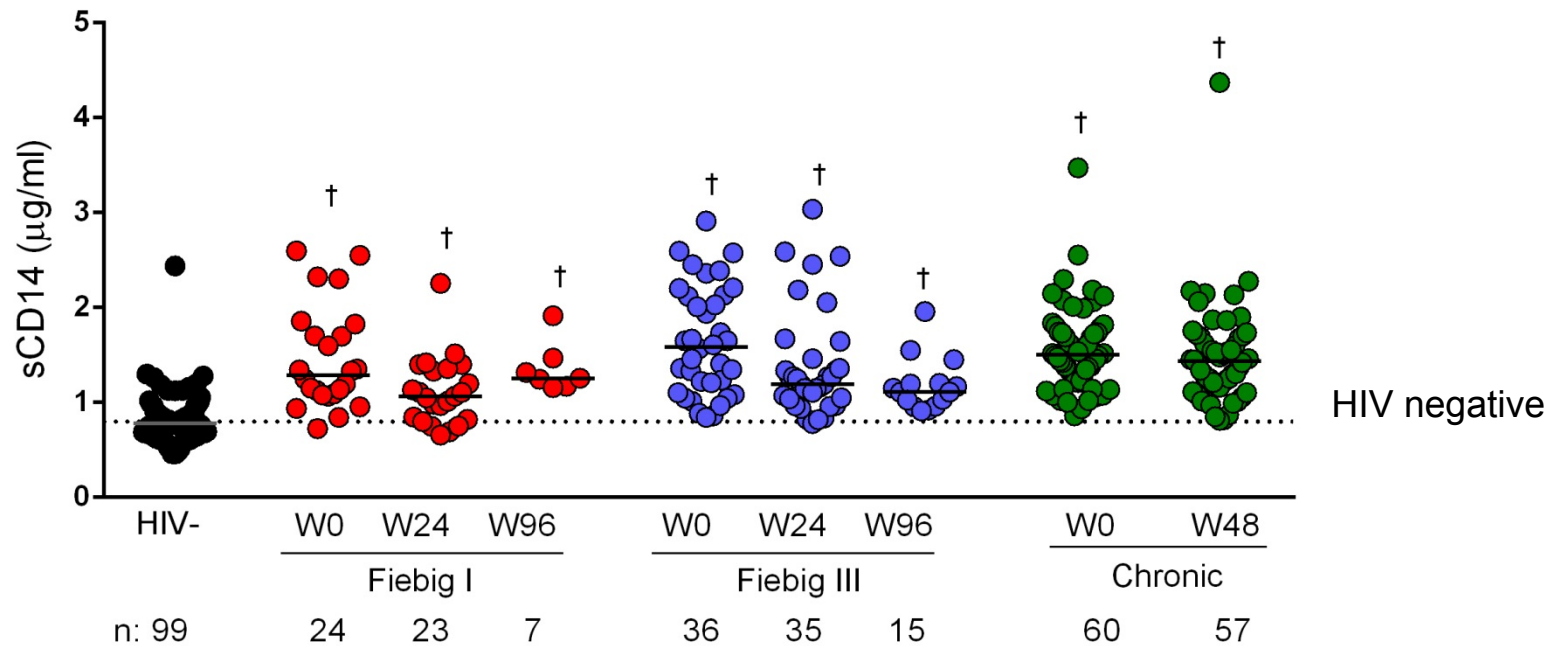


RV254 adults: Baseline DNA values in **memory CD4** predict their reservoir after ART

Limited CD4 Recovery in the Lamina Propria of Gastrointestinal tract

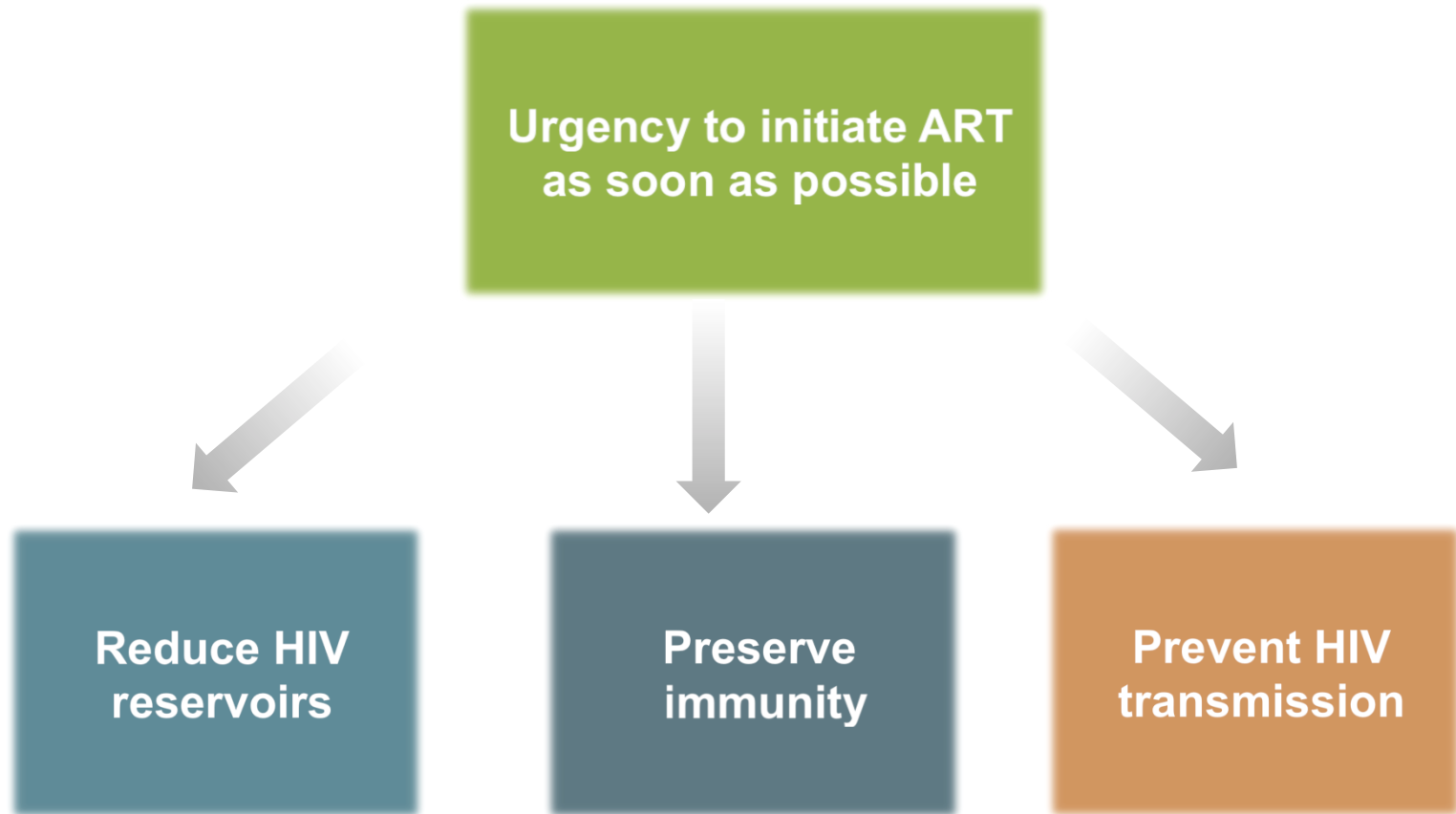


Elevated plasma sCD14 after early ART

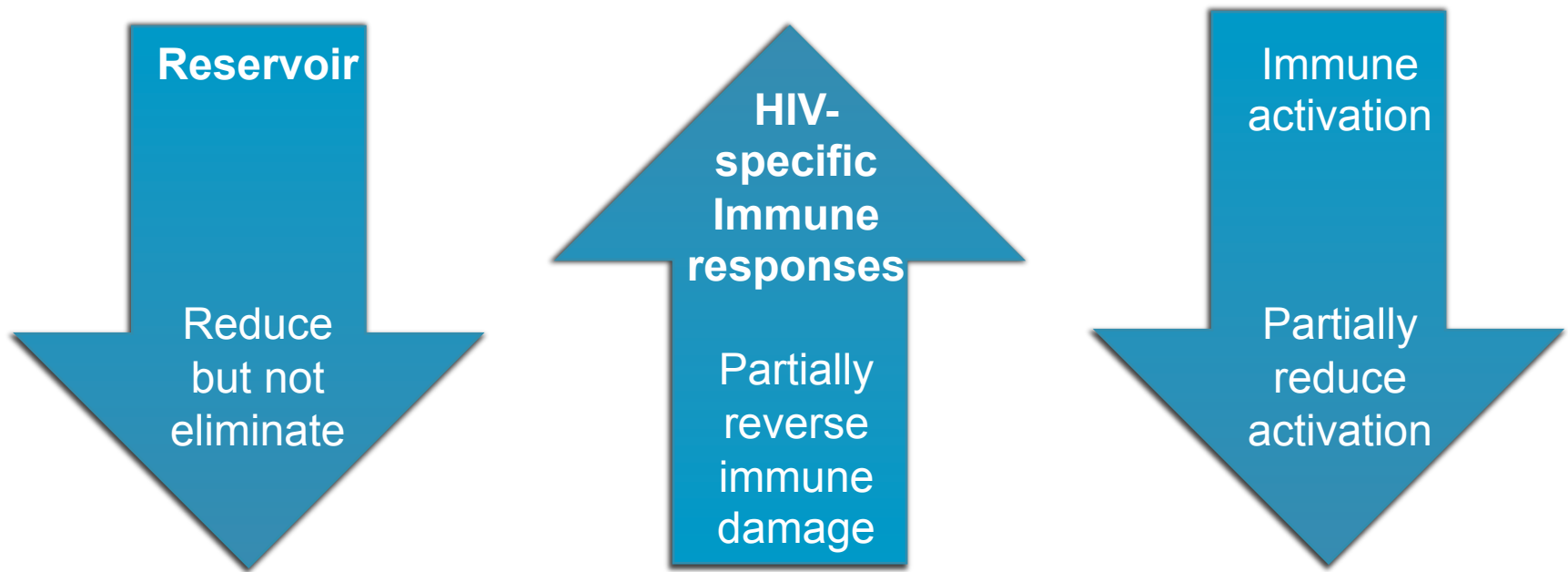


†p<0.05 compared to HIV-

Diagnosis of Acute HIV Infection

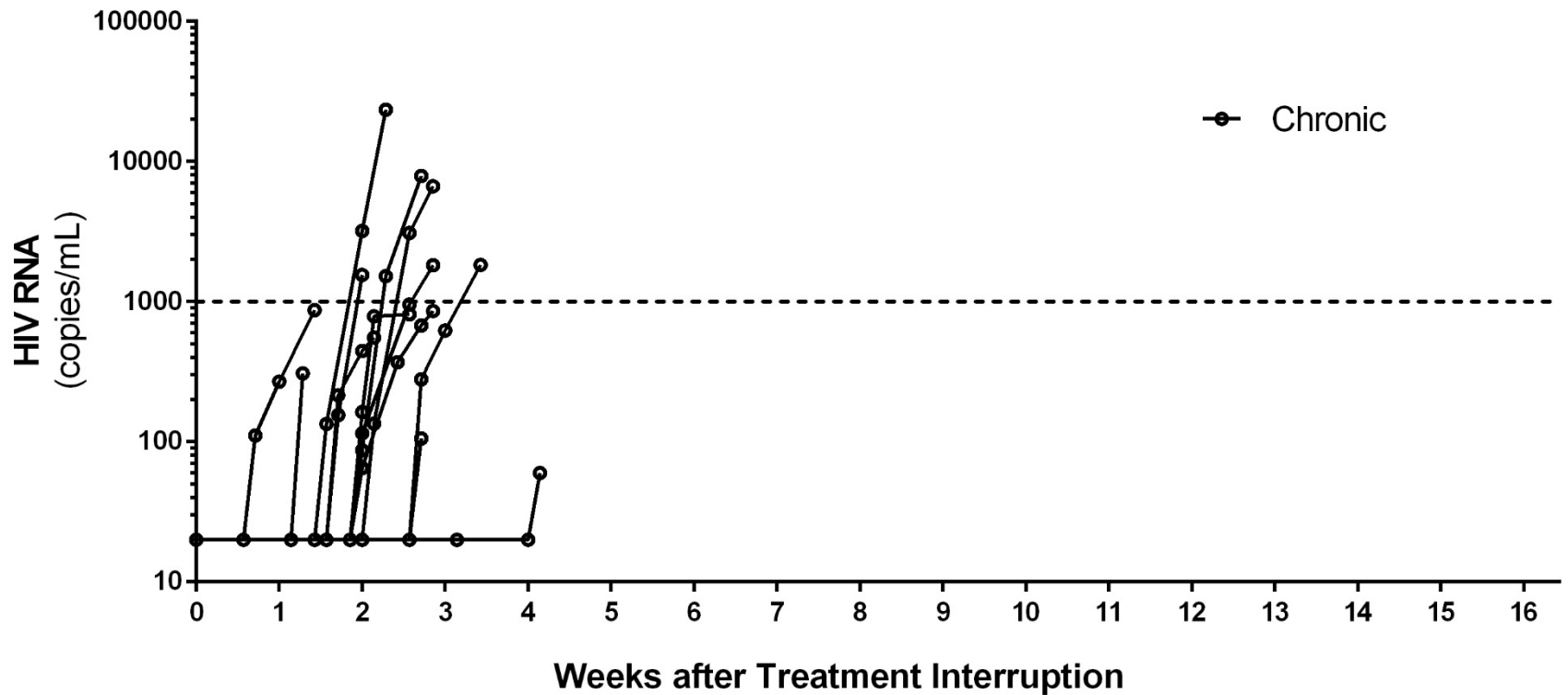


What can early treatment do and not do to help reach HIV remission?



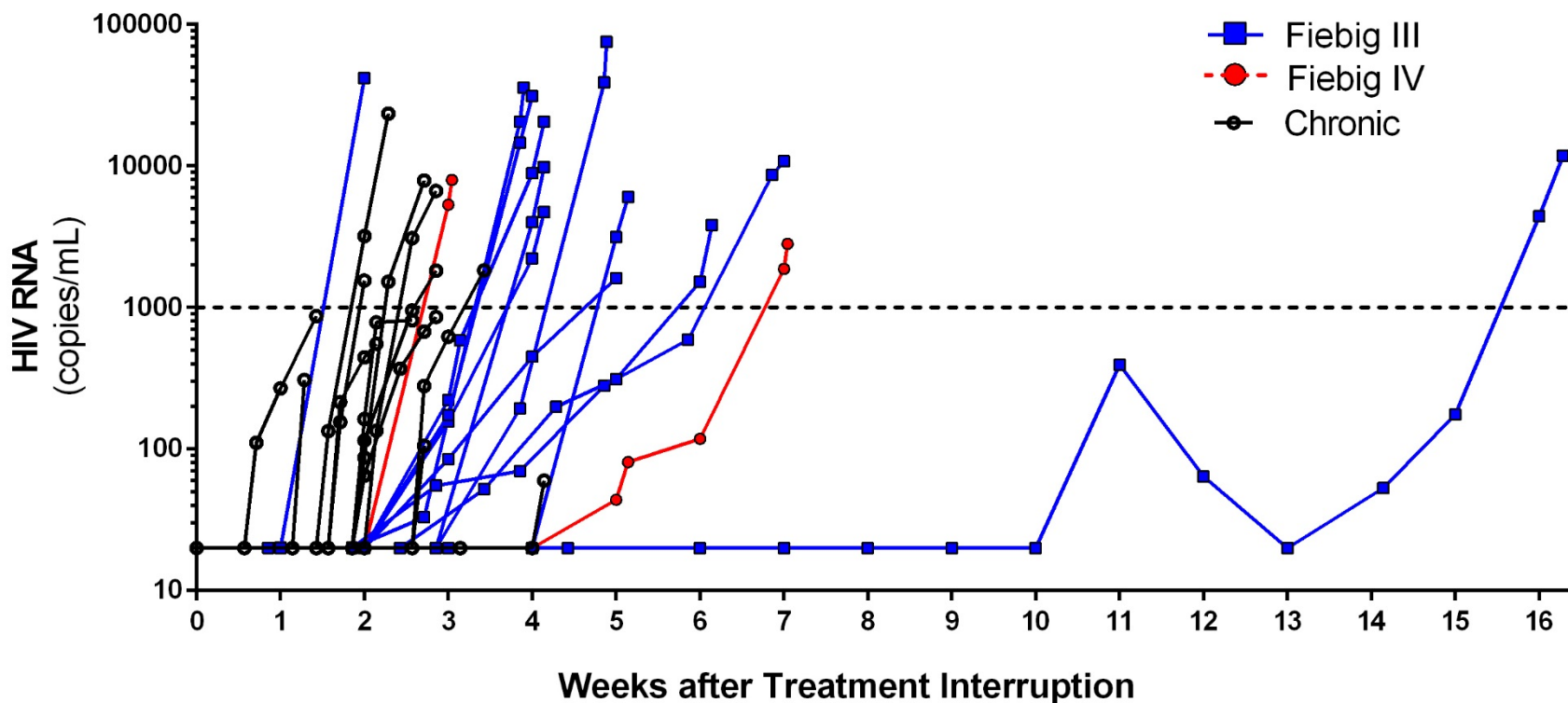
Does Early ART in RV254 Delay Time to Viral Load Rebound after Treatment Interruption?

Viral Load Rebound post-Treatment Interruption



Median (range) time to viral load rebound: 14 (5-29) days

Viral Load Rebound post-Treatment Interruption



SEARCH 019: Chloroquine + Maraviric + Vorinostat

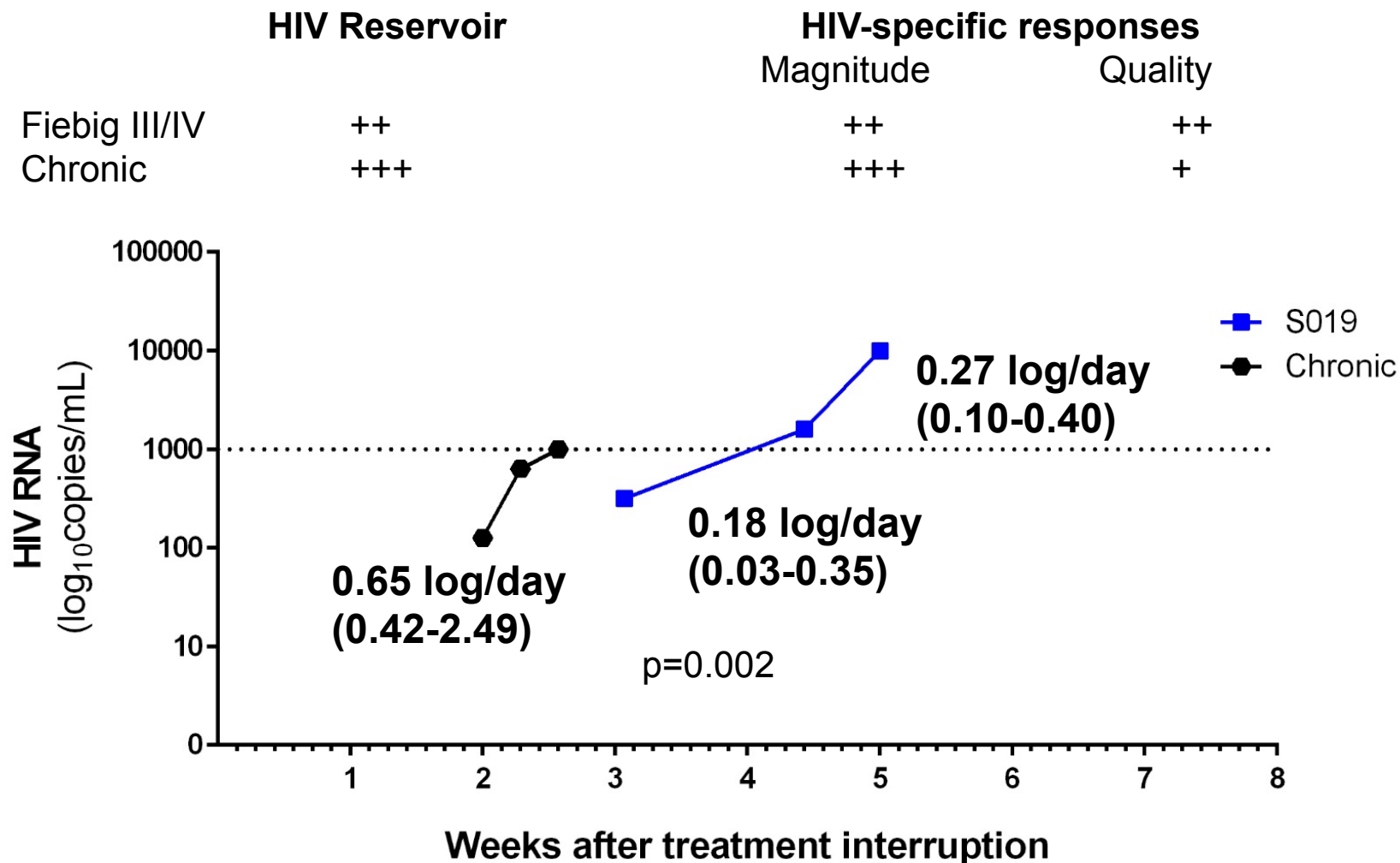
Median (range) time to viral load rebound

Chronic: 14 (5-29) days

Fiebig III/IV: 22 (21-77) days

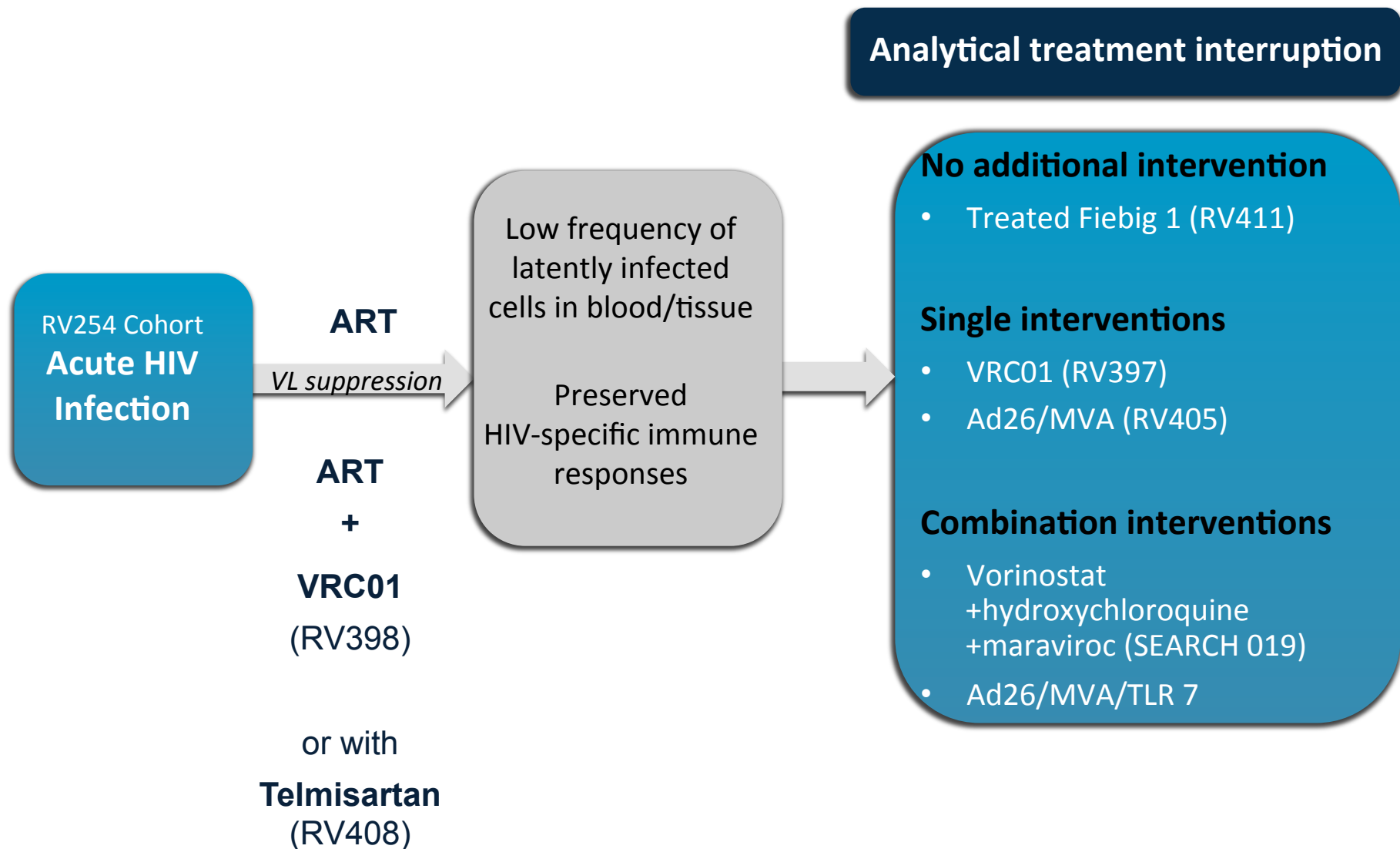
$p=0.002$

Rates of Viral Load Rise following Treatment Interruption



Immune therapeutics will be needed in addition to early ART for durable remission

MHRP-related HIV Remission Trials



MHRP-related HIV Remission Trials

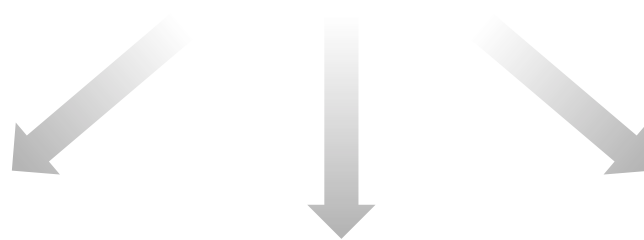
To limit the establishment of the reservoir



Early ART

**Acute cohorts
Fiebig I ATI**

To reduce the size of the reservoir



**Latency
Reversing
agent**

Vorinostat

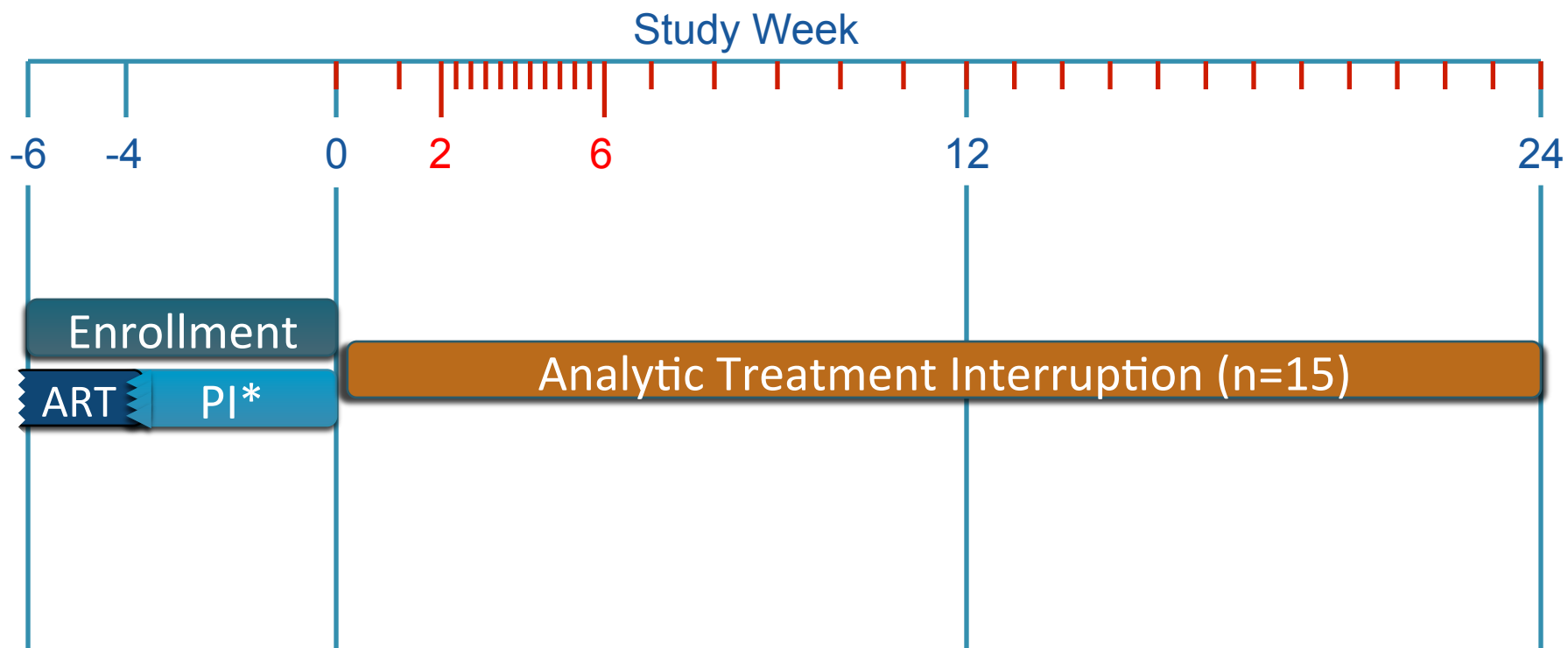
**Immune
therapies**

**Ad26/MVA, DC
VRC01**

**Anti-
inflammation**

Telmisartan

RV 411: Treatment interruption of treated Fiebig I participants



Volunteers from Thai Red Cross

- ≥18 years old
- Started on ART during **Fiebig 1**
- Prescribed ART for ≥24 mo
- HIV-1 RNA <50 copies/mL for ≥12 mo
- CD4 >400 cells/mm³

***4-week** PI substitution for subjects prescribed NNRTI

Intermediate Endpoint (Futility):

- Virologic control (RNA <50 copies/mL)
- 1 of first 8 subjects must meet this endpoint

Primary Endpoint:

- Virologic control (RNA <50 copies/mL)

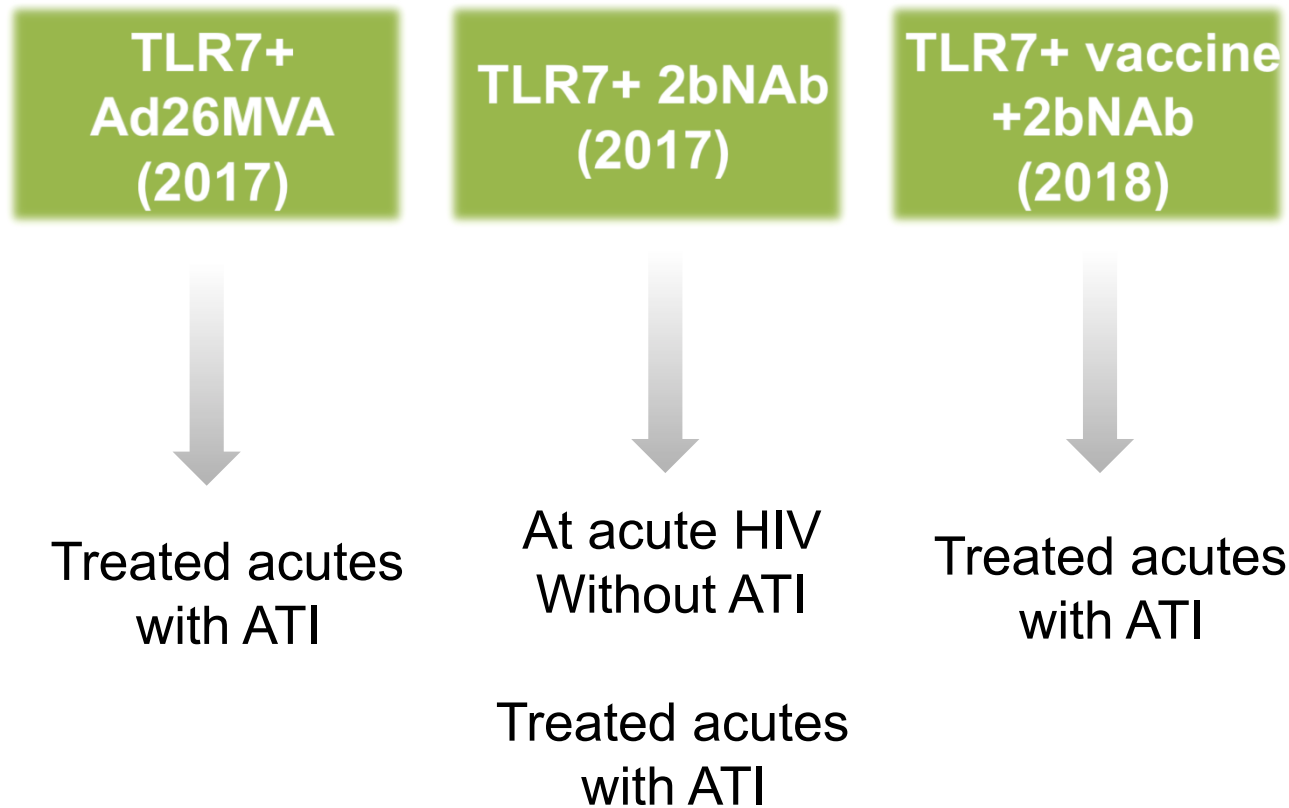
I = HIV RNA Assessment

Any positive HIV RNA prompts repeat quantitative testing at least every 3 days until negative or ART resumed

Criteria for ART Resumption

- **HIV-1 RNA >1,000 copies/mL on 2 consecutive determinations at least 1 day apart**
- Any HIV-1 RNA >10,000 copies/mL
- CD4 <350 cells/mm³ twice over 2 weeks
- CD4 decline > 50% from baseline prior to ATI
- Clinical progression to CDC Category B or C disease
- Acute retroviral syndrome
- Pregnancy

Possible new proposals of combination strategies

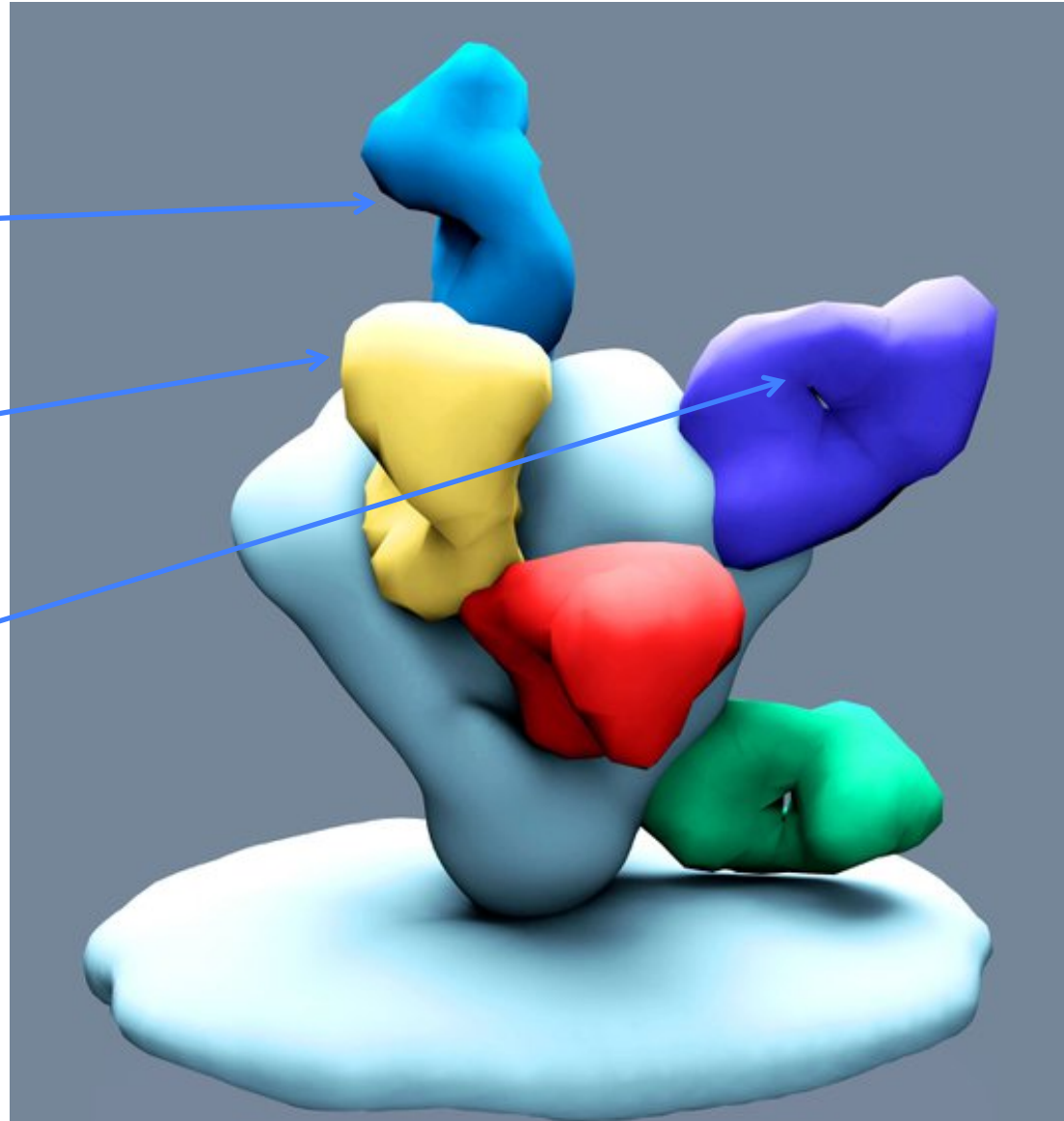


Broadly Neutralizing Monoclonal Antibody (bNabs) Targets

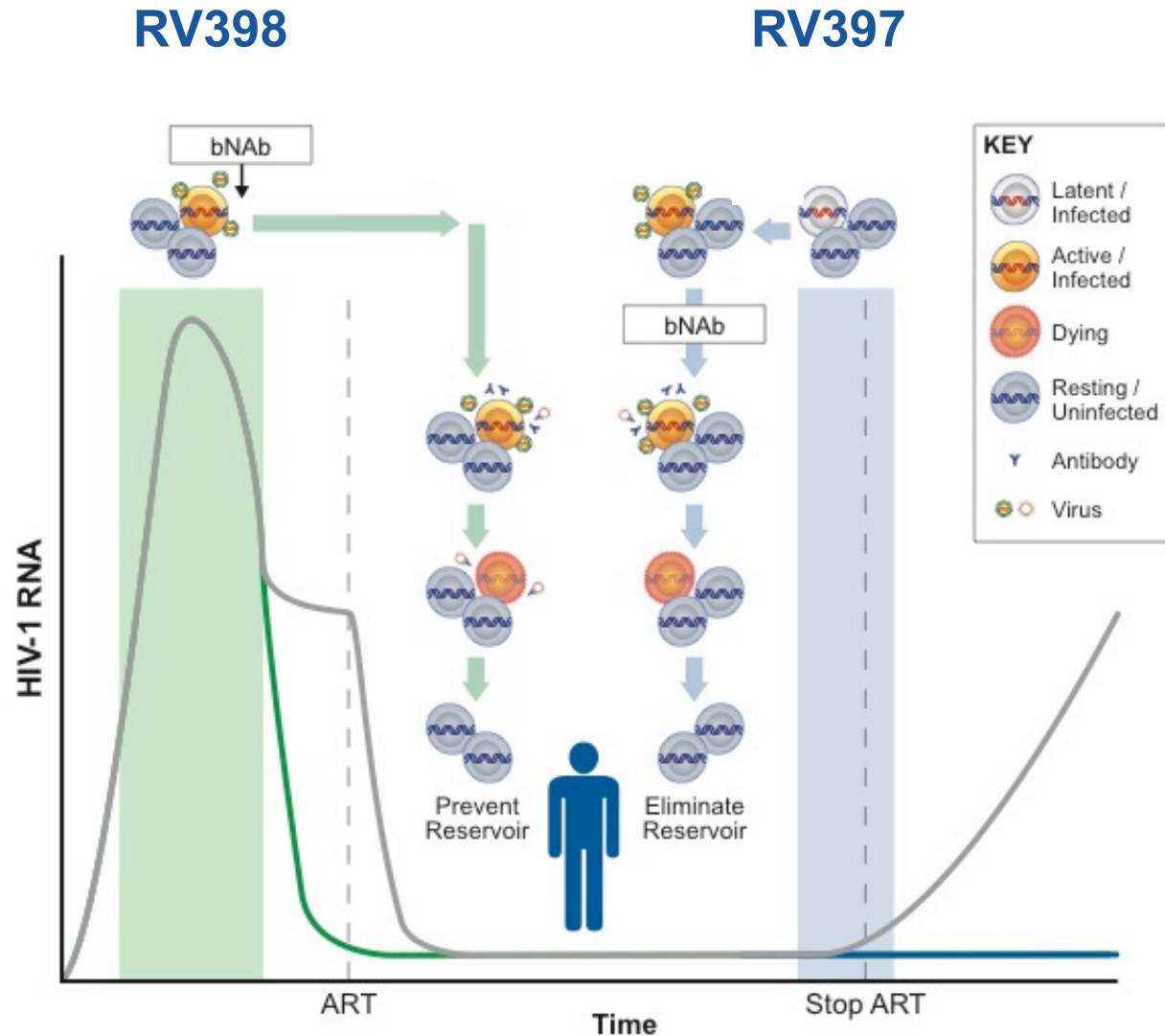
V2
(PGDM1400, CAP256)

CD4bs
(VRC01, 3BNC117)

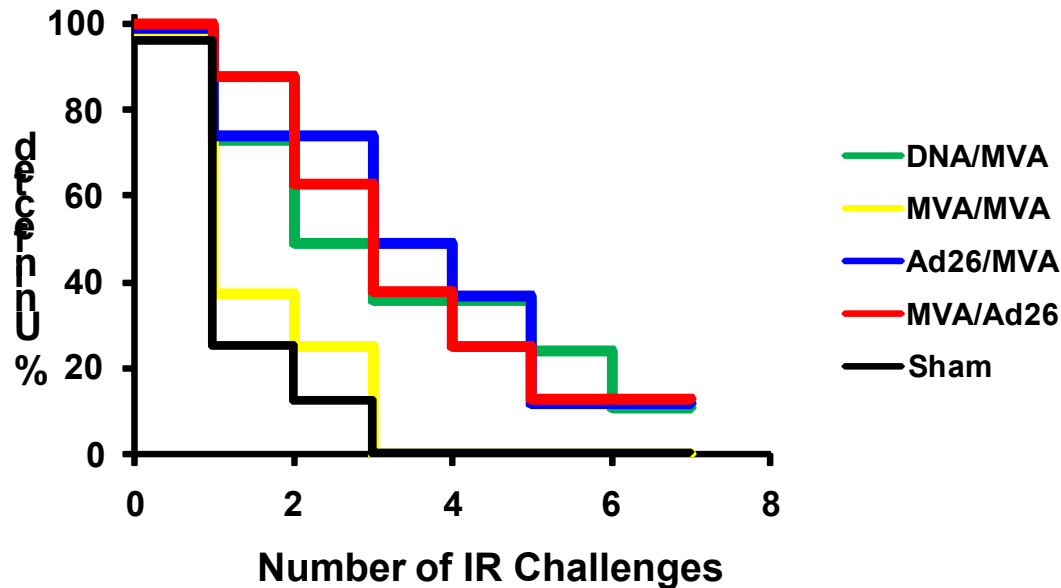
V3
(PGT121, 10-1074)



Broadly Neutralizing Antibody Studies in Early Treated Individuals



NHP SIV-MAC251 Challenge



	# Challenges for 50% Infection	P-Value vs Sham*	Hazard Ratio (95% Conf. Interval)	Per-Exposure Risk of Infection
DNA/MVA	2	0.0055	0.186 (0.057-0.611)	0.269
MVA/MVA	1	0.5587	0.725 (0.247-2.129)	0.615
Ad26/MVA	3	0.0037	0.174 (0.053-0.567)	0.250
MVA/Ad26	3	0.0062	0.198 (0.062-0.632)	0.269
Sham	1	N/A	1	0.727
*Chi-square test, proportional hazard model				

Figure 2a

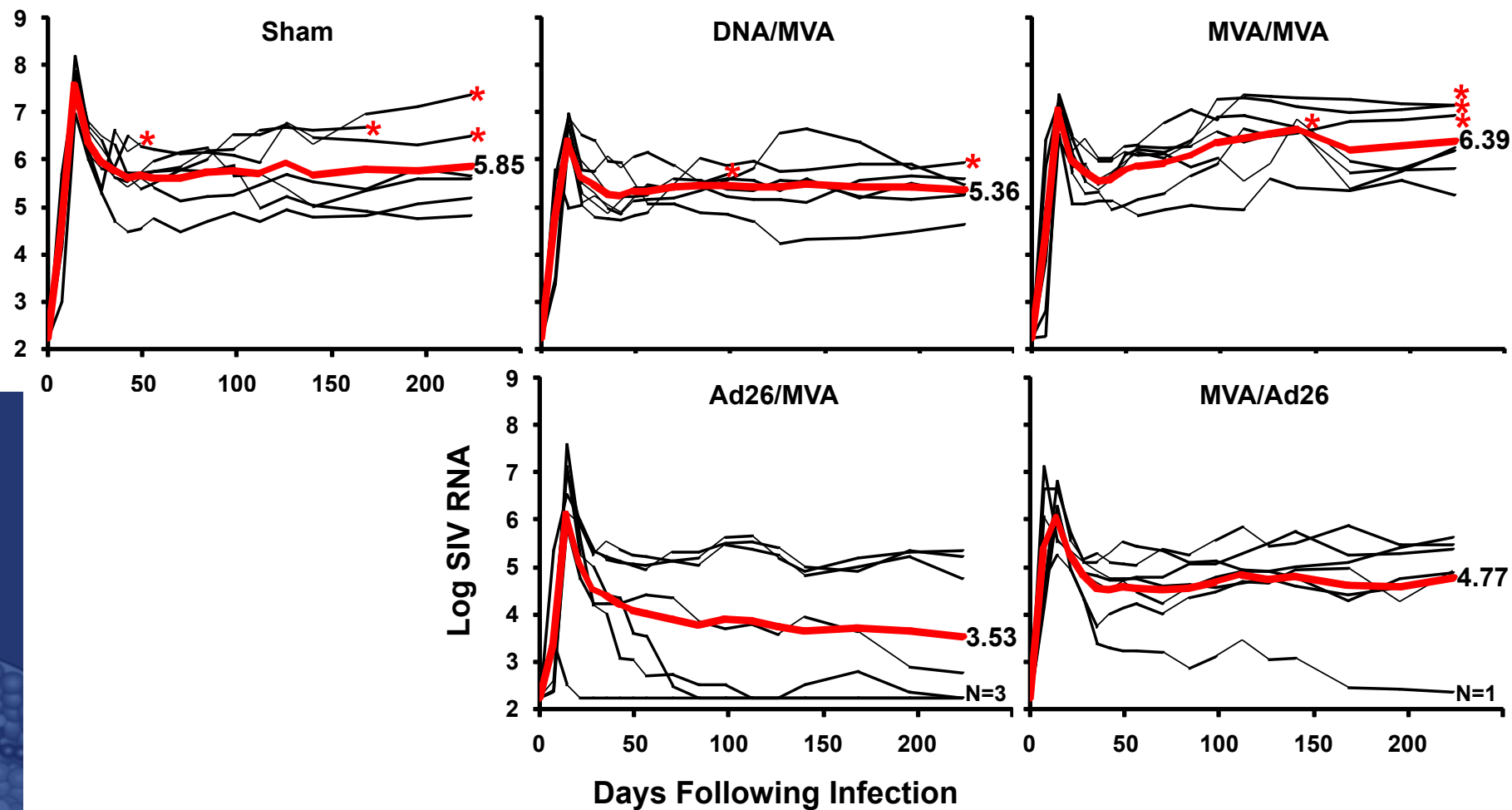
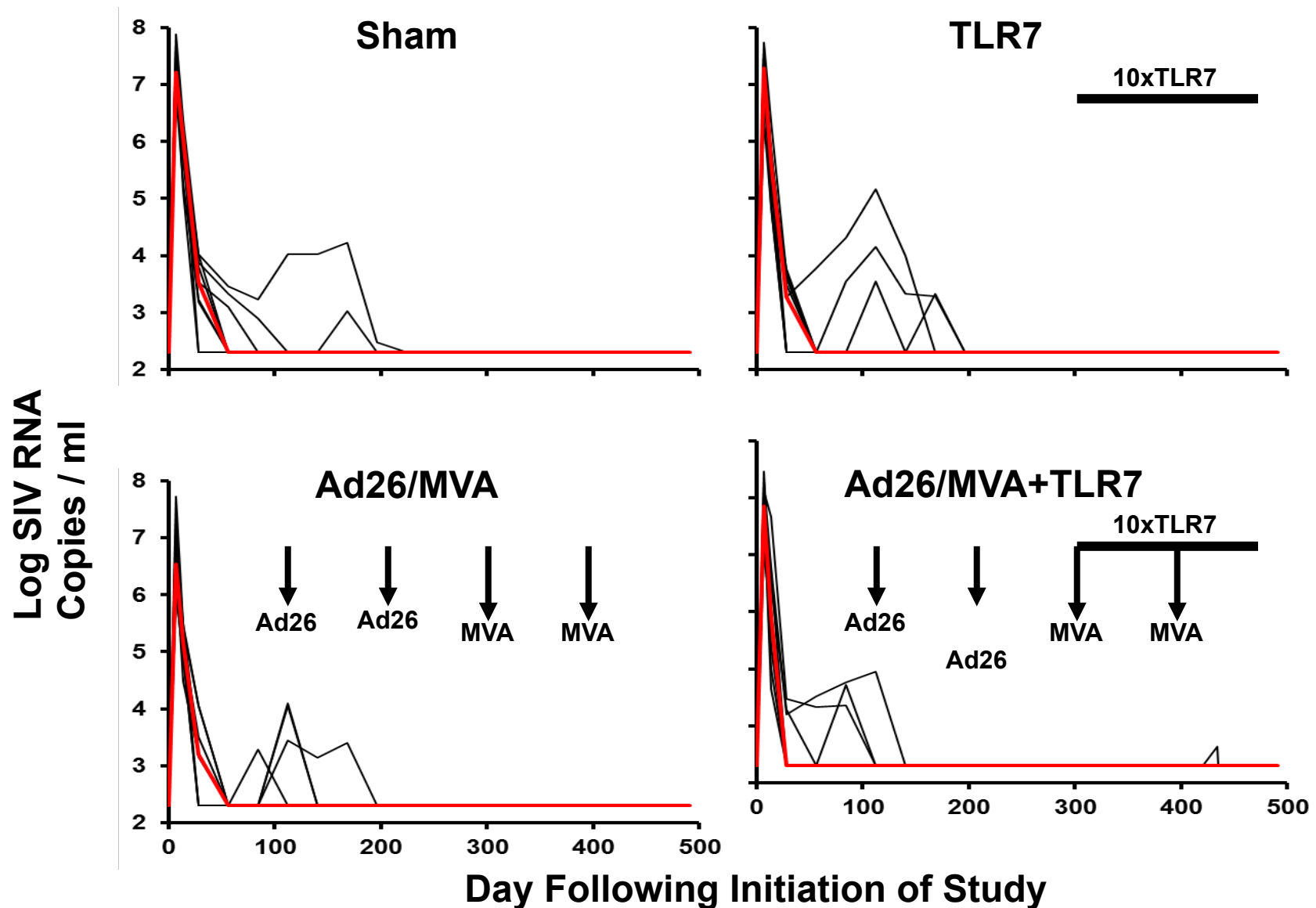
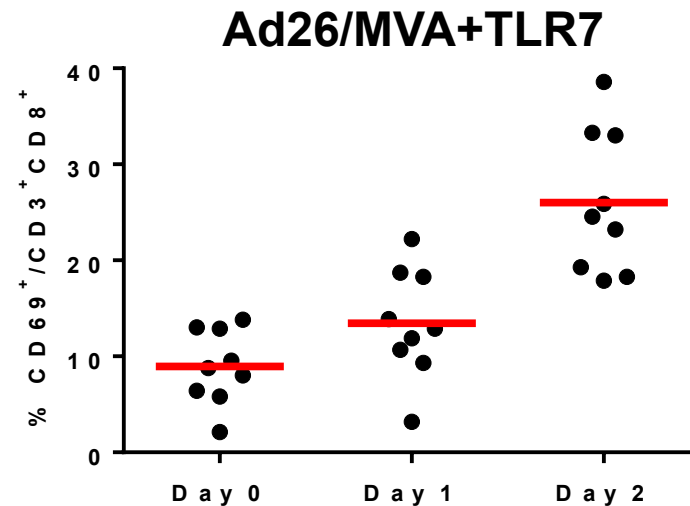
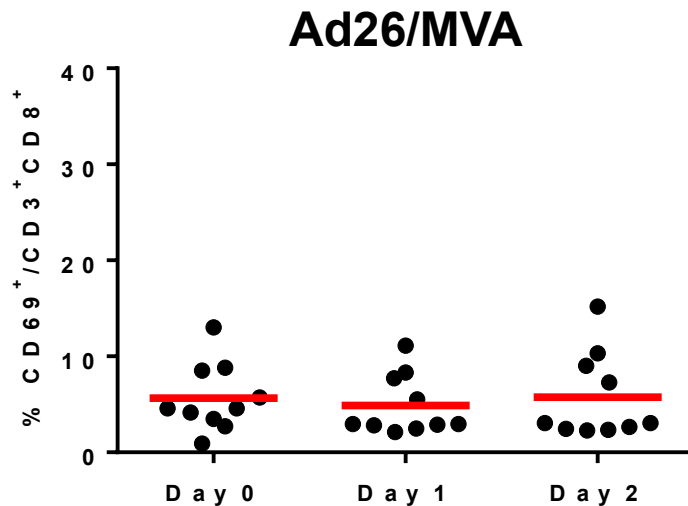
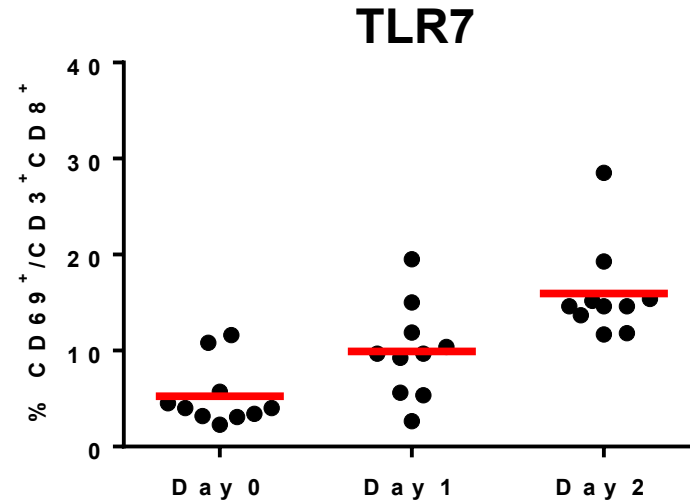
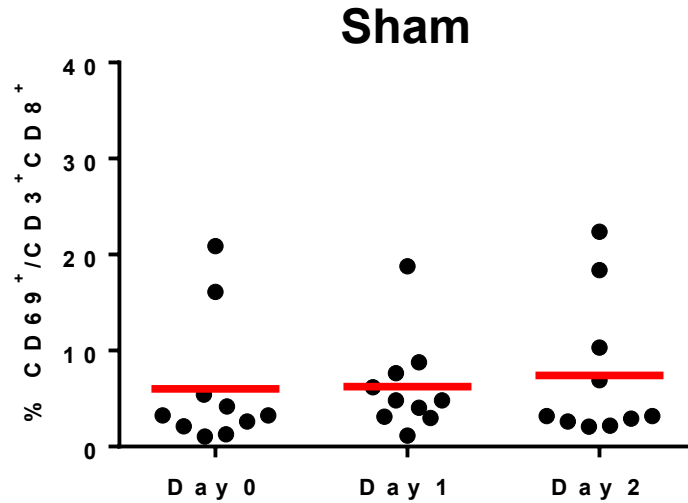


Figure 2b

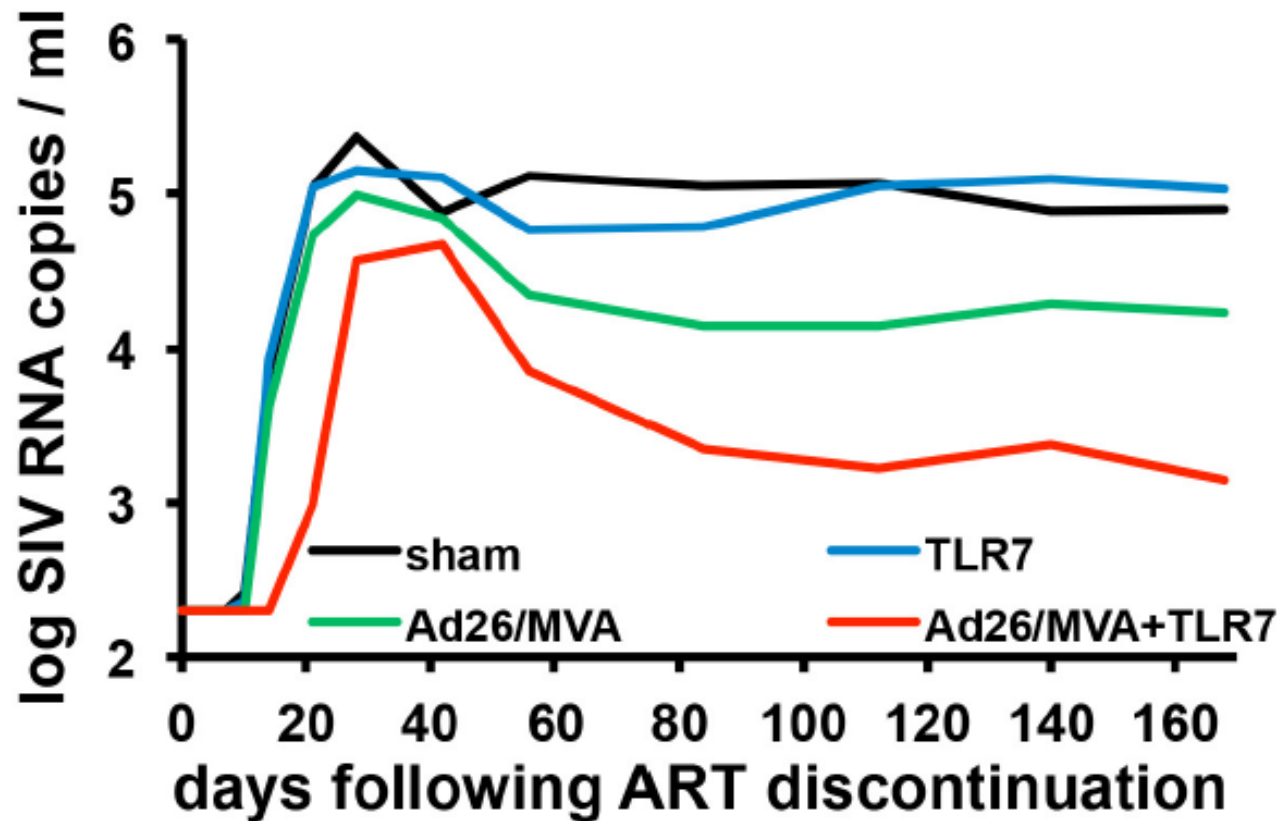
SIV RNA Following ART Initiation on day 7



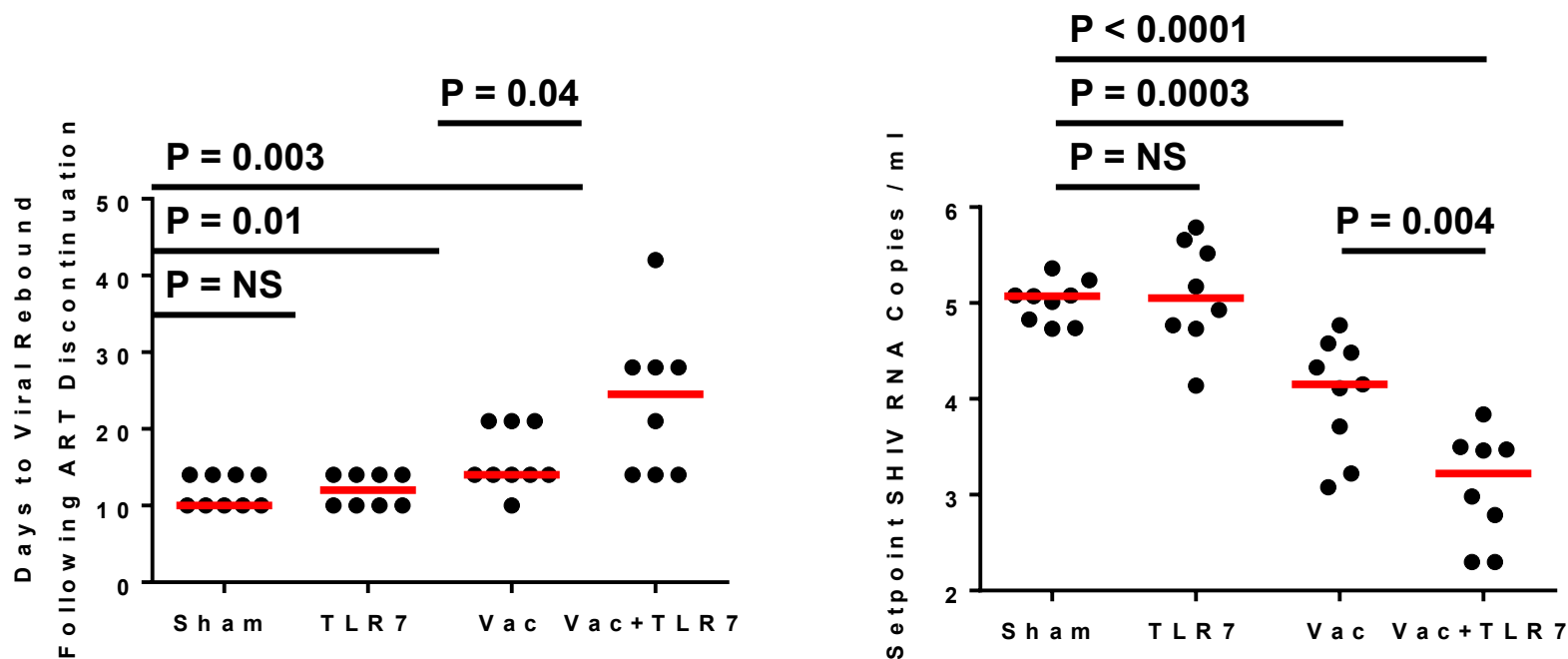
CD8+ T Cell Activation Following TLR7 Agonist



TLR7 Agonist+Ad26MVA Vaccine Reduced Viral Load in Monkeys after ART Discontinuation

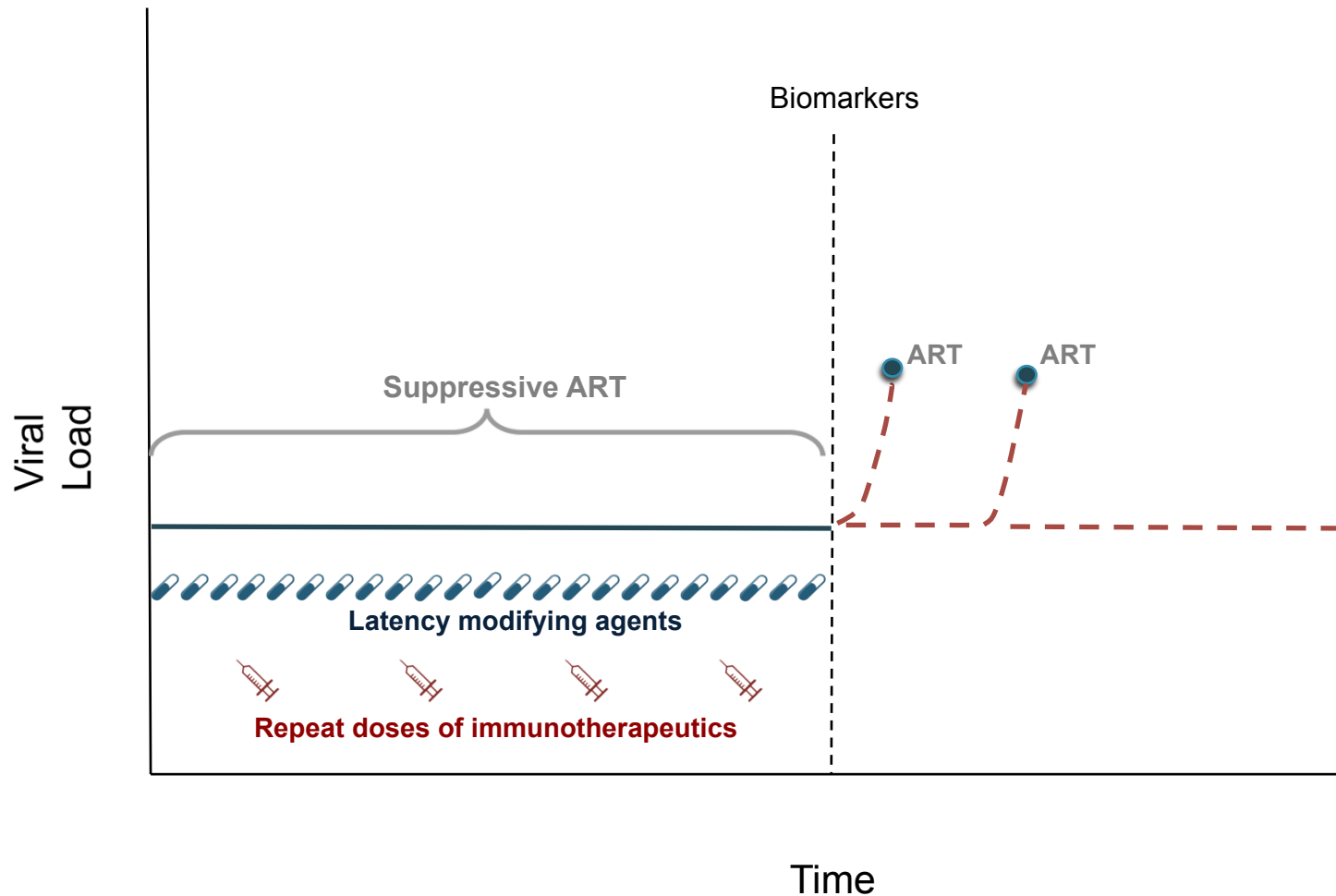


Delay of Viral Rebound and Reduction of Setpoint Viral Loads by Ad26/MVA Vaccine + TLR7 Agonist Following ART Discontinuation



What might HIV remission strategies look like?

What might HIV remission treatment look like?



Lessons Learned So Far from the MHRP Studies

- Delayed in time to viral load rebound with early ART
 - Statistically significant but not clinically meaningful (Fiebig III/IV vs. chronic)
- Treatment interruption can be conducted safely
 - Frequent viral load monitoring and ART resumption at 1000 copies/ml
- Designing treatment interruption trials with immunotherapeutics
 - **Benefits may be missed with the current designs**
 - **SIV models showing viremic control after rebound events**
 - Risks and benefits must be weighed very carefully
 - Stronger scientific rationale is needed
 - Step-wise approach with gate keeper endpoints to indicate responses to interventions before allowing longer and higher viremia

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