Factors Associated with Viral Control after Structured Treatment Interruption

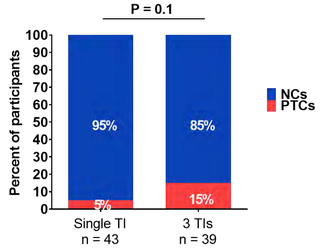
Nikolaus Jilg[1], Behzad Etemad[2], Ruth Dele-Oni[2], Colline Wong[2], Jesse M. Fajnzylber[2], Abbas Mohammadi[2], Evgenia Aga[3], Ronald J. Bosch[3], Daniel R. Kuritzkes[2], Ian Frank[4], Jeffrey M. Jacobson[5], Jonathan Z. Li[2]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA [3]Harvard T. H. Chan School of Public Health, Boston, MA
[4]Hospital of the University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA [5]Case Western Reserve University, Cleveland, OH

Background

- In the CHAMP study, HIV post-treatment controllers (PTCs) were enriched among individuals randomized to receive structured treatment interruptions (STIs) in the A5068 trial **(Figure 1)**.
- ACTG A5068 was a randomized trial in participants with chronic HIV infection (18% female) receiving continuous ART versus STIs with or without therapeutic vaccine.

Figure 1: Enrichment of PTCs in Participants Undergoing Multiple Structured Treatment Interruptions (TIs) in A5068



Objective

Identify virologic determinants of post-treatment control in the participants of A5068 who underwent STIs

Methods

- Participants in the STI arms underwent two short (~4 wks) TIs (STI1 and 2) and a subsequent extended analytical TI (ATI). STI1 and 2 were followed by 16 wks of ART.



- We compared plasma viral load (pVL) dynamics after each STI between PTCs and post-treatment non-controllers (NCs). Single-genome sequencing (SGS) of *pol* (1.7kb) from plasma HIV RNA was performed for 6 PTCs and 7 NCs.
- Confirmatory long-range SGS of the *pol-env* region (6.7kb) was performed for a subset of time points.
- Viral diversity was calculated by average pairwise distance (APD) at one time point and viral divergence was calculated by APD between sequences of different time points.

Results

Figure 2: Peak Viral Loads during STI1 and STI2 Predict Post-Treatment Control

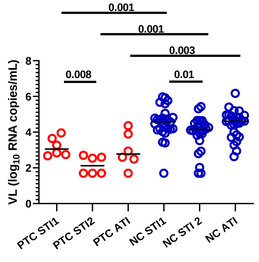


Table 1: Test Characteristics

STI 1	PTC	NC	
VL < 10,000	6	4	*PPV = 60%*
VL ≥ 10,000	0	23	*NPV = 100%*
	Sens = 100%	*Spec = 85%*	

STI 2	PTC	NC	
VL < 1,000	6	5	*PPV = 55%*
VL ≥ 1,000	0	22	*NPV = 100%*
	Sens = 100%	*Spec = 81%*	

Table 2: Proposed Prediction Algorithm

	PTC	NC	
<10k @ STI1 *and* <1k @ STI2	6	1	*PPV = 86%*
(at least one of) *either* >10k @ STI1 *or* >1k @ STI2	0	26	*NPV = 100%*
	Sens = 100%	*Spec = 96%*	

Figure 3: Single Genome Sequences - Neighbor Joining Trees for (A) 625 Pro-RT Sequences, and (B) a Representative PTC

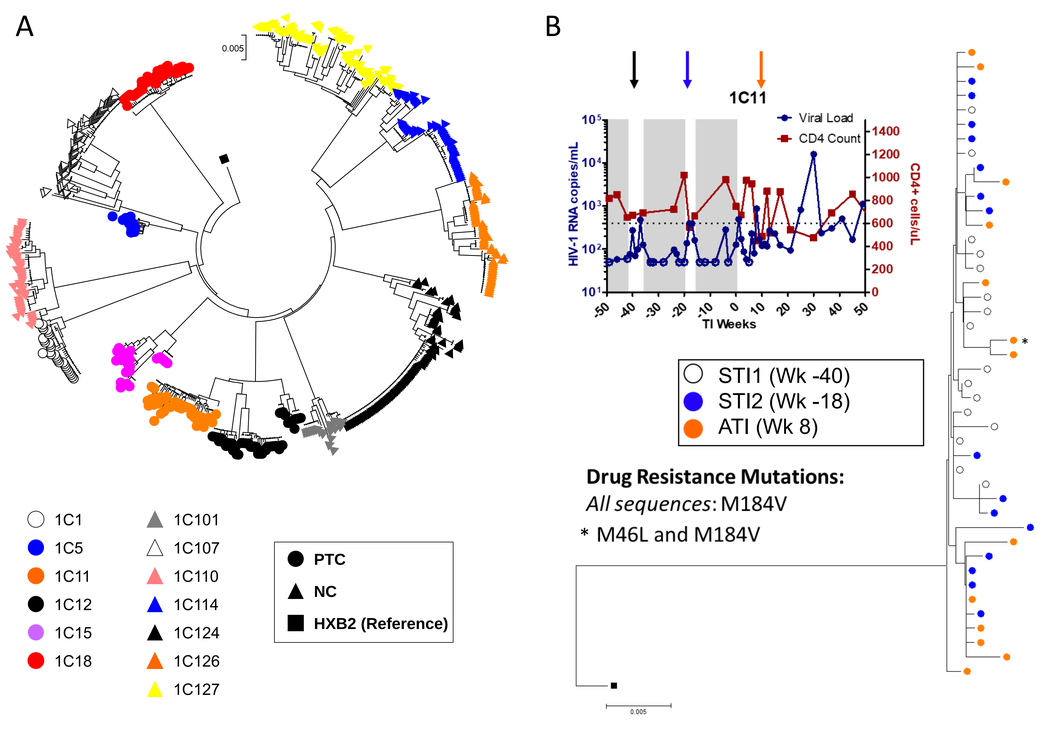
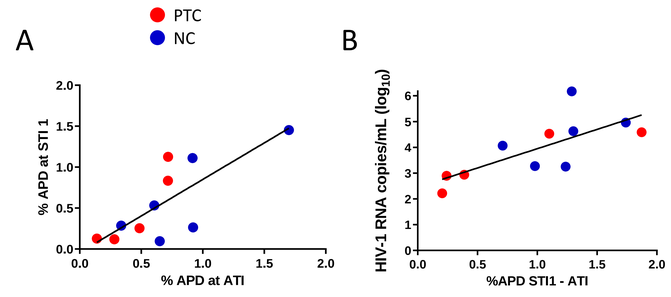


Figure 4: Correlation between (A) Diversities during STI1 and ATI, and (B) Divergence (from STI1 to ATI) and ATI Peak Viral Load



- For both the first and second STI, PTCs (n=6) had significantly lower peak pVLs compared to NCs (n=27; median pVL [Q1, Q3] for PTCs vs. NCs at the first STI [log_{10}]: 3.1 [2.7, 3.7] vs. 4.6 [3.2, 4.8] HIV-1 RNA copies/mL, p=0.001; and second STI: 2.3 [<1.7, 2.6] vs. 4.2 [3.9, 4.5] HIV-1 RNA copies/mL, p=0.001) **(Figure 2).**
- A retrospectively-derived algorithm that used a combination of peak pVL<10,000 HIV-1 RNA copies/mL during STI1 and peak pVL<1,000 HIV-1 RNA copies/mL during STI2 accurately predicted that all 6 PTCs would achieve HIV control and that 26/27 NCs would not (**Table 1, Table 2**).
- In addition, we have generated 625 plasma HIV single-genome sequences for the PTCs and NCs during the TIs (**Figure 3A**). Individual data for a representative PTC, including viral load and CD4 count, a neighbor joining tree comprising sequences from 3 timepoints is shown (**Figure 3B**).
- Higher plasma HIV diversity during STI1 correlated with higher diversity in ATI (Spearman r=0.67, p=0.02) (**Figure 4A**).
- Increasing viral divergence from STI1 to ATI was associated with a higher peak pVL at ATI (Spearman r=0.69, p=0.02) (**Figure 4B**).

Conclusions

- **In participants undergoing structured treatment interruptions, lower peak viral loads during the first two short treatment interruptions may predict post-treatment control.**
- **Emergence of divergent viral populations during the third treatment interruption may compromise the ability to achieve viral control.**

Acknowledgements

We thank the A5068 study participants, the A5068 study team, as well as the site staff of all the AIDS Clinical Trials Group clinical research sites. This study was funded in part by NIH grants U01 AI068636 (ACTG), AI068634 (SDAC) a subcontract from UM1 AI068636 to the Harvard Virology Support Laboratory. NJ has been supported by a T32 institutional training grant (PI: Dr. D. Kuritzkes, Harvard Medical School) and a Harvard University Centers for AIDS Research (HU CFAR) Development Award.