LONGITUDINAL DYNAMICS OF POLYADENYLATED HIV TRANSCRIPTS DURING TREATMENT INTERRUPTION

D-04: 361

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BACKGROUND.

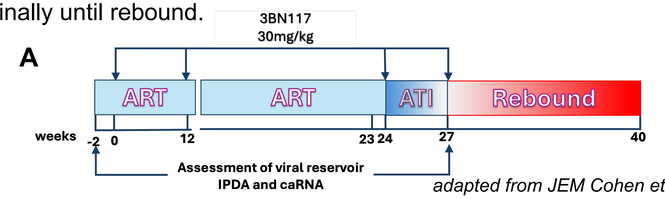
Individuals living with HIV require antiretroviral therapy (ART) to suppress viral replication. When therapy is stopped, most experience virologic rebound, but the interval between cessation and rebound varies widely, and the events preceding rebound are poorly understood. In this study, we examined how levels of cell-associated polyadenylated HIV transcripts (poly-A CA-RNA) change during analytic treatment interruption (ATI), hypothesizing that transcript levels would rise as rebound approached.

METHODS.

Table 1: We analyzed five individuals with subtype B HIV-1 who had previously enrolled in broadly neutralizing antibody (bnAb) ATI trials.

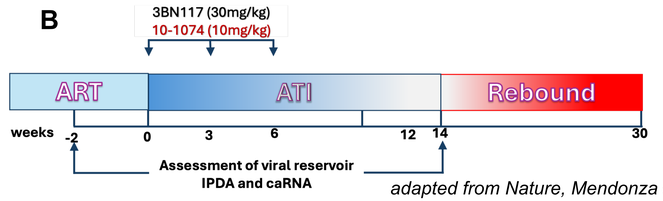
DonorID	Sex	Age	Race	Year ART started	Interventions	Protocol	Citation
601	M	56	White	1997	3BNC117	MCA-866	JEM Cohen et al 2018
602	M	49	White	2011	3BNC117	MCA-866	JEM Cohen et al 2018
609	M	39	White	2014	3BNC117	MCA-866	JEM Cohen et al 2018
614	M	58	Black	2000	3BNC117	MCA-866	JEM Cohen et al 2018
9201	M	43	White Hisp	2015	3BNC117 + 10-1074	MCA-906	Nature 2018 Mendonza, PNAS 2018 Lu

Figure 1A: Four Donors (IDs 601, 602, 609, and 614) received 3BNC117 during ART and ATI; time-to-rebound was between 3 to 6 weeks. Peripheral blood mononuclear cells (PMBC) were collected at screening and longitudinally until rebound.



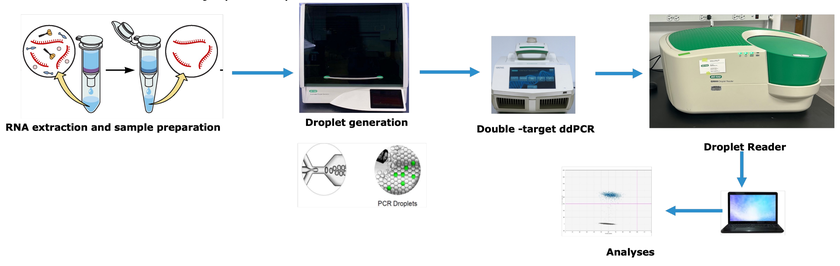
adapted from JEM Cohen et al., 2018

Figure 1B: Donor ID 9201 received 3BNC117 + 10-1074 after ATI initiation and rebounded at week 15. PBMC were collected at screening and longitudinally until rebound.



adapted from Nature, Mendonza et al., 2018

Figure 2: CD4⁺ cells were isolated from PBMC. Poly-A CA-RNA were extracted and quantified by droplet digital PCR for unspliced (LTRgag), 3'UTR-containing, and total poly-A species. Proviral load was measured using Intact Proviral DNA Assay (IPDA).

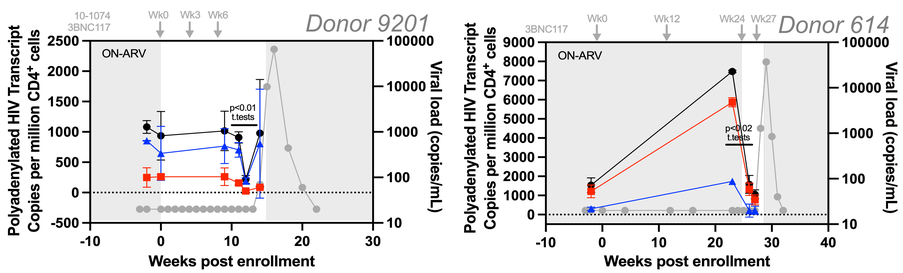


Polyadenylated viral transcripts unexpectedly declined before virologic rebound, suggesting possible transient immune control during ATI.

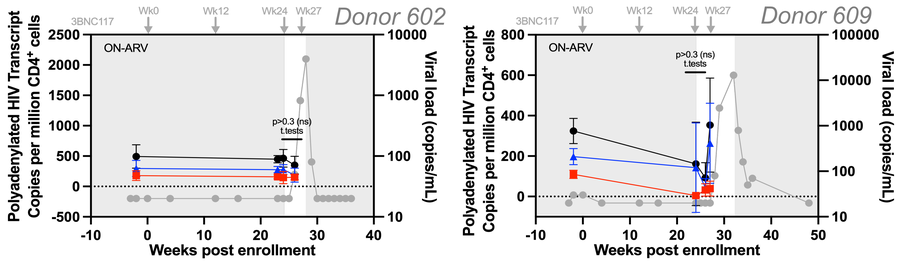
RESULTS.

Figure 3. Contrary to our initial hypothesis, poly-A CA-RNA declined in 4 of the 5 study donors during ATI immediately before virologic rebound.

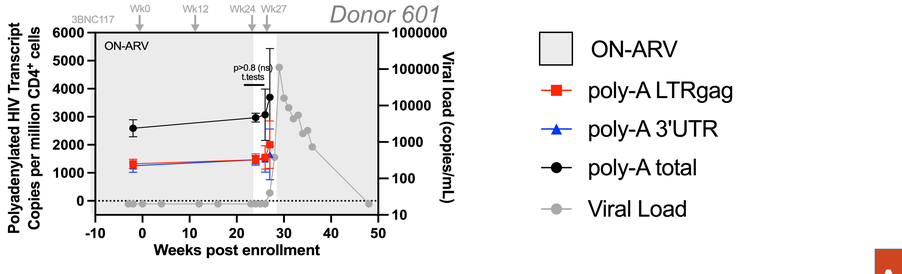
Two persons experienced sudden, statistically significant drop in CA-RNA.



Two persons experienced non-statistically-significant drop in CA-RNA.



One person showed a slight trend of increase in CA-RNA.



CONCLUSIONS. Poly-A viral transcripts, essential for viral protein production and rebound, unexpectedly decreased in most individuals before rebound, contrary to our initial hypothesis of a gradual increase. These findings suggest dynamic regulation and possible transient immune control immediately before viremia. Larger studies should investigate mechanisms of transcript suppression and its relationship to immune responses during ATI.

Figure 4. Intact, defective and total proviral load did not decrease significantly immediately before rebound (IPDA), but some individuals showed trends of decrease.

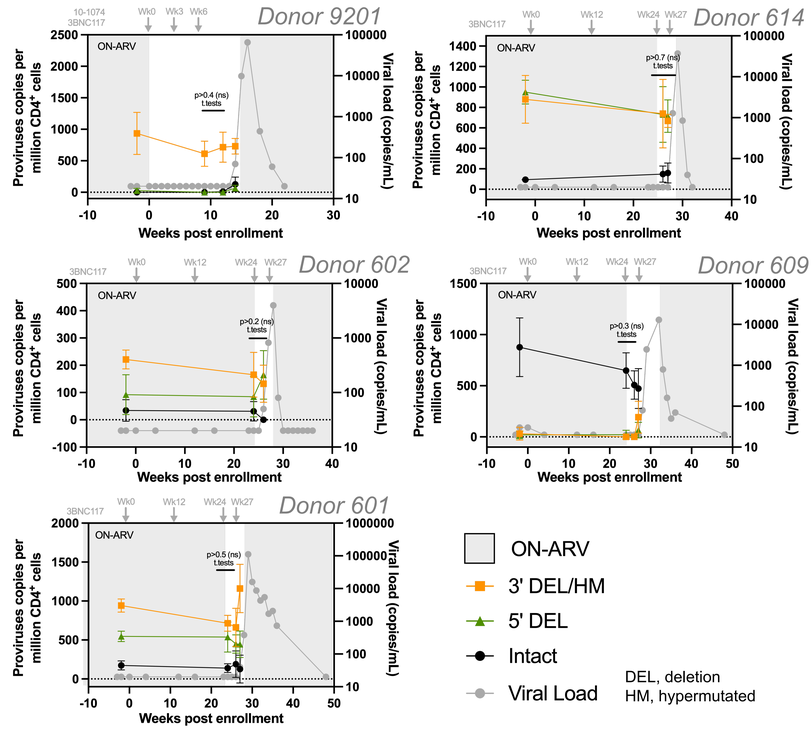


Table 2. Polyadenylated transcript levels correlates strongly/moderately with 3' and 5' IPDA reservoir size measurements, respectively.

Spearman ρ_s

	CA-RNA, average across all time points			CA-RNA, baseline (Week -2) only		
	LTRgag	3'UTR	Total	LTRgag	3'UTR	Total
IPDA 3' DEL/HM	1*	0.7	0.9	0.9	0.7	0.9
IPDA 5' DEL	0.9	0.6	0.7	0.7	0.6	0.7
IPDA Intact	0.3	0.2	0.1	0.1	0.2	0.1

*p-value 0.0167; all other pairs were non-significant (ns)

ρ_s 0.70 – 1.00 → very strong association
ρ_s 0.40 – 0.69 → moderate association
ρ_s 0.10 – 0.39 → weak association
ρ_s < 0.10 → negligible

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