Dynamics of Intact HIV Reservoir During ART Following Analytical Treatment Interruption

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Background and Rationale

- Current antiretroviral therapy (ART) has proven to be successful in suppressing plasma viremia in people living with HIV (PLWH); however, eradication of the virus has not been possible using ART alone.[1]
- Therapeutic strategies aimed at achieving ART-free virologic suppression in PLWH require analytical treatment interruption (ATI) to asses efficacy.[2]
- Previous studies have shown that ATI can cause an expansion of the HIV viral reservoir.[3]
- The effects ATI has on the intact viral reservoirs in PLWH who initiated ART during the acute/early phase compared to those treated during the chronic phase of infection have not been fully delineated.

Materials and Methods

Study Population: We studied two cohorts of PLWH who initiated ART during the acute/early (A/E, n=24, ClinicalTrials.gov ID NCT01859325) or the chronic (Chronic, n=19, ClinicalTrials.gov ID NCT03225118) phase of infection. Timepoints studied were prior to ATI (Pre-ATI), 24 weeks after ART reinitiation (Post-ATI 1), and 52 weeks after ART reinitiation (Post-ATI 2). Blood products were collected from study participants in accordance with clinical protocols approved by the Institutional Review Board approved protocol at the National Institutes of Health.

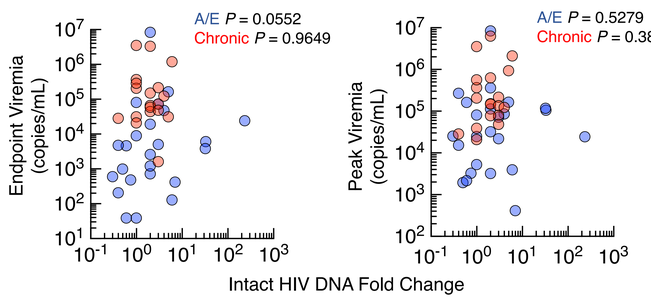
HIV Reservoir Quantification: PCR-based assays were used to measure the intact and defective HIV DNA.

Immunologic Parameters: HIV-specific immune responses were measured by intracellular cytokine staining and flow cytometry following stimulation with HIV-1 Gag peptides. Immunologic phenotyping was done using flow cytometry and biomarkers were measured in the plasma using an automated ELISA.

Table

Clinical characteristics of study participants

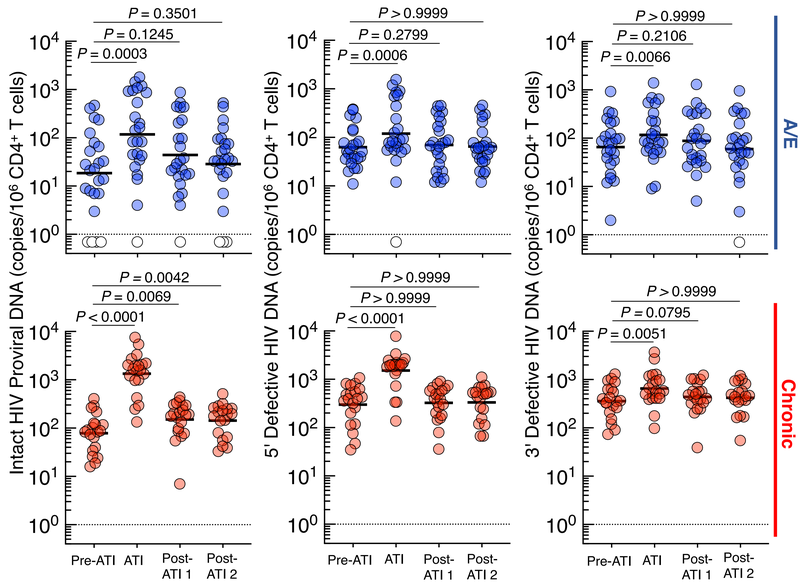
	A/E (N=24)	Chronic (N=19)	P-values
Sex, no. (%) Male Female	24 (100) 0	17 (89) 2 (11)	$P = 0.1894$
Age Mean (Range)	42(21-65)	51(38-61)	**$P = 0.0009$**
CD4⁺ T Cell Count (cells/mm³) Prior to ATI Median(Range)	738(363-2162)	724(466-1778)	$P = 0.5569$
CD4⁺ T Cell % (cells/mm³) Prior to ATI Median(Range)	39(29-62)	42(29-51)	$P = 0.1984$
CD8⁺ T Cell Count (cells/mm³) Prior to ATI Median(Range)	522(307-1600)	648(296-1587)	$P = 0.2715$
CD8⁺ T Cell % (cells/mm³) Prior to ATI Median(Range)	31(14-53)	34(21-52)	$P = 0.2258$
Duration of ART (yrs) Median(Range)	3(1-19)	8(2-16)	**$P = 0.0307$**
Duration of ATI (days) Median(Range)	121(47-319)	34(8-107)	**$P < 0.0001$**
Peak Plasma Viremia (copies/mL) During ATI Geometric Mean(Range)	31,598(416-8,405,097)	229,077(20,922-6,315,485)	**$P = 0.0018$**



- There was no significant correlation between the Pre-ATI and Post-ATI 1 intact HIV DNA fold change and the study endpoint nor peak plasma viremia.

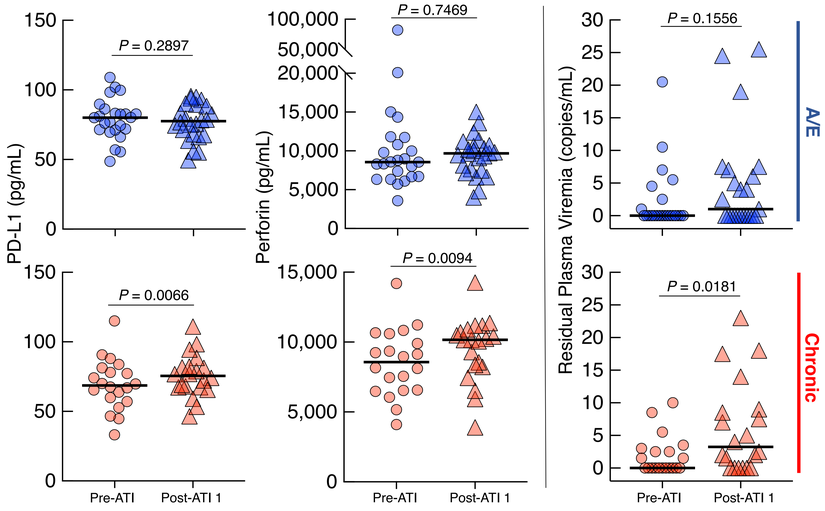
Results

Analysis of Intact and Defective HIV Proviral DNA Reservoirs



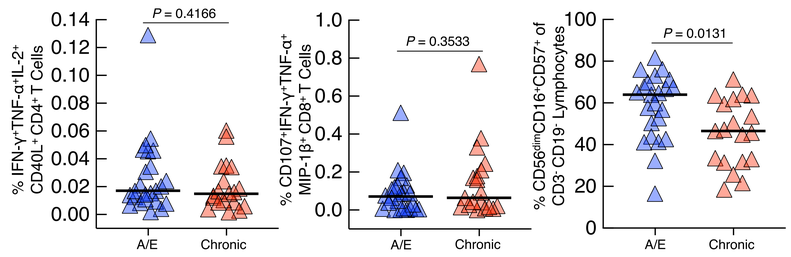
- The levels of intact HIV proviral DNA normalized to the baseline levels by Post-ATI 1 in the A/E group while the Chronic group remained significantly elevated at both Post-ATI 1 and Post-ATI 2.

Levels of Plasma Biomarkers and Residual Plasma Viremia



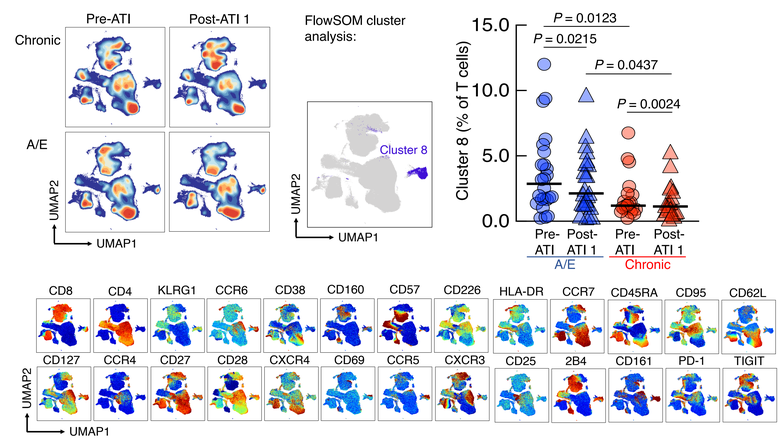
- The levels of PD-L1, Perforin, and residual plasma viremia remained elevated at Post-ATI 1 compared to the baseline in the Chronic group while no difference was observed in the A/E group.

HIV-Specific Immune Response and Natural Killer Cell Phenotype at Post-ATI 1



- HIV Gag-specific CD4 and CD8 T cell response was comparable between the A/E and Chronic group at Post-ATI 1.
- The levels of NK cells with higher effector cytolytic capacity ($CD56^{dim}CD16^{+}CD57^{+}$) were significantly higher in the A/E compared to the Chronic group at Post-ATI 1.

T Cell Phenotypic Analysis at Pre-ATI and Post-ATI 1



- The levels of T cell cluster 8 corresponding to the Mucosal Associated Invariant T (MAIT) cell phenotype were significantly higher in at both Pre-ATI and Post-ATI 1 in the A/E group compared to the Chronic group.

Conclusions

- Our data suggests that the degree of plasma viral rebound during ATI is not the determining factor of the normalization of the intact HIV reservoir following the re-initiation of ART.
- The persistence of elevated immune activation and residual plasma viremia and at the Post-ATI 1 time point in the Chronic group may have contributed toward delayed normalization of infected CD4⁺ T cells carrying intact HIV proviral DNA.
- It is plausible that the A/E group had a stronger innate immune response to HIV leading to a faster decay of the intact HIV DNA reservoir following the re-initiation of ART.
- Delineating the underlying mechanism by which the A/E group achieved faster normalization compared to the Chronic group of immunologic and virologic markers could be informative for future therapies and clinical trials.

References

1. Chun, Tae-Wook et al. "HIV reservoirs as obstacles and opportunities for an HIV cure." *Nature immunology* vol. 16,6 (2015): 584-9.
2. Julg, Boris et al. "Recommendations for analytical antiretroviral treatment interruptions in HIV research trials-report of a consensus meeting." *The lancet. HIV* vol. 6,4 (2019): e259-e268.
3. Wen, Ying et al. "Lessons learned from HIV antiretroviral treatment interruption trials." *Current opinion in HIV and AIDS* vol. 13,5 (2018): 416-421.