Distinct Integration Sites of Intact HIV-1 Proviruses in Post-Treatment Controllers

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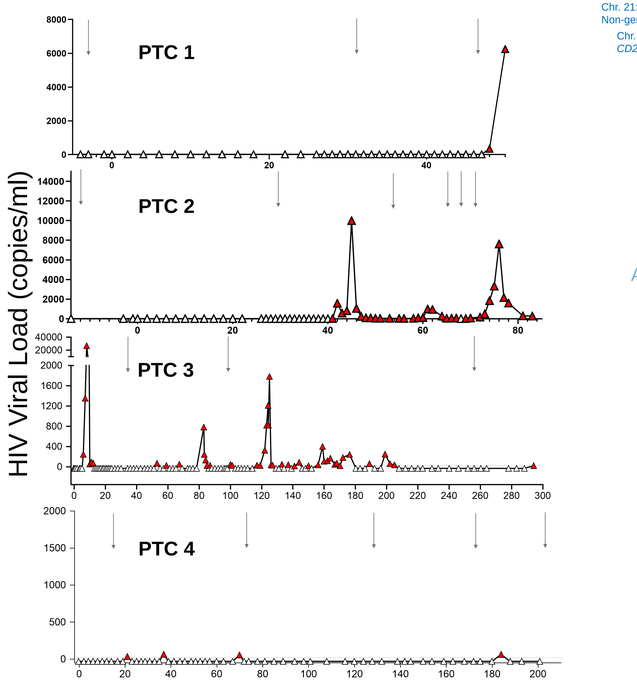
BACKGROUND

- For people living with HIV, the discontinuation of antiretroviral therapy (ART) typically results in rapid viral rebound.
- However, a small number of individuals, called post-treatment controllers (PTCs), can exhibit viral suppression for months or years following ART interruption.
- We previously found that in elite controllers (ECs), intact proviruses are frequently integrated in "blocked and locked" positions in heterochromatin (1).
- We hypothesize that proviral integration sites may play a role in one's ability to sustain viral suppression following ART interruption.

METHODS

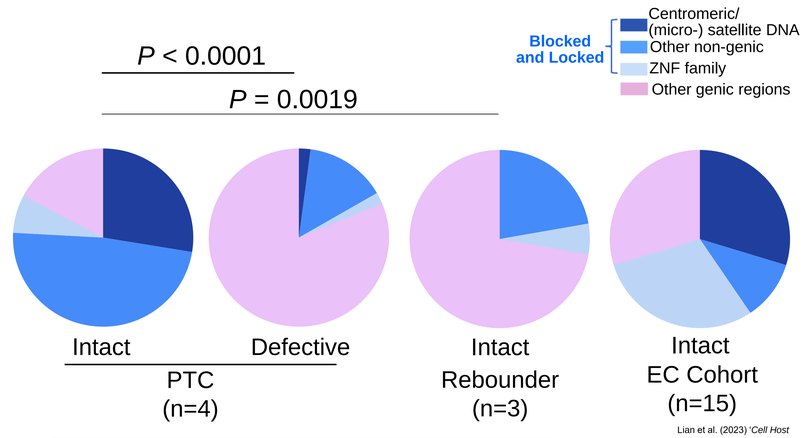
- **Full-length Individual Proviral sequencing (FLIP-seq)**
  - Near-full-length sequencing assay to characterize HIV reservoir in PBMCs (2)
- **Matched Integration site and Proviral sequencing (MIP-seq)**
  - Near-full-length sequencing assay with integration site mapping of individual proviruses using **Integration Site Loop Amplification (ISLA)** (3)

CLINICAL DATA

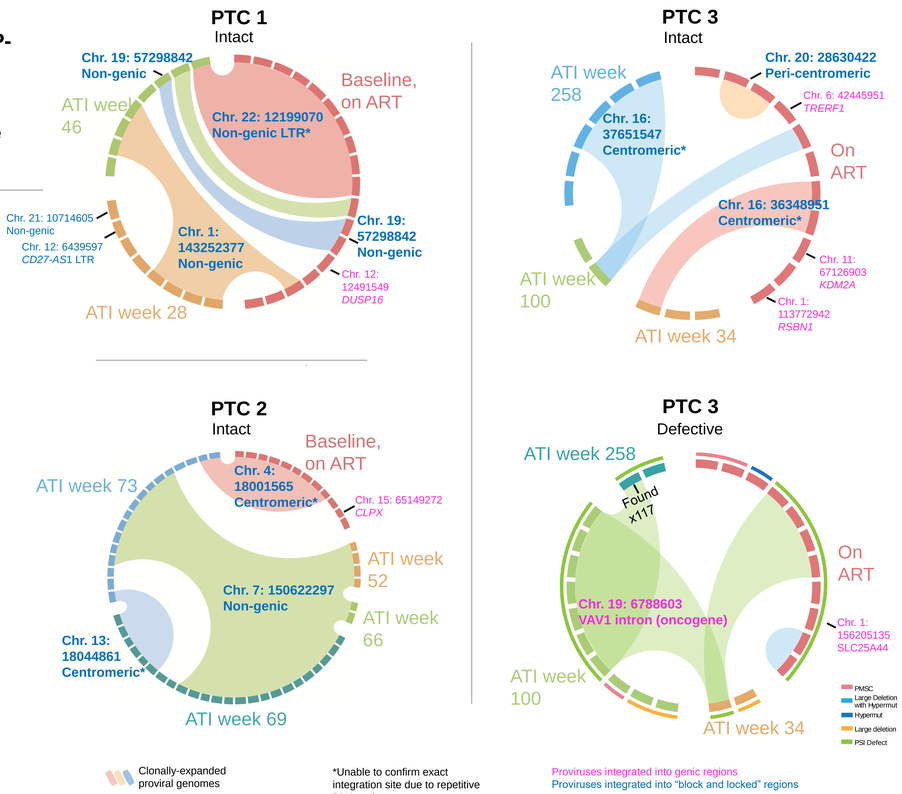


Post-treatment controllers tend to have a higher proportion of **intact proviruses** integrated into **blocked and locked** DNA regions at a **pre-treatment interruption** timepoint.

INTEGRATION SITE PROFILE SUMMARY



LONGITUDINAL RESERVOIR PROFILES



Clonally-expanded proviral genomes

*Unable to confirm exact integration site due to repetitive DNA regions

Proviruses integrated into genic regions
Proviruses integrated into "block and locked" regions

CELLS ASSAYED

PTC 1
2.49E+07 cells total
1.08E+07 cells baseline
6.52E+06 cells ATI week 28
7.54E+06 cells ATI week 19

PTC 2
1.04E+08 cells total
5.38E+06 cells baseline
2.01E+07 cells ATI week 28
5.87E+07 cells ATI week 52
8.76E+06 cells ATI week 66
4.61E+06 cells ATI week 69
1.74E+07 cells ATI week 73

PTC 3
1.06E+08 cells total
1.66E+07 cells on ART
2.55E+07 cells ATI week 34
2.81E+07 cells ATI week 100
3.61E+07 cells ATI week 258

PTC 4
3.52E+07 cells total
6.60E+06 cells On ART
3.21E+06 cells ATI week 17
5.76E+06 cells ATI week 74
1.03E+07 cells ATI week 128
6.09E+06 cells ATI week 175
3.25E+06 cells ATI week 201

CONCLUSIONS

- PTCs tend to have a higher proportion of intact proviruses integrated into regions associated with deep latency.
- These data suggest that there is an underlying immune mechanism selecting for the elimination of intact proviruses integrated into highly expressed genic regions.
- Intact proviruses integrated in heterochromatin may only be poorly rebound-competent and contribute to spontaneous control of HIV after treatment interruption.
- However, subdominant intact proviruses or tissue reservoirs may contribute to viral rebounds in PTCs at a later time during ATI.

Acknowledgements: Our collaborators, funding organizations, and study participants

References:
(1) Jiang et al. (2020) 'Distinct viral reservoirs in individuals with spontaneous control of HIV-1', *Nature*.
(2) Lee and Lichterfeld (2022) 'Near-full-length single genome HIV-1 DNA sequencing', *Methods and Mol Bio*.
(3) Einkauf et al. (2019) 'Intact HIV-1 proviruses accumulate at distinct chromosomal positions during prolonged antiretroviral therapy', *J Clin Invest*.
(4) Lian et al. (2023) '*Cell Host & Microbe*'.

BEAT-HIV DELANEY COLLABORATORY

NIH National Institute of Allergy and Infectious Diseases · NIH National Institute on Drug Abuse · NIH National Heart, Lung, and Blood Institute

Ragon Institute