Low Frequency of Immune Escape Mutations in Intact Proviruses from Elite Controllers

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BACKGROUND

- Rare HIV-1 infected individuals, elite controllers (ECs), maintain undetectable viral loads and normal level of CD4 counts without antiretroviral therapy[1].
- Escape mutations occur during HIV-1 evolution under host immune selection pressure mediated by CTL, bNAbs, innate immune responses and antiretroviral drugs.
- Rare CTL escape mutations were observed among Gag and Nef provirus in defined HIV gene regions from EC but sequence variation on intact proviruses remains unknown[2].

METHODS

- Intact proviruses were obtained from 50 ECs and 37 chronically ART-treated individuals using Full-length Individual Proviral Sequencing (FLIP-Seq)[3].
- CTL optimal epitopes and escape mutations associated with HLA-I alleles were collected from the Los Alamos HIV Immunology Database.
- The numbers of mutations associated with HLA class I-mediated immune pressure were calculated as described by Carlson et al[4].
- Signature sites associated with sensitivity and resistance to 4 types of bNAbs (V1V2, V3, CD4bs, and MPER) were described by Bristine et al[5].

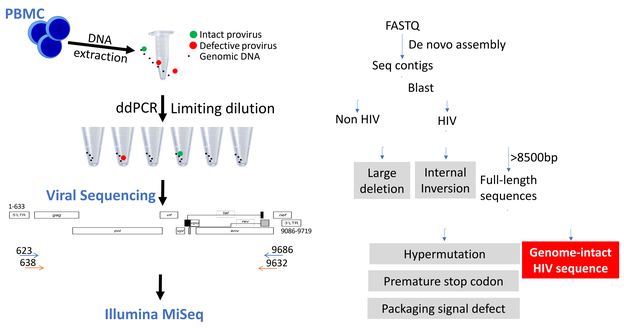


Figure 1 Experimental and computational determination of Full-length Individual Proviral Sequencing.

RESULTS

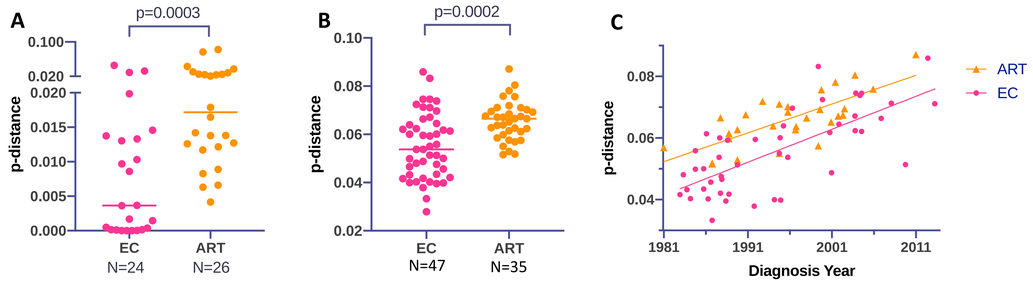


Figure 2 Limit genetic diversity in intact proviruses from ECs.

(A) P-distance between distinct intact provirus obtained from each participant. Participants with at least two detectable intact proviruses are included. **(B-C)** P-distance between intact proviruses and HIV-1 clade B reference sequence. The p-distance values are correlated with diagnosis years. Each dot represents one study participant.

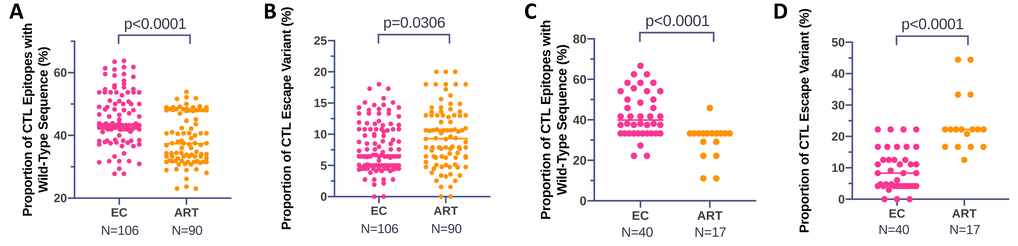


Figure 3 Less mutational CTL escape variants in intact proviruses from ECs.

(A-B) Proportion of HLA class-I alleles restricted CTL epitopes with wild-type sequences (A) and escape variants (B) in all subjects. **(C-D)** Proportion of HLA class-I alleles restricted CTL epitopes with wild-type sequences (C) and escape variants (D) in HLA-B*27/B*57+ subjects. Each dot represents one intact proviral sequence. clonal sequences are counted once.

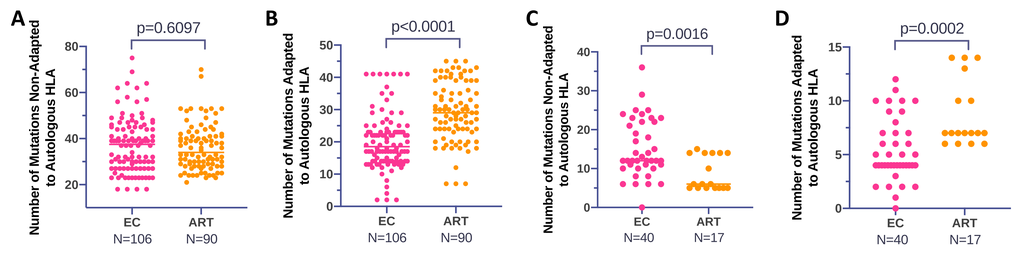


Figure 4 Weaker adaption to HLA-mediated immune pressure in intact proviruses from ECs.

(A-B) Number of polymorphism sites non-adapted (A) and adapted (B) to autologous HLA class I alleles variants in all subjects. **(C-D)** Number of polymorphism sites non-adapted (C) and adapted (D) to autologous HLA class I alleles in HLA-B*27/B*57+ subjects. Each dot represents one intact proviral sequence. clonal sequences are counted once.

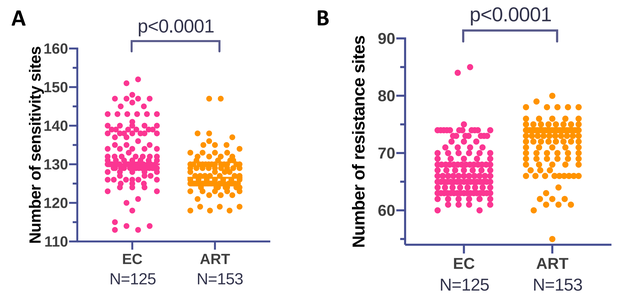


Figure 5 Weaker resistance to bNAbs immune pressure in intact proviruses from ECs.

(A-B) Number of signature sites associated bNAbs sensitivity (A) and resistance (B). Each dot represents one intact proviral sequence. clonal sequences are counted once. All HIV clade sequences are included.

CONCLUSIONS

Elite controllers exhibit low frequencies of immune escape mutations in intact proviruses, despite the absence of antiretroviral therapy, suggesting that intact proviral sequences maintain a state of deep, long-lasting latency through a "block and lock" mechanism.

REFERENCE

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