IMPACT OF HIV RESERVOIR IN THE LOSS OF NATURAL ELITE CONTROL OF HIV-1 INFECTION

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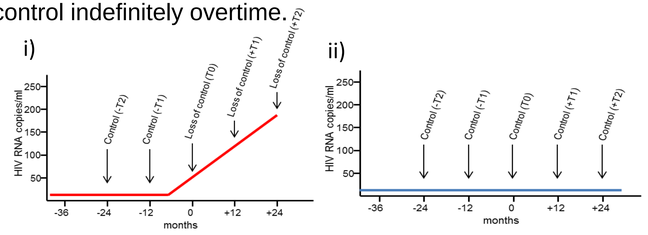
BACKGROUND

Approximately 25% of elite controllers (EC) eventually loss virological control. This has enabled to classify EC in two groups:

i) **Transient elite controllers (TC**), those who eventually lose viremia control (VC).

ii) **Persistent controllers (PC),** those who maintain viremia control indefinitely overtime.



Several studies have shown that PC and TC present different immunological, proteomic, metabolomic and miRNA profiles but in terms of virological factors, it is essential to deeply characterize the quality of HIV reservoirs to distinguish both phenotypes.

METHODS

- Genomic DNA, from 18 PC, 10 TC and 41 antiretroviral-treated participants, was isolated from peripheral blood.
- The characterization of HIV-1 reservoir was performed using **next-generation sequencing techniques**, such as full-length individual proviral sequencing **(FLIP-seq)** and matched integration site and proviral sequencing **(MIP-seq)**.

PC =18
>23 years maintaining the VC
>500 CD4 T-cells (cell/mm^3)

TC = 10
After being EC, detectable viremia for >1 year
0.3-2 years before losing the VC
67-5,580 copies/ml post loss

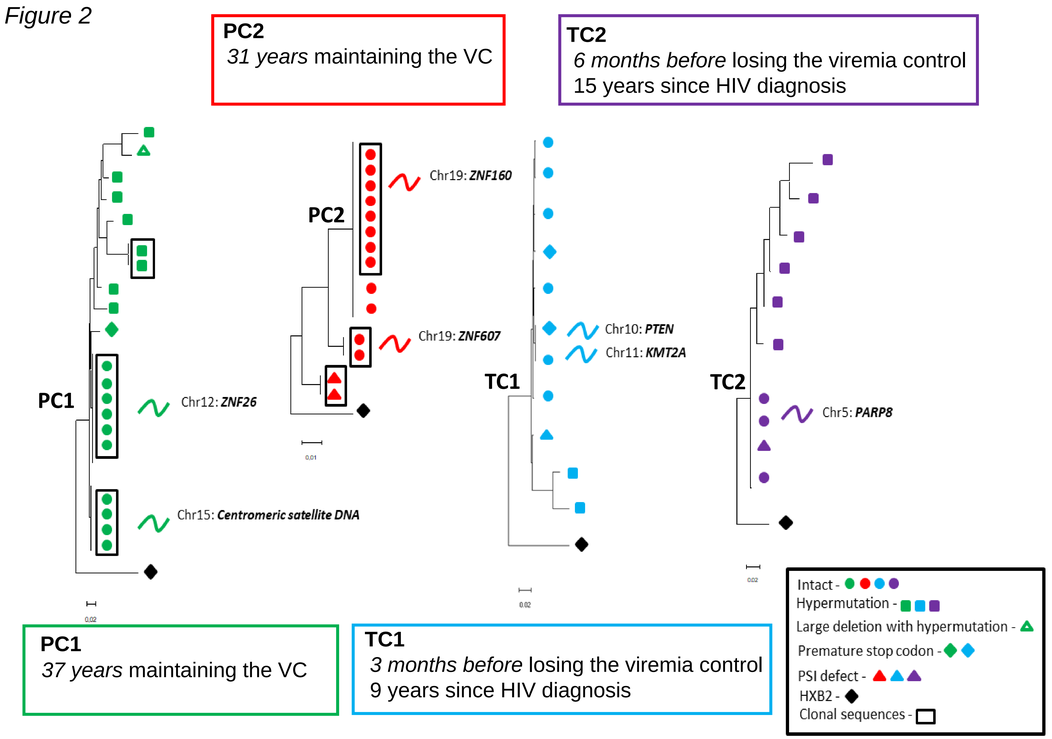
ART= 41
2-19 years

Transient elite controllers present a distinct proviral reservoir landscape, before losing the viremia control, compared to persistent controllers, with higher proportion of intact provirus, no clonally expanded, located in genic regions

RESULTS

- No significant difference was found in total proviruses between PC and TC (*Figure 1, A*).
- Tendency in TC to have higher defective provirus (*Figure 1, B*).
- **Intact proviruses** were **higher in TC** compared to PC (*Figure 1, C*).
- **Intact proviruses were not found in 70% of the PC** (*Figure 1, C*).
- Clonally expanded intact proviruses were not found in TC *(Figure 1, D).*
- Intact proviruses were located in **centromeric satellite DNA** or **zinc-finger genes** (ZNF) in **PC** (*Figure 2, PC1,PC2*).
- Intact proviruses were located in **permissive genic euchromatic** positions in **TC** (*Figure 2, TC1,TC2*).

Figure 2

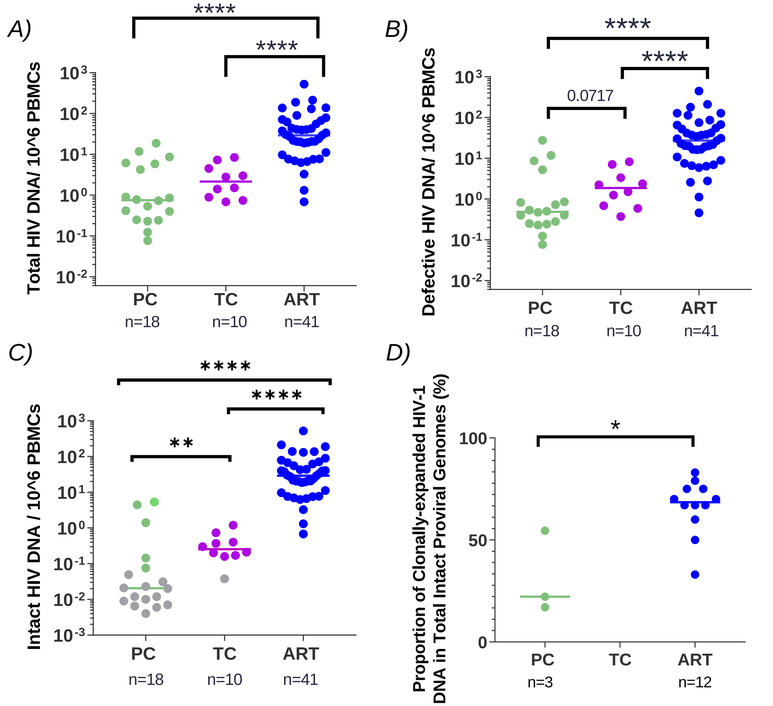


CONCLUSIONS

- PC, TC and ART-treated participants presented a distinct proviral reservoir landscape in PBMCs.
- TC presented more intact provirus than PC before losing the viremia control.
- Clonal expansion of genome-intact HIV-1 was not found in TC.
- Intact provirus from TC were located in permissive genic euchromatic positions in contrast to PC whose intact provirus were located in centromeric satellite DNA or zinc finger genes, both associated with heterochromatin features.

This study goes one step further to identify PC as the right model of functional cure and to determine the causes of the loss of spontaneous viral control

Figure 1



ADDITIONAL KEY INFORMATION

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