Contribution of Diverse CD4+ T-cell Subsets to the HIV Reservoir in ART-suppressed Late Presenters

377

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BACKGROUND

Late presenters (LPs) —individuals diagnosed with advanced HIV disease — often harbor X4-tropic variants that can infect naïve and memory CD4+ T cells, but their contribution to the reservoir under ART is not well defined.

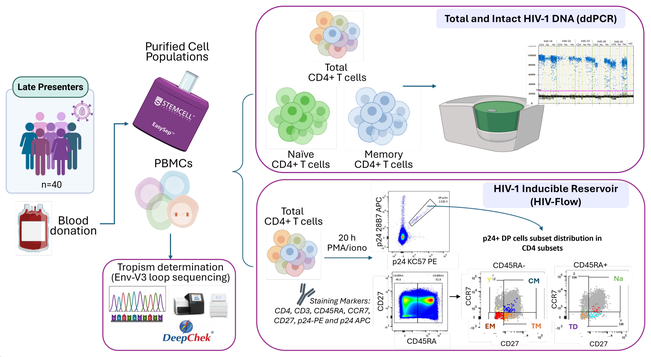
The aim was to assess reservoir composition and inducibility in naïve and memory CD4+ T cells from ART-suppressed LPs.

METHODS

- Cross-sectional study including 40 ART-suppressed LPs (CD4 <350 cells/μL and/or prior AIDS event).
- Excluded individuals with probable acute infection (recent seroconversion <180 days, negative/indeterminate WB or p24 antigenemia, or symptoms of acute retroviral syndrome).
- On ART with HIV-RNA <50 copies/mL for ≥2 years at enrollment.

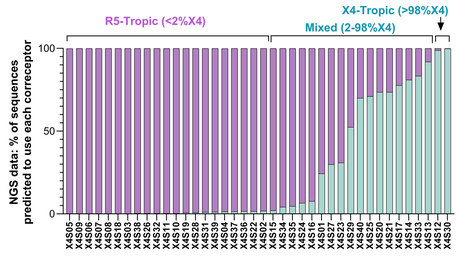
Table 1. Demographic characteristics of the participants (n=40)

Age, *yrs* (median, IQR)	55 (46 – 60)
Gender, n (%)	
Men	36 (90)
Women	3 (7.5)
Transgender	1 (2.5)
Time from diagnosis, *yrs* (median, IQR)	15.2 (10.8 – 24.5)
Time suppressed, *yrs* (median, IQR)	11.1 (8.7 – 14.9)
Nadir CD4, *cells/mm3* (median, IQR)	207 (61 – 278)
CD4 absolute at screening, *cells/mm3* (median, IQR)	578 (415 – 781)



RESULTS

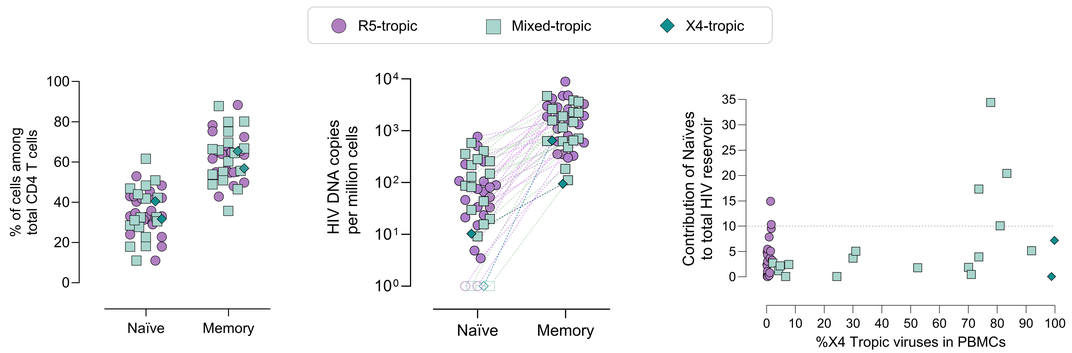
Fig 1: Tropism determined by deep sequencing of Env-V3 loop from cell associated HIV-1 DNA.



- X4-tropic viral variants detected in 19/40 participants.

Naïve CD4+ T cells can constitute a distinct and highly inducible HIV-1 reservoir in some LPs, irrespective of viral tropism, highlighting their relevance for cure-oriented interventions.

Fig 2: Total reservoir size and distribution.

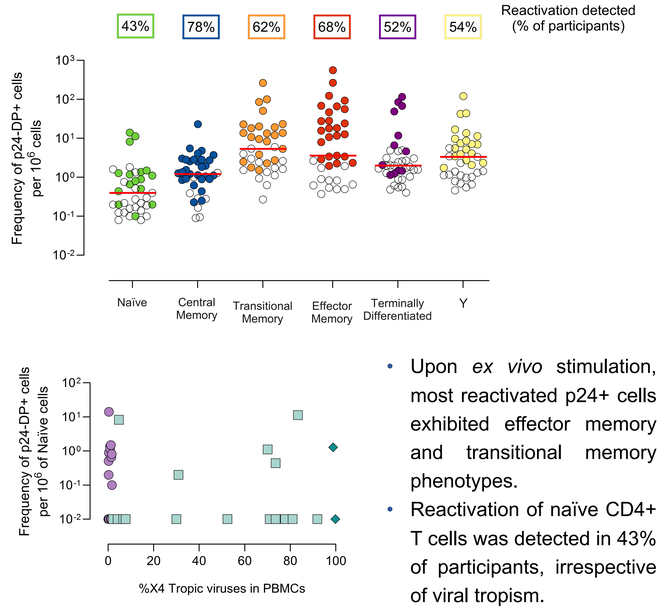


- Memory CD4+ T cells display the highest levels of HIV-1 DNA.
- Naïve CD4+ T-cell contribution to HIV reservoir does not significantly correlate to X4 tropism frequency.
- In 6 participants naïve CD4+ T cells contributed >10% of total HIV reservoir.

Fig 3: Absolute frequency and relative proportion of intact and defective proviruses.

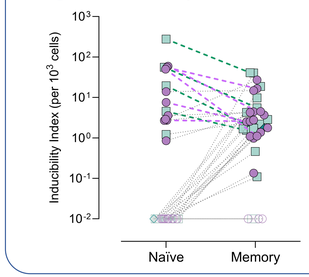
- The reservoir within the naïve subset is enriched in intact proviruses, showing a higher proportion of intact to defective genomes compared with memory.
- In 4 participants, naïve CD4+ T cells even harbored a higher absolute frequency of intact proviruses than the corresponding memory compartment.

Fig 4: Reservoir reactivation evaluated by HIV-Flow.



- Upon *ex vivo* stimulation, most reactivated p24+ cells exhibited effector memory and transitional memory phenotypes.
- Reactivation of naïve CD4+ T cells was detected in 43% of participants, irrespective of viral tropism.

Fig 5: Inducibility index, *how many infected cells can be reactivated?*



$$\text{Inducibility index} = \frac{\text{Frequency of inducible cells (p24+)}}{\text{Frequency of cells harboring HIV DNA}}$$

- In 9 participants, the inducibility index was higher in the naïve CD4+ T cell subset than in memory CD4+ T cells.

CONCLUSIONS

- Memory CD4+ T cells are consistently the primary contributors to the latent and inducible HIV reservoir in LPs, irrespective of viral tropism.
- Naïve cells harbor a substantial proportion of intact proviruses and, in some individuals, display a higher reactivation potential.
- These findings demonstrate a divergent and inducible HIV-1 reservoir within naïve CD4+ T cells in certain LPs, emphasizing the importance of considering this subset in HIV cure strategies.

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