Long-term ART Enhances Cytotoxic Response and Reduces the Reactivation Capacity of HIV-1 Reservoir

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BACKGROUND

- Antiretroviral treatment (ART) successfully blocks HIV-1 replication, although treatment interruption generally results in viral rebound.
- One of the greatest challenges remains the eradication of the virus due to the persistence of a latent viral reservoir, mainly composed of long-lived CD4+ T.
- Long-term ART in people with HIV (PWH) has been related to reduced levels of competent proviruses.

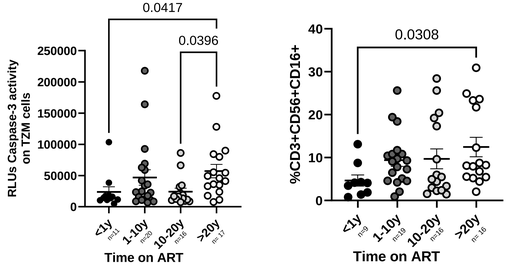
OBJECTIVES

- Evaluate how time on ART affects reservoir size, composition and reactivation capacity.
- Evaluate how time on ART affects CD4+ memory subpopulations and markers of immune activation, exhaustion and senescence.
- Evaluate how time on ART affects the efficacy of cytotoxic response.

Table 1. Clinical and sociodemographic characteristics of the participants.

	<1y n= 11	1-10y n= 20	10-20y n= 16	>20y n= 17	p-value
Demographic characteristics					
Age (years): median (IQR)	30 (24.5-35.5)	42.5 (37.8-49.0)	49.5 (45.8-54.3)	56.0 (54.0-60.0)	**<0.0001**
Gender (male): n (%)	9 (81.8)	17 (85.0)	14 (87.5)	13 (76.5)	0.7661
Clinical chacteristcics of HIV-1 infection					
Time since HIV infection (years): median (IQR)	<1	8.0 (6.0-9.0)	15.0 (13.0-19.0)	28.0 (25.0-31.0)	**<0.0001**
NADIR CD4 (cells/mm3): median (IQR)	334 (196.5-473.0)	331.0 (73.0 -438.0)	210.0 (167.0-307.0)	180.5 (149.8-239.3)	0.5494
CD4 count (cells/mm3): median (IQR)	554.5 (437.0-868.3)	721.0 (502.0-880.3)	905.5 (599.5-1010.3)	898.0 (800.5-991.0)	0.1402
CD8 count (cells/mm3): median (IQR)	1116.0 (904.8-1235.0)	701,5 (607.0-1020.5)	818.0 (552.0-904.8)	862.0 (610.8-1366.3)	0.4328
CD4/CD8 ratio (cells/mm3): median (IQR)	0.52 (0.38-0.78)	0.76 (0.53-1.20)	0.98 (0.77-1.38)	0.86 (0.61-1.23)	0.1862
Viral load (undetectable): n (%)	7 (87.5)	14 (87.5)	14 (87.5)	16 (100)	0.7887
Antiretroviral treatment					
Time on ART (years): media	<1	7.0 (5.8-8.0)	14.0 (12.0-15.5)	25.0 (23.0-30.0)	**<0.0001**
Time on current ART (years)	<1	3.0 (1.8-3.5)	2.4 (1.0-3.5)	3.4 (2.9-4.2)	**0.0111**
2 NRTI + INI	4 (36.4)	10 (50.0)	6 (37.5)	2 (11.8)	0.0909
NRTI + INI	3 (27.3)	8 (40.0)	7 (43.8)	6 (35.3)	0.8754
2 NRTI + PI	1 (9.1)	1 (5.0)	1 (6.2)	4 (23.5)	0.3591
NNRTI + INI	0	0	1 (6.2)	1 (5.9)	0.6726
2 NRTI + NNRTI	0	0	1 (6.2)	3 (17.6)	0.1207
Unknown	3 (27.3)	1 (5.0)	0	1 (5.9)	0.2762

Figure 1. Cytotoxic response against infected TZM cells was higher in >20y, which could be related to enhanced NKT subpopulations.



PWH on long-term ART showed reduced capacity for proviral reactivation with improved cytotoxic response against HIV-1-infected cells.

RESULTS

Figure 2. Despite no significant changes in total reservoir size, proviral reactivation in CD4 was lower as time on ART progressed, which correlated with lower pSAMHD1 levels in CD4 from >20y than in <1y and a smaller proportion of infact provirus.

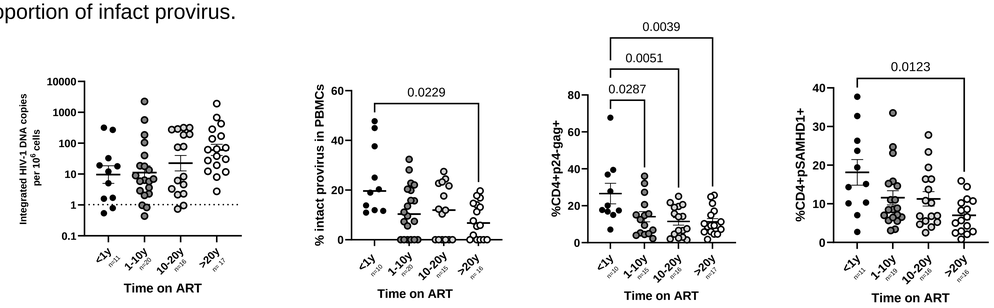
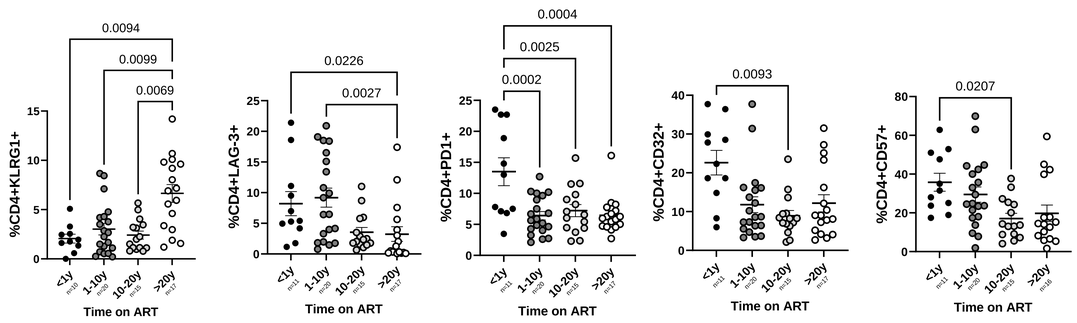


Figure 3. Senescence marker KLRG1 was increased in >20y. However, CD4 of <1y and 1-10y showed higher levels of immune exhaustion markers LAG-3 and PD1 than cohorts with longer time on ART, as well as increased levels of activation markers CD32 and CD57.

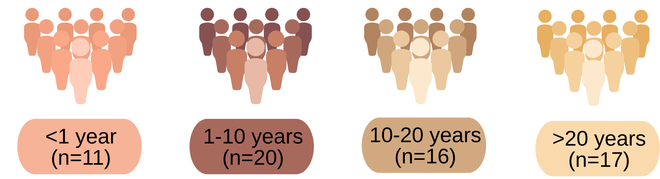


CONCLUSIONS

- PWH on long-term ART showed reduced capacity for proviral reactivation and lower expression of exhaustion markers in CD4+ T cells, with improved cytotoxic response against HIV-1-infected cells.
- Time on ART should be considered for HIV cure interventions to achieve higher efficacy.

METHODS

Cross-sectional study with PWH (n= 64) who were on ART for different durations:



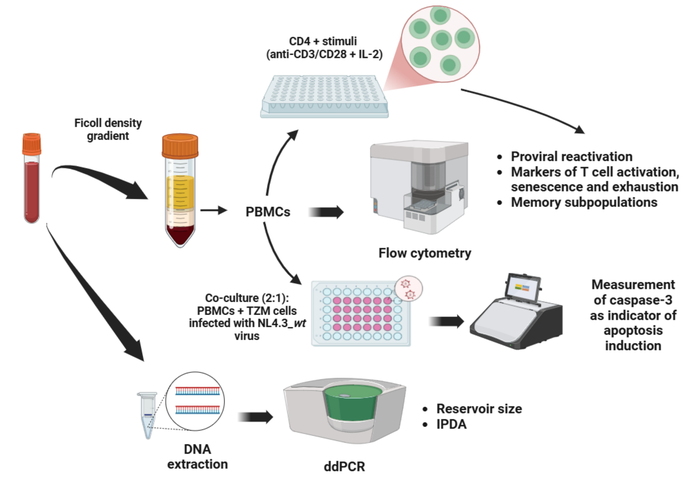
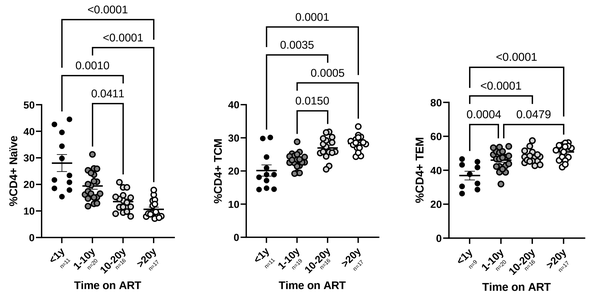


Figure 4. CD4+ naïve cells decreased with longer ART duration, while TCM and TEM increased. There were no differences in TEMRA cells (not shown).



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