Impact of age on T cell exhaustion in children, adolescents and adults with vertically acquired HIV infection

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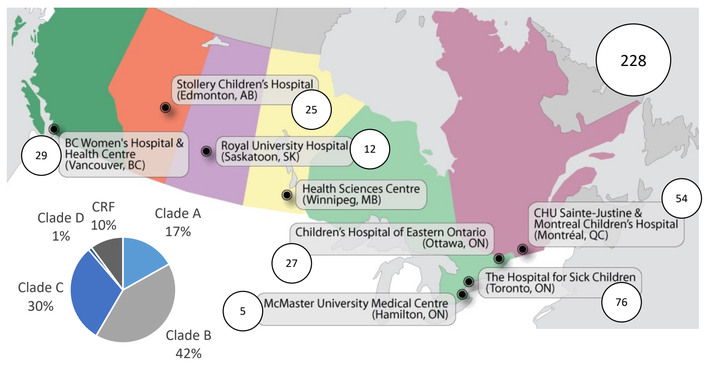
BACKGROUND

In adults with chronic viral infections, including HIV/AIDS, persistent antigen exposure leads to progressive loss of T cell function and T cell exhaustion, which interferes with the efficacy and maintenance of virus-specific cell-mediated immunity.

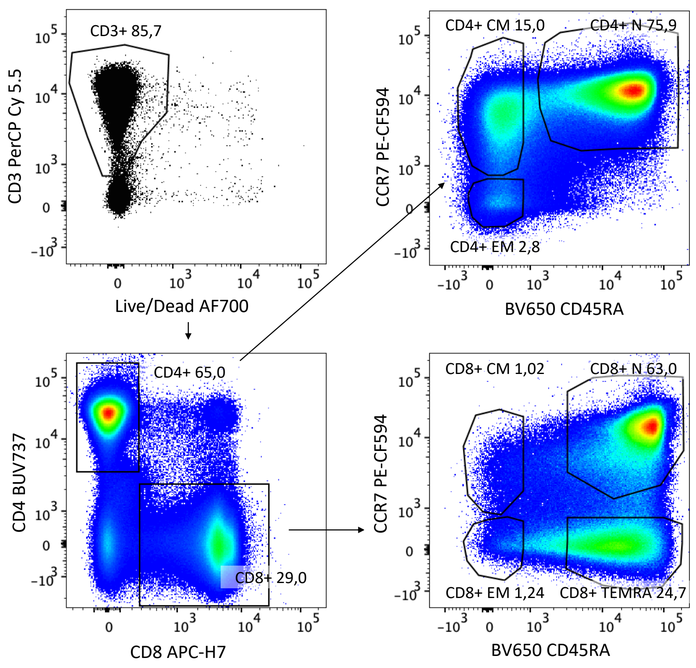
To determine whether the extent and dynamics of T cell exhaustion vary as a function of age, we characterized cell surface expression of immune checkpoint inhibitors (ICIs) that are associated with T cell exhaustion in children, adolescents and young adults who were infected with HIV by vertical transmission.

METHODOLOGY

Study participants were enrolled in the Early Pediatric Initiation, Canada Child Cure Cohort Study (EPIC[4]).



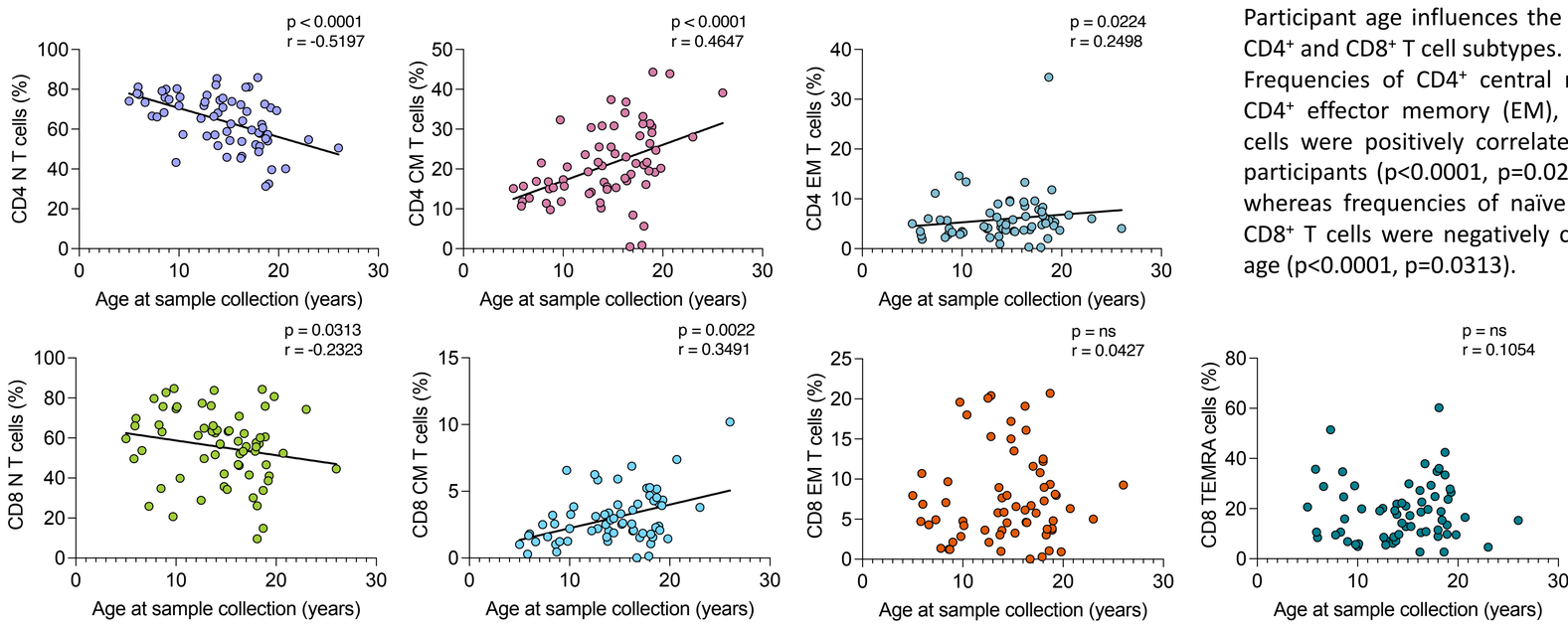
Multiparameter flow cytometry was used to measure expression of cell-surface markers associated with T cell exhaustion (PD-1, CD160, CTLA-4, LAG-3, TIGIT, Tim-3) in CD4⁺ and CD8⁺ T cell subsets isolated from peripheral blood mononuclear cells.



STUDY PARTICIPANTS

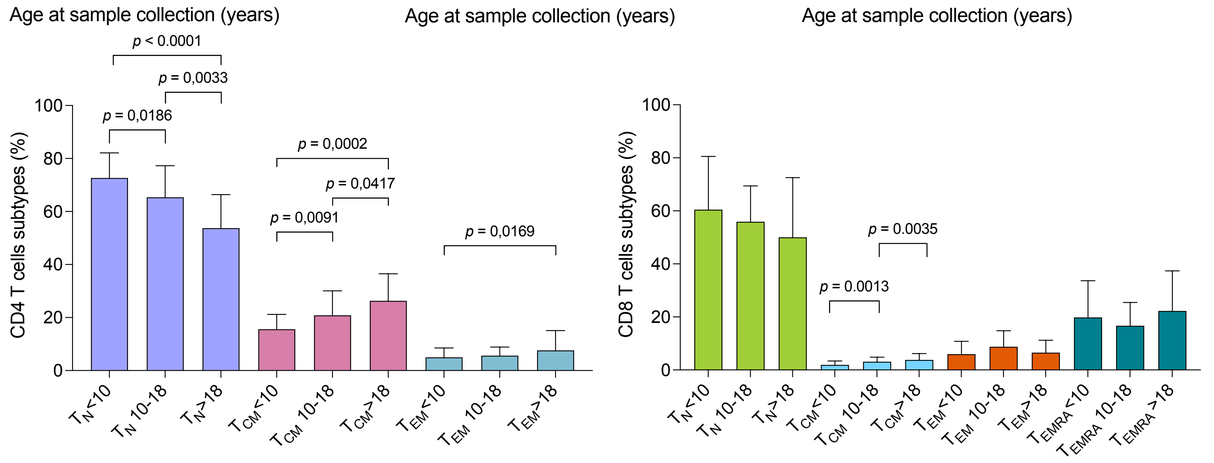
		Age <10 years	Age 10-18 years	Age >18 years
Number of participants (n)		15	34	16
Age (years; median, IQR)		8.33 (6.00-9,00)	14.81 (13.57-16.48)	18.91 (18.43-19.65)
Sex (n, %)	Male	8 (53.33)	17 (50.00)	6 (37.50)
	Female	7 (46.67)	17 (50.00)	10 (62.50)
HIV clade (n, %)	A	3 (20.00)	3 (8.82)	4 (25.00)
	B	4 (26.67)	1 (2.94)	5 (31.25)
	C	6 (40.00)	10 (29.41)	2 (12.50)
	Other	2 (13.33)	6 (17.65)	5 (31.25)
Age at ART initiation (years; median, IQR)		1.12 (0.00-3.36)	1.51 (0.36-5.99)	1.99 (0.98-8.48)
HIV-1 viral load (RNA copies per ml plasma; median, range)		40 (<40-<40)	40 (<40-<40)	40 (<40-<40)
SVS at sample collection (<40 copies per ml plasma; n, %)	Yes	12.00 (80.00)	29 (85.29)	14 (87.50)
	No	3.00 (20.00)	13 (14.71)	2 (12.50)
Proportion of life under SVS (PLUS) (median, IQR)		0.4871 (0.0669-0.6470)	0.2141 (0.0365-0.5845)	0.3719 (0.1421-0.5547)

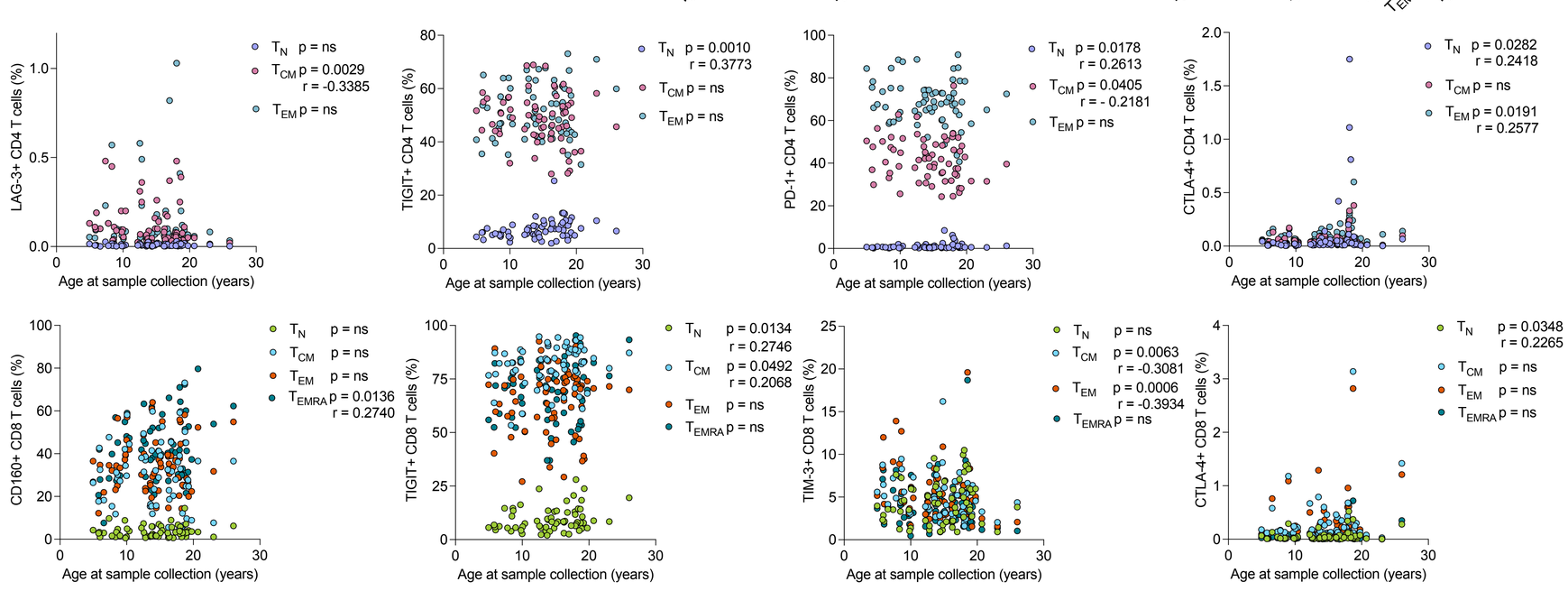
RESULTS



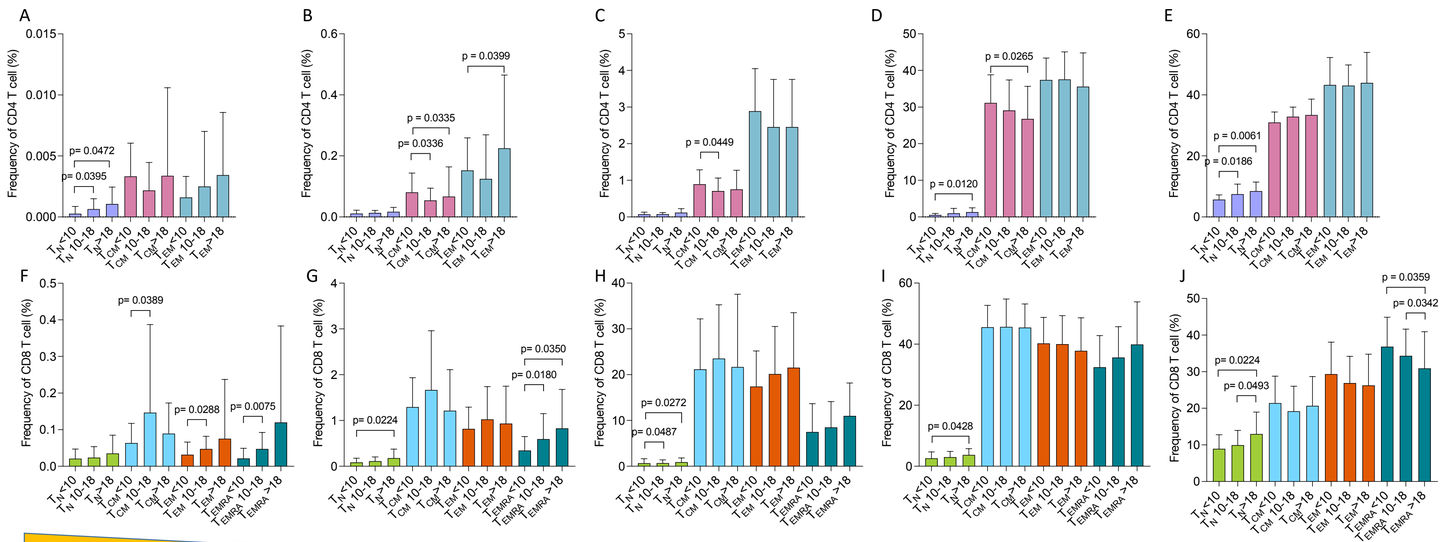
Participant age influences the distribution of CD4⁺ and CD8⁺ T cell subtypes.
Frequencies of CD4⁺ central memory (CM), CD4⁺ effector memory (EM), and CD8⁺ CM cells were positively correlated with age of participants (p<0.0001, p=0.0224, p=0.0022), whereas frequencies of naïve (N) CD4⁺ and CD8⁺ T cells were negatively correlated with age (p<0.0001, p=0.0313).

Participants were stratified based on their age (children = 0-10 years, adolescents = 10-18 years, young adults = 18-26 years). A significant difference was observed in CD8⁺ T cell frequencies between older subjets (<18 years old) and adolescents (10-18 years old). More statisatically significant differences were observed in CD4⁺ T cells subsets than in CD8⁺ T cells subsets.



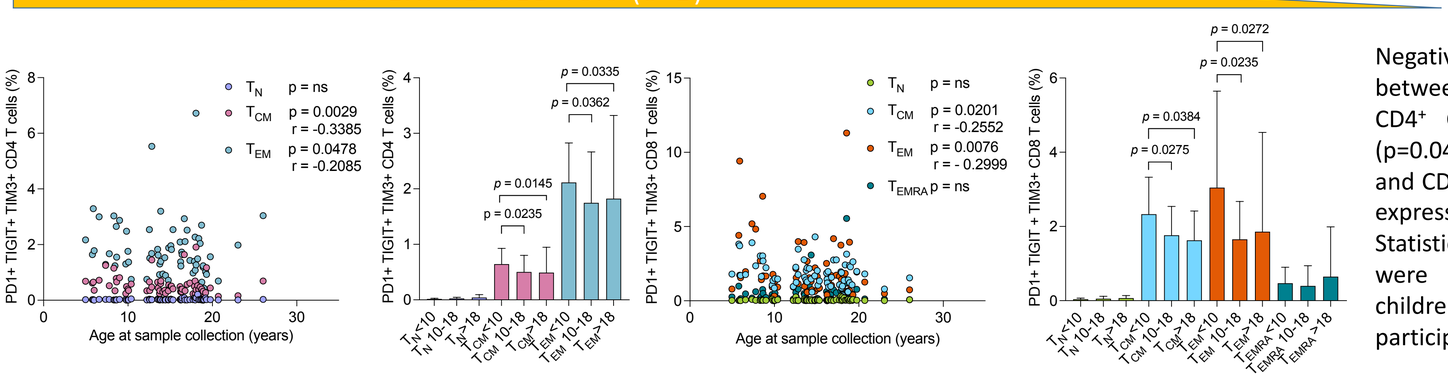


A significantly higher proportion of CD8⁺ CM and CD8⁺ EM expressing Tim-3 and of CD4⁺ CM expressing LAG-3 was observed in younger as compared to older participants. Also, a higher proportion of CD4⁺ CM expressing PD-1 was observed in younger study participants.



Degrees of T cell exhaustion are defined by the number of ICIs expressed at their cell surface. Shown are quintuple (A,F), quadruple (B,G), triple (C,H), double (D,I) and single expression (E,J) of combinations of 6 ICIs (PD-1, CD160, CTLA-4, LAG-3, TIGIT, Tim-3) in CD4⁺ and CD8⁺ T cell subsets. In general, lower frequencies of cells co-expressing ICIs were observed in children.

NUMBER OF CO-EXPRESSED ICIs (5-1)



Negative correlations were found between age and frequencies of CD4⁺ CM (p=0.0029), CD4⁺ EM (p=0.0478), CD8⁺ CM (p=0.0201) and CD8⁺ EM (p=0.0076) T cells co-expressing PD-1, TIGIT, and Tim-3. Statistically significant differences were also observed betwen children and the 2 other groups of participants.

DISCUSSION

Our results showed that the distribution of T cell subsets was age dependent. As previously described, younger participant had more naive T cells but less memory T cells and less CD4⁺ T cells as a whole. Higher frequencies of cells co-expressing ICIs were observed in older participants, which could be explained by a higher degree of exposure to HIV antigens resulting from a lower proportion of life under SVS and initiation of cART later in life. The higher frequency of cells co-expressing PD-1, TIGIT and Tim-3 in CD4⁺ T cells observed in younger participants could be related to the fact that a large proportion of the HIV-1 viral reservoir resides within CD4⁺ T cells expressing PD-1 and TIGIT. T cells expressing Tim-3 are known to exhibit dysfunctional capacities to proliferate or to produce cytokines. Higher frequencies of CD8⁺ T cells expressing PD-1, TIGIT, and Tim-3 could explain in part why HIV infection progresses faster in children.

CONCLUSION

Overall, older participants had higher frequencies of cells co-expressing ICIs. The higher proportions of CD4⁺ and CD8⁺ CM and EM T cells co-expressing PD-1, TIGIT, and Tim-3 in younger children as opposed to adolescents and adults suggest a differential involvement of T cell exhaustion in the pathogenesis of pediatric HIV and in the composition of the viral reservoir as a function of age in vertically acquired HIV infection.

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