Evolving expression of co-inhibitory receptors and plasma cytokines in children living with perinatal HIV.

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Hinatea Dieumegard[1,2], Mojahidul Islam[3], Haliya Johnson[3], Jade Canape[1,2], Madeleine Aby Diallo[1,2], Fatima Kakkar[4,5], Ari Bitnun[6,7], Jason Brophy[8,9], Lindy Samson[9], Stanley Read[6,7], Michael T. Hawkes[10], Rafick-P. Sekaly[3], Ann Chahroudi[11], Ashish Arunkumar Sharma[3], Hugo Soudeyns[1,2,3,4,5], EPIC[4] Study Group. [1]Viral Immunopathology Unit, Centre de recherche Azrieli du CHU Sainte-Justine, Montreal, Canada. [2]Department of Microbiology, Infectiology and Immunology, Faculty of Medicine, Université de Montréal, Montreal, Canada. [3]Pathology Advanced Translational Research Unit (PATRU), Department of Pathology and Laboratory Medicine, Emory University, Atlanta GA. [4]Centre d'infectiologie mère-enfant (CIME), CHU Sainte-Justine, Montreal, Canada. [5]Department of Pediatrics, Faculty of Medicine, Université de Montréal. [6]Hospital for Sick Children, Toronto, Canada. [7]Department of Pediatrics, University of Toronto, Toronto, Canada. [8]Children's Hospital of Eastern Ontario, Ottawa, Canada. [9]Department of Pediatrics, University of Ottawa, Ottawa, Canada. [10]Department of Pediatrics, University of British Columbia, Vancouver, Canada. [11]Department of Pediatrics, Emory University, Atlanta GA.

BACKGROUND

HIV disease in children differs from that seen in adults. The objective of this study was to test the association between HIV reservoir size and the development of antiviral immunity between childhood, adolescence and young adulthood in terms of a) expression of co-inhibitory receptors; and b) expression of plasma cytokines.

METHODS

Expression of co-inhibitory receptors was measured by flow cytometry. Levels of 33 plasma cytokines and chemokines were assessed using the Meso Scale Discovery platform. Total HIV DNA was measured by qRT-PCR and inducible HIV RNA levels were measured following prostratin stimulation. HIV-specific cell-mediated immune responses were measured using IFN-γ ELISPOT.

RESULTS

The study was conducted on 65 participants of the EPIC4 Cohort (47.4% male) who were stratified as children (<10 yrs; n=15), adolescents (10-18 yrs n=34) or young adults (>18; n=16). Median viral load was <40 RNA copies/mL plasma (range=<40-8473 copies). Frequencies of CD4⁺ T cells expressing PD-1 or TIGIT and of CD8⁺ T cells expressing PD-1, TIGIT or CD160 significantly increased with age. Total HIV DNA and inducible HIV RNA levels were positively correlated with frequencies of PD-1⁺ (p≤0.033) and TIGIT⁺ (p≤0.032) CD4⁺ T cells and of PD-1⁺ (p<0.001), TIGIT⁺ (p≤0.080) and CD160⁺ (p≤0.021) CD8⁺ T cells.

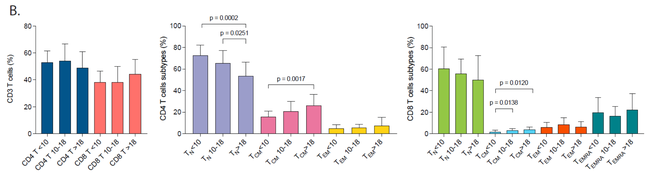


Figure 1. Frequency of naive T cells goes down with age.

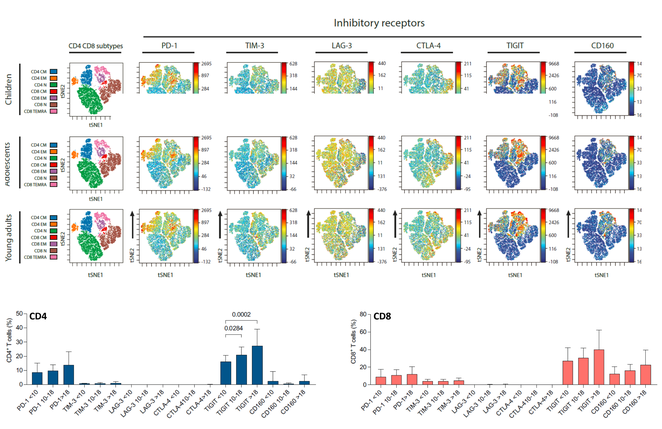


Figure 2. Frequency of inhibitory receptor expression increases with age.

Expression of a set of co-inhibitory receptors (PD-1, TIGIT, CD160) and evolution of cytokine profiles were associated with age and total and inducible HIV reservoir size in children and adolescents living with vertically-acquired HIV. This highlights *major longitudinal shifts in mobilization of immune pathways* and informs the differential pathology of pediatric HIV disease.

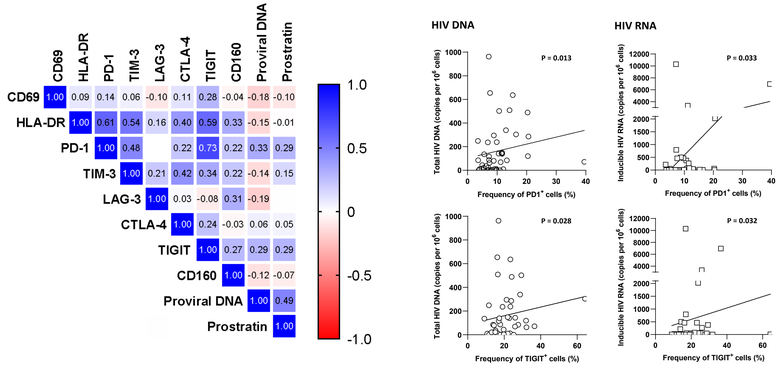


Figure 3. Inhibitory receptor expression in CD4⁺ cells correlates with reservoir size.

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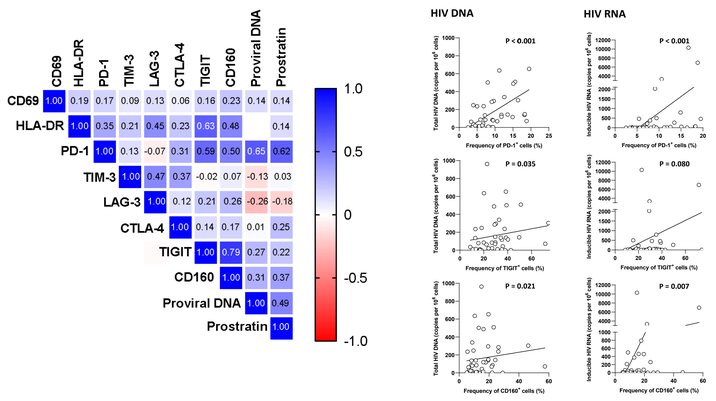


Figure 4. Inhibitory receptor expression in CD8⁺ cells correlates with reservoir size.

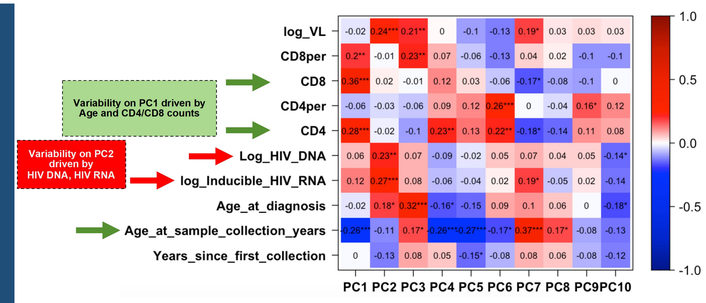


Figure 5. Age and HIV-DNA levels associated with variability explained by principal component 1 and principal component 2.

RESULTS

Unbiased PCA showed that global variability in the plasma cytokine profile on the first PC (27.4% variability) was significantly ($p<0.05$) associated with age at sample collection, while the second PC (15.04% variability) was linked to HIV reservoir size. Plasma levels of TGF-β and TH2 cytokines (e.g., IL-4) were significantly elevated in children <10. A subset of older participants (>10 years) with high TGF-β levels did not exhibit high levels of inducible HIV RNA. Conversely, older participants with reduced levels of TGF-β showed higher levels of IL-17A, IFN-α, total HIV DNA and inducible HIV RNA.

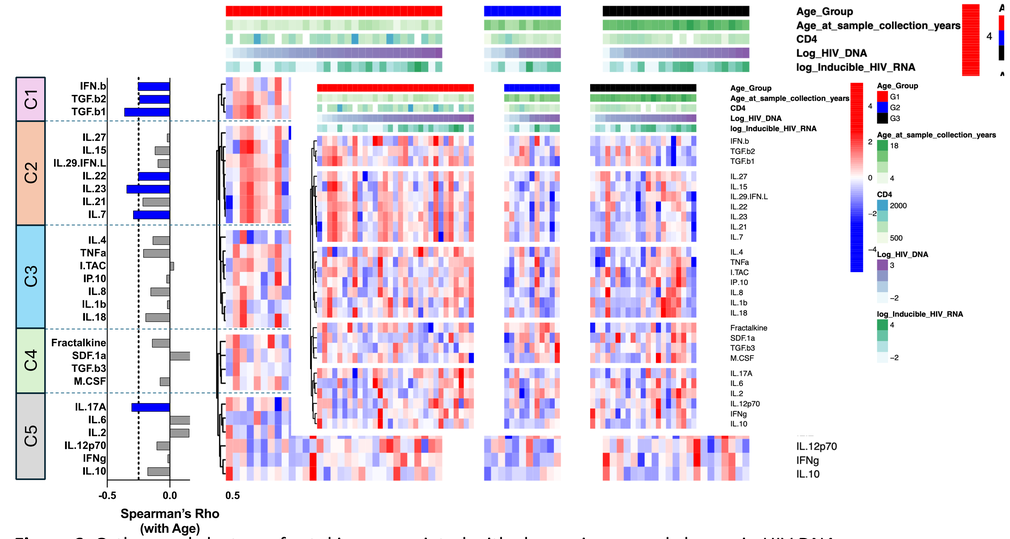


Figure 6. Orthogonal clusters of cytokines associated with change in age and change in HIV DNA per age group. Row normalized heatmap showing the levels of cytokines and chemokines (5 clusters) across the 3 different age groups (columns). Cytokines in clusters 1 and 2 are reduced in the highest age group and include TGF-β1, TGF-β2, IL-7 and IL-21). Levels of HIV-DNA in younger participants were associated with T cell activation and differentiation cytokines (IL-2, IL-4 and IFN-γ) while HIV-DNA in older participants was associated with higher expression of chemokines. < 0.01(**) , p < 0.05 (*) , p<0.1(#).

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CANFAR Canadian Foundation for AIDS Research
the CTN CIHR Canadian HIV Trials Network