Impact of cumulative proportion of life under sustained viral suppression on HIV-specific immune responses and T cell exhaustion in children and adolescents with perinatally-acquired HIV infection

Hinatea Dieumegard[1,2], Doris G. Ransy[1], Ari Bitnun[3], Jason Brophy[4], Lindy Samson[4], Fatima Kakkar[5,6], Michael T. Hawkes[7], Stanley Read[3], Armelle Le Campion[2], Hugo Soudeyns[1,2,5,6], EPIC[4] Study Group.

[1]Unité d'immunopathologie virale, Centre de recherche du CHU Sainte-Justine, Montréal; [2]Département de microbiologie, infectiologie et immunologie, Faculté de médecine, Université de Montréal; [3]Hospital for Sick Children, Toronto; [4]Children's Hospital of Eastern Ontario, Ottawa; [5]Centre d'infectiologie mère-enfant, Centre de recherche du CHU Sainte-Justine, Montréal; [6]Département de pédiatrie, Faculté de médecine, Université de Montréal; [7]Department of Pediatrics, University of Alberta, Edmonton.

I have no conflicts of interest to disclose.

BSP10.09

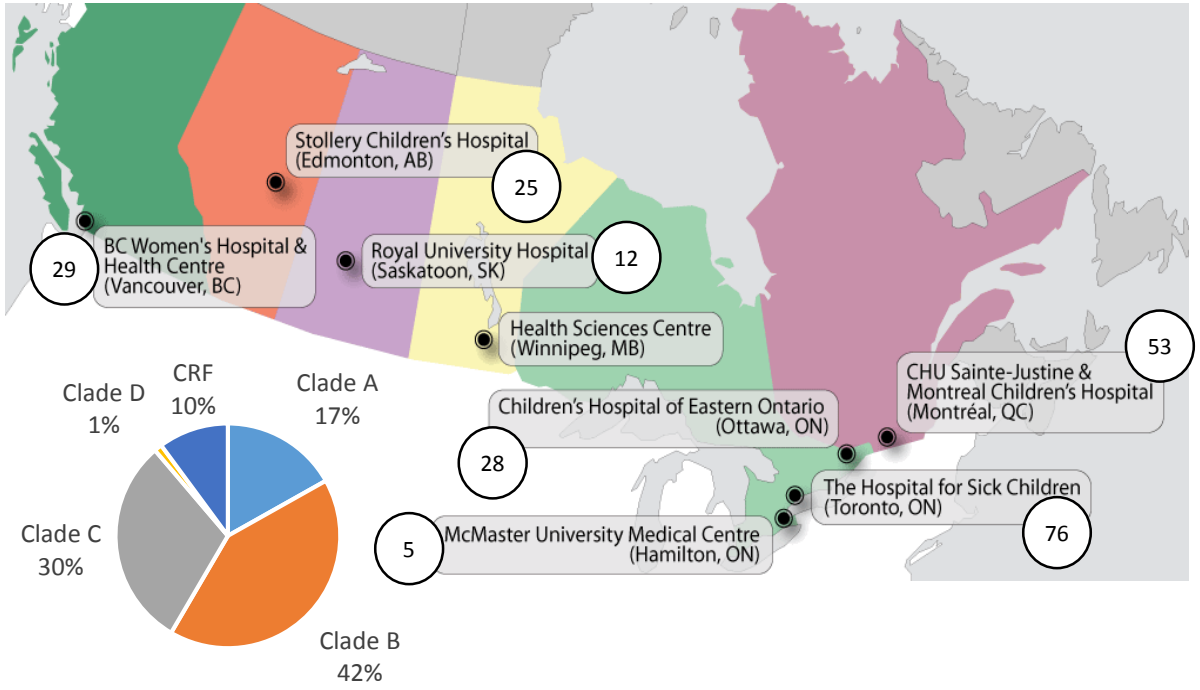
E-mail: hinatea.dieumegard@gmail.com

BACKGROUND

Sustained viral suppression (SVS) is critical to prevent HIV transmission and HIV disease progression. Both antiretroviral therapy (ART) and HIV-specific cell-mediated immunity contribute to the establishment and maintenance of SVS. We explored associations between cumulative proportion of life under SVS (cPLUS), HIV-specific cell-mediated immune responses, and expression of cell surface markers of T cell exhaustion in children and adolescents with perinatally-acquired HIV infection.

EPIC[4] COHORT

Multicenter prospective study involving 9 major pediatric HIV care centers across Canada.



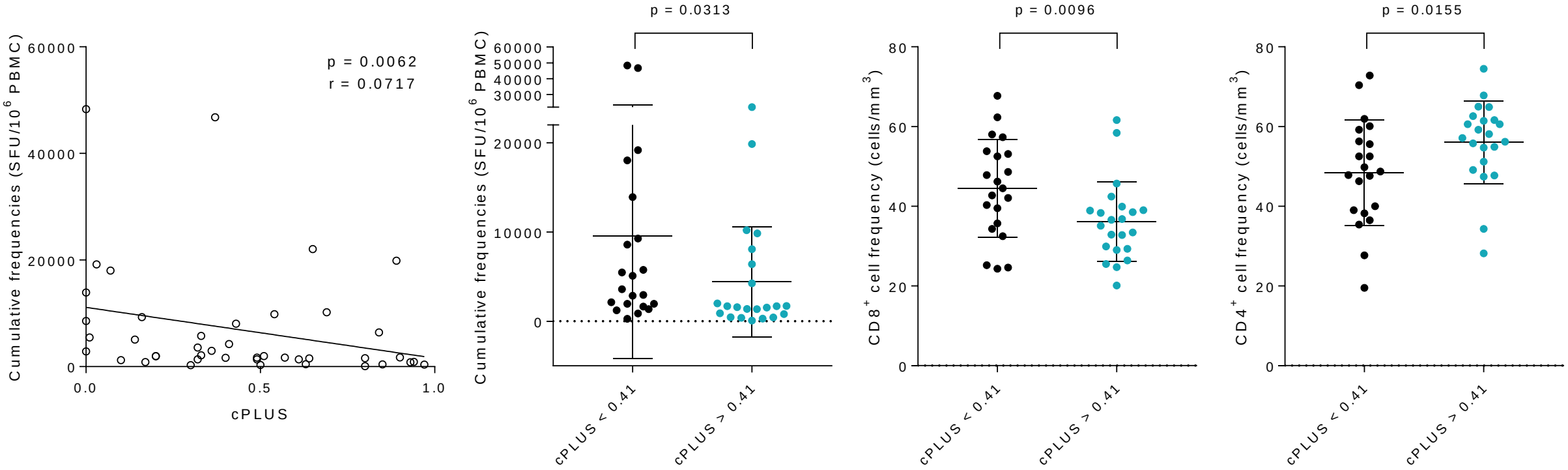
METHODS

Study participants (n=43; median age=14 years, interquartile range=10-18 years) were stratified based on the median value of cPLUS (cPLUS <41 %, n = 21; cPLUS ≥41 %, n=22).

Peripheral blood mononuclear cells (PBMC) obtained from HIV-infected children and adolescents were used in ELISpot assays to measure IFN-γ production [expressed as spot-forming units (SFU)/10^6 PBMC] following stimulation with clade-matched HIV-1 Gag peptide pools. ELISpot positivity was defined according to standard criteria (>50 spot-forming units [SFU] per 10^6 cells and 2 SD over negative controls). The magnitude (cumulative SFU/ 10^6 cells) and breadth (proportion of pools inducing IFN-γ production) were compared with age and duration of SVS.

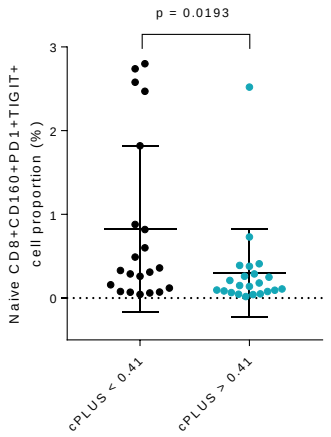
The expression of T cell exhaustion markers (PD-1, CD160, CTLA-4, LAG-3, TIGIT, Tim-3) was measured using 14-color flow cytometry.

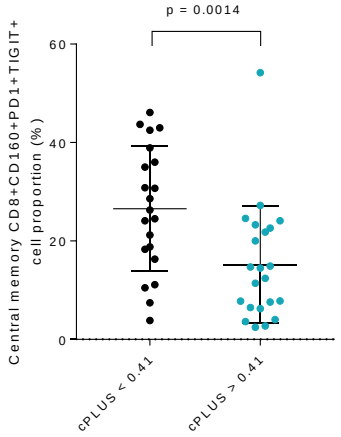
RESULTS

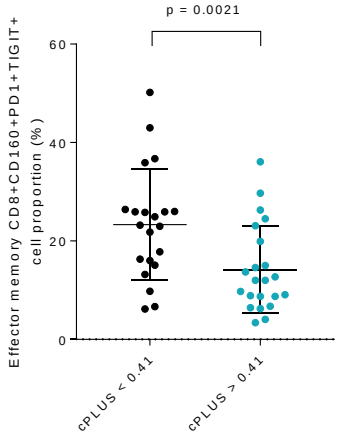


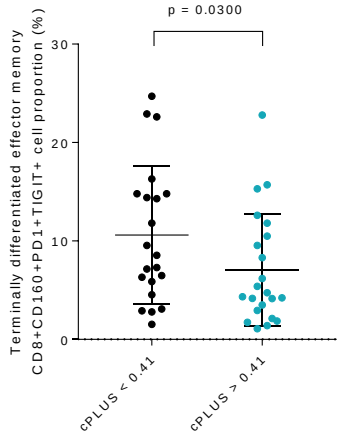
A negative correlation was observed between the cumulative frequencies and the cumulative Proportion of Life Under Sustained viral suppression (cPLUS). Participants with lower cPLUS exhibited higher magnitude of HIV-specific IFN-γ responses (p=0.0313), and had higher frequencies of CD8+ T cells and lower frequencies of CD4+ T cells (p=0.0096 and p=0.0155, respectively).

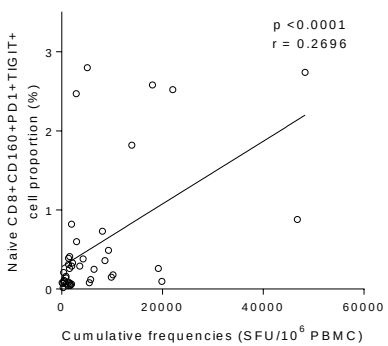
RESULTS

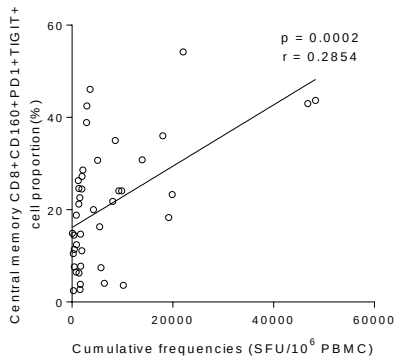


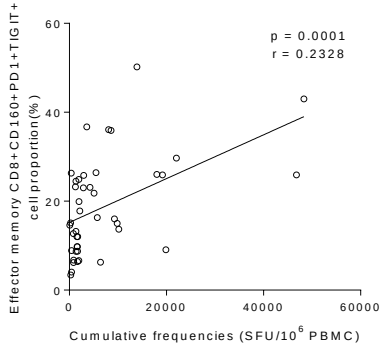


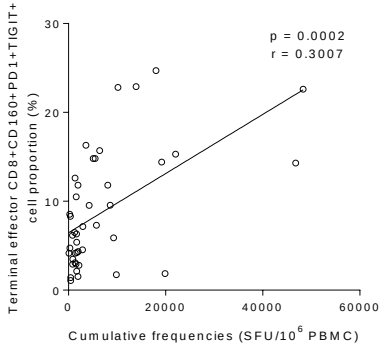


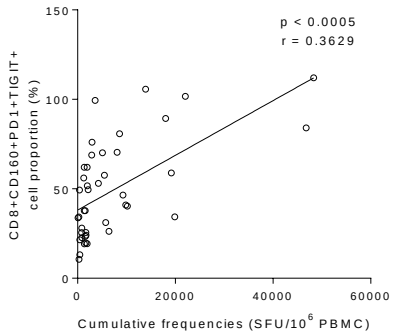












Finally, a positive correlation was observed between the frequencies of CD8+ T cells co-expressing CD160, PD-1 and TIGIT, and HIV-specific IFN-γ responses ($p<0.0005$).

Higher proportions of cells co-expressing of CD160, PD-1 and TIGIT were observed in naive ($p=0.0193$), central memory ($p=0.0014$), effector memory ($p=0.0021$), and terminally differentiated effector memory ($p=0.0300$) CD8+ T cells in participants with low cPLUS as compared to participants with high cPLUS.

A positive correlation was also observed between frequencies of CD8+ T cells subpopulations co-expressing CD160, PD-1 and TIGIT, and HIV-specific IFN-γ responses.

DISCUSSION

A negative correlation between the cumulative frequencies of HIV-specific IFN-γ-producing T cells and cPLUS was observed in our cohort. As the cPLUS reflects the duration and level of exposure to HIV antigens, the immune response deployed against HIV infection is proportional to the degree of antigen exposure. Participants with lower cPLUS exhibited higher magnitude of HIV-specific IFN-γ responses and had higher frequencies of CD8+ T cells and lower frequencies of CD4+ T cells, highlighting the key role of CD8+ T cells in HIV-specific cell-mediated immune reponse and the loss of CD4+ T cells with the progression of HIV infection in children and adolescents.

As the immune response is highly solicited, participants with lower cPLUS exhibed higher proportion of cells co-expressing of CD160, PD-1 and TIGIT in all subpopulation of CD8+ compared to participants with higher cPLUS. A positive correlation was also observed between frequencies of CD8+ T cells subpopulations co-expressing CD160, PD-1 and TIGIT, and HIV-specific IFN-γ responses.

CONCLUSION

These results indicate that greater overall exposure to HIV-1 antigens (lower cPLUS) is associated with a higher magnitude of HIV-specific IFN-γ responses and up-regulation of markers of immune exhaustion (CD160, PD-1 and TIGIT) in multiple CD8+ T cell subpopulations. These results underline the importance for paediatric patients to reach an undetectable viral load under treatment and maintain SVS over a long period.

ACKNOWLEDGMENTS

CHILDREN'S HOSPITAL OF EASTERN ONTARIO
- Jennifer Bowes

HOSPITAL FOR SICK CHILDREN
- Cheryl Arneson

STOLLERY CHILDREN'S HOSPITAL
- Christine Bon

CHU SAINTE-JUSTINE
- Silivie Valois
- Martine Caty

MCMASTER UNIVERSITY MEDICAL CENTRE
- Laura Puri

MONTREAL CHILDREN'S HOSPITAL
- Danny Dong Hyun

ROYAL UNIVERSITY HOSPITAL
- Nicole Kimball

B.C. WOMEN'S HOSPITAL & HEALTH CENTRE
- Annie Qiu