CMV co-infection drives T cell differentiation but not reservoir size among children with HIV

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BACKGROUND

CMV co-infection is common among children living with HIV (CLWH), though its impact on HIV disease control is not clear.

Study rationale: What is the impact of CMV co-infection on HIV reservoir size and T cell subset distribution among CLWH?

METHODS

Study design, setting and populations.

- Sub-study of a prospective, multicenter Early Pediatric Initiation Canada Child Cure Cohort study (EPIC[4]) designed to assess HIV reservoir in children.
- Cohort of 228 Canadian children and young adults living with perinatally acquired HIV-1
- Recruited from the 8 major pediatric HIV care centers across Canada
- Followed every 3-6 months from December 2014 to December 2018
- CMV serostatus (IgG) was determined at baseline using Architect CMIA assay.

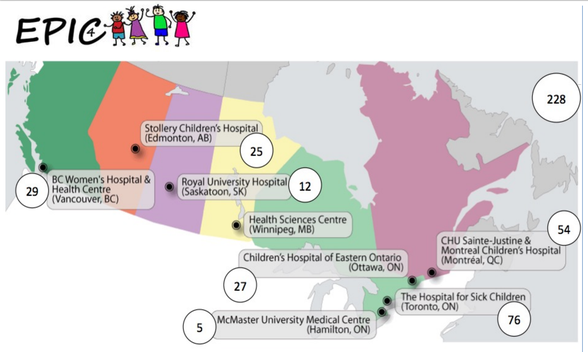
Objective #1: Determine the impact of CMV co-infection on T cell subset distribution

- CD4+ and CD8+ naïve-memory-effector T cell subsets were examined using flow cytometry
- Participants in the EPIC[4] cohort who had accessible T cell subsets were included.

Objective #2: Determine the impact of CMV co-infection on HIV reservoir size

- HIV-1 reservoir size was estimated by measuring total HIV-1 DNA by PCR in unsorted peripheral blood mononuclear cells and inducible cell-free HIV-1 RNA in CD4+T cells using a prostration analog stimulation assay
- Participants in the EPIC[4] cohort with cART (Combination antiretroviral therapy)and sustained viral suppression (SVS) for ≥ 1 year.

RESULTS



N=225 participants	
Median age at baseline entry:	**13.8 year (IQR 9.3-17)**
Female	121 (53.8%)
Canadian-born	99 (44%)
Receiving cART at baseline	222 (98.7%)
HIV Viral suppression at baseline	**182 (81%)**
CMV IgG positive at baseline	**192 (85.3%)**

Objective #1: Determine the impact of CMV co-infection on T cell subset distribution among CLWH.

228 participants → 65 participants with analyse available → 52 CMV seropositive at baseline (80%)

Characteristics	CMV seropositive (n=52)	CMV seronegative (n=13)	p
Female	27 (51.9%)	7 (53.8%)	0.51
Median age (years), IQR	14.4 (9.8-17.5)	14.8 (12.6-17.5)	0.54
Immigrated to Canada	28 (53.8%)	1 (7.7%)	**0.007**
Receiving cART at baseline	50 (96.2%)	13 (100%)	0.23
Age at cART initiation, IQR	3.4 (0.8-9.2)	1.2 (0.4-3.6)	0.35
Viral suppression at baseline	40 (76.9%)	13 (100)	0.13
At least one episode of HIV Viremia occurrence during study	24 (46.2%)	2 (15.4%)	0.09

**Adjusted for HIV viremia during study, age, age at treatment initiation, any treatment interruption during study and migration status.*

N=65		CMV seropositive (n=52)	CMV seronegative (n=13)	Adjusted*
CD4⁺ T cell subsets	CD4⁺ T cell frequency	52.5 (47.0-59.8)	59.2 (54.7-62.6)	0.24
	CD4⁺ T_{CM}, %	20.9 (15.0-28.1)	16.7 (15.3-20.2)	0.25
	CD4⁺ T_{EM}, %	5.7 (4.0-7.5)	3.7 (3.3-4.0)	**0.044**
	CD4⁺ T_{Naive}, %	63.4(54.2-73.6)	73.6 (69.3-74.9)	**0.015**
CD8⁺ T cell subsets	CD8⁺ T cell frequency	39.7 (33.3-47.7)	31.8 (29.6-38.9)	0.37
	CD8⁺ T_{CM}, %	2.5 (1.7-4.1)	2.9 (2.2-3.3)	0.88
	CD8⁺ T_{EM}, %	6.8 (3.8-11.0)	4.6 (2.1-6.6)	0.14
	CD8⁺ T_{EMRA}, %	54.6(40.7-63.3)	70.9(57.6-77.4)	**0.005**
	CD8⁺ T_{Naive}, %	19.5(10.8-27.4)	9.6(6.8-12.9)	**0.002**

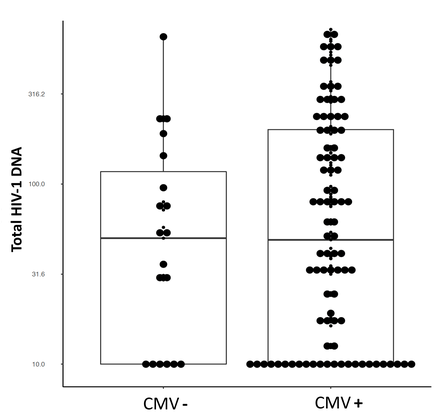
Objective #2: Determine the Impact of CMV co-infection on HIV reservoir size

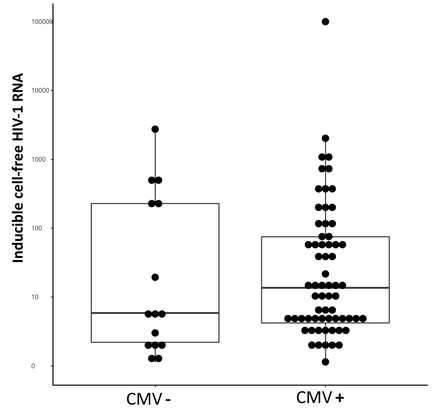
228 participants → 108 with inclusion criteria → 89 CMV seropositive at baseline (82%)

Characteristics	CMV seropositive (n=89)	CMV seronegative (n=19)	p
Female	43(48.3)	10 (52.6)	0.929
Median age (years) at reservoir collection	14.6	16.7	0.28
Median Age (years) at cART initiation	2.2	1.2	0.31
Duration (years) of SVS in years	7.2	6.2	0.51
Peak lifetime HIV viral load	87773	427000	**0.005**

Characteristics	CMV seropositive (n=89)	CMV seronegative (n=19)	P	Adjusted*
Total HIV-1 DNA Median log_{10} HIV DNA copies per 10^6 cells (IQR)	1.7 (1.04-2.31)	1.71 (1.04-2.07)	0.55	0.56
Inducible cell-free HIV-1 RNA Median log10 HIV RNA copies per 106 cells (IQR)	0.79 (0:1.72)	0.6 (0.36:1.8)	0.91	0.93

**Adjusted for age, age at treatment initiation, duration of SVS, and peak lifetime HIV viral load*





KEY POINTS: CMV CO-INFECTION AMONG CHILDREN LIVING WITH HIV IN CANADA

- **Was NOT** significantly associated with HIV reservoir size ,
- **WAS** associated with a change in the the naïve-memory-effector profile of CD4+ and CD8+ T cells, independent of achievement of SVS.
- **MAY** be contributing to in immune exhaustion and inflammation despite effective viral control

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