STRONG INTERFERON-GAMMA RESPONSES AND LIMITED HIV RESERVOIRS IN ADOLESCENT VIROLOGIC CONTROLLERS

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BACKGROUND

- The "Mississippi" baby and the outcomes post-treatment interruption in the Visconti cohort shed light on the potential benefit of early ART after primary HIV infection.
  - To limit reservoir size and possibly allow for viral control in the absence of ART
- The recently described "French teenager" represents another case of pediatric post-treatment control in a child treated with effective ART from 3 months of age). The patient maintained sustained virologic suppression for 11 years after treatment discontinuation at 6 years of age
  - She exhibited weak HIV-specific cell mediated immune (CMI) responses suggesting that factors other than CMI were contributing to her sustained immunologic control.
- The role of CMI in elite and post-treatment control is not well understood especially amongst perinatally infected infants, children, and adolescents.

OBJECTIVE

- To describe two perinatally infected adolescents with virologic control without ART – one who is a treatment naïve elite controller and the other a post-treatment controller

METHODS

- These adolescents participated in the *Early Pediatric Initiation – Canadian Child Cure Cohort (EPIC4).*
- Retrospective review was conducted of each participant's clinical course and antiretroviral treatment, as well as routine virologic and immunologic parameters monitored since diagnosis.
- The following study investigations were conducted:
  - HIV reservoir size was assessed using:
    - TILDA
    - qRT-PCR for total and integrated HIV DNA
  - CMI responses to HIV were assessed using pooled clade-matched HIV-1 Gag peptide panels in matrix format and IFN-g ELISpot and expressed as spot-forming units (SFU) per 10^6 PBMC.
  - HLA typing for protective alleles was determined.

CLINICAL HISTORY – CASE 1

- African-born female, came to Canada at age 7 years
- Diagnosed with HIV at age 10 years after mother's diagnosis
- Asymptomatic at the time of diagnosis
- Initial CD4 count 768 cells/µL (32%), viral load <50 copies/mL. HIV serology repeatedly positive. HIV DNA PCR positive.
- Family members' HIV confirmed Clade C (unable to test patient).
- Since diagnosis, only 2 detectable VLs of 71 copies/mL at age 12 years and 57 copies/mL at age 17 years.
- Now 17 years she remains asymptomatic with normal CD4 counts throughout.

CLINICAL HISTORY – CASE 2

- Canadian-born female of African descent.
- Diagnosed at age 11 months while still breastfeeding; viral load at diagnosis 128,400 copies/mL, clade D.
- Initial CD4 count 1170 cells/µL (14%); CD4 nadir 1170 cells/µL (18%).
- Fully suppressed viral load on cART from 2.3 to 12 years of age
- Self interrupted treatment at age 12 years (without notifying health care providers). Maintained viral load <50 copies/mL and normal CD4 cell counts (range 400-600 cells/µL) for 5 years.
- At 16.5 years of age viral load undetectable and proviral DNA 879 copies/10^6 PBMCs.
- ART commenced at age 17 years for a decrease in CD4 count to 326 cell/µL and viral load 51 copies/mL concomitant with an intercurrent illness. One month later, CD4 count had risen to 511 cells/µL and viral load was 50 copies/mL.
- Now 18 years, viral loads have been consistently detectable for past year, up to 300 copies/mL, with intermittent adherence to cART.

RESULTS

	Case 1	Case 2
Age at time of assessment	17 years	18 years
HLA typing	A*02–A*36; B*53–B*53; C*04–C*04	A*01–A*30; B*15–B*81; C*02–C*18
CCR-5 Δ32 status	Wild type	Wild type
Cell-associated total HIV DNA	470 copies/10^6 CD4+ T cells	1076 copies/10^6 CD4+ T cells
Cell-associated integrated DNA	102 copies/10^6 CD4+ T cells	564 copies/10^6 CD4+ T cells
TILDA	Detected 1.5 cells/10^6 CD4+ T cells	Detected 1.5 cells/10^6 CD4+ T cells
Plasma viremia ‡	168 copies/mL	294 copies/mL

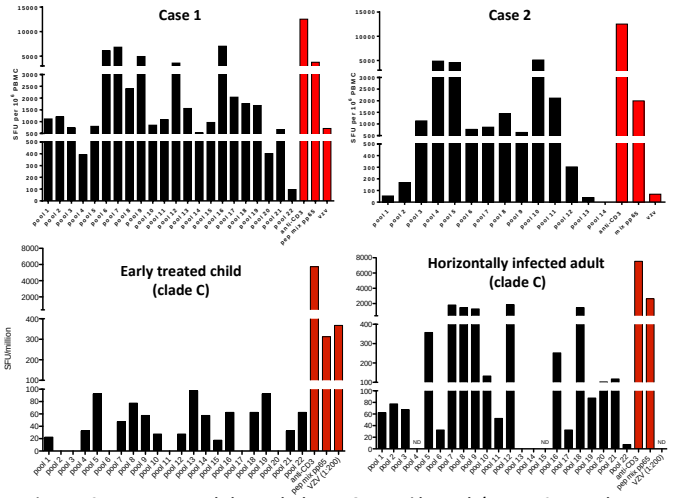


Figure 1: CMI responses to clade-matched HIV-1 Gag peptide panels (IFN-g ELISpot results, expressed as SFU/10^6 PBMCs) for Cases 1 & 2, a child treated from birth with sustained virologic suppression, and a pregnant woman with horizontal HIV infection. CMI for Cases 1 & 2 are in the top quartile compared to chronically infected children and adults.

CASE 1

- TILDA: 1.5 cells/10^6 CD4+ T cells
- HIV DNA: 479 and 102 copies/10^6 CD4+ T cells
- IFN-γ responses: 97-7032 SFU/10^6 PBMC; 22/22 peptide pools recognized.
- HLA: no genotypes predictive of elite control

CASE 2

- TILDA: 1.5 cells/10^6 CD4+ T cells
- HIV DNA: 1076 and 564 copies/10^6 CD4+ T cells
- IFN-γ responses: 0-5103 SFU/10^6 PBMC; 13/14 peptide pools recognized
- HLA: one protective haplotype identified (HLA-B*81)

SUMMARY & CONCLUSIONS

- Our findings contrast with the weak CMI responses recently reported for the "French teenager" post-treatment controller
  - Our subjects (one elite controller, one post-treatment controller) demonstrated HIV-specific CMI responses that were more robust and broad than those of pediatric or adult patients with ongoing viral suppression on cART.
- These results underscore the potential impact of enhanced CMI responses in virologic remission in perinatally infected youth and provide further evidence supporting inquiry into immunotherapeutic strategies such as vaccination in early treated perinatally infected children.