

In HIV-1-infected children CMV rather than HIV triggers the outgrowth of cytolytic CD8⁺CD45RA⁺CD27⁻ T cells.

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Introduction

- Cytolytic T lymphocytes (CTL) or CD8⁺ T cells are recognized as important cells to fight intracellular infections, such as viruses.
- In contrast to CD4⁺ T cells, no change in the number of CD8⁺ T cells is seen during treatment with HAART.
- CD8⁺ T cells can be divided into 4 different subsets: CD8⁺CD45RA⁺CD27⁻ naïve, CD8⁺CD45RA⁻CD27⁺ memory, CD8⁺CD45RA⁻CD27⁻ memory/effector and CD8⁺CD45RA⁺CD27⁻ effector T cells
- Little is known about the way CD8⁺ T cells mature after activation during primary infection or after establishing viral latency in children as seen during CMV infection.
- Cytomegalovirus (CMV) establishes a latent infection, characterized by reactivation.
- HIV-positive patients who are also CMV-seropositive were found to have a higher chance of having disease progression than patients who are CMV-seronegative, even in the era of HAART.
- In a healthy HIV-negative pediatric cohort an association between the outgrowth of CD8⁺CD45RA⁺CD27⁻ effector T cells and CMV was found.
- We studied the association between CMV-infection in HIV-1-infected children and immunophenotypic changes during HAART, the effect of CMV on the outgrowth of effector CD8⁺ T cells (i.e. CD45RA⁺CD27⁻) and their relation to CMV shedding in the urine.

Methods

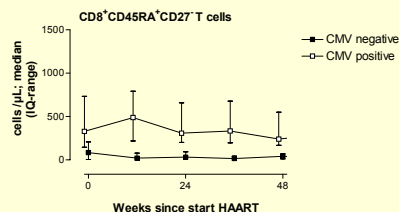
- Prospective observational cohort study.
- Patients included all children and young adolescents under the age of 18 with a proven HIV-1-infection routinely followed-up and treated with HAART at our institution between 1997 and 2002.
- Lymphocyte enumeration and subtyping was done using FACS-analyses.
- Urine culture of CMV was done prospectively in 25 CMV-positive children.
- CMV-specific CD4⁺ and CD8⁺ T cell IFN- γ production was measured after incubation of PBMCs with pp65 lysate and peptide pool respectively.
- A Mann-Whitney-U test was performed to analyze continuous data. Spearman's correlation was used for continuous data, a logistic regression model was built using the median of the group as cut-off for a binary variable.

1. Baseline characteristics of study patients at start HAART

Number of patients, n	52
Median age, years (range)	5.0 (0.8-17.9)
Race/ethnicity, n (white vs. non-white)	5/47
Sex, n (female/male)	29/23
Mode of transmission (vertically vs. sexually)	43/9
CDC-classification, n*	
Non C	29
C	23
Prior treatment	
None	37
Mono/Duotherapy	15
CD4 cell number (cells/ μ L), median (IQR)	480 (175-835)
CD8 cell number (cells/ μ L), median (IQR)	1230 (763-2203)
Plasma HIV-1 RNA, median log copies/mL (IQR)	4.95 (4.25-5.78)
CMV IgG (Number positive)	37

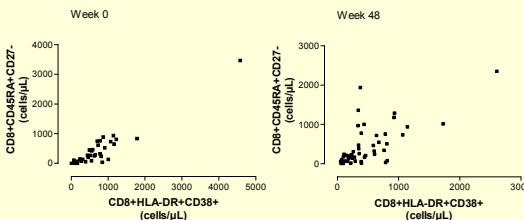
2. Independent of the plasma HIV-1 RNA and the response to HAART there was a higher CD8⁺CD45RA⁺CD27⁻ count in CMV seropositive than in seronegative children.

(Week 0, p=0.008; week 48, p<0.001)



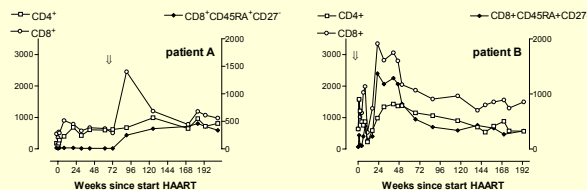
3. The expansion of CD8⁺ effector T cells is associated with chronic immune activation.

CD8⁺CD45RA⁺CD27⁻ effector T cells and activated (i.e. HLA-DR⁺CD38⁺) CD8⁺ T cells are correlated at baseline (r=0.82, p<0.001) and after 48 weeks (r=0.61, p<0.001).

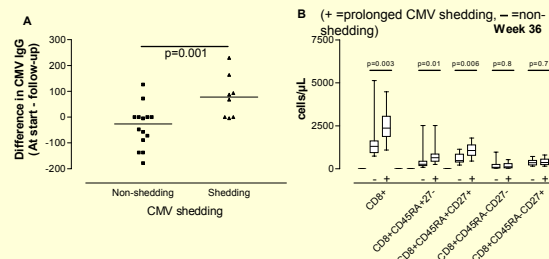


4. After seroconverting for CMV there is an increase in CD8⁺CD45RA⁺CD27⁻ T cells.

(\cup = seroconversion)



5. Prolonged urinary CMV secretion is associated with an increase in CMV-specific IgG and a higher number of CD8⁺CD45RA⁺CD27⁻ T cells.

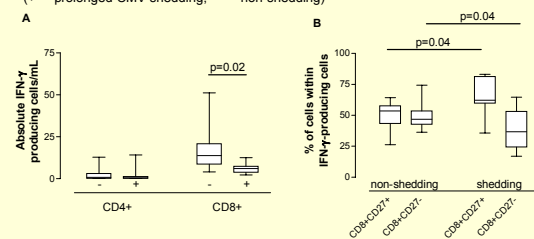


6. Adjusted for age CMV secretion gave a higher risk of having more than the median number (421 cells/ μ L) of CD8⁺CD45RA⁺CD27⁻ T cells at week 36 (OR 7.9; p=0.04).

In contrast to CD8⁺ effector T cells, high naïve CD8⁺ T cells were independently associated with younger age. The same association was found for the total (p=0.03), naïve (p=0.04) and memory (p=0.04) CD4⁺ T cells at 36 weeks.

7. CMV specific CD8⁺ T cell responses are lower and less differentiated in children with prolonged CMV secretion, in contrast to CD4⁺ T cell responses.

(+ = prolonged CMV shedding, - = non-shedding)



Conclusions

- CMV correlates with an outgrowth of CD8⁺CD45RA⁺CD27⁻ cytolytic T cells in HIV-1-infected children.
- Shedding of CMV is associated with an increase in CMV specific IgG and increased numbers of CD8⁺CD45RA⁺CD27⁻ cytolytic T cells.
- Frequencies of CMV-specific IFN- γ -producing CD8⁺ T cells were lower in children with CMV shedding, while CD4⁺ T cell responses were equally present.
- These data demonstrate that in HIV-1-infected children, apart from the effects of HIV itself, ongoing CMV replication may contribute to chronic alteration of the immune system.