Early CMV and EBV Acquisition Predict HIV DNA Levels in Infants on Suppressive ART

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Background

- Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infect nearly all Kenyan HIV-infected infants in the first two years of life.
- Both viruses are poorly contained during primary infection in HIV-infected infants.
- A small number of reports suggest CMV[1,2] and EBV[1] viremia in blood may be associated with higher levels of HIV DNA in blood following HIV RNA suppression on antiretroviral therapy (ART).
- If CMV and/or EBV contribute to HIV DNA levels post-ART, antiviral suppression of these viruses may limit HIV reservoir formation.

Hypothesis

CMV viral load → + Activated CD4+ T cells → + HIV DNA levels

- Systemic CMV replication increases frequencies of activated T cells during acute HIV/CMV co-infection, creating more activated CD4+ T cells which are the primary target cell for HIV.
- Children who have higher CMV viremia and more activated CD4+ T cells may also have higher HIV DNA reservoirs following effective suppression on ART.
- EBV may be related to HIV DNA levels in a similar way. EBV activates CD4+ T cells (to a smaller extent than CMV) and B cells.

Specific Aims

In a cohort of infants with early ART initiation, who suppressed HIV RNA by 18 months post-ART, our aims are:

Aim 1: To compare HIV DNA levels at 24 months between children with early versus later CMV and EBV acquisition.

Aim 2: To assess the association between cumulative CMV and EBV replication and HIV DNA levels at 24 months post ART.

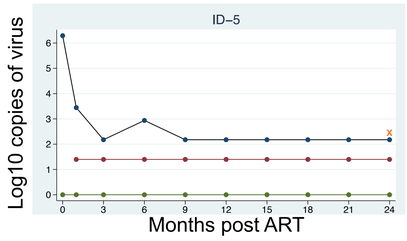
Methods & Study Cohort

- Optimizing Pediatric HIV Treatment (OPH) Cohort[3] (NCT00428116)
- 140 HIV infected children enrolled in Nairobi, Kenya
- Early empiric ART initiation, before 12 months of age
- Followed from 2007-present
- Subset presented here began ART <6 months of age and had HIV RNA suppression to <100 copies/ml by 18 months post-ART (n=23)
- Quantitative PCR of CMV and EBV viral loads in plasma at 3 monthly intervals
- Serology to confirm infection status in those with no CMV, EBV DNA
- ddPCR for HIV DNA from PBMC, HIVpol (LOD 5copies/10^6 cells)
- AUC (area-under-the-curve) calculated for CMV and EBV viral load over first 21 months of ART, simple imputation for missing values

Population Characteristics	n (%), mean (SD) or median (IQR)
Number of infants	23*
Median age in months at enrollment	3.8 (3.0-4.2)
Median age in months at ART initiation	4.4 (3.6-4.8)
Mean log_{10} HIV ca-DNA copies/10^6 PBMC[4]	2.4 (±0.44)
CMV infected by 2 years	21 (91%)
Peak log_{10} CMV DNA copies/ml in plasma	4.4 (±0.93)
EBV infected by 2 years	21 (91%)
Peak log_{10} EBV DNA copies/ml in plasma	2.5 (±0.63)
EBV negative and CMV negative	1 (4.3%)

**27 more infants are in the testing pipeline for testing, who started ART between 6-12 months of age.*

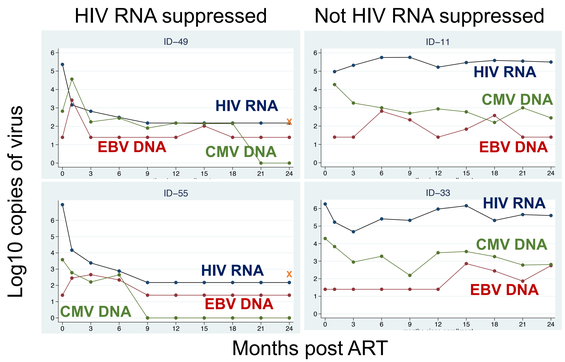
Single EBV and CMV Uninfected Infant



**LOD=limit of detection, CMV LOD shown at zero to discriminate from EBV line*

X HIV DNA LOD 5 c/10^6 cells
HIV RNA LOD 100 c/ml
EBV DNA LOD 50 c/ml
CMV DNA LOD 50 c/ml

CMV and EBV Containment



- Infants who suppressed HIV rapidly also had good control over CMV and EBV
- Infants who remained HIV RNA viremic had poor containment of CMV and EBV

Correlates of HIV DNA Levels

	Unadjusted		Adjusted for Age at ART initiation	
	Coefficient [95%CI]	P value	Coefficient [95%CI]	P
Age at ART initiation*	0.17 [-0.040, 0.38]	0.1	(not shown)	
Baseline log_{10} HIV RNA	0.037 [-0.23, 0.30]	0.8		
Pre- ART CD4 percent	-0.0075 [-0.032, 0.017]	0.5		
CMV infected at enrollment	**0.56 [0.13, 1.0]**	**0.01**	**0.52 [0.092, 0.95]**	**0.02**
CMV DNA AUC	0.000034 [-0.00031, 0.00038]	0.8		
Months of EBV infection**	**0.023 [0.0046-0.042]**	**0.02**	**0.022 [0.0039, 0.040]**	**0.02**
Log_{10} EBV DNA AUC	**5.5 [1.7-9.3]**	**0.006**	**5.0 [1.19, 8.8]**	**0.01**

**While age at ART initiation did not reach significance in this subset of 23 infants, it was a significant predictor of HIV DNA level in the overall cohort of 50 HIV RNA suppressed children.*

***To include EBV-negatives, duration of EBV infection was calculated as [24 months]-[age EBV first detected]*

Conclusions, Interpretation & Next Steps

- Acquisition of CMV or EBV at <6 months of age, or poorly contained EBV was associated with higher HIV DNA levels after HIV suppression.
- Poor containment of CMV or EBV when starting ART during acute HIV infection may have implications for HIV reservoir formation.
- 27 more infants are in the pipeline, who started ART at 6-12 months.

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[1]Gianella, J Virology 2016; [2]Payne, CROI 2015; [3]Wamalwa AIDS 2016; [4]Pankau, Open Forum Infect Dis. 2017

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