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Detectable CMV in PBMC is Associated with Slower HIV DNA Decay during Suppressive ART

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Background

- Asymptomatic CMV replication in the setting of HIV infection is associated with increased immune activation, T cell proliferation and HIV disease progression.
- A previous cross-sectional study demonstrated an association between asymptomatic CMV replication and higher levels of CD4-associated HIV DNA in blood. (Gianella et al. JVI 2014).

Objective

To determine if persistent CMV replication influences HIV DNA dynamics longitudinally after initiation of antiretroviral therapy (ART) during early HIV infection.

Methods

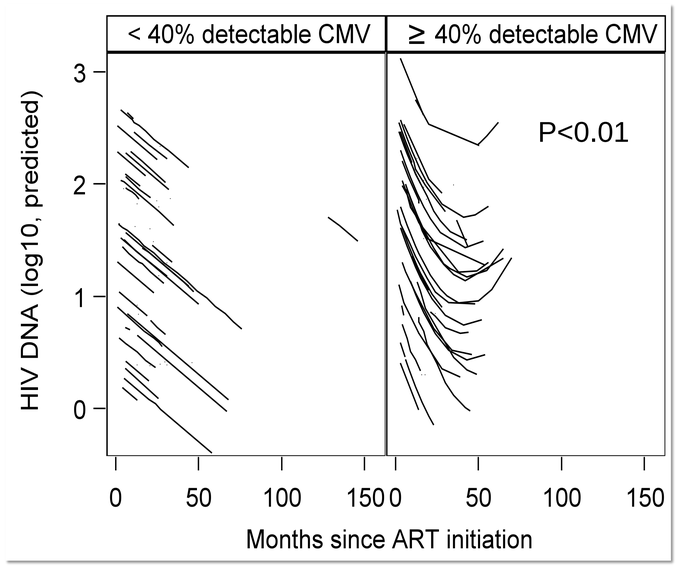
- We investigated 397 peripheral blood mononuclear cell (PBMC) samples collected longitudinally from 96 CMV-seropositive, HIV-infected men who started ART during early infection (**table 1**).
- Levels of CD4-associated HIV DNA and CMV DNA were measured by droplet digital PCR for each time-point (median 3 time-points/participant).
- Using a general linear mixed-effect regression model, we evaluated associations between HIV DNA decay and frequency of detectable CMV, age, nadir CD4 count, peak HIV RNA level, time from EDI to ART start, and time from ART start to virologic suppression.

Table 1: Baseline characteristics were comparable

Characteristic	Total (N=96)	Median (IQR) < 40% detectable CMV (N=48)	≥ 40% detectable CMV (N=48)
Months from HIV infection to ART start	3 (2 – 7)	3 (1 – 11)	3 (3 – 5.5)
Months from ART start to viral suppression	6 (4 – 9)	6 (4 – 10)	6 (4 – 9)
Months of follow-up	11.5 (0 – 31.5)	9.5 (0 – 24.5)	13.5 (0 – 43.5)
Median number of follow-up time points	3 (1 – 6)	3 (1 – 5)	4.5 (1 – 8)
Baseline CD4 T-cell (count/µl)	488 (345 – 595)	520 (329 – 604)	460 (357 – 589)
Peak $\log_{10}$ HIV RNA (copies/ml)	5.7 (5.1 – 6.5)	5.7 (5.1 – 6.5)	5.7 (5.1 – 6.5)

Groups were divided using the median frequency of CMV detection (40%). This is an interim analysis, measurements on additional longitudinal time-points are in progress.

Figure 1: Different HIV DNA decay dynamics depending on frequency of CMV (> or < 40% detectable shedding)



Legend: A linear model fit HIV DNA decay kinetics significantly better in the group of participants with infrequent CMV in PBMC (left panel), while HIV DNA clearance was quadratic (U-shaped) in participants with a higher frequency of detectable CMV DNA (right panel) (p<0.01).

Results

- Higher peak HIV RNA levels and higher frequency of detectable CMV in PBMC (>40% of sampled time-points) were associated with increased levels of HIV DNA during ART (p<0.01).
- Both factors were independently associated with higher HIV DNA in multivariable analysis (p<0.01). No other variable contributed significantly.
- The pattern of HIV DNA decay during ART also differed significantly between participants with higher versus lower frequency of detectable CMV in PBMC (> vs < 40% of samples, p<0.01; see **figure**).

Conclusions

- **Detectable CMV DNA in PBMC was longitudinally associated with higher HIV DNA levels, even among individuals who started ART early during HIV infection, suggesting that CMV replication may help maintain the stability of the HIV DNA reservoir.**
- **Future studies with anti-CMV therapeutics could help determine underlying mechanisms and if causal associations exist.**

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