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Subclinical CMV and EBV DNA and Non-AIDS Events during Antiretroviral Therapy-mediated Viral Suppression.

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Background

Despite antiretroviral therapy (ART), HIV infection remains associated with higher morbidity/mortality, linked to increased inflammation.

Objective

To explore associations between Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) in peripheral blood cells with occurrence of non-AIDS events and mortality during ART.

Cohort and Sampling

445 participants (140 cases who experienced non-AIDS events, 305 matched controls, 929 samples total).

- ART naive when enrolled into an ACTG clinical trial.
- Plasma HIV-1 RNA load <400 copies/mL at week 48 after ART initiation and thereafter.

Cases: Individuals who died from a non-accidental non–AIDS-related event, or had a myocardial infarction (MI), stroke, non–AIDS-defining malignancy or serious bacterial infection subsequent to week 48 (median of 2.9 years post ART start).

Controls: For each case, we identified 2 or 3 controls who had an endpoint-free follow-up time equal or greater than that of the case and were matched by:

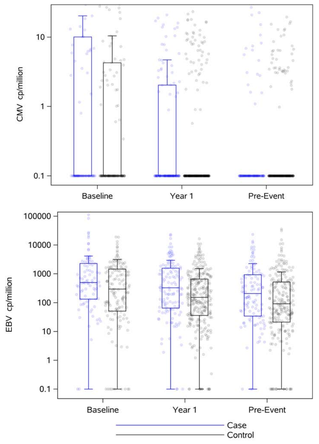
- Age (within 10 years; median 45 years).
- Sex (84% male).
- Baseline CD4+ T cell count (within 50 cells/mm^3; median 219 cells/mm^3).
- ART regimen at week 48 (whether it contained a protease inhibitor or abacavir)
- ACTG parent study.

Data Generated and Statistical Analysis

- Levels of CMV and EBV DNA were measured in PBMC by droplet digital PCR.
- Levels of CMV and EBV IgG were measured at year 1 in plasma by ELISA.[1]
- Other cellular and soluble biomarkers were obtained from previous projects.[2,3]
- Conditional logistic regression analysis assessed associations of CMV and EBV DNA with events, adjusted for relevant covariates. Correlation between biomarker levels were assessed with Spearman's correlations among controls.

Results

Figure 1. CMV DNA was detected in PBMC in 25% of participants, while EBV DNA was detected in >90%.



Legend. Levels of CMV and EBV DNA per million of mononuclear cells at each time-point (baseline, year 1 and pre-event) for cases (in blue) and controls (black). Bars show medians and interquartile ranges.

Figure 2. Higher levels of EBV DNA at all time points were associated with increased risk of events.

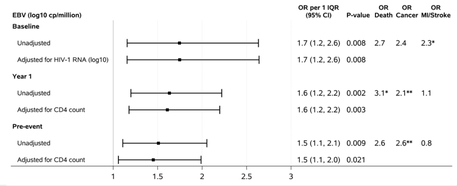
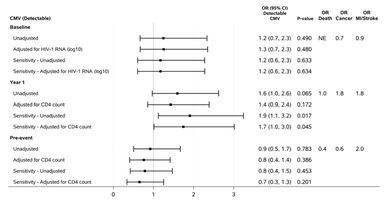
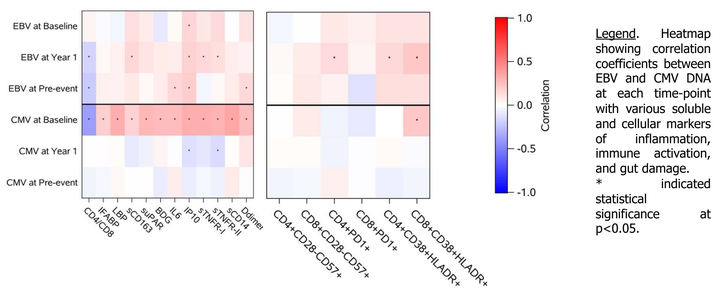


Figure 3. At year 1, having detectable CMV DNA was associated with increased risk of events.



Legend. Figure shows unadjusted analysis and analysis adjusted for HIV RNA ($\log_{10}$) at baseline and for CD4 count at year 1 and pre-event (where CD4 count adjustment includes quadratic and cubic terms). Sensitivity analyses excluded negative CMV DNA results from samples with low cell yield * indicated statistical significance at p<0.05 while ** indicated p<0.01.

Figure 4. Levels of CMV DNA were correlated with all soluble markers at baseline. Levels of EBV DNA were correlated with some biomarkers at multiple time points.



Legend. Heatmap showing correlation coefficients between EBV and CMV DNA at each time-point with various soluble and cellular markers of inflammation, immune activation, and gut damage.
* indicated statistical significance at p<0.05.

CMV and EBV DNA levels were correlated only at the pre-event time point (r=0.18, p<0.0001), (Not shown).
Levels of EBV DNA were associated with EBV IgG (r=0.37, p<0.0001), while CMV DNA levels were not associated with CMV IgG (Not shown)

Conclusions

➢ **Clinical trials of anti-viral therapy or vaccines may help to understand how EBV and CMV DNA might influence non-AIDS events.**

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Reference. 1. Hodowanec, Pathogen and Immunity, 2019, In press **2.** Tenorio et al JID, PMID: 24795473 **3.** Hoenigl M, CID, 2018, PMID: 30418519