Poster 602

LATENT VIRAL INFECTIONS ARE ASSOCIATED WITH VETERANS AGING COHORT STUDY INDEX IN PEOPLE WITH HIV (PWH)

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BACKGROUND

- CMV and EBV contribute to persistent inflammation, comorbidities, and expansion of the HIV reservoir in PWH.
- Unclear if direct viral effects and/or immune response
- Better understanding the role of latent herpesvirus in the elevated mortality and morbidity risk for PWH on ART may lead to therapeutic interventions
- **Aim: Determine relationships among quantitative viral cell associated DNA (ca-DNA), IgG, and VACS index**

METHODS

- Participants and study design. Cross-sectional analysis of 485 virally suppressed PWH (HIV RNA<200 copies/mL).
- Quantitative viral measures. Plasma EBV VCA IgG and CMV IgG were measured by ELISA (n=461). Digital droplet PCR quantified cellular CMV, EBV, and HIV GAG DNA in PBMCs (n=485) per 10^6 cells. Total globulins calculated (plasma total protein – albumin).
- VACS Mortality Index v1.0 is a validated mortality risk score associated with many other adverse clinical outcomes in PWH. VACS includes: age, CD4+, HIV RNA, hemoglobin, FIB-4 index, eGFR, HCV coinfection.
- Statistical Analysis. Relationships between viral DNA, IgG, and VACS tested with linear regression. All model estimates were adjusted for sex, race, ethnicity, estimated duration of HIV infection (EDI), and AIDS diagnosis.

RESULTS: COHORT CHARACTERISTICS

Table 1: Cohort		n=485	Table 2: Viral Measures	
Age		54 [47,60]	CMV IgG+ (n=461)	445 (97%)
Sex (female)		84 (17%)	CMV IgG (IU/ml)	38 [29,44]
Race	White	283 (59%)	CMV DNA +	230 (48%)
	Black	144 (30%)	CMV DNA/10^6cell	0 [0.0,5.3]
Hispanic		89 (18%)	EBV IgG+ (n=461)	461 (100%)
HCV+		344 (71%)	EBV IgG (U/mL)	835 [387,1710]
EDI (years)		20 [14,26]	EBV DNA +	460 (96%)
Current CD4+		615 [432,825]	EBV DNA/10^6cell	102 [27,605]
CD4+ Nadir		159 [36,300]	HIV DNA +	481 (99%)
AIDS diagnosis		320 (66%)	HIV DNA/10^6cell	186 [82,343]

Mortality risk (VACS index) in PWH is associated with higher CMV IgG levels but not EBV IgG, total globulins, or cell associated viral DNA (CMV, EBV, or HIV) in PBMCs

RESULTS: PRIMARY OUTCOMES

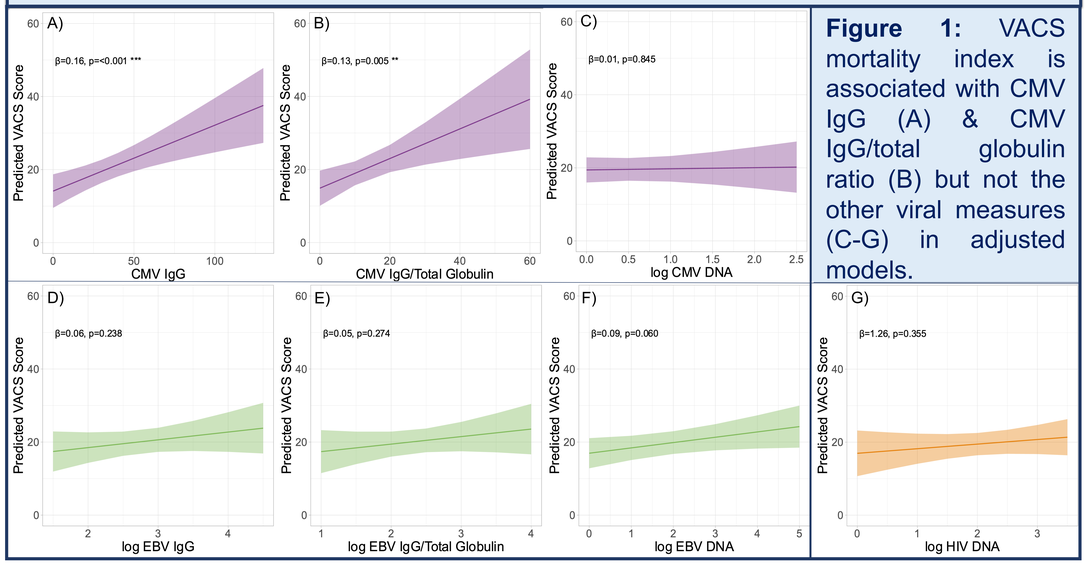
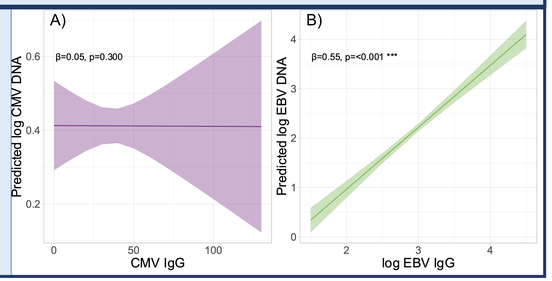


Figure 1: VACS mortality index is associated with CMV IgG (A) & CMV IgG/total globulin ratio (B) but not the other viral measures (C-G) in adjusted models.

RESULTS: SECONDARY OUTCOMES

Figure 2: CMV and EBV have very different relationships between quantitative viral ca-DNA in PBMCs and IgG levels:
2A) CMV ca-DNA in PBMCs is not associated with CMV IgG levels (same in subgroup with detectable CMV ca-DNA)
2B) EBV ca-DNA is strongly associated with EBV IgG levels



CONCLUSIONS

- Individual host immune responses to CMV may be an important predictor of adverse clinical outcomes in PWH.
- The association between CMV IgG and VACS was CMV – specific, rather than nonspecific hypergammaglobulinemia:
  - Remained significant when CMV IgG adjusted for total globulins
  - Not seen with EBV or total globulin levels.
- CMV ca-DNA was not associated with either VACS or CMV IgG. This may be because:
  - Ca-DNA in PBMCs may not reflect CMV activity as the majority of the CMV reservoir is in the tissues **and/or**
  - Immune dysregulation triggered by CMV may reflect host factors beyond the size of CMV reservoir.
- In this study, EBV (IgG and DNA) and HIV DNA were not associated with the VACS index in adjusted analyses but additional investigation with other clinical outcomes is still warranted.

FUTURE DIRECTIONS

- Longitudinal studies with clinical outcome measures to assess:
  - If CMV IgG titer is an independent predictor of adverse outcomes
  - Causality
- Broader investigation of CMV specific immune response
- Measures of CMV, EBV and HIV cell associated DNA and antigen production in tissues (not PBMCs)
- Deeper characterization of these host and viral features are needed to identify:
  - Potential therapeutic targets
  - The individuals most likely to benefit from treatment

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