Cell-Mediated Cytomegalovirus Response in HIV-Infected Persons with Impaired Physical Function

KM Erlandson. AA Allshouse. R Rapaport. BE Palmer. CC Wilson. S MaWhinney. TB Campbell.

University of Colorado; Aurora, CO, USA

Contact: Kristine.Erlandson@ucdenver.edu

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ABSTRACT

Background: Immune responses to human cytomegalovirus (CMV) increase with age and HIV-infection and correlate with cardiovascular disease markers. We previously demonstrated greater odds of functional impairment among HIV-infected persons with higher CMV IgG concentrations, immune activation (%CD38HLA-DR on CD8+ T cells) and inflammation (IL-6, TNF-alpha). Here we evaluated the hypothesis that cell-mediated CMV responses were associated with functional impairment and inflammation/activation in persons aging with HIV infection.

Methods: Case-control study of 45-65 year-old HIV-infected subjects, on antiretroviral therapy >6 months, plasma HIV-1 RNA <48 c/mL. Low function (LF) cases and high function (HF) controls were identified by clinical criteria, and matched by age, gender, and time since HIV diagnosis. CMV-specific T cell responses were determined by the proportion of CD4+ and CD8+ T cells expressing IFN-γ after stimulation with CMV pp65 peptides and described using geometric mean and 95% confidence intervals (CI). Odds of LF was estimated by conditional logistic regression. Associations between continuous variables were described by Spearman correlation.

Results: 30 LF cases were matched to 48 HF controls; mean (SE) age 53 ± 0.8 years; 21% female; 76% Caucasian and 17% Hispanic. Compared to controls cases had similar current CD4 (549 ± 49 vs 639 ± 40 cells/μL, p=0.16), lower nadir CD4 (110 ± 27 vs 178 ± 22 cells/μL, p=0.04) and greater smoking prevalence (48% vs 20%, p=0.01). As previously reported, higher CMV IgG was associated with a 5-fold greater odds of LF (CI 1.5, 17.0) per $\log_{10}$ increase in CMV IgG (p=0.01) and was correlated with markers of inflammation: IL-6 (r=0.37, p<0.001), hs-CRP (r=0.29, p=0.01), TNF-alpha (r=0.24, 0.04); activation: %CD38+HLA-DR+ CD8+ T cells (r=0.21, p=0.07); and immune senescence: %CD28-CD8+ T cells (r=0.27, p=0.02). Odds of LF were not significantly different by CMV-specific CD8+ T cells (1.08; 0.92, 1.28; p=0.35) or CD4+ T cells (OR 0.99; CI 0.76, 1.29; p=0.95). Correlation was detected between CMV IgG and CMV-specific CD8+ T cells (r=0.30, p=0.007) but not CMV-specific CD4+ T cells (r=0.17, p=0.15). CMV-specific CD8+ T cells were not correlated with inflammation, activation, or senescence markers; all r≤|0.12|, p≥0.31. CMV-specific CD4+ T cells were correlated with CD28-CD4+ T cells (r=0.37, p<0.001), but not inflammation or activation markers; all r≤|0.11|, p≥0.36.

Conclusions: Cell-mediated immune response to CMV was not a significant predictor of low physical function and was not associated with inflammation/activation among HIV-infected adults on effective ART. CMV-specific humoral responses are more strongly correlated with functional impairment and related inflammation, activation and senescence.

BACKGROUND

- Cytomegalovirus is a nearly ubiquitous virus that establishes life-long, typically asymptomatic infection.
- *Among elderly HIV-uninfected persons*:
  - Reactivations of CMV lead to clonal expansion of CMV-specific T-cells, thought to contribute to “inflammaging” and immunosenescence
  - CMV IgG has been associated with mortality, frailty, and neurocognitive pathology
- *Among HIV-infected persons*, CMV is frequently implicated as a contributing factor to the inflammation and immune activation underlying complications of aging (i.e., cardiovascular disease).
- We have previously shown a strong association between markers of inflammation or immune activation and physical function impairment (a complication of aging) in HIV-infected older adults.

- **We hypothesized that the % CMV-specific CD8+ T-cells would be associated with physical function impairment, through increases in inflammation and immune activation.**

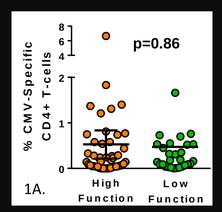
METHODS

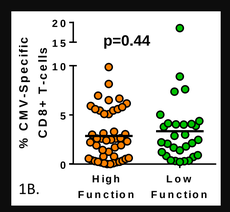
- Nested case-control analysis of HIV-1 infected subjects aged 45-65 years, on effective combination ART ≥ 6 months, at least 1 plasma HIV-1 RNA below the limits of detection.
- Low and high functioning subjects were identified by combined deficits on the Short Physical Performance Battery, a 400-m walk and the Frailty Phenotype.
- High function controls were matched to low function cases by age, gender, and estimated duration of HIV diagnosis.
- Plasma CMV IgG concentration was quantified by enzyme-linked immunosorbent assay; senescence and activation markers were measured by flow cytometry; serum IL-6 and TNF-alpha by ELISA and hs-CRP by immunoturbidimetrics
- CMV-specific T cell responses were determined by the proportion of CD4+ and CD8+ T cells expressing IFN-γ after stimulation with a CMV pp65 peptide pool and described using geometric mean and 95% confidence intervals (CI).
- Odds of being low function were estimated by conditional logistic regression.
- Group means were compared using mixed-effects regression. Relationships between log-transformed CMV IgG or % CMV-specific T-cells and markers of immune activation, inflammation and senescence were described by Spearman correlation (with cases and controls combined).

RESULTS

Table 1. Characteristics of study population by low and high function

Characteristic	Low Function N=30	High Function N=48	*P value*
Age (years)	52.8 (0.8)	52.9 (0.7)	*0.94*
Gender (female)	8 (27)	10 (21)	*0.56*
Caucasian	22 (73)	37 (77)	*0.71*
Hispanic	7 (23)	6 (13)	*0.22*
Current tobacco use	15 (50)	10 (21)	*0.009*
Current CD4 count (cells/μL)	562 (54)	647 (37)	*0.18*
Nadir CD4 count (cells/μL)	111 (23)	181 (24)	*0.05*
Detectable HIV-1 RNA	1 (3)	2 (4)	*0.85*
Time since HIV diagnosis (years)	15.1 (1.5)	15.8 (1.1)	*0.68*

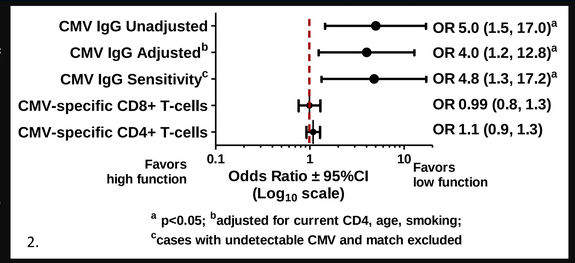




Figures 1A & B. Mean % CMV-Specific CD4+ (A) and CD8+ (B) T-cells in high and low function groups

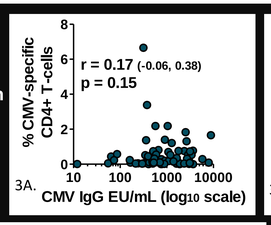
RESULTS

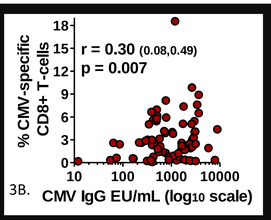
Odds of Being Low Function per 1 $\log_{10}$ in CMV IgG or 0.1% increase in % IFN-γ CMV-Specific T-cells



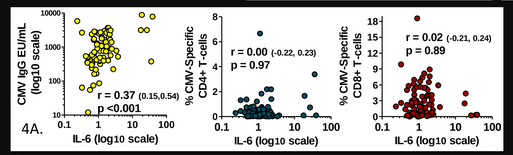
[a] p<0.05; [b]adjusted for current CD4, age, smoking; [c]cases with undetectable CMV and match excluded

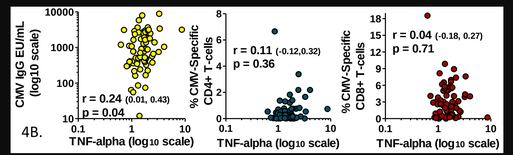
Figure 2. The odds of being low function increased 5-fold per log increase in plasma CMV IgG, but was not associated with an increase in CMV-specific CD4+ or CD8+ T-cells.

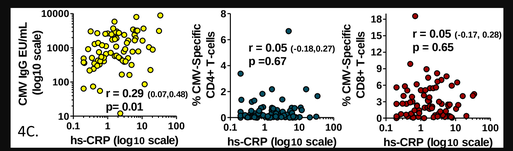




Figures 3A and 3B. Plasma CMV IgG was moderately correlated with % CMV-specific CD8+ T-cells but not % CMV-specific CD4+ T-cells.

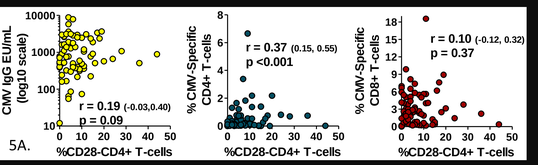


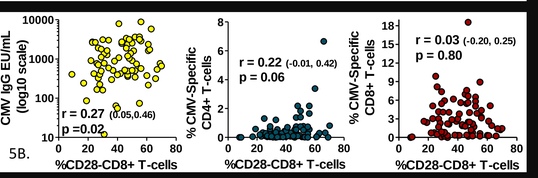


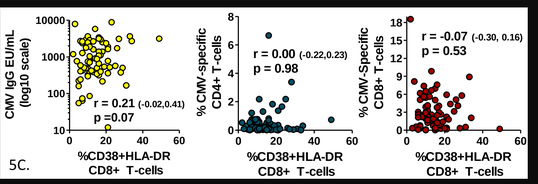


Figures 4A, 4B, and 4C. Serum/plasma markers of inflammation (IL-6, TNF-alpha, and hs-CRP) were moderately correlated with plasma CMV IgG but not % CMV-specific CD4+ or CD8+ T-cells.

Figures 5A, 5B, and 5C. Markers of immune senescence were weakly to moderately correlated with plasma CMV IgG and % CMV-specific CD4+ T-cells, but not % CMV-specific CD8+ T-cells. Activation was not significantly correlated with any CMV markers.







CONCLUSIONS

- **Cell-mediated immune response to CMV was not a significant predictor of low physical function and was not associated with inflammation/activation among HIV-infected adults on effective ART.**
- **CMV-specific humoral responses were more strongly correlated with functional impairment and related inflammation, activation and senescence.**
- **Whether CMV infection *leads* to physical function impairment, or is just associated with another covariate that causes physical function impairment cannot be determined from this study.**
- **Future studies should:**
- **1) evaluate the ability of plasma CMV IgG to predict subsequent physical function impairment**
- **2) Determine whether an intervention to prevent CMV or limit reactivations would prevent subsequent physical function impairment**