Longitudinal Association of Systematic Inflammation with Frailty in HIV-infected Men

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BACKGROUND

- HIV-infected (HIV+) people have higher risk of age-related diseases and syndromes, including frailty, than similar HIV-uninfected (HIV-) people(reviewed in [1,2])
- Frailty, a state of increased vulnerability to stressors, predicts adverse outcomes, such as disability and death[3–5]
- Chronic inflammation, which has been associated with HIV infection[6], may lead to frailty[7]
- Cytomegalovirus (CMV) infection and/or T cell responses to it may drive chronic inflammation[8–12]
- T cell responses to CMV may also reduce inflammation by controlling CMV reactivation[11,13]
- Inflammatory mediators may increase or decrease CMV reactivation:
  - increase: IL-6 [14,15], IL-8[16,17], MCP-1[18], and Eotaxin-3[19]
  - decrease: MIP-1α[18,20], TARC, IFN-γ, TNF-α, IL-10, and IL-12
- %CMV-specific CD4 T cells producing IFN-γ only (single-producers, SP) predicted onset of frailty; positively in HIV-, but negatively in HIV+[21]
- Therefore, we explored the relationship between systematic inflammation, CMV-specific T cell responses, and onset of frailty inHIV- and HIV+ men, accounting for the opposing effect of inflammatory markers and T cell responses

METHODS

- **Study Population**: 21 men (11 virologically suppressed HIV+, 10 HIV−) followed semiannually in the Baltimore-DC center of Multicenter AIDS Cohort Study[11]
- **Frailty**: assessed by Fried frailty phenotype (FFP) at each study visit[11]. Baseline nonfrailty was defined as absence of FFP at two consecutive visits[3]
- **Inflammatory markers**:
  - Serum concentrations of inflammatory markers were measured by multiplex electrochemiluminescence
  - Z-scores* for each marker for each individual were generated from distributions of log-transformed concentrations[22]
  - Inflammatory markers were divided into two categories: promote (a) or reduce (b) CMV reactivation.
  - Composite inflammatory score (CIS) for each person: sum of the z-scores for category subtracts the sum of z-scores for category b.
- **Polyfunctional T cells**: Production of IFN-γ, TNF-α, and/or IL-2 by T cells in response to peptide pools spanning 19 CMV open reading frames was assessed by intracellular cytokine staining flow cytometry at baseline [11]
- **Follow-up**: a median of 6.5 years (IQR: 1.5) after baseline
- **Statistical Analysis**: Mann-Whitney U Test, Kaplan-Meier estimators, exact log-rank test, and Spearman's correlation coefficients

* z-score= $\frac{(\text{concentration}^{l}\text{-mean of the concentration})}{\text{standard deviation of the concentration}}$ [l] log-transformed

A *composite inflammatory score* accounting for the opposing effects of cytokines and chemokines related to CMV reactivation and to T cell functions predicted onset of frailty in *HIV*+ but not HIV- men

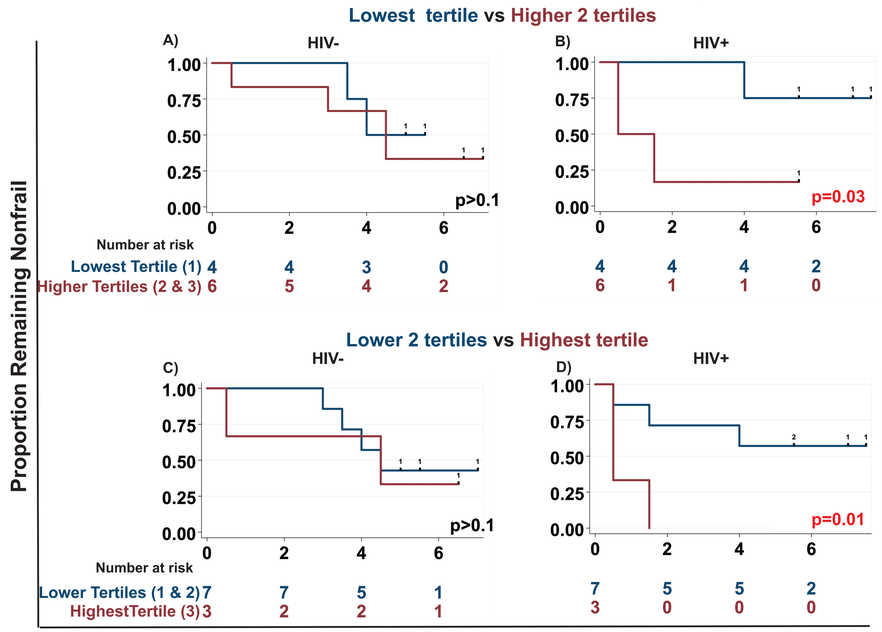
RESULTS

Table 1. Serum Concentrations of Cytokines and Chemokines in the Study Population, Stratified by HIV Status

Variable	Total	HIV Status	
	n=21	HIV- (n=10)	HIV+ (n=11)
Chemokines			
IL-8	10.4(7.6)[a]	10.9(6.6)	10.4(10.3)
Eotaxin-3	19.2(29.0)	26.2(36.8)	0(22.7)
MCP-1	293.8(113.0)	310.7(93.1)	276.5(144.3)
MIP-1α	0(19.5)	0(19.5)	0(19.5)
TARC	511.5(257.3)	504.6(209.1)	511.5(499.6)
Cytokines			
IFN-γ	4.6(2.9)	4.9(3.5)	4(2.9)
TNF-α	2.4(0.6)	2.2(1.1)	2.6(0.8)
IL-6	0.6(0.6)	0.7(0.6)	0.6(0.9)
IL-10	0.1(0.3)	0.2(0.3)	0(0.3)
IL-12	0(0.2)	0(0.2)	0(0.0)

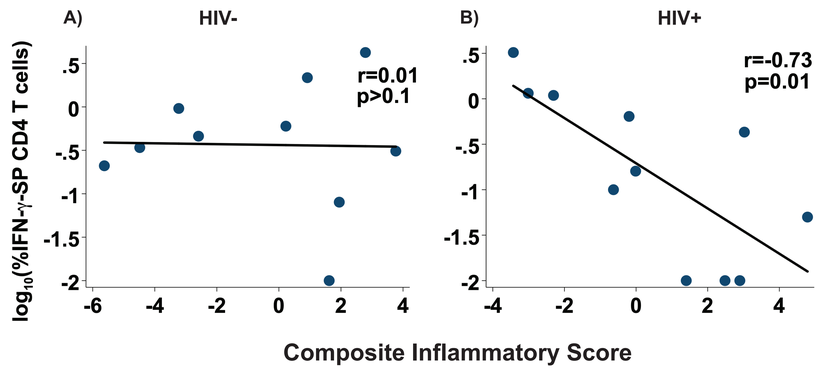
[a] Median (Interquartile range) in pg/mL

Fig. 1. A Higher Composite Inflammatory Score (CIS)* Predicted Onset of Frailty in HIV+, but not HIV-, men



*CIS=(z-IL-8[l] + z-IL-6 + z-Eotaxin-3 + z-MCP-1)-
(z-MIP-1α + z-TARC + z-IFN-γ + z-TNF-α + z-IL-10 + z-IL-12) [l]z-score for IL-8

Fig. 2. %(CMV-Specific-IFN-γ⁺-Single-producing (SP)) CD4 T Cells Were Negatively Correlated with CIS in HIV+, but not HIV-, Men



CONCLUSIONS

- Concentrations of the cytokines and chemokines studied did not differ significantly by HIV status
- Becoming frail in HIV+ men was predicted by a **higher** CIS, which accounted for the opposing effects of cytokines and chemokines related to CMV reactivation and to T cell functions
- Percentages of CMV-specific-IFN-γ-SP CD4 T cells, which were previously shown to predict onset of frailty negatively in HIV+ men[14], were **negatively correlated** with the CIS in these men
- These data suggest that CMV-specific T cell responses, including IFN-γ-SP CD4 T cells, are important for controlling CMV-induced inflammation and onset of frailty in HIV+ men

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