Association of Polyfunctional CMV-specific T Cells with Frailty in HIV-infected and -uninfected Men

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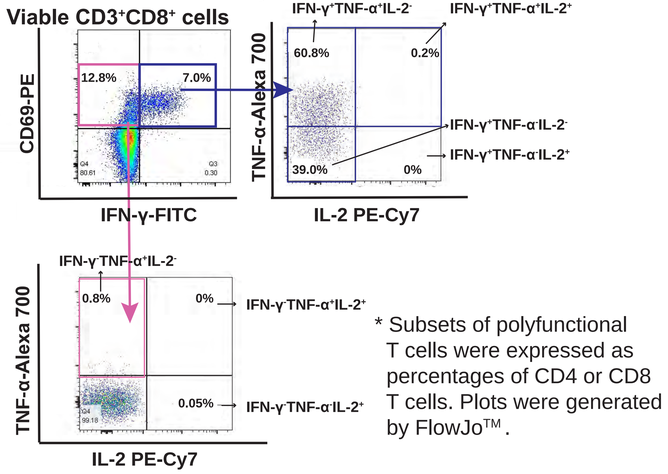
BACKGROUND

- HIV-infected people have higher risk of age-related diseases and syndromes, including frailty[(reviewed in [1,2])]
- Frailty, a state of increased vulnerability to stressors[3], has been associated with chronic inflammation in HIV-infected (HIV+) and -uninfected (HIV-) people[4,5]
- CMV infection may drive chronic inflammation[6-9]
- T cell cytokine responses to CMV were correlated with chronic inflammation, and IL-2-producing CD4 T cells predicted frailty in HIV-, but not HIV+ men[10]
- The relationship between polyfunctional CMV-specific T cells and frailty in HIV+ and HIV- men has not been studied

METHODS

- **Study Population**: 42 men (22 virologically suppressed HIV+, 20 HIV−) followed semiannually in the Multicenter AIDS Cohort Study[10]
- **Frailty**: assesed by Fried frailty phenotype (FFP) at each study visit[11]. Baseline frailty was defined with presence of FFP at two consecutive visits[10]
- **Polyfunctional T cells**: Production of IFN-γ, and/or 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 (Fig. 1)[10]
- **Follow up**: a median of 7 years (IQR: 2) after baseline
- **Statistical Analysis**: Mann-Whitney U Test, Kaplan-Meier estimators, and log-rank test

Fig. 1. Scheme for Identifying Polyfunctional T Cells*

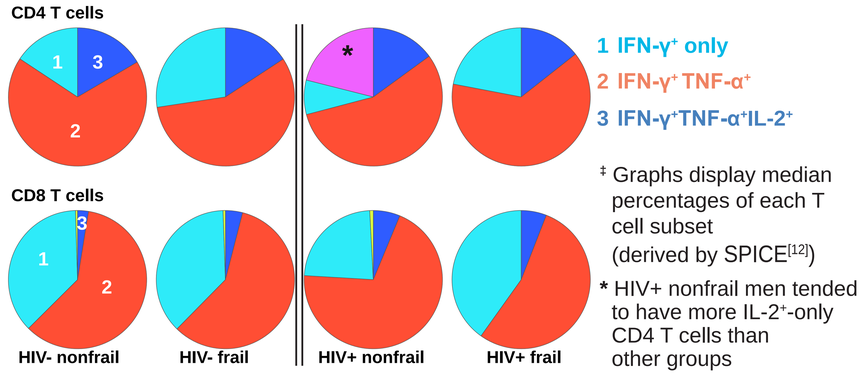


* Subsets of polyfunctional T cells were expressed as percentages of CD4 or CD8 T cells. Plots were generated by FlowJo™.

Percentages of CMV-specific CD4 T cells producing only IFN-γ (IFN-γ⁺TNF-α⁻IL-2⁻) predicted becoming and remaining frail in HIV+ and HIV- men.

RESULTS

Fig. 2. CMV-specific T cells Had Three Main Cytokine Patterns, Which Did Not Differ Significantly by HIV and Frailty Status‡



‡ Graphs display median percentages of each T cell subset (derived by SPICE[12])

* HIV+ nonfrail men tended to have more IL-2+-only CD4 T cells than other groups

Fig. 3. Becoming Frail: % (IFN-γ⁺-only) CD4 T Cells Predicted Frailty: Positively(+) in HIV-, Negatively (-) in HIV+

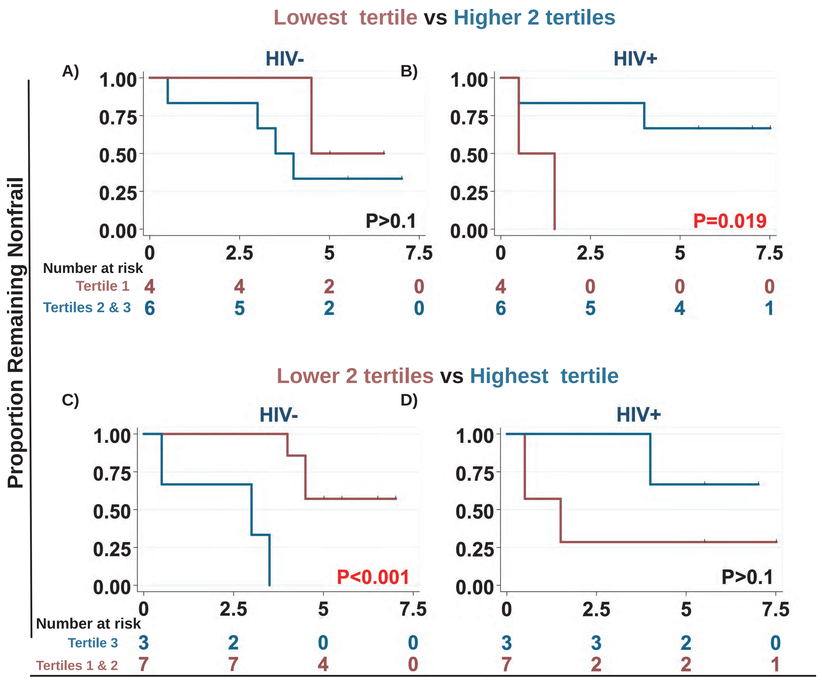
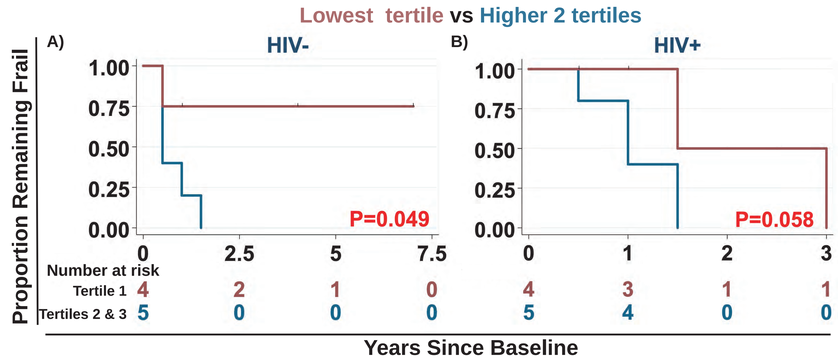


Fig. 4. Remaining Frail: %(IFN-γ⁺-only) CD4 T Cells Were Significantly Associated with Remaining Frail: Negatively (-) in Both HIV- and HIV+



CONCLUSIONS

- Percentages of polyfunctional T cell subsets did not differ significantly by frailty and HIV status in this small study
- Becoming frail was predicted by **higher** percentages of IFN-γ⁺-only CD4 T cells at baseline in HIV-, but by **lower** percentages of these cells in HIV+ men
- Remaining frail was predicted by **higher** percentages of IFN-γ⁺-only CD4 T cells in both HIV- and HIV+ men
- These associations were significant and not seen in analyses of total IFN-γ⁺ CD4 T cells (data not shown)
- These data suggest that HIV status affects the relationship between T cell responses to CMV, systemic inflammation, and pathogenesis of frailty.

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Acknowledgements

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