CMV and HIV: a Double Hit on the CD4/CD8 Ratio

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ABSTRACT

Background: Advanced age is associated with a number of immunologic abnormalities, including a low CD4/CD8 ratio and increased frequency of terminally-differentiated CD8+ T cells ("immunosenescence"). CMV infection significantly contributes to this immunosenescent phenotype. Although HIV infection is associated with high levels of CMV-related inflammatory responses and many of the classic markers of immunosenescence, the relative contribution of CMV and HIV to the development of T cell abnormalities during HIV disease is not known. We examined the impact of CMV and HIV on the CD4/CD8 ratio, which is one of the most validated markers of T-cell senescence.

Methodology: We analyzed 228 subjects, including 8 HIV-CMV-, 15 HIV-CMV+ and 205 HIV+CMV+ individuals [91 controllers (<1000 HIV RNA copies/mL), 91 ART-suppressed and 23 untreated]. We analyzed correlations between the CD4/CD8 ratio and CMV- and HIV-specific T cell responses [proportion of T cells expressing high levels of IFN-gamma, CD107-alpha, TNF-alpha and IL-2 after stimulation by CMV and HIV proteins (IE and pp65, and gag, respectively)].

Results: The CD4/CD8 ratio significantly changed across all subgroups, according to the different immunological background determined by HIV and CMV, as shown in the figure. Among 228 individuals, high CMV-specific IFN-gamma production of CD8 T cells was associated with low CD4/CD8 ratio (Rho -0.30, P<0.01). Similar associations were observed for CMV-specific CD107-alpha, IL-2, and TNF-alpha CD8 T-cell response (all P <0.05). The effect of CMV-specific T cell response on ratio was more consistent than the association with either absolute CD4 or CD8 T cell counts, and was consistent within both the HIV- and the HIV+ ART-suppressed groups (in ART-suppressed, for IFN-gamma CD8 T cell response, Rho=-0.24, P=0.01). The CD4/CD8 ratio was also lower across all groups in subjects with higher HIV-specific CD4 T-cell responses, being the strongest correlations with IFN-gamma (Rho -0.25, P<0.001), IL-2 (Rho -0.23, P=0.001) and TNF-alpha (Rho -0.29, P<0.001) CD4 T-cell responses..

Conclusions: The specific inflammatory responses elicited by CMV and HIV are likely major drivers of a low CD4/CD8 ratio across the whole spectrum of HIV disease. The CD4/CD8 ratio parallels well the progressive decline in immune competence determined by CMV and HIV, and might be considered in clinical settings as a surrogate marker of immunosenescence.

INTRODUCTION

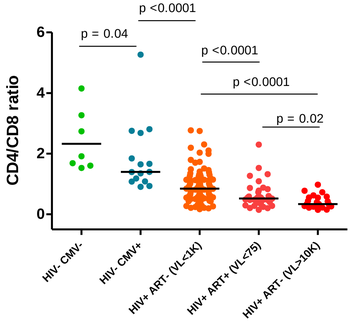
- Advanced age is associated with a number of immunologic abnormalities, including a low CD4/CD8 ratio and increased frequency of terminally-differentiated CD8+ T cells and expansion of CD28- CD8+ T cells ("immunosenescence").
- CMV infection significantly contributes to this immunosenescent phenotype (Hadrup, J Immunol 2006).
- Although HIV infection is associated with high levels of CMV-related inflammatory responses and many of the classic markers of immunosenescence, the relative contribution of CMV and HIV to the development of T cell abnormalities during HIV disease is not known.
- We examined the impact of CMV and HIV on the CD4/CD8 ratio, which is one of the most validated markers of T-cell senescence.

RESULTS

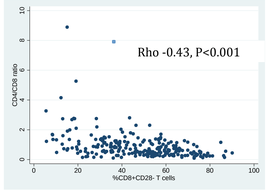
SCOPE cohort: general characteristics of the study population

	HIV-CMV- Median (IQR) (n=8)	HIV-CMV + Median (IQR) (n=15)	*HIV+ART+ Median (IQR) (n=91)	*HIV+ART- Median (IQR) (n=23)	HIV Controllers Median (IQR) (n = 91)
Age, years	47 (35-54)	43 (35-46)	51 (45-57)	43 (41-47)	50 (41 – 54)
Male gender, No. (%)	8 (100%)	15 (94%)	83 (87%)	18 (90%)	24 (26%)
CD4+ Count, cells/mm^3	818 (639-1084)	863 (778-1248)	593 (448-738)	388 (298-495)	759 (620 – 1027)
CD8+ Count, cells/mm^3	357 (272-520)	546 (481-665)	1002 (778-1420)	1098 (825-1415)	569 (428-700)
Proximal HIV RNA Level, log_{10}copies/ mL	NA	NA	≤1.6	4.6 (4.3-5.2)	NA
Pre-ART Nadir CD4+ Count, cells/mm^3	NA	NA	103(24-493)	NA	NA
Duration of Viral Suppression, years	NA	NA	4 (2-9)	NA	NA

CD4/CD8 ratio in different subgroups according to CMV, HIV , ART and VL status

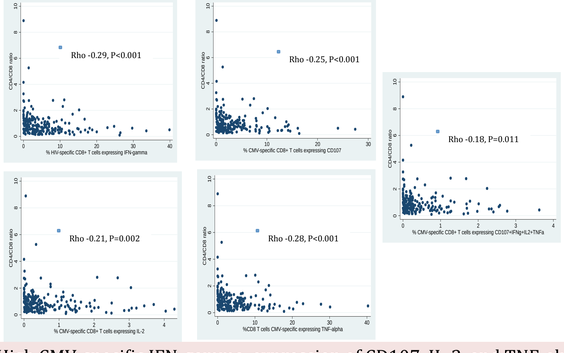


Correlation between the CD4/CD8 ratio and the percentage of senescent (CD28-) CD8+ T cells

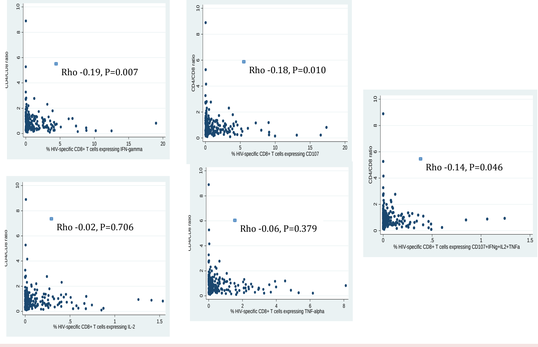


The CD4/CD8 ratio clearly correlated with the % of CD8+CD28- T cells.

Correlations between the CD4/CD8 ratio and CMV-specific CD8+ T cell responses



Correlations between the CD4/CD8 ratio and HIV-specific CD8+ T cell responses



- High CMV-specific IFN-gamma, expression of CD107, IL-2, and TNF-alpha expression of CD8 T cells was associated with low CD4/CD8 ratio.
- The effect of CMV-specific T cell response on ratio was more consistent than the association with either absolute CD4 or CD8 T cell counts.
- In general, the correlations between the CD4/CD8 ratio and CMV- or HIV-specific T cell counts were driven by the CD8 counts.

CONCLUSIONS

- **The specific inflammatory responses elicited by CMV and HIV are likely major drivers of a low CD4/CD8 ratio across the whole spectrum of HIV disease.**
- **The CD4/CD8 ratio parallels well the progressive decline in immune competence determined by CMV and HIV, and might be considered in clinical settings as a surrogate marker of immunosenescence.**

METHODS

- SCOPE: a clinic-based cohort of over 1500 chronically HIV-infected participants and HIV-uninfected controls in San Francisco.
- All T cell studies were performed using freshly collected peripheral blood.
- We determined the CD4/CD8 ratio and CMV- and HIV-specific T cell responses [proportion of T cells expressing high levels of IFN-gamma, CD107-alpha, TNF-alpha and IL-2 after stimulation by CMV and HIV proteins (IE and pp65, and gag, respectively)].
- We analyzed the correlationw between the CD4/CD8 ratio and CMV- and HIV-specific T cell responses.

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