CD8 T-Cell Expansion and Inflammation Linked to CMV Coinfection in ART-treated HIV Infection

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Background

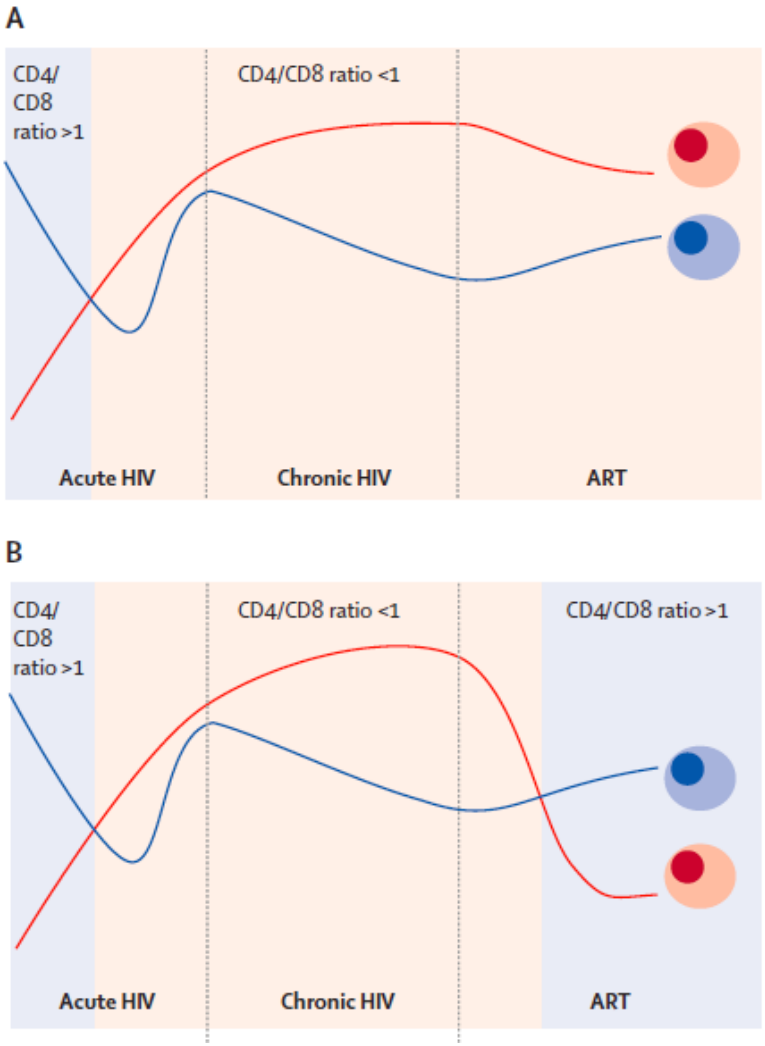
The need of a new biomarker for HIV

- The health benefits of cART in people with HIV are unquestioned.
- The risk of AIDS in this setting is low; however, cART does not fully restore health.
- Several non-AIDS illnesses usually associated with ageing (cardiovascular, renal, liver diseases, non-AIDS cancers, bone disease, etc.) are more likely to occur in people with HIV infection than in those without.
- Because these events occur in patients with undetectable viral loads and high CD4 cell counts, traditional biomarkers for HIV disease are inadequate
- A new biomarker for HIV disease management is needed.

Serrano-Villar S, Deeks SG. Lancet HIV 2015; 2: e67

CD4/CD8 ratio: an emerging biomarker for HIV

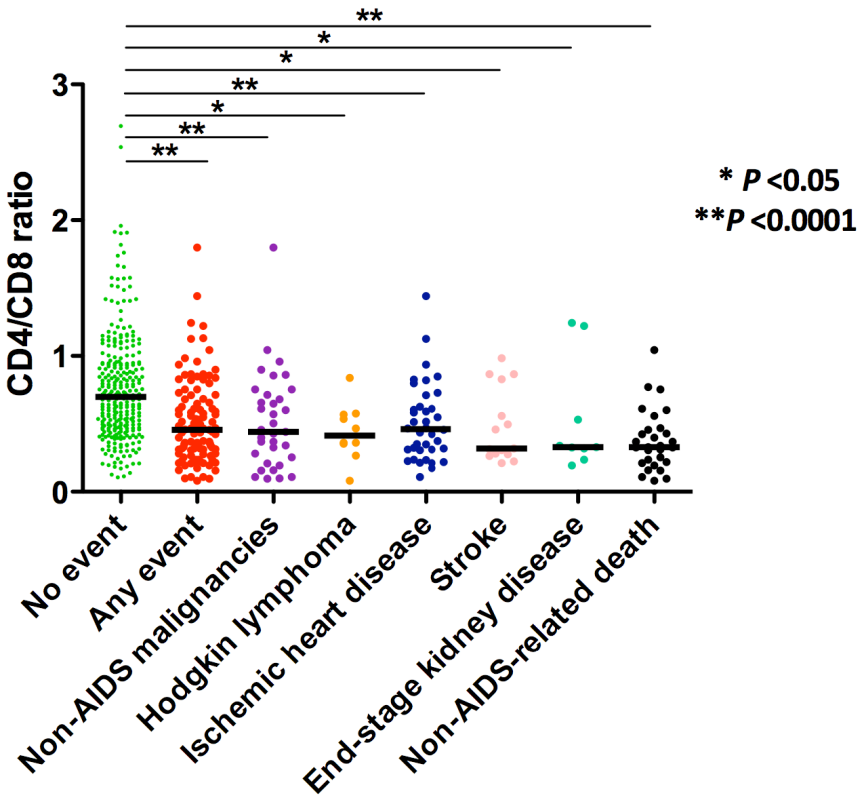
- Many factors contribute to morbidity and mortality in HIV-infected patients on cART.
- These factors include immunological abnormalities commonly found in elderly people (immunosenescence).
  - Low numbers of naïve T cells and circulating CD4 cells
  - High numbers of well differentiated memory CD8 cells
  - Chronic inflammation
- Each of these features is common in patients with HIV.
- This immunological phenotype can be captured by measuring the CD4/CD8 ratio



Serrano-Villar S, Deeks SG. Lancet HIV 2015; 2: e67

Increased risk of serious non-AIDS-related events (NAES) in HIV-infected subjects on cART associated with a low CD4/CD8 ratio

- Case-control study
- 407 cART-treated subjects
  - 109 cases with NAES
  - 298 controls without NAES
- CD4/CD8 ratio was lower in cases than in controls (0.44 vs. 0.70, P<0.001).
- A low CD4/CD8 ratio was strongly associated with the risk of NAES



Serrano-Villar S, et al. PLoS One 2014; 9: e85798

CD4/CD8 ratio and non-AIDS-related events (NAES) in HIV+ with viral load suppression with cART

- 3236 naïve HIV+ patients in ICONA that initiated cART between 1997-2013
- Reached undetectable VL and had CD4/CD8 < 0.8 at the time undetectable VL
- Definition of CD4/CD8 normalization = 2 consecutive values ≥ 1

7305 patient-years of FU

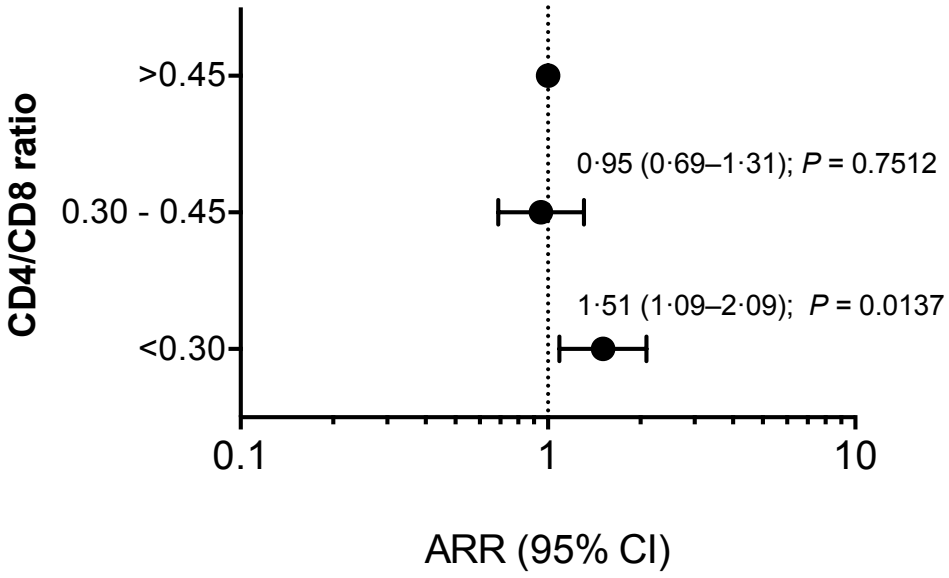
Probability of normalization

- 1 yr. 4·4% (3·7–5·2)
- 2 yrs. 11·5% (10·2–13·0)
- 5 yrs. 29·4% (26·7–32·4)

Rate of NAES (CD4/CD8 ratio)

- > 0.45 2.2 x 100 py (1.7–2.9)
- 0.30–0.45 2.3 x 100 py (2.1–2.5)
- < 0.30 4.2 x 100 py (3.4–5.3)

Adjusted RR of NAES or death



Mussini C. Lancet HIV 2015; 2: e98–106

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Aim

To determine whether persistent CD8 T-cell expansion and increased inflammation observed in ART-treated HIV infection was associated with CMV coinfection.

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Methods

Subjects

- 32 HIV+ CMV- subjects
- 126 HIV+ CMV+ subjects (age, gender & CD4-matched)
- 21 HIV- controls (9 CMV-negative, 12 CMV-positive)

Studies

- CD4+ and CD8+ T-cell counts
- D-dimers
- Interferon gamma-induced protein 10 (IP-10)
- Interleuquin-6 (IL-6)
- Interleuquin-18 (IL-18)
- Soluble CD14 (sCD14)
- Tumor necrosis factor receptor 2 (TNF-RII)

Participant Characteristics

	HIV (+)		
	CMV (-)	CMV (+)	*P*
Number	32	126	
Male – (%)	84.75	84.13	1.00
CMV (+) (%)	0	100	<.001
Median age (y)	41.5	42	>.999
Median time on cART (y)	3.29	3.14	.463
Median CD4 cells/µL	437	490	.420
Median CD4 nadir cells/µL	178.5	180	.653

Participant Characteristics

	HIV (+)			Total		
	CMV (-)	CMV (+)	*P*	HIV (+)	HIV (-)	*P*
Number	32	126		158	21	
Male – (%)	84.75	84.13	1.00	84.18	52.4	.002
CMV (+) (%)	0	100	<.001	79.7	42.9	.028
Median age (y)	41.5	42	>.999	42	37	.053
Median time on cART (y)	3.29	3.14	.463	3.15	NA	NA
Median CD4 cells/µL	437	490	.420	467	907	<.001
Median CD4 nadir cells/µL	178.5	180	.653	180	NA	NA

CD8+ and CD4+ T-cell counts and CD4/CD8 ratio in HIV+/CMV+ individuals

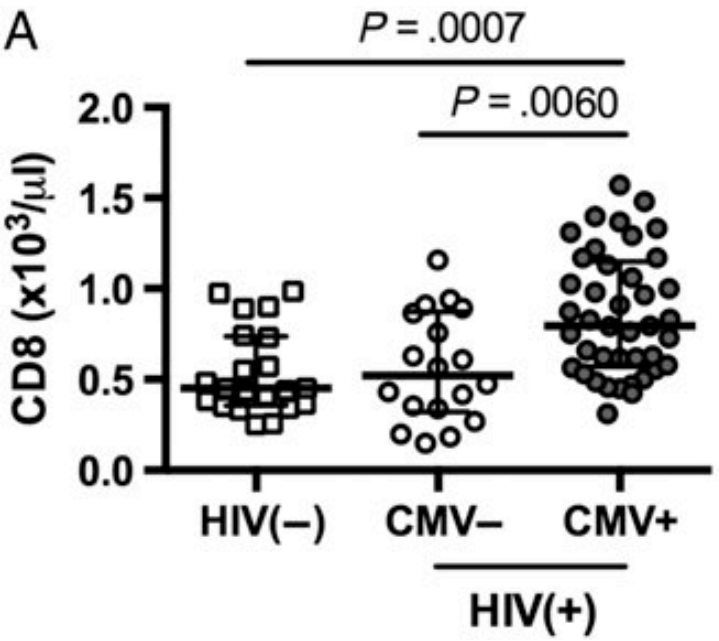


Fig A. CD8 significantly higher in HIV/CMV-coinfected patients than in HIV-monoinfected patients or HIV-uninfected controls.

CD8+ and CD4+ T-cell counts and CD4/ CD8 ratio in HIV+/CMV+ individuals

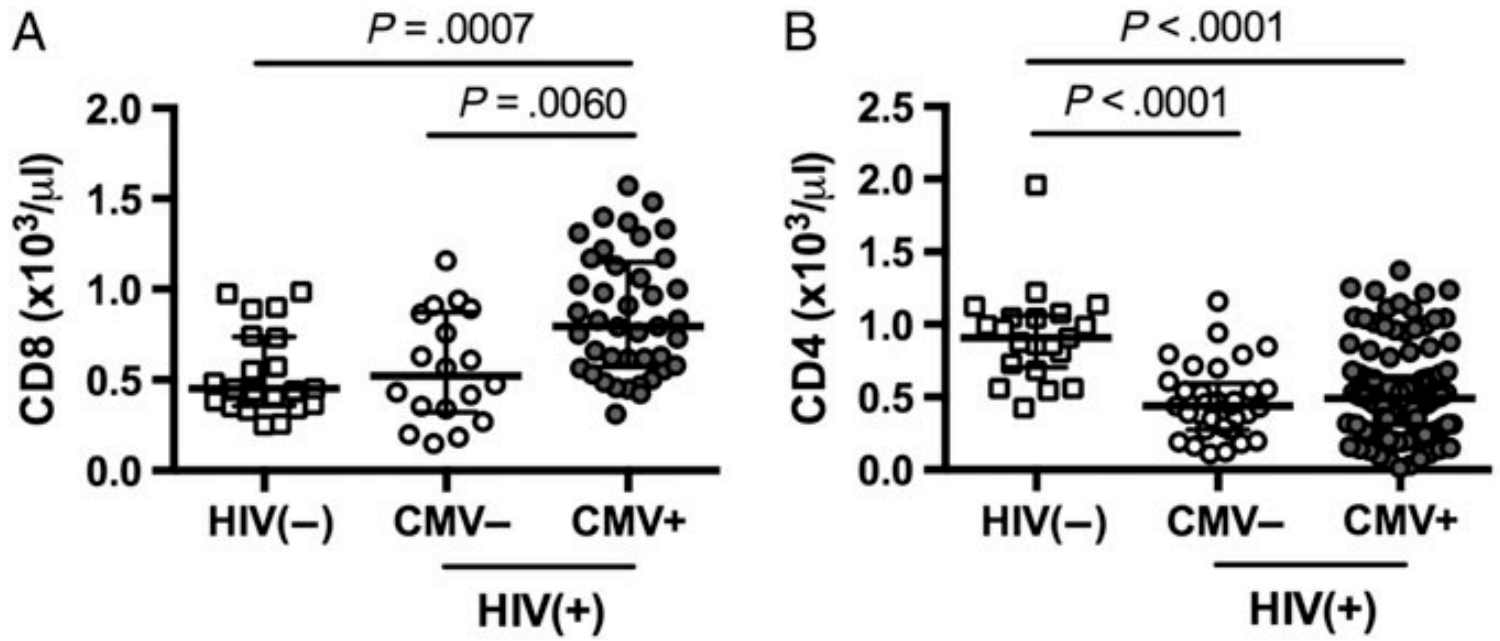


Fig A. CD8 significantly higher in HIV/CMV-coinfected patients than in HIV-monoinfected patients or HIV-uninfected controls.

Fig B. CD4 counts in each HIV-infected group were lower than among HIV-negative controls

CD8+ and CD4+ T-cell counts and CD4/ CD8 ratio in HIV+/CMV+ individuals

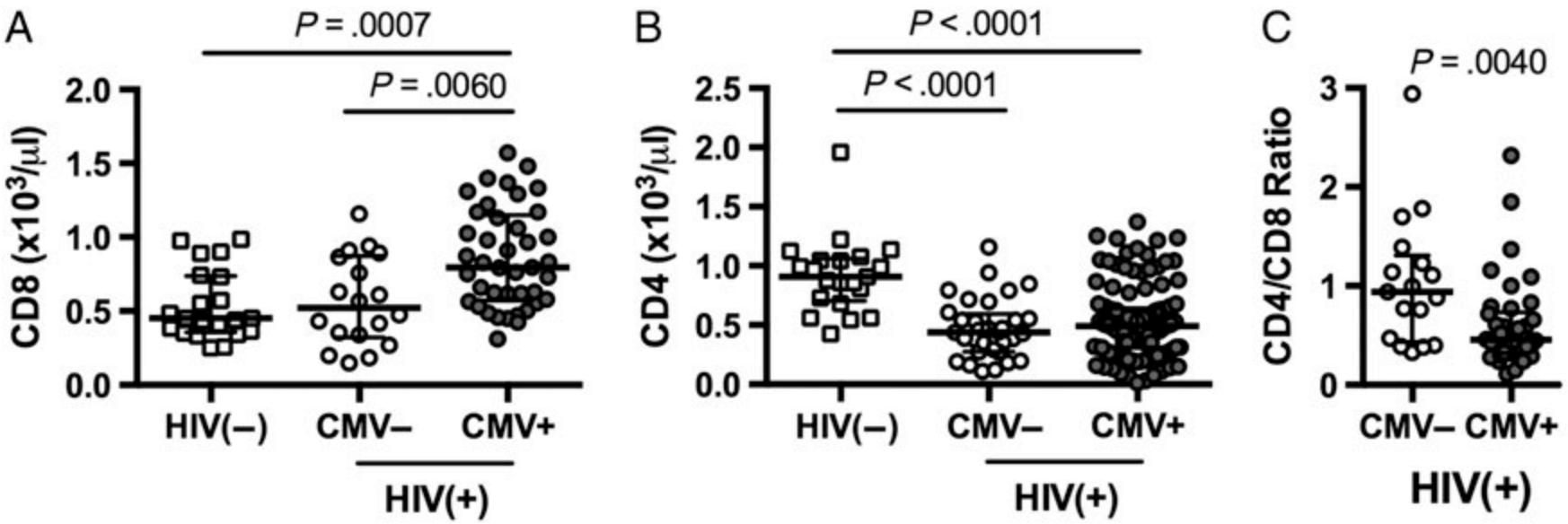
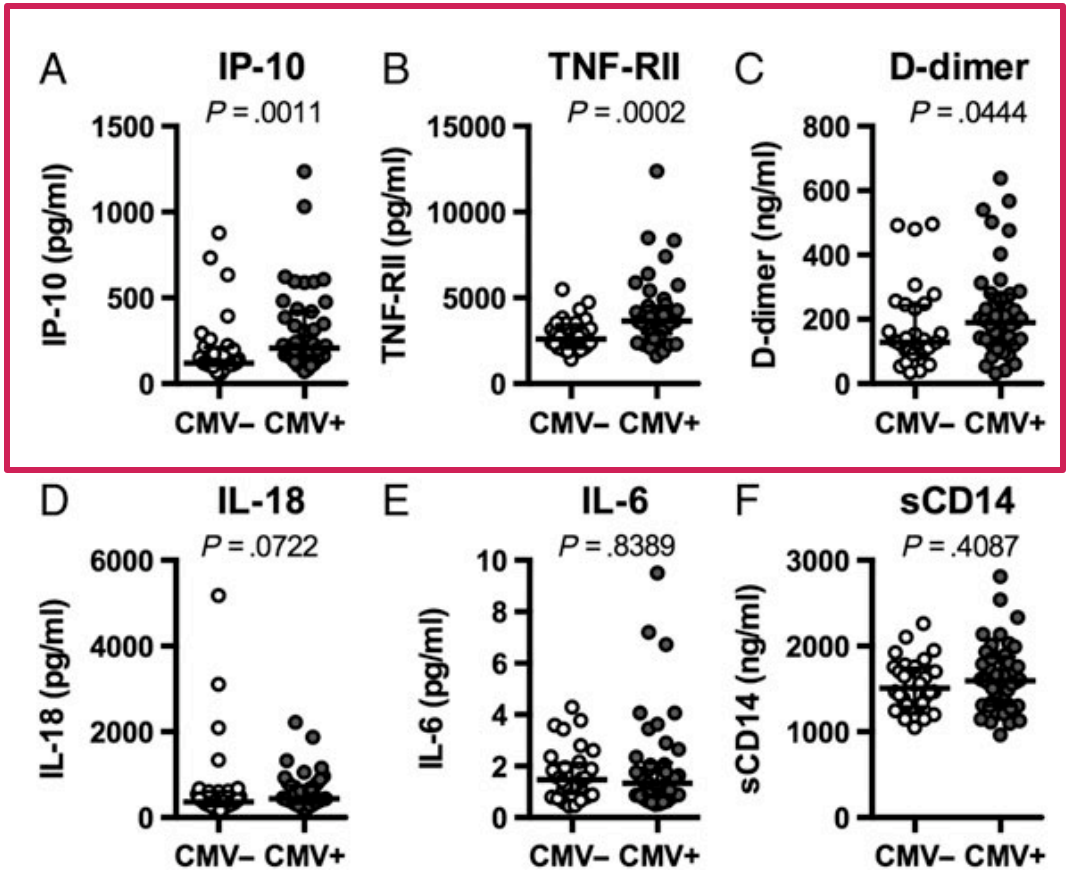


Fig A. CD8 significantly higher in HIV/CMV-coinfected patients than in HIV-monoinfected patients or HIV-uninfected controls.

Fig B. CD4 counts in each HIV-infected group were lower than among HIV-negative controls

Fig C. Significantly lower CD4/CD8 ratio in HIV/CMV-coinfected patients than in HIV-monoinfected patients

Expression of selected markers of inflammation



Higher levels of Interferon gamma-induced protein 10 (IP-10), Tumor necrosis factor receptor 2 (TNF-RII) and D-dimer were also found in HIV/CMV-coinfected patients than in HIV-monoinfected patients

Concluding remarks

- In our age-matched cohorts, we found elevated circulating CD8 T-cell numbers only in individuals coinfected with both CMV and HIV but not in persons infected with HIV alone or CMV alone.

- CMV coinfection was associated with lower CD4/CD8 ratios and higher plasma levels of interferon-inducible protein 10 (IP-10), tumor necrosis factor receptor – type II (TNF-RII), and D-dimers.

- CMV coinfection in HIV-infected persons is a potential contributor to increased inflammation and coagulation observed in HIV disease.

- The mechanisms of how CMV coinfection drives circulating CD8 T-cell persistence and increased inflammation in HIV infection and the role of CMV in the morbid outcomes of treated HIV infection merit further study.