CD4:CD8 Ratio Remains Significantly Depressed Despite Viral Suppression with Effective ART

Brinda Emu[1], Jeffrey N. Martin[2], Douglas F. Nixon[3], Steven G. Deeks[2], Joseph M. Mccune[2]

[1] Yale University; [2]University of California, San Francisco; [3] George Washington University

ABSTRACT

Background: Inverted CD4:CD8 ratio is known to be indicative of advanced, untreated HIV infection. In the HIV-uninfected population, a low CD4:CD8 ratio has also been associated with near-term mortality in the elderly. This study aimed to characterize the CD4:CD8 ratio in untreated and treated HIV-infection, and to determine the relative dynamics of changes in each population over time during effective ART.

Methodology: CD4:CD8 ratio was evaluated in HIV-infected subjects with viral loads >10,000 copies/µl ("non-controllers", n=42), those with undetectable viral loads on ART ("ART-suppressed", n=53), and HIV-uninfected subjects (n=22) from a longitudinal cohort study in San Francisco (SCOPE). In addition, CD4:CD8 ratio, and T cell phenotypes were evaluated in 25 non-controllers, 18 ART-suppressed, and 7 HIV-uninfected subjects.

Results: CD4:CD8 ratio in non-controllers, ART suppressed, and HIV-uninfected subjects was 0.25, 0.48, and 1.95 respectively (P<0.0001 for all comparisons). The increased ratio in ART-suppressed compared to non-controllers was driven by an increase of CD4+ T cells, with limited differences in the expanded CD8+ T cell population. We also studied longitudinal changes in ratio in a a subset of 15 individuals who had been on effective therapy for for a median of 3.7 years (1.0 – 6.9) and who had a median CD4+ T cell count of 482 (range 300-1079) and a ratio of 0.44 (range 0.21-1.52). With additional time on ARV (median of 3.1yrs, range 1.3-4.2 yrs), total CD4+ T cell counts increased by 101 cells/mcl (p=0.02) while CD8+ T cells generally remained stable (p=0.22), resulting in an overall increase in CD4:CD8 ratio from 0.44 to 0.60 (p=0.02).

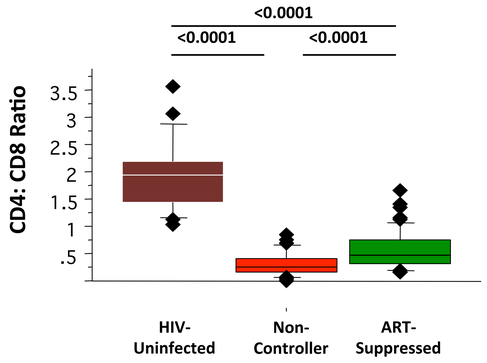
Conclusion: Untreated HIV infection is associated with a low CD4:CD8 ratio. Effective therapy improves the ratio, but this improvement is primarily caused by increases in CD4+ T cell counts. Increases in the ratio are largely due to increased CD4+ T cells, with a persistently expanded CD8+ T cells limiting further normalization of the ratio. Only a minority of individuals demonstrated any further gains in CD4:CD8 ratio with prolonged ARV therapy. A low CD4:CD8 ratio is a biomarker of poor clinical outcomes in the elderly non-HIV infected population, but requires further studies of clinical correlation in HIV-infected individuals.

	HIV-uninfected (n=22)	Non-Controllers (n=42)	ART-Suppressed (n=53)
Age (Yrs)	37 (27-60)	44 (33-62) **	50 (35-64) **!!
Years Infected	NA	18 (6-29)	18 (8-26)
CD4 count/mcl	943 (582-1723)	249 (5-857)***	478 (127-899)*** !!!
CD4 (%)	48 (31-56)	13 (1-38)***	22 (9-47) *** !!
CD8 count/mcl	486 (252-1031)	973 (79-4584)***	1016 (272-3169)*** !!!
CD4:CD8 Ratio	1.95 (1.03-3.54)	0.247 (0.02-0.867)***	0.481 (0.15-1.65)*** !!!
Log viral load	NA	4.24 (4.00-5.61)	1.88 !!!

** = p<0.002; *** = p<0.0001 compared with HIV-uninfected group.
!! = p<0.0005; !!! = p<0.0001
Medians (ranges) reported

Figure 1:
Comparison of CD4:CD8 Ratio in Individuals On and Off ART

A: CD4:CD8 Ratio



B: CD4+ and CD8+ T Cells

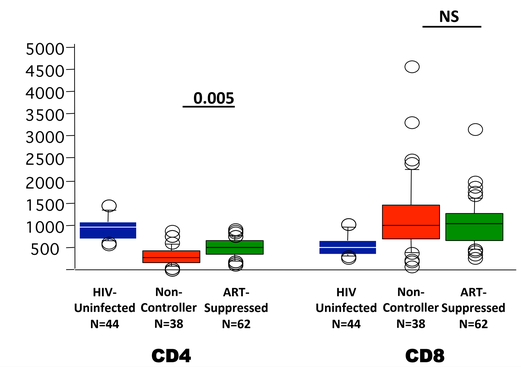


Figure 1: CD4 and CD8 T cell counts were enumerated among different patient groups. Non-controllers are HIV infected individuals with ongoing viral replication. ART-suppressed are HIV-infected individuals with undetectable peripheral viral loads on antiretroviral therapy. HIV-uninfected individuals are controls. CD4:CD8 T cell ratios (A) and individual CD4 and CD8 T cell counts (B) are shown.

Figure 2: Increased CD8+CD28- population and Increased CMV-specific T cell response are associated with low CD4:CD8 Ratio

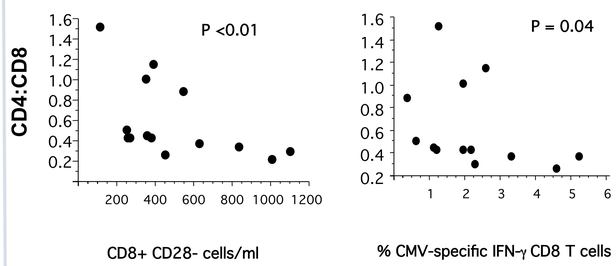


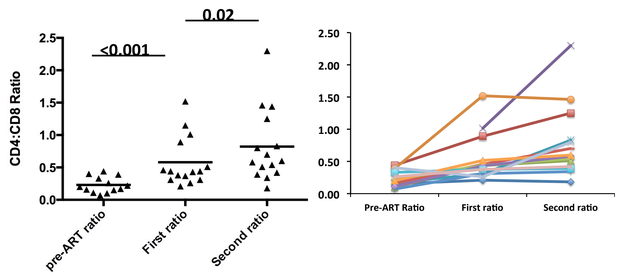
Figure 2: CD4:CD8 ratio is inversely associated with the proportion of CD8+ T cells with a CD28- phenotype. In addition, CD4:CD8 ratio is inversely associated with CD4:CD8 Ratio among individuals with suppressed virus on ART.

Table 2: Longitudinal Evaluation on ART

	Pre-ART (n=15)	First timepoint (n=15)	Second timepoint (n=15)
Age (Yrs)	47 (25-60)	50 (32-61)	56 (34-64)
Years Infected	6 (1-16)	10 (6-20)	13 (7-23)
CD4 count/µl	226 (36-573)	483 (300-1079)**	462 (363-1507)** !
CD8 count/µl	655 (476-1653)!	1023 (484-1662)	828 (353-2192)
CD4:CD8 Ratio	0.20 (0.07-0.44)!	0.44 (0.21-1.52)**	0.60 (0.18-2.30)** !
Log viral load	4.74 (3.88-5.70)	1.88 **	1.88 **
Yrs Suppressive ART	N/A	3.7 (1.0-6.9)	5.5 (3.7-9.5)

! for three subjects, CD8+ T cell counts were not available at the pre-ART timepoint Thus, CD8+ T cell count and CD4:CD8 ratio at the pre-ART timepoint is based on 12 subjects.
** = p<0.001 compared with pre-ART timepoint.
!! = p=0.02 when compared with first on-ART timepoint.

Figure 3:
Evolution of CD4:CD8 Ratio over time on ART



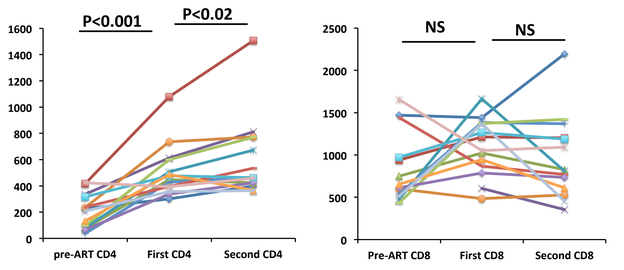


Figure 3: CD4:CD8 ratio in ART-suppressed Individuals at three timepoints (pre-ART, first timepoint on ART and second timepoint on ART). Also shown are individual changes in CD4 and CD8 counts over time in patients. Subjects remained on antiretroviral therapy with suppressed viral load between "first" and "second" timepoint on ART.

Figure 4:
Naïve CD4 and CD8 T cells over time on ART

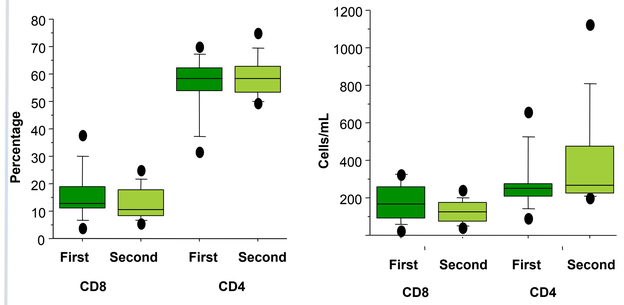
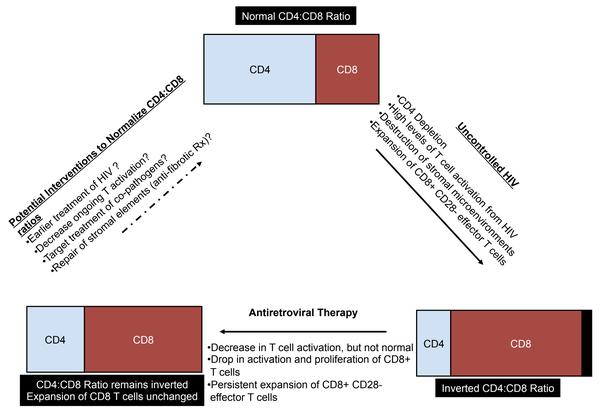


Figure 4: Naïve subpopulations defined as CD27+CD28hiCCR7+CD45RA+. Proportion and absolute number/ml are depicted for the first and second timepoint.



Conclusion: Untreated HIV infection is associated with a low CD4:CD8 ratio. Effective therapy improves the ratio, and this improvement is primarily driven by increases in CD4+ T cell counts, with a persistently expanded CD8+ T cells limiting further normalization of the ratio. Only a minority of individuals demonstrated any further gains in CD4:CD8 ratio with prolonged ARV therapy.

The inability for normalization of the CD4:CD8 ratio in the majority of individuals on ART may reflect a persistent expansion of CD8+ T cells, particularly those of an effector phenotype and decrease in those with a naïve phenotype as we have shown. Decreased CD4:CD8 ratio has been associated with advanced aging and accelerated disease progression in elderly HIV-uninfected adults. The clinical correlation of continued immunologic perturbations is important to pursue given the importance T cell recovery in the defense against new pathogenic infections and tumor surveillance. It remains to be seen whether these persistent deficits portend decreased responses to vaccination and/or serve as a potential etiology for the rise in non-AIDS, age-associated clinical conditions among HIV-infected subjects. Further studies of clinical correlation in HIV-infected individuals is required.

Acknowledgements

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