A Low CD4/CD8 Ratio During Effective ART Predicts Immunosenescence and Morbidity/Mortality

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Abstract #1767

INTRODUCTION

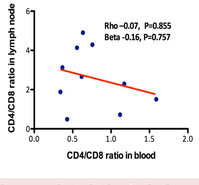
- A subset of HIV-infected adults receiving effective ART fails to normalize the CD4/CD8 ratio, even after achieving successful immunovirological response with adequate CD4 count recovery.
- Among elderly HIV-uninfected adults, inversion of the CD4/CD8 ratio (<1.0) predicts all-cause mortality and is considered part of the immunosenescent phenotype (Hadrup, J Immunol 2006; Wikby, J Gerontol A Biol Sci Med Sci 2005)
- We hypothesized that among ART-treated HIV-infected individuals with CD4 counts ≥500 cells/mm^3, a low CD4/CD8 ratio, may identify individuals with persistent innate and adaptive immune activation at greater risk of serious non-AIDS events.

METHODS

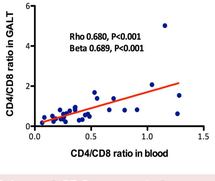
Study subjects were sampled from four cohorts and two clinical trials:
1)SCOPE: a clinic-based cohort of over 1500 chronically HIV-infected participants and HIV-uninfected controls in San Francisco
2)the Study of the Ocular Complications of AIDS (SOCA): a multicenter cohort of over 2200 HIV-infected participants who initiated ART with an AIDS diagnosis
3)OPTIONS: a clinic-based cohort of participants diagnosed during acute/early HIV infection, previously described (Jain, JID 2013),
4)the Madrid cohort: a clinic-based cohort of 2400 ART-treated individuals, 130 of whom developed serious non-AIDS events (Serrano-Villar, PLoS ONE 2014. 5)
5)the raltegravir (Hatano, JID 2011) and maraviroc (Hunt, Blood 2013) ART intensification randomized, placebo-controlled, clinical trials in HIV-infected individuals.

RESULTS

Using data from 10 individuals on ART, in whom the CD4/CD8 ratio in blood was 0.6 (0.4 – 1.1) and in lymph nodes 2.5 (1.5 – 4.1), no significant correlation between the CD4/CD8 ratio in blood and in lymph nodes was detected .



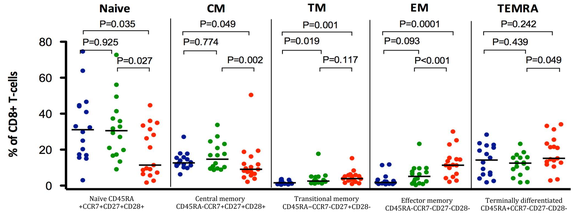
Using data from 32 individuals on ART, in whom the CD4/CD8 ratio in blood was 0.4 (0.2 – 0.6) and in GALT 0.6 (0.4 – 0.9), we found a strong correlation between the the CD4/CD8 ratio in blood and in in rectal mucosa.

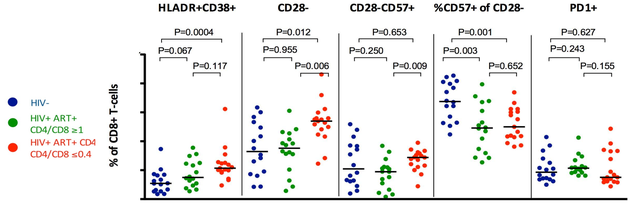


While correlated, the imbalance between CD4+ and CD8+ T-cells is less marked in blood than in GALT.

RESULTS

Low CD4/CD8 ratio during effective ART is associated with altered T cell subsets and heightened T cell activation and senescence



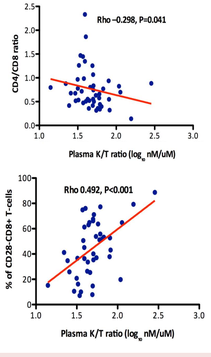


Subjects with a low CD4/CD8 ratio during ART exhibit a skewed T cell phenotype from naïve to TEMRA, whole those with normal ratios showed normal naïve/TEMRA subsets.

Subjects with a low CD4/CD8 ratio during ART exhibit heightened T cell activation and senescence, whole those with normal ratios showed levels closer to normality.

Correlations between the CD4/CD8 ratio and markers of innate immune dysfunction during ART-mediated viral suppression

	Correlations with the CD4/CD8 ratio Rho, P value	
	All subjects (n=192)	Subjects with CD4 ≥500 cells/mm^3
KT ratio	**-0.336 (<0.001)**	**-0.298 (0.041)**
sCD14	**-0.232 (0.002)**	-0.155 (0.303)
hs-CRP	**-0.152 (0.043)**	-0.039 (0.799)
D-dimers	-0.141 (0.060)	0.015 (0.919)
Interleukin-6	**-0.162 (0.031)**	-0.012 (0.930)
IFABP	-0.146 (0.052)	-0.223 (0.134)
Zonulin	0.108 (0.155)	-0.087 (0.569)



- **The CD4/CD8 ratio correlates better with the degree of IDO induction than the CD4 or CD8 counts individually, which becomes especially evident above the threshold of 500 CD4+ T cells/mm^3.**
- **In subjects with low CD4/CD8 ratio, increased IDO induction is associated with an immunosenescent phenotype (expansion of CD28-CD8+ T cells).**

Low CD4/CD8 ratio despite effective ART predicted disease progression beyond the CD4+ and CD8+ T-cell counts

	Beta	P value
Madrid cohort (N=66) (all subjects CD4≥500 cells/mm^3)		
CD4+ T cells	-0.66	0.859
CD8+ T cells	2.29	0.048
CD4/CD8 ratio	-5.08	0.045
SOCA cohort (N=192)		
CD4+ T cells		
All subjects	-1.52	0.009
Subjects with CD4≥500	-4.09	0.525
CD8+ T cells		
All subjects*	0.28	0.392
Subjects with CD4≥500	2.37	0.246
CD4/CD8 ratio		
All subjects	-1.38	0.012
Subjects with CD4≥500	-5.04	0.194

Coefficients are adjusted by age, gender, nadir CD4+ T cell count and duration of viral suppression.

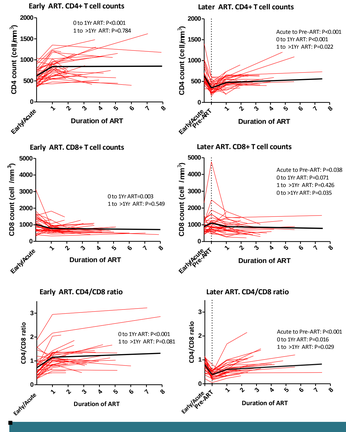
- **Nested case-control study in the Madrid cohort:** ART-suppressed subjects with ≥500 CD4+ T cells/mm^3 where 33 cases who developed serious non-AIDS events were matched to 33 controls by age, gender, nadir CD4 and proximal CD4+ T cell counts.
- Both the CD4/CD8 ratio and CD8 count independently predicted the risk of non-AIDS events, with the coefficient of the CD4/CD8 ratio significantly higher.
- Each 10% decrease in the CD4/CD8 ratio and in the CD8+ T cell counts were associated with 48% and 22% higher odds of serious non-AIDS events, respectively.

- **Nested case-controls study in the SOCA cohort:** ART-suppressed subjects with more advanced HIV infection were 62 cases of death were matched by age, gender, nadir CD4+ T cell count, and duration of viral suppression with 121 controls.
- We observed that both the CD4/CD8 ratio and CD4+ T cells, but not CD8+ T cells, were independent predictors of mortality –for each 10% increase in the CD4/CD8 ratio or in CD4+ T cells and there was a 15% and 13% decrease in the risk of death, respectively.

While the CD4 counts predict mortality in those individuals with low CD4 counts, in those with adequate CD4 recovery, high CD8 counts might drive adverse outcomes. In both scenarios, the CD4/CD8 ratio retains the predictive importance of both CD4+ and CD8+ T cells.

Impact of timing of ART initiation on the dynamics of circulating CD4+ T cells, CD8+ T cells and CD4/CD8 ratio

OPTIONS cohort :recently infected adults who started therapy during the first six months of their infection (early ART) or after two years of untreated infection (later ART)



- After one year of ART, early treated patients showed significantly higher median CD4/CD8 ratio and had fourfold-increased odds of CD4/CD8 ratio normalization (>1) during follow-up (OR, 3.6; 95% CI, 1.2, 10.8; P=0.022).
- The greater effect of early ART compared to later ART on the CD4/CD8 ratio remained statistically significant after adjustment by age, gender, and baseline CD4+ T cell counts using mixed-effects linear models.
- **The CD4/CD8 ratio increased significantly faster among early ART initiators compared to later initiators after one year of ART** (+0.44 vs. +0.25, respectively, P<0.001), **and after a median of 3 years of ART** (+0.61 vs. +0.49, respectively, P<0.001).

Early ART initiators showed a faster CD4/CD8 ratio increase and reached higher CD4/CD8 ratios after a median of 3 years of ART.

CONCLUSIONS

- **A low CD4/CD8 ratio among ART-treated HIV-infected patients with adequate CD4+ T cell counts recovery may define a new clinical phenotype of individuals with:**
  - Higher levels of CD8+ T cell activation and an immunosenescent phenotype
  - Increased IDO activity
  - CD4/CD8 imbalance in GALT
  - Higher risk of morbidity and mortality.
- **Early ART initiation may contribute to more rapid and robust CD4/CD8 ratio normalization.**
- **Monitoring the CD4/CD8 ratio may be useful in clinical settings and become an endpoint for trials evaluating novel therapies for ongoing immune dysfunction during treated infection.**

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