Association of CD4:CD8 with Cause-specific Mortality in 20,464 Patients on Long Term ART

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1. Background

- Patients with advanced HIV disease have low CD4:CD8 ratio which improves with effective ART.
- Increases in the ratio appear largely due to increased CD4 cells.
- A persistent expansion of CD8 cells limits further normalization of the ratio even after 5 years of treatment.
- A low (inverted) CD4:CD8 ratio is associated with mortality in the elderly non-HIV positive population.
- The CD4:CD8 ratio has been suggested as a biomarker for HIV-related immune senescence.

2. Aim

To investigate the association of the CD4:CD8 ratio with cause-specific mortality in long term ART patients followed up for more than 5 years.

3. Methods

Data was used from 13 European and North American cohorts contributing to the **Antiretroviral Therapy Cohort Collaboration (ART-CC)**.

- Adult patients (over 16 years old) were followed up for cause-specific mortality from 5 years after start of ART.
- Baseline measurement of CD4 and CD8 counts were taken as the nearest to 5 years after start of ART within a +/- 3 month window.
- Cox models were used to estimate the hazard ratio (HR) for subsequent all-cause, AIDS-related, and non-AIDS related (excluding unnatural deaths) mortality – competing risks were not used for this.
- We compared patients with a CD4:CD8 ratio ≥0.5 versus <0.5 stratified by CD4 count <350, ≥350, and ≥500 cells/mm^3.
- Three models were fitted, each stratified by cohort: unadjusted; adjusted for CD4; and additionally adjusted for sex, age, IDU transmission group, AIDS and viral suppression at 5 years.
- Causes of death were ascertained using the CoDe procedure.

4. Results

- **20,464 patients** had a CD4:CD8 ratio measured at 5 years after ART start and were included in the analysis.
- The median (inter-quartile range) CD4:CD8 ratio measured at 5 years after start of ART was 0.61 (0.40, 0.89) – figure 1.
- Median (IQR) follow-up was 4.4 (2.0, 7.5) years.
- During 98,438 person-years 902 (4%) of these patients died. The rate of death (95% CI) was 9.2 (8.6, 9.8) per 1000 years.
- At 5 years, only 3,740 (18%) patients had CD4:CD8 >1
- Cause of death was available for 63% of patients.
- The 5 year ratio (IQR) was 0.41 (0.23, 0.72) in patients who died, and 0.23 (0.09, 0.41) and 0.45 (0.27, 0.77) in those who died from AIDS and non-AIDS related causes, respectively.
- Table 2 shows that CD4:CD8 ratio was associated with all-cause mortality in all patients, but this association was completely attenuated by adjustment for CD4 count in those with low, but not medium, CD4 count.
- In patients with CD4 ≥350 cells/mm^3 low CD4:CD8 was associated with both non-AIDS and AIDS-related deaths. However, the confidence intervals were wide.
- In patients with high CD4 (≥500 cells/mm^3) the adjusted all-cause mortality HR (95% CI) for CD4:CD8 ≥0.5 (v. <0.5) was 0.63 (0.48, 0.83).

5. Conclusions

- In the majority of patients on long-term ART, CD4:CD8 ratio was not normalised.
- Low CD4:CD8 ratio was associated with all-cause mortality.
- Further analyses are warranted with more complete causes of death and larger numbers of patients to investigate whether CD4:CD8 ratio may be useful for monitoring patients.

Table 1: Characteristics of patients 5 years after start of ART

Patient characteristics	
Variable	**N (%)**
IDU	1,714 (8%)
Female	5,894 (29%)
AIDS	5,171 (25%)
RNA ≤ 50	14,154 (69%)
CD4:CD8 < 0.5	7,535 (37%)
CD4:CD8 ≥ 0.5	12,929 (63%)
	Median (IQR)
Age	42 (36, 49)
CD4	505 (355, 690)
CD8	830 (596, 1134)

Figure 1: Median CD4, CD8 and CD4:CD8 ratio by years after ART start

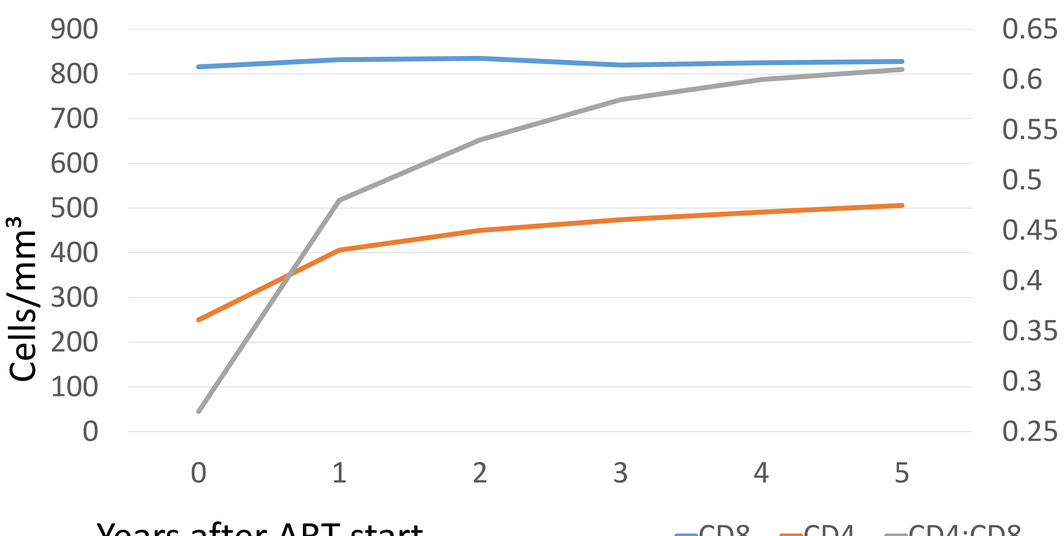

Table 2: Association of CD4:CD8 ratio with mortality stratified by CD4 count

5 year CD4 count		Mortality HR (95% CI) for CD4:CD8 ratio ≥0.5 versus <0.5		
Cells/mm^3	Patients (Deaths)	Unadjusted	Adjusted for CD4	Fully adjusted*
		All-cause mortality		
CD4<350	5016 (424)	0.65 (0.50, 0.85)	0.93 (0.70, 1.22)	1.00 (0.76, 1.33)
CD4≥350	15448 (478)	0.56 (0.47, 0.67)	0.58 (0.47, 0.70)	0.67 (0.55, 0.82)
		AIDS-related deaths		
CD4<350	5016 (97)	0.39 (0.21, 0.77)	1.01 (0.49, 2.05)	1.30 (0.63, 2.70)
CD4≥350	15448 (32)	0.42 (0.21, 0.84)	0.43 (0.20, 0.92)	0.51 (0.23, 1.16)
		Non-AIDS-related deaths		
CD4<350	5016 (156)	0.83 (0.56, 1.22)	1.07 (0.71, 1.61)	1.32 (0.86, 2.02)
CD4≥350	15448 (208)	0.57 (0.43, 0.76)	0.56 (0.41, 0.76)	0.70 (0.51, 0.96)

*Adjusted for CD4, Sex, Age, IDU, AIDS, Viral suppression

ART-CC cohorts contributing to this analysis: the AIDS Therapy Evaluation Project Netherlands (ATHENA); French Hospital Database on HIV (FHDH); Aquitaine Cohort, France; Departments of Internal Medicine at University of Cologne and Bonn, Germany; Italian Cohort of Antiretroviral-Naïve Patients (ICONA); Royal Free Hospital Cohort, London UK; Swiss HIV Cohort Study (SHCS); Southern Alberta Clinic, Canada; HIV Atlanta Veterans affairs Cohort Study (HAVACS), USA; UAB 1917 Clinic Cohort, Birmingham, Alabama, USA; Vanderbilt-Meharry Center for AIDS Research Nashville, Tennessee, USA; Österreichische HIV-Kohortenstudie (OEHIVKOS), Austria; HAART Observational Medical Evaluation and Research (HOMER), Canada.

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