CD4/CD8 AT 2 YEARS OF ANTIRETROVIRAL THERAPY AND INCIDENCE OF SERIOUS NON-AIDS EVENTS

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BACKGROUND

- While a low CD4/CD8 ratio during HIV treatment correlates with immune activation, its predictive value for identifying people living with HIV (PWH) at increased risk of serious non-AIDS events (SNAEs) remains debated.
- We used data from the Spanish CoRIS cohort to assess whether the CD4/CD8 ratio at year 2 of antiretroviral therapy (ART) predicts the incidence of SNAEs in the following 5 years. We then used CD4+ and CD8+ counts as predictor variables in separate models.

METHODS

- **Eligible individuals** were PWH with ART initiation up to 2014 (to allow for a 7-year follow-up) and HIV-RNA <50 copies/mL at 2 years. Participants with a history of AIDS events or SNAEs were excluded.
- We explored the **CD4/CD8 ratio** (0.2, 0.3, 0.4 and 0.5) and **CD4+ count** (200, 350, 500 and 750 cells/µL) **at year two of ART** initiation as **predictor variables**. Moreover, we explored the association of **CD8+ cell count** (800, 1000 and 1500 cells/µL) at year two of ART in the subpopulation of participants with CD4+ counts ≥500 cells/µL.
- The **primary outcome** was the cumulative incidence of the composite endpoint **major adverse cardiovascular event, neoplasia, or death,** over the subsequent 5 years.
- **Follow-up** started at year 2 after ART initiation and ended at the earliest of loss to follow-up, ART discontinuation, or administrative end of follow-up.
- We estimated the **5-year risk** via a double-weighted pooled logistic regression to account for selection bias due to censoring. Covariates included age, sex, date of enrolment, risk group, education level, geographical origin, AIDS diagnosis, HIV-1 RNA at diagnosis, ART regimen, and nadir CD4+ count. CD4+ models also included CD8+ counts at year 2 of ART as covariates.
- We computed **survival curves** introducing a time-varying intercept to allow the hazard to vary over time.

RESULTS

- We included **4625 participants**. Median age was 37 years, 87% were male, median CD4/CD8 ratio at ART initiation was 0.29 (IQR 0.17, 0.46).
- At 2 years after ART initiation, 78%, 71%, 63%, and 53% of participants reached a CD4/CD8 ratio ≥0.2, ≥0.3, ≥0.4, and ≥ 0.5, respectively. Similarly, 78%, 67%, 50%, and 21% reached a CD4+ count ≥ 200, 350, 500, and 750 cells/µL.
- 11% were censored due to loss to follow-up or ART discontinuation, and **4.3% had at least one event during follow-up** (1% MACE, 2.3% NADM, 1.2% death).

- **Figure 1** shows the survival curves and the odds ratio for the event during follow-up. Participants with a CD4/CD8 ratio <0.3 at year 2 of ART had a significantly increased risk of SNAEs.
- Low CD4+ count was associated with an increased risk of events up to the cut-off point of 500 cells/µL (**Figure 2**).
- Among participants with ≥ 500 CD4+, we found an increased risk of event in those with a CD8+ count ≥ 1500 cell/µL at year 2 of ART (**Figure 3**). The CD4/CD8 ratio cut-off predictive of increased event risk in this subpopulation remains <0.3 (OR 0.34 [95% CI 0.14, 0.82], p = 0.016)

When we compared the ability of CD4 counts, CD8 counts, and CD4/CD8 ratio to predict the risk of SNAEs, the ratio (<0.3) was the only variable predicting the risk across the whole range of CD4 counts.

RESULTS

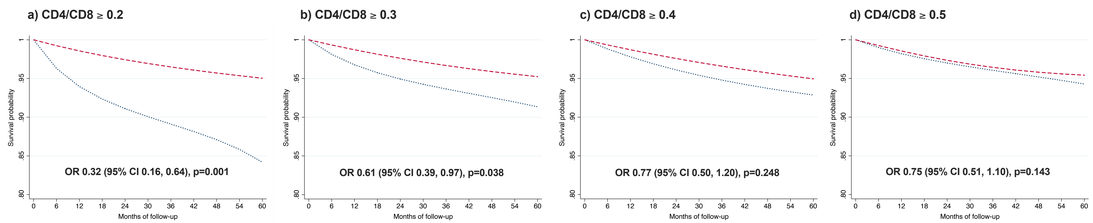


Figure 1. Survival curves for each CD4/CD8 cutoff

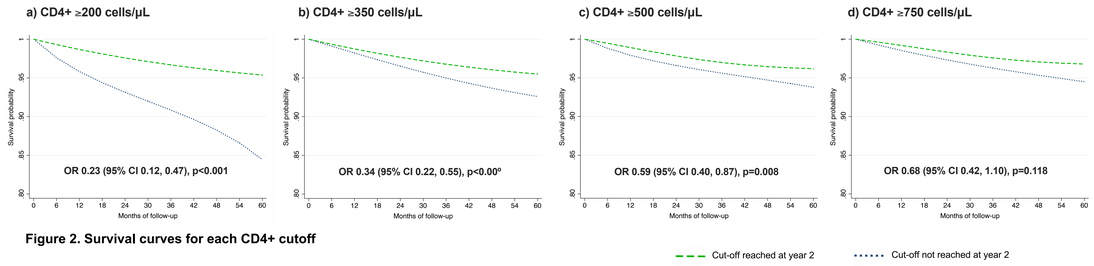


Figure 2. Survival curves for each CD4+ cutoff

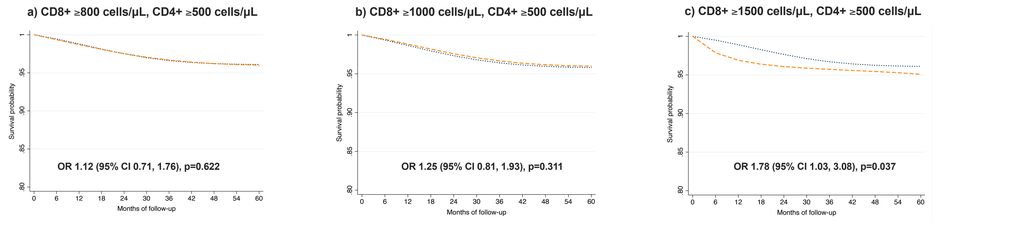


Figure 3. Survival curves for each CD8+ cutoff among participants with ≥500 CD4+

All figures show the adjusted survival curves for participants who reached or did not reach the listed cut-off points at 2 years after ART initiation.
Odds ratio derived from the weighted pooled logistic regression models.

Baseline characteristics	Event (n = 200)	No event (n = 4,425)
Age, median (p25, p75)	37 (30, 43)	45 (39, 54)
Gender, male, n (%)	165 (83)	3687 (83)
Mode of transmission, n (%)		
MSM	75 (38)	2534 (57)
Heterosexual	36 (18)	355 (8)
IDU	81 (41)	1396 (32)
Other	8 (4)	140 (3)
Education level, n (%)		
None – Primary	49 (25)	658 (15)
Secondary – High school	92 (36)	2085 (47)
University	28 (14)	99 (22)
Origin, n (%)		
Spain	137 (69)	2554 (58)
Latin America	23 (11)	726 (16)
Western Europe	32 (16)	773 (17)
Africa	8 (4)	245 (6)
Other	0 (0)	25 (1)
AIDS diagnosis, n (%)	66 (33)	790 (18)
Nadir CD4/CD8 ratio, median (p25, p75)	0.22 (0.12, 0.37)	0.29 (0.17, 0.46)
Nadir CD4+ (cells/µL), median (p25, p75)	173 (56, 264)	250 (135, 342)
ART regimen		
NNRTI	92 (46)	2631 (60)
PI	90 (45)	1408 (31)
INSTI	9 (5)	248 (6)

Abbreviations: ART, antiretroviral therapy; IDU, injecting drug use; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

CONCLUSIONS

- In this observational study, a low CD4/CD8 ratio (<0.3) after two years of successful ART was associated with an increased risk of SNAEs during the following 5 years.
- CD4+ count was significantly associated with higher incidence of SNAEs up to the cutoff point of 500 cells/µL.
- In the subgroup of participants with CD4+ ≥500 cells/µL, we found an increased risk of SNAEs in those with CD8+ ≥1500 cells/µL or a CD4/CD8 ratio <0.3.
- Future studies should address possible differences over the longer term.

ADDITIONAL KEY INFORMATION

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