CD4 and CD4/CD8 as Determinants of Long-Term Risk of Clinical Events After ART Initiation in START

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BACKGROUND

- The START trial randomized ART-naïve participants with CD4 >500 cells/μL to immediate or deferred ART until CD4 declined to 350 cells/μL or AIDS developed.
- From 2015 onward, ART was recommended for all participants; follow-up continued through 2021.
- **Objective**: Evaluate the predictive value of time-updated immunological biomarkers of long-term clinical outcomes after ART initiation.

METHODS

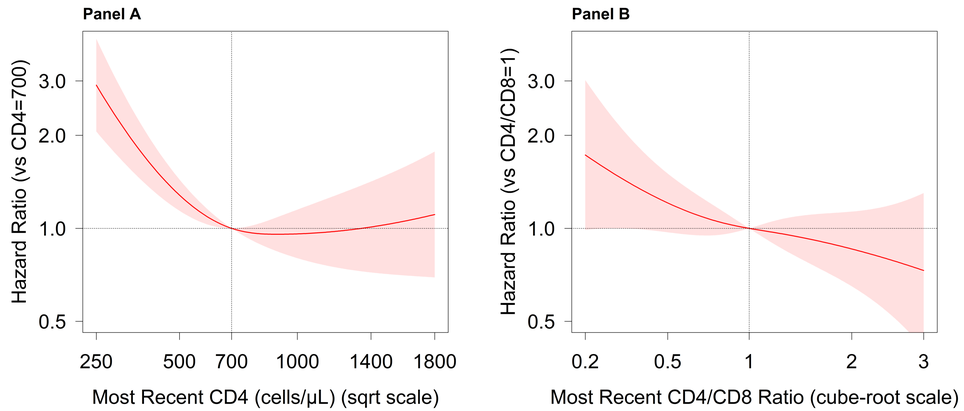
- Cox proportional hazards models were applied to estimate the association between most recent (time-updated) biomarker values and the risk of the primary composite event (serious AIDS, serious non-AIDS event [SNA], or death) after ART initiation.
- Candidate biomarkers were CD4 count, CD4%, CD4/CD8 ratio, HIV-RNA, CD8 count, and CD8%.
- Analyses restricted to participants event-free at ART start.
- The two biomarkers with the best predictive performance based on statistical criteria (AIC) were selected.
- To assess appropriate functional forms, we first explored flexible spline models and then evaluated simpler, more interpretable parameterizations (e.g., piecewise linear terms), as supported by the data.
- Participants were categorized by randomized group and CD4 at ART initiation: Immediate, Deferred >500, Deferred 351–500, and Deferred ≤350 cells/μL.
- To assess whether differences between treatment groups were explained by time-updated biomarkers levels, we compared models with and without biomarkers.
- Analyses were repeated for SNA outcomes (SNA or SNA-related death).

RESULTS

- 4,420 participants initiated ART event-free: 2,302 (51.4%) in the Immediate and 915 (21.0%), 671 (15.5%), 532 (12.1%) in the 3 Deferred (>500, 351–500, and ≤350 cells/μL) groups, respectively.
- A total of 266 primary events occurred: 5.6% in the Immediate vs 5.4%, 6.6%, 8.1% in Deferred groups.
- Eight-year estimated cumulative incidence was 4.2% (95%CI 3.5–5.1) in the Immediate and 5.3% (4.0–7.0), 5.5% (4.1–7.3), 6.3% (4.6–8.6) in the 3 Deferred groups.

Time-updated CD4 count was the strongest predictor of post-ART serious clinical events in START, with steep risk reduction up to ~700 cells/μL and minimal additional benefit above this level. Lower time-updated CD4/CD8 ratio provided a smaller independent contribution. Adjusting for both biomarkers largely eliminated differences between immediate and deferred ART groups.

Figure. Adjusted HRs (95% CI) for the primary event by most recent CD4 (Panel A) and CD4/CD8 ratio (Panel B) from multivariable Cox model with natural splines for √CD4 and (CD4/CD8)^(1/3), adjusted for treatment group, mode of HIV infection, age at ART, and race. Reference values:CD4=700 cells/μL and CD4/CD8=1; axes display original units with square-/cube-root spacing. Range: ~1st to 99th percentile.



- Among candidate biomarkers time-updateCD4 count and CD4/CD8 ratio were the strongest predictors.
- In models using natural splines for √CD4 and (CD4/CD8)^(1/3), estimated risk declined steeply with increasing CD4 counts up to ~700 cells/μL, with minimal change at higher levels; the association with CD4/CD8 ratio was approximately linear across the observed range (Figure).
- A simplified model specification (using linear spline for √CD4 with a knot at 700 cells/μL and a linear term for (CD4/CD8)^(1/3)) was supported by the data (likelihood ratio test compared to model with natural splines: p=0.743) and improved fit (ΔAIC≈7). All subsequent results refer to this model (Table).
- **Primary event**: For CD4<700 cells/μL, risk decreased steeply with higher CD4 (adjusted HR per 1-SD increase on √CD4 = 0.46, 95%CI 0.37–0.57) with no effect above 700 cells/μL. Lower CD4/CD8, on top of CD4 counts, was associated with a modest risk increase (adjusted HR per 1-SD increase on cube-root scale = 0.87, p=0.043; Table).
- **SNA outcomes**: Biomarker's effects were smaller; current CD4 remained predictive when below 700 cells/μL (HR 0.61, p=0.002), whereas CD4/CD8 ratio was not significant (p=0.620; Table).
- Ignoring biomarkers, Deferred 351–500 and ≤350 had higher risk of primary event compared to Immediate [HR 1.47 (95%CI:1.04-2.08) and 1.62 (95%CI:1.14-2.31)]. After adjusting for updated CD4 and CD4/CD8, between-group differences were smaller and no longer significant (global p=0.523).

Table. Multivariable Cox model (piecewise linear for √CD4 and linear for cube-root CD4/CD8) for the hazard of the primary event and cause-specific hazard analysis for SNA outcome.

	Primary event			SNA		
Characteristic	**HR**	**95% CI**	**p-value**	**cHR**	**95% CI**	**p-value**
Most recent CD4 count, per 1-SD higher (square root scale)			<0.001			0.005
Up to 700 cells/μL	0.46	0.37, 0.57	<0.001	0.61	0.45, 0.83	0.002
Above 700 cells/μL	1.16	0.98, 1.38	0.089	1.13	0.94, 1.37	0.195
Most recent CD4/CD8 ratio, per 1-SD higher (cube-root scale)	0.87	0.75, 1.00	0.043	0.96	0.82, 1.12	0.620

HR = Hazard Ratio, cHR = Cause-specific Hazard Ratio, CI = Confidence Interval. Adjusted also for treatment group (4 levels), mode of HIV infection, age at ART, and race.

CONCLUSIONS

- Post-ART risks of serious clinical events were associated with lower current (time-updated) CD4 counts, with additional but smaller effects of CD4/CD8 ratio.
- Risk declined steeply as CD4 increased up to ~700 cells/μL, then levelled off.
- After accounting for time-updated CD4 and CD4/CD8 ratio, differences in event risk between the immediate and deferred ART groups were no longer evident, suggesting that observed treatment group differences were largely explained by achieved immunologic status.
- Ongoing monitoring of CD4 (and, to a lesser extent, CD4/CD8) remains clinically informative for long-term risk assessment after ART initiation, even in the modern treatment era.

PLAIN LANGUAGE SUMMARY

Having a low CD4 count increased the risk of serious health complications. The risk reduced as the CD4 count increased from <350 to 700 cells/ /μL and then leveled off. Having a low CD4/CD8 ratio was also important, but less so. This shows that monitoring the CD4 counts when <700 cells/μL, and to a lesser extend CD4/CD8, is still important, even on effective ART.