CD4 increase < 100 cells/μL/year during 2 years of ART is associated with worse outcomes

Abstract #209

Sol Aldrete[1], Jeong Hoon Jang[2], Kirk A. Easley[2], Jason Okulicz[3], Tian Dai[2], Yi No Chen[4], Brian K. Agan[5], Mirko Paiardini[6,7], Vincent C. Marconi[7]

[1]Infectious Disease Division, Medical College of Wisconsin; [2]Department of Biostatistics and Bioinformatics, Emory University; [4]Division of Internal Medicine and Infectious Disease Service, San Antonio Military Medical Center; [4]Infectious Disease Research Program, Atlanta VA Medical Center; [5]Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences and Henry M. Jackson Foundation for the Advancement of Military Medicine; [6]Yerkes National Primate Research Center; [7]School of Medicine, Emory University

Introduction

- Most individuals who initiate antiretroviral therapy (ART) exhibit sustained increases in their peripheral CD4+ T cell counts.
- Immune non-response (INR) is failure to fully restore CD4 counts despite ART and is associated with increased morbidity and mortality. INR is often defined using the rate of CD4 increase, however cutoffs in the literature vary.
- Several analytical approaches have been used to quantify the relationship between longitudinal CD4 counts and time to event data. However, most published models are not able to fully account for time updated confounders.
- Joint modeling (JM) offers the advantage of being able to more completely account for covariates related to both the exposure and outcome.
- **We aimed to identify a CD4 count recovery pattern most predictive of composite adverse events after two years on ART using a JM approach**

Methods

Participants

- We utilized data from three large cohorts with distinct patient characteristics previously well described: the HIV Atlanta VA Cohort Study (HAVACS), US Military HIV Natural History Study (NHS) and the Infectious Disease Program Cohort (IDP) of the Grady Health System
- Patients were treatment naïve and virologically suppressed ≤6 months on ART and remained suppressed for ≥2 years.

Measurements

- The primary predictor of interest was the CD4 cell recovery pattern in the first two years of ART.
- The composite clinical outcome included mortality, AIDS and serious non-AIDS events starting two years after ART initiation.

Statistical Analysis

- Two approaches were used to evaluate the association between the CD4 recovery pattern and the composite clinical endpoint:
  - (i) Two-stage Modeling
    - ➢ 1st stage: rates of CD4 increase were obtained using a mixed-effects model with a random slope and intercept for each patient.
    - ➢ 2nd stage: the risk of composite endpoint was modeled using the Cox regression model considering rate of CD4 increase as main predictor.
  - (ii) Joint Modeling
    - ➢ Enabled both CD4 measurements and the composite clinical outcome to be modelled together while taking into account the association between the corresponding mixed-effects and Cox proportional hazards models.

The study is a secondary data analysis with data from the Center for AIDS Research [CFAR] HIV Data Registry at Grady Health System. The registry contains data from the electronic health records of patients who received medical treatment at the Ponce the Leon Center IDP.

Results

Table 1. Estimated mean CD4 count (cells/μL) at baseline and average rate of increase in the first 2 years

	Mean CD4 intercept (SE)	Mean Rate of CD4 increase (SE)
All	326 (5)	102 (2)
Cohorts		
HAVACS	361 (11)	102 (6)
IDP	180 (5)	103 (3)
NHS	482 (6)	100 (3)
P-value	<0.0001	0.8044
Age at baseline		
Age >37	269 (6)	99 (3)
Age ≤ 37	377 (7)	104 (3)
P-value	<0.0001	0.1843

Table 2. Association of CD4 recovery pattern (rate of increase) in the first two years on continuous ART with risk of composite endpoint

Two-stage model	Unadjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value
50 cells/μL/year higher	0.88	0.79-0.98	0.019	0.89	0.80-0.99	0.037
100 cells/μL/year higher	0.78	0.63-0.96	0.019	0.80	0.65-0.99	0.037
Joint Model						
50 cells/μL/year higher	0.88	0.80-0.98	0.021	0.90	0.81-0.99	0.041
100 cells/μL/year higher	0.78	0.63-0.96	0.021	0.80	0.65-0.99	0.041

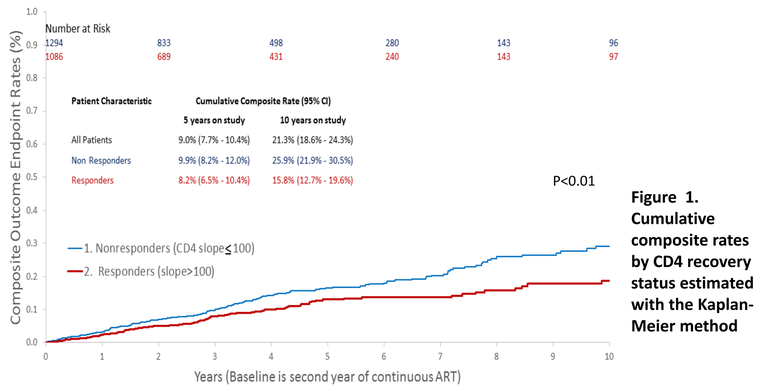

Figure 1. Cumulative composite rates by CD4 recovery status estimated with the Kaplan-Meier method

Key Findings

- The cohort included 2,422 treatment naïve patients
- Median age was 37 years, 86.9% males, 61.6% African-American. Median follow up was 5.4 years for patients without the composite endpoint
- The three cohort groups differed significantly in age at ART initiation, ethnicity, CD4 nadir and CD4 at baseline.
- The average yearly linear CD4 cell count rate of increase was 102 cells/μL/year (95% CI: 98-106 cells/μL/year) during two years of continuous ART.
- When comparing Immune responders (IR) to INR (<100 cells/μL/year), the mean rate of CD4 increase (mean ± SE) was significantly different (IR 178 ±2 vs. INR 38 ±2 cells/μL/year, p<0.0001).
- When evaluating the association between rates of CD4 increase and the composite endpoint in the Joint Model approach, a 50 cell/μL/year increase and a 100 cell/μL/year were both associated with a lower likelihood of developing the composite outcome in the adjusted analysis.
- The 10-year cumulative incidence rate of the composite outcome was 15.8% (95% CI: 12.7%-19.6%) for immune responders (CD4 cell count ≥ 100 cells/μL/year) versus 25.9% (95% CI: 21.9%-30.5%) for INR

Conclusions

- There is no consensus in the literature on how best to define INR and most definitions have not been associated with clinical endpoints.
- This could be related to the complexity associated with performing two-stage modeling and joint modeling analyses but these analyses allow us to obtain less biased estimates and achieve more efficient inferences.
- We propose defining INR as a CD4 increase of <100 cells/μL/year in the first two years of ART. We found that this rate of CD4 increase was predictive of long-term outcomes, even in the adjusted analysis.

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