Effect of Acute HIV Infection on CD4/CD8 Normalization after ART Initiation

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ABSTRACT #291
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Background

- Low CD4/CD8 ratios may be markers of immune activation and chronic inflammation. (1, 2)
- Low CD4/CD8 ratios are associated with increased risk of serious non-AIDS clinical events. (3)
- Earlier antiretroviral therapy (ART) may lead to a higher likelihood of CD4/CD8 normalization. (4)
- We estimated time to CD4/CD8 normalization following ART initiation and hazard ratios of mortality and serious clinical events among acutely and chronically infected patients.

Methods

STUDY PARTICIPANTS

- Acute HIV infection (AHI): acutely HIV-infected patients who initiated ART within 120 days of estimated infection, calculated as 14 days prior to the onset of Acute Retroviral Syndrome
  - AHI is defined as: a) a negative or indeterminate antibody test and reproducibly detectable HIV RNA, or b) a positive antibody test with seronegative documentation within 30 days.
- Chronic HIV infection (CHI): HIV-infected patients who initiated ART on comparable regimens at UNC between 2000 and 2013

DATA SOURCES

- Acute HIV Longitudinal Cohort (AHLC)
- UNC CFAR HIV Clinical Cohort (UCHCC)

OUTCOMES

- CD4/CD8 ratio normalization: ratio ≥ 1
- All-cause mortality
- Composite outcome: all-cause mortality, all non-AIDS defining cancers, myocardial infarction, stroke, end-stage liver disease, end-stage renal disease (all adjudicated)

ART REGIMENS

- 2 NRTIs + NNRTI, boosted PI, or InSTI
- Elvitegravir, Cobicistat, FTC/TDF
- Etravirine + boosted PI

ANALYSIS

- Chi-Square, Wilcoxon Rank-Sums Tests to compare AHI and CHI patients
- Kaplan-Meier curves and multivariable Cox proportional hazards for CD4/CD8 normalization
  - We only included patients who maintained HIV viral load suppression, defined as 2 VL<200 copies/mL at least 14 days apart.
  - Patients censored at virologic failure (2 VL>400 at least 30 days apart), death, loss-to-follow-up, or December 10, 2014.
- Multivariable Cox proportional hazards for mortality and composite outcome, comparing subjects with normal CD4/CD8 ratio at 1 year of ART
  - Patients censored at loss-to-follow-up, or December 10, 2014.

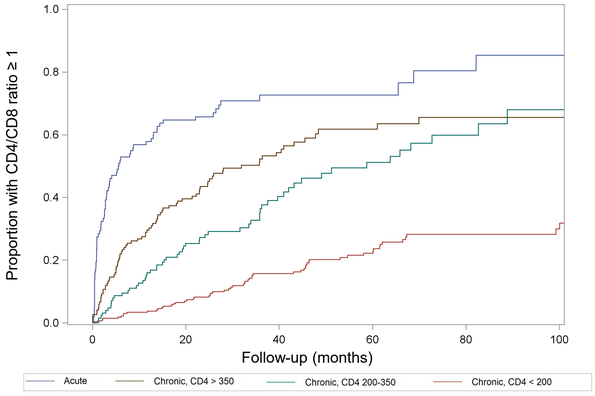
Results

- AHI patients (n=102) were younger, more likely men and had higher baseline CD4 than CHI patients (n=545), (Table 1, both p<0.001).
- 57% and 14% of AHI and CHI patients had normal ratios at 1 year of suppressive ART, respectively (p<0.001).
- Median times to normalization were 6, 28, 51 and >125 months among AHI and CHI patients with ART initiation CD4>350, 200-350 and <200 cells/mm3, respectively (Figure 1, log-rank p<0.001).

Table 1: Baseline characteristics of participants

	Chronic		Acute	
Characteristic	**N**	**%**	**N**	**%**
Total	545	100%	102	100%
Race/Ethnicity				
African-American, non-Hisp.	309	57%	58	57%
White, non-Hisp.	154	28%	40	39%
Hispanic	63	12%	4	4%
Other/Unknown	19	3%	0	0%
Sexual transmission risk group				
MSM	252	46%	81	79%
Hetero men	145	27%	10	10%
Women	148	27%	11	11%
	Median	**IQR**	**Median**	**IQR**
Age (years)				
All participants	38	30-47	28	22-39
Female participants	43	34-48	41	36-44
Male participants	37	29-46	25	21-35
CD4 count (cells/mm^3)	203	56-368	489	346-590
CD4/CD8 ratio	0.2	0.1-0.4	0.4	0.3-0.7
HIV viral load (log copies/mL)	4.8	4.3-5.4	5.2	4.5-5.8

Figure 1: Time from ART initiation to CD4/CD8 normalization



Results

Figure 2: CD4, CD8, and Ratio Trajectories after ART Initiation in Acute vs. Chronic HIV Infection (median, lower and upper quartiles)

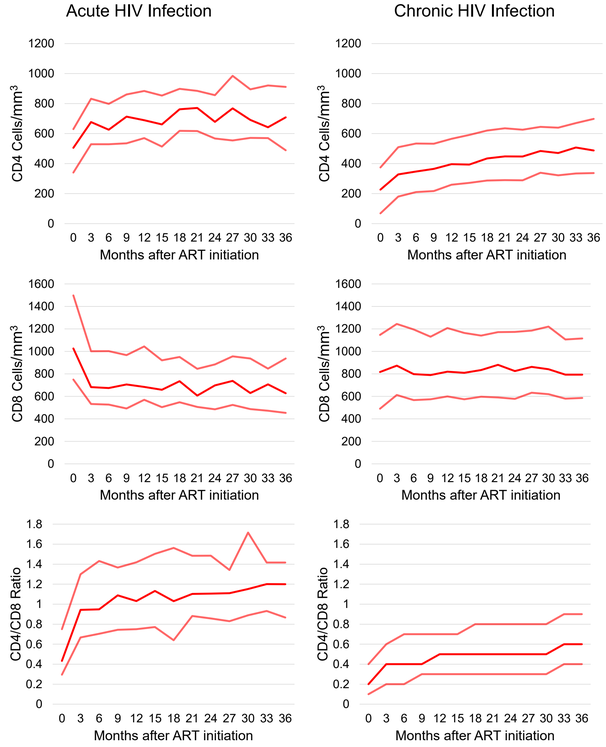


Table 2: Multivariable* Hazard Ratios (HR) and 95% Confidence Intervals (CI) for CD4/CD8 Normalization

Characteristic	HR	95% CI
Acute	2.72	1.00, 3.72
Age, per 10 years increase	1.14	1.02, 1.28
Male sex	0.65	0.49, 0.86
White race	1.00	0.77, 1.29
Baseline CD4, per 100 cells/mm^3 increase	1.33	1.26, 1.40

Results

- In mortality-only analysis, during 4,097 person-years of follow-up, 92 patients died.
- Including mortality and serious non-AIDS clinical outcomes, there were 123 total outcomes. 9 patients had a myocardial infarction, 8 developed end-stage renal disease, 4 had a stroke, 2 developed end-stage liver disease, and 32 developed non-AIDS-defining cancer.

Table 3: Multivariable* Hazard Ratios (HR) and 95% Confidence Intervals (CI) for all-cause mortality and composite outcome

	All-Cause Mortality		Composite Outcome	
Characteristic	**HR**	**95% CI**	**HR**	**95% CI**
Normal ratio at 1 year of ART	0.86	0.40, 1.87	1.03	0.55, 1.92
Baseline CD4, per 100 cells/mm^3	0.82	0.71, 0.95	0.85	0.75, 0.96
Age, per 10 years	1.20	0.98, 1.46	1.29	1.09, 1.53
White race	0.55	0.32, 0.93	0.90	0.60, 1.36
Male sex	0.88	0.55, 1.40	0.75	0.51, 1.11

*Hazard Ratios in tables 2 and 3 are adjusted for baseline CD4, age, race, and sex.

Conclusion

- CD4/CD8 normalization occurred earlier among AHI versus CHI patients.
- Early normalization did not appear to predict mortality and serious non-AIDS events, with study definition of normalization.
- Ratio ≥ 1 is a stringent criterion for normalization, and a lower cut-point may have more predictive power.
- The effect of longitudinal CD4/CD8 ratios on serious clinical events among patients on suppressive ART is important to evaluate given proposed hypotheses of an association with immune activation and immunosenescence.

References

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