Associations between Nadir CD4 and Subsequent Immune Measures with Long-Term Cognitive Function in HAILO (ACTG 5322)

Poster 544

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BACKGROUND

- Older persons with HIV (PWH) experience high rates of cognitive impairment and frailty, and accelerated decline in physical function compared with the general population.
- Relationships between immune measures and long-term cognitive function among virally suppressed PWH receiving ART are unclear.

METHODS

- Among HAILO participants who were virally suppressed with HIV RNA <200 copies/ml ≥75% of time since ART start and had results from ≥2 neurocognitive assessment visits, we analyzed longitudinal data:
  - Immune measures: nadir and current CD4 cells/µl (CD4), time-updated maximum CD4, CD4%, CD4:CD8 ratios
  - Neurocognitive function (NPZ3 scores): combined results from the Trail Making A and B tests and the Wechsler Adult Intelligence Scale-Revised Digit Symbol test

Data Analysis

- Longitudinal linear mixed models with fixed and random effects to assess associations between NPZ3 scores (measured ≥96 weeks post ART start, baseline) and immune measures.
- Models included age, sex, and race/ethnicity (partial adjustment), type and years of ART use, and HCV co-infection (full adjustment).
- Models were Inverse Probability of Censoring (IPC) weighted.

RESULTS

- Among 885 PWH seen 1/1/2000-12/30/2021, median (Q1, Q3) age at ART start was 44 (39, 48) years. Initial ART regimens: 13% included INSTIs, 96% included NRTIs, 37% included NNRTIs, and 56% included PIs. Characteristics at analysis baseline are described in Table 1; median (Q1, Q3) time on ART was 1.8 (1.8, 1.9) years at analysis baseline.
- Higher nadir CD4 was associated with higher baseline NPZ3 but slower NPZ3 increase: PWH with nadir CD4 0-50 had mean NPZ3 increases of 0.067 per year (95% CL = (0.056, 0.077)); PWH with nadir CD4>501 had less yearly increase (0.030 fewer points), 95% CL= (-0.054, -0.007)). Adding any time-updated CD4 measure attenuated effects of nadir CD4, often rendering them non-significant.
- One standard deviation (1SD) (309 cells/µl) higher maximum CD4 was associated with a 0.034 (95% CL=-0.011, 0.080) higher NPZ3 score, and a reduction in NPZ3 score slope of -0.007 (-0.013, -0.002).
- A one standard deviation (10.4) higher CD4% was associated with a 0.074 (0.034, 0.113) higher NPZ3 score and a decrease of -0.009 (-0.015, -0.004) in NPZ3 slope.

CONCLUSIONS

- Lower nadir CD4 was associated with lower NPZ3 score at baseline but greater increases over time.
- Current CD4% and CD4:CD8, but not absolute CD4, had the strongest associations with current NPZ3 score and change over time.

Table 1. Participant characteristics by CD4 nadir group

Characteristic		Total (N=885)	CD4 Nadir Group 0-50 (N=196)	51-200 (N=257)	201-350 (N=290)	351-500 (N=96)	501+ (N=46)
Age (years) at baseline	Min, Max	27, 75	27, 73	30, 72	28, 69	30, 75	37, 65
	Median (Q1, Q3)	46 (41, 50)	45 (40, 50)	46 (41, 51)	45 (40, 50)	46 (40, 51)	46 (43, 50)
	<40	286 (32%)	69 (35%)	74 (29%)	102 (35%)	31 (32%)	10 (22%)
	40-49	424 (48%)	93 (47%)	124 (48%)	133 (46%)	45 (47%)	29 (63%)
	50+	175 (20%)	34 (17%)	59 (23%)	55 (19%)	20 (21%)	7 (15%)
Sex (at birth)	Male	716 (81%)	155 (79%)	217 (84%)	234 (81%)	73 (76%)	37 (80%)
	Female	169 (19%)	41 (21%)	40 (16%)	56 (19%)	23 (24%)	9 (20%)
Race/Ethnicity	White, non-Hispanic	442 (50%)	73 (37%)	120 (47%)	169 (58%)	51 (53%)	29 (63%)
	Black, non-Hispanic	258 (29%)	68 (35%)	78 (30%)	73 (25%)	28 (29%)	11 (24%)
	Hispanic + other	185 (21%)	55 (28%)	59 (23%)	48 (17%)	17 (18%)	6 (13%)
HIV-1 RNA*	<200 copies/ml	862 (97%)	189 (96%)	249 (97%)	283 (98%)	96 (100%)	45 (98%)
Hepatitis C co-infection*	Yes	89 (10%)	14 (7%)	26 (10%)	33 (11%)	10 (10%)	6 (13%)
CD4 (cells/µl)*	Min, Max	23, 1,671	23, 952	104, 1,046	262, 1,211	460, 1,316	648, 1,671
	Median (Q1, Q3)	486 (332, 648)	276 (191, 377)	404 (298, 512)	570 (478, 662)	706 (623, 819)	993 (884, 1,174)
CD4%*	Min, Max	4.0, 62.6	4.0, 44.5	8.3, 46.0	11.0, 56.7	22.7, 62.6	27.2, 55.0
	Median (Q1, Q3)	28.3 (19.7, 35.3)	16.0 (11.5, 20.7)	24.7 (19.3, 30.3)	33.2 (28.0, 37.3)	37.7 (32.8, 42.1)	42.6 (38.7, 47.1)
CD4:CD8 ratio*	Min, Max	0.1, 3.3	0.1, 1.6	0.1, 2.3	0.2, 3.0	0.4, 3.3	0.5, 2.3
	Median (Q1, Q3)	0.7 (0.4, 0.9)	0.3 (0.2, 0.4)	0.5 (0.4, 0.7)	0.8 (0.6, 1.0)	1.0 (0.8, 1.3)	1.3 (1.0, 1.5)
NPZ3 score*	Min, Max	-3.3, 3.0	-3.1, 2.6	-3.3, 3.0	-2.9, 2.3	-2.7, 2.4	-1.8, 2.4
	Median (Q1, Q3)	-0.1 (-0.7, 0.5)	-0.2 (-0.9, 0.6)	-0.0 (-0.7, 0.5)	-0.1 (-0.7, 0.5)	-0.1 (-0.5, 0.7)	-0.2 (-0.8, 0.4)

*Note: * Analysis baseline (96 weeks post ART initiation) value of time-updated variable.*

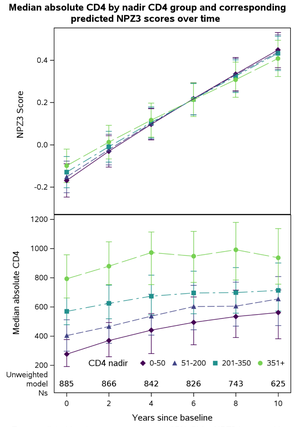
- A 1SD (0.527) higher CD4:CD8 ratio was associated with a 0.060 (0.020, 0.099) higher NPZ3 score and reduction in NPZ3 score slope of -0.007 (-0.012, -0.001).
- When nadir and current CD4 were modeled together, their effects were not statistically significant. Effects were similar in fully-adjusted models
- Current CD4% and CD4:CD8 remained most strongly associated with current NPZ3 score and change over time

- Table 2: Models for current CD4, CD4%, and CD4:CD8 ratio were rerun without nadir CD4.

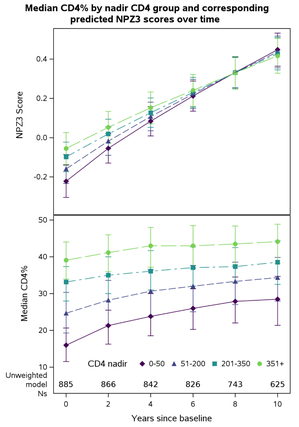
Table 2. Longitudinal associations between NPZ3 Score and individual CD4 measures

Effect	Model 1: Absolute CD4 Estimate	(95% CL)	Model 2: CD4% Estimate	(95% CL)	Model 3: CD4:CD8 ratio Estimate	(95% CL)
Intercept*	0.185	(0.068, 0.302)	0.186	(0.069, 0.303)	0.209	(0.092, 0.326)
CD4 measure	0.039	(0.006, 0.072)	0.075	(0.042, 0.109)	0.070	(0.035, 0.106)
Time (years since baseline)	0.059	(0.054, 0.065)	0.057	(0.051, 0.062)	0.055	(0.050, 0.060)
Time x CD4 measure	-0.007	(-0.011, -0.002)	-0.010	(-0.014, -0.005)	-0.008	(-0.013, -0.004)

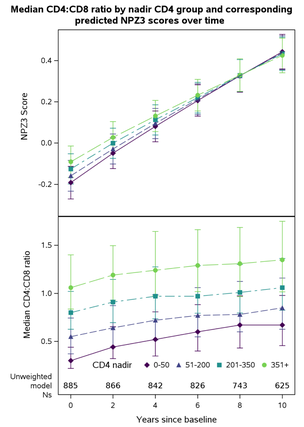
*Note: All models are adjusted for age group, race/ethnicity, and birth sex, and IPC weighted. *Intercept represents White non-Hispanic man, age <40 years. CD4 measures shifted and scaled based on overall standard deviations as follows: current CD4 (cells/µl): centered at 500, 1 unit=288; CD4%: centered at 30, 1 unit=10.4; CD4:CD8 ratio: centered at 0.9, 1 unit=0.527*



Top: predicted least squares means and 95% CI for NPZ3 in men with given absolute CD4 over time. Bottom: median Q1-Q3 absolute CD4 (cells/microliters) by CD4 nadir group over time.



Top: predicted least squares means and 95% CI for NPZ3 in men with given CD4% over time. Bottom: median Q1-Q3 CD4% by CD4 nadir group over time.



Top: predicted least squares means and 95% CI for NPZ3 in men with given CD4:CD8 ratio over time. Bottom: median Q1-Q3 CD4:CD8 ratio by CD4 nadir group over time.

Above:

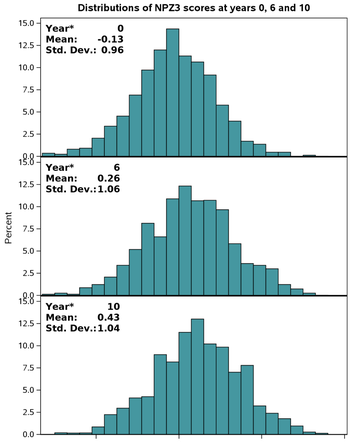
- The bottom panels plot median (Q1-Q3) CD4 stratified by nadir CD4 group with the top 2 CD4 nadir groups combined. The top panels plot the least squares means and 95% confidence intervals for male participants as estimated by the models in Table 2. (Plots use unscaled CD4 measures.)
- Predicted NPZ3 scores converged 6-8 years after baseline for the 4 nadir CD4 groups
- Over time, CD4 nadir groups became somewhat less immunologically distinct, with substantial overlap
- See Table 3 (*below*) for median (Q1, Q3) CD4 at time of NPZ3 convergence.

Table 3. CD4 at year of predicted NPZ3 convergence

Nadir CD4 group	Absolute CD4 (year 6) Med.	(Q1, Q3)	CD4% (year 8) Med.	(Q1, Q3)	CD4:CD8 ratio (year 8) Med.	(Q1, Q3)
0-50	494	(341, 669)	27.9	(22.0, 34.5)	0.67	(0.43, 0.97)
51-200	602	(443, 748)	33.3	(27.0, 38.6)	0.78	(0.60, 1.12)
201-350	696	(554, 845)	37.3	(33.0, 42.5)	1.01	(0.80, 1.30)
351+	948	(769, 1118)	43.5	(37.8, 48.4)	1.31	(0.97, 1.69)

Right:

- Distributions of NPZ3 scores at 0, 6, and 10 years since analysis baseline, IPC weighted.



*Years since analysis baseline; statistics are IPCW weighted.

ACKNOWLEDGEMENTS

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