PREDICTIVE VALUE OF THE CD8 COUNTS AND CD4/CD8 RATIO AT TWO YEARS OF SUCCESSFUL ART

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BACKGROUND

- Individuals on successful antiretroviral therapy (ART) still have increased morbidity and mortality.
- Increased CD8+ T cell counts and low CD4/CD8 ratio during treated HIV correlate with immunosenescence.
- Cohort studies have yielded conflicting results on their additional predictive value to identify HIV-infected individuals at higher risk of clinical events.
- We examined whether CD8+ T cell counts and CD4/CD8 ratio after 2 years of suppressive ART predict the probability of subsequent clinical events through year 7, independently of the CD4 count.

METHODS

Study population:

- Treatment-naïve individuals from ACTG studies: 384, 388, A5095, A5142, A5202, A5257 + ALLRT follow-up.
- N = 5133
- Virologically suppressed (<200 copies/ml) and on ART at year 2.
- CD8+ T cell counts and CD4/CD8 ratio available at year 2.

Clinical events:

- AIDS-defining event (ADE)
- Non-AIDS-defining events: non-accidental death, liver, cardiovascular, renal disease, cancers, fractures, diabetes and serious bacterial infection.

Statistical analysis:

- Individuals were censored at the time of ART interruption, viral failure (2 vRNA ≥ 200 cp/mL) or loss to follow up.
- Inverse probability of censoring weighting (IPCW) method addressed informative censoring.
- Logistic regression models with IPCW weights estimated the association between CD8+ T cell counts and CD4/CD8 ratios at year 2 and clinical events during years 3-7.

RESULTS

1. CD8+ T cell counts at year 2 had the clearest stepwise effect across the full range of values for the association with subsequent clinical events.

2. CD4/CD8 ratio at extremely low values was predictive of greater risk of clinical events especially AIDS-defining events through year 7

Table 1: Demographics and pre-ART variables of individuals (N=5133)

	Clinical events years 3-7			
	Yes (N=385)	No (N=961)	Censored (N=3787)	Total (N=5133)
Male	305 (79%)	788 (82%)	3,081 (81%)	4,174 (81%)
Race/ethnicity: White	188 (49%)	452 (47%)	1,528 (40%)	2,168 (42%)
Black	136 (35%)	260 (27%)	1,335 (35%)	1,731 (34%)
Age (years), Median (IQR)	44 (38, 51)	39 (33, 45)	37 (30, 45)	38 (31, 45)
Injection drug use	41 (11%)	54 (6%)	312 (8%)	407 (8%)
Initial ARVs:				
Boosted PI+NRTI	121 (31%)	213 (22%)	1,521 (40%)	1,855 (36%)
NNRTI +NRTI	149 (39%)	529 (55%)	1,292 (34%)	1,970 (38%)
INSTI+NRTI	29 (8%)	0 (0%)	494 (13%)	523 (10%)
Pre-ART HIV RNA(≤100000 copies/ml)	215 (56%)	576 (60%)	2,461 (65%)	3,252 (63%)
CD4 count at year 2, Median (IQR)	476 (311, 656)	463 (321, 609)	516 (360, 683)	503 (348, 668)
CD8 count at year 2, Median (IQR)	819 (590, 1,059)	770 (586, 1,014)	769 (574, 1,019)	772 (578, 1,022)
<500	61 (16%)	146 (15%)	591 (16%)	798 (16%)
500-1499	293 (76%)	766 (80%)	2,992 (79%)	4,051 (79%)
≥1500	31 (8%)	49 (5%)	204 (5%)	284 (6%)
CD4:8 ratio at year 2, Median (IQR)	0.60 (0.38, 0.92)	0.61 (0.37, 0.88)	0.68 (0.43, 0.97)	0.65 (0.41, 0.95)
<0.15	9 (2%)	12 (1%)	51 (1%)	72 (1%)
0.15-0.3	57 (15%)	143 (15%)	396 (10%)	596 (12%)
>0.3	319 (83%)	806 (84%)	3,340 (88%)	4,465 (87%)
History of a clinical event at year 2	188 (49%)	320 (33%)	1,174 (31%)	1,682 (33%)

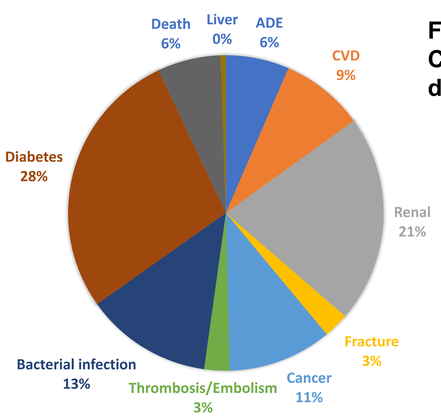


Figure 1: Clinical Events during years 3-7

Table 2: Adjusted odd ratios and 95 percent confidence intervals for the first clinical event during years 3-7

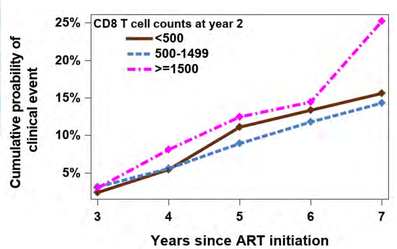
	CD4 adjusted*		Multivariable adjusted**	
Variables	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
CD8+ T-cell at year 2:				
Every 100 cells increase	1.03 (1.01,1.05)	0.003	1.02 (1.00,1.04)	0.04
<500 vs 500-1499	1.14 (0.92,1.42)	0.22	1.12 (0.90,1.41)	0.32
≥1500 vs 500-1499	1.99 (1.51,2.64)	<0.001	1.79 (1.33,2.41)	<0.001
CD4:8 ratio at year 2:				
<0.15 vs >0.3	2.81 (1.61,4.9)	<0.001	1.34 (0.76,2.39)	0.31
0.15-0.3 vs >0.3	1.08 (0.84,1.39)	0.53	0.73 (0.57,0.93)	0.01

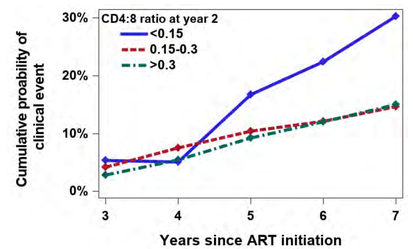
* Each row adjusted for CD4 cells counts at year 2. **Note:** CD4 at year 2: OR (95% CI) =1.02 (0.99,1.06) per 100 cells increase and OR (95% CI) =1.32 (1, 1.75) for CD4≤200 (vs >200).
**Each row adjusted for race/ethnicity, injection drug use, age, initial ARV regimens, pre-ARV HIV viral load and history of clinical events, not adjusted for CD4.

Table 3: CD4-adjusted odd ratios and 95 percent confidence intervals for specific class of event during years 3-7

	AIDS		Infectious non-AIDS		Noninfectious non-AIDS	
Variables	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
CD8+ T-cell at year 2:						
<500 vs 500-1499	1.44 (0.71,2.93)	0.3	1.53 (0.99,2.36)	0.05	1.18 (0.93,1.49)	0.2
≥1500 vs 500-1499	3.86 (1.81,8.20)	<0.001	0.28 (0.07,1.15)	0.08	2.25 (1.68,3.02)	<0.001
CD4:8 ratio at year 2:						
<0.15 vs >0.3	5.11 (1.51,17.31)	0.009			3.01 (1.66,5.47)	<0.001
0.15-0.3 vs >0.3	1.14 (0.51,2.55)	0.7			1.14 (0.87,1.5)	0.3
≤0.3 vs >0.3			0.68 (0.38,1.22)	0.2		

Figure 2: Estimated probability of clinical events over time by CD8 cell counts and CD4:8 ratios





CONCLUSIONS

- The results of this analysis with pooled data from clinical trials support the value of the CD8+ T cell count as a predictor of clinical progression.
- People with very high CD8 counts during suppressive ART might benefit from closer monitoring and could be a target population for novel interventions.

ACKNOWLEDGEMENTS

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