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Intestinal CD4:CD8 ratio and systemic inflammatory parameters in suppressed HIV-1 infection

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BACKGROUND

- With successful antiretroviral therapy (ART), while peripheral CD4+ T cells may reconstitute in most people with HIV, CD8+ T cells often remain elevated.
- Inversion of CD4:CD8 ratio (<1) is associated with adverse clinical outcomes.
- The gut-associated lymphoid tissue (GALT) endures significant CD4+ T cell depletion starting during acute HIV infection.

AIM OF THE STUDY

TI determine the heterogeneity in CD4:CD8 ratio in people with suppressed HIV infection on ART (PWSH), the predictors of intestinal CD4:CD8 ratio reconstitution (CD4:CD8>1) and its impact on systemic inflammation.

METHODS

We enrolled 52 PWSH (peripheral HIV-RNA<20 copies/ml, PWSH) on ART as well as 37 HIV-negative controls (HIV-NC) who underwent colonoscopy **(Table 1).** T-cell subsets were analyzed via multiparameter flow cytometry. Peripheral inflammatory cytokines were analyzed with a multiplexed proteomic inflammation panel (Olink®). Comparisons were performed with Mann-Whitney U test, Chi-square test or Spearman correlation as appropriate. Multiple logistic regression was used to estimate Odds Ratio (OR).

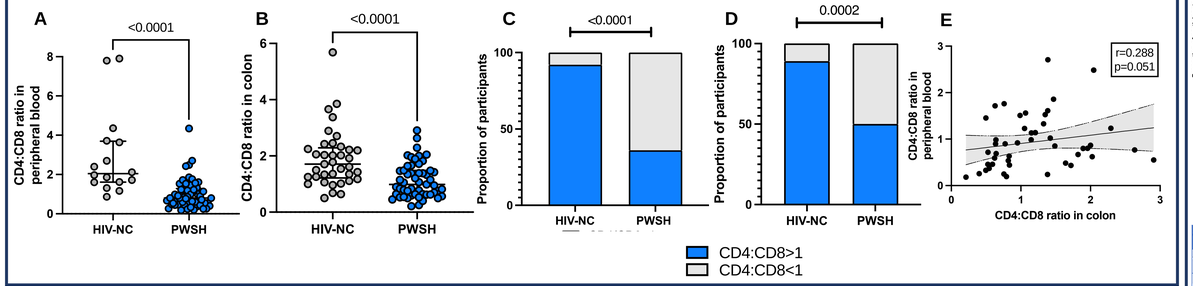
RESULTS

Table 1: Demographics and HIV-related characteristic of study participants.

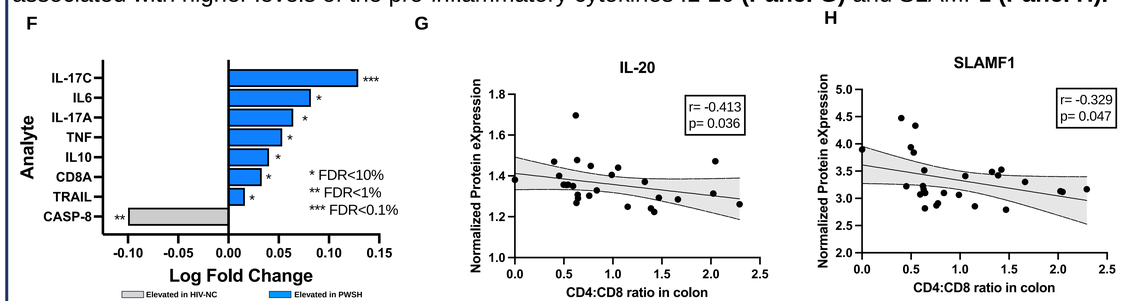
	PWSH	HIV-NC	P value
Female sex, n(%)	16 (31%)	18 (49%)	0.087
Race/ethnicity n(%)			
Caucasian	13 (25%)	14 (38%)	0.0113
African-American	14 (27%)	4 (11%)	
Hispanic/latino	23 (44%)	11 (30%)	
Other	2 (4%)	8 (21%)	
Age, median (IQR)	56 (51 – 61)	57 (46 – 69)	0.776
HIV acquisition risk			
MSM	25 (38%)	-	
Heterosexual contact	23 (35%)		
IVDU	5 (8%)		
Other/NA	12 (18%)		
Years since HIV diagnosis	21 (15 - 26)	-	
Years of last known virological suppression	7 (4 – 11)	-	
Nadir CD4+ T Cells	192 (88 – 228)	-	
CD4+ T Cells at enrollment	594 (451 – 880)	-	

Longer time since HIV diagnosis and higher CD4+ T cells nadir are the best predictors of normalization of intestinal CD4:CD8 ratio in people with suppressed HIV infection

RESULTS: Overall, PWSH had a lower CD4:CD8 ratio both in the peripheral blood [0.8 (0.5 – 1.28) vs 2.05 (1.6 – 3.7) p<0.001] **(Panel A)** and in the colon [0.9 (0.6-1.4 vs 1.7 (1.2-2.9)), p<0.0001] **(Panel B)** compared to HIV-NC. Sixteen (36%) of PWSH had CD4:CD8 ratio>1 in the peripheral blood, compared to 11 (92%) of HIV-NC (**Panel C**); while 26 (50%) PWSH had colonic CD4:CD8 >1 compared to 33 (89%) in HIV-NC **(Panel D)**. In PWSH, colonic CD4:CD8 showed a weak correlation with the peripheral blood CD4:CD8 ratio **(Panel E).**



RESULTS: Higher levels of several pro-inflammatory systemic cytokines were observed in PWSH compared with HIV-NC after correcting for multiple comparisons **(Panel F)** and lower colonic CD4:CD8 ratio was associated with higher levels of the pro-inflammatory cytokines IL-20 **(Panel G)** and SLAMF1 **(Panel H).**



RESULTS

Table 2: PWSH with CD4:CD8 ratio>1 were more likely female **(Panel I)**, diagnosed with HIV for a longer time **(Panel J)**, have longer duration of most recent viral suppression **(Panel K)**, higher CD4+ T cells at enrollment **(Panel L)** and higher CD4+ T cell nadir **(Panel M)**.

	Colon CD4:CD8 ratio >1	Colon CD4:CD8 ratio <1	P value (chi-square or M-W tests)
Female, n(%)	**10 (62%)**	**6 (38%)**	**0.0158**
Race/ethnicity n(%)			
Caucasian	8 (62%)	5 (38%)	0.388
African-American	6 (43%)	8 (57%)	
Hispanic/latino	12 (52%)	11(48%)	
Other	0 (0%)	2 (100%)	
Age, median (IQR)	57 (53 - 61)	53 (50 – 71)	0.1256
HIV acquisition risk			
MSM	12 (48%)	13 (52%)	0.2301
Heterosexual contact	8 (50%)	8 (50%)	
IVDU	0 (0%)	3 (100%)	
Other/NA	5 (71%)	2 (29%)	
Years since HIV diagnosis	**21 (18-32)**	**19 (10-24)**	**0.0347**
Years of last known virological suppression	**7 (4-12)**	**4 (2-8)**	**0.0365**
Nadir CD4+ T Cells	**200 (92-306)**	**162 (39 – 193)**	**0.0413**
CD4+ T Cells at enrollment	**607 (453 - 947)**	**462 (294 - 664)**	**0.0262**

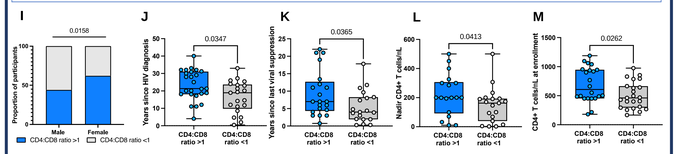


Table 3: Multiple logistic regression showed that duration of HIV infection and CD4+ T cell nadir were associated with colonic CD4:CD8 >1.

Variable	OR	95% CI
Years since HIV diagnosis	**1.129**	**1.019 to 1.304**
CD4+ T cells nadir	**1.007**	**1.001 to 1.016**
Peripheral CD4+ T cells/mcl	1.003	0.9993 to 1.007
Time since last known virological suppression	1.146	0.9921 to 1.374
Female sex	0.8579	0.1134 to 5.910

CONCLUSIONS

In PWSH, CD4:CD8 ratio<1 is associated with persistent elevation of inflammatory parameters. Nadir CD4+ T cells and longer since HIV diagnosisare the best predictors of normalization of intestinal CD4:CD8 ratio

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ADDITIONAL KEY INFORMATION

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