Aging, Trends in CD4/CD8 Ratio and Clinical Outcomes with HIV Suppression

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BACKGROUND

- **Among persons with HIV (PLWH), data addressing the effects of aging on T cell phenotype suggest that advancing age blunts CD4 cell count (CD4) improvements observed with ART-induced viral suppression. [1,2]**
- **ART-induced prolonged viral suppression reduces immune activation, reflected by a rising CD4/CD8 ratio.**
- **We studied CD4/CD8 over time to determine whether it could predict risk for select comorbidities or mortality among aging PLWH with ≥ 1 year virologic control.**

METHODS

- **We analyzed data from HIV Outpatient Study (HOPS) participants seen at 12 U.S. HIV clinics who were followed from 2000-2018.**
- **The first viral load test result < 200 copies/mL while taking ART during 2000-2018 was considered to be the baseline observation date.**
- **Included participants had known baseline CD4, ART history, all viral loads (VL) < 200 copies/mL during 1st observation year, ≥ 1 year of follow up with ≥ 2 CD4/CD8 measures (N=2,480).**
- **We analyzed participants with CD4/CD8 < 0.7 (immune dysregulation) versus ≥ 0.7 by age group.**
- **Cochran-Armitage trend tests were used to compare proportions across time, and by baseline age.**
- **Clinical outcomes we evaluated included non-AIDS non-skin cancer, dyslipidemia, renal disease and all-cause mortality. Outcomes were determined using abstracted data collected by routine medical records review: lab records, treatments (where applicable), and documented diagnoses (as previously described [3]) or death.**
- **Spearman correlations were used to determine associations between baseline CD4/CD8 value and clinical outcomes.**
- **Case-control analyses were performed using conditional logistic regression to assess for associations of baseline CD4/CD8 < 0.7 with clinical outcomes and mortality during observation, matching 1:1 for smoking, sex and age.**

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Table 1: Characteristics at baseline of participants by age group, the HIV Outpatient Study, 2000-2018, (N=2,480)

Baseline characteristic*	N (%)	Age < 40 years	Age 40-49 years	Age ≥ 50 years	P-value†
Overall	2,480 (100.0)	1,145 (46.2)	835 (33.7)	500 (20.2)	
Year of HIV diagnosis, median (IQR)	2000 (1995-2006)	2002 (1997-2008)	1998 (1993-2004)	1999 (1993-2005)	< 0.001
Started ART before 2000	739 (29.8)	292 (25.5)	296 (35.5)	151 (30.2)	
Started ART during 2000-2007	948 (38.2)	443 (38.7)	315 (37.7)	190 (38.0)	< 0.001
Started ART during 2008-2012	558 (22.5)	270 (23.6)	172 (20.6)	116 (23.2)	
Started ART during 2013-2017	235 (9.5)	140 (12.2)	52 (6.2)	43 (8.6)	
Male sex	2,023 (81.6)	925 (80.8)	686 (82.2)	412 (82.4)	0.64
Female sex	457 (18.4)	220 (19.2)	149 (17.8)	88 (17.6)	
White, non-Latinx	1,281 (51.6)	541 (47.2)	459 (55.0)	281 (56.2)	
Black, non-Latinx	778 (31.4)	375 (32.8)	256 (30.7)	147 (29.4)	0.002
Latinx race/ethnicity	322 (13.0)	176 (15.4)	91 (10.9)	55 (11.0)	
Other/Unknown race/ethnicity	99 (4.0)	53 (4.6)	29 (3.5)	17 (3.4)	
MSM HIV risk	1,561 (62.9)	767 (67.0)	522 (62.5)	272 (54.4)	
Heterosexual HIV risk	625 (25.2)	275 (24.0)	209 (25.0)	141 (28.2)	< 0.001
IDU HIV risk	155 (6.3)	38 (3.3)	65 (7.8)	52 (10.4)	
Other HIV risk	139 (5.6)	65 (5.7)	39 (4.7)	35 (7.0)	
Private insurance	1,486 (59.9)	692 (60.4)	520 (62.3)	274 (54.8)	
Public insurance	772 (31.1)	340 (29.7)	245 (29.3)	187 (37.4)	0.013
No insurance	222 (9.0)	113 (9.9)	70 (8.4)	39 (7.8)	
Current/prior smoker-yes	1,185 (47.8)	505 (44.1)	415 (49.7)	265 (53.0)	0.002
Current/prior smoker-no	1,295 (52.2)	640 (55.9)	420 (50.3)	235 (47.0)	
On 1st ART regimen	1,483 (59.8)	757 (66.1)	446 (53.4)	280 (56.0)	
On 2nd ART regimen	238 (9.6)	103 (9.0)	81 (9.7)	54 (10.8)	< 0.001
On 3rd ART regimen	239 (9.6)	106 (9.3)	85 (10.2)	48 (9.6)	
On 4th or higher ART regimen	520 (21.0)	179 (15.6)	223 (26.7)	118 (23.6)	
Nadir CD4+ < 200 cells/mm^3	939 (39.1)	389 (34.0)	363 (43.5)	217 (43.4)	
Nadir CD4+ 200-349 cells/mm^3	687 (27.7)	334 (29.2)	218 (26.1)	135 (27.0)	< 0.001
Nadir CD4+ 350-499 cells/mm^3	437 (17.6)	217 (19.0)	132 (15.8)	88 (17.6)	
Nadir CD4+ ≥ 500 cells/mm^3	387 (15.6)	205 (17.9)	122 (14.6)	60 (12.0)	
Clinical history (pre-baseline*)					
Cardiovascular disease	199 (8.0)	45 (3.9)	72 (8.6)	82 (16.4)	< 0.001
Cancer (non-AIDS, non-skin)	49 (2.0)	12 (1.0)	15 (1.8)	22 (4.4)	< 0.001
Renal disease	144 (5.8)	30 (2.6)	50 (6.0)	64 (12.8)	< 0.001
Dyslipidemia	678 (27.3)	213 (18.6)	247 (29.6)	218 (43.6)	< 0.001
Diabetes	130 (5.2)	26 (2.3)	54 (6.5)	50 (10.0)	< 0.001
Clinical outcomes during follow-up					
Died within 6 months of last HOPS contact	124 (5.0)	20 (1.8)	54 (6.5)	50 (10.0)	< 0.001
Cardiovascular disease	4 (0.2)	3 (0.3)	0 (0.0)	1 (0.2)	0.35
Cancer (non-AIDS, non-skin)	153 (6.2)	29 (2.5)	53 (6.3)	71 (14.2)	< 0.001
Renal disease	16 (0.6)	1 (0.1)	6 (0.7)	9 (1.8)	< 0.001
Dyslipidemia	27 (1.1)	9 (0.8)	14 (1.7)	4 (0.8)	0.13
Diabetes	4 (0.2)	0 (0.0)	2 (0.2)	2 (0.4)	0.14

Abbreviations: ART, antiretroviral therapy; MSM, men who have sex with men; PWID, persons who inject drugs. *Baseline is the date of the first viral load test result < 200 copies/mL. †Yates-corrected chi-square test

RESULTS, Table 1:

- **2,480 participants were included. Median duration of follow up to last HOPS encounter from baseline date was 7.4 years (interquartile range = 4.1-12.2 years).**
- **At the date of first VL < 200 copies/mL (baseline), 46% were < 40 years, 34% were 40-49 years, and 20% were ≥ 50 years of age.**
- **Median baseline age was 41 years; 82% were men; 52% Non-Latinx (NL) white, 32% NL black, and 13% Latinx.**
- **60% were on their 1st ART regimen, 21% on their ≥4th regimen. 39% had a nadir CD4 count < 200 cells/mm^3.**

Figure 1a: Median CD4/CD8 by baseline age group and year of follow-up, the HIV Outpatient Study, 2000-2018, (N=2,480)

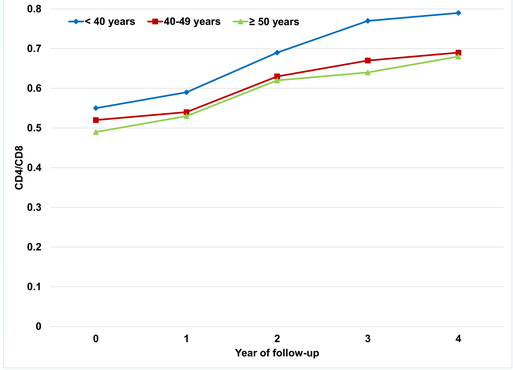
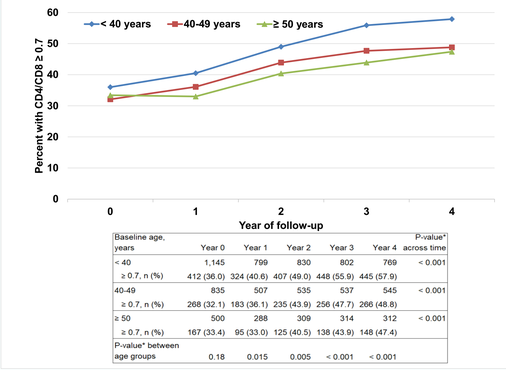


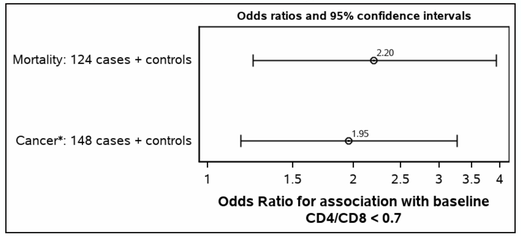
Figure 1b: Percent of participants with CD4/CD8 ≥ 0.7 by baseline age group and year of follow-up, the HIV Outpatient Study, 2000-2018, (N=2,480)



Baseline age, years	Year 0	Year 1	Year 2	Year 3	Year 4	P-value* across time
< 40	1,145	799	830	802	769	< 0.001
≥ 0.7, n (%)	412 (36.0)	324 (40.6)	407 (49.0)	448 (55.9)	445 (57.9)	
40-49	835	507	535	537	545	< 0.001
≥ 0.7, n (%)	268 (32.1)	183 (36.1)	235 (43.9)	256 (47.7)	266 (48.8)	
≥ 50	500	288	309	314	312	< 0.001
≥ 0.7, n (%)	167 (33.4)	95 (33.0)	125 (40.5)	138 (43.9)	148 (47.4)	
P-value* between age groups	0.18	0.015	0.005	< 0.001	< 0.001	

*Cochran-Armitage test of trend

Figure 2: Matched case-control analyses for two selected outcomes, the HIV Outpatient Study, 2000-2018



*Non-AIDS, non-skin cancer.
Note: Cases and controls were matched on smoking status, age range, and sex.

RESULTS

Figure 1a:

- **CD4% declined but CD8% was not observed to increase with age (data not shown).**
- **The median CD4/CD8 value was highest in the youngest age group at baseline and at the end of follow-up, compared to the two older age groups.**

Figure 1b:

- **Baseline CD4/CD8 predicted CD4/CD8 increases through 4y of follow up (P < 0.001 for each follow-up year).**
- **Higher baseline age predicted lesser CD4/CD8 increases through 4y of follow-up with increasing age (P < 0.05 within each follow-up year).**

RESULTS, Figure 2:

- **Matched case-control analyses for death (n=124) and non-AIDS non-skin cancer (n=153) were performed. There were insufficient numbers of outcomes during follow-up for analysis of other co-morbidities.**
- **Of the 153 cases of incident non-AIDS non-skin cancer, 148 had baseline CD4/CD8 data, and all of these 148 were matched to controls.**
- **In matched conditional logistic regressions comparing participants with CD4/CD8 < 0.7 vs ≥ 0.7; mortality (Odds Ratio [OR] 2.20, 95% Confidence Interval [95% CI] 1.24-3.93), and non-AIDS non-skin cancer (OR 1.95, 95% CI 1.17-3.26) were significantly associated with CD4/CD8 < 0.7.**

CONCLUSIONS

- **Among PLWH, immune dysregulation may persist as assessed by CD4/CD8 < 0.7, even with viral suppression over time.**
- **Many co-morbidities were pre-existing prior to baseline among this cohort of virally suppressed PLWH.**
- **After matching on age, smoking status and sex, baseline immune dysregulation was associated with mortality and non-AIDS non-skin cancer.**
- **Our data suggest that there may be clinical consequences to continued immune dysregulation among aging PLWH over time, that warrant continued surveillance, prevention, and treatment.**

The findings and conclusions from this presentation are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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