Higher CD4 at cART Initiation Predicts Long Term Likelihood of CD4 Normalization in the HIV Outpatient Study (HOPS)

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INTRODUCTION

- Higher plasma CD4+ cell counts per mm^3 (CD4) at cART initiation (AI) improve long-term CD4 responses and survival.
- Recent data suggest attaining CD4 > 750 is a clinically significant threshold for AIDS-related illness reduction and immune "normalization".
- We evaluated the effect of CD4 on subsequent long-term immunologic recovery, including the likelihood of achieving CD4 > 750, as well as mortality risk and factors associated with survival.

METHODS

Study Population: ART-naïve HIV-infected participants in the HIV Outpatient Study (HOPS) seen during 1996-2012 who had ≥ 3 years of follow-up after AI.

Statistical Methods:

- Mortality rates per 100 person-years by CD4 at time of cART initiation (AI, baseline) with 95% CIs assuming Poisson distribution.
- CD4 trajectories compared using the Jonckheere-Terpstra test.
- Factors associated with mortality and achieving CD4 > 750 examined using Cox proportional hazards models with backward selection of variables.

RESULTS

- Of 1,327 eligible patients followed a median of 7.9 years, > 85% were prescribed cART at least 75% of follow-up time after AI, and 64 died; Table 1.
- Higher CD4 at AI was associated with:
  1. Increased subsequent median peak CD4+ (p < 0.001 for trend); Table 2.
  2. Lower crude mortality rates (p = 0.005 for trend) and higher CD4 closest to death (p = 0.013 for trend); Table 2.
- Maximal CD4 response and benefit plateaued at about eight years after AI, but differences by CD4 strata at AI persisted (p < 0.001 for trend); Figure 1.
- Increases in median CD4 for persons with CD4 at AI < 50 and 50-199 seemed to converge by eight years after AI (< 50% achieved CD4+ > 750).
- Participants with CD4 > 350 at AI achieved a CD4 > 750 (normalization) by eight years after AI (> 80% of patients); Figure 1.
- In multivariable analyses, higher CD4 at AI was independently associated with achieving a CD4 > 750 during follow-up through last HOPS contact, and having a history of injection drug use HIV risk was inversely associated with this outcome; Table 3.

Table 1: Characteristics of HOPS participants whose first ART regimen was a cART regimen and were followed for at least 3 years after cART initiation: 1996-2012 (N=1,327)

Patient characteristics at cART initiation	CD4+ cell count range (cells/mm^3) at start of observation: n (column %) or median (IQR)					
	< 50	50-199	200-349	350-499	≥ 500	Total
Total patients	261	313	326	215	212	1,327
Total deaths	19	24	9	5	7	64
Start of observation						
1996-2000	108 (41.4)	118 (37.7)	100 (30.7)	81 (37.7)	118 (55.7)	525 (39.6)
2001-2006	118 (45.2)	140 (44.7)	148 (45.4)	72 (33.5)	66 (31.1)	544 (41.0)
2007-2012	35 (13.4)	55 (21.3)	78 (23.9)	62 (28.8)	28 (13.2)	258 (19.4)
Median years follow-up (IQR)	8.2 (5.6-11.5)	7.7 (5.4-11.0)	7.7 (5.0-10.3)	7.3 (4.7-11.5)	8.5 (5.8-13.3)	7.9 (5.3-11.4)
Age in years						
All ages, median (IQR)	38 (33-47)	40 (34-46)	36 (31-44)	38 (31-45)	37 (31-45)	38 (32-45)
< 35	84 (32.2)	89 (28.4)	131 (40.2)	86 (40.0)	89 (42.0)	479 (36.1)
35-44	127 (48.7)	172 (55.0)	161 (49.4)	97 (45.1)	94 (44.3)	651 (49.1)
≥ 45	50 (19.2)	52 (16.6)	34 (10.4)	32 (14.9)	29 (13.7)	197 (14.9)
Sex						
Female	74 (28.4)	65 (20.8)	72 (22.1)	36 (16.7)	42 (19.8)	289 (21.8)
Male	187 (71.6)	248 (79.2)	254 (77.9)	179 (83.3)	170 (80.2)	1,038 (78.2)
Race/Ethnicity						
Black	119 (45.6)	103 (32.9)	109 (33.4)	58 (27.0)	54 (25.5)	443 (33.4)
White	92 (35.3)	147 (47.0)	166 (50.9)	120 (55.8)	128 (60.4)	653 (49.2)
Hispanic	38 (14.6)	52 (16.6)	36 (11.0)	28 (13.0)	20 (9.4)	174 (13.1)
Other/unknown	12 (4.6)	11 (3.5)	15 (4.6)	9 (4.2)	10 (4.7)	57 (4.3)
Insurance						
Private	132 (50.6)	178 (56.9)	200 (61.4)	147 (68.4)	134 (63.2)	791 (59.6)
Public	92 (35.3)	91 (29.1)	76 (23.3)	42 (19.5)	47 (22.2)	348 (26.2)
Other/unknown	37 (14.2)	44 (14.1)	50 (15.3)	26 (12.1)	31 (14.6)	188 (14.2)
HIV risk						
Heterosexual	104 (39.9)	95 (30.4)	88 (27.0)	50 (23.3)	58 (27.4)	395 (29.8)
IDU	16 (6.1)	19 (6.1)	23 (7.1)	7 (3.3)	9 (4.3)	74 (5.6)
MSM	117 (44.8)	177 (56.6)	195 (59.8)	146 (67.9)	133 (62.7)	133 (62.7)
Other/unknown	24 (9.2)	22 (7.0)	20 (6.1)	12 (5.6)	12 (5.7)	12 (5.7)
Percent time prescribed cART in follow-up						
< 75%	30 (11.5)	35 (11.2)	37 (11.4)	31 (14.4)	41 (19.3)	174 (13.1)
75-99%	104 (39.9)	112 (35.8)	108 (33.1)	58 (27.0)	67 (31.6)	449 (33.8)
100%	127 (48.7)	166 (53.0)	181 (55.5)	126 (58.6)	104 (49.1)	704 (53.1)

Abbreviations: cART, combination antiretroviral therapy; IQR, interquartile range; IDU, intravenous drug use; MSM, men who have sex with men.

Table 2: Nadir, peak and most recent CD4 by vital status groups at end of follow-up and by CD4 range at cART initiation:1996-2012 (N=1,327)

Baseline CD4 range, vital status at end of follow-up	Nadir CD4: median (IQR)	p-value*	Peak CD4: median (IQR)	p-value*	Most recent CD4: median (IQR)	p-value*	Years follow-up: median (IQR)	p-value*
< 50 cells/mm^3								
Died, n=19	8 (1-18)	0.005	313 (229-521)	< 0.001	216 (23-484)	0.004	5.8 (4.1-6.0)	< 0.001
Living, n=242	20 (9-28)		543 (383-747)		418 (259-573)		8.6 (5.7-12.0)	
All, n=261	19 (8-28)		531 (354-737)		411 (230-564)		8.2 (5.6-11.5)	
50-199 cells/mm^3								
Died, n=24	103 (63-124)	0.45	445 (298-621)	0.034	188 (87-350)	< 0.001	7.4 (5.5-9.1)	0.18
Living, n=289	98 (64-149)		553 (393-764)		436 (276-621)		7.8 (5.4-11.2)	
All, n=313	98 (64-146)		552 (388-756)		430 (249-608)		7.7 (5.4-11.0)	
200-349 cells/mm^3								
Died, n=9	225 (127-254)	0.10	525 (475-533)	0.002	257 (127-393)	< 0.001	5.2 (4.3-6.3)	0.020
Living, n=317	240 (201-285)		779 (601-960)		600 (453-770)		8.0 (5.2-10.4)	
All, n=326	240 (200-284)		776 (594-957)		587 (439-761)		7.7 (5.0-10.3)	
350-499 cells/mm^3								
Died, n=5	320 (229-384)	0.51	769 (702-960)	0.20	516 (490-832)	0.49	4.3 (3.9-4.6)	0.021
Living, n=210	354 (289-395)		926 (744-1120)		684 (537-857)		7.3 (4.9-11.5)	
All, n=215	353 (287-395)		924 (743-1118)		683 (535-857)		7.3 (4.7-11.5)	
≥ 500 cells/mm^3								
Died, n=7	233 (126-488)	0.08	955 (704-1654)	0.51	436 (305-725)	0.030	7.7 (3.2-8.5)	0.043
Living, n=205	460 (327-553)		1129 (893-1398)		779 (578-999)		8.8 (5.9-13.5)	
All, n=212	456 (325-552)		1127 (882-1399)		767 (563-997)		8.5 (5.8-13.4)	

* Kruskal-Wallis test comparing medians by vital status groups at end of follow-up

Table 3: Factors associated with achieving CD4 > 750 (n=665) in Cox proportional hazards analyses: 1996-2012 (N=1,327)

Patient characteristics at cART initiation	Univariate analysis HR (95% CI)	p-value	Multivariable analysis HR (95% CI)	p-value	Final multivariable model, backward selection HR (95% CI)	p-value
Age per 10 years	0.93 (0.86-1.01)	0.09	1.00 (0.92-1.08)	0.91		
White race	1.41 (1.21-1.65)	< 0.001	1.22 (1.02-1.46)	0.032		
Public insurance	0.78 (0.65-0.93)	0.006	0.99 (0.81-1.22)	0.94		
IDU HIV risk	0.67 (0.46-0.99)	0.046	0.64 (0.43-0.94)	0.023	0.68 (0.47-0.99)	0.042
MSM HIV risk	1.17 (0.99-1.37)	0.06	0.84 (0.69-1.02)	0.08		
CD4 ≥ 500 cells/mm^3	14.1 (10.5-18.9)	< 0.001	12.6 (10.1-15.8)	< 0.001	12.8 (10.2-15.9)	< 0.001
CD4 350-499 cells/mm^3	6.70 (4.97-9.03)	< 0.001	6.07 (4.81-7.66)	< 0.001	6.03 (4.79-7.60)	< 0.001
CD4 200-349 cells/mm^3	3.09 (2.31-4.13)	< 0.001	2.83 (2.26-3.54)	< 0.001	2.83 (2.27-3.53)	< 0.001
CD4 50-199 cells/mm^3	1.19 (0.85-1.66)	0.31				

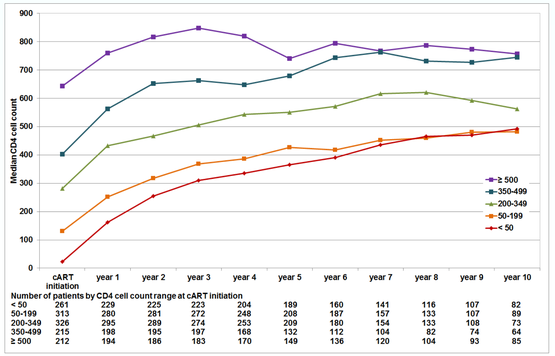
Abbreviations: cART, combination antiretroviral therapy; HR, hazard ratio; CI, confidence interval; IDU, intravenous drug use; MSM, men who have sex with men.

Table 4: Mortality risk factors (deaths=64) in Cox proportional hazards analyses: 1996-2012 (N=1,327)

Baseline Factor*	Univariate analysis HR (95% CI)	p-value	Multivariable analysis HR (95% CI)	p-value	Final multivariable model, backward selection HR (95% CI)	p-value
Age per 10 years	1.94 (1.55-2.44)	< 0.001	1.83 (1.44-2.33)	< 0.001	1.85 (1.45-2.35)	< 0.001
Black race	2.28 (1.40-3.73)	0.001	1.49 (0.87-2.56)	0.15	1.72 (1.04-2.85)	0.036
Public insurance	3.18 (1.94-5.19)	< 0.001	1.71 (0.98-2.97)	0.059	1.96 (1.16-3.32)	0.012
IDU HIV risk	3.86 (2.10-7.11)	< 0.001	3.17 (1.46-6.88)	0.004	2.33 (1.22-4.43)	0.010
Heterosexual HIV risk	1.92 (1.17-3.14)	0.010	1.59 (0.84-3.03)	0.15		
CD4 < 50 cells/mm^3	2.54 (1.23-5.24)	0.011	2.05 (1.09-3.83)	0.025	2.05 (1.09-3.84)	0.025
CD4 50-199 cells/mm^3	2.78 (1.39-5.57)	0.004	2.24 (1.25-4.04)	0.007	2.24 (1.24-4.04)	0.007
CD4 200-349 cells/mm^3	1.04 (0.44-2.47)	0.93				

* Referent groups: non-Black race, Private or no insurance, MSM or other/unknown HIV risk for all analyses, CD4 ≥ 350 cells/mm^3 for univariate analysis, CD4 ≥ 200 cells/mm^3 for both multivariable analyses.
Abbreviations: HR, hazard ratio; CI, confidence interval; IDU, intravenous drug use.

Figure 1: Median CD4 by number of years after cART initiation, stratified by CD4 range at cART initiation, among patients with at least 3 years of follow-up: 1996-2012 (N=1,327)



Number of patients by CD4 cell count range at cART initiation

	cART initiation	year 1	year 2	year 3	year 4	year 5	year 6	year 7	year 8	year 9	year 10
< 50	261	229	225	223	204	189	160	141	116	107	82
50-199	313	280	281	272	248	208	187	157	133	107	89
200-349	326	295	289	274	253	209	180	154	133	108	73
350-499	215	198	195	197	168	132	112	104	82	74	64
≥ 500	212	194	186	183	170	149	136	120	104	93	85

Figure 2: Years after cART initiation to achieving CD4 > 750 by CD4 stratum at cART initiation: 1996-2012 (N=1,327)

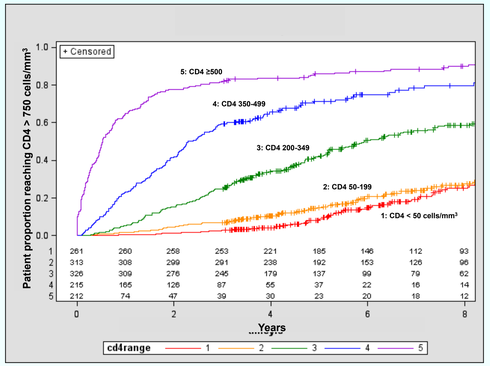
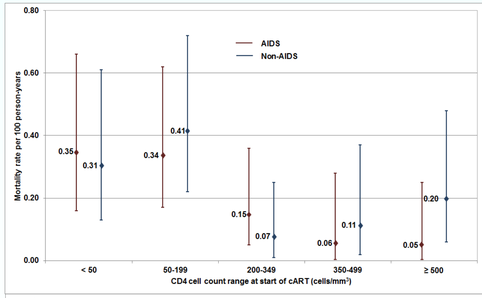


Figure 3: Mortality rates among patients with known causes of death (95% confidence intervals) by CD4 stratum at cART initiation and cause of death (AIDS or non-AIDS)



	< 50	50-199	200-349	350-499	≥ 500
Years follow-up	2,286	2,653	2,691	1,783	1,992
AIDS deaths	8	9	4	1	1
Non-AIDS deaths	7	11	2	2	4

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.

RESULTS, continued

- In multivariable analyses, factors independently associated with mortality were (Table 4):
  1. CD4 at AI < 50 and 50-199 compared with CD4 at AI ≥ 200.
  2. IDU HIV risk.
  3. Public compared with private or no insurance.
  4. Advancing age, per 10 year increment.
  5. Black non-Hispanic race compared with all other race/ethnicities.
- The likelihood of achieving CD4 > 750 by four years after AI increased with each higher stratum of CD4 at AI: 4.3%, 10.5%, 33.8%, 65.8%, and 83.6% of participants with CD4 at AI < 50, 50-199, 200-349, 350-499, and ≥ 500, respectively, achieved a CD4 > 750 (p<0.001); Figure 2.
- For decedents with known primary cause(s) of death (n=49), crude mortality rates for patients with AIDS-related (n=23) and non-AIDS-related causes (n=26) decreased with increasing CD4 at AI (p=0.004 and p=0.009, respectively, comparing CD4 at AI < 200 with CD4 ≥ 200). Among persons with CD4 >50 who died, non-AIDS-related causes predominated (19/34 or 56%); Figure 3.
- Median CD4 near death was 134 for persons with AIDS-related causes and 294 for persons with non-AIDS-related causes (p=0.019).

CONCLUSIONS

- Progressively higher CD4 at cART initiation was associated with greater long-term CD4 gains, greater likelihood of achieving CD4 > 750 ("normalization"), increased unadjusted survival rates, higher CD4 at death, and decreased likelihood of deaths from both AIDS and non-AIDS causes.
- CD4 gains and chances of achieving CD4 >750 peaked at about eight years after cART initiation. Most persons with CD4 >350 at cART initiation eventually achieved CD4 normalization while less than half of persons with CD4 at cART initiation < 50 and 50-199 did. Having a CD4 at cART initiation ≥ 500 optimized the likelihood of CD4 normalization.
- These data confirm the hazards of delayed cART initiation and support cART initiation at CD4 ≥ 500.