CD4 at HAART Initiation Predicts Long Term CD4 Responses and Mortality from AIDS and non-AIDS Causes in the HIV Outpatient Study (HOPS)

#W-103

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ABSTRACT

Background: Initiating HAART at higher CD4 cell counts/mm³ (CD4) has been demonstrated to result in decreased mortality. We sought to assess the impact of earlier (versus later) HAART initiation upon causes of death, CD4 trajectories after HAART initiation, and CD4 at time of death.

Methods: We studied patients with ≥ 6 months (mos) of follow-up (f/u) after starting HAART seen at 10 U.S. clinics during 1996-2007. We analyzed CD4 trajectories (compared using the Jonckheere-Terpstra test) and mortality rate (MR) trends by CD4 at time of HAART start (baseline, BL). We assessed factors associated with mortality using Cox proportional hazards models.

Results: Among 1,378 patients with a CD4 recorded at HAART initiation, median f/u was 4.2 years and 82 died within 6 mos of last contact. By baseline CD4 strata (< 50, 50-199, 200-349, ≥ 350), we found: i) median peak CD4 achieved after BL was progressively higher at each higher BL CD4 stratum: 392, 443, 644, and 956, p<0.001 for trend; ii) the proportions of surviving patients with CD4 ≥350 at 4 years increased: 46%, 59%, 79%, and 95%, p<0.001 for trend; iii) crude MRs per 100 person-years decreased: 2.80, 1.52, 0.60, and 0.53, p<0.001 for trend; and iv) among deaths, higher BL CD4 was associated with higher CD4 near death: 68, 186, 245, and 516, p<0.001 for trend. In multivariable analyses, factors independently associated with mortality were CD4 < 50 (hazard ratio [HR] = 4.6, 95% CI 2.7-7.9) and CD4 50-199 (HR=2.6, 95% CI 1.5-4.8) compared with CD4 ≥ 200, and public insurance (HR=1.73, 95% CI 1.1-2.7). For persons with known primary cause(s) of death (n= 69), crude mortality rates for patients with AIDS-related (n=33) and non-AIDS-related causes (n=36) decreased with increasing BL CD4 (p<0.001 and p=0.005, respectively, for trend); in the two higher BL CD4 strata (200-349 and ≥ 350) deaths from non-AIDS-related causes predominated (13/17 or 76%). Median CD4 near death was 27 for patients with AIDS-related causes and 193 for non-AIDS-related causes (p<0.001). Median CD4 nadir-to-peak increases were greater among persons who survived than among persons who died in the BL CD4 < 50 (401 vs 135, p<0.001; median f/u=57 mos) and BL CD4 50-199 (351 vs 158, p<0.001, median f/u=52 mos) strata, but not in the two higher BL CD4 strata.

Conclusions: Lower BL CD4 at HAART start was associated with lower peak CD4 achieved while on HAART, lower CD4 at time of death, and increased risk of death from AIDS-related and non-AIDS-related causes. Among persons starting HAART with BL CD4 200-349 and ≥ 350, deaths with non-AIDS causes comprised the majority of deaths.

INTRODUCTION

Initiating HAART at higher CD4 cell counts/mm³ (CD4) has been demonstrated to result in decreased mortality. We sought to assess the impact of earlier (versus later) HAART initiation upon causes of death, CD4 trajectories after HAART initiation, and CD4 near time of death.

METHODS

Study Population:

Patients with ≥ 6 months of follow-up after starting HAART seen at 10 U.S clinics during 1996-2007.

Statistical Methods:

- Mortality rates per 100 person-years by CD4 at time of HAART start (baseline) with 95% CIs assuming Poisson distribution.
- CD4 trajectories compared using the Jonckheere-Terpstra test.
- Factors associated with mortality examined using Cox proportional hazards models.

Table 1: Characteristics of HOPS study population whose first ART regimen was a HAART regimen:1996-2007 (N=1,378)

Characteristics of Pts at start of observation	By CD4+ cell count range at start of observation: n (column %) or median (IQR)				
	< 50	50-199	200-349	≥ 350	Total
Total patients	278	323	361	416	1,378
Total deaths	38	23	9	12	82
Start of observation					
1996-1999	106 (38.1)	115 (35.6)	116 (32.1)	197 (47.4)	534 (38.8)
2000-2003	113 (40.7)	113 (35.0)	122 (33.8)	135 (32.5)	483 (35.0)
2004-2007	59 (21.2)	94 (29.4)	123 (34.1)	84 (20.2)	361 (26.2)
Median years	4.4	4.2	3.5	5.1	4.2
follow-up (IQR)	(2.4-7.1)	(2.0-6.9)	(1.9-5.7)	(2.5-8.3)	(2.2-7.2)
Median Age (IQR)	38 (33-46)	40 (34-46)	36 (30-43)	36 (30-43)	37 (31-44)
Male Sex	202 (72.7)	263 (81.4)	282 (78.1)	332 (79.8)	1079 (78.3)
Race/Ethnicity					
Black	132 (47.5)	100 (31.0)	120 (33.2)	111 (26.7)	463 (33.6)
White	92 (33.1)	158 (48.9)	184 (51.0)	251 (60.3)	685 (49.7)
Hispanic	43 (15.5)	49 (15.2)	39 (10.8)	37 (8.9)	168 (12.2)
Other/unknown	11 (3.9)	16 (5.0)	18 (5.0)	17 (4.1)	62 (4.5)
Insurance					
Private	144 (51.8)	205 (63.5)	215 (59.6)	270 (64.9)	834 (60.5)
Public	107 (38.5)	85 (26.3)	95 (26.3)	92 (22.1)	379 (27.5)
Other/unknown	27 (9.7)	33 (10.2)	51 (14.1)	54 (13.0)	165 (12.0)
HIV risk †					
Heterosexual	116 (41.7)	102 (31.6)	102 (28.3)	107 (25.7)	427 (31.0)
IDU	23 (8.3)	21 (6.5)	27 (7.5)	19 (4.6)	90 (6.5)
MSM	115 (41.4)	181 (56.0)	206 (57.1)	273 (65.6)	775 (56.2)
Other/unknown	24 (8.6)	19 (5.9)	26 (7.2)	17 (4.1)	86 (6.2)
% Time taking HAART in follow-up					
< 75%	27 (9.7)	34 (10.5)	43 (11.9)	73 (17.6)	177 (12.8)
75-99%	101 (36.3)	95 (29.4)	104 (28.8)	102 (24.5)	402 (29.2)
100%	150 (54.0)	194 (60.1)	214 (59.3)	241 (57.9)	799 (58.0)

* IQR = Inter-quartile range
† Abbreviations: IDU, intravenous drug user; MSM, men who have sex with men.

RESULTS

Among 1,378 patients median follow-up was 4.2 years and there were 82 deaths.

➢By baseline (BL) CD4 strata (< 50, 50-199, 200-349, ≥ 350):

- Median peak CD4 achieved after BL was progressively higher at each higher BL CD4 stratum: 392, 443, 644, and 956, p<0.001 for trend (Table 3);
- Crude mortality rates per 100 person-years decreased: 2.80, 1.52, 0.60, and 0.53, p<0.001 for trend;
- Proportions of surviving patients with CD4 ≥ 500 at 4 years increased, p<0.001 for trend (Figure 2);
- Higher BL CD4 was associated with higher CD4 near death: 68, 186, 245, and 516, p<0.001 for trend.

➢In multivariable analyses, factors independently associated with increased mortality (Table 2) were:

- CD4 < 50 (hazard ratio [HR] = 4.6, 95% CI 2.7-7.9) and
- CD4 50-199 (HR=2.6, 95% CI 1.5-4.8) compared to CD4 ≥ 200;
- Public insurance (HR=1.73, 95% CI 1.1-2.7).

Table 2: Risk factors for mortality in multivariable Cox proportional hazards analyses

	Univariate analysis		Parsimonious multivariable analysis, stepwise selection	
Baseline Factor*	HR (95% CI)	p-value	HR (95% CI)	p-value
Black race	1.99 (1.29-3.08)	0.002	--	--
Public insurance	2.15 (1.39-3.33)	<0.001	1.73 (1.11-2.70)	0.015
IDU HIV risk	2.13 (1.13-4.03)	0.020	--	--
Heterosexual HIV risk	1.77 (1.14-2.75)	0.011	--	--
CD4 < 50 cells/mm³	5.40 (2.82-10.3)	<0.001	4.60 (2.68-7.90)	<0.001
CD4 50-199 cells/mm³	2.93 (1.46-5.89)	0.003	2.66 (1.47-4.82)	0.001
CD4 200-349 cells/mm³	1.15 (0.48-2.74)	0.75	--	--

* Referent groups: non-Black race, Private insurance, MSM or other/unknown HIV risk, CD4 ≥ 350 cells/mm3 for univariate analysis, CD4 ≥ 200 cells/mm³ for parsimonious multivariable analysis

Table 3: Nadir, peak and most recent CD4+ cell count by vital status at end of follow-up and baseline CD4+ cell count range

Baseline CD4+ range, status at follow-up end	Nadir CD4+: median, (IQR)	p-value*	Peak CD4+: median, (IQR)	p-value	Last CD4+: median, (IQR)	p-value	Years follow-up: median, (IQR)	p-value
< 50								
died, n = 38	9(3-20)	0.003	162(36-313)	<0.001	38(16-156)	<0.001	2.5(1.2-4.1)	<0.001
living, n = 240	20(8-28)		421(290-652)		327(205-492)		4.8(2.8-7.6)	
All n= 278	19(7-28)		392(252-623)		301(149-462)		4.4(2.4-7.1)	
50-199								
died, n = 23	76(42-119)	0.032	226(167-486)	<0.001	173(65-272)	<0.001	1.9(1.0-6.2)	0.010
living, n = 300	102(68-148)		460(315-636)		363(229-535)		4.3(2.1-6.9)	
All n= 323	101(67-147)		443(297-623)		343(204-524)		4.2(2.0-6.9)	
200-349								
died, n = 9	127(47-226)	0.004	475(276-533)	0.016	184(86-260)	<0.001	4.6(2.4-6.3)	0.35
living, n = 352	241(207-284)		653(483-815)		501(357-681)		3.5(1.9-5.7)	
All n= 361	240(204-283)		644(479-812)		495(353-670)		3.5(1.9-5.7)	
350+								
died, n = 12	249(91-406)	0.004	927(703-1131)	0.45	489(281-637)	0.007	3.7(2.6-7.8)	0.45
living, n = 404	399(313-502)		958(760-1217)		701(543-902)		5.1(2.5-8.4)	
All n= 416	393(308-499)		956(760-1217)		697(531-900)		5.1(2.5-8.3)	

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

RESULTS (cont'd)

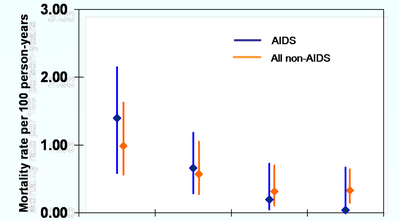
➢Among persons with known primary causes of death (n=69/82 or 84%), crude mortality rates for persons with AIDS-related (n=33) and non-AIDS-related (n=36) causes of death decreased with increasing BL CD4 (p<0.001 and p=0.005, respectively, for trend, Figure 1).

➢In the two higher BL CD4 strata (200-349 and ≥ 350), deaths from non-AIDS related causes predominated (13/17 or 76%).

➢Median CD4 near death was 27 for persons with AIDS-related causes of death and 193 for persons with non-AIDS-related causes (p<0.001).

➢Median CD4 nadir-to-peak increases were greater among persons who survived than among persons who died in the BL CD4 < 50 (401 vs 135, p<0.001; median f/u=57 mos) and BL CD4 50-199 (351 vs 158, p<0.001, median f/u=52 mos) strata, but not in the two higher BL CD4 strata (Table 3).

Figure 1: Mortality rates among patients with a known cause of death (95% confidence intervals) by baseline CD4+ range (cells/mm³) and cause of death (AIDS or non-AIDS)



	< 50	50-199	200-349	≥ 350
Years follow-up	1,356	1,511	1,509	2,267
AIDS deaths	19	0	3	1
Non-AIDS deaths	14	9	5	8

Figure 2: Proportion of patients whose CD4+ cell count has remained below 500 cells/mm3 after starting HAART, stratified by CD4+ cell count at start of HAART (Kaplan-Meier curves)

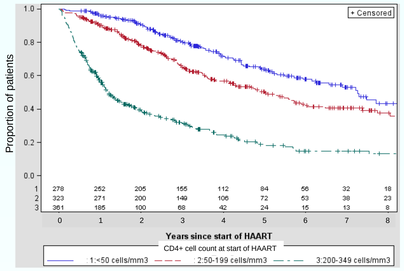
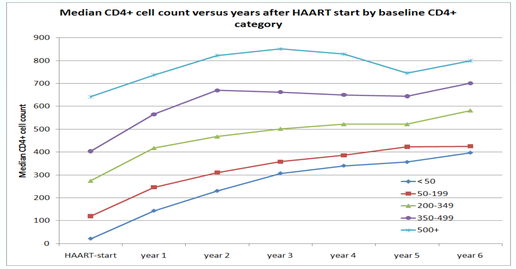


Figure 3: Median CD4+ cell count versus years after HAART-start by baseline CD4+ cell range



N	HAART-start	year 1	year 2	year 3	year 4	year 5	year 6
< 50	278	250	222	189	153	137	109
50-199	323	292	249	205	173	146	123
200-349	361	323	266	204	174	132	101
350-499	198	180	158	141	112	89	73
500+	218	198	177	149	135	112	104

CONCLUSIONS:

➢Lower BL CD4 at HAART initiation was associated with:
- Lower subsequent peak CD4 achieved while on HAART
- Lower CD4 near time of death
- Increased risk of death from AIDS-related and non-AIDS-related causes.

➢Among persons starting HAART with BL CD4 ≥ 200 and CD4 ≥ 350, deaths with non-AIDS causes comprised the majority of deaths.

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