Published in final edited form as:
J Acquir Immune Defic Syndr. 2009 November 1; 52(3): 357–363. doi:10.1097/QAI.0b013e3181b62933.

Effect of Baseline CD4 Cell Counts on the Clinical Significance of Short-Term Immunologic Response to Antiretroviral Therapy in Individuals With Virologic Suppression

The Antiretroviral Therapy Cohort Collaboration

Abstract

Background—Achieving virologic suppression is a clear therapeutic goal for patients receiving combination antiretroviral therapy (cART). However, the effects of immunologic responses, whether measured as CD4 count changes from baseline or CD4 counts at follow-up, in patients with virologic suppression, have not been clearly established.

Methods—Treatment-naive individuals aged ≥16 years, who initiated cART between 1998 and 2005 in participating cohorts of the ART Cohort Collaboration and achieved viral load <400 copies per milliliter 6 months after cART initiation, were included. We used Cox models to examine associations of CD4 change from baseline to 6 months and absolute CD4 counts at 6 months with subsequent rates of mortality and AIDS. Analyses were stratified by baseline CD4 count.

Results—Among 23,679 eligible participants, the median increase in CD4 count at 6 months and the implications of these increases for subsequent mortality and AIDS varied with baseline CD4 count. Mortality hazard ratios for increases of 0–50 cells per microliter, compared with >100 cells per microliter, were 1.87 (95% confidence interval: 1.28 to 2.73), 1.60 (1.13 to 2.28), 0.98 (0.58 to 1.65) and 1.24 (0.70 to 2.18) in participants with baseline CD4 cell count <50, 50–199, 200–349 and >350 cells per microliter, respectively. In contrast, hazard ratios for mortality or AIDS associated with absolute CD4 cell counts at 6 months were similar across all but the highest baseline CD4 cell count strata.

Conclusion—It is not possible to derive thresholds for change in CD4 count that define an adequate immunologic response in individuals receiving cART. Absolute CD4 counts at 6 months are a more useful measure of immunologic response and subsequent prognosis.

Keywords

antiretroviral therapy; CD4 counts; discordant responses; immunologic response; virologic suppression

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

All members of the study group are listed in the online appendix (see Appendix, Supplemental Digital Content 1, http://links.lww.com/QAI/A20).

INTRODUCTION

Both $CD4^+$ T-lymphocyte (CD4) cell counts and plasma HIV-1 viral load (VL) measured after initiation of combination antiretroviral therapy (cART) have been shown to have prognostic value for later morbidity and mortality.[1,2] Achieving the lowest level of viremia to the point of nondetection has been established as a clear therapeutic goal.[3–6] However, definitions of immunologic responses to therapy that have clinical significance have not been clearly established.

Many clinical trials of novel antiretroviral drugs[7,8] and many therapeutic guidelines[9,10] use increases in CD4 cell counts after initiation of therapy as a measure of immunologic response to therapy. Definitions of adequate changes in CD4 cell counts from baseline used in observational studies and guidelines have varied: for example, ≥25 cells per microliter[11,12] or 50 cells per microliter[13–15] at 6 months or 100–150 cells per microliter after 1 year of cART.[5,16] The rationale for these choices, and the implications of such responses for subsequent morbidity and mortality, have often not been well defined.

A previous study from the Antiretroviral (ART-CC) Cohort Collaboration found a strong inverse association between absolute CD4 cell counts at 6 months after cART initiation and subsequent rates of AIDS and death, after adjustment for VL at 6 months.[1] Neither CD4 cell counts at cART initiation nor changes in CD4 cell count from baseline were associated with clinical progression from 6 months, after adjustment for 6-month CD4 cell counts. CD4 cell count changes after initiation of cART are associated with CD4 cell counts at initiation.[11,17,18] Therefore, it is likely that the prognostic value of change in CD4 cell count after starting cART varies with the CD4 cell count at cART initiation.

The aim of this study was to establish the clinical significance of different measures of immunologic response to cART in individuals who have achieved virologic suppression 6 months after cART initiation. We examined CD4 changes from baseline, stratified by baseline CD4 cell count and quantified associations of change in CD4 cell count from baseline with subsequent rates of clinical outcomes in these patients. We also examined the prognostic value of absolute CD4 cell counts at 6 months, when individuals are stratified according to baseline CD4 cell counts.

METHODS

ART-CC was established in 2001 to estimate the prognosis of HIV-1– infected, treatment-naive patients initiating cART. The collaboration includes the following cohort studies from Canada, Europe, and the United States: French Hospital database on HIV, Italian Cohort of Antiretroviral-Naive Patients, Swiss HIV Cohort Study, AIDS Therapy Evaluation project Netherlands, EuroSIDA, Collaborations in HIV Outcomes Research United States, Frankfurt HIV Cohort, Aquitaine Cohort, British Columbia Centre for Excellence in HIV, Royal Free Hospital Cohort, South Alberta Clinic, Koln/Bonn Cohort, PISCIS, 1917 Clinic Cohort, University of Alabama, the University of Washington HIV Cohort, and the Veteran's Aging Cohort Study (VACS) cohort. The 2007 dataset (the second update of the original dataset) contains data on more than 40,000 antiretroviral naive patients who have started cART. As well as patient characteristics at the time of starting cART, the dataset includes CD4 cell count, VL, and treatment regimen closest to 6 months and between 3 and 9 months after starting cART (referred to hereafter as 6-month measurements).

For this analysis, we selected cART-naive individuals ≥16 years of age, who initiated triple drug cART consisting of 2 nucleoside reverse transcriptase inhibitors and either a boosted protease inhibitor, unboosted nelfinavir, a nonnucleoside reverse transcriptase inhibitor, or a third nucleoside reverse transcriptase inhibitor. In addition, subjects were required to have at

least 6 months of follow-up, to have been maintained on their primary drug regimen for the first 6 months of therapy and to have achieved virologic suppression after starting cART. Deaths and new AIDS events occurring during follow-up were determined through physician reports or linkages with vital statistics agencies. The main analyses included participants who initiated cART between January 1998 and December 2005 and used a definition of virologic suppression of a single measurement at 6 months after treatment initiation of ≤400 copies per milliliter.

We examined immunologic responses to cART in terms of CD4 change from baseline with categories of commonly used strata; (increases of <0, 0–50, 51–100, and >100 cells/μL).We stratified analyses by CD4 cell counts at the time of initiation of cART ("baseline CD4"), using categories of <50 cells per microliter, 50–199 cells per microliter, 200–349 cells per microliter, and ≥350 cells per microliter. We compared baseline variables across these baseline CD4 cell count strata using tests for trend based on logistic regression (for binary variables) or linear regression (for continuous variables). We used Cox proportional hazards models to estimate mortality hazard ratios for CD4 change groups according to baseline CD4 stratum and to test for interactions between the effects of baseline CD4 and CD4 response on mortality rates. Models were adjusted for AIDS before cART initiation, before 6 months of follow-up, or both, age, sex, and history of injection drug use and stratified by cohort. We also examined associations of absolute CD4 cell counts at 6 months with subsequent rates of AIDS events and mortality, again stratified according to baseline CD4 cell counts.

We conducted further analyses that varied the definitions of CD4 response categories and of virologic suppression. First, we used the same participants as in the main analysis but with CD4 response defined in terms of quartiles of increase in CD4 cell counts from baseline for each baseline CD4 cell count stratum. Because full virologic suppression to ≤50 copies per milliliter has been shown to maximize immunologic responses to therapy,[19] the main analyses were restricted to participants who initiated cART after January 2000 (after the advent of ultra-sensitive assays) using this more rigorous definition of suppression. Lastly, the main analyses were restricted to participants who had initiated cART after 1998 but with VL ≤400 copies per milliliter at 6 months and 11 months to define virologic suppression.

RESULTS

Of 40,977 patients starting cART between January 1, 1998, and December 30, 2005, 3635 were lost to follow-up or had died within 6 months of cART initiation, and a further 4992 were excluded as they did not have a recorded CD4 cell count at 6 months, leaving 32,370 available for analysis. Of these, 23,679 (73%) achieved VL <400 copies per milliliter at 6 months of therapy. A total of 3969 (17%) initiated cARTwith baseline CD4 cell counts of <50 cells per microliter, 7299 (31%) with 50–199 cells per microliter, 7110 (30%) with 200–349 cells per microliter, and 5301 (22%) with ≥350 cells per microliter (Table 1). Those initiating cART with higher baseline CD4 counts tend to be younger, were less likely to be prescribed protease inhibitor–based cART (compared with nonnucleoside reverse transcriptase inhibitor–based cART), and were more likely to be men who have sex with men.

Median CD4 cell count increases after 6 months of cART were lowest for those who initiated cART with lowest baseline CD4 cell counts: median increases from baseline at 6 months were 94, 110, 123, and 110 cells per microliter and for those with baseline CD4 were <50, 50–199, 200–349, and ≥350 cells per microliter, respectively. A total of 684 deaths and 797 new AIDS events occurred at a median of 37 months after the 6-month CD4 result (interquartile range: 8–59 months), with deaths and events more common at lower

baseline CD4 ($P < 0.001$). Of the 16,496 participants who began cART after the year 2000, 12,274 (74%) also had VL measured as ≤400 copies per milliliter after 6 months of cART.

In the main analysis (Table 2), there was considerable variation in associations of CD4 response with subsequent mortality rates between strata defined by baseline CD4 cell count (interaction $P < 0.001$). For each CD4 change category, compared with increases of >100 cells per microliter, adjusted hazard ratios were greater in participants with baseline CD4 <50 or 50–199 cells per microliter than in participants with baseline CD4 200–349 or >350 cells per microliter. For example, the hazard ratios for an increase of 0–50 cells per microliter were 1.87 (95% confidence interval: 1.28 to 2.73), 1.60 (1.13 to 2.28), 0.98 (0.58 to 1.65), and 1.24 (0.70 to 2.18) in participants with baseline CD4 cell count <50, 50–199, 200–349, and >350 cells per microliter, respectively. For participants with baseline CD4 cell count >350 cells per microliter, there was little evidence of an association between CD4 response and subsequent mortality rates. Similar results were found when examining associations of CD4 change from baseline with subsequent rates of AIDS. Thus, the prognostic values of changes in CD4 cell count after starting cART varies according to baseline CD4 cell count.

Web Tables 1 and 2 show results of analyses restricted, respectively, to participants who initiated cART after January 2000 and had 6-month VL ≤50 copies per milliliter and to participants who initiated cART after 1998 and had VL ≤400 copies per milliliter at 6 months and 11 months (see Appendix, Supplemental Digital Content 2, http://links.lww.com/QAI/A21). There was again substantial variation in the prognostic value of CD4 response for subsequent rates of AIDS and death between categories of baseline CD4 cell count.

Table 3 shows the results of analyses, based on the same participants as in the main analyses presented in Table 2, in which CD4 response categories were defined using quartiles of CD4 change. The ranges of CD4 changes in each quartile group generally increased with increasing baseline CD4. Quartiles 3 and 4 (those with the greatest increases in CD4 cell count) corresponded approximately to divisions of participants with increases of >100 cells per microliter: there was little evidence that rates of progression differed between these quartiles in any of the strata defined by baseline CD4. In contrast to the results presented in Table 2, the association between quartiles of CD4 change and subsequent mortality seemed stronger in individuals with baseline CD4 50–199 than <50 cells per microliter. Associations with quartiles of CD4 change were weaker in participants with baseline CD4 200–349 and >350 cells per microliter than in those with baseline CD4 50–199 cells per microliter. Results were similar in analyses with AIDS events as the outcome.

The proportion of participants achieving different absolute CD4 cell count strata at 6 months are shown in Table 4. As expected, CD4 cell count at 6 months is strongly related to baseline CD4 cell count: 83% of patients with baseline CD4 count <50 cells per microliter had CD4 counts <200 cells per microliter at 6 months, whereas 71% of patients with baseline CD4 cell count >350 cells per microliter had CD4 counts ≥500 cells per microliter at 6 months. Because there was such strong variation in the number of patients in different strata of 6-month CD4 cell count between groups defined by baseline CD4 cell count, we could not estimate hazard ratios comparing the different strata. Instead, the prognostic value of 6-month CD4 cell counts was modeled as hazard ratios (for AIDS and death after 6 months) per 100 cells per microliter increase in 6-month CD4 cell count. Table 4 shows that these hazard ratios were similar across all baseline CD4 cell count strata except for baseline CD4 >350 cells per microliter: mortality hazard ratio (HR) = 0.72 (0.58 to 0.89) for baseline CD4 count <50 cells per microliter; HR = 0.69 (0.61 to 0.78) for baseline CD4 counts of 50–199 cells per microliter; HR = 0.77 (0.68 to 0.87) for baseline CD4 counts of 200–349 cells

per microliter; and HR = 0.99 (0.91 to 1.08) for baseline CD4 cell counts of ≥350 cells per microliter. Similar results were found using AIDS events as the outcome.

DISCUSSION

Clinical trials of novel antiretroviral drugs, and therapeutic guidelines, often use thresholds of CD4 change from baseline to define successful immunologic responses to cART. However, the magnitude of immunologic responses after 6 months of cART, in the presence of virologic suppression, varies according to CD4 cell count at initiation of therapy, with lower median responses in individuals with lower baseline CD4 cell counts. Furthermore, the magnitude of associations of immunologic responses with subsequent rates of AIDS and death also depends on the baseline CD4 cell count. These findings hold whether immunologic responses are defined in terms of commonly used ranges, or in terms of quartiles of responses in different baseline CD4 strata, and when more rigorous definitions of virologic suppression are used. It is therefore not possible to define a single threshold for change in CD4 cell count from baseline that has a useful clinical interpretation, independent of baseline CD4 cell count. This implies that immunologic response endpoints in either clinical trials or observational cohorts which are defined as changes in CD4 counts from baseline should be analyzed and interpreted with great caution.

In contrast, absolute CD4 cell count measurements at 6 months after cART initiation seem to provide relatively consistent prognostic value across all baseline CD4 cell count strata up to 350 cells per microliter. This is consistent with previous work showing that absolute CD4 cell counts measured 6 months after initiation of cART have greater prognostic value for subsequent rates of AIDS and death than change in CD4 cell counts from baseline.[1] Therefore, clinically important CD4 cell count responses are likely to be better defined in terms of absolute post-cART CD4 cell counts, rather than change from baseline.

Although it is desirable to use thresholds for clinical decision making, our results suggest that, particularly for baseline CD4 counts below 200 cells per microliter, the greater increase in CD4 cell count, the lower are the subsequent rates of clinical outcomes. A previous study reported that each increase of 50 cells per microliter in CD4 cell count was associated with a 60% reduction in risk for opportunistic infections after 6 months of cART.[20] The results presented here suggest that such findings represent an average of varying reductions of risk across ranges of increase and levels of baseline CD4 cell count; treatment guidelines should be modified to reflect this. Similarly, although many studies use CD4 change from baseline as important clinical outcomes,[21–24] it is likely that these outcomes would be better characterized on the basis of posttreatment absolute CD4 cell counts, adjusted for baseline CD4 when appropriate.

Variation in CD4 responses with baseline CD4 cell counts has been described in other studies; however, the results have been conflicting. Smith et al[25] found that among 596 cART-naive individuals, of whom 80% achieved VLs <400 copies per milliliter at 6 months, CD4 responses after 3 months of cART were lower in those with higher baseline CD4 counts. Similarly, Hunt et al18 found that among 423 patients with VLs <1000 copies per milliliter receiving cART, achieving a CD4 cell count ≥200 cells per microliter after 4 years of follow-up, was associated with a lower baseline CD4 cell count. However, others have found similar results to the present study whereby greater CD4 responses are associated with higher baseline CD4 cell counts.26–28 These differences may be due to the measurement of CD4 response as a categorical or continuous variable, the duration of follow-up, the proportion of study subjects who achieved virologic suppression, and variations in the covariates (such as hepatitis C coinfection29) examined.

Despite the large number of contributing cohorts to this collaboration, we were limited by the small number of clinical events in the group with highest baseline CD4 cell count and in some of the strata in the subanalysis using the more rigorous definition of virologic suppression. Further, there was a wide range of baseline CD4 cell counts (median 463; interquartile range: 394–573 cells/μL) among individuals who initiated cART at CD4 ≥350 cells per microliter. This may have masked associations of CD4 responses with clinical events at the lower baseline CD4 cell counts within this stratum. The main analyses included some patients who initiated cART with regimens containing older drugs such as saquinavir and indinavir, which are not commonly used in HIV care today. We restricted our analysis to CD4 responses 6 months after cART initiation. Some guidelines recommend thresholds based on immunologic responses after 12 months of cART.[5] However, given our desire to assist clinicians in identifying patients at risk for adverse clinical outcomes while virologically suppressed on cART, to intervene, it makes sense to try to identify poorly responsive individuals as early as possible.

In conclusion, immunologic responses to cART are associated with subsequent mortality rates among individuals who achieve virologic suppression after 6 months of therapy. However, it is not possible to derive thresholds for, or categories of, change in CD4 count because initiation of therapy that define an adequate immunologic response for all individuals receiving cART. This is because both average CD4 responses and their prognostic value for subsequent rates of AIDS and death, vary greatly depending on CD4 cell counts at initiation of therapy. Absolute CD4 cell counts at 6 months are a more useful measure of immunologic response to therapy and marker of subsequent prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to acknowledge the participating members of ART-CC. We are grateful to all patients, doctors, and study nurses who were involved in the participating cohort studies. The ART-CC is supported by the UK Medical Research Council grant number G0700820.

Supported by the Agence Nationale de Recherche contre le SIDA (ANRS); the Institut National de la Santé et de la Recherche Médicale (INSERM); the French, Italian, Spanish, and Swiss Ministries of Health; The Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (Grant No. 33CSC0-108787), the Stichting HIV Monitoring; the European Commission; the British Columbia and Alberta Governments; the Michael Smith Foundation for Health Research; the Canadian Institutes of Health Research; the VHA Office of Research and Development; and unrestricted grants from GlaxoSmithKline, Roche, and Boehringer-Ingelheim. Support was also provided by the "Spanish Network for AIDS Research (RIS; ISCIII-RETIC RD06/006).

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TABLE 1

Characteristics of 23,679 Patients Included in the Main Analysis

	Baseline CD4 Cell Count (cells/μL)				
	<50	**50–199**	**200–349**	**>350**	***P* for Trend**
Participants, n (%)	3969 (16.8)	7299 (30.8)	7110 (30.0)	5301 (22.4)	NA
Age (yrs), median (IQR)	39 (34–47)	39 (33–47)	37 (31–45)	36 (31–43)	<0.001
Sex					
Female, n (%)	890 (22)	1996 (27)	2016 (28)	1263 (24)	0.280
Presumed mode of transmission, n (%)					
MSM	1112 (28)	2296 (31)	2435 (34)	2165 (41)	<0.001
Heterosexual contact	1693 (43)	3085 (42)	2959 (42)	1781 (34)	
Injection drug use	437 (11)	861 (12)	866 (12)	743 (14)	
Others or unknown	727 (18)	1057 (14)	850 (12)	612 (12)	
Clinical AIDS, n (%)					
Before starting cART	2381 (60)	1972 (27)	668 (9)	358 (7)	<0.001
Within 6 months of cART	500 (13)	361 (5)	125 (2)	58 (1)	<0.001
CD4 count (cells/μL), median (IQR)					
Baseline	20 (10–32)	125 (85–164)	267 (232–303)	463 (394–573)	NA
6-month increase	94 (55–144)	110 (53–189)	123 (50–209)	110 (10–231)	<0.001*
Baseline plasma HIV-1 RNA (log_{10} copies/mL), median (IQR)	5.30 (4.91–5.68)	5.04 (4.62–5.50)	4.76 (4.28–5.18)	4.64 (4.11–5.07)	<0.001
Initial cART regimen, n (%)					
NNRTI based	1047 (26)	2619 (36)	3142 (44)	2076 (39)	<0.001
PI based	2676 (67)	3973 (54)	2947 (41)	2464 (46)	
Triple NRTI	134 (3)	534 (7)	839 (12)	566 (11)	
Year of initiation of cART, median (IQR)	2001 (1999–2002)	2001 (1999–2003)	2001 (1999–2003)	2000 (1999–2002)	<0.001
1998–1999, n (%)	1151 (29)	1887 (26)	1816 (26)	2329 (44)	
2000–2001, n (%)	1266 (32)	2149 (29)	1904 (27)	1474 (28)	
2002–2003, n (%)	1030 (26)	2059 (28)	1966 (28)	970 (18)	
2004–2005, n (%)	522 (13)	1204 (16)	1424 (20)	528 (10)	
Duration of follow-up from 6 months (yrs), median (IQR)	3.24 (1.66–4.92)	2.89 (1.37–4.64)	2.76 (1.28–4.67)	3.91 (1.99–5.62)	<0.001
Deaths, n (%)	174 (4.4)	250 (3.4)	160 (2.3)	100 (1.9)	<0.001

	Baseline CD4 Cell Count (cells/μL)				
	<50	**50–199**	**200–349**	**>350**	***P* for Trend**
AIDS events (post 6m), n (%)	235 (6.3)	275 (3.8)	160 (2.3)	127 (2.4)	<0.001
Deaths per 100 person-years	1.3	1.1	0.7	0.5	<0.001
AIDS events post 6 months (per 100 person-years)	2.2	1.4	0.8	0.7	<0.001

Cell entries are number (%) of participants unless otherwise indicated. Participants started cART in 1998 or later and had HIV1 RNA ≤ 400 copies per milliliter after 6 months of cART.

* Test for trend also performed with baseline CD4 strata 200–349 and >350 combined: $P < 0.001$.

IQR, interquartile range; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

TABLE 2

Associations of CD4 Change from Baseline at 6 Months, With Rates of Death and AIDS After 6 Months on CART, for Individuals With a Single VL ≤400 Copies Per Milliliter at 6 Months After Initiation and Who Started CART After January 1, 1998

Change in CD4 Cell Count From Baseline to 6 Months	Baseline CD4 Cell Count							
	<50 Cells/μL (n = 3969)		50–199 Cells/μL (n = 7299)		200–349 Cells/μL (n = 7110)		>350 Cells/μL (n = 5301)	
	Events/n	HR (95% CI)	Events/n	HR (95% CI)	Events/n	HR (95% CI)	Events/n	HR (95% CI)
Analyses with death as outcome (n = 23,679)								
>100	59/1841	1 (Ref)	94/3948	1 (Ref)	73/4085	1 (Ref)	53/2778	1 (Ref)
51–100	53/1241	1.28 (0.88 to 1.86)	57/1612	1.49 (1.07 to 2.08)	27/1239	1.26 (0.81 to 1.97)	7/632	0.59 (0.27 to 1.31)
0–50	53/814	1.87 (1.28 to 2.73)	48/1179	1.60 (1.13 to 2.28)	18/911	0.98 (0.58 to 1.65)	16/657	1.24 (0.70 to 2.18)
Decrease	9/73	3.70 (1.81 to 7.55)	51/560	3.60 (2.55 to 5.08)	42/875	2.31 (1.56 to 3.40)	24/1234	0.88 (0.54 to 1.44)
Analyses with AIDS as outcome (n = 23,649)								
>100	87/1838	1 (Ref)	123/3939	1 (Ref)	70/4084	1 (Ref)	71/2777	1 (Ref)
51–100	66/1236	1.08 (0.78 to 1.49)	63/1611	1.23 (0.90 to 1.66)	31/1238	1.45 (0.95 to 2.21)	11/632	0.71 (0.38 to 1.35)
0–50	70/813	1.75 (1.27 to 2.42)	57/1178	1.42 (1.04 to 1.95)	27/911	1.68 (1.07 to 2.62)	14/657	0.86 (0.48 to 1.53)
Decrease	12/71	3.82 (2.07 to 7.05)	32/559	1.77 (1.20 to 2.62)	32/873	2.02 (1.32 to 3.09)	31/1232	0.92 (0.60 to 1.41)

HR estimated using Cox proportional hazards regression, adjusted for AIDS at baseline, during first 6 months of cART, or both, age, sex, and history of injection drug use and stratified by cohort.

CI, confidence interval.

TABLE 3

Associations of Quartiles of CD4 Change from Baseline At 6 Months, in Groups Defined by Baseline CD4 Count, With Rates of Death and AIDS After 6 Months on CART, for Individuals With a Single VL ≤400 Copies Per Milliliter at 6 Months After Initiation and Who Started CART After January 1, 1998

	Baseline CD4 cell count					
	<50 Cells/μL (n = 3969 for Death, 3958 for AIDS)			50–199 Cells/μL, (n = 7299 for Death, 7287 for AIDS)		
Quartile of Change in CD4 count	Quartile Range (cells/μL)	Events/n	HR (95% CI)	Quartile Range (cells/μL)	Events/n	HR (95% CI)
Analyses with death as outcome (n = 23,679)						
4	144–771	33/1000	1 (Ref)	189–1629	41/1831	1 (Ref)
3	94–144	36/1001	0.96 (0.60 to 1.54)	110–189	44/1886	1.21 (0.79 to 1.86)
2	55–94	39/997	1.08 (0.68 to 1.72)	53–110	65/1782	1.82 (1.23 to 2.70)
1	−30 to 55	66/971	1.80 (1.18 to 2.77)	−170 to 53	100/1800	2.57 (1.78 to 3.71)
Analyses with AIDS as outcome (n = 23,649)						
4	144–771	53/990	1 (Ref)	189–1629	47/1828	1 (Ref)
3	94–144	40/989	0.72 (0.48 to 1.08)	110–189	64/1880	1.43 (0.98 to 2.08)
2	55–94	54/1011	0.86 (0.58 to 1.27)	53–110	73/1781	1.64 (1.13 to 2.37)
1	−30 to 55	88/968	1.58 (1.12 to 2.24)	−170 to 53	91/1798	1.91 (1.34 to 2.73)
	200–349 Cells/μL (n = 7110 for Death, 7106 for AIDS)			>350 Cells/μL (n = 5301 for dDeath, 5298 for AIDS)		
Quartile of Change in CD4 count	Quartile Range (cells/μL)	Events/n	HR (95% CI)	Quartile Range (cells/μL)	Events/n	HR (95% CI)
Analyses with death as outcome (n = 23,679)						
4	209–1245	32/1783	1 (Ref)	231–1741	30/1326	1 (Ref)
3	123–209	28/1785	0.89 (0.53 to 1.47)	110–231	22/1340	0.66 (0.38 to 1.15)
2	50–123	42/1811	1.33 (0.83 to 2.11)	10–110	22/1314	0.74 (0.42 to 1.28)
1	−273 to 50	58/1731	1.64 (1.06 to 2.54)	−1961 to 10	26/1321	0.72 (0.42 to 1.24)
Analyses with AIDS as outcome (n = 23,649)						
4	209–1245	27/1783	1 (Ref)	231–1741	36/1325	1 (Ref)
3	123–209	33/1784	1.22 (0.73 to 2.04)	110–231	33/1340	0.90 (0.56 to 1.44)
2	50–123	41/1810	1.49 (0.91 to 2.43)	10–110	24/1314	0.73 (0.43 to 1.22)
1	−273 to 50	59/1729	2.16 (1.36 to 3.43)	−1961 to 10	34/1319	0.88 (0.55 to 1.42)

HR estimated using Cox proportional hazards regression, adjusted for AIDS at baseline, during first six months of cART, or both, age, sex, and history of injection drug use and stratified by cohort.

CI, confidence interval.

TABLE 4

Distribution of 6-Month CD4 Counts, and Hazard Ratios for Association With Subsequent Rates of Death and AIDS, According to Baseline CD4 Count, for 23,679 Individuals With a Single VL ≤400 Copies Per Milliliter at 6 Months After CART Initiation and Who Started CART After January 1, 1998

	Baseline CD4 Cell Count			
	<50 Cells/μL (n = 3969)	**50–199 cells/μL (n = 7299)**	**200–349 Cells/μL (n = 7110)**	**>350 Cells/μL (n = 5301)**
CD4 count at 6 months, n (%)				
<50	490 (12)	52 (0.7)	8 (0.1)	3 (0.06)
50–199	2815 (71)	2547 (35)	268 (4)	33 (0.6)
200–349	565 (14)	3295 (45)	2304 (32)	301 (6)
350–499	78 (2)	1113 (15)	2970 (42)	1219 (23)
>500	21 (0.5)	292 (4)	1560 (22)	3745 (71)
HR (95% CI) for death per 100 cells/μL increase in 6 month CD4 cell count	0.72 (0.58 to 0.89)	0.69 (0.61 to 0.78)	0.77 (0.68 to 0.87)	0.99 (0.91 to 1.08)
HR (95% CI) for AIDS per 100 cells/μL increase in 6 month CD4 cell count	0.85 (0.71 to 1.01)	0.78 (0.70 to 0.88)	0.75 (0.66 to 0.85)	1.02 (0.95 to 1.10)

HR estimated using Cox proportional hazards regression, adjusted for AIDS at baseline, during first 6 months of cART, or both, age, sex, and history of injection drug use and stratified by cohort.

CI, confidence interval.