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# CD4 cell count at initiation of ART, long-term likelihood of achieving CD4 >750 cells/mm$^3$ and mortality risk

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**Objectives:** We sought to evaluate associations between CD4 at ART initiation (AI), achieving CD4 >750 cells/mm$^3$ (CD4 >750), long-term immunological recovery and survival.

**Methods:** This was a prospective observational cohort study. We analysed data from ART-naive patients seen in 1996–2012 and followed ≥3 years after AI. We used Kaplan–Meier (KM) methods and log-rank tests to compare time to achieving CD4 >750 by CD4 at AI (CD4-AI); and Cox regression models and generalized estimating equations to identify factors associated with achieving CD4 >750 and mortality risk.

**Results:** Of 1327 patients, followed for a median of 7.9 years, >85% received ART for ≥75% of follow-up time; 64 died. KM estimates evaluating likelihood of CD4 >750 during 5 years of follow-up, stratified by CD4-AI <50, 50–199, 200–349, 350–499 and 500–750, were 20%, 25%, 56%, 80% and 87%, respectively (log-rank $P<0.001$). In adjusted models, CD4-AI ≥200 (versus CD4-AI <200) was associated with achievement of CD4 >750 [adjusted HR (aHR)=4.77]. Blacks were less likely than whites to achieve CD4 >750 (33% versus 49%, aHR=0.77). Mortality rates decreased with increasing CD4-AI ($P=0.004$ across CD4 strata for AIDS causes and $P=0.009$ for non-AIDS death causes). Among decedents with CD4-AI ≥50, 56% of deaths were due to non-AIDS causes.

**Conclusions:** Higher CD4-AI resulted in greater long-term CD4 gains, likelihood of achieving CD4 >750, longer survival and decreased mortality regardless of cause. Over 80% of persons with CD4-AI ≥350 achieved CD4 >750 by 4 years while 75% of persons with CD4-AI <200 did not. These data confirm the hazards of delayed AI and support early AI.

## Introduction

Highly effective combination ART (cART) has been associated with marked and sustained reductions in HIV-associated mortality and opportunistic disease.[1,2] In recent years, data from large observational cohorts of HIV-infected persons have demonstrated that earlier ART initiation (AI) improves survival[3–6] and reduces the risks of both AIDS- and non-AIDS-associated outcomes.[7,8] Furthermore, deaths among ART-treated persons are increasingly likely to result from chronic non-infectious comorbidities that are traditionally considered age-related.[9,10]

Long-term immunological responses differ among HIV-infected individuals by CD4 cell count (CD4) per mm$^3$ at AI (CD4-AI). ART-treated persons with higher CD4-AI have been shown to attain greater CD4 levels after several years of follow-up than persons initiating at lower CD4-AI, even if absolute CD4 increases among CD4-AI groups are similar.[11,12] While all of the clinical benefits of achieving substantial restoration in CD4 cell counts have not been well quantified, one recent report demonstrated marked reduction in risk of opportunistic illness after attaining and maintaining CD4 >750 cells/mm$^3$ (CD4 >750) compared with lower thresholds[13] and, hence, that CD4 >750 represents a threshold of immune reconstitution that is clinically significant.

In the present study, we characterized long-term CD4 trajectories, death rates and causes of death in a large and diverse group of HIV-infected persons stratified by CD4-AI. Our primary objective was to evaluate the association between CD4-AI and subsequent long-term immunological recovery, clinical course and mortality risk.

## Methods

### The HIV Outpatient Study (HOPS)

The HOPS is an ongoing prospective observational cohort study of HIV-infected adults receiving care at nine HIV clinics (university-based, public and private) in six US cities (Chicago, IL; Denver, CO; Stony Brook, NY; Philadelphia, PA; Tampa, FL; and Washington, DC) since 1993. Patient data, including socio-demographic characteristics, symptoms, diagnoses, treatments and laboratory values, are abstracted from medical charts and entered into an electronic database (Discovere©; Cerner Corporation, Kansas City, MO, USA) by trained staff. These data are reviewed for quality and analysed centrally. Up to June 2013, the HOPS had collected information on >10000 patients at >430000 clinical encounters.

### Ethics

Since its inception, the HOPS protocol has been reviewed and approved annually by CDC (Atlanta, GA, USA), Cerner Corporation (Kansas City, MO, USA) and each local site's institutional review board. All participants provided written informed consent. The study protocol conforms to the guidelines of the US Department of Health and Human Services for the protection of human subjects in research. The present analysis is based on the HOPS data current up to 30 June 2013.

### Study population

We included ART-naive patients who initiated ART after 1 January 1996, had at least 3 years duration between AI and their last HOPS contact and had a CD4 count recorded near the time of AI (from 183 days before to 14 days after) that could be considered for this analysis as the CD4-AI and was defined as the 'baseline' CD4.

### Measurements and definitions

Demographic variables included sex, race/ethnicity (black non-Hispanic/Latino, white non-Hispanic/Latino, Hispanic/Latino or other/unknown race/ethnicity), insurance (private, public or none), HIV transmission risk (ordered using the following priority: IVDU, MSM, heterosexual and other/unknown) and age in years at date of AI. CD4-AI was categorized as: <50, 50–199, 200–349, 350–499 and ≥500 cells/mm$^3$. Endpoints of interest included most recent CD4 by vital status at end of follow-up, achievement of CD4 >750 and mortality rates by CD4-AI. Variables assessed during follow-up included percentage of time prescribed ART, nadir CD4 (at any time before AI to end of follow-up), CD4 trajectories after AI and most recent CD4. We also characterized the median percentage of patients with an undetectable plasma HIV RNA level [viral load (VL)] while on ART by CD4-AI.

Median CD4 cell counts, stratified by CD4-AI category and years since AI, were calculated as follows: for each patient, CD4 counts with dates closest to the date of AI and each year thereafter were selected from CD4 counts with dates within 6 months of these dates of interest. The median value for each year of observation was then calculated for each CD4-AI stratum and displayed graphically to describe trajectories for each stratum.

For analysis of factors associated with achieving CD4 >750, patients whose baseline CD4 was ≤750 were followed from baseline until first documented CD4 >750 after baseline or, if not achieved, then until last CD4 value measured or last patient contact.

We analysed deaths that occurred within 183 days after last HOPS contact, consistent with previously published HOPS analyses that have used mortality as an endpoint.[2,3,9,14] Cause of death was ascertained by systematic review of death records within the HOPS database and additional information from medical providers and source records at HOPS sites. Causes of death and associated data were reviewed by a HOPS physician (F. J. P.) and were considered to be AIDS related if attributable to an AIDS-defining illness per CDC AIDS case definition.[15] The HOPS sites routinely use the US Social Security Death Index[16] to ascertain which patients are deceased.

For analysis of factors associated with mortality, the time origin was re-set such that patient follow-up began 3 years after baseline (since all analysed patients were required to have at least 3 years of follow-up) until the earliest of death (as described above), last HOPS contact plus 183 days or 30 June 2013. Unadjusted mortality rate estimates were calculated for deaths determined to be either AIDS or non-AIDS related; patients with unknown causes were excluded from these calculations.

### Statistical analyses

We generated descriptive summaries of the data and compared nadir and most recent median CD4 within each CD4-AI category (regardless of vital status) across the five CD4-AI groups, using the Kruskal–Wallis test. We used the Jonckheere–Terpstra test of trend to compare nadir and most recent CD4 and years of follow-up across CD4-AI strata. We used Kaplan–Meier (KM) time-to-event analyses and log-rank tests to compare KM curves across CD4-AI strata. Median CD4 by CD4-AI strata was plotted over years since AI. Factors associated with achieving CD4 >750 and mortality were assessed using Cox proportional hazards regression models, with censoring as defined above. All variables of interest were analysed in both univariate and multivariable Cox regression models to obtain unadjusted HR and adjusted HR (aHR) and associated 95% CI. Factors associated with achieving CD4 >750 were also assessed using generalized estimating equations (GEEs) to account for within-person correlations due to repeated CD4 count measurements over time during the duration of follow-up, in models controlling for CD4-AI, age, race/ethnicity and health insurance or payer. We calculated unadjusted mortality rates by CD4-AI and their associated CIs assuming a Poisson distribution, and compared mortality rates by CD4-AI <200 versus ≥200 using Open-Epi, Version 3,[17] an open-source calculator of person-time. For all other analytical purposes we used SAS version 9.4 (SAS Institute, Cary, NC, USA). Statistical results with $P<0.05$ were considered significant.

## Results

### Study sample

Of the 10116 patients enrolled in the HOPS up to 30 June 2013, 1327 met inclusion criteria for our analysis. Please see the patient eligibility flow diagram (Figure S1, available as Supplementary data at *JAC* Online). Patients were excluded if they did not have complete ARV history documentation ($n=3850$), had non-cART as their first ARV regimen ($n=3300$), were not followed for at least 3 years ($n=933$) and did not have a recorded CD4 cell count from 6 months before to 2 weeks after start date of first cART ($n=706$). Analyses of factors associated with achieving CD4 >750 during follow-up were restricted to the 1279 patients with CD4-AI ≤750.

The 1327 eligible patients analysed had a baseline median age of 38 years, 22% were women, 49% were white non-Hispanic/Latino race/ethnicity, 40% had either public sources of payment for healthcare or no insurance at all and 43% had CD4-AI <200 (Table 1). Median follow-up was 7.9 years (IQR 5.3–11.4), during which time patients had a median of 18 CD4 measurements (IQR 12–28) available for analysis. The majority of patients were prescribed ART continuously during follow-up; 64 died during the study observation period (Tables 1 and 2). The majority of patients receiving ART achieved an undetectable VL level and remained virologically suppressed while receiving ART: the median percentage of ART recipients over time across CD4-AI strata who had undetectable VL levels was 78 (IQR 54–94).

**Table 1.** Demographics and other characteristic of study patients followed for ≥3 years after AI, HOPS, 1996–2012 ($N$=1327)

| | CD4 cell count (cells/mm$^3$) at AI | | | | | |
|---|---|---|---|---|---|---|
| Patient characteristics at AI | total | <50 | 50–199 | 200–349 | 350–499 | ≥500 |
| Total patients, *n* | 1327 | 261 | 313 | 326 | 215 | 212 |
| Total deaths, *n* (%) | 64 (4.8) | 19 (7.3) | 24 (7.7) | 9 (2.8) | 5 (2.3) | 7 (3.3) |
| Start of observation, *n* (%) | | | | | | |
| 1996–2000 | 525 (39.6) | 108 (41.4) | 118 (37.7) | 100 (30.7) | 81 (37.7) | 118 (55.7) |
| 2001–06 | 544 (41.0) | 118 (45.2) | 140 (44.7) | 148 (45.4) | 72 (33.5) | 66 (31.1) |
| 2007–12 | 258 (19.4) | 35 (13.4) | 55 (17.6) | 78 (23.9) | 62 (28.8) | 28 (13.2) |
| Follow-up time (years), median (IQR) | 7.9 (5.3–11.4) | 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 (5.8–13.4) |
| Age (years) | | | | | | |
| all ages, median (IQR) | 38 (32–45) | 38 (33–47) | 40 (34–46) | 36 (31–44) | 38 (31–45) | 37 (31–45) |
| <35, *n* (%) | 479 (36.1) | 84 (32.2) | 89 (28.4) | 131 (40.2) | 86 (40.0) | 89 (42.0) |
| 35–44, *n* (%) | 651 (49.1) | 127 (48.7) | 172 (55.0) | 161 (49.4) | 97 (45.1) | 94 (44.3) |
| ≥45, *n* (%) | 197 (14.9) | 50 (19.2) | 52 (16.6) | 34 (10.4) | 32 (14.9) | 29 (13.7) |
| Sex, *n* (%) | | | | | | |
| female | 289 (21.8) | 74 (28.4) | 65 (20.8) | 72 (22.1) | 36 (16.7) | 42 (19.8) |
| male | 1038 (78.2) | 187 (71.6) | 248 (79.2) | 254 (77.9) | 179 (83.3) | 170 (80.2) |
| Race/ethnicity, *n* (%) | | | | | | |
| black non-Hispanic/Latino | 443 (33.4) | 119 (45.6) | 103 (32.9) | 109 (33.4) | 58 (27.0) | 54 (25.5) |
| white non-Hispanic/Latino | 653 (49.2) | 92 (35.3) | 147 (47.0) | 166 (50.9) | 120 (55.8) | 128 (60.4) |
| Hispanic/Latino | 174 (13.1) | 38 (14.6) | 52 (16.6) | 36 (11.0) | 28 (13.0) | 20 (9.4) |
| other/unknown | 57 (4.3) | 12 (4.6) | 11 (3.5) | 15 (4.6) | 9 (4.2) | 10 (4.7) |
| Insurance, *n* (%) | | | | | | |
| private | 791 (59.6) | 132 (50.6) | 178 (56.9) | 200 (61.4) | 147 (68.4) | 134 (63.2) |
| public | 348 (26.2) | 92 (35.3) | 91 (29.1) | 76 (23.3) | 42 (19.5) | 47 (22.2) |
| other/unknown/none | 188 (14.2) | 37 (14.2) | 44 (14.1) | 50 (15.3) | 26 (12.1) | 31 (14.6) |
| HIV transmission factor[a], *n* (%) | | | | | | |
| heterosexual | 395 (29.8) | 104 (39.9) | 95 (30.4) | 88 (27.0) | 50 (23.3) | 58 (27.4) |
| IVDU | 74 (5.6) | 16 (6.1) | 19 (6.1) | 23 (7.1) | 7 (3.3) | 9 (4.3) |
| MSM | 768 (57.9) | 117 (44.8) | 177 (56.6) | 195 (59.8) | 146 (67.9) | 133 (62.7) |
| other/unknown | 90 (6.8) | 24 (9.2) | 22 (7.0) | 20 (6.1) | 12 (5.6) | 12 (5.7) |
| During follow-up | | | | | | |
| number of CD4 measurements, median (IQR) | 18 (12–28) | 19 (12–29) | 19 (12–29) | 17 (11–27) | 18 (11–30) | 20 (13–30) |
| percentage of time prescribed ART, *n* (%) | | | | | | |
| <75% | 174 (13.1) | 30 (11.5) | 35 (11.2) | 37 (11.4) | 31 (14.4) | 41 (19.3) |
| 75%–99% | 449 (33.8) | 104 (39.9) | 112 (35.8) | 108 (33.1) | 58 (27.0) | 67 (31.6) |
| 100% | 704 (53.1) | 127 (48.7) | 166 (53.0) | 181 (55.5) | 126 (58.6) | 104 (49.1) |

The median percentage of ART recipients over time across CD4-AI strata who had undetectable VL levels was 78% (IQR 54%–94%).
[a]Ordered by the following priority: IVDU, MSM, heterosexual and other/unknown.

### *Most recent CD4 by vital status at end of follow-up and CD4-AI*

Using CD4-AI strata of <50, 50–199, 200–349, 350–499, ≥500, the median most recent CD4 was progressively higher for each successively higher stratum: 411, 430, 587, 683 and 767, respectively ($P$<0.001; Table 2). Among the 1279 patients with CD4-AI ≤750, the percentage of patients achieving CD4 >750 by 4 years after AI increased with each higher CD4-AI stratum: 4 ($n$=221), 11 (238), 34 (179), 66 (55) and 81 (27), respectively (log-rank $P$<0.001; Figure 1). Similarly, the percentages achieving CD4 >750 by 7 years after AI were 20 ($n$=112), 25 (126), 56 (79), 80 (16) and 87 (15) for the respective CD4-AI strata (log-rank $P$<0.001).

### *Factors associated with achieving CD4 >750*

Among the 1279 patients with baseline CD4 ≤750, baseline variables significantly associated with achieving CD4 >750 in the

**Table 2.** Nadir and most recent CD4-AI cell count (cells/mm$^3$) by vital status at end of follow-up stratified by baseline CD4 cell count among patients followed for ≥3 years after AI, HOPS, 1996–2012 ($N$=1327)

| | Nadir CD4 | | Most recent CD4 | | Years follow-up | |
|---|---|---|---|---|---|---|
| Baseline CD4 range, vital status at end of follow-up | median (IQR) | $P^a$ | median (IQR) | $P^a$ | median (IQR) | $P^a$ |
| <50 cells/mm$^3$ | | | | | | |
| died, $n$=19 | 8 (1–18) | 0.005 | 216 (23–484) | 0.004 | 5.8 (4.1–6.0) | <0.001 |
| living, $n$=242 | 20 (9–28) | | 418 (259–573) | | 8.6 (5.7–12.0) | |
| all, $n$=261 | 19 (8–28) | | 411 (230–564) | | 8.2 (5.6–11.5) | |
| 50–199 cells/mm$^3$ | | | | | | |
| died, $n$=24 | 103 (63–124) | 0.45 | 188 (87–350) | <0.001 | 7.4 (5.5–9.1) | 0.18 |
| living, $n$=289 | 98 (64–149) | | 436 (276–621) | | 7.8 (5.4–11.2) | |
| all, $n$=313 | 98 (64–146) | | 430 (249–608) | | 7.7 (5.4–11.0) | |
| 200–349 cells/mm$^3$ | | | | | | |
| died, $n$=9 | 225 (127–254) | 0.10 | 257 (127–393) | <0.001 | 5.2 (4.3–6.3) | 0.020 |
| living, $n$=317 | 240 (201–285) | | 600 (453–770) | | 8.0 (5.2–10.4) | |
| all, $n$=326 | 240 (200–284) | | 587 (439–761) | | 7.7 (5.0–10.3) | |
| 350–499 cells/mm$^3$ | | | | | | |
| died, $n$=5 | 320 (229–384) | 0.51 | 516 (490–832) | 0.49 | 4.3 (3.9–4.6) | 0.021 |
| living, $n$=210 | 354 (289–395) | | 684 (537–857) | | 7.3 (4.9–11.5) | |
| all, $n$=215 | 353 (287–395) | | 683 (535–857) | | 7.3 (4.7–11.5) | |
| ≥500 cells/mm$^3$ | | | | | | |
| died, $n$=7 | 233 (126–488) | 0.08 | 436 (305–725) | 0.030 | 7.7 (3.2–8.5) | 0.043 |
| living, $n$=205 | 460 (327–553) | | 779 (578–999) | | 8.8 (5.9–13.5) | |
| all, $n$=212 | 456 (325–552) | | 767 (563–997) | | 8.5 (5.8–13.4) | |
| All patients, test for trend across CD4-AI strata[b] | | <0.001 | | <0.001 | | 0.73 |
| Expired patients, test for trend of most recent CD4 across CD4-AI strata | | | | 0.013 | | |

Nadir and most recent CD4 levels were, respectively, the lowest (from 183 days before date of AI to end of observation) and most recent during the observation.
[a]Kruskal–Wallis test.
[b]Five-group comparison using Jonckheere–Terpstra test of trend.

multivariable model were CD4-AI 200–349 (aHR 3.16, 95% CI 2.35–4.23), CD4-AI 350–499 (aHR 7.02, 95% CI 5.20–9.49) and CD4-AI 500–750 (aHR 12.78, 95% CI 9.40–17.38), each compared with CD4-AI <50 (referent) (Table 3). Additionally, black non-Hispanic/Latinos were less likely to achieve CD4 >750 compared with white non-Hispanic/Latinos (aHR 0.77, 95% CI 0.62–0.95) (Table 3). In additional analyses of repeated CD4 cell count measurements over time using GEE methods for within-person correlations, we found similar results, i.e. that higher CD4-AI was associated, in a similar dose–response fashion, with greater odds of achieving CD4 >750 and that non-Hispanic blacks were less likely to achieve this endpoint than whites, after controlling for insurance and HIV risk group (data not shown). Among patients followed for ≥3 years, the trajectories of the median CD4 converged by ∼8 years after AI for patients with CD4-AI <50 or CD4-AI 50–199 and similarly converged for the patients with CD4-AI 350–499 or 500–750 (Figure 2).

### *Mortality and CD4-AI*

Crude all-cause mortality rates per 100 person-years of observation decreased with increasing CD4-AI: mortality rates were 0.83, 0.90, 0.33, 0.28 and 0.35 for patients with CD4-AI <50, 50–199, 200–349, 350–499 and ≥500, respectively (generalized linear model $P$=0.005). Additionally, crude mortality rates decreased for AIDS-related deaths with increasing CD4-AI stratum ($P$<0.001). Among patients with known causes of death, compared with CD4-AI <200, having CD4-AI >200 was associated with decreased risk of death from both AIDS-related and non-AIDS-related causes ($P$=0.004 for AIDS-related death rates and $P$=0.009 for non-AIDS-related death rates) (Figure 3). Higher CD4-AI was associated with higher median CD4 at death: 216, 188, 257, 516 and 436, respectively ($P$=0.013) (Table 2).

### *Factors associated with mortality*

Variables significantly associated with mortality at baseline plus 3 years in the multivariable model were increasing age (aHR 1.82 per 10 years, 95% CI 1.44–2.30), having public insurance (aHR 2.92, 95% CI 1.53–5.58), CD4 ≥500 (aHR 0.07, 95% CI 0.03–0.18), CD4 350–499 (aHR 0.21, 95% CI 0.08–0.51), CD4 200–349 (aHR 0.23, 95% CI 0.10–0.55) and CD4 50–199 (aHR 0.38, 95% CI 0.16–0.90), compared with CD4 <50 (Table 4).

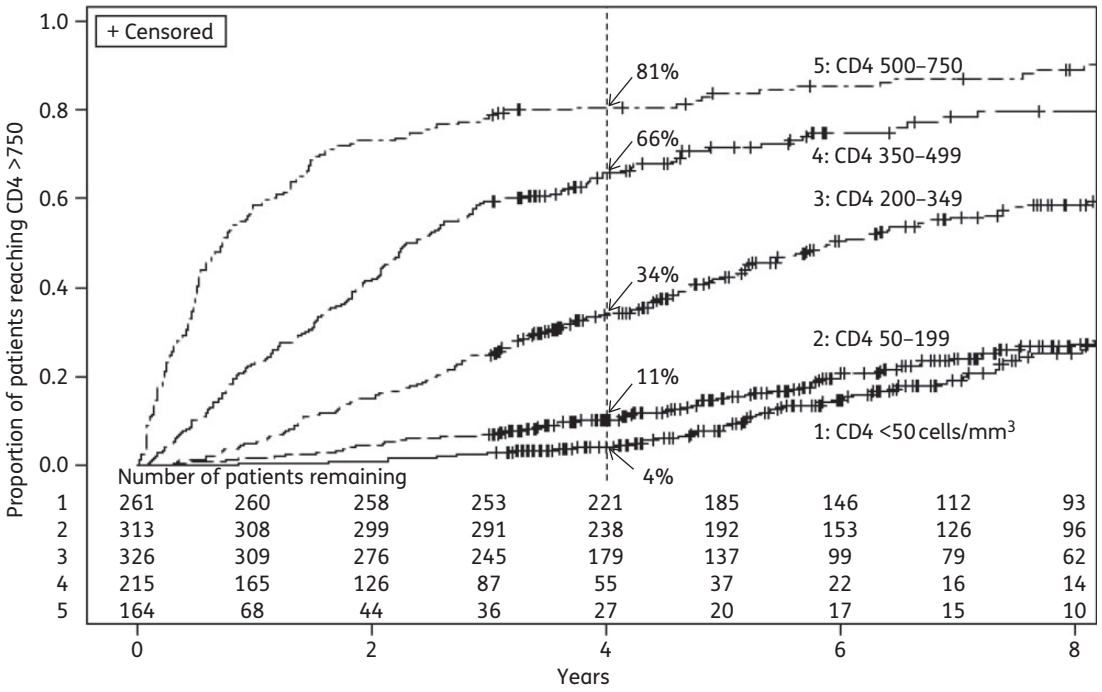
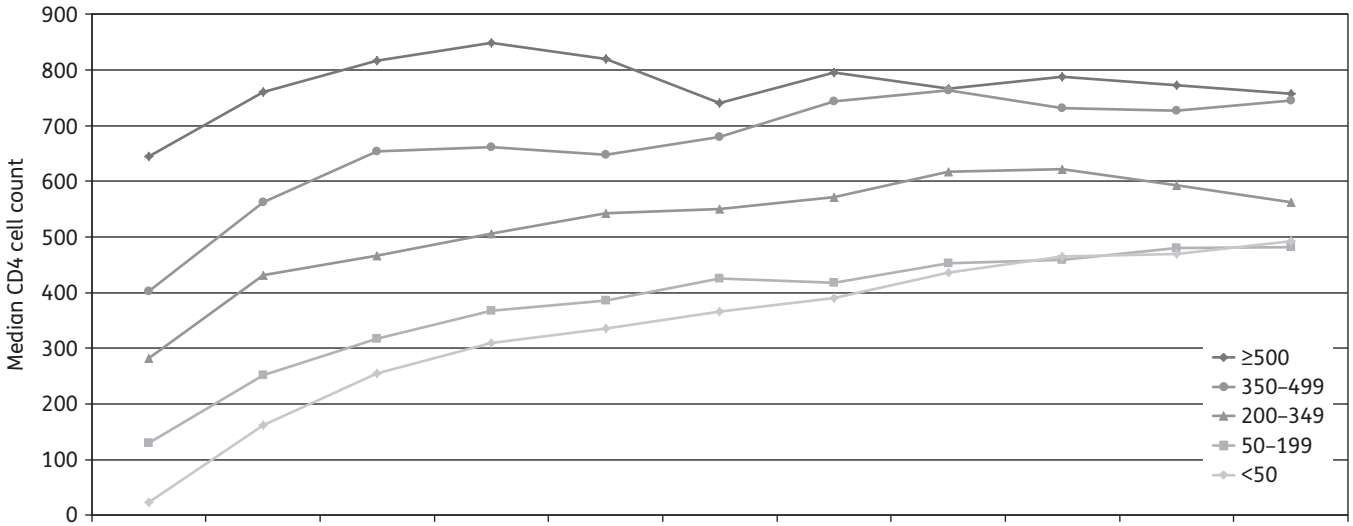



**Figure 1.** Time to achieving CD4 >750 cells/mm$^3$ among evaluable patients followed for ≥3 years after AI, stratified by CD4 at AI, HOPS, 1996–2012 ($N$=1279).

**Table 3.** Factors[a] associated with achieving CD4 >750 cells/mm$^3$ among evaluable patients followed for ≥3 years after AI, HOPS, 1996–2012 ($N$=1279)

| | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|
| Patient characteristics at AI | HR (95% CI) | *P* | aHR (95% CI) | *P* |
| Age per 10 years | 0.93 (0.86–1.01) | 0.09 | 1.00 (0.92–1.09) | 0.98 |
| Race/ethnicity | | | | |
| black non-Hispanic/Latino | 0.70 (0.58–0.84) | <0.001 | 0.77 (0.62–0.95) | 0.014 |
| Hispanic/Latino | 0.75 (0.58–0.96) | 0.024 | 0.92 (0.70–1.20) | 0.53 |
| other | 0.95 (0.64–1.41) | 0.80 | 0.99 (0.67–1.48) | 0.97 |
| white non-Hispanic/Latino | referent | | referent | |
| Payer | | | | |
| public insurance | 0.77 (0.64–0.94) | 0.008 | 1.01 (0.81–1.27) | 0.90 |
| no insurance | 1.01 (0.81–1.27) | 0.91 | 1.23 (0.97–1.55) | 0.08 |
| private insurance | referent | | referent | |
| HIV risk | | | | |
| IVDU | 0.60 (0.41–0.87) | 0.008 | 0.82 (0.55–1.24) | 0.35 |
| heterosexual | 0.86 (0.72–1.02) | 0.09 | 1.24 (1.00–1.55) | 0.06 |
| other/unknown | 0.79 (0.56–1.11) | 0.17 | 0.98 (0.69–1.39) | 0.93 |
| MSM | referent | | referent | |
| CD4 cell count (cells/mm$^3$) | | | | |
| 500–750 | 12.81 (9.47–17.33) | <0.001 | 12.78 (9.40–17.38) | <0.001 |
| 350–499 | 6.97 (5.17–9.40) | <0.001 | 7.02 (5.20–9.49) | <0.001 |
| 200–349 | 3.13 (2.34–4.19) | <0.001 | 3.16 (2.35–4.23) | <0.001 |
| 50–199 | 1.19 (0.85–1.66) | 0.30 | 1.18 (0.85–1.65) | 0.33 |
| 0–49 | referent | | referent | |

Number of patients achieving CD4 >750 cells/mm$^3$=620.
[a]From the Cox proportional hazards regression model.




Number of patients by CD4 cell count range at cART initiation

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| <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 |

IQR of median CD4 cell count values

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| <50 | 14–36 | 105–225 | 175–359 | 197–435 | 231–475 | 215–540 | 259–584 | 295–581 | 325–644 | 340–675 | 353–709 |
| 50–199 | 87–171 | 172–352 | 228–433 | 236–488 | 235–534 | 255–611 | 283–606 | 288–632 | 292–646 | 285–653 | 290–634 |
| 200–349 | 243–321 | 328–538 | 361–615 | 389–685 | 393–705 | 427–717 | 428–754 | 450–758 | 445–789 | 450–793 | 437–771 |
| 350–499 | 370–452 | 462–672 | 476–823 | 520–825 | 513–801 | 548–851 | 597–915 | 621–911 | 545–915 | 552–893 | 544–893 |
| ≥500 | 557–752 | 599–896 | 623–1001 | 592–1064 | 624–988 | 551–988 | 583–1049 | 542–1020 | 526–1088 | 485–1044 | 524–998 |

**Figure 2.** Unadjusted median CD4 cell count/mm$^3$ by years among patients followed for ≥3 years after AI, stratified by CD4 cell count/mm$^3$ at AI, HOPS, 1996–2012 ($N$=1327).

## Discussion

In this well-characterized, demographically diverse cohort of HIV-infected outpatients, progressively higher CD4 cell counts at AI were associated with greater CD4 cell count gains over 10 years of follow-up, greater chances of achieving CD4 >750 (a CD4 threshold that may be clinically significant), decreased crude mortality rates, decreased risk of death from AIDS-related and non-AIDS-related causes and higher CD4 near to time of death (usually within 6 months). These findings corroborate prior results reported from our and other cohorts that have documented the clinical and immunological benefits of earlier AI[3,4,6,12] and support the current clinical standards of care[18] regarding early diagnosis and treatment of HIV infection regardless of CD4.

Our analysis contributes several unique and new findings, in part because the extended duration of patient follow-up provided the opportunity to observe trends in CD4 cell counts among ART recipients up to 10 years after initiating ART. First, we found that CD4 gains and chances of reaching CD4 >750 appeared to peak by ~7 years after AI for persons in most CD4-AI strata. Our data suggested a convergence of median CD4 cell counts at ~8 years after AI within the two lowest CD4-AI strata (<200) and among the two highest CD4-AI strata (≥350). Also, our findings are in some ways distinct from those of other cohorts that did not observe a 'plateauing' effect of median CD4 cell count increases years after AI,[19] regardless of CD4-AI.[8]

Second, we observed that most persons with CD4-AI ≥350 eventually achieved CD4 cell counts >750 while fewer than half with CD4-AI <200 did. Persons with CD4-AI 500–750 had the greatest likelihood of achieving CD4 >750, which is not surprising since lesser CD4 increases on ART were necessary for these persons to achieve CD4 >750 than for persons whose CD4-AI was lower; however, our finding of roughly parallel and largely non-overlapping CD4 trajectories over time by CD4-AI (especially after ~3 years after AI), as shown in Figure 1, corroborates earlier findings from our and other cohorts[8,9,19] and suggests the possible existence of an absolute quantitative CD4 recovery capacity that is achievable per unit of time regardless of CD4-AI.

Blacks were less likely to achieve a CD4 >750 compared with whites. Reasons for this are unclear but may involve factors that were not directly measured, such as access to care, medication payment (including financial and/or insurance factors) or medication adherence issues. Healthcare providers and medical resource administrators should be cognizant of such potential issues when formulating strategies to optimize treatment outcomes for black HIV-infected persons.

Consistent with previous reports,[3,6] we observed marked clinical benefit associated with higher CD4-AI in terms of overall mortality reduction and reduced likelihood of death from both AIDS

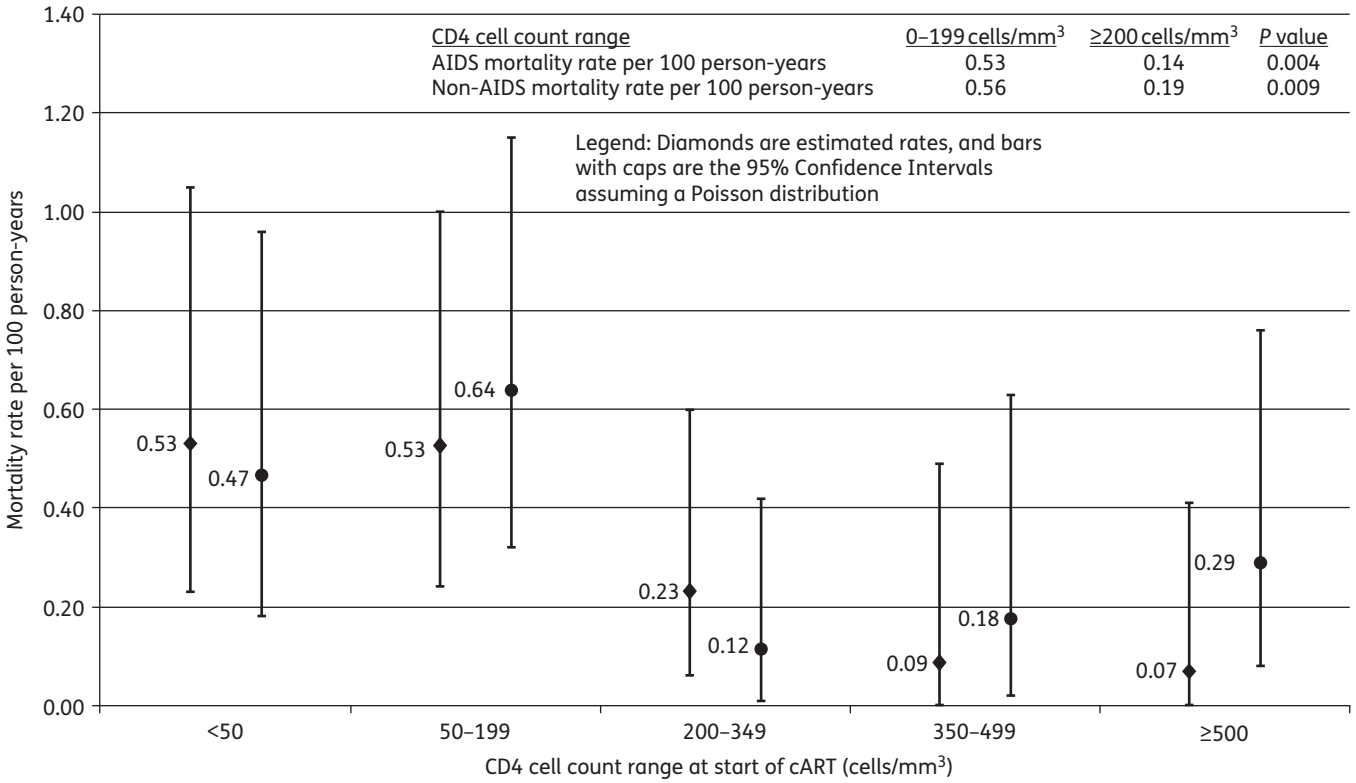



**Figure 3.** Unadjusted mortality rates among patients followed for ≥3 years after AI and with a known cause of death by CD4 cell count/mm$^3$ at AI, HOPS, 1996–2012 ($N$=1327). Mortality rates were calculated beginning at 3 years after start of cART. Diamonds, AIDS; circles, non-AIDS. *P* values are Mid-P Exact (OpenEpi.com).

and non-AIDS causes. Higher CD4-AI was in turn associated with attainment and maintenance of higher CD4 during follow-up. Others have shown that peak CD4 achieved while prescribed virally suppressive ART correlates with mortality risk.[20–22] We observed that higher CD4-AI was associated with higher CD4 at death (Table 2) and that among persons with CD4-AI 50–199 and CD4-AI ≥350, deaths from non-AIDS causes predominated slightly. While our data did not allow us to ascertain whether differential absolute increases in CD4 from baseline over time (stratified by CD4-AI) independently predicted mortality (due to a limitation of an overall low number of deaths observed), our data nonetheless support the following observations: (i) achieving and maintaining higher CD4 while receiving ART correlates with reduced mortality from both AIDS-related and non-AIDS-related causes; (ii) persons who initiated ART at a higher CD4 (i.e. ≥350) were more likely to achieve or maintain CD4 >750 over time; and (iii) the absolute CD4 attainable may be limited by the CD4 at which ART is initiated.

Our analysis has several limitations. Because the median follow-up in our open cohort analysis approached 8 years, with 25% of patients having <5 years of follow-up, we have less confidence in the precision and generalizability of the median CD4 values in later years of follow-up, when increasingly fewer patients contributed CD4 data. Additionally, some patients have become lost to follow-up (e.g. transitioned to other HIV clinics or disengaged from HIV care) and thus the observed median CD4 values may incorrectly estimate the population values that would be expected if we had more complete long-term observation of all patients, as modelled by Luz *et al.*[11] However, we found no evidence of differential attrition or censoring by CD4-AI strata, which reduces the concern about bias in comparison of CD4 trajectories among the different CD4-AI categories. Lastly, our overall observed death rates (as presented in Figure 3) were quite low and hence may be subject to some instability; this concern is valid for both AIDS-related and non-AIDS-related deaths.

There may have been factors that influenced CD4 trajectories, mortality and their relationship that we did not or could not account for nor adjust for analytically. Despite such potential unmeasured confounding, our findings are consistent with other reports[8,11,13] and possess biological plausibility. We relied upon observational cohort data involving a diverse and heterogeneous group of patients for whom the frequency of CD4 monitoring was determined by clinical practice and necessity; the decision to measure CD4 may have included consideration of patient-level factors that we did not measure (e.g. perceived ART medication adherence) or reflected patients' adherence to clinical visits, and in such ways may have influenced our outcome measures. Nevertheless, no significant differences in longitudinal CD4 measurement frequency were apparent by CD4-AI (data not shown). We did not systematically evaluate how the trajectories would differ if based on CD4 percentages rather than absolute CD4 cell counts or the associations of CD4 percentages at AI with mortality. However, at least one other cohort has identified modest disparities between absolute CD4 counts and CD4 percentages over time and in association with clinical events.[23]

**Table 4.** Risk factors[a] for all-cause mortality among evaluable patients followed for ≥3 years after AI, HOPS, 1996–2012 ($N$=1327)

| | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|
| Patient characteristics at cART initiation+3 years | HR (95% CI) | $P$ | aHR (95% CI) | $P$ |
| Age per 10 years | 1.94 (1.55–2.44) | <0.001 | 1.82 (1.44–2.30) | <0.001 |
| Race/ethnicity | | | | |
| black non-Hispanic/Latino | 2.69 (1.54–4.69) | <0.001 | 1.22 (0.63–2.40) | 0.56 |
| Hispanic/Latino | 2.07 (0.97–4.42) | 0.06 | 0.96 (0.41–2.24) | 0.92 |
| other | 0.67 (0.09–4.97) | 0.69 | 0.50 (0.07–3.79) | 0.50 |
| white non-Hispanic/Latino | referent | | referent | |
| Payer | | | | |
| public insurance | 5.12 (2.95–8.90) | <0.001 | 2.92 (1.53–5.58) | 0.001 |
| no insurance | 1.19 (0.40–3.52) | 0.75 | 1.25 (0.42–3.79) | 0.69 |
| private insurance | referent | | referent | |
| HIV risk | | | | |
| IVDU | 6.48 (3.20–13.13) | <0.001 | 1.69 (0.74–3.85) | 0.22 |
| heterosexual | 2.99 (1.67–5.35) | <0.001 | 1.17 (0.57–2.43) | 0.67 |
| other/unknown | 1.96 (0.67–5.77) | 0.22 | 0.75 (0.24–2.32) | 0.62 |
| MSM | referent | | referent | |
| CD4 cell count (cells/mm$^3$) | | | | |
| ≥500 | 0.06 (0.02–0.14) | <0.001 | 0.07 (0.03–0.18) | <0.001 |
| 350–499 | 0.18 (0.08–0.43) | <0.001 | 0.21 (0.08–0.51) | <0.001 |
| 200–349 | 0.25 (0.11–0.59) | 0.002 | 0.23 (0.10–0.55) | <0.001 |
| 50–199 | 0.50 (0.22–1.17) | 0.11 | 0.38 (0.16–0.90) | 0.029 |
| 0–49 | referent | | referent | |

Number of patients who died during follow-up=64.
[a]From the Cox proportional hazards regression model.

In summary, higher baseline CD4 was associated with greater long-term CD4 values, greater chances of achieving CD4 >750 and decreased risk of death from all causes of death, including both AIDS-related and non-AIDS-related causes. These findings confirm the clinical and immunological hazards of delayed AI and support early AI regardless of CD4-AI as recommended by current US HIV treatment guidelines. Our observation that most persons with baseline CD4 ≥350 eventually achieved CD4 >750 while fewer than half of persons with baseline CD4 <200 did not is consistent with the possible existence of a finite absolute quantitative CD4 recovery threshold.

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### *HOPS Investigators*

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## Transparency declarations

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## Disclaimer

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

## Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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