Mortality by baseline CD4 cell count among HIV patients initiating antiretroviral therapy: evidence from a large cohort in Uganda

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Objective: Evaluations of CD4 cell count and other prognostic factors on the survival of HIV patients in sub-Saharan Africa are extremely limited. Funders have been reticent to recommend earlier initiation of treatment. We aimed to examine the effect of baseline CD4 cell count on mortality using data from HIV patients receiving combination antiretroviral therapy (cART) in Uganda.

Design: Observational study of patients aged at least 14 years enrolled in 10 clinics across Uganda for which The AIDS Support Organization (TASO) has data.

Methods: CD4 cell count was stratified into categories (<50, 50–99, 100–149, 150–199, 200–249, 250–299, ≥300 cells/μl) and Cox proportional hazards regression was used to model the associations between CD4 cell count and mortality.

Results: A total of 22 315 patients were included. 1498 patients died during follow-up (6.7%) and 1433 (6.4%) of patients were lost to follow-up. Crude mortality rates (CMRs) ranged from 53.8 per 1000 patient-years [95% confidence interval (CI) 48.8–58.8] among those with CD4 cell counts of less than 50, to 15.7, (95% CI 12.1–19.3) among those with at least 300 cells/μl. Relative to a baseline CD4 cell count of less than 50 cells/μl, the risk of mortality was 0.75 (95% CI 0.65–0.88), 0.60 (95% CI 0.51–0.70), 0.43 (0.37–0.50), and 0.41 (0.33–0.51) for those with baseline CD4 cell counts of 50–99, 100–149, 150–249, and ≥250 cells/μl, respectively.

Conclusion: Earlier initiation of cART is associated with increased survival benefits over deferred treatment.

AIDS 2011, **25**:851–855

Keywords: antiretroviral therapy, CD4, HIV, mortality, sub-Saharan Africa, Uganda

Introduction

CD4 cell count at initiation of combination antiretroviral therapy (cART) is known as one of the most important predictors of patient survival [1–3]. In many resource-constrained settings, such as sub-Saharan Africa, patients initiate cART very late, often with a very low CD4 cell count [4–6]. The latest guidelines of the World Health

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Received: 5 November 2010; revised: 15 January 2011; accepted: 4 February 2011.

DOI:10.1097/QAD.0b013e32834564e9

ISSN 0269-9370 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins

Organization (WHO) recommend that asymptomatic patients initiate cART at CD4 cell count 350 cells/μl or less [7], whereas the International AIDS Society recommends that such patients initiate cART even earlier, at CD4 cell count 500 cells/μl or less [8]. Current guidance is based upon discordant evidence from wealthy settings [9,10] and a single small randomized trial [11]. However, there is concern that resource limitations in sub-Saharan Africa may prevent many health services from managing the increased workload of earlier initiation, and some international donors are reluctant to support initiation of cART at CD4 cell counts higher than 200 cells/μl [12].

Evaluations of CD4 cell count and other prognostic factors on the survival of HIV patients in sub-Saharan Africa are typically limited by small sample sizes and the relative homogeneity of low CD4 cell counts among patients starting cART [13–15]. Using data from a large observational cohort of HIV patients receiving cART in Uganda, our present study is the largest to examine the effect of baseline CD4 cell count on mortality in sub-Saharan Africa.

Methods

We used data from The AIDS Support Organization (TASO) in Uganda. The program and data collection process have been published previously [6,16]. Briefly, patients aged at least 14 years who initiated cART at TASO clinics in Uganda between 1 January 2000 and 1 February 2010 were included in this study. These patients were followed until either the time of death or the end of the study period (1 February 2010). For each patient, we recorded age at the start of cART (years), sex, baseline CD4 cell count (<50, 50–99, 100–149, 150–249, 250–299, and ≥300 cells/μl), WHO clinical disease stage (I, II, III, IV), loss to follow-up (defined as a 3-month untraceable absence from a clinic), year cART started, date last seen for care, and when applicable, date of death. Patient adherence to cART was defined as at least 95% or below 95% and determined by a composite of pharmacy refill records, 3-day self-report, and drug possession ratio.

Analyses

We assessed survival according to CD4 status at baseline, in categories of below 50, 50–99, 100–149, 150–199, 200–249, 250–299, and at least 300 cells/μl. We also examined the Ugandan guidance on initiation of cART before and after CD4 depletion at 250 cells/μl [17]. Survival distributions by CD4 cell count were estimated using Kaplan–Meier methods and compared using the log-rank test. These analyses were conducted for the overall cohort and for those with 12 or more months of follow-up. Patients lost to follow-up were censored at the date when they were last seen, and patients alive at the date when the study ended were censored at this date. We applied a weighted analysis whereby 30% of patients lost to follow-up were assumed dead, weighted by baseline CD4, age and male sex [16,18]. Survival times were expressed in months. Unadjusted and adjusted Cox proportional hazards regression [19] was conducted in order to quantify the effect of CD4 cell count on survival, adjusting for age, sex, and WHO clinical disease stage. This analysis included point and confidence interval (CI) estimates for the hazard ratios of death for each factor. Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals. To account for missing baseline CD4 cell counts we also conducted our analyses using the multiple imputation method [20]. All significance tests were two-sided with a P value of less than 0.05 considered significant. All analyses were conducted using SAS version 8 (SAS Institute, Cary, North Carolina, USA).

Institutional review

Approval to conduct this study was received from the administrative headquarters ethics board of TASO Uganda, and the Research Ethics Boards of the University of Ottawa and the University of British Columbia in Canada.

Results

Characteristics of included population

We included 22 315 individuals at least 14 years of age who initiated cART at TASO clinics in Uganda between 2004 and 2010. Patients were followed for a median of 31 months [interquartile range (IQR) 19–45]. Web-appendix Table 1, http://links.lww.com/QAD/A122 shows the demographic and clinical characteristics of patients. The median age among patients was 37 years (IQR 31–43 years), and the majority (69.4%) of patients were women. The median CD4 cell count at cART initiation was 142 cells/μl (IQR 70–206 cells/μl) (72.5% initiated cART with a CD4 cell count <200 cells/μl). A higher percentage of patients (58.1%) started cART with a WHO disease stage of either II or III. Adherence was high among patients, with 85.8% maintaining at least 95% adherence.

Mortality

One thousand, four hundred and ninety-eight (6.7%) patients died during follow-up and 1433 (6.4%) of patients were lost to follow-up. Web-appendix Table 2, http://links.lww.com/QAD/A122 shows the crude mortality rates by baseline CD4 cell count. Rates are presented overall and for the first year after cART initiation and subsequent years combined. The highest death rates were observed among patients initiating cART with a CD4 cell count below 50 cells/μl. Death rates were also highest within the first year of cART initiation. Of note, as baseline CD4 cell count decreased, the death rate generally increased.

When we applied the Ugandan criteria for initiation, those patients who initiated cART were in the CD4 cell

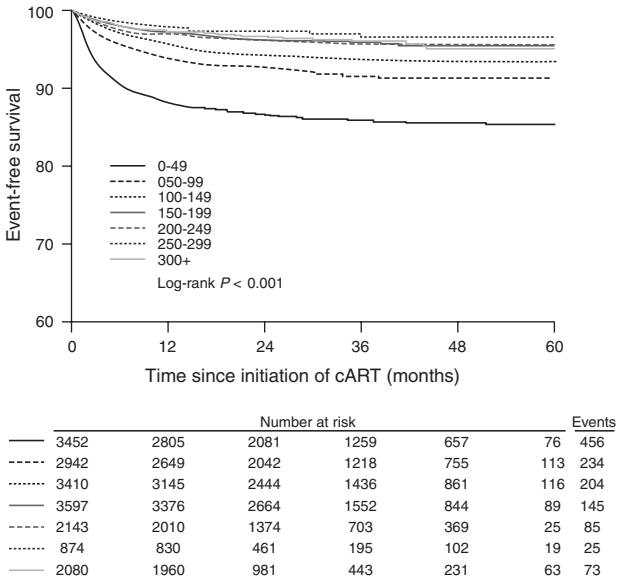

Fig. 1. Kaplan–Meier estimates for the probability of survival by CD4 strata (0–49, 50–99, 100–149, 150–199, 200–249, 250–299, ≥300 cells/μl).

count categories below 250 and at least 250 cells/μl. The estimated probability of survival after 12 months of follow-up was 94.2% (95% CI 93.9–94.5) for patients who initiated cART with a CD4 cell count less than 250 cells/μl, and 97.4 (95% CI 96.9–97.9) for patients who initiated cART with a CD4 cell count at least 250 cells/μl. By 36 months, this was 92.3 (95% CI 91.9–92.7) and 96.2 (95% CI 95.4–97.0). We observed a significant difference between the CD4 cell count categories over time (log-rank test, $P < 0.001$). When we restricted the analysis to only patients with 12 or more months of follow-up, a significant difference was maintained between the CD4 cell count categories (log-rank test, $P = 0.02$).

Figure 1 shows the Kaplan–Meier survival estimates for patients who initiated cART in the CD4 cell count categories below 50, 50–99, 100–149, 150–199, 200–249, 250–299, and at least 300 cells/μl. We observed a significant difference between the CD4 cell count categories over time (log-rank test, $P < 0.001$). When we considered only patients with 12 or more months of follow-up, a significant difference was also observed between the CD4 cell count categories (log-rank test, $P < 0.001$).

Regression analyses

Table 1 shows the results of the unadjusted and adjusted Cox proportional hazards models of time to death. The adjusted model indicated that the risk of mortality increased significantly with decreasing CD4 cell count, after adjusting for sex, WHO disease stage, and year of cART initiation. Relative to a baseline CD4 cell count of below 50 cells/μl, the risk of mortality was 0.75 (95% CI 0.65–0.88), 0.60 (95% CI 0.51–0.70), 0.43 (0.37–0.50), and 0.41 (0.33–0.51) for those with baseline CD4 cell counts of 50–99, 100–149, 150–249, and at least 250 cells/μl, respectively. Using the multiple imputation method to account for missing baseline CD4 cell count values, we found that the risk of mortality was comparable: relative to a baseline CD4 cell count of less than 50 cells/μl, the risk of mortality was 0.66 (95% CI 0.57–0.76), 0.56 (95% CI 0.49–0.65), 0.44 (0.39–0.49), and 0.44 (0.37–0.51) for those with baseline CD4 cell counts of 50–99, 100–149, 150–249, and at least 250 cells/μl.

Table 1. Unadjusted and adjusted Cox proportional hazard models of time to death among patients initiating cART at TASO clinics in Uganda.

Variable		Unadjusted hazard ratio (95% confidence interval)	*P* value	Adjusted hazard ratio (95% confidence interval)	*P* value
Age (continuous)	(per decade increase)	1.08 (1.03–1.14)	0.004		
Age (categorical)	14–19	1.00 (–)		1.00 (–)	
	20–29	0.81 (0.54–1.21)	0.301	0.83 (0.56–1.25)	0.383
	30–39	0.82 (0.55–1.21)	0.312	0.79 (0.53–1.16)	0.227
	40–49	0.78 (0.53–1.16)	0.225	0.73 (0.49–1.09)	0.128
	≥50	1.06 (0.71–1.60)	0.773	1.05 (0.69–1.57)	0.833
Sex	Male	1.54 (1.39–1.71)	<0.001	1.48 (1.33–1.65)	<0.001
CD4 cell count (cells/μl) (continuous)	(per 100 cells increase)	0.63 (0.59–0.67)	<0.001		
CD4 cell count (cells/μl) (categorical)	<50	1.00 (–)		1.00 (–)	
	50–99	0.76 (0.66–0.88)	<0.001	0.75 (0.65–0.88)	<0.001
	100–149	0.56 (0.48–0.66)	<0.001	0.60 (0.51–0.70)	<0.001
	150–249	0.37 (0.32–0.43)	<0.001	0.43 (0.37–0.50)	<0.001
	≥250	0.32 (0.26–0.40)	<0.001	0.41 (0.33–0.51)	<0.001
WHO clinical disease stage	Stage I	1.00 (–)		1.00 (–)	
	Stage II	1.05 (0.65–1.69)	0.845	1.24 (0.77–1.99)	0.382
	Stage III	2.28 (1.42–3.65)	<0.001	2.21 (1.37–3.54)	0.001
	Stage IV	4.49 (2.77–7.29)	<0.001	4.71 (2.90–7.67)	<0.001
	Missing	1.97 (1.23–3.15)	0.005	1.39 (0.87–2.22)	0.174
Year cART started (continuous)	(per year increase)	0.70 (0.67–0.73)	<0.001	0.69 (0.66–0.72)	<0.001

Discussion

The study is the largest cohort study to examine the effect of baseline CD4 cell counts on mortality in sub-Saharan Africa. The results of this study clearly indicate that CD4 cell count is an important prognostic factor in HIV patients on cART in Uganda. Specifically, this study found that initiating cART with low CD4 cell count levels is significantly associated with reduced survival time.

There are several features of this study that should be highlighted. Although many programs in Africa are affected by major loss to follow-up [21], TASO employs a specific mobile team on motorcycles that consistently track patients, thereby reducing overall loss to follow-up. Although loss to follow-up is low in TASO programs, compared with other sub-Saharan sites, we found that about 6.4% of patients were lost once they initiated cART. In a previous analysis, we found that about 26% of eligible patients at baseline will not initiate cART and are lost to follow-up prior to initiation, a third of whom were dead [16]. We aimed to reduce any bias associated with lost patients by applying a sensitivity analysis that assumes that 30% of those patients were deceased, based on findings from our previous tracking study and a similar analysis at a relevant local Ugandan setting [16,18]. Additionally, monitoring and adherence counseling at TASO is superior to that found in more developed settings, as adherence counselors and database managers are employed at each TASO clinical site. From the early years of the AIDS epidemic in Uganda TASO has been involved with peer support groups and psychosocial support.

We note that 3817 (17.1%) patients were missing baseline CD4 cell count data. We examined the effect of this using sensitivity analysis with multiple imputation. The absence of complete CD4 cell count data is a reflection of the constrained resources and diverse settings in Uganda and has been demonstrated in other resource-constrained settings [22]. Additionally, routine patient data on HIV viral load or antiretroviral resistance testing are not available at TASO. Therefore, it was not possible to understand the impact of these factors on mortality among patients at TASO. Furthermore, since this is an observational study, conclusions about causality should not be made. As with all observational studies, although we adjusted our analyses for several demographic and clinical factors, unmeasured differences may exist among the study population.

Our study examined baseline CD4 levels as a predictor of mortality and found consistent effects demonstrating lower CD4 status is associated with increased mortality. It is important to emphasize that the optimal time for initiation of therapy cannot be determined from this work. We demonstrate that decreased CD4 status at treatment baseline is a strong predictor of mortality. Differences in treatment effectiveness may differ when a CD4 cell count is at high levels. Further, our study did not account for lead-time bias, that is, the number of patients who may have died prior to accessing therapy at any CD4 category [10]. It is possible, though unlikely, that any patients dying prior to treatment would offset our study findings.

Uganda is frequently cited as a leader in the response to HIV/AIDS. In the context of improving access to treatment, Uganda has issued guidance that patients initiate at a CD4 cell count 250 cells or less, and will soon strive to increase this to 300 cells. Although these thresholds are arbitrary, they are based on the efforts of the Ministry of Health to be progressive in achieving improved health. Any increase in CD4 access appears to offer reduced mortality compared to late initiation. Benefits of early initiation may extend beyond mortality alone to decreased co-infections, decreased resource costs and possibly even prevention efforts [23].

Acknowledgements

The Canadian Institutes of Health Research (CIHR) funded this study. TASO receives core funding from the US Presidents Emergency Plan for AIDS Relief. The Canada-Africa Prevention Trials (CAPT) Network Scholarship supports J.B. The Ontario HIV Treatment Network Career Award supports C.C. A CIHR Canada Research Chair in Global Health supports E.J.M.

Author contributions: Study conception: E.M., C.B., J.B., R.M., N.F., C.C., R.H. Data acquisition: E.M., C.B., J.B., R.M., N.F., C.C., R.H. Data analysis: E.M., C.B., J.B., R.M., N.F., C.C., R.H. Interpretation: E.M., C.B., J.B., R.M., N.F., C.C., R.H. Drafting manuscript: E.M., C.B., J.B., R.M., N.F., C.C., R.H. Revisions: E.M., C.B., J.B., R.M., N.F., C.C., R.H. Approval of final manuscript: E.M., C.B., J.B., R.M., N.F., C.C., R.H.

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