The prognostic value of baseline CD4$^+$ cell count beyond 6 months of antiretroviral therapy in HIV-positive patients in a resource-limited setting

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Objective: The risk of death is highest in the first few months after initiation of antiretroviral therapy (ART). We examined whether initial CD4$^+$ cell count maintains a strong prognostic value among patients with at least 6 months follow-up after the initiation of ART.

Design: Observational study of HIV patients in Uganda aged 14 years or older enrolled in 10 clinics across Uganda.

Methods: Baseline CD4$^+$ cell count of patients with more than 6 months of follow-up were stratified into categories (<50, 50–99, 100–149, 150–249, >250 cells/μl). A Kaplan–Meier survival analysis and Cox proportional hazards regression was used to model the associations between baseline CD4$^+$ cell count and mortality.

Results: Of 22 315 patients, 20 730 (92.8%) had more than 6 months of follow-up. Six hundred and eleven (2.9%) patients died during follow-up and 737 (3.6%) were lost to follow-up. Relative to a baseline CD4$^+$ cell counts of less than 50 cells/μl, the adjusted hazard ratios for death were 0.83 [95% confidence interval (CI) 0.67–1.02], 0.71 (95% CI 0.57–0.88), 0.52 (95% CI 0.42–0.64), and 0.55 (95% CI 0.42–0.70) favouring those with baseline CD4$^+$ cell counts of 50–99, 100–149, 150–249, and at least 250 cells/μl, respectively. Differing ages and male sex increased the likelihood of mortality.

Conclusion: Among patients with more than 6 months of follow-up after initiation of ART, baseline CD4$^+$ cell count at initiation still has important prognostic value. This suggests that active engagement and earlier treatment initiation is important for long-term survival.

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Keywords: antiretroviral therapy, CD4$^+$, HIV, prognosis, sub-Saharan Africa, Uganda

Introduction

CD4$^+$ cell count is a strong prognostic indicator of mortality among individuals infected with HIV in Africa [1–3], and treatment initiation decisions are based on CD4$^+$ status [4]. In 2010, the WHO issued guidance to resource-constrained settings to expand the eligibility of the treated population by recommending initiation of

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ART when a patient's $CD4^+$ T-cell count reached 350 cells/μl or less, or clinically necessitated [5], but in practice, many patients continue to start treatment at much lower $CD4^+$ cell counts. The average $CD4^+$ cell count among patients initiating ART in sub-Saharan Africa multicountry studies is between 100 and 130 cells/μl [6].

The majority of death among patients who begin ART occurs in the first 3 months of therapy [7]. Patients who survive this initial period are typically considered to have a better likelihood of long-term survival [8,9]. Although $CD4^+$ cell counts are increasingly used for determining ART eligibility in many global settings, $CD4^+$ cell counts are costly and are rarely done for clinical follow-up in resource-limited settings. Our study aims to examine whether initial $CD4^+$ cell count maintains a strong prognostic value beyond 6 months of ART in a large observational cohort in sub-Saharan Africa.

Methods

Setting

Our study used data collected by the AIDS Support Organization (TASO). Since its foundation in 1987, TASO has been providing care to over 200 000 patients in Uganda, counselling, free access to ART, and regular healthcare for treatment of opportunistic infections, while actively attempting to retain patients and avoiding loss to follow-up. It began free distribution of antiretrovirals in 2004; currently, TASO services 24 000 patients at 11 sites throughout Uganda. We have previously reported on clinical outcomes within this cohort [10–13]. The TASO cohort is one of the largest in Africa and is generalizable to many resource-limited settings, as it receives funding primarily from the United States Presidents Emergency Plan for AIDS Relief (via CDC) and clinical practice is guided by clinical monitoring rather than regular $CD4^+$ cell counts or any virological monitoring.

Cohort characteristics

The cohort for this analysis involved patients initiated since 2004 and receiving treatment for a minimum duration of 6 months. Patients older than 14 years of age initiated between 1 January 2000 and 1 February 2010 were included in this study. These patients were followed until either until the time of death or the end of the study period (1 February 2010). For each patient, we recorded age at the start of antiretroviral therapy (years), sex, baseline $CD4^+$ cell count, WHO clinical disease stage, loss to follow-up (defined as a 3-month untraceable absence from a clinic), year of start of antiretroviral therapy, date last seen for care, and, where applicable, date of death. Patient adherence to ART was defined as more than 95% or less than 95% and determined by a composite of pharmacy refill records, 3-day self-report, and drug possession ratio. The cohort profile has been previously published [10].

Analysis

The $CD4^+$ cell counts were stratified into the following categories: less than 50, 50–99, 100–149, 150–249, and more than 250 cells/μl. Patients' survival estimates were assessed according to baseline $CD4^+$ cell counts. Survival probabilities based on baseline $CD4^+$ cell count were estimated using a Kaplan–Meier plot using the 6-month period after initiation as the starting date and compared using the log-rank test. Patients lost to follow-up were censored at the date they were last seen. Patients alive at the date when the study ended were censored at that particular date. A weighted analysis was applied, whereby 30% of patients lost to follow-up were assumed dead, weighted by baseline $CD4^+$ cell count, age, and male sex, consistent with published data and modelling studies [14,15]. Unadjusted and adjusted Cox proportional hazards regression were conducted in order to quantify the impact of initial $CD4^+$ cell count on the probability of survival after 6 months of treatment, adjusting for three covariates selected *a priori*: age, sex, and WHO clinical disease stage [16]. Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals. To account for missing baseline $CD4^+$ cell counts, we also conducted analyses using the multiple imputation method [17]. All significance tests were two-sided with a P value less than 0.05. 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

Patient demographics

Of the 22 315 patients aged at least 14 years in the TASO program between 2000 and 2010, 20 730 (92.8%) patients had more than 6 months of follow-up and were thus included in this study. Baseline characteristics are summarized in Web Appendix 1, http://links.lww.com/QAD/A219. Patients were followed for a median period of 33 months [interquartile range (IQR) 31–45 months] and the majority, 70.2%, were of female sex. The median patient age was 37 years (IQR 31–43 years) and the median $CD4^+$ cell count was 146 cells/μl (IQR 75–208) with 71.6% of the patients having $CD4^+$ cell counts below 200 cells/μl at the initiation of treatment. Most patients

were classified into WHO disease stage II (55.8%) or III (33.5%). Eighty-five percent of patients maintained at least 95% adherence.

Mortality

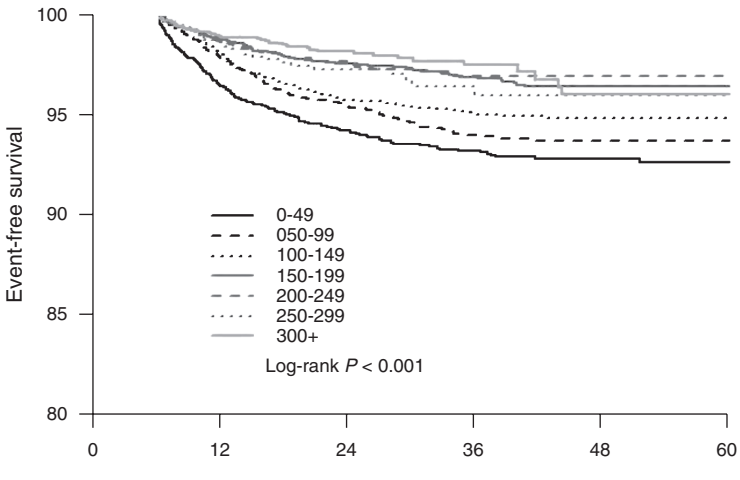
The majority of deaths (59%) occurred in the first 6 months. Of patients with more than 6 months of follow-up, 611 (2.9%) died and 737 (3.6%) were lost to follow-up. Figure 1 shows a Kaplan–Meier graph that projects the survival of patients on ART with more than 6 months of follow-up, with different baseline CD4$^+$ cell count ranges. Higher baseline CD4$^+$ cell counts were consistently associated with probability of survival in the long term. For patients starting treatment with low CD4$^+$ cell counts (<150 cells/μl), these strata continue to be at a higher risk of mortality, after accounting for 6 months of treatment. Those at greatest risk continued to be those who initiated ART with the lowest CD4$^+$ cell counts (<50 cells/μl).

Table 1 displays the unadjusted and adjusted Cox proportional hazard models for patients with 6 or more months of follow-up. The adjusted model indicates that, relative to the lowest CD4$^+$ strata, baseline CD4$^+$ cell count increases in patients with more than 6 months of treatment, after adjusting for sex, advanced WHO disease stage, and year of ART initiation. Male sex is an important predictor of mortality.

Discussion

The high risk of early mortality among patients presenting with low CD4$^+$ cell counts is well established. Trials are planned to assess interventions to reduce early mortality among patients with low CD4$^+$ cell counts [18]. Our study demonstrates that even after surviving the most difficult first few months of treatment, baseline CD4$^+$ cell count remains a strong prognostic factor of future mortality. Patients starting ART with a lower baseline CD4$^+$ cell count continue to be at significantly higher risk of mortality than those with higher CD4$^+$ cell counts. Earlier recruitment into care through active case finding and earlier initiation of treatment may have important long-term benefits.

Our study has low rates of death despite a poorly resourced environment. Strengths of ART delivery in this setting include its community-based approach and directed efforts at improving retention and adherence. It is possible that our findings would differ in cohorts with larger attrition and poor adherence support. We did not assess CD4$^+$ cell count changes between baseline and the 6-month point to assess their prognostic value. However, our goal was to examine patients who had survived and were followed beyond the 6-month period; our assessment of vital status is reliable, as reported elsewhere [10–13,19–21]. In a previous analysis, we found that about 26% of eligible patients at baseline will not initiate



	Number at risk						Events
0-49	2937	2805	2081	1259	657	76	187
050-99	2731	2649	2042	1218	755	113	147
100-149	3229	3145	2444	1436	861	116	146
150-199	3443	3376	2664	1552	844	89	100
200-249	2048	2010	1374	703	369	25	53
250-299	845	830	461	195	102	19	25
300+	1997	1960	981	443	231	63	41

Fig. 1. Kaplan–Meier probability plot of mortality for patients beginning 6 months after initiation of antiretroviral therapy.

Table 1. Unadjusted and adjusted Cox proportional hazard models of patients with more than 6 months follow-up.

Variable	Unadjusted hazard ratio (95% CI)	*P*	Adjusted hazard ratio (95% CI)	*P*
Age				
14–19 years	0.92 (0.54–1.57)	0.758	0.97 (0.57–1.67)	0.919
20–29 years	0.60 (0.47–0.78)	<0.001	0.67 (0.52–0.87)	0.003
30–39 years	0.67 (0.55–0.83)	<0.001	0.67 (0.55–0.83)	<0.001
40–49 years	0.72 (0.58–0.89)	0.002	0.69 (0.55–0.85)	<0.001
>50 years	1.00		1.00	
Male sex	1.40 (1.22–1.61)	<0.001	1.40 (1.21–1.62)	<0.001
$CD4^+$ cell count at ART initiation				
<50 cells/μl	1.00		1.00	
50–99 cells/μl	0.84 (0.68–1.04)	0.108	0.83 (0.67–1.02)	0.080
100–149 cells/μl	0.68 (0.55–0.85)	<0.001	0.71 (0.57–0.88)	0.002
150–249 cells/μl	0.47 (0.38–0.57)	<0.001	0.52 (0.42–0.64)	<0.001
>250 cells/μl	0.45 (0.35–0.58)	<0.001	0.55 (0.42–0.70)	<0.001
WHO at ART initiation				
Stage 1	1.00		1.00	
Stage 2	0.82 (0.52–1.28)	0.369	0.97 (0.62–1.52)	0.898
Stage 3	1.37 (0.92–2.04)	0.120	1.39 (0.94–2.06)	0.102
Stage 4	1.79 (1.10–2.91)	0.020	2.03 (1.25–3.28)	0.005
Year on ART	0.61 (0.58–0.65)	<0.001	0.62 (0.58–0.66)	<0.001

ART, antiretroviral therapy; CI, confidence interval.

ART and are lost to follow-up prior to initiation, a third of whom were dead [15]. 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, a method we and others have used previously [14,15,20].

Although our hazard ratios were adjusted to account for other factors such as patient age and sex, these factors are also important variables affecting mortality of HIV patients undergoing ART in Uganda. In this study, men were 40% more likely to die during the follow-up period of more than 6 months. Men are inconsistently represented in treatment programmes in Africa, evident in the significant sex disparity in our patient distribution [22]. Fewer men begin treatment, and many are initiated at lower $CD4^+$ cell counts, and thus generally fare worse than their female counterparts [12,13]. These factors were associated with the higher risk of mortality after 6 months of treatment in male patients that was found in our data. We also have found a higher rate of mortality among young people and older adults. Both groups are under-represented in African cohorts and their higher death rates are largely attributable to the fact that they have historically had poor access to ART and many adolescent patients were likely infected at birth [13,21].

The findings of the study have important prognostic implications for HIV treatment in sub-Saharan Africa. Our results indicate that nadir $CD4^+$ cell counts maintain their predictive value of death, even after 6 months of ART treatment. Uganda has recently changed its target $CD4^+$ cell count for initiation to less than 350 cells/μl, yet many African countries have low thresholds [23]. However, Uganda and many other resource-limited settings have important challenges in even meeting this threshold and more effort needs to go into diagnosing and linking patients into care and treatment programs earlier [24]. The added benefits of earlier initiation include the reduced sexual transmission of the virus [25] and increased life expectancy [20], a finding that may indicate treatment of infected patients is ultimately cost-saving [26].

In conclusion, our study demonstrates that in Uganda, baseline $CD4^+$ cell count prior to initiation of ART remains a strong prognostic factor even after 6 months of treatment. Early recruitment into care and early initiation of ART remains the best approach to decreasing mortality associated with HIV. Special attention should be devoted to ensuring equitable access to care among more vulnerable including men, adolescents, and the elderly.

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Conflicts of interest

There are no conflicts of interest.

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