Association of aging and survival in a large HIV-infected cohort on antiretroviral therapy

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Objective: To examine if there is a significant difference in survival between elderly (>50 years) and nonelderly adult patients receiving combination antiretroviral therapy in Uganda between 2004 and 2010.

Design: Prospective observational study.

Methods: Patients 18–49 years of age (nonelderly) and 50 years of age and older enrolled in the AIDS Support Organization Uganda HIV/AIDS national programme were assessed for time to all-cause mortality. We applied a Weibull multivariable regression.

Results: Among the 22 087 patients eligible for analyses, 19 657 (89.0%) were aged between 18 and 49 years and 2430 (11.0%) were aged 50 years or older. These populations differed in terms of the distributions of sex, baseline CD4 cell count and death. The age group 40–44 displayed the lowest crude mortality rate [31.4 deaths per 1000 person-years; 95% confidence interval (CI) 28.1, 34.7) and the age group 60–64 displayed the highest crude mortality rate (58.9 deaths per 1000 person-years; 95% CI 42.2, 75.5). Kaplan–Meier survival estimates indicated that nonelderly patients had better survival than elderly patients ($P < 0.001$). Adjusted Weibull analysis indicated that elderly age status was importantly associated (adjusted hazard ratio 1.23, 95% CI 1.08–1.42) with mortality, when controlling for sex, baseline CD4 cell count and year of therapy initiation.

Conclusion: As antiretroviral treatment cohorts mature, the proportion of patients who are elderly will inevitably increase. Elderly patients may require focused clinical care that extends beyond HIV treatment.

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Introduction

Little attention has been given to the prognosis of elderly patients under antiretroviral care in developing settings, even though recent estimates suggest approximately 3 million elderly individuals in Africa are living with HIV infection, approximately 14% of all HIV infections [1].

Reliable estimates of HIV prevalence of elderly individuals aged 50 and over are unavailable due to limitations in monitoring systems in resource-constrained countries [1,2]. However, secondary peaks of HIV incidence have appeared among older persons in several regions of Africa, including Uganda [3]. This may be partially attributed to the maturation of the epidemic and the high infection rates among divorced and widowed persons who have become more numerous as the epidemic has progressed [2,3]. A recent community mortality analysis from Kenya found that about 17% of mortality above the age of 50 was attributable to AIDS, as determined by verbal autopsy, with no ascertainment of AIDS exacerbated deaths [4,5]. Survival data among older HIV patients starting combination antiretroviral therapy (cART) in resource-constrained settings, like Uganda, are, to our knowledge, rarely available in the published literature and no estimates of mortality rates or comparisons with other age groups are reported [6–10]. Using data from a national cohort of HIV patients in Uganda, we assessed survival between older patients initiating cART relative to younger patients in this resource-constrained setting.

Methods

Programme

We used data from the AIDS Support Organization (TASO) in Uganda. The programme and data collection process have been published previously [11,12]. Briefly, we included data on all patients initiated on cART from 2004 to January 2010. We excluded patients from one clinic site due to concerns of the data integrity and system. The current life expectancy in Uganda is 52 years. For each patient, we recorded age at the start of the antiretroviral therapy (years), sex (male, female), baseline CD4 cell counts ($<$50, 50–99, 100–199, 200–299 and $\geq$300 cells/μl), WHO clinical disease stage (I, II, III and IV), whether or not they were lost to follow-up (yes, no), year of therapy initiation (years), date when they were last seen and, in which applicable, date of death.

Analyses

Patients were divided into two groups: elderly (aged 50 years or older according to WHO classification) [13,14] and nonelderly (aged between 18 and 49 years). Patient characteristics for the two groups were compared using χ^2-test to detect significant differences. Age-specific crude mortality rates (CMRs) were computed for the age groups 18–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64 and above 65 and expressed as deaths per 1000 person-years. Corresponding 95% confidence intervals (CIs) accompanying the rates were derived using Poisson approximation.

To address mortality status in lost to follow-up patients, we considered 50% of lost to follow-up patients as dead, in keeping with recommended distributions of death per proportion lost [15]. We weighted this assumption according to CD4 cell counts at initiation and age. We calculated CMRs. Survival distributions for elderly and nonelderly patients were estimated using the Kaplan–Meier method and compared by log-rank test. Survival was calculated from the start date of cART to the date of death. Survival times were expressed in months.

Univariate Cox regressions were performed to identify factors significantly associated with survival among age status, sex, baseline CD4 cell counts, prior history of tuberculosis, loss to follow-up and adherence to cART, and multivariate Cox regression model was built to quantify the effect of age status on survival, adjusting for those variables found to be important ($P < 0.1$) at univariate analysis. Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals. In order to assess the influence of the missing values for CD4 cell counts in the adjusted model, a sensitivity analysis was performed using the Markov chain Monte Carlo method for multiple imputation to fill in the missing CD4 cell status [16]. The resulting model was consistent with the original model.

All analyses were performed using the statistical software package R, version 2.10.0 (R Foundation for Statistical Computing, Vienna, Austria) [17]. All tests of significance were two-sided, with *P*-values less than 0.01 indicating statistical significance of test results. A significance level of 0.05 and 95% CIs for parameters of interest are reported. An academic statistician conducted all analyses.

Institutional review

The administrative headquarters of TASO Uganda, Mbale Research Ethics Board and the University of British Columbia Ethical Review Board approved this study. This study received funding from the Canadian Institutes of Health Research.

Results

Characteristics of nonelderly and elderly patients

Table 1 shows the characteristics of the 22 087 elderly and nonelderly patients included in this study. One thousand, four hundred and eighty-one patients were documented

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Table 1. Characteristics of the nonelderly and elderly patients who initiated combination antiretroviral therapy at the AIDS Support Organization.

Variable	Nonelderly patients ($n = 19\,657$)	Elderly patients ($n = 2\,430$)	*P*-value
Sex			
Female	13 949 (71.0%)	1392 (57.3%)	<0.001
Male	5708 (29.0%)	1038 (42.7%)	
CD4 cell counts (cells/μl) (baseline)[a]			
<50	3129 (19.3%)	265 (12.8%)	<0.001
50–99	2590 (16.0%)	326 (15.7%)	
100–199	6138 (37.8%)	810 (39.0%)	
200–299	2574 (15.9%)	419 (20.2%)	
≥300	1801 (11.1%)	257 (12.4%)	
WHO disease stage (baseline)[a]			
Stage I	403 (3.1%)	59 (3.6%)	0.208
Stage II	6984 (54.2%)	914 (56.1%)	
Stage III	4414 (34.3%)	519 (31.8%)	
Stage IV	1074 (8.3%)	138 (8.5%)	
Year of first therapy[a]			
Median (interquartile range)	2007 (2005–2007)	2007 (2005–2007)	0.357
Death			
No	18 383 (93.5%)	2223 (91.5%)	<0.001
Yes	1274 (6.5%)	207 (8.5%)	
Loss to follow-up			
No	18 386 (93.5%)	2284 (94.0%)	0.405
Yes	1271 (6.5%)	146 (6.0%)	

[a]Characteristic at initiation of combination antiretroviral therapy.

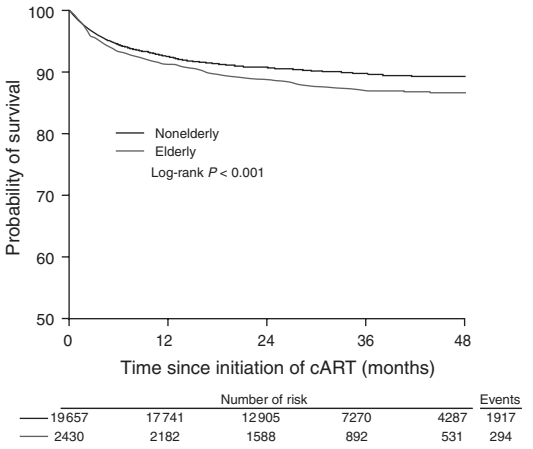
as deaths and we imputed a further 730 deaths from lost to follow-up patients. Among the patients included in the analyses, 19 657 (89.0%) were aged between 18 and 49 years and 2430 (11.0%) were aged 50 years or older. χ^2-test analyses indicated that the distributions of sex, baseline CD4 cell count and deaths differed significantly between nonelderly and elderly patients. There was no significant difference between nonelderly and elderly patients in terms of the distribution of WHO clinical disease stage at baseline, loss to follow-up and year of first therapy. Patients lost to follow-up had a lower median CD4 than those not lost [144 interquartile range (IQR) 73–207 vs. 105, IQR 34–181, $P \leq 0.001$].

Age-specific crude mortality rates

Web appendix Table 1, http://links.lww.com/QAD/A109, shows the age-specific CMRs. Generally, as age increases so does the mortality rate. Elderly patients had a pooled CMR of 45.6 deaths per 1000 person-years (95% CI 40.4–50.8), whereas younger patients had a pooled CMR of 36.5 deaths per 1000 person-years (95% CI 34.9–38.2). The age group 40–44 displayed the lowest CMR (31.4 deaths per 1000 person-years; 95% CI 28.1, 34.7) and the age group 60–64 displayed the highest CMR (58.9 deaths per 1000 person-years; 95% CI 42.2, 75.5).

Comparison of survival distributions for elderly and nonelderly patients

The nonelderly patients were followed-up for a median of 32 months (IQR 19–45 months), whereas the elderly patients were followed-up for a median of 31 months (IQR 19–45 months). The estimated probability of survival (for nonelderly and elderly, respectively) after 3 months on treatment was 96.3% (95% CI 96.0–96.5%) and 95.7% (95% CI 94.9–96.5%); at 6 months was 94.4% (95% CI 94.1–94.8%) and 93.5% (95% CI 92.5–94.5%); at 1 year of follow-up was 92.5% (95% CI 92.1–92.8%) and 91.3 (95% CI 90.2–92.4%); and at 4 years of follow-up was 89.4% (95% CI 88.9–89.8%) and 86.5% (95% CI 85.2–88.1%). Estimated probabilities of survival at other time points are provided in Fig. 1, which also shows



Months of follow-up	Cumulative survival at a specific time point (95% confidence interval)		Number of patients at risk	
	Nonelderly patients	Elderly patients	Nonelderly patients	Elderly patients
12	92.5 (92.1, 92.8)	91.3 (90.2, 92.4)	17741	2182
24	90.6 (90.2, 91.1)	88.7 (87.4, 90.0)	12905	1588
36	89.7 (89.3, 90.2)	87.1 (85.7, 88.5)	7270	892
48	89.4 (88.9, 89.8)	86.6 (85.2, 88.1)	4287	531

Fig. 1. Kaplan–Meier product limit estimates of cumulative survival. cART, combination antiretroviral therapy.

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Kaplan–Meier product limit estimates of the survival distribution for the elderly and nonelderly patients, and show that the nonelderly group had better survival than the elderly group (log-rank $P < 0.001$). Web appendix Figure 1, http://links.lww.com/QAD/A109, displays this by age-specific mortality.

Unadjusted and adjusted Weibull hazard regression analyses

Web appendix Table 2, http://links.lww.com/QAD/A109, shows the distribution of the variables that were considered for inclusion in the Weibull regression, whereas web appendix Table 3, http://links.lww.com/QAD/A109, presents the unadjusted and adjusted hazard ratios for each variable. The adjusted analysis indicated that elderly patients were 1.23 (95% CI 1.08, 1.42) times more likely to die when compared with nonelderly patients. We also found that male sex, baseline CD4 cell counts and year of therapy initiation were independently associated with mortality.

Discussion

Our study demonstrates elevated mortality rates as patient's age, regardless of the duration of therapy. The findings contribute to the limited understanding of the impact of HIV and cART among the elderly in sub-Saharan Africa in particular, and resource-constrained settings throughout the world more generally. Our analyses indicate that elderly patients receiving cART tend to have a poorer survival outcome compared with nonelderly patients independent of disease state.

Prior to the widespread use of cART, many studies conducted in resource-rich countries reported poorer survival in patients 50 years of age and older [18–21]. Even following the introduction of cART, short-term mortality rates have been reported to be higher in older HIV patients [22]. Some have attempted to explain this as a consequence of diminished immune recovery with antiretroviral therapy [23,24]. However, other studies conducted in resource-rich regions suggest that elderly patient response to cART is comparable with younger individuals [25–27]. This may be true in the period immediately following initiation of cART. However, differences in mortality rates become more evident over time [22]. An increased rate of non-AIDS defining illnesses including cardiovascular disease, liver disease, renal impairment and malignancy contribute to increased mortality in older HIV patients [28]. Of course, the risk for these illnesses increases in the non-HIV population with aging as well. There continues to be great debate regarding the relative contribution of the natural aging process, immune senescence, smoking, antiretroviral-specific toxicities and HIV itself in impacting the mortality rate in those living with HIV [29].

There are several features of this study that should be highlighted. Due to active tracing, we had relatively low loss to follow-up, around 7%. We weighted loss to follow-up patients in this analysis by CD4 cell counts at initiation, sex and age, reflecting the likely scenario that patients lost to follow-up have worse clinical outcomes [15]. We did not define AIDS deaths in our cohort as it is becoming increasingly acknowledged that age-related diseases are modified by HIV infection and, thus, even chronic diseases like early cardiovascular disease may be considered AIDS-related [30].

There were incomplete CD4 cell counts at cART initiation among some patients included in this study, both at initiation and follow-up. This lack of complete CD4 cell counts is a reflection of the diverse settings in which TASO works in Uganda, as well as the funding challenges faced by antiretroviral providers in these settings. This problem is common in other resource-constrained settings as well [31], although emerging evidence indicates clinical care results in similar outcomes as laboratory informed care [32]. Additionally, routine patient data on HIV viral load or antiretroviral resistance testing are not available at TASO. Therefore, we cannot be sure of the number of virological failures. Although we adjusted our analyses for several demographic and clinical characteristics, we acknowledge that unmeasured differences may exist among the population studied in this observational cohort analysis.

Around one in 10 people in our cohort were considered elderly. We expect that as the availability and effectiveness of antiretroviral therapy in resource-limited settings increase so will the proportion of elderly patients. There is, therefore, a pressing need to better understand the reasons for higher mortality, to develop effective prevention interventions and to adapt clinical and programmatic approaches to improve survival among this group.

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The study conception was contributed by C.B., J.B., R.M., N.F., C.L.C., J.B.N., E.W., R.S.H. and E.J.M.

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Interpretation of the data was performed by C.B., J.B., R.M., N.F., C.L.C., K.C., C.A.-Y., J.B.N., E.W., R.S.H., M.D. and E.J.M.

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