Association between older age and adverse outcomes on antiretroviral therapy: a cohort analysis of programme data from nine countries

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Context: Recent studies have highlighted the increased risk of adverse outcomes among older patients on antiretroviral therapy (ART). We report on the associations between older age and adverse outcomes in HIV/AIDS antiretroviral programmes across 17 programmes in sub-Saharan Africa.

Methods: We included data from nine countries: Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Ethiopia, Nigeria, Republic of Congo, Uganda, Zambia and Zimbabwe. We describe survival probability for progression to death and loss to follow-up for patients initiating ART aged less than 50 years and at least 50 years. Multivariate Cox proportional hazards models were used to assess the association between age (15–39, 40–49, 50–59, 60–69 and 70–94 years) and adverse outcomes adjusting for confounders identified *a priori*.

Results: Our analysis included 17 561 patients followed for a median of 12 months. The majority (65%) were female and 6672 (38%) were severely immunosuppressed at baseline. Median age at ART initiation was 36.0 years (interquartile range 30.1–42.8); 11.4% of patients were aged at least 50 years. Median gain in CD4 cell count at 6 and 12 months was significantly higher in patients less than 50 years old compared with those at least 50 years (134 vs. 112 cells/μl at 6 months; 170 vs. 139 cells/μl at 12 months; both $P < 0.001$). In multivariate analysis, there was a significant increased risk of mortality beyond 3 months after ART initiation in all age groups of at least 40 years of age compared with less than 40 years [40–49 years adjusted hazard ratios (aHRs) 1.59, $P < 0.001$; 50–59 years aHR 1.58, $P = 0.002$; 60–69 years aHR 2.63, $P < 0.001$; 70–94 years aHR 3.64, $P = 0.004$).

Conclusion: Older age groups represent an important proportion of the overall treatment cohort in these sub-Saharan Africa programmes, and risk of mortality increased as age increased. Future research should be directed at further understanding the reasons for higher mortality, and defining simple interventions that are feasible in highly under-resourced settings to allow for adapted follow-up and care approaches for older age groups.

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Introduction

Increased access to antiretroviral therapy (ART) in resource-limited settings over the last decade has resulted in substantial reductions in AIDS-related illness and death [1,2] for people living with HIV/AIDS.

Concern about heightened vulnerability within specific age groups has tended to focus on the lower extreme, particularly infants and children [3], and more recently adolescents [4]. Vulnerability at the other age extreme has received less attention. The need to focus on older age groups has recently been highlighted by reports from sub-Saharan Africa showing higher mortality in people aged 50 years and older [5–9]. This has led to calls for greater attention to be paid to the specific vulnerabilities of older populations in HIV/AIDS programmes [10].

In this study, we report on the association between older age and adverse outcomes in HIV/AIDS programmes across nine countries in sub-Saharan Africa.

Methods

This analysis is based on data from 17 programmes from nine countries in sub-Saharan Africa: Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Ethiopia, Nigeria, Republic of Congo, Uganda, Zambia and Zimbabwe. At each site, data were routinely collected by clinical staff using standardized forms and entered into an electronic database (*FUCHIA*, Epicentre, Paris, France). This database has been described in detail elsewhere [11]. Data for all adult patients (15 years or older) initiating ART between September 2003 and March 2010 were included in this study.

Descriptive analyses were based on percentages and frequencies for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Baseline characteristics were described for the cohort overall and separately for patients aged less than 50 years and at least 50 years. Continuous variables were assessed for skew and as all demonstrated nonnormality they were compared using the Wilcoxon rank-sum test. Proportions were compared using the χ^2-test.

We used Kaplan–Meier estimates to describe the cumulative probability of progression to death and loss to follow-up for patients aged less than 50 years and at least 50 years across all projects. Loss to follow-up was defined as missing a scheduled appointment by 2 months or more. Multivariate Cox proportional hazards models were used to model the association between age and adverse outcomes (death and loss to follow-up). Age was assessed as a categorical variable (15–39, 40–49, 50–59, 60–69 and 70–94 years). These models adjusted for the following potential confounders defined *a priori*: sex (male or female), BMI (kg/m^2) at ART initiation, clinic setting (urban or rural), tuberculosis (TB) at ART initiation and severe immunosuppression at ART initiation (defined as WHO stage IV or CD4 cell count $\leq$100 cells/μl). Models were segmented by time of follow-up (mortality $>0-\leq3$ and $>3-\leq42$ months of follow-up; loss to follow-up $>0-\leq12$, $>12-\leq24$ and $>24-\leq42$ months of follow-up) and hazard proportionality assessed by analysis of scaled Schoenfeld residuals. We performed sensitivity analyses to assess the potential influence of a specific programme on the overall mortality estimate by leaving out each programme in separate regressions, and assessing the potential effect of misclassification of mortality among patients lost to follow-up using a competing risks framework [12]. All reported P values are exact and two-tailed, and for each analysis $P < 0.05$ was considered significant. All analyses were carried out in STATA 10.1 and 11.0 (StataCorp, College Station, Texas, USA).

The analysis was based on routine clinical data; therefore, ethical review and individual patient consent were not sought. All patient information was entered into a database using coded identification numbers, and no information that could reveal patient identity was entered into the databases.

Results

Characteristics of included population

We included 17 561 patients who were followed on ART for a median of 12 months, and a median ART start date of 30 October 2007. The majority (65%) were female, and 6672 (38%) were considered severely immunosuppressed at baseline (Table 1). Median age at ART initiation was 36.0 years (IQR 30.1–42.8). Most patients (65.8%) were aged less than 40 years, whereas 3995 patients (22.8%) were aged 40–49 years, 1566 patients (8.9%) were aged 50–59 years, 367 patients (2.1%) were aged 60–69 years and 78 patients (0.44%) were aged 70–94 years. The proportion of patients aged at least 50 years was similar across countries (Table 2).

More adult patients aged less than 50 years were female (66 vs. 51%; $P < 0.001$), had a diagnosis of TB at ART initiation (8 vs. 6%; $P < 0.001$), and were treated in an urban clinic setting (45 vs. 40%; $P < 0.001$) than patients aged at least 50 years (Table 1). Patients in both age groups were recorded as having similar rates of severe immunosuppression (38 vs. 37%; $P = 0.14$).

Immune restoration, mortality and loss to follow-up

Patients were followed for an average of 1 year (IQR 0.34–1.92 years) with patients aged less than 50 followed for slightly less time than those at least 50 years (1.00 vs.

Table 1. Baseline characteristics of patients at antiretroviral therapy initiation.

	15–49 years ($n=15584$)	50–95 years ($n=1977$)	*P*-value	Total
Female, *n* (%)	10350 (66)	1010 (51)	<0.001	11360 (65)
Current tuberculosis diagnosis, *n* (%)	1302 (8)	121 (6)	<0.001	1423 (8)
BMI, median (IQR)	19.8 (17.6, 22.2)	19.9 (17.9, 22.5)	0.021	19.8 (17.7, 22.2)
CD4*, median (IQR) ($n=12143$)	139 (65, 205)	139 (71, 201)	0.54	139 (67, 204)
CD4 <100 *n* (%)	3968 (37%)	497 (36%)	0.30	4465 (37%)
CD4 100 <200 *n* (%)	3949 (37%)	542 (39%)		4491 (37%)
CD4 200 <350 *n* (%)	2373 (22%)	302 (22%)		2675 (22%)
CD4 ≥350 *n* (%)	462 (4%)	50 (4%)		512 (4%)
Clinical WHO stage 4, *n* (%)	2897 (19)	309 (16)	0.001	3206 (19)
Clinical WHO stage 1–3, *n* (%)	12334 (81)	1619 (84)		13953 (81)
Severe immunosuppression†, *n* (%)	5951 (38)	721 (37)	0.14	6672 (38)
Programme in an urban setting, *n* (%)	7069 (45)	791 (40)	<0.001	7860 (45)

IQR, interquartile range. *CD4 from up to 3 months before up until ART initiation available for 69% patients ($n=10752$) aged less than 50 years, 70% patients ($n=1391$) aged at least 50 years. †Severe immunosuppression: WHO stage IV or CD4 cell count ≤100 cells/μl.

1.08 years, $P=0.007$). The crude mortality rate for patients aged at least 50 years was significantly higher than for those aged less than 50 years [rate ratio (RR) 1.22, 95% confidence interval (CI) 1.03–1.43, $P=0.016$], whereas the rate of loss to follow-up was not significantly different (RR 1.07, 95% CI 0.96–1.18, $P=0.19$). The median gain in CD4 cell count at 6 and 12 months was significantly higher in patients less than 50 years old compared with those at least 50 years (134 vs. 112 at 6 months; 170 vs. 139 at 12 months; both $P<0.001$). Only 28 and 21% of patients overall (similar by age group) had CD4 cell count measurements at both baseline and 6 or 12 months, respectively, and although most variables differed between those who did and did not have CD4 cell count measurements, there was no significant difference in median age (results not shown).

Cox proportional hazards analysis found that all patients aged at least 40 years were at increased mortality risk from more than 3 to 42 months on ART after adjusting for sex, current TB, BMI, severe immunosuppression and clinic setting [40–49 years: adjusted hazard ratio (aHR) 1.59, 95% CI 1.29–1.96, $P<0.001$; 50–59 years: aHR 1.58, 95% CI 1.19–2.11, $P=0.002$; 60–69 years: aHR 2.63, 95% CI 1.66–4.16, $P<0.001$; 70–94 years: aHR 3.64, 95% CI 1.51–8.77, $P=0.004$; Table 3; Fig. 1a]. In addition, there was a significantly increased risk of mortality in those aged 70–94 years compared with patients aged 15–39 years during the first 3 months on ART (aHR 3.18, 95% CI 2.12–4.77; $P<0.001$). Severe immunosuppression at ART initiation was most strongly associated with mortality (>0–3 months follow-up: aHR 2.19, 95% CI 1.83–2.63, $P=0.008$; >3–42 months follow-up: aHR 1.83, 95% CI 1.52–2.21, $P<0.001$), and each unit increase in BMI reduced risk of mortality (aHR 0.88 and 0.91 for >0–3 months and >3–42 months follow-up, respectively, $P<0.001$). Rural clinic setting was protective against mortality in the first 3 months of ART (aHR 0.80, 95% CI 0.68–0.95, $P=0.009$) but a risk thereafter (aHR 1.27, 95% CI 1.05–1.52, $P=0.013$). Conversely, increasing age was not associated with risk of loss to follow-up in any of the

Table 2. Age distribution by project location with effect of leaving each project out on mortality adjusted hazard ratio for age per 10 year increase.

	15–49 years	50–95 years	Total	aHR (95% CI)	*P* value
Abdurafi, Ethiopia	376	20 (5.0%)	396	1.14 (1.07, 1.21)	<0.001
Baraka, Democratic Republic of Congo (DRC)	150	23 (13.3%)	173	1.14 (1.08, 1.21)	<0.001
Boguila, Central African Republic	171	13 (7.1%)	184	1.15 (1.09, 1.22)	<0.001
Bukavu, DRC	1409	167 (10.6%)	1576	1.16 (1.09, 1.23)	<0.001
Danane, Côte d'Ivoire	567	46 (7.5%)	613	1.15 (1.09, 1.22)	<0.001
Dubie, DRC	84	11 (11.6%)	95	1.15 (1.08, 1.21)	<0.001
Epworth, Zimbabwe	3922	444 (10.2%)	4366	1.12 (1.06, 1.19)	<0.001
Gweru, Zimbabwe	4644	832 (15.2%)	5476	1.12 (1.05, 1.20)	<0.001
Humera, Ethiopia	838	56 (6.3%)	894	1.14 (1.08, 1.21)	<0.001
Kindamba, Republic of Congo (RoC)	10	13 (56.5%)	23	1.15 (1.09, 1.22)	<0.001
Kitgum, Uganda	222	32 (12.6%)	254	1.14 (1.08, 1.21)	<0.001
Kinkala, RoC	49	2 (3.9%)	51	1.14 (1.08, 1.21)	<0.001
Kilwa, DRC	36	5 (12.2%)	41	1.14 (1.08, 1.21)	<0.001
Lagos, Nigeria	1738	180 (9.4%)	1918	1.15 (1.08, 1.22)	<0.001
Mindouli, RoC	203	19 (8.6%)	222	1.15 (1.08, 1.21)	<0.001
Nchelenge, Zambia	1139	111 (8.9%)	1250	1.15 (1.08, 1.22)	<0.001
Walikale, DRC	26	3 (10.3%)	29	1.14 (1.08, 1.21)	<0.001
Total	15584	1977 (11.3%)	17561	1.14 (1.08, 1.21)	<0.001

aHR, adjusted hazard ratio; CI, confidence interval.

Table 3. Unadjusted and adjusted risk of death.

	>0–3 months of follow-up				>3–24 months of follow-up			
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Age*								
15–39 years	1		1		1		1	
40–49 years	1.17 (0.98–1.39)	0.09	1.21 (1.00–1.46)	0.050	1.53 (1.26–1.85)	<0.001	1.59 (1.29–1.96)	<0.001
50–59 years	1.12 (0.83–1.51)	0.45	1.16 (0.83–1.63)	0.39	1.53 (1.18–1.99)	0.001	1.58 (1.19–2.11)	0.002
60–69 years	1.22 (0.77–1.95)	0.39	1.44 (0.89–2.31)	0.14	2.76 (1.84–4.14)	<0.001	2.63 (1.66–4.16)	<0.001
70–94 years	2.35 (1.36–4.05)	0.002	3.18 (2.12–4.77)	<0.001	3.49 (1.60–7.62)	0.002	3.64 (1.51–8.77)	0.004
Sex								
Female	1		1		1		1	
Male	1.33 (1.14–1.54)	<0.001	1.20 (1.01–1.41)	0.035	1.34 (1.13–1.59)	0.001	1.02 (0.84–1.22)	0.87
Current TB diagnosis*								
No	1		1		1		1	
Yes	1.25 (0.99–1.60)	0.065	1.05 (0.81–1.34)	0.72	1.46 (1.11–1.92)	0.006	1.34 (0.99–1.80)	0.055
BMI* (per 1 kg/m^2 increase)	0.86 (0.84–0.88)	<0.001	0.88 (0.86–0.90)	<0.001	0.89 (0.86–0.92)	<0.001	0.91 (0.88–0.94)	<0.001
Severe immunosuppression*								
No	1		1		1		1	
Yes	2.81 (2.40–3.29)	<0.001	2.19 (1.83–2.63)	0.008	2.09 (1.77–2.48)	<0.001	1.83 (1.52–2.21)	<0.001
Setting								
Urban	1		1		1		1	
Rural	1.00 (0.86–1.17)	1.00	0.80 (0.68–0.95)	0.009	1.43 (1.21–1.70)	<0.001	1.27 (1.05–1.52)	0.013
Schoenfelds *P*				0.83				0.23

Age categorized for patients with >0–3 months or >3–42 months of follow-up. ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; TB, tuberculosis. *At ART initiation.

periods of follow-up assessed after adjusting for sex, current TB, BMI, severe immunosuppression and clinic setting (Table 4; Fig. 1b). The most significant factor associated with loss to follow-up was the clinic being in a rural setting, with risk increasing with greater follow-up time (Table 4).

The association between increasing age and mortality in the adjusted model was robust to leaving out any single country (Table 2), and a regression that assessed the potential for loss to follow-up as a competing risk (subhazard ratio 1.15, 95% CI 1.08–1.21).

All of the models displayed proportional hazards except for loss to follow-up up until 12 months on ART (Schoenfeld residual $P = 0.002$, Table 4), primarily because of the BMI variable, even after applying a range of statistical contingencies to attempt to obtain proportionality, including categorization, transformation, removal of data outliers and assessment of possible interactions.

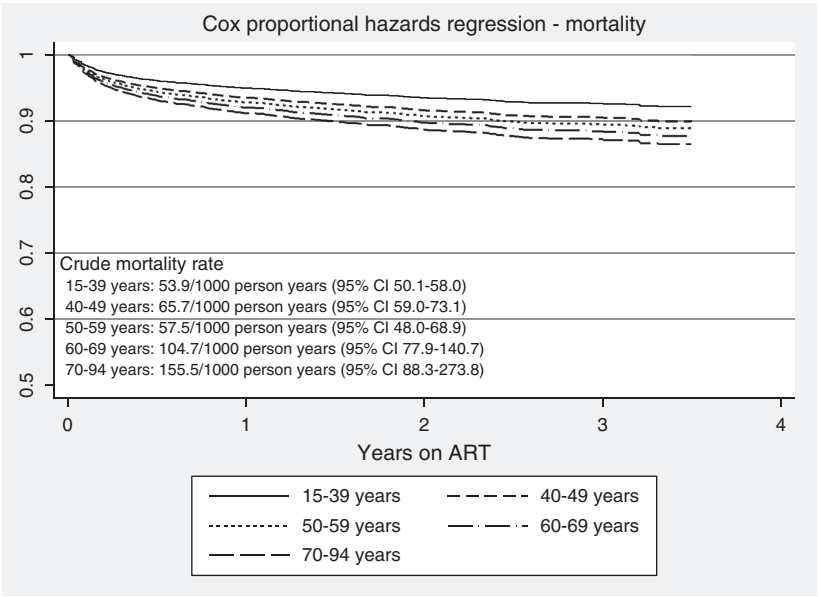
Discussion

HIV/AIDS has resulted in a dramatic decline in life expectancy in sub-Saharan Africa, [13] but with ART, people living with HIV/AIDS can enjoy almost normal life expectancy [14]. The neglect of older age groups in the HIV/AIDS response in sub-Saharan Africa is partly due to a perception that populations in the most affected countries are unlikely to achieve old age anyway and so a focus on younger patients represents a more reasonable public health approach. However, our study shows that older age groups represent an important proportion of the overall ART population. More than one in 10 people on ART in this study were found to be aged 50 years or over, a proportion consistent across most of the nine sub-Saharan Africa countries under review.

Previous studies have reported that people aged 50 or over were at higher risk of mortality compared with younger adults [5–7]. In this study, we found that mortality risk increased as age increased after 3 months on ART, suggesting that a simple age cut-off may not be sufficient for defining older groups at heightened risk of death.

In developed countries, the increased risk of death among HIV patients in older age groups is explained by the increased risk of development of non-AIDS-defining illnesses such as cardiovascular and liver disease, renal impairment and malignancies [15]. A recent study from Botswana found increased risk of non-AIDS-defining illnesses among higher age groups, with standardized rates higher than reported in the United States [16]. Although this is likely to explain some of the excess mortality observed in our cohorts, it is important to note that older age groups are also at greater risk of infectious diseases, particularly TB, as a result of declines in immunity associated with older age [17].

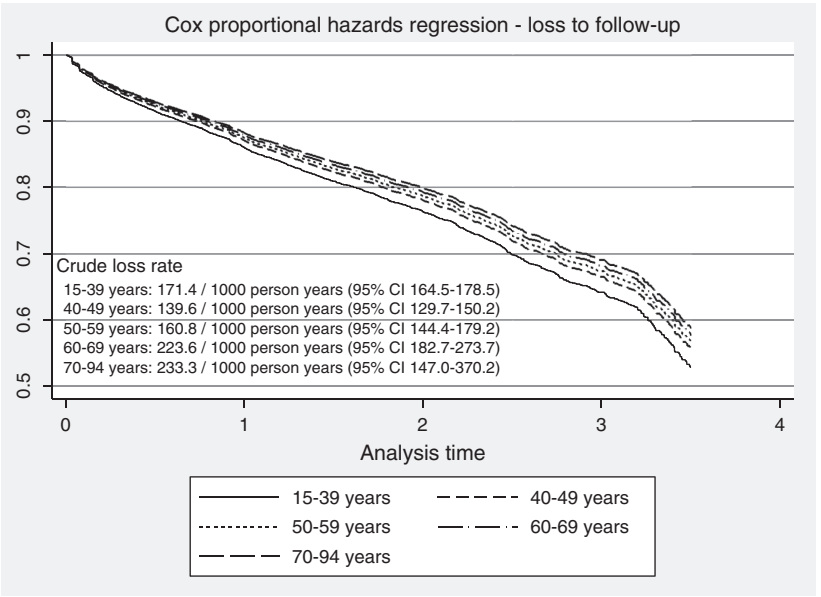
The reason for higher mortality among older people with HIV/AIDS is multifactorial, with the natural aging process, immune senescence, antiretroviral drug toxicities and HIV infection all suggested to play a role [18,19]. We found that patients aged at least 50 years had a significantly



(a)

Number at risk

Years on ART	0	1	2	3
15-39 y	11121	5646	2543	589
40-49 y	3874	2090	1020	300
50-50 y	1518	852	418	107
60-69 y	356	172	73	22
70-94 y	73	33	9	2



(b)

Fig. 1. Cox proportional hazards regression plots. Plots of the adjusted risk of (a) death and (b) loss to follow-up after initiation of antiretroviral therapy.

lower CD4 gain at 6 and 12 months on ART, a finding consistent with those from a large observational cohort study from 33 European cohorts which found that the probability of immunological response reduced in those aged 60 years or older [20]. This gives further cause for concern about potential vulnerability to incident opportunistic infections and suggests a need for rapid ART initiation as soon as clinically eligible.

Our results are based on data pooled from different programmes in which HIV care was provided both as a disease-specific programme and integrated into general healthcare, in urban and rural areas and across a number of countries. This allows some confidence in the generalizability of our findings to other programmes in sub-Saharan Africa. Leaving out any single country did not importantly influence the role of age on mortality. We

Table 4. Unadjusted and adjusted risk of loss to follow-up.

	>0–12 months follow-up				>12–24 months follow-up				>24–42 months follow-up			
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value	HR (95% CI)	*P* value	aHR (95% CI)	*P* value	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Age*												
15–39 years	1		1		1		1		1		1	
40–49 years	0.83 (0.75–0.93)	0.001	0.83 (0.74–0.93)	0.002	0.88 (0.73–1.05)	0.15	0.91 (0.76–1.11)	0.38	0.97 (0.79–1.19)	0.78	0.96 (0.77–1.19)	0.70
50–59 years	0.91 (0.78–1.07)	0.24	0.88 (0.74–1.04)	0.13	1.14 (0.91–1.43)	0.25	1.05 (0.82–1.34)	0.71	1.22 (0.93–1.58)	0.15	1.15 (0.86–1.52)	0.35
60–69 years	1.27 (0.98–1.65)	0.07	1.28 (0.97–1.68)	0.08	1.05 (0.67–1.65)	0.84	0.91 (0.57–1.46)	0.70	1.43 (0.85–2.39)	0.18	1.04 (0.60–1.80)	0.88
70–94 years	1.00 (0.55–1.83)	0.99	0.86 (0.47–1.59)	0.63	1.19 (0.52–2.77)	0.69	1.08 (0.44–2.62)	0.87	2.44 (0.92–6.46)	0.07	2.18 (0.85–5.60)	0.10
Sex												
Female	1		1		1		1		1		1	
Male	1.06 (0.97–1.16)	0.20	1.07 (0.97–1.18)	0.17	0.95 (0.82–1.11)	0.54	0.94 (0.80–1.11)	0.47	0.90 (0.75–1.08)	0.25	0.85 (0.70–1.03)	0.10
Current TB diagnosis*												
No	1		1		1		1		1		1	
Yes	0.65 (0.54–0.78)	<0.001	0.76 (0.63–0.93)	0.007	0.69 (0.51–0.93)	0.017	0.99 (0.71–1.40)	0.97	0.66 (0.45–0.97)	0.034	1.11 (0.74–1.67)	0.61
BMI* (per 1 kg/m^2 increase)	0.99 (0.98–1.00)	0.06	1.01 (0.99–1.02)	0.36	0.99 (0.97–1.01)	0.18	1.21 (0.99–1.04)	0.14	1.00 (0.97–1.02)	0.78	0.99 (0.96–1.01)	0.26
Severe immunosuppression*												
No	1		1		1		1		1		1	
Yes	1.28 (1.17–1.39)	<0.001	1.22 (1.11–1.34)	<0.001	0.92 (0.80–1.06)	0.26	0.94 (0.81–1.11)	0.48	0.75 (0.64–0.90)	0.001	0.68 (0.57–0.82)	<0.001
Setting												
Urban	1		1		1		1		1		1	
Rural	2.30 (2.08–2.54)	<0.001	2.23 (2.00–2.50)	<0.001	3.71 (3.14–4.38)	<0.001	3.55 (2.96–4.27)	<0.001	6.53 (5.10–8.36)	<0.001	6.47 (4.99–8.38)	<0.001
Schoenfelds *P*				0.002				0.47				0.23

Age categorized for patients with >0–12, >12–24 or >24–42 months of follow-up. aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; TB, tuberculosis. *At ART initiation.

were able to control for a number of patient and programme-level variables, but cannot exclude the possibility of residual confounding. Despite various attempts to obtain proportionality, one of the Cox hazards models did not adhere to the assumption of proportional hazards; however, BMI was retained in the model as a clinically important factor related to poor outcomes. The likely effect of a nonproportional predictor is that the power of the test for this variable is reduced, such that any association may be missed, and the concurrent model predictors that do satisfy proportionality also suffer from decreased power associated with a poorer overall model fit [21]. Finally, we were unable to report on a number of important variables due to the limits of routine programme reporting. In common with reports from other routine programmes in sub-Saharan Africa [22], CD4 cell counts were not available for a substantial number of patients. Thus, we are unable to report on the association between excess mortality and age-related decline in immune status; nevertheless, higher mortality at older age groups was still seen after controlling for a composite measure of immunosuppression combining CD4 cell count and WHO stage. Specific causes of death could also not be reported because this was not routinely reported and links to death registries were not established in these settings. We could not assess association of HIV status and expected risk of mortality with age in these settings, as data was from routine monitoring of dedicated HIV programmes.

In conclusion, this study provides further evidence that older age groups are a vulnerable group in ART programmes and suggests that, although it is important to identify groups in need of more careful follow-up and earlier initiation on ART, the application of crude age categories may result in patients at higher risk being overlooked. Future research is now needed to understand the reasons for higher mortality in older age groups, and defining simple interventions that are feasible in highly under-resourced settings to allow for adapted follow-up and care approaches for older age groups.

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Conflicts of interest

There are no conflicts of interest.

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