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Trends in one-year cumulative incidence of death between 2005 and 2013 among patients initiating antiretroviral therapy in Uganda

Lisa M Bebell[1,2], Mark J Siedner[1,2], Nicholas Musinguzi[3], Yap Boum II[3,4], Bosco M Bwana[3], Winnie Muyindike[5], Peter W Hunt[6], Jeffrey N Martin[7] and David R Bangsberg[1,2]

Abstract

Recent ecological data demonstrate improving outcomes for HIV-infected people in sub-Saharan Africa. Recently, Uganda has experienced a resurgence in HIV incidence and prevalence, but trends in HIV-related deaths have not been well described. Data were collected through the Uganda AIDS Rural Treatment Outcomes (UARTO) Study, an observational longitudinal cohort of Ugandan adults initiating antiretroviral therapy (ART) between 2005 and 2013. We calculated cumulative incidence of death within one year of ART initiation, and fit Poisson models with robust variance estimators to estimate the effect enrollment period on one-year risk of death and loss to follow-up. Of 760 persons in UARTO who started ART, 30 deaths occurred within one year of ART initiation (cumulative incidence 3.9%, 95% confidence interval [CI] 2.7–5.6%). Risk of death was highest for those starting ART in 2005 (13.0%, 95% CI 6.0–24.0%), decreased in 2006–2007 to 4% (95% CI 2.0–6.0%), and did not change thereafter ($P = 0.61$). These results were robust to adjustment for age, sex, CD4 cell count, viral load, asset wealth, baseline depression, and body mass index. Here, we demonstrate that one-year cumulative incidence of death was high just after free ART rollout, decreased the following year, and remained low thereafter. Once established, ART programs in President's Emergency Fund for AIDS Relief-supported countries can maintain high quality care.

Keywords

Death, mortality, HIV, antiretroviral therapy, Africa, antiretroviral, early, clinical outcomes

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Introduction

Recent ecological data have demonstrated decreasing mortality of HIV-infected persons accessing antiretroviral therapy (ART) in sub-Saharan Africa, particularly in countries targeted by the President's Emergency Fund for AIDS Relief (PEPFAR) and other international HIV treatment programs.[1–3] Cohort studies in South Africa have documented a decline in mortality and increase in life expectancy for people living with HIV/AIDS (PLWHA) as ART has become widely available.[4,5] Elsewhere in sub-Saharan Africa, progress diagnosing HIV and linking PLWHA into care has been slower and sometimes erratic,[6–8] with much of the benefit of expanded ART access confined to women.[9] The Uganda National Antiretroviral Treatment Guidelines[10] have changed since PEPFAR

[1]Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, USA
[2]Massachusetts General Hospital Center for Global Health, Boston, MA, USA
[3]Mbarara University of Science and Technology, Mbarara, Uganda
[4]Epicentre Research Base, Mbarara, Uganda
[5]Department of Medicine, Mbarara Regional Referral Hospital, Mbarara, Uganda
[6]Department of Medicine, University of California, Berkeley, CA, USA
[7]Department of Epidemiology and Biostatistics, University of California, Berkeley, CA, USA

Corresponding author:
Lisa M Bebell, Department of Infectious Diseases, Massachusetts General Hospital Center for Global Health, 55 Fruit Street, GRJ-504, Boston, MA 02115, USA.
Email: lbebell@mgh.harvard.edu

first began ART rollout in 2004. The threshold for ART initiation was a CD4 count ≤ 200 cells/μl (or World Health Organization Stage III/IV) until late 2011 when it increased to 350 cells/μl. Recently, Uganda has experienced a recent resurgence in both HIV incidence and prevalence,[11] but trends in HIV-related deaths have not been well described and mortality data are scant. Accurate estimates of trends in risk of early death over time are critical to providing successful linkage of PLWHA to care and to maximizing quality of care. However, correct classification of patient death remains a challenge in mortality assessment throughout sub-Saharan Africa.[12,13] Biased estimates result from failure to differentiate between patient death, default, or transfer of care among disengaged patients.[12]

To investigate whether one-year cumulative incidence of death has changed over calendar time in PLWHA initiating ART in Uganda, we examined associations between year of ART initiation and cumulative incidence of death in a cohort of ART-naïve PLWHA enrolled between 2005 and 2013. To minimize bias in estimating outcomes among patients lost to follow-up, all participants disengaging from care were physically tracked to enable accurate allocation of outcome. We hypothesized that one-year cumulative incidence of death would decrease over time, due to increased access to HIV testing leading to earlier diagnosis and presentation for treatment.

Methods

Study participants and procedures

Data from this study were collected as part of the Uganda AIDS Rural Treatment Outcomes (UARTO) Study, described previously.[14,15] In brief, UARTO (NCT01596322) is an observational longitudinal cohort study of ambulatory adults initiating ART at the Immune Suppression Syndrome (ISS) Clinic at the Mbarara Regional Referral Hospital in Mbarara, Uganda, an HIV treatment clinic located approximately 290 km southwest of Kampala. The cohort began in 2005, enrolled individuals until August 2013, and followed participants until they died, withdrew, moved out of the catchment area, or August 2015, whichever came last. Inclusion criteria were age ≥ 18 years, documented HIV-1 infection, ART-naïve at enrollment, and living within 60 km of the clinic. The only exclusion criterion was inability to provide written consent. The ISS Clinic has provided ART free of charge to approximately 10,000 PLWHA since 2004. The clinic prescribes ART on the basis of CD4+ T-cell (CD4) count or clinical status, according to the Uganda National Antiretroviral Treatment Guidelines.[10] These guidelines changed over the observation period.

Participants completed study visits 3–4 times per year, each with structured interviews and laboratory testing for CD4 count and plasma HIV-1 RNA viral loads (VL). We included all study participants who started ART in our analyses, regardless of duration of therapy or retention in care. For participants missing baseline CD4 or HIV VL measures within 90 days of ART initiation, the CD4 value was imputed as the median CD4 count for participants entering the cohort that same year. Missing baseline HIV VL and body mass index (BMI) were imputed as the mean for the entire UARTO cohort. Participant observation continued until August 2015, ensuring a minimum follow-up time of at least two years for the last enrolled participant. Participants missing from the study were tracked at home to determine their vital status and whether they had transferred care to another clinic. Reported deaths were confirmed using verbal autopsy. The study was approved by the institutional ethics review boards at Mbarara University of Science and Technology, Partners Healthcare, and the Uganda National Council of Science and Technology.

Statistical analyses

Descriptive statistics were used to characterize the cohort. To summarize baseline participant characteristics and changes in characteristics over calendar time, the cohort was divided into five strata based on year of entry into the cohort (2005, 2006–2007, 2008–2009, 2010–2011, and 2012–2013), to account for changes in clinical infrastructure and national treatment guidelines.

Our primary outcome of interest was death from any cause within 365 days of ART initiation. Success was defined as a participant confirmed alive at 365 days after ART initiation, including those who transferred care or those known to have disenrolled from study but were confirmed alive. Failure was defined in any participant confirmed dead at or before 365 days after ART initiation. Participants not meeting either definition were excluded from the cumulative incidence of death analysis and considered as failures in the death or loss-to-follow-up secondary analysis. Participants who were initially thought LTFU at 365 days but later were found to have been alive or dead at 365 days were assigned as 365-day successes or failures, respectively. The primary predictor of interest in the analysis was period of enrollment, classified by year of cohort entry and divided into five time periods as described above. We abstracted data from the ISS HIV treatment clinic where study participants received ART and summarized the number of new patients each year and cumulative patient load. We plotted crude one-year

cumulative incidence of death by year of enrollment to depict trends over time.

Cumulative one-year incidence of death and 95% confidence intervals (CI) were calculated from the number of deaths over number of persons enrolled in a given cohort period. To estimate trends in cumulative incidence of death over calendar time, we fit a Poisson model with robust variance estimators to estimate the effect of calendar time on risk of death, with cumulative incidence of death within 365 days of ART initiation as the outcome variable and period of cohort entry as a categorical explanatory variable, referenced to the 2006–2007 enrollment period. A second model was then fitted with a composite outcome of death or loss to follow-up (LTFU) within 365 days of ART initiation as the outcome of interest, in which participants lost to follow-up before 365 days were included as failures. To obtain adjusted estimates, we fitted multivariable models including gender, age, enrollment CD4 count divided into strata (<100, 100–250, 251–349, ≥350 cells/μl), $\log_{10}$ HIV-1 RNA VL, educational attainment, marital status, household asset wealth,[16] baseline depression (Hopkins Symptoms Checklist score as a dichotomous variable with a cutoff of >1.75), BMI divided into strata (<18, 18–25, >25), and employment status; using backward stepwise regression modeling with a threshold of $P < 0.25$. We fit a final model comparing one-year risk of death between participants enrolled in 2005 with those enrolled between 2006 and 2013.

We graphically depicted trends in one-year cumulative incidence of death using a time-to-event analysis to generate a Kaplan–Meier survival curve. The left-censor date for the Cox model was calendar date of antiretroviral start, and the right-censor date was the date of death or LTFU, counted in days. All analyses were performed using STATA software (Version 12.0, StataCorp, College Station, TX).

Results

Of 5199 persons screened for enrollment into UARTO, 760 started ART and were included in this analysis.

Table 1. Patient characteristics by year of enrollment into the UARTO cohort, divided into five groups to demonstrate trends over time.

Characteristic	Total cohort (2005–2013) $N = 760$	2005 $N = 61$	2006–2007 $N = 303$	2008–2009 $N = 137$	2010–2011 $N = 99$	2012–2013 $N = 160$	*P*-value*
Age in years, median (IQR)	34 (28, 39)	34 (30, 39)	35 (30, 40)	33 (27, 39)	33 (28, 42)	29.5 (25, 37.5)	0.003
Female, *n* (%)	525 (69)	39 (64)	215 (71)	97 (71)	67 (68)	108 (68)	0.82
Married ($n = 759$), *n* (%)	379 (50)	28 (46)	133 (44)	61 (45)	62 (63)	95 (59)	0.001
Achieved more than primary education ($n = 730$), *n* (%)	205 (28)	20 (36)	74 (27)	32 (23)	27 (27)	52 (33)	0.26
Lowest quartile of household asset index ($n = 754$), *n* (%)[a]	192 (25)	19 (31)	84 (28)	46 (34)	15 (15)	28 (18)	0.02
Employed, *n* (%)	578 (76)	51 (84)	235 (78)	86 (63)	81 (81)	125 (78)	0.001
BMI category, *n* (%)							
<18	83 (11)	18 (30)	29 (10)	19 (14)	9 (9)	8 (5)	<0.001
18–25	547 (72)	38 (62)	232 (77)	100 (73)	72 (73)	105 (63)	
>25	130 (17)	5 (8)	42 (14)	18 (13)	18 (18)	47 (29)	
Baseline CD4 lymphocyte count, mean (SD)	203 (158)	120 (112)	142 (95)	175 (116)	305 (196)	312 (187)	<0.001
Baseline CD4 lymphocyte count category							<0.001
< 100, *n* (%)	202 (27)	34 (56)	108 (36)	34 (25)	10 (10)	16 (10)	
100–250, *n* (%)	340 (45)	22 (36)	163 (54)	78 (57)	30 (30)	47 (29)	
251–349, *n* (%)	114 (15)	2 (3)	23 (8)	16 (12)	30 (30)	43 (27)	
≥ 350, *n* (%)	104 (14)	4 (5)	9 (3)	9 (7)	29 (29)	54 (34)	
Baseline HIV viral load (Log_{10}), mean (SD)	4.9 (0.8)	5.1 (0.6)	5.0 (0.8)	4.9 (0.8)	4.8 (0.7)	4.7 (1.0)	<0.001

BMI: body mass index; CD4: CD4+ T-cell; HIV: human immunodeficiency virus; IQR: interquartile range; SD: standard deviation.

[a]This variable was calculated using an internal principal components analysis. By definition, the within-cohort mean is equal to zero. Positive scores indicate increasing wealth, and negative scores indicate decreasing wealth

*P-values represent comparison between the five cohort groups using Chi-squared, Wilcoxon Rank Sum or t-test, where appropriate.

Baseline CD4 count was imputed for 15 (2.0%) and baseline HIV VL was imputed for 11 (1.4%) participants, who did not have these measures recorded within 90 days of ART start. Baseline BMI was imputed for 22 (2.9%). There were no significant differences between complete cases and persons with missing data for any of the variables of interest. There were 525 women (69.1%) and 235 men (30.9%) in the sample. Average age at cohort entry was 34.4 (range 18–75) years old. Mean BMI at enrollment increased significantly over time, from 20.6 in 2005 to 23.3 in 2013 ($P < 0.001$) and median CD4 at enrollment increased from 81 in 2005 to 288 in 2013 ($P < 0.001$). There was no difference in baseline CD4 count between men and women (190.7 versus 209.0 cells/mm^3, $P = 0.14$), though men had higher baseline $\log_{10}$ HIV VL (5.10 versus 4.83, $P < 0.001$). Baseline characteristics are presented in Table 1.

Among the 760 enrolled and initiated on ART and followed for at least 365 days, there were 57 deaths (7.5%) in the cohort at the time of last follow-up in August 2015. Of these, 30 (52.6%) occurred within 365 days of initiating ART, for a cumulative one-year incidence of death of 3.9% (95% CI 2.7–5.6%). Of 30 deaths, 18 (60.0%) of were women. At 365 days after ART initiation, 20 people (2.6%), 12 women (60.0%) and 8 men, were unable to be contacted to determine their vital status and were designated as LTFU. The remaining 710 were confirmed alive at 365 days post-ART initiation, and 495 (69.7%) were women. There were no differences in risk of death or LTFU at one year between women and men ($P = 0.36$).

Crude one-year cumulative incidence of death did not change significantly over calendar time in this cohort, compared to the reference period 2006–2007 (Figure 1). Crude one-year cumulative incidence of death was highest in 2005 at 13% (95% CI 6–24%), decreased to 4% (95% CI 2–6%) in the 2006–2007 enrollment period, and did not change significantly thereafter (Figure 2). Cumulative incidence ratios (CIR) comparing other enrollment periods to the 2006–2007 reference period were 3.78 (95% CI 1.59–8.98, $P < 0.003$) for 2005, 0.82 (95% CI 0.27–2.53, $P = 0.73$) for 2008–2009, 0.27 (95% CI 0.04–2.08, $P = 0.21$) for 2010–2011, and 1.03 (95% CI 0.39–2.73, $P = 0.96$) for 2012–2013. These results did not change meaningfully after adjustment for age, sex, baseline CD4 stratum, baseline HIV-1 RNA VL, asset index quartile, baseline depression, and BMI category, or in

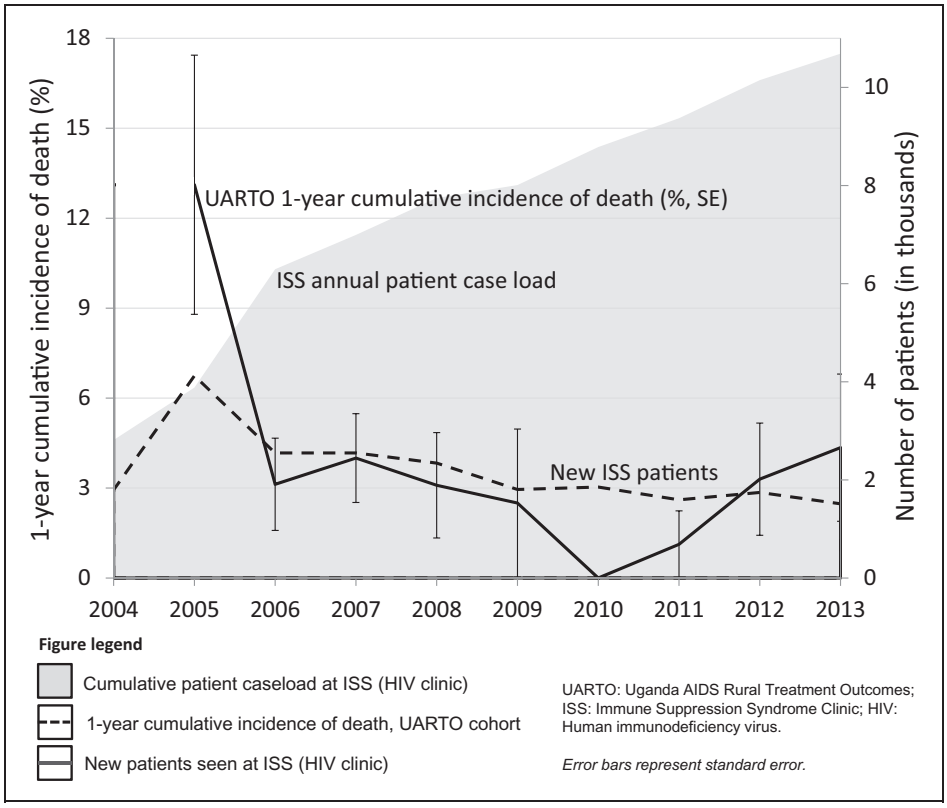

Figure 1. Line graph demonstrating crude one-year cumulative incidence of death by year of ART start, plotted against ISS clinic annual patient case load and number of new patients seen annually at ISS.
ART: antiretroviral therapy; ISS: immune suppression syndrome.

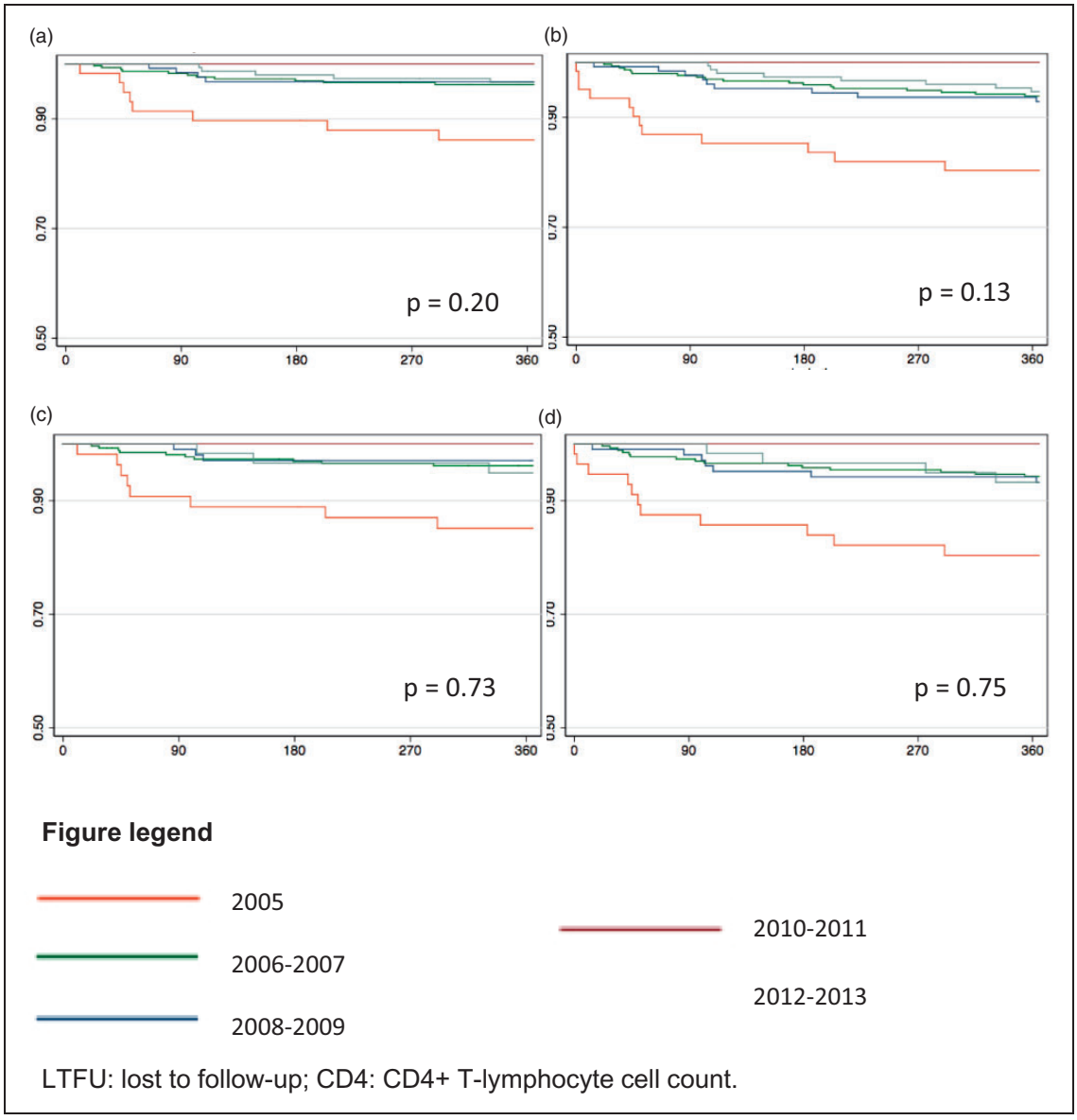

Figure 2. Kaplan–Meier survival plots for one-year cumulative of outcome after starting antiretroviral therapy. (a) death, (b) death or LTFU, (c) death, restricted to CD4<250 and (d) death or LTFU, restricted to CD4<250.

models with death or LTFU as the outcome of interest (Table 2). Baseline depression was the only significant predictor ($P \leq 0.05$) of one-year cumulative incidence of death in the multivariable model, and baseline depression and male sex were the only significant predictors of death or LTFU.

In a model comparing participants enrolled in 2005 to those enrolled from 2006 to 2013, participants enrolled in 2005 had a CIR for death within one year of starting ART of 4.36 (95% CI 2.03–9.35, $P < 0.001$). Similarly, the CIR for death or LTFU was 3.62 (95% CI 2.00–6.56, $P < 0.001$) for participants enrolled in 2005 compared to those enrolled later. This relationship remained significant, although with decreased magnitude in a multivariable model (3.03, 95% CI 1.42–6.47, $P = 0.004$), and in a model with death or LTFU as the primary outcomes of interest (adjusted for age, sex, BMI category, baseline CD4 stratum, baseline $\log_{10}$ VL asset wealth, baseline depression).

Discussion

In this analysis of a prospectively enrolled cohort of ART-naïve PLWHA, we demonstrate that risk of early death in this cohort was low overall, with an overall one-year cumulative incidence of death at 365 days of 3.9% (95% CI 2.7–5.6%) within one year of ART initiation and no association between baseline low

Table 2. CIR and AIR for outcome of death at 365 days after ART initiation and death or LTFU at 365 days after ART initiation by period of enrollment.

	Univariable model		Multivariable model[a]	
Outcome: Death By enrollment period	CIR (95% CI)	*P*-value	AIR (95% CI)	*P*-value
2005	3.78 (1.59–8.98)	0.003	3.27 (1.41–7.55)	0.006
2006–2007	1.0 (Ref)	–	1.0 (Ref)	–
2008–2009	0.82 (0.27–2.53)	0.73	0.97 (0.31–3.05)	0.97
2010–2011	0.27 (0.04–2.08)	0.21	0.58 (0.07–5.20)	0.63
2012–2013	1.03 (0.39–2.73)	0.96	1.76 (0.61–5.12)	0.30
Outcome: Death or LTFU By enrollment period	CIR (95% CI)	*P*-value	AIR (95% CI)	*P*-value
2005	3.31 (1.68–6.52)	0.001	2.76 (1.42–5.36)	0.003
2006–2007	1.0 (Ref)	–	1.0 (Ref)	–
2008–2009	1.23 (0.58–2.59)	0.59	1.26 (0.59–2.69)	0.55
2010–2011	0.17 (0.02–1.26)	0.08	0.23 (0.03–2.00)	0.18
2012–2013	0.95 (0.44–2.06)	0.89	1.03 (0.41–2.57)	0.95

AIR: adjusted cumulative incidence ratio; ART: antiretroviral therapy; CIR: cumulative incidence ratio; LTFU: lost to follow-up. [a]Adjusted for age, sex, CD4 stratum, baseline $\log_{10}$ human immunodeficiency virus viral load, asset index quartile, baseline depression, BMI category. Significant in multivariable model for risk of death ($P \leq 0.05$): baseline depression. Significant in multivariable model for risk of death or LTFU ($P < 0.05$): male sex and baseline depression.

CD4 count and mortality. Our findings are similar or lower overall to early risk of death in other large sub-Saharan African cohorts. The ART-LINC Collaboration, which analyzed data from 18 cohorts with active follow-up across the developing world, reported a one-year mortality average of 6.4% (95% CI 5.1–7.7%).[17] In that study, mortality was lower in programs from high-income countries, at 1.8% (95% CI 1.5–2.2%).[17] After 2005, one-year risk of death among UARTO cohort participants approached mortality rates in high-income settings, ranging from 1.0 to 3.8% in subsequent enrollment periods. However, during the first year of UARTO enrollment (2005), risk of death within one year of initiation ART was estimated at 13.1% (95% CI 5.8–24.2%), similar to the risk observed in another Ugandan prospective cohort of urban ART-naïve PLWHA. In this cohort enrolled from 2004 and 2005, the probability of death was high within one year of starting ART (15.0%, 95% CI 12.0–18.0%).[18]

PEPFAR began rolling out free ART in Uganda in 2004. By 2005, very few rural Ugandans had been started on treatment.[19] In this early phase of ART roll-out, we found that one-year cumulative incidence of death was relatively high, and hypothesize that high risk of death was partially due to PLWHA presenting for care in 2005 at late stages of HIV disease, compared to later enrollment periods. This hypothesis is supported by the fact that over 50% of patients enrolling in 2005 had a CD4 count at enrollment <100 cells/μL, which gradually decreased to 10% by 2013. However, even after multivariable adjustment (including CD4 count), one-year cumulative incidence of death in 2005 remained significantly higher than other cohort periods. We attribute this difference to challenges in effective ART delivery early in the program implementation. After 2005, we found a rapid and persistent decrease in risk of death during the first year after ART initiation in this cohort. Between 2006 and 2013, one-year death risk did not significantly change, and we suspect a ceiling effect due to delivering optimal care. The low risk of death in this cohort from 2006 on may be the result of HIV provider and clinic excellence in addition to intensive efforts to track patients after missing clinic visits and reengage them in HIV care. Importantly, we found stable, low one-year risk of death during a period in Uganda when HIV incidence and prevalence increased, suggesting that clinical programs remain capable of improving outcomes even while prevention and other HIV strategies appeared to be less successful.

Strengths of our analysis include the large cohort size, rare missing data, and near complete ascertainment of outcomes, including care transfer and death. There are limitations to our analysis. First, these results may not be generalizable to all ART treatment centers in low-resource settings, as the study was conducted at a single center, enrollment was limited to those residing within 60 km of the clinic, and we implemented patient

tracking and adherence measures that are not routine in most ART clinics. Although we might have misclassified participants LTFU among those who could not be tracked, the addition of LTFU in a composite outcome did not change our estimates meaningfully, mitigating any effect of misclassification. There may be unmeasured or residual confounding affecting the relationship between calendar date at ART initiation and one-year cumulative incidence of death. In our adjusted analysis, we corrected for known potential confounders and the relationship between calendar date and the outcome of one-year cumulative incidence of death remained similar.

Conclusions

After the first year of PEPFAR scale-up, one-year cumulative incidence of death was persistently low during 2006–2013 in this prospectively followed cohort of rural Ugandan PLWHA initiating ART. Our findings suggest that with multilateral support and intensive follow-up high-quality HIV care can be achieved early and sustained in PEPFAR focus countries. Future studies should evaluate the success of former PEPFAR programs in the post-PEPFAR era.

Authors' contributions

LMB – data analysis and interpretation, manuscript preparation and revision.
MJS – data analysis and interpretation, manuscript preparation and revision.
NM – data analysis and interpretation, manuscript revision.
YB – study design and data acquisition, manuscript revision.
BMB – study design and data acquisition, data interpretation, manuscript revision.
WM – data acquisition, data interpretation, manuscript revision.
PWH – study design and data acquisition, data interpretation, manuscript preparation and revision.
JNM – study design and data acquisition, data interpretation, manuscript preparation and revision.
DRB – study design and data acquisition, data interpretation, manuscript preparation and revision.
All authors have read and approved the final manuscript.

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Declaration of conflicting interests

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