



Original Contribution

Mortality Rate in a Cohort of People Living With HIV in Rural Tanzania After Accounting for Unseen Deaths Among Those Lost to Follow-up

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Mortality assessment in cohorts with high numbers of persons lost to follow-up (LTFU) is challenging in settings with limited civil registration systems. We aimed to assess mortality in a clinical cohort (the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO)) of human immunodeficiency virus (HIV)-infected persons in rural Tanzania, accounting for unseen deaths among participants LTFU. We included adults enrolled in 2005–2015 and traced a nonrandom sample of those LTFU. We estimated mortality using Kaplan-Meier methods 1) with routinely captured data (method A), 2) crudely incorporating tracing data (method B), 3) weighting using tracing data to crudely correct for unobserved deaths among participants LTFU (method C), and 4) weighting using tracing data accounting for participant characteristics (method D). We investigated associated factors using proportional hazards models. Among 7,460 adults, 646 (9%) died, 883 (12%) transferred to other clinics, and 2,911 (39%) were LTFU. Of 2,010 (69%) traced participants, 325 (16%) were found: 131 (40%) had died and 130 (40%) had transferred. Five-year mortality estimates derived using the 4 methods were 13.1% (A), 16.2% (B), 36.8% (C), and 35.1% (D), respectively. Higher mortality was associated with male sex, referral as a hospital inpatient, living close to the index clinic, lower body mass index, more advanced World Health Organization HIV clinical stage, lower CD4 cell count, and less time since initiation of antiretroviral therapy. Adjusting for unseen deaths among participants LTFU approximately doubled the 5-year mortality estimates. Our approach is applicable to other cohort studies adopting targeted tracing.

HIV; loss to follow-up; mortality; proportional hazards models; Tanzania

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range; KIULARCO, Kilombero and Ulanga Antiretroviral Cohort; LTFU, loss/lost to follow-up; WHO, World Health Organization.

Survival among human immunodeficiency virus (HIV)-infected persons receiving treatment is approaching that of the general population in resource-rich settings (1–3) but not yet in resource-limited settings (4). Estimation of mortality remains challenging in settings with high numbers of persons lost to follow-up (LTFU) and differential risk of mortality among those who remain in care versus those LTFU (5). In a 2009 meta-analysis assessing mortality among patients LTFU in antiretroviral therapy (ART) programs in resource-limited settings, Brinkhof et al. (6) found that 46% of those LTFU and traced had died. There was an inverse relationship between the proportion of patients LTFU and the mortality

rate among those LTFU, with higher mortality being seen among those LTFU in cohorts with lower overall LTFU. In an updated 2017 meta-analysis, Zürcher et al. (7) found an overall mortality prevalence of 34% among those LTFU, with substantial declines as ART was scaled up over calendar time.

While passive surveillance of deaths captured in routine care is insufficient to estimate true mortality (8–13), active surveillance involves tracing a subset of patients LTFU, known as “double sampling” (14), and those found to be alive but not under care are encouraged to return to the clinic. In a 2013 systematic review, McMahan et al. (15) found that

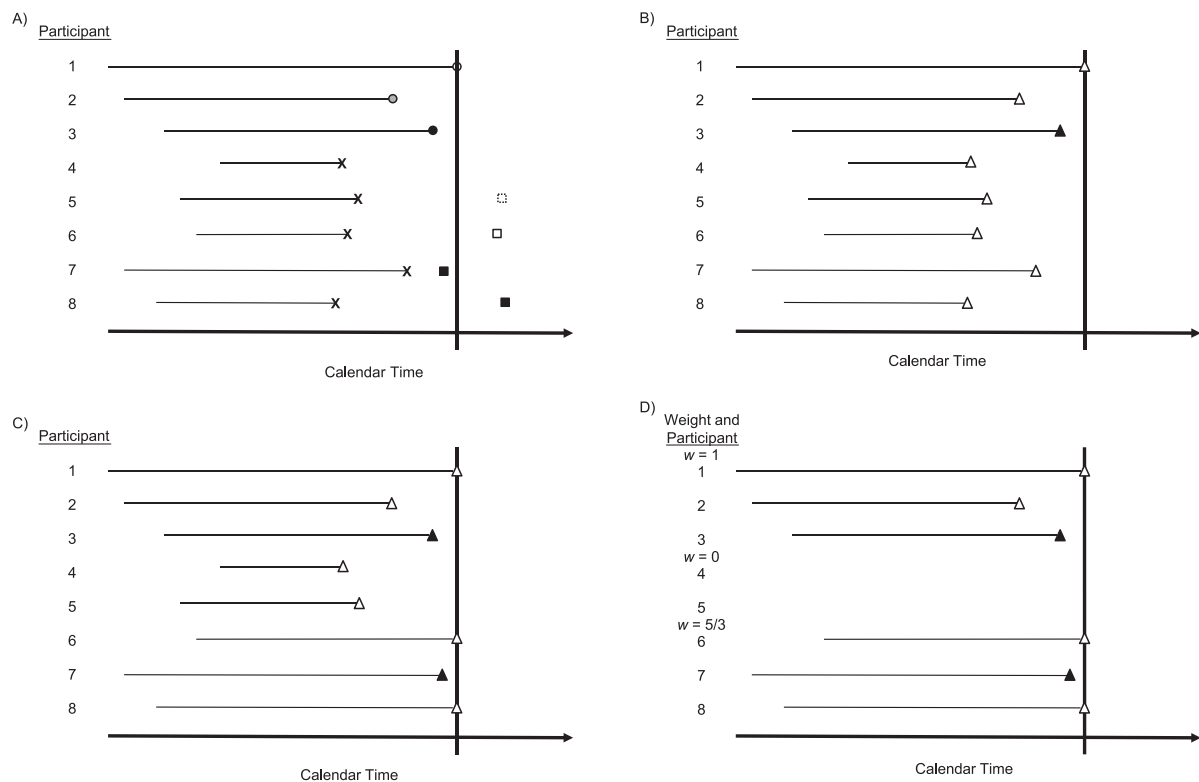


Figure 1 Continues

treatment programs with routine tracing had lower LTFU than those without it because of the determination of outcomes among those LTFU, and more importantly because of reengagement of patients in care after tracing. However, deaths determined through tracing cannot simply be pooled with those captured routinely: Appropriate statistical methods are required to adjust mortality estimates to account for the patients who were LTFU and not traced or who remained LTFU despite tracing efforts (8, 11, 12, 14).

Our objective in this study was to estimate mortality and associated factors among HIV-infected adults enrolled in an open cohort in Ifakara, rural Tanzania, incorporating additional information ascertained through tracing. We used previously developed methods (10, 12–14) plus a 2-step weighting approach which has previously been proposed but not yet implemented (16) and which accounts for the probabilities of being selected for tracing and of being found after tracing has been attempted. These methods allow unbiased estimation of mortality rates under the hypothetical scenario of being able to observe all outcomes, that is, without masking of outcomes due to LTFU.

METHODS

Study design and population

Since 2005, consenting HIV-infected persons visiting the Chronic Disease Clinic in Ifakara at St. Francis Referral Hospital in Ifakara, Tanzania, have been invited to enroll in

the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO), described previously (17, 18). Since 2013, comprehensive data have been systematically captured in electronic medical records, including information on demographic characteristics, ART use, and clinical outcomes (limited data were captured on paper previously). We included data from adults (ages ≥ 15 years) enrolled since 2005, with administrative censoring on November 15, 2015.

Outcomes and tracing

During the study period, participant clinical outcomes were assessed at every visit. Transfers to other clinics were captured if reported in advance by the participant, and deaths were reported by a relative or treatment supporter. In the 3-monthly data export, participants were identified as LTFU if they were more than 60 days late for their last scheduled appointment. Visits were scheduled 3-monthly for persons on ART and 6-monthly for persons not on ART. Nonrandom samples of LTFU participants were traced between February 2016 and July 2017. Participant selection for tracing was done pragmatically, based on logistical considerations (i.e., participants living in the same village were traced at the same time) and operational capacity, after administrative database closure. Tracing was attempted by making up to 3 telephone calls to the participant, household head, treatment supporter, and/or community (10-cell) leader, and if phone calls were unsuccessful, we communicated with community

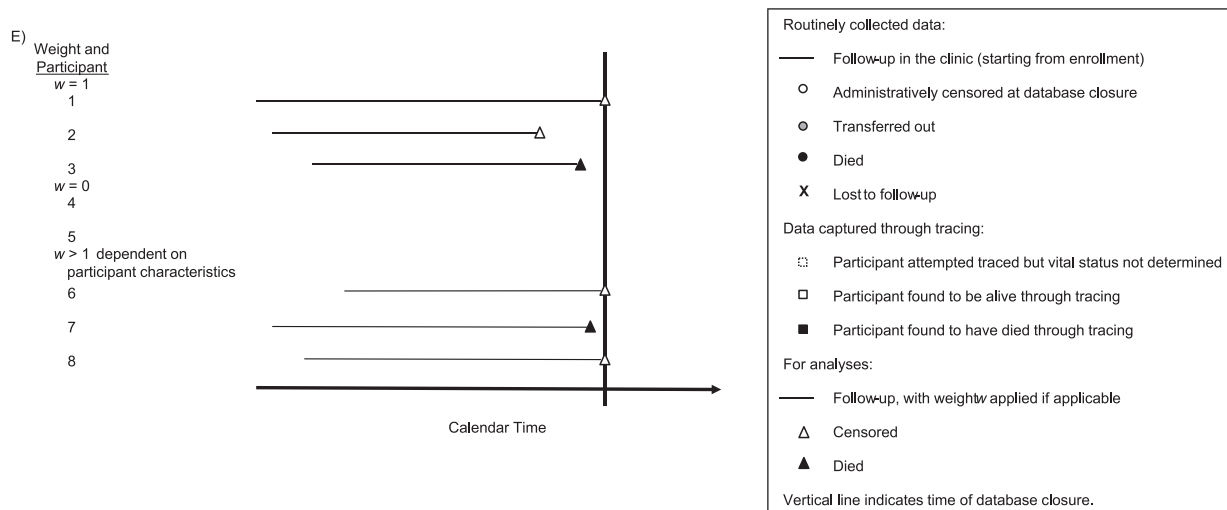


Figure 1. Data captured routinely and through tracing among KIULARCO participants and how it translated to analysis, Ifakara, Tanzania, 2005–2015. A) Illustration of data captured routinely and through tracing for 10 example participants. The horizontal lines indicate follow-up in the clinic starting from enrollment, and the vertical line indicates database closure. Participant 1 remained under active follow-up until administrative censoring (white circle) at database closure. Participant 2 transferred to another clinic, and this was captured in the routine database (gray circle). Participant 3 died, and this was captured in the routine database (black circle). Participants 4–8 were lost to follow-up from the routine database (“X”). Participant 4 was not selected for tracing. An attempt was made to trace participant 5, but vital status was not determined; therefore, no further data were available beyond those in the routine database (the dotted white square indicates the time at which tracing was attempted, but this has no other implication for data interpretation for this participant). Participant 6 was successfully traced and found to be alive (the white square indicates the time at which tracing was performed and therefore the time at which the participant was last known to be alive). Participant 7 was successfully traced and was found to have died before database closure (black square indicates date of death). Participant 8 was successfully traced and was found to have died after database closure (black square indicates date of death). B) Illustration of how the data were used in the analysis under method A (see text for methods) using data captured routinely (straightforward time-to-event analysis). The participants contributed follow-up time as indicated by the horizontal lines, and all participants were censored (white triangles), except for participant 3, who died (black triangle). C) Illustration of how the data were used in the analysis under method B, that is, updating the routinely collected data with information obtained through tracing. Participants 1–5 were included as for method A. Participants 6 and 8 were included as alive until censored at database closure. Participant 7 was included up to the point of death (before database closure) as indicated. D) Illustration of how the data were used in the analysis under method C. Participants 1–3 were included as for methods A and B (weight $w = 1$). Participants 4 and 5 were excluded because they were lost to follow-up and not successfully traced (weight $w = 0$). Participants 6–8 were included with weights $w = 5/3$, that is, upweighted to account for the exclusion of participants 4 and 5. As for method B, participants 6 and 8 were included as alive up to the date of database closure, and participant 7 was included up to the point of death. E) Illustration of how the data were used in the analysis under method D. The approach was the same as that for method C, except that the weights applied to participants 6–8 were based on participant characteristics, through the probabilities of being attempted traced and successfully traced. KIULARCO, Kilombero and Ulanga Antiretroviral Cohort.

health workers for home visits. Participants who were found to be alive and not under care were counseled to return to the clinic. In this article, we refer to those participants who were LTFU and for whom tracing was attempted as “attempted traced” and those whose vital status was determined (regardless of outcome) as “successfully traced.” This information was used to define the participants’ vital status as of the date of administrative censoring for analysis under methods B–D (see below). In particular, 7 participants who were determined through tracing to have died a median of 8 months after administrative censoring were considered to have been alive at the time of censoring in November 2015.

Statistical methods

Our aim was to estimate mortality in the whole cohort population, under the hypothetical scenario that outcomes were observed in all participants. Notably, this is not the

same estimand as mortality among the cohort population if all participants had (hypothetically) remained in care, which was not the objective of this analysis. We estimated mortality using Kaplan-Meier estimation, with 4 methods. Time was measured from enrollment. Participants with intermittent periods of LTFU or transfers to other clinics could reenter the risk set if they returned to the index clinic (the Chronic Disease Clinic in Ifakara) (19). The methods differed in the data used and the weights applied (Figure 1). Figure 1A illustrates data captured routinely and through tracing for 10 example participants. Method A used data captured routinely in the clinic, ignoring tracing data (Figure 1B). Method B used tracing data to update outcomes (and date last known to be alive or to have died) which had been determined through tracing, with no further statistical adjustment (Figure 1C). Method C used the weighting methods of Frangakis and Rubin (14) to correct for unobserved deaths among those who remained

LTFU (9, 20). That is, participants not LTFU were assigned a weight of 1; those LTFU but not successfully traced were given a weight of 0 (i.e., excluded); and those LTFU and successfully traced were assigned a weight given by the number of participants who were LTFU divided by the number who were successfully traced (i.e., upweighted to account for those LTFU and not successfully traced) (Figure 1D). While a single weight is used, some authors refer to this as “time-dependent weighting” because of the way the risk set changes over time (9).

In method D, we extended the Frangakis and Rubin approach to estimate the weights in a 2-step process based on the probabilities of being attempted traced and successfully traced, accounting for participant characteristics, as proposed previously (16). Firstly, we estimated the probability of a participant being attempted traced among those LTFU. Secondly, we estimated the probability of a participant being successfully traced among those attempted traced. For both steps, we used logistic regression models incorporating baseline covariates (see Web Table 1, available at <https://academic.oup.com/aje>) and variables determined at the time of LTFU: year of LTFU, time since ART initiation during follow-up, and number of gaps in care (transient periods of LTFU). Lastly, we included time between LTFU and attempted tracing in the model for successful tracing. The weights were calculated as the product of the inverse of the probabilities of being attempted traced and successfully traced and were applied to the participants who were successfully traced. The weights for those LTFU and successfully traced differed by participant, since they were based on participant characteristics. As for method C, participants not LTFU received a weight of 1, and participants LTFU but not successfully traced were excluded (Figure 1E). For methods C and D, 95% confidence intervals were estimated using a bootstrap of the weighted data with 1,000 replications.

If mortality were similar among participants LTFU and not LTFU, then all methods would unbiasedly estimate mortality in the cohort population. However, we found through tracing that mortality was higher among those LTFU than among those not LTFU (see Results section). Therefore, methods A and B will yield biased mortality estimates. Under the assumption that participants were randomly selected and successfully traced (i.e., the probability of being selected for tracing or successfully traced was not dependent on participant characteristics), method C would yield unbiased mortality estimates. Method D yields unbiased mortality estimates under the assumption that there are no unmeasured confounders for the probabilities of being selected for tracing or successfully traced.

For all 4 methods, we assessed factors associated with mortality using Cox proportional hazards models. We fitted univariable and multivariable models, with the latter including all covariates (no model selection performed). We included the same baseline covariates as in the weighting models, with some variables categorized to aid interpretation, plus time-dependent variables of time since ART initiation during follow-up and number of gaps in care (Web Table 1). In addition, models under methods C and D used weights calculated as described above. We performed

sensitivity analyses with the weights truncated at a maximum of 20 (corresponding to the upper third percentile in our data) (21). Results are presented as hazard ratios and 95% confidence intervals. For the models, missing data on baseline covariates (Table 1) were imputed using multiple imputation with chained equations, assuming data were missing at random (22, 23). For the imputation, we used truncated regression with lower limits of 0 for square-root CD4 cell count and 3 for square-root body mass index, logistic regression for binary variables, and multinomial regression for the remaining categorical variables. Variables included in the imputation models were the baseline covariates plus indicators for each of the outcomes “attempted traced,” “successfully traced,” and “died”; the Nelson-Aalen estimator of the baseline cumulative hazard (23); time since ART initiation during follow-up; and number of gaps in care. We used 15 imputations, based on the approximate fraction of missing information (22). In sensitivity analyses, we fitted the same models only in participants with complete baseline data (“complete cases”). In further analyses, we used the same methods and multiply imputed data to assess factors associated with mortality among participants observed to initiate ART (with time at risk from ART initiation, and weights estimated among this subset of participants).

Finally, we evaluated the impacts of tracing by assessing outcomes captured in the routine database by January 2018 among participants who were LTFU in November 2015. Analyses were conducted in Stata (24).

Ethical considerations

The institutional review board of the Ifakara Health Institute and the National Health Research Ethics Review Committee of the National Institute for Medical Research of Tanzania provided ethical approval for KIULARCO. Written informed consent was sought from all participants at registration at the Chronic Disease Clinic in Ifakara; those who refused were excluded. Data are stored on a secure server and were deidentified before analysis.

RESULTS

Among 7,460 adults, 4,850 (65% of participants with a response) were female and 5,029 (67%) were aged 25–44 years (Table 1). At enrollment, 5,059 (72% of those with a response) did not know their partner’s HIV status, 4,080 (68%) had disclosed their HIV status, 342 (5%) were inpatients, and 3,100 (50%) were living in the town of Ifakara. Large proportions of participants were underweight ($n = 1,001$; 25%), were classified as being in World Health Organization (WHO) HIV clinical stage 3/4 ($n = 2,694$; 41%), or had a CD4 cell count less than 200 cells/mm³ ($n = 1,890$; 47%), and 635 (9%) participants had tuberculosis. Overall, 11% of baseline covariate data were missing across all participants, mostly for body mass index, WHO stage, and CD4 cell count. ART was started within 30 days of enrollment in 3,173 (43%) participants. Overall, 5,471 (73%) participants initiated ART after a median of 0.5 months (interquartile range (IQR), 0.1–5).

Table 1. Characteristics of KIULARCO Participants by Outcome at Administrative Censoring on November 15, 2015, Ifakara, Tanzania, 2005–2015

Participant Characteristic	Outcome at Administrative Censoring in November 2015								Total	
	Died		Transferred Out		LTFU		In Active Care			
	No.	% ^a	No.	% ^a	No.	% ^a	No.	% ^a	No.	% ^a
Total	646	9	883	12	2,911	39	3,020	40	7,460	100
<i>At Enrollment</i>										
Year of enrollment										
2005–2007	324	18	212	12	832	46	444	25	1,812	100
2008–2009	202	8	401	17	1,112	47	663	28	2,378	100
2010–2012	71	4	162	10	712	43	704	43	1,649	100
2013–2015	49	3	108	7	255	16	1,209	75	1,621	100
Sex										
Male	263	10	306	12	1,102	42	932	36	2,603	100
Female	383	8	571	12	1,809	37	2,087	43	4,850	100
Missing data	0	0	6	86	0	0	1	14	7	100
Age, years										
15–24	46	8	59	11	247	45	200	36	552	100
25–34	190	8	290	12	1,049	43	907	37	2,436	100
35–44	236	9	323	12	950	37	1,084	42	2,593	100
≥45	174	9	211	11	665	35	829	44	1,879	100
Marital status										
Married/cohabiting	287	8	454	12	1,443	38	1,628	43	3,812	100
Never married	149	11	152	11	639	45	467	33	1,407	100
Separated/divorced	86	7	132	11	455	37	553	45	1,226	100
Widowed/other	68	9	107	14	287	37	316	41	778	100
Missing data	56	24	38	16	87	37	56	24	237	100
HIV status of partner										
Positive	49	5	124	13	300	31	492	51	965	100
Negative	35	7	53	11	181	36	232	46	501	100
Unknown	517	10	629	12	2,210	44	1,703	34	5,059	100
Not applicable	23	4	43	8	77	14	405	74	548	100
Missing data	22	6	34	9	143	37	188	49	387	100
Disclosure of HIV status										
No	109	6	205	11	855	45	749	39	1,918	100
Yes	282	7	501	12	1,431	35	1,866	46	4,080	100
Missing data	255	17	177	12	625	43	405	28	1,462	100
Referral to clinic as hospital inpatient										
No	527	8	777	12	2,543	39	2,725	41	6,572	100
Yes	29	8	30	9	120	35	163	48	342	100
Missing data	90	16	76	14	248	45	132	24	546	100

Table continues

Table 1. Continued

Participant Characteristic	Outcome at Administrative Censoring in November 2015								Total	
	Died		Transferred Out		LTFU		In Active Care			
	No.	% ^a	No.	% ^a	No.	% ^a	No.	% ^a	No.	% ^a
Distance of ward of residence from clinic, km										
1	295	10	223	7	1,071	35	1,511	49	3,100	100
2–49	58	5	69	6	384	35	602	54	1,113	100
50–79	88	11	105	14	385	50	195	25	773	100
≥80	82	7	277	23	496	40	373	30	1,228	100
Missing data	123	10	209	17	575	46	339	27	1,246	100
Smoking status										
Never/former smoker	477	8	707	12	2,267	38	2,536	42	5,987	100
Current smoker	95	11	110	12	419	47	263	30	887	100
Missing data	74	13	66	11	225	38	221	38	586	100
Pregnant										
No	375	8	547	12	1,699	37	1,980	43	4,601	100
Yes	8	3	24	10	110	44	107	43	249	100
Body mass index ^b										
Underweight (<18.5)	111	11	102	10	386	39	402	40	1,001	100
Normal (18.5–24.9)	142	6	273	11	857	35	1,209	49	2,481	100
Overweight (25.0–29.9)	13	3	40	8	154	33	266	56	473	100
Obese (≥30.0)	4	3	6	5	40	31	78	61	128	100
Missing data	376	11	462	14	1,474	44	1,065	32	3,377	100
WHO HIV clinical stage										
1	116	5	286	12	1,033	42	1,041	42	2,476	100
2	102	7	174	12	548	38	628	43	1,452	100
3	182	10	242	13	756	42	636	35	1,816	100
4	169	19	116	13	372	42	221	25	878	100
Missing data	77	9	65	8	202	24	494	59	838	100
CD4 cell count, cells/mm ³										
<100	119	11	121	11	398	36	456	42	1,094	100
100–199	48	6	104	13	262	33	382	48	796	100
200–349	41	5	97	11	303	35	428	49	869	100
≥350	48	4	119	9	543	43	555	44	1,265	100
Missing data	390	11	442	13	1,405	41	1,199	35	3,436	100
Tuberculosis										
No	585	9	804	12	2,708	40	2,728	40	6,825	100
Yes	61	10	79	12	203	32	292	46	635	100
Initiated ART within 30 days of enrollment										
No	451	11	505	12	1,924	45	1,407	33	4,287	100
Yes	195	6	378	12	987	31	1,613	51	3,173	100

Table continues

Table 1. Continued

Participant Characteristic	Outcome at Administrative Censoring in November 2015								Total	
	Died		Transferred Out		LTFU		In Active Care			
	No.	% ^a	No.	% ^a	No.	% ^a	No.	% ^a	No.	% ^a
<i>At End of Follow-up</i>										
Time since ART initiation during follow-up, months										
Not yet initiated	302	15	274	13	1,260	62	194	10	2,030	100
0.1–5.9	185	15	141	12	555	46	333	27	1,214	100
6.0–11.9	39	6	86	13	277	42	250	38	652	100
≥12.0	120	3	382	11	819	23	2,243	63	3,564	100
No. of gaps in care (periods of LTFU)										
0	448	17	376	14	0	0	1,783	68	2,607	100
1	162	5	368	11	2,064	62	731	22	3,325	100
2	27	3	90	9	568	58	301	31	986	100
≥3	9	2	49	9	279	51	205	38	542	100

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; KIULARCO, Kilombero and Ulanga Antiretroviral Cohort; LTFU, lost to follow-up; WHO, World Health Organization.

^a Row percentage.

^b Weight (kg)/height (m)². Data were missing for pregnant women.

Outcomes

In the routinely collected data, 646 (9%) participants died, 883 (12%) transferred to another clinic, 2,911 (39%) were LTFU, and 3,020 (40%) were in care at administrative censoring (Figure 2). The median follow-up times for each outcome category were 0.4 (IQR, 0.1–1.5), 1.6 (IQR, 0.5–3.1), 0.8 (IQR, 0.4–2.3), and 4.0 (IQR, 1.4–6.8) years, respectively. Participants living far away from the Chronic Disease Clinic in Ifakara were more likely to have transferred out or been LTFU than those living closer (Table 1). Women were more likely to remain in care than were men. Participants with poorer health status (body mass index, WHO stage, and CD4 cell count) were more likely to have died than those with better health. Those who initiated ART were more likely to have transferred to another clinic or remained in care than those who did not initiate ART. Overall, 4,853 (65%) participants had at least 1 LTFU episode (median, 1 LTFU episode per participant; maximum = 12). There were 7,227 LTFU episodes, following which participants returned to care 3,848 (53%) times, after a median of 2 months following the date on which they were declared LTFU (IQR, 0.4–5).

Tracing

Tracing attempts were made for 2,010 (69%) participants who were LTFU (Figure 2). Tracing attempts were more likely for participants who lived close to the clinic than

for those living further away (Web Table 2). Among these 2,010 participants, 325 (16%) were successfully traced, with a median time between LTFU and attempted tracing of 6.0 years (IQR, 3.7–7.8). Comparing participants who were and were not successfully traced, characteristics were similar except that those living closer to the clinic were slightly less likely to have been successfully traced and those who did not initiate ART at enrollment were more likely to have been successfully traced (Web Table 3). The proportions of participants attempted traced and successfully traced were similar according to the year in which the participant was LTFU (Web Table 4).

Among the 325 participants successfully traced, 131 (40%) had died, 130 (40%) had transferred to another clinic, 7 (2%) were reported to have returned to the Chronic Disease Clinic in Ifakara, and 57 (18%) were alive but refused care (Figure 2). Those who were enrolled in earlier years were more likely to have died or transferred to another clinic; women and those living further from the clinic were more likely to have transferred; and those with poorer health status were more likely to have died (Web Table 5). Further, those who initiated ART at enrollment were more likely to have died, which is attributable to those with poorer health status being more likely to have initiated ART in the years before implementation of the test-and-treat strategy for HIV.

Weights

Under method C, the weight applied to those LTFU and successfully traced was 9.0 (2,911/325). Under method D,

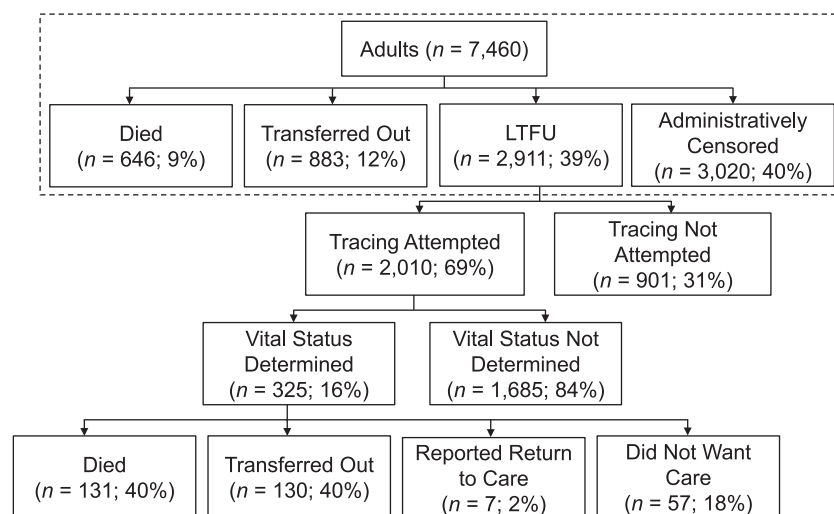


Figure 2. Outcomes among KIULARCO participants determined by means of routinely captured data and through tracing, Ifakara, Tanzania, 2005–2015. Data captured routinely are shown in the dashed box; the remaining data were determined through tracing. KIULARCO, Kilombero and Ulanga Antiretroviral Cohort; LTFU, lost to follow-up.

the weights applied to those LTFU and successfully traced varied by person (Table 2). Notably, for every additional month of delay in tracing (time between being lost and attempted traced), the odds of being successfully traced decreased by 2% (odds ratio = 0.98, 95% confidence interval (CI): 0.96, 1.00).

Mortality

Under method A, mortality estimates were 6.8% (95% CI: 6.2, 7.4) at 1 year and 13.1% (95% CI: 12.1, 14.3) at 5 years (Figure 3). Under method B, mortality was slightly higher at 7.3% (95% CI: 6.7, 8.0) and 16.2% (95% CI: 15.0, 17.5), respectively. Under method C, mortality was substantially higher, at 11.5% (95% CI: 10.2, 12.8) and 36.8% (95% CI:

33.2, 40.3), respectively. Similar results were obtained under method D, with mortality of 11.1% (95% CI: 9.8, 12.4) and 35.1% (95% CI: 31.2, 38.6), respectively.

Factors associated with mortality

In the multivariable model, higher mortality was associated with male sex (vs. being a nonpregnant female), HIV status disclosure (methods A and B only), referral as an inpatient (weaker evidence for method A), living in the town of Ifakara versus further away, lower body mass index, WHO stage 3/4, lower CD4 cell count, and less time on ART (Table 3). Associations between mortality and enrollment year differed by method: Mortality was higher in earlier years under method A, yet highest in 2010–2012 under

Table 2. Weights Used Under Mortality Estimation Method D^a for KIULARCO Participants Who Were Lost to Follow-up and Successfully Traced, Ifakara, Tanzania, 2005–2015

Participant Outcome	For Probability of Being Attempted Traced		For Probability of Being Successfully Traced		Overall ^b	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
LTFU and successfully traced	1.5 (0.6)	1.0–6.0	6.0 (3.0)	2.2–32	8.6 (4.8)	3.0–43
Died					7.9 (4.1)	3.6–27
Transferred to another clinic					9.8 (5.8)	3.0–43
Reported returning to care or did not want care					7.7 (3.1)	3.0–16

Abbreviations: KIULARCO, Kilombero and Ulanga Antiretroviral Cohort; LTFU, lost to follow-up; SD, standard deviation.

^a Extension to the Frangakis and Rubin (14) method; see Methods section of text.

^b For attempted tracing and successful tracing combined.

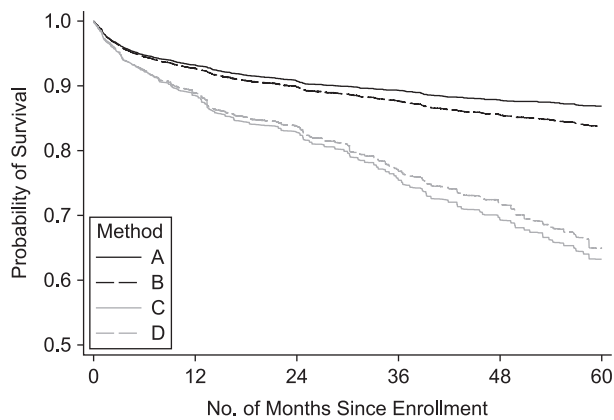


Figure 3. Probability of survival following enrollment in the Kilombero and Ulanga Antiretroviral Cohort, estimated according to 4 different methods, Ifakara, Tanzania, 2005–2015. Method A, routine data; method B, routine data plus tracing data; method C, Frangakis and Rubin (14) method; method D, extension to the Frangakis and Rubin method. See Methods section of text for more details.

methods C and D. Under methods A and B, any gaps in care were strongly associated with lower mortality risk, whereas under methods C and D, a single gap in care was strongly associated with higher risk (95% confidence intervals were wide for 2 or ≥ 3 gaps in care). Similar results were obtained after truncating weights at 20. In sensitivity analyses among complete cases, results were broadly similar except that 1) the 95% confidence intervals tended to be wider, 2) the point estimates for smoking reversed direction (but they remained nonsignificant across all methods), and 3) there was stronger evidence of both 1 and 2 gaps in care being associated with higher mortality under methods C and D (Web Table 6).

Mortality among persons who initiated ART

Among 5,430 participants with follow-up after ART initiation, 344 (6%) died, 609 (11%) transferred to another clinic, 1,651 (30%) were LTFU, and 2,826 (52%) were in care at administrative censoring. Among those LTFU, attempts were made to trace 1,144 (69%), and 186 (16%) were successfully traced. Of those successfully traced, 76 (41%) had died, 74 (40%) had transferred, 4 (2%) were reported to have returned to the index clinic, and 32 (17%) were alive but refused care. Mortality estimates were all somewhat lower than those in the whole population (when time was measured from enrollment) but displayed similar patterns (Web Figure 1). The factors associated with mortality were similar to those in the whole cohort, except for 1) some evidence of higher mortality risk at older ages, 2) current smoking being associated with higher mortality under methods A and B, 3) weaker associations of mortality with WHO stage and CD4 cell count, and 4) much higher mortality risk with a greater number of gaps in care under methods C and D (Web Table 7).

Impacts of tracing

Of the 2,911 participants LTFU at administrative censoring in November 2015, 13 were not included in the database by January 2018 (e.g., consent withdrawal). Routine data on the remaining 2,898 participants showed that the majority (2,421; 84%) remained LTFU, 53 (2%) returned for ≥ 1 visit but again became LTFU, 121 (4%) died, 143 (5%) transferred out, and 160 (6%) returned to care (Table 4). Among the deaths and transfers, 91 of 121 (75%) and 104 of 143 (73%), respectively, had been determined through the tracing efforts of this study. Among the 64 participants who had been traced and found to be alive but not under care, 15 (23%) returned for a clinic visit after 2015.

DISCUSSION

In this large cohort of people living with HIV in rural Tanzania, LTFU was high at 39%, in line with other estimates from the region (25, 26). Among participants who were successfully traced, mortality was much higher than that among those not LTFU. The substantial tracing efforts resulted in only 23% ($n = 15$) of those found alive through tracing actually returning to care, indicating that tracing alone was not successful in encouraging participants to reengage in care in this population, in contrast to other settings (15, 27). Among those LTFU, approximately 75% of outcomes captured within the following 2 years were a direct result of the tracing, with relatively few reports of death or transfers out being provided to the clinic directly. While outcome status was determined in only about 10% of those LTFU, incorporation of this information through appropriate statistical methods had substantial impacts on the mortality estimates, essentially doubling the uncorrected ones which underestimate death in those LTFU and not traced. Our 1-year (corrected) mortality estimates of around 11% (9% among those initiating ART) were in line with those of other studies (9, 11, 28, 29). Our 5-year mortality estimates of 27%–29% among persons initiating ART were in line with those of an analysis of 34 cohorts in sub-Saharan Africa (29) while markedly higher than those from another analysis of 57 cohorts in sub-Saharan Africa, but only from 2009 onwards (26).

There were a number of similarities in the determinants of survival across the methods. However, we found that gaps in care were associated with higher mortality risk after accounting for the unseen mortality among those LTFU, which was missed in the models which did not account for this. There were also some differences in the mortality risk by year of enrollment. However, we did not observe large differences in the results under our extended approach as compared with the Frangakis and Rubin method (14). As indicated in the Methods section, these results should be interpreted as factors associated with survival under the hypothetical scenario that all outcomes had been observed. Alternative approaches would be required if instead one wanted to address the hypothetical scenario that all participants could be retained in care (30).

A number of previous studies have attempted to correct mortality estimates for the unseen mortality among

Table 3. Factors Associated With Mortality in KIULARCO Participants Under 4 Different Methods of Mortality Estimation^a, Ifakara, Tanzania, 2005–2015

Participant Characteristic	Method A: Data as Captured in Database		Method B: Incorporating Tracing Outcomes		Method C: Frangakis and Rubin (14) Approach		Method D: Extension to Frangakis and Rubin (14) Approach	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<i>Baseline Covariates</i>								
Year of enrollment								
2005–2007	0.94	0.67, 1.32	0.87	0.63, 1.21	0.58	0.37, 0.91	0.62	0.39, 1.00
2008–2009	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2010–2012	0.69	0.51, 0.92	0.98	0.76, 1.26	1.86	1.32, 2.62	1.84	1.30, 2.63
2013–2015	0.37	0.23, 0.59	0.52	0.34, 0.80	1.18	0.55, 2.50	1.17	0.59, 2.33
Sex								
Male	1.24	1.03, 1.50	1.29	1.08, 1.53	1.32	1.00, 1.73	1.38	1.05, 1.80
Female	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Age, years								
15–24	1.05	0.72, 1.53	0.92	0.64, 1.33	0.56	0.31, 0.99	0.56	0.32, 0.99
25–34	0.85	0.69, 1.05	0.88	0.73, 1.07	0.85	0.62, 1.15	0.86	0.63, 1.18
35–44	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
≥45	1.09	0.89, 1.34	1.12	0.93, 1.35	1.01	0.75, 1.36	0.98	0.73, 1.30
Marital status								
Married/cohabiting	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Never married	1.08	0.86, 1.35	1.03	0.84, 1.28	1.04	0.73, 1.47	0.99	0.70, 1.40
Separated/divorced	0.89	0.68, 1.16	0.92	0.72, 1.16	0.96	0.66, 1.39	1.00	0.69, 1.45
Widowed/other	0.88	0.66, 1.18	0.86	0.65, 1.13	0.82	0.50, 1.35	0.82	0.50, 1.36
HIV status of partner								
Positive	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Negative	1.29	0.82, 2.05	1.21	0.79, 1.85	1.08	0.55, 2.12	1.07	0.55, 2.10
Unknown	1.22	0.86, 1.74	1.35	0.98, 1.87	1.41	0.86, 2.31	1.45	0.87, 2.40
Not applicable	1.85	0.99, 3.46	1.95	1.08, 3.52	2.39	0.89, 6.41	2.01	0.78, 5.18
Disclosure of HIV status								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	1.34	1.06, 1.69	1.28	1.03, 1.59	1.03	0.77, 1.38	1.04	0.76, 1.42
Referral to clinic as hospital inpatient								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	1.49	0.99, 2.25	1.45	1.00, 2.11	1.76	1.09, 2.83	1.69	1.02, 2.80
Distance of ward of residence from clinic, km								
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2–49	0.62	0.46, 0.84	0.61	0.46, 0.81	0.64	0.41, 1.00	0.66	0.42, 1.04
50–79	0.91	0.69, 1.18	0.80	0.62, 1.04	0.51	0.31, 0.86	0.53	0.33, 0.84
≥80	0.64	0.48, 0.84	0.65	0.50, 0.85	0.79	0.52, 1.18	0.75	0.49, 1.15

Table continues

Table 3. Continued

Participant Characteristic	Method A: Data as Captured in Database		Method B: Incorporating Tracing Outcomes		Method C: Frangakis and Rubin (14) Approach		Method D: Extension to Frangakis and Rubin (14) Approach	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Smoking status								
Never/former smoker	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Current smoker	1.22	0.92, 1.61	1.23	0.94, 1.61	1.44	0.99, 2.08	1.39	0.95, 2.02
Pregnant								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.99	0.49, 2.03	1.26	0.71, 2.19	0.95	0.34, 2.59	1.11	0.41, 2.98
Body mass index ^b								
Underweight (<18.5)	1.51	1.16, 1.98	1.56	1.22, 2.00	1.60	1.17, 2.20	1.58	1.15, 2.17
Normal-weight (18.5–24.9)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Overweight (25.0–29.9)	0.66	0.41, 1.07	0.63	0.40, 1.00	0.66	0.32, 1.35	0.73	0.34, 1.56
Obese (≥30.0)	0.44	0.14, 1.36	0.32	0.11, 0.94	0.16	0.03, 0.81	0.15	0.03, 0.84
WHO HIV clinical stage								
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	1.44	1.08, 1.94	1.45	1.12, 1.89	1.52	1.05, 2.20	1.39	0.95, 2.02
3	1.90	1.46, 2.49	2.10	1.65, 2.68	2.43	1.69, 3.48	2.32	1.62, 3.32
4	3.31	2.47, 4.44	3.43	2.60, 4.53	3.16	2.01, 4.99	3.01	1.90, 4.77
CD4 cell count, cells/mm ³								
<100	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
100–199	0.73	0.54, 0.97	0.73	0.55, 0.96	0.67	0.42, 1.07	0.65	0.41, 1.04
200–349	0.57	0.41, 0.79	0.59	0.45, 0.78	0.59	0.39, 0.90	0.58	0.39, 0.87
≥350	0.32	0.22, 0.46	0.33	0.23, 0.47	0.25	0.15, 0.43	0.24	0.14, 0.43
Tuberculosis								
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	1.00	0.75, 1.33	0.90	0.69, 1.18	0.75	0.48, 1.19	0.71	0.46, 1.10
<i>Time-Dependent Covariates</i>								
Time since ART initiation during follow-up, months								
Not yet initiated	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
0.1–5.9	0.23	0.18, 0.29	0.34	0.27, 0.42	0.63	0.47, 0.86	0.6	0.43, 0.84
6–11.9	0.04	0.02, 0.05	0.06	0.04, 0.08	0.16	0.10, 0.26	0.13	0.08, 0.22
≥12	0.03	0.02, 0.05	0.03	0.02, 0.04	0.02	0.01, 0.03	0.01	0.01, 0.02
No. of gaps in care (periods of LTFU)								
0	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
1	0.17	0.13, 0.21	0.35	0.29, 0.43	2.30	1.72, 3.06	1.95	1.46, 2.61
2	0.18	0.11, 0.28	0.24	0.17, 0.36	0.71	0.36, 1.39	0.71	0.37, 1.37
≥3	0.17	0.08, 0.35	0.27	0.16, 0.46	1.27	0.58, 2.78	0.98	0.42, 2.28

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; KIULARCO, Kilombero and Ulanga Antiretroviral Cohort; LTFU, lost to follow-up; WHO, World Health Organization.

^a Results were derived from multivariable Cox proportional hazards models adjusting for all variables shown in the table, with multiple imputation for missing baseline covariates (see Methods section of text for details).

^b Weight (kg)/height (m)².

Table 4. Subsequent Follow-up of KIULARCO Participants Who Were Lost to Follow-up at Administrative Censoring on November 15, 2015, Ifakara, Tanzania, 2005–2015

Participant Outcome ^a	Year of Last Visit										Total ^b	
	2005–2007		2008–2009		2010–2012		2013–2015		2016–2018			
	No. (n = 445)	% ^c (15 ^d)	No. (n = 808)	% ^c (28 ^d)	No. (n = 863)	% ^c (30 ^d)	No. (n = 544)	% ^c (19 ^d)	No. (n = 238)	% ^c (8 ^d)		No. (n = 2,898)
Died	15	3	42	5	44	5	16	3	4	2	121	4
Transferred to another clinic	10	2	51	6	30	3	31	6	21	9	143	5
LTFU	420	94	715	88	789	91	497	91	53	22	2,474	85
In active care	0	0	0	0	0	0	0	0	160	67	160	6

Abbreviations: KIULARCO, Kilombero and Ulanga Antiretroviral Cohort; LTFU, lost to follow-up.

^a As captured at administrative censoring in January 2018.

^b Excludes 13 participants who were LTFU in November 2015 but were not included in the January 2018 database (because of a change in consent, for example).

^c Column percentage.

^d Row percentage.

participants LTFU, using a range of approaches: by tracing participants LTFU and using weighted estimation as in this study (9–11, 14, 20, 31); by assuming that a proportion of those LTFU had died based on previously reported estimates (26, 32); by imputing survival times using results of a meta-regression (33); by using a nomogram (28, 29, 34); or by linking participants to national registries (5, 16, 35, 36). Assuming a mortality risk among those LTFU based on previously reported estimates is simple to implement but does not allow for changing LTFU and mortality risks over time or across different settings. The nomogram approach provides an estimate of mortality among those LTFU based on the observed LTFU within a particular cohort (28); this approach is also simple to apply but is limited to the estimation of mortality at 1 year following ART initiation. Few settings, especially in sub-Saharan Africa, have adequate civil registration and vital statistics systems in place to allow linkage (37). Other researchers have used a combination of these methods, while also accounting for a limited set of participant characteristics (38, 39). Other methods have been used to model the missingness mechanism—for example, by incorporating the “sensitivity” of routinely detecting a death (9) or using multiple imputation (16). An alternative approach is to use a multistage sampling approach to obtain a representative sample of those LTFU (31). In a recent paper, Jannat-Khah et al. (40) compared complete-case analysis with 2 principled approaches: 1) using multiple imputation for missing baseline covariates and outcomes and 2) using inverse probability weighting methods after tracing to account for unseen deaths among those LTFU, which is similar to our approach but based only on successful tracing. Further, the authors did not use multiple imputation to account for missing baseline covariates in the latter approach, as we have done. Our extension to the Frangakis and Rubin method explicitly models the 2 steps of the missingness mechanism, accounting for measured differences in the participant characteristics between those who were 1) attempted traced and 2) successfully traced versus those who remained LTFU.

This study had a number of limitations. Firstly, a low proportion of participants were successfully traced. This reflects the challenges involved in locating participants and leads us to advocate for prompt tracing. This low tracing success may partly explain the similar results between our 2-step approach and the Frangakis and Rubin method. Another reason may be the similarities in characteristics between persons attempted traced and not attempted traced and between those successfully traced and not successfully traced; the impact of our method may be greater in other cohorts with more pronounced differences in those traced, for example with targeted tracing. Secondly, our 2-step approach assumes that there is no residual unmeasured confounding in the models for attempted and successful tracing and for mortality, which is not straightforward to assess. Thirdly, we assumed that the risk of death among participants successfully traced was the same as that among those who remained LTFU despite tracing efforts, which is not typically possible to assess (8). Lastly, to implement the multiple imputation, we assumed that the data were missing at random. This assumption could not be tested directly in

the data, but we increased the plausibility by including a broad range of covariates (22).

In conclusion, our study demonstrates the challenges associated with tracing participants who are LTFU, with a relatively low proportion being successfully traced and with little impact on participants subsequently returning to care at our HIV clinic. However, even with somewhat limited tracing information, incorporating tracing outcomes with appropriate statistical adjustment resulted in considerable changes in mortality estimates, demonstrating the importance of accounting for unseen mortality among those LTFU. The method of Frangakis and Rubin (14) has the advantage of being simple to apply and does not need measurement of covariates. However, it requires tracing to be performed in a random sample of participants LTFU. In practice, this may not be possible or even desirable. For example, individual clinics may wish to perform targeted tracing based on measured risk factors, and national programs may pool such clinic data for informing monitoring and evaluation assessments. In such circumstances, the Frangakis and Rubin method will yield biased estimates of mortality. We have demonstrated the application of a method which should be used to compensate for such nonrandom sampling to account for differential mortality among persons who have become LTFU from HIV programs. Our method can equally be applied in any setting where LTFU is of concern.

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