# Estimation of mortality among HIV-infected people on antiretroviral treatment in east Africa: a sampling based approach in an observational, multisite, cohort study

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## Summary

**Background** **Mortality in HIV-infected people after initiation of antiretroviral treatment (ART) in resource-limited settings is an important measure of the effectiveness and comparative effectiveness of the global public health response. Substantial loss to follow-up precludes accurate accounting of deaths and limits our understanding of effectiveness. We aimed to provide a better understanding of mortality at scale and, by extension, the effectiveness and comparative effectiveness of public health ART treatment in east Africa.**

**Methods** **In 14 clinics in five settings in Kenya, Uganda, and Tanzania, we intensively traced a sample of patients randomly selected using a random number generator, who were infected with HIV and on ART and who were lost to follow-up (>90 days late for last scheduled visit). We incorporated the vital status outcomes for these patients into analyses of the entire clinic population through probability-weighted survival analyses.**

**Findings** **We followed 34 277 adults on ART from Mbarara and Kampala in Uganda, Eldoret, and Kisumu in Kenya, and Morogoro in Tanzania. The median age was 35 years (IQR 30–42), 11 628 (34%) were men, and median CD4 count count before therapy was 154 cells per μL (IQR 70–234). 5780 patients (17%) were lost to follow-up, 991 (17%) were selected for tracing between June 10, 2011, and Aug 27, 2012, and vital status was ascertained for 860 (87%). With incorporation of outcomes from the patients lost to follow-up, estimated 3 year mortality increased from 3·9% (95% CI 3·6–4·2) to 12·5% (11·8–13·3). The sample-corrected, unadjusted 3 year mortality across settings was lowest in Mbarara (7·2%) and highest in Morogoro (23·6%). After adjustment for age, sex, CD4 count before therapy, and WHO stage, the sample-corrected hazard ratio comparing the settings with highest and lowest mortalities was 2·2 (95% CI 1·5–3·4) and the risk difference for death at 3 years was 11% (95% CI 5·0–17·7).**

**Interpretation** **A sampling-based approach is widely feasible and important to an understanding of mortality after initiation of ART. After adjustment for measured biological drivers, mortality differs substantially across settings despite delivery of a similar clinical package of treatment. Implementation research to understand the systems, community, and patients' behaviours driving these differences is urgently needed.**

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## Introduction

Although worldwide investments in HIV/AIDS care and treatment have helped to deliver highly effective antiretroviral therapy to 13 million individuals (ART),[1] an understanding of the effectiveness and comparative effectiveness across settings of this public health investment depends on our ability to assess survival after treatment initiation. Although the antiretroviral regimens routinely used in resource-limited settings have reliable and potent pharmacological ability to suppress HIV RNA replication, the actual attainment of viral control, restoration of health, and achievement of long-term survival in the real world is far less certain. To achieve optimum effectiveness, HIV drugs must be delivered by adequately staffed clinics with qualified and motivated providers, accompanied by clinical and laboratory monitoring and taken by engaged patients with high day-to-day adherence. Barriers to these behaviours are common: poverty is prevalent,[2] transportation is unreliable,[3] free drugs incur ancillary and opportunity costs (eg, loss of wages),[4] provider burnout and long waiting times are commonplace,[5] and stigma and depression remain widespread.[6] Quantification of mortality after ART initiation is therefore urgently needed to understand the effectiveness and comparative effectiveness of global HIV treatment programmes.

To date, however, uncertainty remains about mortality in HIV-infected patients after starting ART. Existing reports from programmatic settings[7–9] likely miss many deaths because of loss to follow-up.[10–12] For example, the Antiretroviral Therapy in Lower Income Countries (ART-LINC) cohorts reported mortality of 1·8–6·0% in 30 clinics in Africa at 1 year after ART initiation, but those researchers noted that these figures were related to how active follow-up (and therefore ascertainment) was at each site.[13] By

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contrast, interval research cohorts or randomised trials of clinical interventions can show mortality more completely.[14] These studies, however, select individuals who are willing and able to comply with research protocols and often offer special services (such as transportation). Finally, international agencies provide estimates of HIV mortality on treatment.[15] These figures, however, come from models that rely, in turn, on inputs from epidemiological studies. Models also generally offer national figures and do not shed light on site-to-site variability needed to inform practice behaviours at the front lines of the response to HIV.

We have previously developed a sampling-based approach to obtain more valid estimates of mortality in real-world, clinic-based cohorts of HIV patients in treatment programmes in Africa.[16,17] This approach is based on identification of a numerically small but randomly selected sample of patients lost to follow-up, intensive searching for their outcomes in the community, and incorporation of these findings to correct estimates in the entire clinic population by use of a probability weight. Previous work has been done in single clinic sites.[18,19] In this paper, we apply this approach in a network of clinics in east Africa to better understand mortality at scale, and by extension, the effectiveness and comparative effectiveness of public health ART treatment in Africa.

## Methods

### Patients and setting

We assessed adult patients on ART in 14 clinics and five programmes in east Africa that operate in five locations: Mbarara, Uganda; Eldoret, Kenya; Kisumu, Kenya; Kampala, Uganda; and Morogoro, Tanzania. All programmes deliver a similar package of simplified and standardised care, which consists of a few first-line regimens based on non-nucleoside reverse-transcriptase inhibitors (NNRTIs), no assigned stable provider for patients, the absence of routine HIV RNA testing, and HIV genotype resistance assays.[20] The clinics included participate in the East Africa International Epidemiologic Databases to Evaluate AIDS (IeDEA), which is a National Institutes of Health-funded consortium that pools and harmonises data generated in routine care but does not affect delivery of clinical care at those sites. We included patients who had a visit in each programme in the 2·5 years before the sampling was done. This definition includes patients already on ART at the start of the observation period and patients who started ART during the observation period. We believe this population represents the contemporary experience of the clinic. Patients were followed until death, transfer out of the facility, loss to follow-up, or database closure. The study was approved by the institutional review boards of relevant institutions involved. Informed consent was already obtained for patient tracing already carried out at all sites for programme purposes (>99% of patients at all sites). Some sites required additional verbal consent from patients in order for tracers to ask patients questions that would be used for research.

### Procedures

Sociodemographic (eg, sex) and clinical (eg, CD4 cell count at ART initiation) data were obtained from routine care records. As previously described, a random number generator in statistical software was used to produce a random sample of patients lost to follow-up (defined as >90 days late for last visit as of sampling date) who were then intensively sought in the community to find their vital status.[16,21] Patients who were known to have died or left the clinics with transfers were not counted as lost to follow-up. We targeted a 10–20% sample of lost patients on the basis of practical considerations about an absolute number that could be intensively traced with the resources available at the sites. Ascertainers, hired through existing departments in every programme, sought the lost patients. For patients who had died, we documented the date of death and basic information about the cause of death (eg, illness, accident, suicide, homicide, or childbirth).

### Statistical analysis

We used the Kaplan-Meier method to estimate mortality after ART initiation overall and by setting. Because some patients in our cohort started ART before we began to observe them (inclusion was defined by any visit to clinic in the 2·5 years before sampling was done), their observation time was treated as left-truncated. Left-truncated survival estimates are analogous to life-expectancy estimates, which provide an estimate of expected longevity given survival to the present era,[22] but do not account for patients who ceased to access care before the observation period (eg, died or were lost to follow-up). We therefore also estimated mortality restricted to new ART initiators. For all Kaplan-Meier estimates, we first did a naive analysis, which used only deaths known to the clinic before tracing. Second, as described in previous work,[23] we did a revised estimate of mortality that incorporated outcomes in a random sample of lost patients through probability weights. In this approach, patients who remain under observation (who are not lost to follow-up) receive a weight of 1, patents who have unknown outcomes a weight of 0, and patients with outcomes identified through tracing are given a weight inverse to the probability of outcome ascertainment. Weights were derived separately in every clinic. CIs for descriptive estimates were obtained with bootstrapping. We applied a competing risk approach to estimate the occurrence of deaths in care (defined as deaths within 30 days inclusive of their last clinic visit, irrespective of the next assigned appointment date) in the presence of deaths after a period of absence at the original clinic (defined as deaths that occurred more than 30 days after their last clinic visit).[24–26]

We used multivariable Cox proportional hazards regression to estimate the association between setting

| | Mbarara, Uganda | | | | Eldoret, Kenya | | | | Kisumu, Kenya | | | | Kampala, Uganda | | | | Morogoro, Tanzania | | | | All | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All | LTFU | Sampled LTFU | Traced patients | All | LTFU | Sampled LTFU | Traced patients | All | LTFU | Sampled LTFU | Traced patients | All | LTFU | Sampled LTFU | Traced patients | All | LTFU | Sampled LTFU | Traced patients | All | LTFU | Sampled LTFU | Traced patients |
| Number | 7515 | 907 | 113 | 95 | 15568 | 2220 | 441 | 367 | 4261 | 639 | 114 | 110 | 3611 | 697 | 148 | 132 | 3322 | 1317 | 175 | 156 | 34277 | 5780 | 991 | 860 |
| Age (years)* | 35 (29–41) | 33 (27–40) | 32 (28–40) | 32 (28–40) | 36 (31–43) | 35 (30–42) | 35 (30–42) | 35 (30–42) | 31 (26–38) | 29 (24–35) | 29 (22–36) | 29 (23–36) | 34 (28–40) | 32 (27–39) | 31 (26–38) | 31 (26–38) | 37 (31–44) | 36 (31–44) | 37 (31–45) | 37 (31–44·5) | 35 (30–42) | 34 (28–41) | 34 (28–41) | 34 (28–41) |
| Sex | | | | | | | | | | | | | | | | | | | | | | | | |
| Men | 2811 (37%) | 409 (45%) | 56 (50%) | 47 (50%) | 5503 (35%) | 821 (37%) | 181 (41%) | 158 (43%) | 1343 (32%) | 197 (31%) | 34 (30%) | 32 (29%) | 1019 (28%) | 231 (33%) | 48 (32%) | 43 (33%) | 952 (29%) | 375 (29%) | 58 (33%) | 50 (32%) | 11628 (34%) | 2033 (35%) | 377 (38%) | 330 (38%) |
| Non-pregnant women | 4022 (54%) | 431 (48%) | 46 (41%) | 40 (42%) | 8829 (57%) | 1203 (54%) | 215 (49%) | 172 (47%) | 2323 (55%) | 339 (53%) | 63 (55%) | 62 (56%) | 2461 (68%) | 448 (64%) | 98 (66%) | 88 (67%) | 2296 (69%) | 911 (69%) | 111 (63%) | 101 (65%) | 19931 (58%) | 3332 (58%) | 533 (54%) | 463 (54%) |
| Pregnant women | 682 (9%) | 67 (7%) | 11 (10%) | 8 (8%) | 1236 (8%) | 196 (9%) | 45 (10%) | 37 (10%) | 595 (14%) | 103 (16%) | 17 (15%) | 16 (16%) | 131 (4%) | 18 (3%) | 2 (1%) | 1 (1%) | 74 (2%) | 31 (2%) | 6 (3%) | 5 (3%) | 2718 (8%) | 415 (7%) | 81 (8%) | 67 (8%) |
| CD4 count at ART initiation (cells per µL)† | 164 (75–235) | 147 (56–223) | 168 (89–238) | 167 (90–239) | 143 (64–218) | 138 (58–230) | 124 (54–225) | 125 (61–228) | 194 (94–275) | 156 (59–238) | 162 (79–247) | 162 (80–254) | 167 (92–239) | 147 (65·5–215) | 126·5 (42–206) | 124 (42–207) | 126·5 (55–208) | 123 (51–202) | 130 (55–222) | 126 (48–213) | 154 (70–234) | 138 (57–222) | 136 (60–225) | 137 (61–227) |
| WHO stage‡ | | | | | | | | | | | | | | | | | | | | | | | | |
| I | 1763 (24%) | 153 (17%) | 24 (22%) | 21 (23%) | 4481 (31%) | 537 (27%) | 102 (26%) | 84 (25%) | 1080 (26%) | 140 (22%) | 27 (24%) | 25 (23%) | 576 (16%) | 102 (15%) | 17 (12%) | 15 (11%) | 133 (5%) | 43 (4%) | 8 (5%) | 6 (5%) | 8033 (25%) | 975 (19%) | 178 (20%) | 151 (19%) |
| II | 2178 (30%) | 245 (28%) | 33 (30%) | 28 (30%) | 2842 (19%) | 368 (18%) | 61 (16%) | 55 (17%) | 1218 (28%) | 147 (23%) | 22 (20%) | 22 (20%) | 1458 (41%) | 255 (38%) | 67 (46%) | 57 (43%) | 624 (23%) | 250 (23%) | 28 (19%) | 24 (18%) | 8320 (26%) | 1265 (24%) | 211 (23%) | 186 (23%) |
| III | 2616 (36%) | 352 (40%) | 36 (33%) | 30 (33%) | 5886 (40%) | 867 (43%) | 178 (46%) | 154 (47%) | 1575 (37%) | 266 (43%) | 53 (47%) | 52 (48%) | 1515 (33%) | 236 (35%) | 46 (31%) | 44 (33%) | 1576 (58%) | 598 (56%) | 94 (62%) | 85 (63%) | 12804 (39%) | 2319 (42%) | 407 (45%) | 365 (46%) |
| IV | 814 (11%) | 138 (16%) | 16 (15%) | 13 (14%) | 1464 (10%) | 228 (11%) | 47 (12%) | 38 (12%) | 366 (9%) | 82 (13%) | 10 (9%) | 9 (8%) | 357 (10%) | 87 (13%) | 17 (12%) | 16 (12%) | 400 (15%) | 180 (17%) | 21 (14%) | 19 (14%) | 3401 (11%) | 715 (14%) | 111 (12%) | 95 (12%) |
| NNRTI component of first regimen§ | | | | | | | | | | | | | | | | | | | | | | | | |
| Nevirapine | 5556 (74%) | 689 (76%) | 89 (79%) | 75 (79%) | 10839 (78%) | 1439 (75%) | 278 (74%) | 233 (74%) | 2703 (69%) | 422 (75%) | 85 (84%) | 81 (84%) | .. | .. | .. | .. | 2026 (64%) | 850 (67%) | 93 (57%) | 83 (57%) | 21124 (74%) | 1233 (27%) | 545 (73%) | 472 (72%) |
| Efavirenz | 1938 (26%) | 214 (24%) | 24 (21%) | 20 (21%) | 3119 (22%) | 469 (25%) | 96 (26%) | 84 (27%) | 1209 (31%) | 138 (25%) | 16 (16%) | 16 (17%) | .. | .. | .. | .. | 1151 (36%) | 412 (33%) | 71 (43%) | 63 (43%) | 7417 (26%) | 3400 (73%) | 207 (28%) | 183 (28%) |
| NRTI in first regimen¶ | | | | | | | | | | | | | | | | | | | | | | | | |
| Zidovudine | 1780 (24%) | 202 (22%) | 27 (24%) | 20 (21%) | 9272 (64%) | 1339 (67%) | 260 (66%) | 219 (66%) | 2050 (49%) | 386 (62%) | 72 (64%) | 70 (65%) | .. | .. | .. | .. | 1782 (56%) | 766 (61%) | 80 (49%) | 70 (48%) | 14894 (51%) | 2693 (56%) | 439 (56%) | 379 (56%) |
| Stavudine | 5117 (68%) | 628 (69%) | 77 (68%) | 66 (70%) | 4337 (30%) | 621 (31%) | 129 (33%) | 111 (33%) | 1474 (35%) | 210 (34%) | 36 (32%) | 35 (32%) | .. | .. | .. | .. | 1385 (44%) | 496 (39%) | 84 (51%) | 76 (52%) | 12313 (42%) | 1955 (41%) | 326 (42%) | 288 (42%) |
| Tenofovir | 616 (8%) | 77 (9%) | 9 (8%) | 9 (10%) | 808 (6%) | 54 (3%) | 6 (2%) | 4 (1%) | 659 (16%) | 30 (5%) | 4 (4%) | 3 (3%) | .. | .. | .. | .. | 0 | 0 | 0 | 0 | 2083 (7%) | 161 (3%) | 19 (2%) | 16 (2%) |
| Care status | | | | | | | | | | | | | | | | | | | | | | | | |
| In care at observation start | 4238 (56%) | 465 (51%) | 58 (51%) | 45 (47%) | 8464 (54%) | 1012 (46%) | 195 (44%) | 171 (47%) | 706 (17%) | 144 (23%) | 33 (29%) | 32 (29%) | 1239 (34%) | 265 (38%) | 55 (38%) | 50 (38%) | 1549 (47%) | 644 (49%) | 71 (40%) | 65 (42%) | 16196 (47%) | 2530 (44%) | 412 (42%) | 363 (43%) |
| New to care during observation period | 3277 (44%) | 442 (49%) | 55 (47%) | 50 (53%) | 7104 (46%) | 1208 (54%) | 246 (56%) | 196 (43%) | 3555 (83%) | 495 (78%) | 81 (71%) | 78 (71%) | 2372 (66%) | 432 (62%) | 93 (63%) | 82 (62%) | 1773 (47%) | 673 (51%) | 104 (59%) | 91 (58%) | 18081 (53%) | 3250 (56%) | 579 (58%) | 497 (58%) |

Data are number of patients, median (IQR), or number of patients (%). Data for antiretroviral therapy regimen is missing from Kampala sites. Fraction of deaths among those found through tracing and additional information on missing data can be found in the appendix p 1. LTFU=lost to follow-up. NNRTI=non-nucleoside reverse-transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitors. *Missing in 638 (2%). †Missing in 4950 (14%). ‡Missing in 1719 (5%). §Missing in 5736 (17%). ¶Missing in 4987 (15%).

***Table 1:*** **Patient characteristics of 34 277 patients in clinic populations assessed in this analysis**

and mortality adjusted for sociodemographic, clinical, and laboratory factors. Using predicted mortality at each of these timepoints, we also quantified the variability of mortality across programmes as absolute risk differences at 1, 2, and 3 years. We took the inverse of the risk differences to provide number-needed-to-treat values, which in this case is number of patients who need to be treated in one setting to avoid one death compared with another setting. A directed acyclic graph of the assumed underlying causal relation did not identify backdoor paths in a model including all available predictors, we therefore did not do univariate analysis to identify candidate factors for a multivariate model. Continuous variables were categorised on the basis of customary cutoff points. Time on treatment before the observation period began was accounted for through a restricted cubic spline of the time between observation start and ART initiation. We used multiple imputation to address missing predictor values.[27] The imputation model included all variables in the main effects model and an interaction term between outcome and log-transformed observation time. We explored potential multiplicative interactions between programme and two patient factors: CD4 cell count before therapy and sex. All analyses, including multiple imputation, were done with STATA version 13.0.

### Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Overall, we assessed 34 277 adults on ART in 14 clinics in five different settings during 63 390 person-years and for an average of 1·85 years per person. The programme in Mbarara contributed 7515 patients from a single clinic site, Eldoret 15 568 from five sites, Kisumu 4261 from four sites; Kampala 3611 from three clinics, and Morogoro 3322 from one site. The median (IQR) age of patients was 35 years (30–42), 11 628 (34%) were men, median (IQR) CD4 count before therapy was 154 cells per μL (70–234), and 18 081 patients (53%) had newly started ART after observation began for the current analysis (table 1). Overall demographic characteristics were not substantially different across settings.

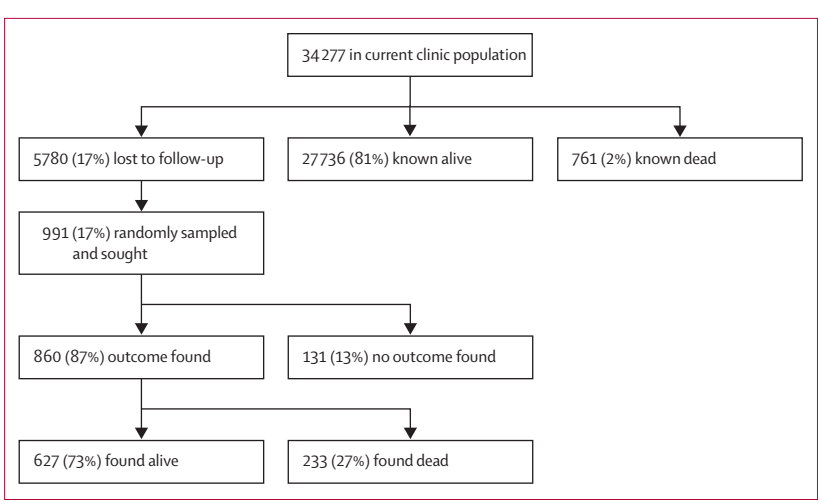



*Figure 1:* **Study population**

5780 patients (17%) were lost to follow-up, of whom 991 (17%) were selected at random for tracing, which was done at all sites between June 10, 2011, and Aug 27, 2012. When stratified by setting, the fraction of the sampled successfully traced was 87% overall, 84% in Mbarara, 83% in Eldoret, 86% in Kisumu, 89% in Kampala, and 89% in Morogoro. Patients lost to follow-up were more likely to be men, had slightly lower CD4 cell counts at ART initiation, and more often started ART after observation in the cohort began (table 1). The median time between loss to follow-up and tracing was 1·2 years (IQR 0·7–1·8). We ascertained vital status for 860 (87%) of 991 attempted cases. Of these, 135 outcomes (16%) were found through chart review alone; the remaining were found through tracing activities. As expected, the characteristics of the randomly selected lost patients were very similar to those of all lost patients (table 1). Of the 860 patients for which an outcome was ascertained, 233 (27%) had died (figure 1), yielding a cumulative mortality among the patients lost to follow-up at 30 days after the last visit of 9·8% (95% CI 8·0–12·0), at 90 days of 15·6% (13·3–18·2), at 180 days of 18·7% (16·3–21·5), and at 365 days of 23·4% (20·7–26·4). When stratified by programme, the 1 year cumulative mortality among patients lost to follow-up ranged from 20·1% in Eldoret to 29·2% in Morogoro (figure 2).

In all patients, the naive (unweighted) mortality estimate at 1 year after ART initiation (which does not account for deaths among the lost) was 2·7% (95% CI 2·5–3·0), at 3 years 3·9% (3·6–4·2), and at 5 years 5·2% (4·8–5·6). After incorporation of updated vital status information in the patients lost to follow-up obtained through tracing, mortality at 1 year was 7·1% (95% CI 6·4–7·7), at 3 years 12·5% (11·8–13·3), and 5 years 15·8% (14·8–16·2; figure 3). Sample-corrected estimates of 3 year mortality in individual settings were two times to ten times higher than in the naive (ie, unweighted) analyses (figure 4). Mortality varied substantially across settings. The lowest mortality was noted in Mbarara, where the corrected 3 year cumulative mortality was 7·2%. The highest mortality was observed at Morogoro, where the corrected 3 year cumulative mortality was 23·6% (figure 5). An analysis restricted to patients newly starting ART during the observation period was very similar and showed overall mortality at 1 year was 8·1% (95% CI 6·9–9·3) and at 2 years was 12·4% (10·5–14·0; figure 5). When stratified by programme, the 2 year mortality among patients starting ART during the

observation period ranged from a low of 7·7% (95% CI 4·5–10·8) in Mbarara to 23·7% (17·7–29·7) in Morogoro.

In the competing risk analysis, the fraction of patients who died in care (ie, within 30 days of last actual visit inclusive) was highest soon after ART initiation for all locations, whereas deaths after 30 or more days of absence from initial clinic rose slowly with time (figure 6). In the estimates pooled across settings, 1 year after ART initiation, the fraction of deaths that occurred after 30 days of absence from the initial clinic exceeded deaths that occurred within 30 days of the last visit (figure 6). The proportion of deaths in care versus out of care over time, however, varied from programme to programme: in Mbarara, deaths out of care exceeded deaths in care by 6 months after ART initiation, in Morogoro, even after 2 years, deaths in care exceeded deaths out of care.

In multivariable analyses, after adjustment for biological and clinical factors and the time the patients had been on ART before observation, the hazard ratio for mortality associated with setting was 2·2 (95% CI 1·5–3·3) when comparing Morogoro (setting with the highest mortality) with Mbarara (the setting with lowest mortality; table 2). The adjusted risk difference in 1 year mortality between these two settings was 6·5% (95% CI 1·0–11·9), 2 year mortality 9·0% (2·6–15·4), and 3 year mortality 11·3% (5·0–17·7): number needed to treat (NNT) 15 for 1 year, 11 for 2 years, and nine for 3 years. Male sex, older age, advanced WHO stage, and lower CD4 cell counts before therapy were also associated with higher mortality (table 2). A naive analysis including only outcomes known before tracing to show the potential distorting effects of loss to follow-up noted falsely increased associations between Eldoret and mortality (where the HR rose from 1·47 to 2·73 compared with Mbarara), and falsely diminished associations between Morogoro and mortality (where the HR fell from 2·24 to 1·52) and Kampala and mortality (where HR fell from 1·45 to 0·48). In this naive, unweighted analysis, the adjusted 2 year risk difference between the settings with the highest and lowest mortality was 4·8% (95% CI 2·6–7·0), yielding an NNT of 21—substantially higher than the 11 at the same time obtained from the sample-weighted estimates.

## Discussion

In a network of clinics providing facility-based care in east Africa, accounting for outcomes among lost patients through a sampling based approach led to an increase of greater than 3 times the estimated 3 year mortality as compared with an estimate using only outcomes known to the clinic through routine practices. The resulting corrected mortality estimate of 12·5% is substantially higher than pooled estimates from Europe.[28,29] A comparison of the corrected mortality estimates across settings showed a 2·2-times difference between settings after adjustment for clinical predictors of mortality such as WHO stage and CD4 level at ART initiation. On an

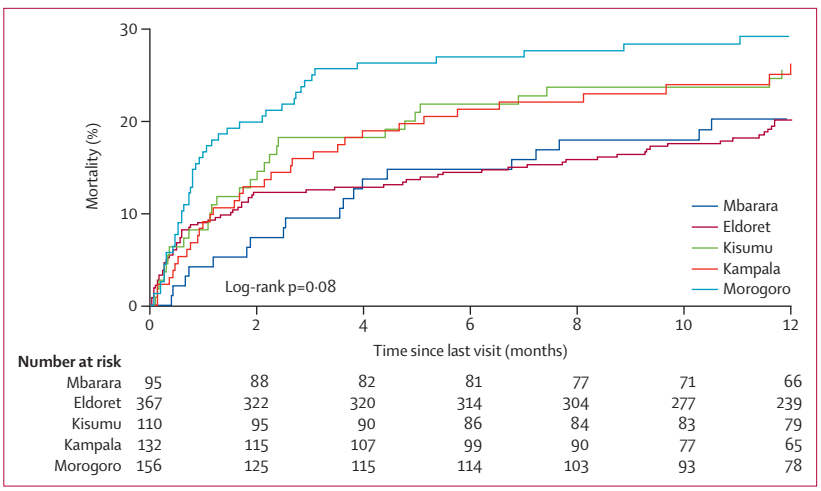



***Figure 2:*** **Mortality among the sample of patients lost to follow-up, successfully sought, with outcomes**
p value is comparison of equality of survival distributions.

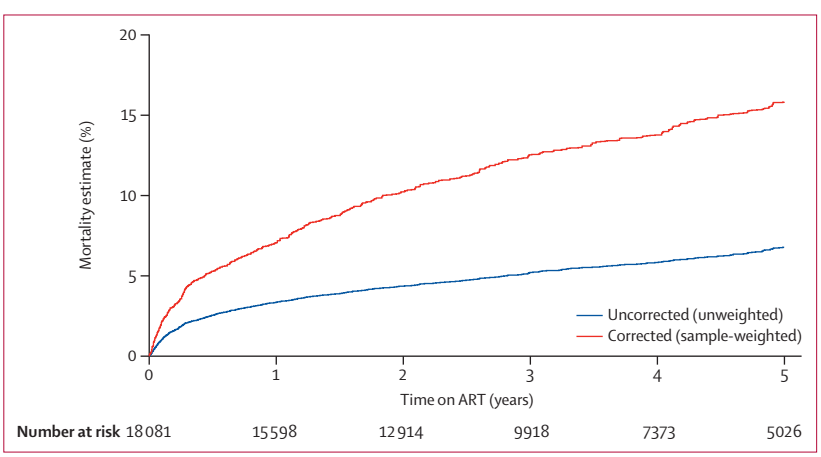



***Figure 3:*** **Overall mortality estimates**
Uncorrected and corrected estimates of mortality for all patients in the current clinic population (N=34 277). ART=antiretroviral treatment.

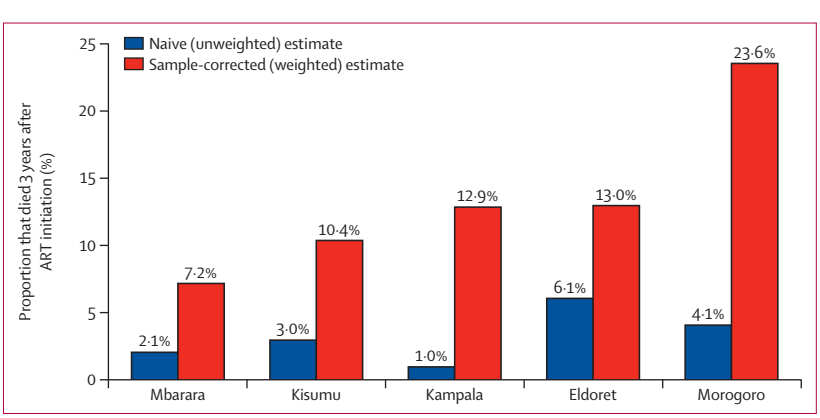
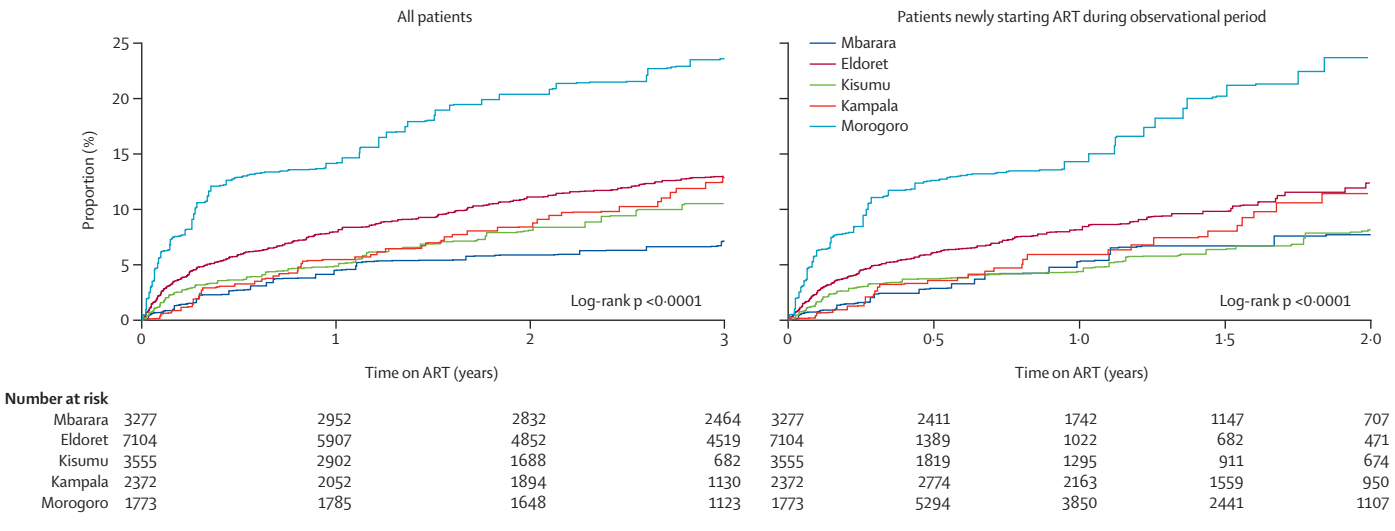



***Figure 4:*** **Corrected mortality estimates by setting**
Naive (unweighted) and corrected (sample-weighted) 3 year cumulative incidences of mortality for all programmes. ART=antiretroviral treatment.




**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Mbarara | 3277 | 2952 | 2832 | 2464 | 3277 | 2411 | 1742 | 1147 | 707 |
| Eldoret | 7104 | 5907 | 4852 | 4519 | 7104 | 1389 | 1022 | 682 | 471 |
| Kisumu | 3555 | 2902 | 1688 | 682 | 3555 | 1819 | 1295 | 911 | 674 |
| Kampala | 2372 | 2052 | 1894 | 1130 | 2372 | 2774 | 2163 | 1559 | 950 |
| Morogoro | 1773 | 1785 | 1648 | 1123 | 1773 | 5294 | 3850 | 2441 | 1107 |

***Figure 5:*** **Sample-corrected mortality estimates**
Kaplan-Meier estimates of mortality among all patients (N=34 277) and new ART initiators during observation period (N=18 081) after ART initiation, stratified by programme, corrected to include outcomes in patients lost to follow-up through sampling-based approach. ART=antiretroviral treatment.

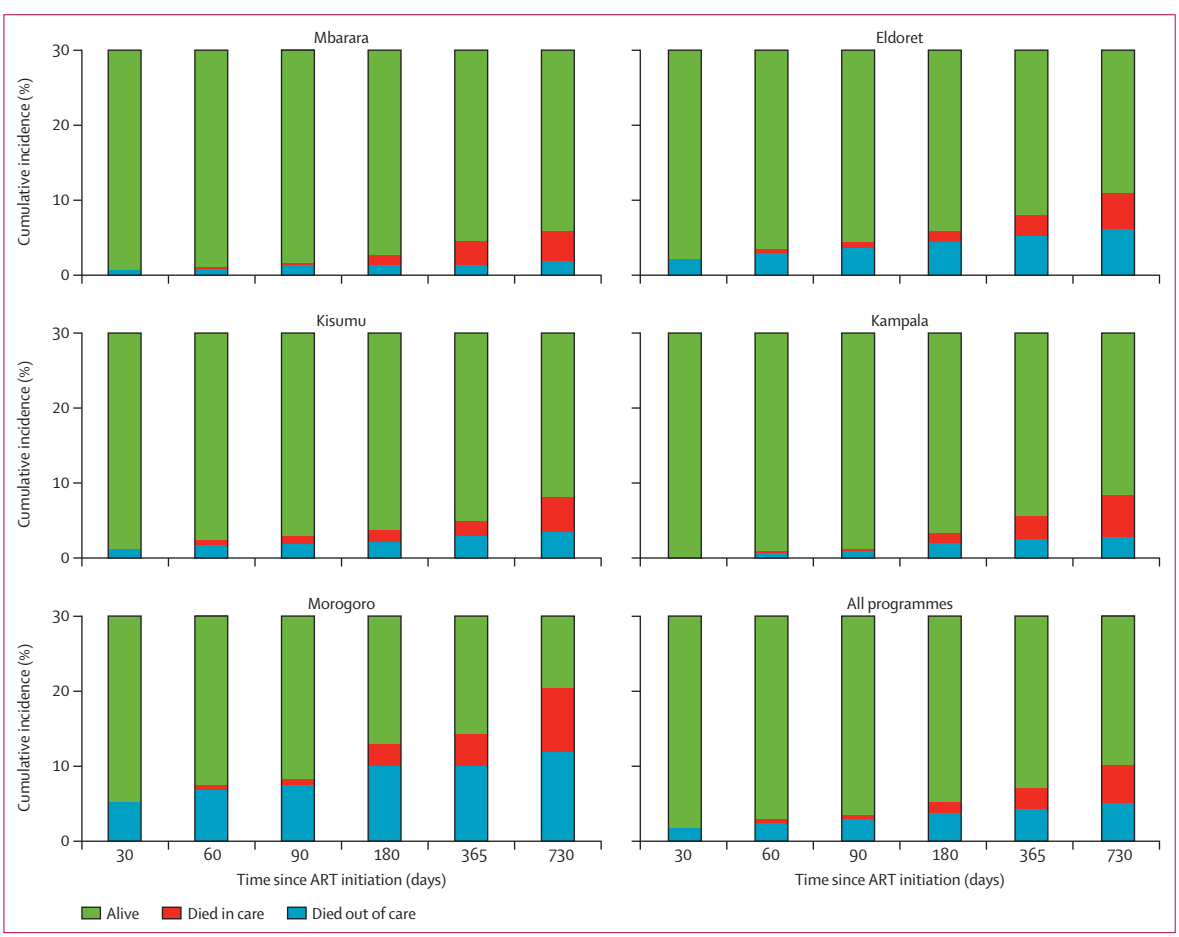



***Figure 6:*** **Competing risk analysis of deaths in and out of care**
Deaths in care and deaths after lapse in care at original clinic site among new ART initiators (N=18 081). ART=antiretroviral treatment.

absolute scale, the adjusted risk difference for mortality at 3 years between the sites with the highest and lowest mortalities is as high as 11%, corresponding to an NNT of 9. Overall, we conclude that accounting for outcomes among the lost is needed to understand the scale of mortality in diverse settings; the corrected mortality are higher than previously believed; and that after adjustment for clinical characteristics, the effectiveness of treatment differs substantially across settings, despite application of broadly similar clinical packages of care.

Our study in a network of 14 clinics is on a larger scale than previous sampling-based studies (panel). These results on a larger scale imply that such an approach is not only widely feasible, but also has widespread importance in settings where vital registries are not robust. Global health programmes are increasingly focused on patients' outcomes: a 2013 report from the US Government's Accounting Office was titled *Shift Toward Partner Country Treatment Programs will Require Better Information on Results*[35] and recent statements from the incoming US Global AIDS Coordinator emphasise the importance of outcomes.[36] At present efforts to obtain these results in the presence of high loss to follow-up include a nomogram to apply a correction factor to mortality estimates derived from summaries of existing cohort studies in which outcomes in a non-probability sample of lost patients were identified.[37] Although useful at the macroscopic level, in our study, the nomogram did not provide enough resolution in individual settings: estimates of 3 year mortality with the nomogram ranged from a 77% underestimate to a 30% overestimate compared with a sampling-based approach. Other strategies, such as inverse probablility of censoring weights,[38] assume that outcomes are missing at random after accounting for available covariates. This assumption is unlikely to be met in settings where rich time-varying covariates are not available, deaths are many times higher among lost patients,[39] and death is itself a cause for an unknown outcome.[40] Sampling offers an immediately feasible and effective strategy that does not rely on these assumptions to obtain inferences about effectiveness and effect.

The corrected mortality estimates of 8·1% at 1 year in patients starting ART and 15·8% at 3 years in all patients are a sobering assessment of the effectiveness of ART treatment in Africa. These findings are higher than those from previous reports from several large, multisite cohort analyses. ART LINC, which included sites from southern, eastern, and western Africa, reported a pooled death rate of 5% 1 year after starting ART.[13] South Africa's public sector programmes in four provinces followed 44 177 patients and observed 6·6% mortality at 1 year and 9·7% at 3 years after starting ART.[41] Both analyses, however, included high fraction of loss to follow-up. Accounting for deaths among the lost to follow-up might explain increased mortality observed in our analysis. Recent reports from European and American cohorts suggest an overall mortality of 1·1 to 1·8 deaths per 100 person-years among adults starting ART with similar CD4 cell counts to the CD4 counts in the patients in our study,[29] which is substantially lower than the overall estimates of mortality we noted. This difference implies that although the global response to treatment of HIV has made huge strides in Africa, further improvements are needed. Strategies to enhance both the supply side (eg, improvement of the quality of care[42]), and the demand side (eg, enhancement of satisfaction, social marketing) are the next generation of public health challenges that must be overcome to reach optimum outcomes.

Mortality across settings in east Africa, or the comparative effectiveness of treatment across these settings, differed substantially and emphasises the urgency of more deeply understanding the nature of organisational

| | Corrected (sampled-weighted) | | Naive (unweighted) | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) | p value |
| Setting | .. | 0·0005 | .. | <0·0001 |
| Mbarara, Uganda | .. | .. | .. | .. |
| Eldoret, Kenya | 1·47 (1·04–2·10) | .. | 2·73 (2·12–3·50) | .. |
| Kisumu, Kenya | 1·19 (0·78–1·80) | .. | 1·39 (1·01–1·92) | .. |
| Kampala, Uganda | 1·45 (0·97–2·16) | .. | 0·48 (0·30–0·78) | .. |
| Morogoro, Tanzania | 2·24 (1·49–3·38) | .. | 1·52 (1·09–2·10) | .. |
| Age, per 10 years | 1·13 (1·02–1·24) | 0·017 | 1·07 (0·99–1·17) | 0·087 |
| Sex | .. | 0·002 | .. | 0·015 |
| Non-pregnant women | .. | .. | .. | .. |
| Men | 1·34 (1·12–1·60) | .. | 1·24 (1·06–1·44) | .. |
| Pregnant women | 0·76 (0·43–1·32) | .. | 0·89 (0·58–1·36) | .. |
| CD4 count at ART initiation (cells per μL) | .. | <0·0001 | .. | <0·0001 |
| ≥350 | .. | .. | .. | .. |
| 200–349 | 0·92 (0·55–1·52) | .. | 0·91 (0·61–1·37) | .. |
| 50–199 | 1·42 (0·90–2·25) | .. | 1·60 (1·12–2·29) | .. |
| 0–49 | 2·58 (1·62–4·13) | .. | 2·64 (1·83–3·82) | .. |
| WHO stage at ART initiation | .. | <0·0001 | .. | <0·0001 |
| I | .. | .. | .. | .. |
| II | 1·39 (0·97–1·98) | .. | 1·25 (0·93–1·69) | .. |
| III | 2·34 (1·70–3·22) | .. | 2·31 (1·78–2·99) | .. |
| IV | 3·74 (2·62–5·34) | .. | 3·98 (2·99–5·30) | .. |
| NNRTI component of first regimen | .. | 0·925 | .. | 0·419 |
| Efavirenz | .. | .. | .. | .. |
| Nevirapine | 1·01 (0·80–1·28) | .. | 1·08 (0·90–1·29) | .. |
| NRTI component of first regimen | .. | 0·320 | .. | 0·115 |
| Zidovudine | .. | .. | .. | .. |
| Stavudine | 0·86 (0·68–1·09) | .. | 0·83 (0·70–1·00) | .. |
| Tenofovir | 0·74 (0·45–1·21) | .. | 1·00 (0·72–1·40) | .. |

All factors are adjusted for all other factors displayed in the table as well as time on ART before entry into observation modelled as a restricted cubic spline (N=34 277). ART=antiretroviral treatment. NNRTI=non-nucleoside reverse-transcriptase inhibitor. NRTI=nucleoside reverse-transcriptase inhibitor.

***Table 2:*** **Factors associated with mortality in a multivariable Cox proportional hazards regression model**

*Panel:* Research in context

**Systematic review**

We searched PubMed for cohort studies that offered estimates of adult mortality after antiretroviral therapy initiation in the east African countries of Uganda, Kenya, or Tanzania from Dec 17, 2009, to Dec 17, 2014, with the search terms ([hiv] AND [antiretroviral therapy)] AND (mortality) AND cohort study AND adult) AND ((kenya OR uganda OR tanzania OR "eastern africa")) , which yielded 133 total publications. Several studies estimated mortality within randomised trials, which might not reflect "real world" outcomes.[30–32] Other studies reporting mortality also observed substantial loss to follow-up but did not incorporate outcomes in those lost to follow-up in mortality estimates.[33,34]

**Interpretation**

Our study offers a unique cross-setting assessment of mortality after initiation of antiretroviral therapy in east Africa, which accounts for outcomes in patients lost to follow-up. Substantial changes in estimates of mortality support the widespread feasibility and use of a sampling-based approach. The overall 3 year estimate of mortality of 12·5% suggests that the delivery of HIV treatment is not optimally effective. Great variation in mortality between settings motivates further research to unpack and reproduce characteristics of care in the most effective settings.

patient and provider behaviours at the front lines. On the surface, all settings in this study delivered a similar package of public health services: NNRTI-based first-line ART, clinics staffed by the ministries of health, a clinic-based model that does not support one-to-one longitudinal provider–patient relationships, and no routine access to HIV RNA quantification or HIV resistance mutation genotyping. However, despite this fairly standardised approach,[20] large differences in outcomes were noted, which were not explained by obvious factors: for example, both Mbarara and Morogoro are semi-urban hubs in rural environments but outcomes differed greatly, despite similar per capita GDP of US$598 in Uganda and $695 in Tanzania. Candidate determinants that lie just beneath the surface include patient–provider trust, communication, and quality of care. Research to identify, isolate, replicate, and disseminate the behaviours that lead to the best outcomes must be urgently pursued. The stakes are high: as shown in our multivariable regression model, the adjusted association between setting and mortality was similar in scale to the effect of a CD4 count of 200–350 cells per μL versus less than 50 cells per μL at ART initiation.

The timing of deaths in relation to the last clinic visit might yield additional insights into organisational and systems drivers of mortality. Because many deaths occurred within a month of the last visit to the original clinic and therefore occurred in care, the timing of these events implies that facility-based opportunities to intervene are present. Anecdotally, we noted that in settings where a standardised and simplified approach to patients is taken, systems are not optimally positioned to detect and respond to the individuals who have signs and symptoms of an acute illness. In previous work, we reported that mortality among the lost could be predicted by clinical characteristics at last clinic visit.[16] Efforts to optimise the speed and quality of medical care, perhaps with algorithmic strategies for empirical treatment, could affect outcomes in these situations.

Our study has several limitations. We did not find 100% of patients who were lost to follow-up: residual selection bias might be present. The fraction ascertained, however, was high overall (87%) and was similar across patients' characteristics (eg, sex and age) and tracing process factors (eg, time from last visit to tracing). Furthermore, the between-site variability in outcomes ascertainment did not have an obvious relation with the corrected mortality estimates: the site with the highest (Morogoro) and lowest (Mbarara) mortalities ascertained outcomes in very similar proportions of those sampled (85% and 83%). Second, the settings in this study were not sampled from a larger pool of sites, but rather represent a convenience sample of programmes. These results, therefore, cannot be directly interpreted as signifying performance in certain regions, much less countries. Third, as in many real-world settings, some data about patients' characteristics were missing. The overall level of missing data, however, was low and similar across settings, with the exception of ART regimen in Kampala, which we were unable to collect and is therefore categorically missing. Fourth, we did not have detailed measurements of the nature of care in these settings: for example we did not have data for provider-to-patient ratios, waiting times, adherence, or other factors that would be associated with mortality. Therefore, although we document differences, we are not well positioned to explain these differences. Finally, although analysis of predictors of mortality included standard metrics of illness severity at ART initiation, such as WHO stage and CD4 cell counts, these markers might not capture the complete clinical picture and therefore residual bias could be present.

In summary, we applied a sampling-based approach to obtain more accurate estimates of mortality in HIV treatment programmes in east Africa and noted striking variability in survival outcomes across settings, which persisted after adjustment for CD4 cell counts, WHO stage, and other demographic characteristics. This unexpected variability implies that organisational, provider, and patients' behaviours in delivery of a similar clinical package is a crucial, but an incompletely understood dimension, in the public health response to HIV. The presence of such heterogeneity is a clarion call for implementation science, which at this point in the response to the HIV epidemic, could offer a greater potential for immediate public health impact than clinical

or basic research. Research to conceptualise,[43] describe, measure, and specify implementation processes[44] is needed to identify and ultimately replicate high-quality practices at the front lines of the public health response to HIV/AIDS. A sampling-based approach is an efficient strategy to ascertain outcomes where loss to follow-up is high, and can be applied in other steps of the cascade as well to inform our understanding of the effectiveness of the HIV response. Epidemiological networks such as the East Africa International Epidemiologic Databases to Evaluate AIDS, which pool data across diverse settings, can show heterogeneity not apparent to investigators working in one programme, region, or even country.

#### Contributors

EHG and JNM led the overall design and execution of the study. EHG led the analysis and writing of the first draft of the report. TAO, REL, AN-M, LD, MB, WM, PB, GRS, AK, EAB, MW, KKW-K, and CYT contributed to the concept development, measurement design, execution of study procedures, review and writing of the report, and interpretation of the results. JNM, DVG, and CTY provided analytic oversight. JNM and CTY provided organisational support.

#### Declaration of interests

We declare no competing interests.

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