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

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Abstract

Background—Mortality after initiation of antiretroviral treatment (ART) among HIV-infected patients in resource limited settings is a critical measure of the effectiveness and comparative effectiveness of the global public health response. Unknown outcomes due to high loss to follow-up (LTFU) preclude accurate accounting of deaths and limit our understanding of effectiveness.

Methods—We evaluated in HIV-infected adults on ART in 14 clinics in five settings in Kenya, Uganda and Tanzania using a sampling-based approach in which we intensively traced a random sample of lost patients (> 90 days late for last scheduled visit) and incorporated their vital status outcomes into analyses of the entire clinic population through probability-weighted survival analyses.

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Contributions

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

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We declare that we have no conflicts of interest

Findings—We followed 34,277 adults on ART from Mbarara and Kampala, Uganda; Eldoret and Kisumu, Kenya; and Morogoro, Tanzania. The median age was 35 years, 34% were men, and median pre-therapy CD4 count was 154 cells/μl. Overall 5,780 (17%) were LTFU, 991 (17%) were randomly selected for tracing and vital status was ascertained in 860 of 991 (87%). Incorporating outcomes among the lost increased estimated 3-year mortality from 3.9% (95% CI: 3.6%-4.2%) to 12.5% (95% CI: 11.8%-13.3%). The sample-corrected, unadjusted 3-year mortality across settings ranged from 7.2% in Mbarara to 23.6% in Morogoro. After adjustment for age, sex, pre-therapy CD4 value, and WHO stage, the sample-corrected hazard ratio comparing the setting with highest vs. lowest mortality 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 for understanding mortality after starting 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 patient behaviors driving these differences is urgently needed.

Keywords

Antiretroviral therapy; Africa; loss to follow-up; mortality; effectiveness

Although global investments in HIV/AIDS care and treatment have reached 13 million individuals with highly efficacious antiretroviral therapy (ART) (1), understanding the effectiveness – and comparative effectiveness across settings – of this public health investment depends on our ability to assess survival after ART initiation. While the antiretroviral regimens routinely used in resource limited settings (RLS) have reliable and potent pharmacologic 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 optimal effectiveness, HIV medications 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 behaviors are common: poverty is prevalent (2), transportation is unreliable (3), “free” medications entail ancillary and opportunity costs (e.g., loss of wages) (4), provider burn out and long waiting times are commonplace (5), and stigma and depression remain widespread (6). Quantifying mortality after ART initiation is therefore urgently needed to understand the effectiveness – and comparative effectiveness – of global HIV treatment programs.

To date, however, surprising uncertainty remains about mortality among HIV-infected patients after starting ART. Existing reports from programmatic settings (7-9) likely miss a significant number of deaths due to loss to follow-up (10-12). For example, the Antiretroviral Therapy in Lower Income Countries (ART-LINC) cohorts reported mortality of 1.8% to 6% in 30 clinics in Africa at one year after ART initiation, but the authors noted that these figures were related to how active follow-up (and therefore ascertainment) was at each site (13). Interval “research” cohorts or randomized trials of clinical interventions, on the other hand, are able to report 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 which in turn rely on inputs from epidemiologic studies. Models also generally offer national figures, and do not shed light on site-to-site variability needed to inform practice behaviors 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 programs in Africa (16, 17). This approach is based on identifying a numerically small but randomly selected sample of lost to follow-up patients, intensively seeking their outcomes in the community, and incorporating these findings to correct estimates in the entire clinic population using a probability weight. Previous work has been carried out 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 evaluated patients on ART in 14 clinics and five programs in East Africa that operate in five locations: Mbarara, Uganda; Eldoret, Kenya; Kisumu, Kenya; Kampala, Uganda; and Morogoro, Tanzania. All programs deliver a similar package of simplified and standardized care which consists of a restricted number of non-nucleoside reverse transcriptase (NNRTI) –based first line combinations, 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 (East Africa – IeDEA), which is an NIH-funded consortium that pools and harmonizes data generated in routine care but does not influence delivery of clinical care at those sites (21). We included patients who had a visit in each program in the 2.5 years before the sampling was carried out. This definition includes patients already on ART at the start of the observation period as well as 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, loss to follow-up or database closure.

Measurements and Procedures

Socio-demographic (e.g., sex) and clinical (e.g., CD4 level at ART initiation) data were obtained from routine care records. As previously described, a random sample of patients lost to follow-up (defined as > 90 days late for last visit as of sampling date) were intensively sought in the community to find their vital status (16, 22). Patients who had died or left the clinics with transfers were not counted among the lost. We targeted a 10%-20% sample of lost patients based on practical considerations about an absolute number that could be intensively traced by resources available at that site. Ascertainers, hired through existing departments in each program, sought the lost patients. For patients found to have died, we documented the death date and basic information about the cause of death (e.g., illness, accident, suicide, homicide or childbirth).

Analyses

We used the Kaplan-Meier (KM) method to estimate mortality after ART initiation overall and by setting (e.g., Mbarara, Kisumu). Since 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 the sampling was carried out), 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 (23), but which does not account for patients who ceased to access care before the observation period (e.g., died or were lost to follow-up). We therefore also estimated mortality restricted to new ART initiators. For all KM estimates, we first conducted a "naïve" analysis which used only deaths known to the clinic before tracing. Second, as described in previous work (24), we carried out a revised estimate of mortality by incorporating outcomes among 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 receive a weight of zero; patients who are found through tracing are given a weight inverse to the probability of outcome ascertainment. Weights were derived separately in each clinic. Confidence intervals for descriptive estimates were obtained via 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) (25-27).

We carried out multivariable Cox proportional hazards regression to estimate the association between setting (e.g., Mbarara, Kampala) and mortality adjusted for socio-demographic, clinical and laboratory factors. We also quantified the variability of mortality across programs as absolute risk differences at 1, 2 and 3 years using predicted mortality at each of these time points. We took the inverse of the risk differences to provide number-needed-to-treat (NNT) values, which in this case is number of patients who need to be treated in one setting to avoid one death as compared to another setting. A directed acyclic graph of the assumed underlying causal relationships did not identify backdoor paths in a model including all available predictors – we therefore did not carry out univariate analysis to identify candidate factors for a multivariate model. Continuous variables were categorized based on customary cut-points. Time on treatment before 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 (28). The imputation model included all variables in the main effects model as well as an interaction term between outcome and log-transformed observation time. We explored potential multiplicative interactions between program and two patient factors: pre-therapy CD4 level and sex. All analyses, including multiple imputation, were conducted using STATA 13.0 (College Station, TX). The study was approved by the institutional review boards of relevant institutions involved.

The sponsor of the study had no role in 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

Patient Characteristics

Overall, we evaluated 34,277 adults on ART in 14 clinics in five different settings over a total of 63,390 person years and for an average of 1.85 years per person. The program in Mbarara contributed 7,515 from a single clinic site; Eldoret contributed 15,568 patients from five clinic sites; Kisumu provided 4,261 from four sites; Kampala provided 3,611 patients from three clinics and Morogoro observed 3,322 patients from one clinic site. Patients had a median age of 35 years, 33.9% were men, median CD4 level at ART initiation was 154 /μl (IQR: 70-234) and 52.8% newly started ART after observation began for the current analysis (Table 1). Overall patient demographic characteristics were not markedly different across settings.

Patients lost to follow-up

Of 34,277 total patients, 5,780 (17%) were lost to follow-up and 991 of 5,780 (17%) were randomly selected for tracing, which was carried out at all sites between June 10, 2011 and August 27, 2012. When stratified by setting, the fraction of the sampled successfully traced was 84% in Mbarara, 83% in Eldoret, 86% in Kisumu, 89% in Kampala and 89% in Morogoro. Lost patients were more likely to be men, had slightly lower CD4 levels at ART initiation, and more often started ART after observation in the cohort began. The median time between loss and tracing was 1.2 years (IQR: 0.7 to 1.8). In 860/991 (87%) of attempted cases, updated vital status was ascertained. Of these 860, 135 (15.6%) outcomes were found through chart review alone and the remaining were found through tracing activities. As expected, the characteristics of the randomly selected lost patients were very similar to all lost patients (Table 1). Among the 860 cases where an outcome was ascertained, in 233 (27%) the patient was found to have died (Figure 1), yielding a cumulative incidence of mortality among the lost at 30, 90, 180 and 365 days after the last visit of 9.8% (95% CI: 8.0%-12.0%); 15.6% (95% CI: 13.3%-18.2%); 18.7% (95% CI: 16.3%-21.5%); and 23.4% (95%CI: 20.7%-26.4%). When stratified by program, the 1-year cumulative incidence of mortality among patients lost to follow-up ranged from a low of 20.1% in Eldoret to 29.2% in Morogoro (Figure 2). Changes in the rate of mortality after ART initiation differed from site to site (Figure 2).

Naïve and Corrected Mortality Estimates

Among all patients, the “naïve” mortality estimate at 1, 3, and 5 years after ART initiation (which does not account for deaths among the lost) was 2.7% (95% CI: 2.5%-3.0%), 3.9% (95% CI: 3.6%-4.2%), and 5.2% (95% CI: 4.8%-5.6%). After incorporating updated vital status information among the lost patients obtained through tracing, mortality at the same time points was estimated to be 7.1% (95% CI: 6.4%-7.7%), 12.5% (95% CI: 11.8%-13.3%) and 15.8% (95% CI: 14.8%-16.2%) (Figure 3). Sample-corrected estimates of three-year mortality in individual settings were two-fold to over 10-fold higher compared to the “naïve”

(i.e., unadjusted) ones (Figure 4). Mortality varied markedly across settings. The lowest mortality was observed in Mbarara, where the corrected 3 year cumulative incidence of mortality was 7.2%. The highest mortality was observed at Morogoro, where the corrected 3 year cumulative incidence of mortality was 23.6% (Figure 5). An analysis restricted to patients newly starting ART during the observation period was very similar and found an overall mortality at one year was 8.1% (95% CI: 6.9% - 9.3%) and at year two was 12.4% (95% CI: 10.5% −14.0%) When stratified by program the two-year mortality among patients starting ART during observation period differed markedly as well and ranged from a low of 7.7% (4.5% - 10.8%) in Mbarara to 23.7% (95% CI: 17.7 - 29.7%) in Morogoro.

Deaths in relation to last visit

In the competing risk analysis, the fraction of patients who died in care (i.e., within 30 days of last actual visit inclusive) was highest soon after ART initiation while deaths after 30 or more days of absence from initial clinic rose slowly over time (Figure 6). In the estimates pooled across settings, approximately 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. The proportion of deaths in care vs. out of care over time, however, varied from program to program: in Mbarara, deaths out of care exceeded deaths in care by 6 months after ART initiation, in Morogoro, even after two years, deaths in care exceeded deaths out of care.

Predictors of mortality

In multivariable analyses, after adjustment for biological and clinical factors as well as the time the patients had been on ART before observation, the hazard ratio for mortality associated with setting was 2.2 fold (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, 2 and 3-year mortality between these two settings was 6.5% (95% CI: 1.0%-11.9%); 9.0% (95% CI: 2.6%-15.4%); and 11.3% (95% CI: 5.0%-17.7%) respectively, which translated into a number needed to treat of 15, 11 and 9 at each of those time points. Male sex, advancing age, more advanced WHO stage and lower pre-therapy CD4 levels were also associated with higher rates of mortality (Table 2). A “naïve” analysis including only outcomes known before tracing to illustrate the potential distorting effects of loss to follow-up found spuriously elevated associations between Eldoret and mortality (where the HR rose from 1.5 to 2.7 as compared with Mbarara), as well as a spuriously diminished associations between Morogoro and mortality (where the HR fell from 2.2 to 1.5) and Kampala and mortality (where HR fell from 1.5 to 0.5). In this naïve, 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 a NNT of 21 – markedly higher than the estimated NNT of 11 at the same time obtained from the sample weighted estimates.

Discussion

We report mortality among HIV infected patients receiving ART in network of clinics providing facility-based care in East Africa which accounts for deaths normally unknown due to loss to follow-up. Carrying out the sampling approach “at scale” in a network of 14

clinics extends previous sampling-based estimates at a smaller number of sites by expanding the overall scope as well as providing comparison between treatment settings. Accounting for outcomes among lost patients led to a 2.5-fold increase in estimated two-year mortality in the entire patient population. The resulting estimated mortality of 12.5% is substantially higher than pooled estimates from Europe. A comparison of the corrected mortality estimates across settings showed a 2.2-fold difference between settings after adjustment for clinical predictors of mortality such as WHO stage and CD4 level at ART initiation. On an absolute scale, the adjusted risk difference for mortality at 3 years between the site with the highest and lowest mortality was as high as 11%, corresponding to a number needed to treat of 9. Overall, we conclude that (1) accounting for outcomes among the lost is requisite for understanding the magnitude of mortality in diverse settings; (2) the corrected mortality rates are higher than previously believed; and (3) after adjustment for clinical characteristics, the effectiveness of treatment differs substantially across settings, despite application of a broadly similar clinical package of care.

These results imply that a sampling-based approach is not only widely feasible, but also has widespread importance in settings where vital registries are not robust. Global health programs are increasingly focused on patient 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" (29) and recent statements from the incoming US Global AIDS Coordinator emphasize the importance of outcomes (30). Currently 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 non-probability sample of lost patients were identified (31). Although useful at the macroscopic level, in our study the nomogram did not provide enough resolution in individual settings: estimates of three year mortality using the nomogram ranged from a 77% underestimate to a 30% overestimate as compared to a sampling-based approach. Other strategies such as inverse probably of censoring weights (32) 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 fold higher among lost patients (33), and death is itself a cause for an unknown outcome (34). Sampling offers an immediately feasible and impactful strategy that does not rely on these assumptions to obtain inferences about effectiveness and impact.

The corrected mortality estimates we observed of 8.1% at one year among new ART starters and 15.8% at three years in all patients' offers a sobering assessment of the effectiveness of ART treatment in Africa. These findings are higher than previous reports from several large, multi-site cohort analyses. ART LINC, which included sites from southern, eastern, and western Africa, reported a pooled death rate of 5% one year after starting ART (13). South Africa's public sector programs in four provinces followed 44,177 patients and observed 6.6% and 9.7% mortality at one and three years after starting ART (35). Both analyses, however, included high fraction of loss to follow up. Accounting for deaths among the lost to follow-up may explain higher mortality observed in our analysis. Recent reports from European cohorts suggest an overall mortality of 1.1 deaths per 100 person-years among adults starting ART with similar CD4 levels (36), which is substantially lower than the

overall estimates of mortality we observed. This difference implies that while the global response to treating HIV has made huge strides in Africa, further improvements are needed. Strategies to enhance both the supply side (e.g., improving the quality of care (37)), as well as the demand side (e.g.,enhancing satisfaction, social marketing) are the next generation of public health challenges that must be overcome to reach optimal outcomes.

Mortality across settings in East Africa, or the “comparative effectiveness” of treatment across these settings, differed markedly and highlights the urgency of more deeply understanding the nature of organizational as well as patient and provider behaviors 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, ministry of health (MOH)-staffed clinics, a clinic-based model that does not support one-to-one longitudinal provider-patient relationship, and no routine access to HIV RNA quantification or HIV resistance mutation genotyping. Yet, despite this relatively standardized approach (20), large differences in outcomes were observed which were not explained by obvious factors: for example, both Mbarara and Morogoro are semi-urban hubs in a rural environment yet outcomes differed markedly despite similar per capita GDP of 598 USD in Uganda and 695 USD in Tanzania. Candidate determinants which lie just beneath the surface include patient-provider trust, communication, and the quality of care. Research to identify, isolate, replicate and disseminate the behaviors 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 magnitude to the effect of a CD4 count of 200-350/μl vs. <50 /μl at ART initiation.

The timing of deaths in relation to the last clinic visit may yield additional insights into organizational and systems drivers of mortality. Since 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 observed that in settings where a standardized 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 found mortality among the lost could be predicted by clinical characteristics at last clinic visit (16). Efforts to optimize the speed and quality of medical care, perhaps using algorithmic strategies for empiric treatment, may influence outcomes in these situations.

There are a number of limitations in this study. We did not find 100% of patients who were lost to follow-up: residual selection bias may be present. The fraction ascertained, however, was high overall (87%) and was similar across patient characteristics (e.g., sex, age) and tracing process factors (e.g., time from last visit to tracing). Furthermore, the site to site variability in outcomes ascertainment did not have an obvious relationship with the corrected mortality estimates: the site with the highest mortality (Morogoro) ascertained vital status in 85% of the sampled, whereas the site with the lowest mortality (Mbarara) ascertained outcomes in a very similar fraction of 83%. Second, the settings in this study were not sampled from a larger pool of sites, but rather represent a convenience sample of programs. 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

patient characteristics was 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 which is therefore categorically missing. Fourth, we also lacked more detailed measurements of the nature of care in these settings: for example we did not have data on provider to patient ratios, waiting times, adherence or other factors that would be associated with mortality. Therefore, while we document differences, we are not well positioned to explain these differences. Finally, while analysis of predictors of mortality included standard metrics of illness severity at ART initiation such as WHO stage and CD4 levels, these markers may not capture the complete clinical picture and therefore residual bias may be present.

In summary, we applied a sampling-based approach to obtain more accurate estimates of mortality in HIV treatment programs in East Africa and found striking variability in survival outcomes across settings, which persisted after adjustment for CD4 level, WHO stage and other demographic characteristics. This unexpected variability implies that organizational, provider and patient behaviors in delivery of a similar clinical package is a critical, 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, is likely to offer a greater potential for immediate public health impact than clinical or basic research. Research to conceptualize (38), describe, measure and specify implementation processes (39) 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. Epidemiologic networks such as the East Africa International Epidemiologic Databases to Evaluate AIDS, which pool data across diverse settings, can demonstrate heterogeneity not apparent to investigators working in one program, region or even country.

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Evidence in Context

Search

We searched for cohort studies which offered estimates of adult mortality after antiretroviral therapy initiation in the Eastern African countries of Uganda, Kenya or Tanzania over the last five years using Pubmed. The search terms ((((hiv) AND antiretroviral therapy) AND mortality) AND cohort study AND adult) AND ((kenya OR uganda OR tanzania OR "eastern africa")) yielded 133 total publications. A number of studies estimated mortality within randomized trials, which may not reflect “real world” outcomes (40-42). Other studies reporting mortality also observed high levels of loss to follow-up, but did not incorporate outcomes among those lost into mortality estimates (43, 44).

Interpretation

In the context of present literature, this study offers a unique cross-setting evaluation of mortality after starting antiretroviral therapy in Eastern Africa that accounts for outcomes among patients lost to follow-up. Substantial changes in estimates of mortality support the widespread feasibility and utility 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. Marked variation in mortality between settings motivates further research to unpack and reproduce characteristics of care in most effective settings.

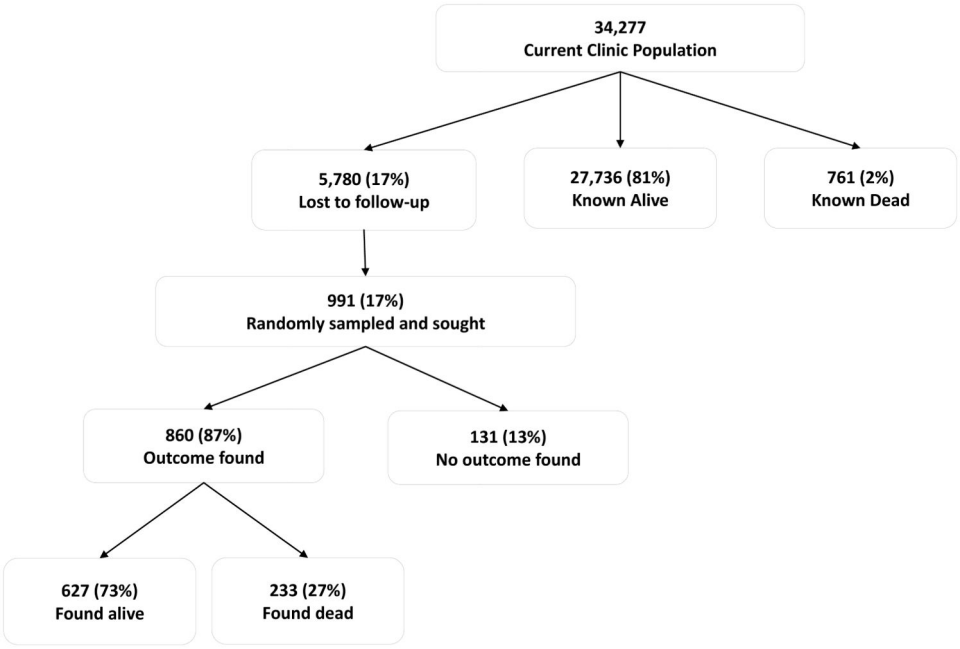

Figure 1.
Flow chart of study population.

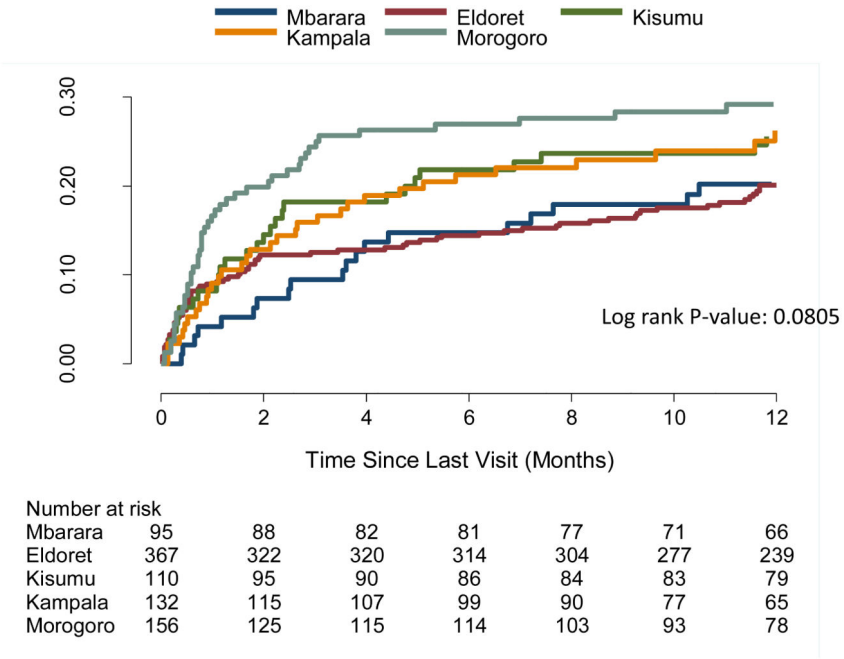

Figure 2.

Mortality among a sample of patients lost to follow-up. Incidence and the hazard of mortality among a random sample of patients lost to follow-up and successfully sought in the community, stratified by program.

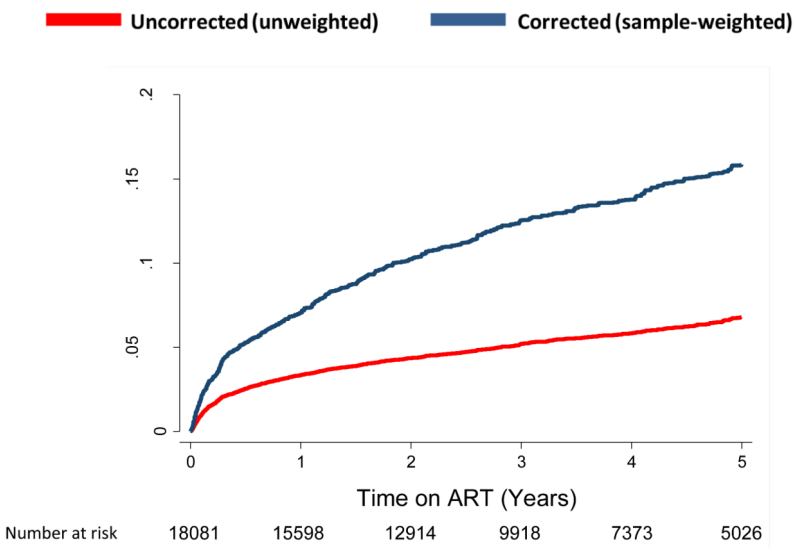

Figure 3.

Overall mortality estimates. Uncorrected and corrected estimates of mortality for all patients in the current clinic population (N=34,277).

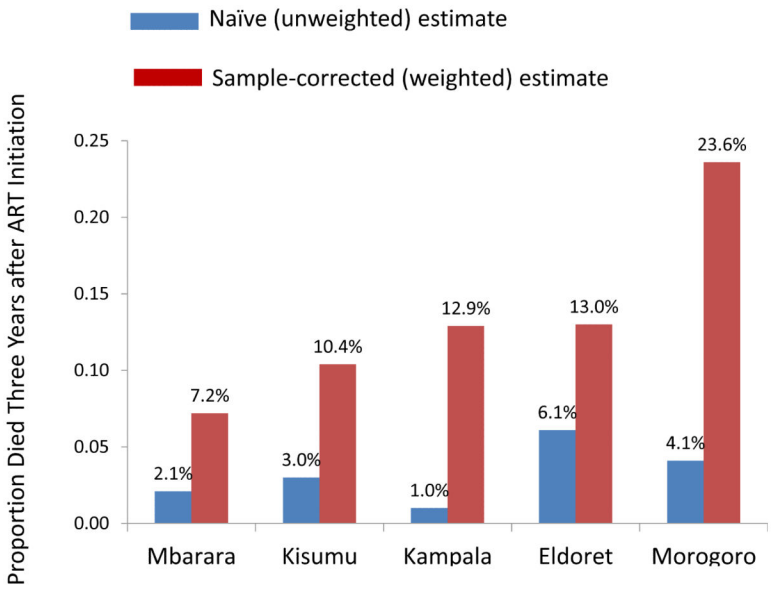

Figure 4.

Corrected mortality estimates by setting. “Naïve” (unweighted) and corrected (sample-weighted) three year cumulative incidences of mortality at each program.

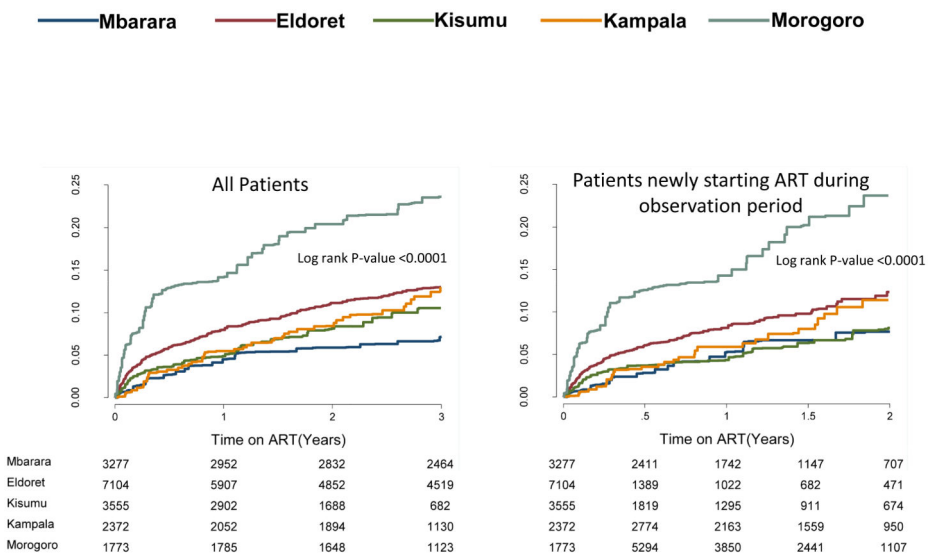

Figure 5.

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 program, corrected to include outcomes among patients lost to follow-up through sampling-based approach.

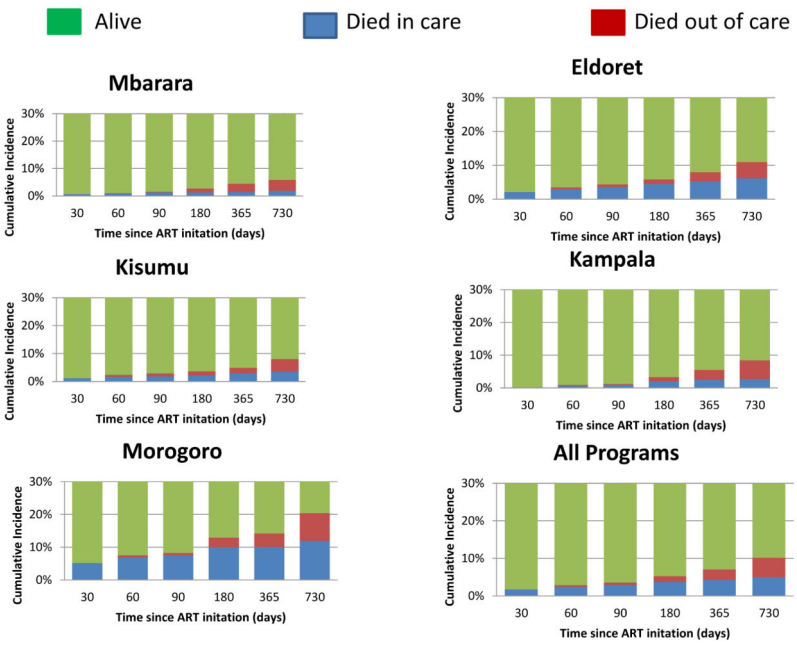

Figure 6.

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).

Table 1

Patient characteristics of 34,277 patients in the current clinic populations evaluated in this analysis, by setting and overall. Antiretroviral therapy regimen is missing from Kampala sites.

Characteristic	Mbarara, Uganda				Eldoret, Kenya				Kisumu, Kenya			
	All patients	Lost to follow-up patients	Lost patients randomly sampled for tracing	Successfully traced patients	All patients	Lost to follow-up patients	Lost patients randomly sampled for tracing	Successfully traced patients	All patients	Lost to follow-up patients	Lost patients randomly sampled for tracing	Successfully traced patients
Number	7515	907	113	95	15568	2220	441	367	4261	639	114	110
Age - years, median (IQR) *	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)
Sex, n (%)												
male	2811 (37.4)	409 (45.1)	56 (49.6)	47 (49.5)	5503 (35.4)	821 (37.0)	181 (41.0)	158 (43.1)	1343 (31.5)	197 (30.8)	34 (29.8)	32 (29.1)
non pregnant female	4022 (53.5)	431 (47.5)	46 (40.7)	40 (42.1)	8829 (56.7)	1203 (54.2)	215 (48.8)	172 (46.9)	2323 (54.5)	339 (53.1)	63 (55.3)	62 (56.4)
pregnant female	682 (9.1)	67 (7.4)	11 (9.7)	8 (8.4)	1236 (7.9)	196 (8.8)	45 (10.2)	37 (10.1)	595 (14.0)	103 (16.1)	17 (14.9)	16 (15.6)
CD4 level at ART initiation – cells/µl, median (IQR) †	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)
WHO Stage, n (%) ‡												
WHO Stage I	1763 (23.9)	153 (17.2)	24 (22.0)	21 (22.8)	4481 (30.5)	537 (26.9)	102 (26.3)	84 (25.4)	1080 (25.5)	140 (22.1)	27 (24.1)	25 (23.2)
WHO Stage II	2178 (29.6)	245 (27.6)	33 (30.3)	28 (30.4)	2842 (19.4)	368 (18.4)	61 (15.7)	55 (16.6)	1218 (28.7)	147 (23.2)	22 (19.6)	22 (20.4)
WHO Stage III	2616 (35.5)	352 (39.6)	36 (33.0)	30 (32.6)	5886 (40.1)	867 (43.4)	178 (45.9)	154 (46.5)	1575 (37.2)	266 (41.9)	53 (47.3)	52 (48.2)
WHO Stage IV	814 (11.0)	138 (15.5)	16 (14.7)	13 (14.1)	1464 (10.0)	228 (11.4)	47 (12.1)	38 (11.5)	366 (8.6)	82 (12.9)	10 (8.9)	9 (8.3)
NNRTI component of first regimen §												
NVP	5556 (74.1)	689 (76.3)	89 (78.8)	75 (79.0)	10839 (77.7)	1439 (75.4)	278 (74.3)	233 (73.5)	2703 (69.1)	422 (75.4)	85 (84.2)	81 (83.5)
EFV	1938 (25.9)	214 (23.7)	24 (21.2)	20 (21.1)	3119 (22.4)	469 (24.6)	96 (25.7)	84 (26.5)	1209 (30.9)	138 (24.6)	16 (15.8)	16 (16.5)
NRTI in first regimen ¶												
AZT	1780 (23.7)	202 (22.3)	27 (23.9)	20 (21.1)	9272 (64.3)	1339 (66.5)	260 (65.8)	219 (65.6)	2050 (49.0)	386 (61.7)	72 (64.3)	70 (64.8)
D4T	5117 (68.1)	628 (69.2)	77 (68.1)	66 (69.5)	4337 (30.1)	621 (30.8)	129 (32.7)	111 (33.2)	1474 (35.2)	210 (33.6)	36 (32.1)	35 (32.4)
TDF	616 (8.2)	77 (8.5)	9 (8.0)	9 (9.5)	808 (5.6)	54 (2.7)	6 (1.5)	4 (1.2)	659 (15.8)	30 (4.8)	4 (3.6)	3 (2.8)
Care status												
In care at observation	4238 (56.4)	465 (51.3)	58 (51.3)	45 (47.4)	8464 (54.4)	1012 (45.6)	195 (44.2)	171 (46.6)	706 (16.6)	144 (22.5)	33 (29.0)	32 (29.1)

start												
New to care during observation period	3277 (43.6)	442 (48.7)	55 (46.7)	50 (52.6)	7104 (45.6)	1208 (54.4)	246 (55.8)	196 (43.4)	3555 (83.4)	495 (77.5)	81 (71.1)	78 (70.9)
Characteristic	**Kampala, Uganda**				**Morogoro,** Tanzania				**All**			
	All patients	Lost to follow-up patients	Lost patients randomly sampled for tracing	Successfully traced patients	All patients	Lost to follow-up patients	Lost patients randomly sampled for tracing	Successfully traced patients	All patients	Lost to follow-up patients	Lost patients randomly sampled for tracing	Successfully traced patients
Number	3611	697	148	132	3322	1317	175	156	34277	5780	991	860
Age - years, median (IQR) *	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, n (%)												
male	1019 (28.2)	231 (33.1)	48 (32.4)	43 (32.6)	952 (28.7)	375 (28.5)	58 (33.1)	50 (32.1)	11628 (33.9)	2033 (35.2)	377 (38.0)	330 (38.4)
non pregnant female	2461 (68.2)	448 (64.3)	98 (66.2)	88 (66.7)	2296 (69.1)	911 (69.2)	111 (63.4)	101 (64.7)	19931 (58.2)	3332 (57.7)	533 (53.8)	463 (53.8)
pregnant female	131 (3.6)	18 (2.6)	2 (1.4)	1 (0.8)	74 (2.2)	31 (2.4)	6 (3.4)	5 (3.2)	2718 (7.9)	415 (7.2)	81 (8.2)	67 (7.8)
CD4 level at ART initiation - cells/ul, median (IQR) †	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, n (%) ‡												
WHO Stage I	576 (16.3)	102 (15.0)	17 (11.6)	15 (11.4)	133 (4.9)	43 (4.0)	8 (5.3)	6 (4.5)	8033 (24.7)	975 (18.5)	178 (19.6)	151 (19.0)
WHO Stage II	1458 (41.2)	255 (37.5)	67 (45.6)	57 (43.2)	624 (22.8)	250 (23.3)	28 (18.5)	24 (17.9)	8320 (25.6)	1265 (24.0)	211 (23.3)	186 (23.3)
WHO Stage III	1515 (32.5)	236 (34.7)	46 (31.3)	44 (33.3)	1576 (57.7)	598 (55.8)	94 (62.3)	85 (63.4)	12804 (39.3)	2319 (42.0)	407 (44.9)	365 (45.8)
WHO Stage IV	357 (10.1)	87 (12.8)	17 (11.6)	16 (12.1)	400 (14.6)	180 (16.8)	21 (13.9)	19 (14.2)	3401 (10.5)	715 (13.6)	111 (12.2)	95 (11.9)
NNRTI component of first regimen §												
NVP	--	--	--	--	2026 (63.8)	850 (67.4)	93 (56.7)	83 (56.9)	21124 (74.0)	1233 (26.6)	545 (72.5)	472 (72.1)
EFV	--	--	--	--	1151 (36.2)	412 (32.7)	71 (43.3)	63 (43.2)	7417 (26.0)	3400 (73.4)	207 (27.5)	183 (27.9)
NRTI in first regimen ¶												
AZT	--	--	--	--	1782 (56.4)	766 (60.7)	80 (48.8)	70 (48.0)	14894 (50.9)	2693 (56.0)	439 (56.0)	379 (55.5)
D4T	--	--	--	--	1385 (43.6)	496 (39.3)	84 (51.2)	76 (52.1)	12313 (42.0)	1955 (40.7)	326 (41.6)	288 (42.2)
TDF	--	--	--	--	0	0	0	0	2083 (7.1)	161 (3.4)	19 (2.4)	16 (2.3)
Care status												
In care at observation start	1239 (34.3)	265 (38.0)	55 (37.2)	50 (37.9)	1549 (46.6)	644 (48.9)	71 (40.4)	65 (41.7)	16196 (47.3)	2530 (43.8)	412 (41.6)	363 (42.2)
New to care during	2372 (65.7)	432 (62.0)	93 (62.8)	82 (62.1)	1773 (46.6)	673 (51.1)	104 (59.4)	91 (58.3)	18081 (52.8)	3250 (56.2)	579 (58.4)	497 (57.8)

observation period

[*] missing in 638 (1.9%);

[†] missing in 4,950 (14.4%);

[‡] missing in 1,719 (5.0%);

[§] missing in 5,736 (16.7%) ;

[¶] missing in 4,987 (14.5%)

Table 2

Factors associated with mortality in a multivariable Cox proportional hazards regression model. All factors are adjusted for all other factors displayed in the table as well as time on ART before entry into observation modeled as a restricted cubic spline (N=34,277).

Factor	***Corrected (sampled-weighted)***		***Naive (unweighted)***	
	Hazard Ratio (95% CI)	**P-Value**	**Hazard Ratio (95% CI)**	**P-Value**
Setting		0.001		<0.001
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
Gender		0.002		0.015
Non-pregnant female	--		--	
Male	1.34 (1.12-1.60)		1.24 (1.06-1.44)	
Pregnant female	0.76 (0.43-1.32)		0.89 (0.58-1.36)	
CD4 level at ART initiation - cells/μl		<0.001		<0.001
>=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		<0.001		<0.001
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				0.419
EFV		0.925		

Factor	*Corrected (sampled-weighted)*		*Naive (unweighted)*	
	Hazard Ratio (95% CI)	**P-Value**	**Hazard Ratio (95% CI)**	**P-Value**
NVP	1.01 (0.80-1.28)		1.08 (0.90-1.29)	
NRTI component of first regimen		0.320		0.115
AZT	--		--	
D4T	0.86 (0.68-1.09)		0.83 (0.70-1.00)	
TDF	0.74 (0.45-1.21)		1.00 (0.72-1.40)	