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Mortality trends in the era of antiretroviral therapy: evidence from the Network for Analysing Longitudinal Population based HIV/AIDS data on Africa (ALPHA)

Georges Reniers[a], Emma Slaymaker[a], Jessica Nakiyingi-Miiro[b], Constance Nyamukapa[c], Amelia Catharine Crampin[a,d], Kobus Herbst[e], Mark Urassa[f], Fred Otieno[g], Simon Gregson[c,h], Maquins Sewe[g], Denna Michael[f], Tom Lutalo[i], Victoria Hosegood[e,j], Ivan Kasamba[b], Alison Price[a,d], Dorean Nabukalu[i], Estelle Mclean[a], Basia Zaba[a], on behalf of the ALPHA Network

Background: The rollout of antiretroviral therapy (ART) is one of the largest public health interventions in Eastern and Southern Africa of recent years. Its impact is well described in clinical cohort studies, but population-based evidence is rare.

Methods: We use data from seven demographic surveillance sites that also conduct community-based HIV testing and collect information on the uptake of HIV services. We present crude death rates of adults (aged 15–64) for the period 2000–2011 by sex, HIV status, and treatment status. Parametric survival models are used to estimate age-adjusted trends in the mortality rates of people living with HIV (PLHIV) before and after the introduction of ART.

Results: The pooled ALPHA Network dataset contains 2.4 million person-years of follow-up time, and 39114 deaths (6893 to PLHIV). The mortality rates of PLHIV have been relatively static before the availability of ART. Mortality declined rapidly thereafter, with typical declines between 10 and 20% per annum. Compared with the pre-ART era, the total decline in mortality rates of PLHIV exceeds 58% in all study sites with available data, and amounts to 84% for women in Masaka (Uganda). Mortality declines have been larger for women than for men; a result that is statistically significant in five sites. Apart from the early phase of treatment scale up, when the mortality of PLHIV on ART was often very high, mortality declines have been observed in PLHIV both on and off ART.

Conclusion: The expansion of treatment has had a large and pervasive effect on adult mortality. Mortality declines have been more pronounced for women, a factor that is often attributed to women's greater engagement with HIV services. Improvements in the timing of ART initiation have contributed to mortality reductions in PLHIV on ART, but also

[a]Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK, [b]Research Unit on AIDS, Medical Research Council/Uganda Virus Research Institute, Entebbe, Uganda, [c]Manicaland HIV/STD prevention project, Biomedical Research and Training Institute, Harare, Zimbabwe, [d]Karonga Prevention Study, London School of Hygiene and Tropical Medicine, Chilumba, Malawi, [e]Africa Centre for Health and Population Studies, University of KwaZulu Natal, Somkhele, South Africa, [f]TAZAMA project, National Institute for Medical Research, Mwanza, Tanzania, [g]Kenya Medical Research Institute / Centers for Disease Control and Prevention, Kisumu, Kenya, [h]School of Public Health, Faculty of Medicine, Imperial College, London, UK, [i]Rakai Health Sciences Program, Makerere University School of Public Health, Rakai, Uganda, and [j]Department of Social Statistics and Demography, Southampton University, Southampton, UK.

Correspondence to Georges Reniers.

E-mail: georges.reniers@lshtm.ac.uk

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among those who have not (yet) started treatment because they are increasingly selected for early stage disease.

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Introduction

The expansion of HIV care and treatment services is one of the largest public health interventions in sub-Saharan Africa of recent times, but it is notoriously difficult to evaluate its population-wide impact because many of the countries that are hardest hit by the epidemic have poor registration of vital events. Clinical cohort studies fill part of the information gap, and suggest that the mortality levels of patients who start treatment early and do not default approaches that of HIV-negative individuals of the same age [1–3]. Clinical studies have also shown, however, that late presentation and patient attrition continue to limit the efficacy of ART [3–5]. The true magnitude of the mortality associated with these phenomena is harder to estimate. Intensive patient tracing studies have shed light on the mortality of patients who are lost to follow-up [6], but estimating mortality in HIV positives who never make contact with the health system remains intractable with clinic-based study designs.

This situation thus calls for a population-based assessment of mortality trends, and in this contribution we use data from seven demographic and HIV surveillance sites in six eastern and southern African countries. Several of these studies have previously reported on the impact of HIV on adult mortality [7–12]. This study differs from earlier analyses because the data range is extended to 2011, and thus covers several years during which ART was locally available. We also use individually-linked information on HIV testing and treatment uptake, which allows us to estimate the mortality trends of people living with HIV (PLHIV), and disaggregate those estimates by their treatment status.

Most of our estimates are presented for men and women separately. Gender equity in the uptake of ART has been a concern since the early days of the treatment scale up; initially because of women's elevated HIV prevalence and concerns that men had privileged access to treatment in places where it was offered under a patient copay scheme [13,14]. Current programme statistics suggest the opposite gender disparity: nationally representative surveys from Africa consistently report higher female HIV Testing and Counseling (HTC) coverage rates [15], and a disproportionately large number of women are on ART compared with estimated need in both sexes [16,17]. Women are also less likely to enroll with advanced disease, and tend to have lower attrition and mortality rates following treatment initiation [17–21].

Methods

ALPHA Network study sites and data

Data for this study come from seven members of the Network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (http://alpha.lshtm.ac.uk/), located in six countries as shown in Fig. 1. ALPHA Network study sites cover populations ranging from 20 000 to 200 000 in size. With the exception of the Manicaland study (wherein the individuals consist of residents in a set of eight noncontiguous areas chosen to represent distinct socioeconomic zones), the surveillance sites exhaustively cover the entire population of a circumscribed area. Demographic information is collected through regular censuses, generally conducted as

Fig. 1. Location of the ALPHA Network sites contributing data to this study. We use location names to refer to the study sites. Other names are sometimes used for Kisesa (Magu Demographic Surveillance System), Kisumu (Kenya Medical Research Institute/Centers for Disease Control and Prevention, KEMRI/CDC HDSS), Masaka (General Population Cohort in the Kyamulibwa sub-district), and uMkhanyakude (Africa Centre Demographic Information System, ACDIS).

interviews with a senior household member who acts as a proxy respondent on behalf of the whole household. Prepopulated lists of household members from the last census round are used by the fieldworker to inquire about the residency and survival status of all household residents. In Karonga, village informants assist with the demographic surveillance [22]. The size of the study sites and the intervals at which demographic surveillance is carried out vary across sites and have a bearing on the range of analyses possible with each site's data and the precision of the resulting estimates.

Along with the demographic surveillance, all ALPHA members organize post-mortem interviews with relatives of deceased residents (verbal autopsies) and repeated population-based HIV serosurveys, either via home visits or mobile HIV testing centers to which residents are invited. HIV testing protocols and participation rates have varied over time and between sites. Prior to the availability of rapid HIV tests and treatment, residents were often referred to a medical facility in the vicinity for the return of their test results, or directed to a separate testing and counseling service. In recent serosurveys, most ALPHA Network studies give residents the opportunity to receive standard HTC in the same visit that specimens for a research test are collected. The serosurveys also use individual interviews to collect behavioral data, including information about utilization of HIV and AIDS care services.

The demographic surveillance data used in this study are continuously updated – the dataset used in this analysis was assembled in September 2014, spans the period 2000–2011, and thus covers several years before and after the introduction of ART. Several study sites started HIV surveys later than the demographic surveillance, so their HIV status information is restricted to a narrower time span. The date ranges used for overall mortality estimates and mortality estimates by HIV status are stipulated for each study site in the first column of Table 1. Most ALPHA Network members have published cohort profiles with detailed descriptions of the population characteristics and fieldwork procedures [22–25], and in some cases also methodological studies describing the HIV serosurveys, nonresponse rates, and associated bias in HIV prevalence estimates [26,27].

Our measure of exposure time for the risk of dying comes from the residence episodes of men and women in the

Table 1. Site-specific characteristics of the study populations, and HIV+/HIV− mortality rate ratios.

Study site, country		Individuals, person-years and deaths by HIV status				Mortality rates and RR			
						2000–2003		2009–2011	
Dates, all-cause mortality Dates, mortality by HIV	Average HIV%[a]	HIV status	Individuals (ages 15–64)	Person-years	Deaths	Death rate (per 1000)	HIV+/HIV− RR (95% CI)	Death rate (per 1000)	HIV+/HIV− RR (95% CI)
Karonga, MAW	11.3	All	30 397	144 479	1486	14.6	ND	7.6	3.9
2003–2011		HIV−	17 156	47 204	230	ND		5.3	(3.0–5.1)
2006–2011		HIV+	1761	5320	149	ND		20.8	
		HIV unknown[b]	29 384	91 955	1107	ND		10.8	
Kisesa, TAZ	5.9	All	45 540	171 619	1791	12.5	8.4	8.0	5.3
2000–2011		HIV−	18 192	82 108	697	9.1	(6.7–10.7)	7.0	(3.8–7.3)
2000–2011		HIV+	1507	4750	275	76.9		36.9	
		HIV unknown[b]	40 018	84 761	819	12.3		7.4	
Kisumu, KEN	24.6	All	229 177	901 590	17 289	25.6	ND	15.0	2.6
2003–2011		HIV−	68 128	110 874	1369	ND		12.4	(2.4–2.8)
2008–2011		HIV+	13 901	32 153	1752	ND		32.3	
		HIV unknown[b]	222 641	758 564	14 168	ND		14.3	
Manicaland, ZIM	21.9	All	67 225	319 384	3908	16.8	12.3	7.2	6.5
2000–2010		HIV−	28 330	99 621	579	4.7	(10.1–15.1)	4.3	(5.0–8.6)
2000–2010		HIV+	6604	29 861	1406	58.5		28.1	
		HIV unknown[b]	59 060	189 903	1923	16.8		5.7	
Masaka, UGA	9.4	All	21 999	105 860	1412	16.4	8.5	10.7	2.6
2000–2011		HIV−	17 342	81 138	772	10.6	(7–10.2)	8.6	(1.9–3.6)
2000–2011		HIV+	1873	7753	390	90.0		22.7	
		HIV unknown[b]	11 221	16 970	250	14.1		14.9	
Rakai, UGA	12.5	All	67 909	296 723	3668	16.9	21.2	9.2	6.6
2000–2010		HIV−	34 331	148 308	559	4.5	(18.2–24.6)	3.4	(5.0–8.8)
2000–2010		HIV+	5538	20 493	1210	96.2		22.5	
		HIV unknown[b]	59 194	127 922	1899	18.5		13.8	
uMkhanyakude, RSA	35.4	All	88 230	467 619	9560	22.7	9.5	16.4	2.4
2001–2011		HIV−	26 294	76 450	791	7.4	(4.4–20.6)	15.1	(2.1–2.7)
2004–2011		HIV+	12 314	37 565	1711	69.9		36.0	
		HIV unknown[b]	87 791	353 603	7058	22.7		11.5	
Total	18.5	All	550 477	2407,275	39 114	19.4	11.6	12.9	3.3
		HIV−	209 773	645 704	4997	6.7	(10.7–12.7)	9.5	(3.1–3.5)
		HIV+	43 498	137 894	6893	77.8		31.6	
		HIV unknown[b]	509 309	1623 677	27 224	21.0		12.2	

CI, confidence interval; KEN, Kenya; MAW, Malawi; ND, no data; RR, rate ratio; RSA, South Africa; TAZ, Tanzania; UGA, Uganda; ZIM, Zimbabwe.
[a]Average HIV prevalence = HIV+ person-years/(HIV+ person-years + HIV− person-years). These prevalence estimates are relatively high because we include HIV status information from medical facilities and treatment clinics, which increases the fraction of known HIV positives in our dataset.
[b]HIV unknown includes all the persons-years of exposure before the start of the HIV surveillance in the study site, and individual time prior to first HIV test.

study areas, and the nature of the terminating events of residence episodes (administrative censoring, death, or migration). HIV status information comes from community-based serological surveys, supplemented by self-reports, proxy reports in post-mortem interviews, and from record-linkage with health facilities used by residents. The latter is also an important source for retrieving data on the uptake of treatment. A few of the ALPHA Network members have established reliable record linkage between the demographic surveillance and medical facility data with unique identifiers common to individuals in clinic and community records (e.g., Karonga, Masaka, and uMkhanyakude), whereas others (e.g., Kisumu) have piloted probabilistic record linkage. To allocate person-time to HIV status and treatment categories, we adopted a set of rules for censoring HIV status and service use information. Individuals with a report of an HIV-negative followed by an HIV-positive test are assumed to have seroconverted at the midpoint between the last negative and first positive test dates, and allocate HIV-positive and HIV-negative exposure time accordingly. Persons who are HIV positive at the time of their first HIV test have all their observed exposure time following the test classified as HIV positive. To calculate mortality of HIV-negative individuals who remain uninfected throughout the study, we classify all their exposure time between tests as HIV negative. Following their last negative test, they are classified as HIV negative for a period of time corresponding to the 95% probability of their age group remaining uninfected given the site and sex-specific HIV incidence rates. Following that cut-off point, their HIV status is considered unknown. Time lived by individuals prior to the first recorded HIV test is also classified as HIV status unknown. We classify individuals as having received ART from the date on which they were first recorded as receiving treatment. No attempt is made to account for treatment adherence, interruption, or cessation.

Statistical methods

We first present trends in the all-cause mortality rates of adults aged 15–64 by sex, HIV status, and treatment status. This is followed by parametric survival analysis of the mortality hazards in HIV positives, whereby individual age (radix at exact age 15) serves as a measure of time. Among several possible distributions of the outcome, the Weibull model, which describes mortality patterns that increase steadily with age, was chosen on the basis of Akaike's Information Criterion, a statistic that values both model fit and efficiency. Hazard ratio estimates from the Weibull models are not qualitatively different from semiparametric survival analysis, which supports our choice for the Weibull distribution. Under the proportional hazards specification of the Weibull model and given a set of covariates, X_j, the age-specific mortality hazard is given by:

$$h(age_t|X_j = pt^{p-1}\exp(\beta_0 + X_j\beta_X)$$

where p represents the change in mortality by age. In this application, we expect $p > 1$, which implies that the hazard is monotone increasing with age.

As covariates, we consider calendar year, sex, and the interaction between both. To investigate changes in the mortality of HIV positives following the introduction of ART, we fit separate models for the pre-ART and post-ART period, whereby the coefficients for calendar year quantify the impact of ART as the average annual change in the mortality hazard of HIV-positive adults. In the post-ART period, we also allow the mortality rates for HIV-positive men and women to differ by their treatment status. The representation of calendar time is made using two dichotomous variables: one that captures the period in which treatment started to become locally available, and one for subsequent years. This distinction is made because the first year(s) of treatment rollout may feature uncharacteristically high-mortality rates as a backlog of patients with severe immunosuppression are quickly ushered onto treatment. The case of Kisumu is special because ART was introduced in 2007, but service provision was severely affected by the violence that started after the presidential elections of 27 December and lasted until a truce was signed on 28 February 2008 [28]. Kisumu was one of the areas heavily implicated in the protests against the ruling government and some excess mortality may be associated with the protest itself.

Given declining incidence trends observed in some surveys, and expected increases in longevity because of treatment, there is a general lengthening of the duration postinfection among PLHIV in the post-ART period. However, the known seroconverters for whom duration post infection can be measured constitute less than 12% of PLHIV in the pooled dataset, so it is not practical to introduce duration postinfection as another metric of exposure.

Results

The pooled dataset contains 550477 individuals between exact ages 15 and 65 (43498 with a known HIV positive status), who jointly contribute 2.4 million person-years of follow up time, and 39114 deaths (6893 to PLHIV). A site-specific breakdown of these statistics is given in Table 1. This table also contains crude mortality rates and the rate ratios for HIV-positive over HIV-negative mortality for the period 2000–2003, when ART was not yet available in any of the sites, and for the period 2009–2011, when ART was locally available in all of the study sites. These provide an indication of the mortality reductions that have taken place since the rollout of ART. In the early 2000s, the HIV+/HIV− mortality rate ratios varied between 8.4 [Kisesa, 95% confidence interval (CI): 6.7–10.7] and 21.2 (Rakai, 95% CI: 18.2–24.6).

Between 2009 and 2011, these rate ratios ranged from 2.4 (uMkhanyakude, 95% CI: 2.1–2.7) to 6.6 (Rakai, 95% CI: 5.0–8.8).

Figures 2 and 3 provide detailed descriptions of trends in mortality rates by HIV status and treatment status. The background shading in these illustration marks the years that ART was locally introduced (between 2004 and 2007, depending on the site), and the years wherein the rollout had been completed (between 2005 and 2009). In an online appendix, we present mortality estimates by study site, sex, HIV status, and selected calendar years in

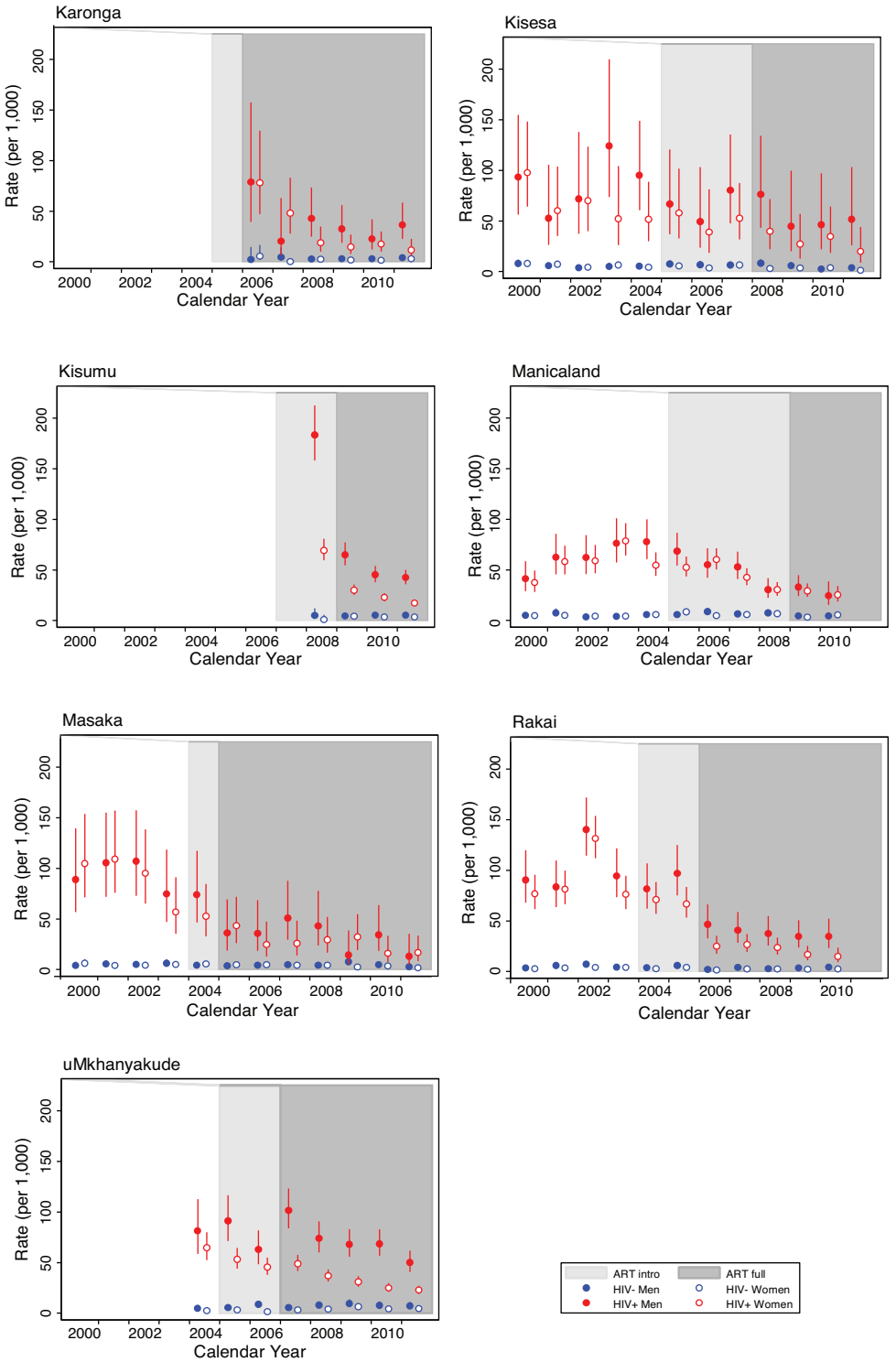

Fig. 2. All-cause death rates, and 95% confidence intervals, by study site, HIV status and sex (ages 15–64).

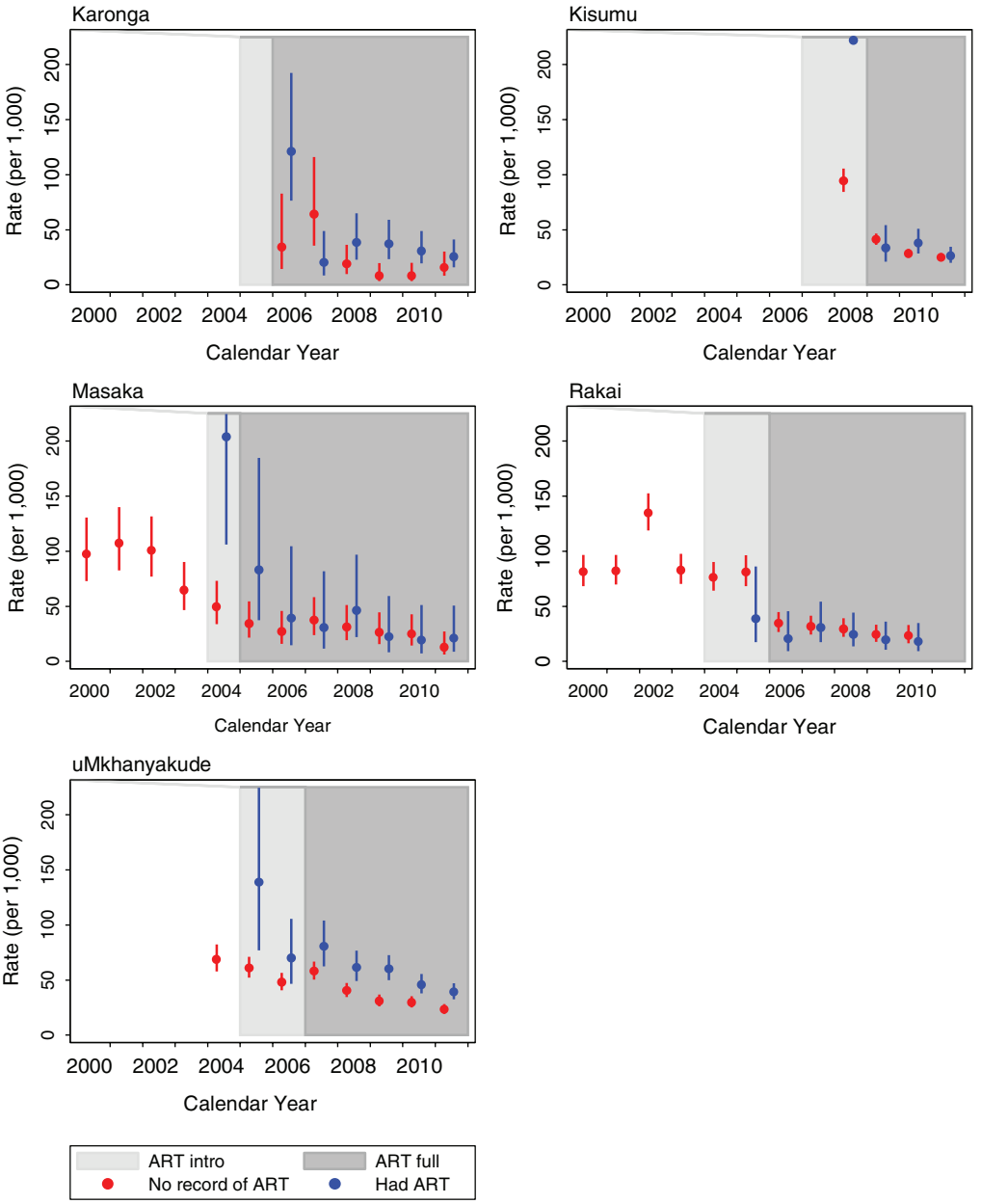

Fig. 3. All-cause death rates and 95% confidence intervals among PLHIV, by study site and treatment status (ages 15–64, both sexes). In a few instance, the estimates and confidence intervals have been truncated or modified to maintain the readability of the plots. This affects the following estimates: Kisumu, 2008, had ART: 528 (95% confidence interval (CI): 374–747); Masaka, 2004, had ART: 204 (95% CI: 106–392); and uMkhanyakude, 2005, had ART: 139 (95% CI: 77–251). Insufficient treatment uptake data in Kisesa and Manicaland to conduct this analysis.

table format (Table A.1, http://links.lww.com/QAD/A591), and also compare overall mortality with the mortality for men and women whose HIV status has not been measured in the study (Figure A.1, http://links.lww.com/QAD/A591). The latter demonstrates that mortality trends of men and women with an unknown HIV status closely match overall mortality trends, which suggest that there is no strong selection bias in HIV status information in our datasets. uMkhanyakude is the only site where the mortality rates of men and women with unknown HIV status are consistently different for a prolonged period of time. In this case, they are lower than the overall mortality rate suggesting that HIV-negative individuals are more likely to have an HIV status that is unknown to the study.

The mortality rates of HIV-positive men and women before the availability of treatment often exceeded 100 per thousand, without a clear upwards or downwards trend (Fig. 2). Modest mortality declines in the last year before the local introduction of ART are perhaps an exception. The latter is most clearly visible in the

illustration for Masaka. Mortality declines are much more pronounced in the period that ART was being rolled out to health facilities located in the study sites. Compared with the pre-ART years, total reductions in adult mortality exceed 58% in all study sites. The mortality rate for HIV-positive women in Masaka declined from 104.7 (95% CI: 71.3–153.8) in the year 2000 to 16.7 (95% CI: 8.4–33.4) in 2011, or, a total decline of 84% (Table A.1, http://links.lww.com/QAD/A591).

In 2011, all-cause death rates among HIV-positive women ranged from 11.7 (Karonga, 95% CI: 6.1–22.5) to 22.7 per thousand (uMkhanyakude, 95% CI: 19.1–27.1); the ones for men varied between 13.3 (Masaka, 95%–CI: 5.0–35.3) and 51.7 per thousand (Kisesa, 95%-CI: 25.8–103.3).

Rapid falls in the mortality of HIV positives have contributed to a decline in overall adult mortality rates. In 2003, these still ranged between 8.2 (Kisesa, 95% CI: 6.2–10.7) and 20.5 (Kisumu, 95% CI: 19.1–22.0) per thousand for women, and between 10.1 (Kisesa, 95% CI: 7.9–13.0) and 23.5 (uMkhanyakude, 95% CI: 21.1–26.1) per thousand for men. By 2011, adult female mortality rates ranged between 2.9 (Kisesa, 95% CI: 1.9–4.5) and 9.9 (uMkhanyakude, 95% CI: 8.7–11.3) per thousand. Male, adult death rates are now as low as 4.6 per thousand in Masaka (95% CI: 2.9–7.2). The highest observed value for men is 12.5 per thousand (uMkhanyakude, 95% CI: 10.9–14.4). The results presented in Fig. 2 and Table A.1, http://links.lww.com/QAD/A591 are not suggestive of clear trends in the mortality rates of HIV-negative individuals.

Figure 3 shows that there has been a decline in the mortality of HIV positives who ever started treatment, but also among PLHIV without a record of treatment initiation. The mortality rates of men and women who started ART is often very high during the first year(s) that ART became available in the study sites. In subsequent years, both the level and trend in mortality rates are comparable in the two treatment status categories. uMkhanyakude is the only study site with consistent and relatively large differences in the mortality of HIV positives with and without ART.

The assessment of trends in the mortality rates of HIV-positive men and women is extended in Table 2, which contains site-specific estimates of the mortality hazard ratios from parametric survival models. The auxiliary parameter of the Weibull model (p) captures the rising mortality risk with age. More pertinent for the current discussion is the change in age-adjusted mortality rates over time. Separate models fitted for the pre-ART and post-ART period indicate that age-adjusted mortality rates among PLHIV only started declining after the local introduction of ART (none of the hazard ratios for calendar year in the pre-ART period were significantly smaller than 1). The coefficients for the post-ART period are indicative of an average annual decline in the mortality hazard ranging from 13% in Kisesa (hazard ratio 0.87, 95% CI: 0.83–92) to 38% in Kisumu (hazard ratio 0.62, 95% CI: 0.59–0.65).

Pre-ART mortality rates among HIV positive men and women are comparable, but gender differences became more pronounced following the introduction of treatment. Gender differences are statistically significant in five out of seven study sites in the post-ART era (Karonga, Kisesa, Kisumu, Rakai, and uMkhanyakude), and the female advantage increases over time in two of the study sites (Rakai and uMkhanyakude) as shown by the interaction between sex and calendar year.

Table 2 also formalizes the comparison of adult mortality rates among HIV positives who initiated ART and HIV positives without a record of treatment. The mortality levels and trends in both groups are generally comparable, but the early years of local ART availability are an important exception. In three of the four study sites with available data, the mortality hazard is significantly elevated among patients who accessed treatment in the early rollout stages. The highest ratio of mortality hazards is observed in Kisumu (hazard ratio 6.23, 95% CI: 4.68–8.29). In later years, the mortality hazard in patients who ever started treatment is sometimes higher (e.g., uMkhanyakude), sometimes lower (e.g., Rakai), and often not significantly different (e.g., Kisumu and Masaka).

Discussion

Our results demonstrate the large impact of AIDS treatment programmes on adult mortality in eastern and southern Africa. In most study sites, the mortality of HIV positives had been relatively stable with some signs of a mortality decline just prior to the local introduction of ART. This decline could result from increased efforts to treat opportunistic infections, or, from patients receiving treatment at medical facilities outside of the actual study sites. However, the local rollout of ART had a much more sizable and sustained effect. All study sites have witnessed average annual reductions in the mortality hazards of HIV-positive adults in excess of 10% ever since, and total mortality declines following the expansion of ART vary between 58 and 84%. The largest mortality reduction has been recorded in Kisumu, but its mortality rates for 2008, the year following the introduction of ART, were exceptionally high and probably associated with the postelectoral violence and interruption of medical services. Despite the strong mortality reductions among PLHIV in all study sites, the morality rates of HIV-positive adults are still between 2.4 and 6.6 times higher than those of HIV negatives (both sexes combined), which underlines that there is still much room for improving ART coverage and impact.

Table 2. All-cause mortality in HIV-positive individuals, hazard ratios and 95% confidence interval (Weibull regression).

Study site – Country code	Karonga – MAW	Kisesa – TAZ	Kisumu – KEN	Manicaland – ZIM	Masaka – UGA	Rakai – UGA	uMkhanyakude – RSA
Pre-ART period		2000–2004		2000–2004	2000–2003	2000–2003	2004
Calendar year (annual change)	ND	0.95 (0.84–1.06)	ND	1.09 (1.03–1.16)	0.88 (0.78–1.00)	1.05 (0.98–1.13)	ND
Women (ref.)							
Male	ND	1.16 (0.82–1.63)	ND	1.03 (0.87–1.22)	0.98 (0.73–1.31)	1.01 (0.86–1.19)	ND
Interaction: male x calendar year	ND	NS	ND	NS	NS	NS	ND
p (age)	ND	2.39 (1.85–3.09)	ND	2.15 (1.84–2.51)	1.64 (1.18–2.26)	1.79 (1.48–2.15)	ND
N		868		4029	927	3175	
Deaths		133		583	188	665	
Post-ART period	2006–2011	2005–2011	2008–2011	2005–2010	2004–2011	2004–2010	2005–2011
Calendar year (annual change)	0.86 (0.75–0.99)	0.87 (0.83–0.92)	0.62 (0.59–0.65)	0.85 (0.83–0.87)	0.80 (0.76–0.84)	0.75 (0.72–0.78)	0.83 (0.80–0.85)
Women (ref.)							
Men	1.66 (1.14–2.41)	1.29 (1.01–1.65)	2.14 (1.92–2.39)	1.03 (0.93–1.15)	1.09 (0.88–1.34)	0.99 (0.86–1.15)	1.16 (0.90–1.48)
Interaction: male x calendar year	NS	NS	NS	NS	NS	1.11 (1.05–1.18)	1.09 (1.04–1.14)
No record of ART (ref.)							
Had ART – early	ND	ND	6.23 (4.68–8.29)	ND	3.11 (1.60–6.04)	0.58 (0.26–1.29)	1.93 (1.06–3.51)
Had ART – late	1.78 (1.20–2.65)	ND	1.07 (0.87–1.30)	ND	1.20 (0.81–1.77)	0.67 (0.49–0.91)	1.39 (1.24–1.56)
p (age)	1.72 (1.09–2.72)	2.19 (1.79–2.69)	1.43 (1.25–1.63)	2.06 (1.86–2.29)	1.57 (1.23–2.01)	1.97 (1.73–2.23)	2.15 (1.98–2.34)
N	1672	1488	13193	6824	1813	5535	12129
Deaths	111	266	1347	1406	358	1208	1633

Estimates from site-specific and period-specific regression models. The analysis of the pre-ART period is restricted to the study sites that conducted population-based HIV serosurveys before the local introduction of ART. Pre-ART years, where available, contribute to the analyses for the post-ART period but are all coded 0; starting with the year wherein ART was first made locally available, the following calendar years are coded with consecutive numbers. ART, antiretroviral therapy; KEN, Kenya; MAW, Malawi; ND, no data to estimate coefficient(s); ref., reference category; RSA, South Africa; TAZ, Tanzania; UGA, Uganda; ZIM, Zimbabwe.

Gender differences in the mortality rates of PLHIV only started to appear as treatment was being rolled out. The estimated mortality hazards for men are now significantly higher in five of the seven study sites and have been increasing over time in two of those five sites. Our results thus corroborate earlier findings that women have benefitted more from the expansion of treatment programmes, either through a higher uptake of ART, better treatment outcomes, or both. Despite the more successful engagement of women in HIV care and treatment programmes, it is premature to conclude that this has created a new gender disparity whereby men are most disadvantaged. First, it is unclear whether the larger mortality reductions among HIV-positive women have reversed the burden of HIV in terms of the life years lost to HIV. Second, a lower uptake of treatment among men could imply that their female partners will not be as well protected against infection as the male partners of HIV-positive women. In other words, gender disparities in the utilization of HIV services may sustain previously observed gender disparities in the number of new infections, which have generally been higher in women.

In most of the study sites, the mortality trend of PLHIV who started ART is comparable with the trend of those not (yet) on treatment. This is a good indication that programmes are increasingly successful in ensuring timely transitions along the cascade of HIV care and treatment: as PLHIV initiate treatment earlier, treatment failures are reduced, but importantly, pretreatment mortality also declines as those with advanced disease are selected onto treatment, leaving an increasingly healthy not-on-ART population. Other factors, such as changes in treatment eligibility criteria and the availability of better drugs, will complement or enhance this pattern. Despite broad similarities in the mortality trends of PLHIV who have and have not initiated treatment, there are a couple of notable differences. First, the mortality of PLHIV on treatment during the rollout phase was generally much higher, probably because PLHIV who began treatment as soon as it became locally available had advanced disease progression at the time of initiation. Second, there are a couple of sites, uMkhanyakude and to a lesser extent Karonga, where the mortality of PLHIV who started ART continues to be higher than among those for whom we do not have a record of treatment initiation. This may indicate either that linkage to care is more efficient in these settings (lowering pretreatment mortality), or that mortality following treatment initiation is higher for other reasons.

The population perspective offered by the ALPHA Network data is an invaluable attribute for studying the impact of treatment scale-up in the region, but the close monitoring of HIV status, services uptake and vital events is only practically feasible in relatively small populations, and these come with their own limitations. An often-cited drawback of demographic surveillance sites is their lack of generalizability, but the consistency of findings across study sites strengthens our belief that results are not driven by the particularities of each study site (including variations in data collection protocols). Small populations are typically also affected by high levels of mobility in and out of the study sites, and previous work has demonstrated its association with HIV status [29–31]. How these relationships may have changed following the expansion of treatment programmes is not clear, and we reserve this subject for future inquiry.

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Conflicts of interest

There are no conflicts of interest.

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