Age-specific mortality patterns in HIV-infected individuals: a comparative analysis of African community study data

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Objectives: Describe age-specific mortality patterns of HIV-infected adults in African communities before introduction of HAART.

Methods: Mortality data (deaths and person-years observed) for HIV-positive subjects aged 15–65 from six African community studies in five different countries were pooled, combining information from 1793 seroconverters and 8534 HIV positive when first tested. Age-specific mortality hazards were modelled using parametric regression based on the Weibull distribution, to investigate effects of sex, and site-specific measures of mean age at incidence, crude mortality rate of uninfected, and measures of epidemic maturity.

Results: The combined studies yielded a total of 31 777 person-years of observation for HIV-positive subjects, during which time 2602 deaths were recorded. Mortality rates rose almost linearly with age, from below 50/1000 at ages < 20 years, up to 150/1000 at 50 years +. There was no significant difference between men and women in level or age pattern of mortality. Weibull regression analysis suggested that intersite variation could be explained by HIV prevalence trend, and by the ratio of HIV proportional mortality to current HIV prevalence. A model representation was constructed with a common age pattern of mortality, but allowing the level to be adjusted by specifying HIV prevalence indicators.

Conclusion: The linear age trend of mortality in HIV-infected populations was satisfactorily represented by a Weibull function providing a parametric model adaptable for representing different levels of HIV-related mortality. This model might be simpler to use in demographic projections of HIV-affected populations than models based on survival post-infection.

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Introduction

Worldwide concern about HIV/AIDS stems from its devastating impact on mortality, but direct information on HIV mortality is very incomplete; official publications give far more information on proportions of living people infected with HIV than on proportions of deaths attributable to HIV, or about the age pattern of HIV deaths, although estimates are often provided about the impact of HIV on life expectancy [1,2]. Cohort studies

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contributing material to this volume have focussed on analysing proportions surviving post-infection, to facilitate comparisons independent of population structure and epidemic maturity, and to provide input for models and projections of epidemic spread [3,4]. Information on age-specific mortality among the HIV-infected is, however, of interest in its own right, as a measure of the demographic impact of the epidemic. It also has important practical advantages over survival data when it comes to measurement. First, it does not require the identification of seroconverters as it is only necessary to know the current HIV status of the dead and those exposed to risk. Second, it does not take as long to collect, because it is not necessary to follow seroconverters over long periods of time. Third, much smaller overall sample sizes are required to ascertain mortality rates reasonably accurately, as total numbers of HIV-infected individuals in the study populations are much larger than the numbers of identified seroconverters.

Robust model schedules of age-specific mortality among the HIV-infected would constitute a useful additional tool for demographic projection, allowing the development of projection packages based on knowledge of time series estimates of age-specific HIV prevalence. This would represent a simplification of currently used methods that require knowledge of age-specific HIV incidence schedules (which cannot usually be observed directly) and computer programs that track individuals by age and time since infection [4].

This paper introduces a theoretical discussion of indicators that could be used to measure epidemic maturity, because such measures are required as inputs into a statistical model of age-specific HIV mortality. The Methods section deals with strategies employed for pooling data from the different sites, and explains the statistical methodology. The Results section describes the data, including comparisons between sites, presents the statistical analysis, and shows how closely the final model fits the site-specific data. The Discussion touches on the applications of this model in demographic and epidemiological projections.

Theoretical justification for the statistical model

As the mortality of seroconverters is known to increase with the time since infection [5,6], the mortality of infected individuals should be higher, overall, in a mature epidemic than in one that is just unfolding, because the proportion of individuals infected for a long time must be higher in the former. This proportion is expected to be particularly high in a population that is experiencing declining prevalence as a result of deaths of HIV-infected individuals exceeding new infections.

These relationships are illustrated in Figure 1, a chart based on a projection of the natural course of the HIV epidemic made using the UNAIDS estimation and projection package (EPP) model [3]. The proportionate rate of change of prevalence is defined by:

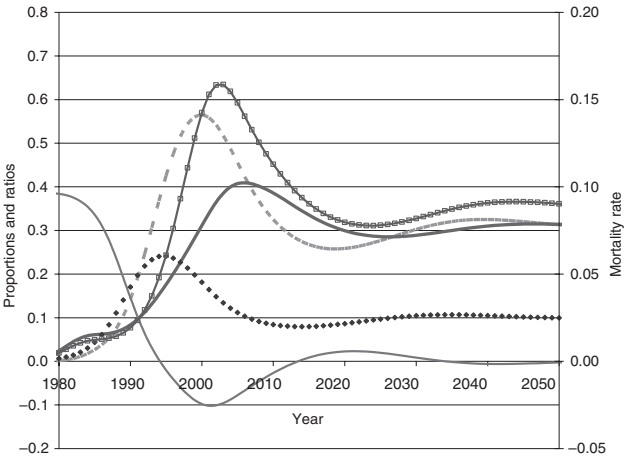

Fig. 1. Theoretical relationships between HIV prevalence and mortality indicators. The dead/living HIV prevalence ratio is scaled by a factor of 1/10 so it can be plotted on the left-hand axis with other indicators. ◆ Prevalence of HIV; - - proportional HIV mortality; ——— dead/living HIV prevalence ratio; ——— rate of change of HIV prevalence; —▫— mortality rate of HIV-infected individuals.

$$\frac{1}{\bar{p}} \cdot \frac{\Delta p}{\Delta t}$$

where Δp is the change in prevalence, Δt is the time interval, and $\bar{p}$ is the mean prevalence in the interval. This attains its minimum (negative) value at the time that mortality peaks. The way that these two curves mirror each other suggests that the negative value of the rate of change of prevalence could be used to predict the mortality rate among the infected. The relationship is not proportionate or even linear, however, because a long-term zero rate of prevalence change (from 2030 onwards, when prevalence reaches an endemic equilibrium) corresponds to a non-zero mortality rate among those infected with HIV, which is very different from the HIV-infected mortality rate in 1994, which also coincides with a zero prevalence change rate (corresponding to the local maximum of the prevalence curve).

Proportional HIV mortality, $d = \frac{D_i}{D}$

(deaths among those infected with HIV, D_i, as a proportion of all deaths, D) follows a similar time pattern to the HIV mortality rate [7], which typically lags proportional mortality by a few years. Proportional mortality cannot, however, be used as a predictor of mortality of HIV-infected individuals across different populations, because it clearly depends on epidemic scale: epidemics with higher prevalence levels would produce higher proportional mortality, but not necessarily higher levels of mortality among those infected with HIV. A

possible 'scale-free' predictor of mortality among the HIV-infected is the ratio, *r*, of HIV proportional mortality to HIV prevalence (the ratio of prevalence among the dead to prevalence among the living).

$$r = \frac{d}{p}$$

This curve is also shown in Figure 1, it lags the HIV-infected mortality curve by approximately 3 years.

The EPP model represents crude patterns, it does not account for age and sex-specific factors, which might be expected to influence mortality patterns and levels among the HIV positive. In real populations, we would also expect differences as a result of uneven rates of epidemic growth and decline, especially decline caused by successful preventative strategies. The prevalence peak in the illustrative example in Figure 1 is only caused by the lag between infection and death, corresponding to the mean survival time after infection, which is a variable input parameter of the EPP model. The possibility of modelling and thereby predicting age-specific HIV mortality patterns and levels in real populations without tracking individuals from the point at which they become infected needs to be investigated in real populations with good data on HIV mortality.

This paper compares age-specific mortality rates among HIV-infected individuals in six African population-based cohort studies. Following from the above theoretical consideration of the expected relationships between mortality patterns and epidemic maturity, it proposes a data-based regression model that will allow the prediction of mortality rates by age among the HIV-infected in populations without access to antiretroviral therapy (ART). Such mortality estimates should provide a useful baseline against which to measure the future impact of ART.

Methods

Data sources

Six member sites of the ALPHA network [8] provided data on sex, date of birth, date of entry into observation, date of exit from observation, and dates of HIV tests for all members of their study population. Associated with these dates was information on method of entry (baseline interview, birth or in-migration); method of exit (censored at end of study, death, out-migration or loss to follow-up); and results of HIV tests. Each site also reported when ART became available in their study area. Further information on fieldwork methods used in each site is available from past publications and site-specific papers in this volume [9–19].

To compare mortality across sites, data were left truncated at the later of (age 15 years, date of the first HIV test); and right censored at the earlier of (age 65 years, start of the year in which ART became available in the study community, age left study site). ART was available from 2004 in the Uganda studies, and 2005 in the Tanzanian and Malawi studies. The graphs show estimates of mortality rates for consecutive single-year age ranges in which the numbers at risk are over 10. This limits the display of data over the age of 55 years, but in two studies (Manicaland and Karonga) data for those under 20 years of age are also curtailed. All the data were used in regression analyses and in characterising individuals as HIV-infected or uninfected. Seroconverters contribute data on deaths and person-years at risk to the HIV-infected population after their first HIV-positive test. They also contribute data on person-years at risk to the HIV-negative population before their last negative test, and are censored during the interval between the last negative and the first positive test.

Data on those who were not infected (or not yet infected) are used to calculate annual time series of HIV prevalence estimates, and to derive indicators and explanatory variables at site level. Four studies (Karonga, Kisesa, Masaka and Rakai) had data spanning 10 years or more; for those sites a dividing year was chosen that approximately split the total person-years exposure of the HIV-infected into equal groups, and separate estimates were made for the early and late time periods for those studies. This enabled us to characterise time periods more accurately in sites experiencing changes in prevalence trend.

For each time interval the following outcome statistics and indicators were calculated: 5-year age-specific mortality rates for the HIV-infected, crude death rate among those not infected with HIV, HIV proportional mortality (equals deaths of HIV-infected individuals as a fraction of all deaths), average period prevalence, percentage rate of change of prevalence (slope of annual prevalence estimates/average period prevalence), and mean age at HIV infection. All the indicators and outcome statistics were calculated separately for men and women. Period prevalence is defined as the person-years lived by HIV-infected as a fraction of total person-years lived by individuals of known HIV status, and refers to ages 15–65 years.

Some of the indicators could not be measured for Karonga, as data from Karonga are based on a retrospective cohort [9] unlike the data from the other studies that are prospective. Briefly, the retrospective cohort was formed by selecting all individuals with an HIV-positive sample from blood tests during two community-wide surveys in the 1980s, each with two matched initially HIV-negative controls. Survivors from these individuals were followed up again with HIV tests in the late 1990s, and their subsequent survival has been monitored. The

data on mortality of HIV-positive individuals can be treated in the same way as those from the prospective studies; however, to obtain the indicators based on prevalence and incidence statistics, it was not possible to use the data on HIV-negative controls. Period prevalence estimates were taken from published modelling work for that study [20].

Each study site was covered by ethical approval from its national regulatory authority. Data sharing between sites was covered by the ALPHA network data sharing agreement [8].

Statistical analysis and modelling

Statistical analyses were carried out using Stata version 9 (Stata Corp., College Station, Texas, USA). Allowance was made for clustering at the study level when calculating standard errors. Graphical results are shown using smoothed hazard curves (using a Gaussian function and band-width of 3 years) rather than 5-year age-specific mortality rate estimates, to aid comparisons across sites and to emphasise the overall trend with age. Observed and predicted 5-year age-specific mortality rates are used to examine the goodness of fit of the regression models.

Mortality was analysed on a natural age scale. After examining various parametric forms to represent the age pattern of mortality variation, the Weibull was selected as fitting the age pattern most closely. A multi-level regression model was constructed using individual-level predictor variables (sex, age and time period in which individual exposure occurred) and population level variables (study site, mean age at infection, mortality rate among the uninfected, HIV prevalence trend, and ratio of HIV prevalence among those who died to prevalence among the living). A combination of population-level predictor variables was sought whereby the addition of study site would not significantly increase the likelihood ratio.

Results

Numbers at risk and crude rates

Data on 10 327 eligible individuals from six studies were available for analysis, representing 31 777 years of follow-up, during which 2602 deaths were observed (Table 1). The average individual follow-up time was 3.1 years, ranging from 1.6 years in Hlabisa to 6.9 years for Karonga. Approximately 20% of the observation time was contributed by individuals who seroconverted while under observation in the studies, with Karonga, Kisesa and Masaka having over 30% of their data contributed by known seroconverters, whereas the newer studies (Hlabisa and Manicaland) had under 10% of their data from the follow-up of newly infected. Time between the last negative and the first positive test was over 4 years for 88% of the seroconverters in Karonga, and 29% of seroconverters in Kisesa, and less than 20% in other studies.

Table 1. HIV-infected individuals by site and infection history, with observed deaths, person-years of follow-up and crude death rates.

	Masaka 1989–2003	Rakai 1991–2003	Kisesa 1994–2004	Karonga 1985–2004	Manicaland 1998–2006	Hlabisa 2003–2006
Individuals						
Seroconverters	369	487	404	67	294	172
Seroprevalent	1089	2075	1006	166	1489	2709
All infected individuals	1458	2562	1410	233	1783	2881
Deaths						
Seroconverters	100	66	44	24	8	2
Seroprevalent	491	945	192	102	416	212
All infected individuals	591	1011	236	126	424	214
Person-years						
Seroconverters	1823[a]	1782[b]	1548[c]	508[d]	666	256
Seroprevalent	3595	7541	2702	1103	5779	4467
All infected individuals	5425	9323	4250	1611	6445	4723
Crude mortality rates with 95% CL						
Seroconverters	0.055	0.037	0.028	0.047	0.012	0.008
	0.046–0.065	0.030–0.047	0.022–0.038	0.032–0.070	0.006–0.027	0.002–0.077
Seroprevalent	0.137	0.125	0.071	0.093	0.072	0.047
	0.125–0.149	0.118–0.133	0.062–0.082	0.076–0.112	0.065–0.079	0.042–0.054
All infected individuals	0.109	0.108	0.056	0.078	0.066	0.045
	0.101–0.118	0.102–0.115	0.049–0.063	0.066–0.093	0.060–0.072	0.040–0.052
Uninfected individuals	0.009	0.006	0.006	0.011	0.006	0.003
	0.009–0.010	0.005–0.006	0.006–0.007	0.008–0.014	0.005–0.007	0.003–0.004
Ratio of death rates Infected/uninfected	12.1	18.0	9.3	7.1	11.0	15.0

CL, Confidence limit.
[a]Includes estimates for 76 seroconverters (21%) with seroconversion interval greater than 4 years.
[b]Includes estimates for 58 seroconverters (12%) with seroconversion interval greater than 4 years.
[c]Includes estimates for 116 seroconverters (29%) with seroconversion interval greater than 4 years.
[d]Includes estimates for 59 seroconverters (88%) with seroconversion interval greater than 4 years.

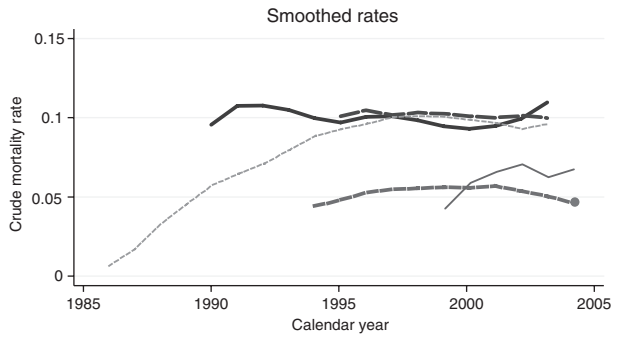

Fig. 2. Trends in crude mortality rate among HIV-infected, by site. ——— Masaka; – – – Rakai; - - - - Kisesa; ····· Karonga; ——— Manicaland; • Hlabisa.

The ratio of crude mortality rates in infected and uninfected individuals, ranged from seven in Karonga to 18 in Rakai. The overall mortality of prevalent cases was significantly higher (by a factor of approximately 2.5 in long running studies) than the mortality of seroconverters. Figure 2 shows the smoothed trends in crude death rate of all infected individuals by calendar year. In general the level was steady, although there was a clear rise over time in Karonga between 1985 and 1995, a slight increase in Manicaland before 2002, and a slight fall in Masaka in the early 1990s. In all studies the mean age of infected individuals rose steadily over time (by 3.8 years per decade, on average), and infected men were older than infected women (by 3.7 years, on average).

Explanatory variables

Variables thought to be associated with mortality differences between study sites or in the same study over time are shown in Table 2. Prevalence was highest in Manicaland and Hlabisa, and higher in women than men in all studies. The mean age at infection is younger in women than men, younger in Hlabisa than elsewhere, rose over time in Kisesa, but fell slightly in Masaka. The prevalence rate of change indicator is very high in Hlabisa and in Karonga between 1981 and 1995, and fairly high in Kisesa between 1994 and 1999. It is negative in Manicaland and in the Ugandan studies. The dead/living prevalence ratio has generally increased slightly over time in the long running studies, except for Kisesa where it fell sharply. The ratio is generally slightly higher among women than men.

Age-specific mortality and hazard comparisons

Age-specific mortality patterns (smoothed hazards) are shown in Figure 3a, for the HIV-infected of both sexes in each site, over the whole time period for which data were available. The sites fall into two groups: the two Ugandan sites, Rakai and Masaka, have higher overall mortality (and thus a more steeply rising age curve) than all the other sites. Up to approximately the age of 50 years, when small numbers under observation start to become a problem, the curves are remarkably linear. Some curves show a downturn at the oldest ages for which data are available; this is probably an artefact caused by decreasing numbers at risk coupled with boundary effects associated with the smoothing algorithm.

Table 2. Person-years of observation of HIV-infected at ages 15–65 years and characteristics of study populations.

Site and time period	Sex	Person-years of observation	Crude death rate of infected	Crude death rate for uninfected	Average period prevalence	Mean age at infection	Rate of change of prevalence	Dead/living prevalence ratio
Masaka								
1989–1996	Men	1255	0.106	0.011	7.1	34.4	−5.5	6.8
	Women	1585	0.095	0.010	8.3	28.6	−3.2	6.2
1997–2003	Men	1858	0.076	0.010	5.8	33.8	−4.2	7.1
	Women	2292	0.072	0.009	7.2	27.7	−3.9	6.3
Rakai								
1993–1998	Men	1845	0.117	0.008	13.3	31.8	−2.4	5.4
	Women	2965	0.101	0.005	17.6	30.1	−1.9	4.8
1999–2003	Men	2496	0.090	0.006	12.8	31.6	−1.6	5.8
	Women	3536	0.077	0.005	15.3	30.9	−3.9	5.1
Kisesa								
1994–1999	Men	945	0.048	0.004	5.1	30.1	8.3	9.1
	Women	1269	0.043	0.003	7.1	29.6	6.5	8.2
2000–2004	Men	1431	0.046	0.008	6.3	31.0	2.4	5.2
	Women	1817	0.039	0.009	7.3	31.1	−0.4	4.1
Karonga[a]								
1985–1993	Men	672	0.060	0.009	6.0[a]	35.0	14.3[a]	3.9[a]
	Women	1145	0.046	0.007	6.0[a]	30.1	14.3[a]	3.9[a]
1994–2004	Men	289	0.060	0.015	12.0[a]	35.8	0.0[a]	4.2[a]
	Women	571	0.061	0.015	12.0[a]	29.7	0.0[a]	4.2[a]
Manicaland								
1998–2006	Men	2620	0.065	0.006	22.0	31.9	−1.4	3.5
	Women	4485	0.057	0.006	24.7	30.0	−1.5	3.2
Hlabisa								
2003–2006	Men	1295	0.060	0.005	13.4	28.4	17.1	4.9
	Women	3548	0.038	0.002	25.1	26.2	15.9	3.5

[a]Prevalence statistics based on modelling results for Karonga [20].

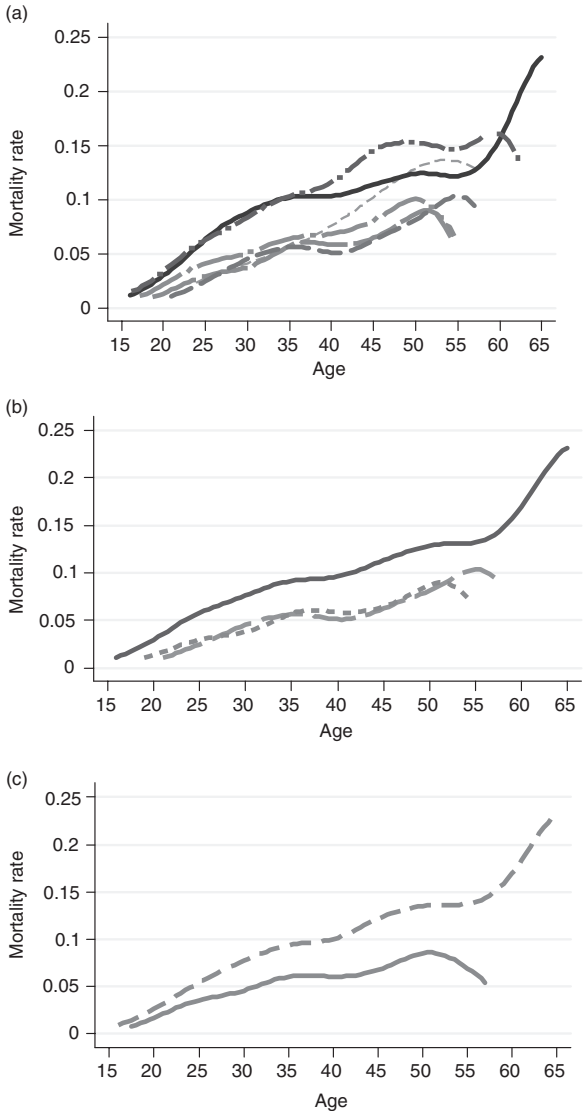

Fig. 3. Age-specific mortality patterns for HIV-infected, by study site. (a) By study site. ——— Masaka; —·—·— Rakai; – – – Kisesa; ------ Karonga; —·— Manicaland; —— Hlabisa. (b) By prevalence trend in subpopulation. ——— Declining; —— steady; ------ increasing. (c) By ratio of dead to living prevalence. – – – 4 and over; ——— below 4.

Using the pooled dataset, (broken down by sex and time period), but excluding Karonga from the analysis, hazard ratios were compared. Compared with Masaka the mortality hazard was slightly greater in Rakai [hazard ratio (HR) 1.09, 95% confidence interval (CI) 0.99–1.22], but was 35–50% lower in the other sites with a hazard ratio of 0.52 (95% CI 0.45–0.60) in Kisesa, 0.66 (95% CI 0.85–0.75) in Manicaland, and 0.53 (95% CI 0.45–0.62) in Hlabisa. Hazard ratios associated with individual-level variables: sex (HR 0.93, 95% CI 0.83–1.04) and time period (HR 0.98, 95% CI 0.72–1.34) were not significantly different from one; nor were two site-level variables: crude death rate among the uninfected (HR 1.16, 95% CI 0.80–1.67) or mean age at infection (HR 1.09, 95% CI 0.84–1.41). We have not illustrated the breakdowns for sex or other non-significant factors.

Combining sex and period-specific datasets (from Masaka, Rakai, Kisesa and Hlabisa men) in which the dead to living prevalence ratio exceeds 4, the mortality hazard is 65% higher (HR 1.65, 95% CI 1.28–2.13) than in datasets with lower ratios (Manicaland and Hlabisa women). Mortality in datasets with declining prevalence (Masaka, Rakai, Manicaland and Kisesa women in the later time period) is 68% higher (HR 1.68, 95% CI 1.27–2.22) than in datasets in which the prevalence is steady or rising (remaining Kisesa datasets and Hlabisa). These results are highly significant, and age-specific patterns for these categories are also illustrated, in Figures 3b and c. The curvature of the age-specific pattern (governed by the shape parameter) is not affected by controlling for (or stratifying by) any of these variables; the shape parameter is never significantly different from 2.34, the value observed when a Weibull model is fitted to the pooled dataset characterised only by the age of the individual.

Multi-level statistical analysis

When adjusting for declining prevalence trend and the ratio of dead to living prevalence, there are no significant changes between crude and adjusted hazard ratios or slope parameters. This analysis suggests that a reasonably discrete model for predicting mortality in the different study populations could be obtained using the declining prevalence trend and ratio of dead to living prevalence higher than 4. The actual (exponential) coefficients of the regression model are 0.49 (95% CI 0.32–0.67) for the declining prevalence trend indicator; 0.48 (0.35–0.61) for the ratio indicator. The constant in the regression is −9.02 (−9.71 to −8.34), and the shape parameter for the Weibull curve is 2.36 (2.23–2.50). This means that mortality at age a, $m(a)$ in the predictive model can be specified as:

$$m(a) = \phi\lambda a^{\phi-1} \text{ where } \phi = 2.36 \text{ and } \lambda \text{ is given by:}$$

$$\lambda = \exp\{-9.02 + 0.49|_{(\text{if prevalence is declining})} + 0.48|_{(\text{if ratio} > 4)}\}$$

Age-specific mortality rates generated by this model are illustrated in Figure 4.

As parameters for the two indicators are very similar, the model appears to have just three outcomes, the upper line corresponding to the situation in which prevalence is declining and the dead/living prevalence ratio is higher than 4, the two overlapping middle lines when only one of these two conditions is true, and the bottom line when neither is true. If we apply estimates from the model to the data from all six sites shown in Table 2, the upper line would model the mortality pattern for both time periods in the Uganda studies and women in Kisesa in the later

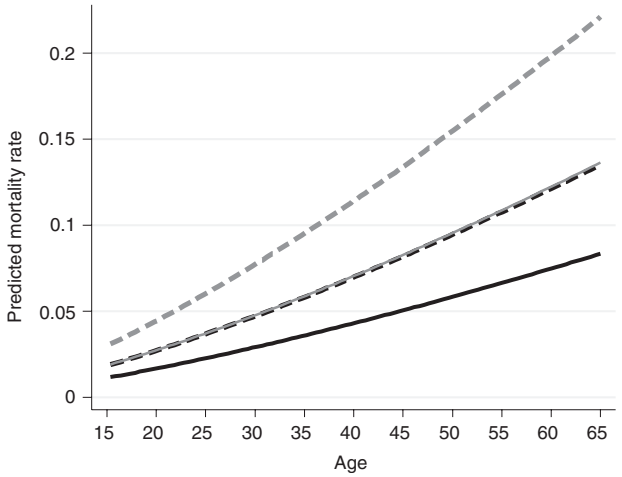

Fig. 4. Model age-specific mortality patterns based on prevalence trend and dead to living prevalence ratio. - - - - - Prevalence declining ratio exceeds 4; ——— prevalence declining ratio less than 4; **-----** prevalence rising/steady ratio exceeds 4; ——— prevalence rising/steady ratio less than 4.

period (2000–2004); the middle line would model the mortality pattern for all the other study episodes in Kisesa, Hlabisa and Manicaland, as well as the later period in Karonga. The early period in Karonga (1985–1993) for which indicator estimates were obtained from published modelling results [20], would have a mortality pattern represented by the lower line.

Figure 5 shows how closely the model mortality rates fit the actual data in the six sites. Each point on these graphs corresponds to a 5-year age group (for both sexes across the whole period of observation). No smoothing has been employed, but data points based on fewer than 10 individuals per year of observation are omitted. The panel for Karonga is an out-of-sample prediction, as it was not used in the regression fitting. The relatively poor fit of the model to the data for Masaka is mainly caused by the large difference between the observed mortality rate (0.13, 95% CI 0.08–0.20) and the model mortality rate (0.19) for the age group 55–59 years.

Discussion

Main findings

We have used empirical data on deaths of HIV-infected and uninfected individuals, and on HIV prevalence from six study sites, and calculated age and sex-specific mortality rates and simple parameters describing the epidemic dynamics, classified by sex, time period and site. The pooled mortality data were then analysed using a multi-level regression approach.

The analysis revealed strong regularities in age-specific patterns of mortality of HIV-infected individuals. In the Ugandan study sites, which experienced declining HIV prevalence, infected individuals have age-specific mortality rates up to twice as high as in study sites where HIV prevalence was still rising, or had recently stabilised. This was an expected finding, as at times of declining prevalence there are higher proportions of individuals infected for a relatively long time, and survival analysis has shown that HIV mortality increases steeply with the duration of infection [6,21]. The new and unexpected findings highlighted in the Results section, are the linear age patterns (seen in populations with increasing, stagnating and declining prevalence) and the similarity of age patterns in men and women, in spite of differences between the sexes in mean age at infection.

Full use has been made of data on the distribution of deaths and exposure to risk of dying by age among HIV-infected individuals from all the ALPHA network member studies, without confining attention to those with known seroconversion dates. This has increased the amount of data available for mortality analysis: between them, the six studies have almost four times as much data on prevalent cases (over 25 000 person-years of observation) compared with the follow-up of incident cases (approximately 6500 person-years). Even studies with short follow-up periods (Hlabisa and Manicaland), which have not yet accumulated data on the survival of seroconverters contributed data, enabling comparisons across a wider geographical area.

Critical appraisal of the statistical model

Karonga data could not be analysed in the same way as data from the other studies, although age-specific mortality rates for the infected population conformed to the general pattern. The number of infected individuals observed was small (233, only one-sixth of Kisesa, the next smallest site), but the long period of observation meant that their contribution in terms of person-years (1611) was large enough to avoid small number problems even after breaking down by sex, time period and 5-year age group. However, the design of the sample: a retrospective cohort based on individuals providing blood samples tested in the early 1980s, meant that the sample was not continually replenished by newly diagnosed infected individuals until after the follow-up survey performed in 1999. This would imply that the average time since infection in the Karonga dataset would be longer than in the other studies, and would get progressively longer over time, implying higher mortality in the closed cohort than might be expected based on indicators of prevalence trend and epidemic maturity. This explains the relatively poor fit of the out-of-sample prediction for Karonga, where model mortality rates are systematically lower than observed.

The fit of the model to the Masaka data at ages 55–59 years is less than satisfactory. The Weibull model (Fig. 4) predicts that mortality rates should rise steadily

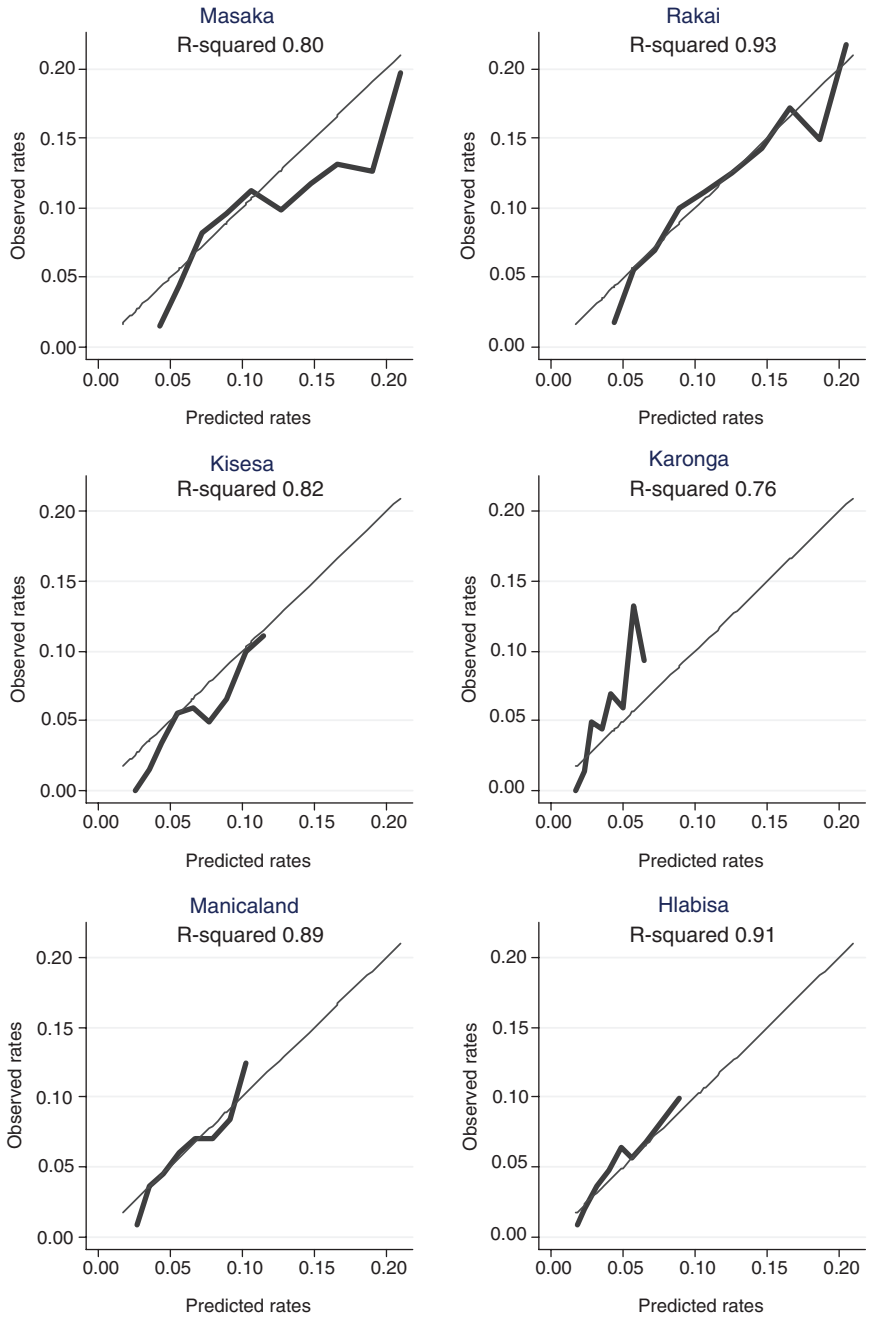

Fig. 5. Model fits to observed age-specific data by site (summary for both sexes over entire study period).

with age, with the mortality increase accelerating slightly at older ages, whereas the empirical data for Masaka (Fig. 3a) seem to indicate a dip around the age of 55 years, although there is a sharp rise after 60 years; so for the 60–64 years age group the model fits the data quite well.

The mean seroconversion interval in the Karonga dataset is 7.2 years, the mean interval in the Kisesa study is 3.6 years, in other studies the mean interval length is less than 3 years. Relatively long intervals between serological surveys, or high proportions of individuals not participating in every survey will mean that a relatively high proportion of seroconversions may not be detected at all, with the result that a significant number of infected individuals will be wrongly classified as uninfected. This will mean that period prevalence measures will be biased downwards and mortality estimates among the uninfected will be biased upwards. Mortality estimates for infected individuals will probably also be biased upward as those with a short duration of infection will be under-represented. The movement of infected individuals shortly before death (seeking treatment or care) could bias mortality rate estimates up (movement into the study area) or down (movement out).

Possible uses of the statistical model

The explanatory variables used in the regression model for age-specific mortality were the proportional rate of change in prevalence and the ratio of prevalence among the dead to prevalence in the living. A consideration of the theoretical behaviour of these indicators showed that the statistical relationship discovered in the data (a negative association between mortality level and prevalence change, and a positive association between mortality level and the ratio of proportional mortality to prevalence) is very much what would have been expected from their behaviour in long-term projections of the natural dynamics of the epidemic. This theoretical underpinning is important, because our observations mainly cover epidemics that are approaching or are just past their peak prevalence. Further empirical and modelling work would be needed to confirm that the associations found above, and the Weibull representation of age-specific mortality, are applicable to epidemics in their starting and endemic phases.

Given the differences in survival post-infection between African epidemics and those of Thailand and Haiti, described elsewhere in this volume [6], the statistical model described here is unlikely to give a useful representation of age-specific mortality outside of Africa. Nor should it be used to estimate the mortality of infected individuals in populations in which substantial numbers are already receiving ART treatment; the relationships for these populations would need to be investigated afresh.

Age at infection has repeatedly been shown to be a powerful determinant of survival post-infection [5,21], with those infected at young ages surviving longer, so it may seem surprising that it did not emerge as an important determinant of HIV age-specific mortality patterns. The explanation lies in the fact that for a fixed current age, an individual who seroconverted at a younger age will have been infected for longer than an older seroconverter, so that the advantage conferred by young age at infection will be balanced by a longer exposure to the virus. These counter-acting forces might balance out in the opposite way, so that other things being equal, a population with a younger pattern of age at infection would have higher age-specific mortality among its HIV-infected population. Compared with the effect of epidemic maturity and prevalence trend the population-level effect of the age pattern of infection would have a second-order effect on age-specific mortality among the infected, and will need to be investigated using a combination of techniques, including modelling and studies of mortality among individuals with reasonably accurately known dates of seroconversion.

The emphasis on measuring survival post-infection has meant that hitherto little attention has been devoted to developing this type of model which could make 'back of the envelope' estimates of expected deaths among infected individuals, required for planning the estimated need of ART, for example, a much simpler procedure. In many ways a continuous formulation would be more useful for such an application, allowing the model to be tailored more closely to observed prevalence trends in a population, but even a categorical model such as this, fitting the data for the six study sites could be used. Application of this model to demographic updates and projections of HIV-affected African populations using the census rounds of the 1990s as a baseline and HIV prevalence estimates based on antinatal clinic (ANC) surveillance should provide a useful test of its robustness and validity.

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