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Survival and mortality of people infected with HIV in low and middle income countries: results from the extended ALPHA network

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This supplement brings together analyses and papers from the ALPHA network, a collaboration aimed at maximizing the usefulness of data generated in community-based longitudinal HIV studies in sub-Saharan Africa [1]. The network organized a workshop in Entebbe, Uganda, in November 2006, to which additional cohort study sites from low and middle income countries in different regions of the world were invited. At this workshop, study sites presented their preliminary findings on survival and mortality, and discussed appropriate definitions and methods.

Published at a time when antiretroviral treatment (ART) is rapidly being scaled up in most low and middle income countries [2], this collection of papers represents a major collaborative effort to quantify and analyse the survival from HIV seroconversion to death in the absence of ART. The advent of effective treatment means it will not be possible to conduct any further studies of this nature in the future, so the results from these analyses together with a small number of previously published survival studies will serve as a baseline against which to assess the impact of ART in low and middle income countries. In addition, this new information is important for deriving parameters to model HIV epidemics.

Several papers examine the survival period from seroconversion to death, before ART became available in the study sites. Figure 1 shows the geographical spread of the study sites represented. Most of these studies were conducted in Africa, including three community-based studies in Kisesa, Tanzania [3], Rakai, Uganda [4], and Masaka, Uganda [5], and one among pregnant women recruited at an antenatal clinic in Kigali, Rwanda [6]. Two studies were conducted in Thailand, one among military recruits [7] and one among blood donors and their partners [8].

Todd *et al.* [9] bring together in a single collaborative analysis the data from the above study sites and from a large cohort study among South African miners. Survival was strongly

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associated with age at infection. Adjusted to age 25–29 years at seroconversion, the median survival time was 11.1 years in the East African community-based studies [95% confidence interval (CI) 8.7–14.2], 11.6 years among South African miners (95% CI 9.8–13.7), 7.5 years in Thailand (95% CI 5.4–10.4) and 8.3 years in Haiti (95% CI 3.2–21.4).

Marston *et al.* [10] describe a methodology for deriving HIV-specific ('net') mortality (i.e. mortality directly attributable to HIV infection excluding non-AIDS-related mortality), and compare net survival across study sites and by covariates. The overall effect of the net mortality adjustment was to proportionately increase survivorship by between 2 and 5% after 6 years post-infection, although background mortality is more important at older ages. This information will also be very useful for model representations of HIV epidemics, as these generally try to take account of background mortality.

These joint analyses suggest that the survival of people infected with HIV in low and middle income countries is broadly similar to survival in developing countries before ART became available [11], and that the survival functions are closer than previously believed.

Mortality patterns by age and sex are described for community-based studies in Hlabisa, South Africa [12], and Manicaland, Zimbabwe [13], with the latter also examining trends in mortality. These patterns of mortality are important as few direct data on AIDS-specific mortality are currently available. A joint analytical paper explores the relationship between mortality patterns among the HIV-infected population and the overall magnitude and trend of the HIV epidemic [14]. The paper by Murray *et al.* [15] examines the specific causes of mortality among a group of HIV-infected miners in South Africa.

A paper from Karonga, Malawi, is only the second community-based study to quantify the number of people who are eligible for ART [16,17], and estimates that approximately 31% of all people living with HIV are in need of ART, which is more than previously estimated [18]. The same study suggested that checklist-based field screening and clinical screening by medical assistants did not perform adequately in identifying people in need of ART.

Although the survival analysis in Todd *et al.* [9] represents a large variety of viral subtypes and of the genetic background of the study participants, the regions of Eastern Europe, Latin America, west and central Africa, and large parts of Asia are not represented among the study sites. The value of collaborative analyses of the kind that the ALPHA network has generated resides in the large denominators that can be achieved by pooling several study sites and the resulting statistical power, as well as the variety in the sample. Furthermore, these collaborative analyses provide the opportunity to make the statistical methods comparable across sites, which facilitates the interpretation of the study results for the different sites (e.g. adopting common definitions of censoring, as described in the Technical annex). Similar collaborative analyses elsewhere have generated very important information [11,19], and more collaborative projects of this kind should be encouraged.

Todd *et al.* [9] show that survival in the two Thai studies is significantly shorter than in the African studies. In this supplement, Rangsin *et al.* [7] and Nelson *et al.* [8] suggest that this may be because of the difference in viral subtype, with the Thai study populations being almost entirely composed of people infected with subtype E (recombinant form

CRF01_AE). Although not significant, Lutalo *et al.* [4] also suggest a shorter survival for subtype D compared with A, similar to findings in other studies in east Africa [20–22]. Although it is possible that survival differs by subtype, and notably that subtypes E and D may have more rapid progression and shorter survival compared with other subtypes, it is important to recognise that worldwide subtypes E and D are estimated to represent only approximately 5 and 3%, respectively, of all HIV infections [23].

To explore differences in mortality between populations infected with different HIV-1 subtypes further, future studies will not be able to estimate the survival time from seroconversion to death in the absence of ART, but it will still be possible to compare the time from seroconversion to ARTeligibility, and to compare the survival patterns of those on ART.

The new evidence resulting from the joint analyses [9,10] is important for modelling HIV epidemics. Preliminary results from the ALPHA workshop were presented to the UNAIDS Reference Group on Estimates, Modelling and Projections at a meeting in December 2006. Based on the new evidence the Reference Group recommended that, for the purpose of modelling national epidemics, the assumption about average net survival in most low and middle income countries be changed from 9 years to 11 years, and be kept at 9 years in countries where subtype E is dominant [24,25].

The estimates of numbers of new HIV infections and the numbers of deaths caused by AIDS are based on HIV prevalence over time combined with the assumed median survival [26]. The new survival assumption has resulted in lower estimates of numbers of new HIV infections and AIDS mortality in many countries, and this is reported in the 2007 AIDS Epidemic Update report [27]. This constitutes an example of the rapid incorporation of new evidence in the methodology for HIV and AIDS estimates. It is vital that estimates of the burden of infection, morbidity and mortality be based on research findings and that new evidence be quickly incorporated in the estimation methods and assumptions. Collaborative analyses of the sort produced by the ALPHA network facilitate this process.

Technical annex

The difference between years of exposure to HIV infection and years of follow-up in cohort studies

In all the cohort studies reported in this special issue the exact time or age at seroconversion is not known; it is estimated as occurring at a plausible point between when an individual last tested negative (or could safely be assumed to be uninfected) and their first positive test. When the time interval between the last negative test and the first positive test is short (less than 2 years) it is conventionally assumed that infection occurred at the mid-point of the interval. If the same assumption is made for intervals of more than two years, survival estimates may be substantially biased [28]. The estimated seroconversion time is the point from which exposure to HIV infection is measured, and terms that are used to designate the years that have elapsed between this point and death are ‘years of HIV exposure to risk of dying’ or ‘years from HIV seroconversion’. Similarly, for other HIV-related events such as the onset of AIDS, we refer to ‘years of exposure to risk of developing AIDS’ and measure

this from the estimated point of seroconversion. An individual is exposed to the risk of dying (or developing AIDS) from the moment that he or she is infected.

As we do not know that the individual is infected until they have had an HIV test, we do not know what happens to the whole population of seroconverters between infection and the first positive test. We know that those people who had a first test survived from infection to test, but we do not know how many people in the population under study became infected but did not survive long enough to be tested. The longer the interval the more likely it becomes that people with short survival times are excluded. The interval between the estimated date of infection and the first test date is not used in analysis, and is referred to as 'left truncated at the date of the first positive HIV test' (see Fig. 2). Truncated refers to the fact that we do not have any information about the events of interest (deaths, development of AIDS) that may have occurred during this time in the population as a whole. Left means that when time is represented as a line running from left to right, the interval in question for a particular individual lies to the left of the time period for which we have follow-up information (after the first test). Allowing for left truncation in survival analysis minimizes bias that would arise from excluding those with shorter survival times [29].

Once an individual has had a positive test most studies keep track of them by repeatedly interviewing the individual (or their family) or by searching official documents (e.g. death registers) to check whether that individual is still alive. Some studies also make further biological measurements (e.g. CD4 cell counts) if they can access the individual in person. As long as the people running the study know that an individual is alive and HIV positive the individual is described as 'under follow-up' (see Fig. 2). If the study loses contact with the individual and their family, or if the individual leaves the country so that their death would not be reported in the national death register, the individual is described as 'lost to follow-up'. When describing survival probabilities, or studying mortality rates, the time after the first positive test and whichever comes first: death; loss to follow-up; last interview when the individual was known to be alive; and study cut-off time is referred to as 'years of follow-up'.

Another name for the time in which events can no longer be observed after the follow-up years is 'right censored', because it lies at the right hand end of the time line (see Fig. 2). Right censored time includes years lived after loss to follow-up, years lived after the study cut-off date, and years lived after the last study interview in those studies in which an individual's survival is only assessed in household interviews (as opposed to record searches).

So 'years of HIV exposure' include left-truncated time, but 'years of follow-up' exclude left-truncated time. Conventionally, both years of exposure and years of follow-up exclude right-censored time (even though an individual who is lost to follow-up remains at risk of dying).

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Fig. 1. Geographical location of study sites reporting on survival from HIV seroconversion to death before antiretroviral treatment became available.

Fig. 2. Examples of left truncation and right censoring.