Gender differences in AIDS mortality since the introduction of antiretroviral therapy in Ethiopia

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Abstract

The rollout of antiretroviral treatment (ART) in eastern and southern Africa will be one of the most important public health interventions in the years to come. Among the lingering dangers in that effort is that inequalities in infection rates will be compounded by inequities in the access to treatment. Because of a lack of vital registration systems, however, the settings where these concerns are probably most legitimate go without monitoring. We use 5-year data from an ongoing surveillance of burials at all cemeteries of Addis Ababa to investigate the population level impact of antiretroviral treatment on sex-specific adult mortality trends. To that end, we use life table techniques as well as methods that are based on the lay reports of the causes of death. Preliminary results suggest that AIDS mortality indeed declined since the introduction of ART, but more so for men than for women.

Extended abstract

1. Introduction

The provision of ART will be one of the most important public health interventions in sub-Saharan Africa in the decade to come. Among the lingering threats in the large scale provision of ART is that it will compound inequality in the risk of infection with inequity in the access to treatment (Loewenson and McCoy 2004; Egger, Boulle, Schechter, and Miotti 2005; McCoy et al. 2005; Rosen, Sanne, Collier, and Simon 2005). It is more common, however, to find this concern expressed in editorials or viewpoints rather than reports of research findings because most settings where ART has been and will be rolled-out most extensively simply lack the monitoring systems necessary to reach these conclusions (Cleland 1996; Cooper, Rotimi, Kaufman, and Lawoyin 1998; Diaz, Loth, Whitworth, and Sutherland 2005). HIV prevalence figures no longer provide solace, as they have become a confounded measure of the scope of the epidemic as well as our success of combating it. The few studies on inequities in the impact of ART in developed countries as well as Brazil, have reached mixed conclusions (McNaghten, Hanson, Dworkin, and Jones 2003; Antunes, Waldman, and Borrell 2005; Gebo et al. 2005). Reports from sub-Saharan Africa are non-existing, or have not yet been published.

This new stage in the fight against AIDS thus poses new challenges to demographers and epidemiologists to review their toolbox of methods to come up with reasonably timely data and reasonably accurate measures for monitoring the effectiveness of ART and biases in their delivery schemes. Population-based mortality data are the ultimate outcome measure in this respect and that is evocative of vital registration type data collection systems. These are, as most of us have come to realize, notoriously difficult to set up and maintain in resource-constrained settings. In this contribution we use an ongoing registration of burials at all cemeteries of Addis Ababa as an exemplary alternative approach. A surveillance of burials is relatively simple logistical endeavour as it taps into an existing infrastructure of cemeteries. In some of the cemeteries under surveillance, a rudimentary registry of burials existed prior to the initiation of our project.

Since February 2001 cemetery clerks collect background socio-demographic characteristics and the lay report of the cause of death from close relatives or friends while making the arrangements for burial. So far, we have used these data to document the high impact of HIV on adult mortality (Sanders et al. 2003; Araya et al. 2004; Reniers, Araya, and Sanders Under review), and as a sampling frame for verbal autopsies that were conducted in 2001 and 2004. The current paper examines trends in AIDS mortality over five years during which ART was introduced. To that end we use life table techniques and a method that relies on lay reports of causes of death. We are particularly sensitive to diverging trends in AIDS mortality by sex because a previous study in Addis Ababa has pointed at a gender bias in hospital services utilization (Reniers et al. 2005).

2. The setting

Addis Ababa has an estimated population of close to 3 million and is one of the largest urban centers in East-Africa. As is the case for many urban areas in the region, Addis Ababa is severely affected by the HIV/AIDS epidemic. For 2003, urban HIV prevalence is estimated at 12.6% (MOH 2004), and this has obvious repercussions for the distribution of causes of death. For 2001, between 60-70 % of adult deaths (aged 20-54) are attributed to AIDS (Araya et al. 2004; Reniers et al. Under review).

Since 1999, a limited number of AIDS patients have been receiving antiretroviral medication through the informal market and usually at a very high cost. In July 2003, the Ethiopian government adopted a policy for the provision of antiretrovirals through a co-pay scheme ranging from 30 to 80US$ per month. For most Ethiopians this is still a substantial amount because the monthly salary of an entry-level administrative government employee is less than 50US$. Nonetheless, well over 10,000 patients were receiving antiretroviral drugs in Ethiopia by the end of 2004. In March 2005, the government launched a free ART program in which new patients are enrolled as well as transferred from the fee based schemes.

Exhaustive and detailed data on the number of patients on ART's are not easy to come by, but in 13 governmental and private hospitals in the capital for which data are available, a combined number of 6,605 patients have been receiving ART between July 2003 and December 2004[1]. The sex ratio of these patients is 1.19 suggesting that men do have privileged access to ART; most likely because of greater control over the necessary economic resources. An alternative explanation is that there is simply many more male than female AIDS patients and that a random selection from this pool would result in more men on ART than women. This is unlikely to explain the full extent of the difference: 10 years prior to the initiation of ART, the ratio of male to female infections was already close to unity (Fontanet et al. 1998).

[1] Data provided by the Addis Ababa Regional Health Bureau. This list of hospitals is thought to comprise most important providers of ART, but it is not exhaustive.

3. The data

The burial surveillance was initiated at all cemeteries of Addis Ababa in February 2001 and records information for an average of over 20,000 deaths a year. The surveillance currently covers 55 Orthodox, 9 Muslim, 1 Catholic, 1 Jewish and 8 municipal cemeteries. The largest of the municipal cemeteries, *Baytewar*, buries persons without close relatives or friends to facilitate a funeral[2]. In 2001, Baytewar alone accommodated 14% of the burials. Many of these are infant corpses delivered by obstetrics wards of hospitals. Most persons (61.5%) buried at Baytewar remain unidentified.

The surveillance is assisted by cemetery clerks who were trained in a two-day workshop. Twelve supervisors closely monitor the work of the clerks and report to the project office on a weekly basis. The cemetery clerks collect information on the date of burial, age, name, sex, address, and presumed cause of death (i.e. the lay report of the cause of death) from relatives or close friends while they are making arrangements for burial. Marital status, region of birth, ethnicity and religion were added to this list in 2002.

Because life tables methods are used to estimate HIV/AIDS mortality, the quality of age reporting is of primary concern. For the first year of the surveillance, 6.3% of the records have missing values for age. Excluding Baytewar, only 1.5% of cases have missing values for age. Age heaping is serious (Whipple Index of 283) and we therefore grouped ages into five-year intervals. Cubic spline smoothing is done on the age distribution of deaths above age 50 because this age range is characterised by a strong digit preference for 0. Age over-reporting is a potentially more serious problem because it leads to underestimates of mortality (Ewbank 1981; Coale and Kisker 1986). Both in the burial surveillance data as well as in other published reports on mortality for Addis Ababa, there is evidence of age over-reporting[3], and this casts doubt on the utility of old age mortality schedules for any analytical purpose.

Because infant deaths occurring before the naming ceremony (40 days for boys and 80 days for girls) are often not given an official funeral, the burial surveillance is prone to underreporting of infant mortality. The under-reporting of infant deaths is the main reason why we concentrate on adult mortality. After correcting for the underreporting of early childhood deaths, the crude death rate (CDR) estimated from the burial surveillance oscillates between 9 and 10 per 1000 (Reniers et al. Under review). This figure is higher than the official estimate of 7.6, but is still on the low side for a population that is severely affected by the HIV/AIDS epidemic and suggest that there may be sources for the under-reporting of adults as well[4]. One source of bias is that the project only registers regular Addis Ababa residents buried on the territory of the city[5]. This strategy misses out on all residents buried elsewhere and is not compensated by non-residents buried in Addis Ababa. Other sources for under-reporting are the return of terminally sick migrants to their families for care (Urassa et al. 2001), the repatriation of bodies for burial, and possibly also illegal burials. The only category of burials outside the capital that are represented in the surveillance is that of Orthodox Christians that are referred to sacred burial sites outside Addis Ababa because there are first registered in one of the local churches.

4. Methods

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[2] Baytewar is an Ethiopian Amharic word that is used to refer to a stranger or someone who is socially isolated.

[3] To give only one example, the reported value of 13.5 for e_{70} in a life table for 1984 for males (CSA 1987) would imply an e_0 value of 76 and 80 years in the North and West model life tables respectively. This is an unrealistic value and probably not only due to age over-reporting but also to the under-reporting of deaths.

[4] There are two potentially useful strategies for identifying the completeness of the burial registration that will not be further explored in this paper. Indirect methods often assume stability and/or that the population is closed to migration (Bennet and Horiuchi 1981; Preston 1984) and these assumptions are too stringent for the current context. A second approach is to identify deaths in the community through an independent system and assess to what extent these deaths can be traced in the burial registration system. Preston (1984) labelled this a direct method for assessing the completeness of a death registration system and it has previously been applied in Abidjan and Dakar (Garenne and Zanou 1995). We hope to pursue a similar effort in the future.

[5] In the third year of the surveillance this policy was changed to record all burials on Addis Ababa territory.

To estimate trends in AIDS estimates, we use two methods. The first is based on life table techniques; the second relies on the predictive value of the lay reports of causes of death. Each of these methods is discussed below.

4.1 Life table estimates

The approach to estimating AIDS mortality from these data is straightforward: 1) we construct an empirical life table for 2001 using the burial surveillance data and projected 1994 census data; 2) we match the empirical life table with Coale-Demeny model life tables (Coale and Demeny 1983) on an age range that is not affected by AIDS mortality[6] and 3) we assign excess adult mortality to HIV/AIDS. The parameter used for matching both life tables ${}_{10}q_8$. This age range is chosen because AIDS mortality in this interval is negligible (UNAIDS Reference Group 2002), and because it is not likely to be affected by extreme forms of age misreporting. An attractive feature of this procedure is that it automatically accounts for under-reporting of deaths as long as the under-reporting in each age group is proportional to the under-reporting in the age range that is used for matching. For the same reason we also chose to disregard cases with missing information on sex and age in the life table analyses.

Among the other issues that could compromise our estimates is that relatively few deaths occur in the age range 8-17 (2.4% in the burial surveillance data). Our results are therefore anchored on the reliability of reporting for a relatively small fraction of deaths. Secondly, not all change in mortality can be automatically assigned to HIV/AIDS and temporary fluctuations in the frequency of external injuries (cfr. the student riots of April 2001 and June 2005) may bias AIDS estimates upward or downward depending on the age-groups wherein it is concentrated. A third issue is that we need to make assumptions about AIDS mortality in order to make projections of the population at risk. We accommodate this problem by an iterative procedure: first, we project the population at risk without assuming an AIDS effect and the resulting estimates of age-specific AIDS mortality rates are used as an input to run the projections again until the difference between two subsequent projection rounds is negligible. In these projections, we assume that AIDS mortality rates increases exponentially. The baseline population for the projections is derived from the 1994 census (CSA 1999). The fertility assumptions come from the DHS survey of 2000 (CSA and ORC Macro 2001) and, in accordance with the official high-range population projections, net immigration is assumed to remain constant at the 1994 level (CSA 1999).

4.2 Extrapolations from lay reports of causes of death

The second and perhaps more innovative method is based on the lay report of the cause of death. In a first step, we investigate the diagnostic validity of the lay diagnoses of causes of death, and subsequently use the diagnostic indicators (sensitivity, specificity and positive predictive value (PPV)) from that analysis to extrapolate estimates of AIDS mortality to the total population of Addis Ababa. For investigating the diagnostic value of the lay reports, we use three gold standards: a) the hospital discharge diagnosis in the set of burial records that were matched with a record from the one year surveillance of hospital deaths (2001, N=858), b) the physician review of the verbal autopsies (2004, N=750), and c) a combination of serostatus and admission diagnosis in a set of burial records linked with a record from a 9-month surveillance in the Zewditu Memorial Hospital (2003-2004, N=150). Estimation of diagnostic indicators is done by means of logistic regression, and the regression parameters are used for modeling the share of AIDS mortality under the simple assumption that the sensitivity and PPV are unbiasedly estimated in the sample of matched records (i.e. the samples with info on the gold standard). The share of AIDS deaths is then simply

[6] We chose for a model life table because no reliable life table exists for the pre-AIDS period. One 1983-life-table based on a census question of the number of household deaths (CSA 1987) in the year preceding the census is characterized by serious under-reporting of mortality at older ages (see earlier). We only report results using the Coale-Demeney West model life table. We tested the sensitivity of the results to the use of other model life tables but the ensuing estimates not change much.

calculated as the number of cases in the population with an AIDS-indicative lay diagnosis times the PPV divided by the product of the total number of deaths times the sensitivity of the AIDS indicative lay diagnoses. Compared to an earlier study where we used a similar approach (Araya et al. 2004), the greater sample sizes now allow us to break down estimates of the diagnostic indicators (hence AIDS mortality) by age and sex.

5. Preliminary results

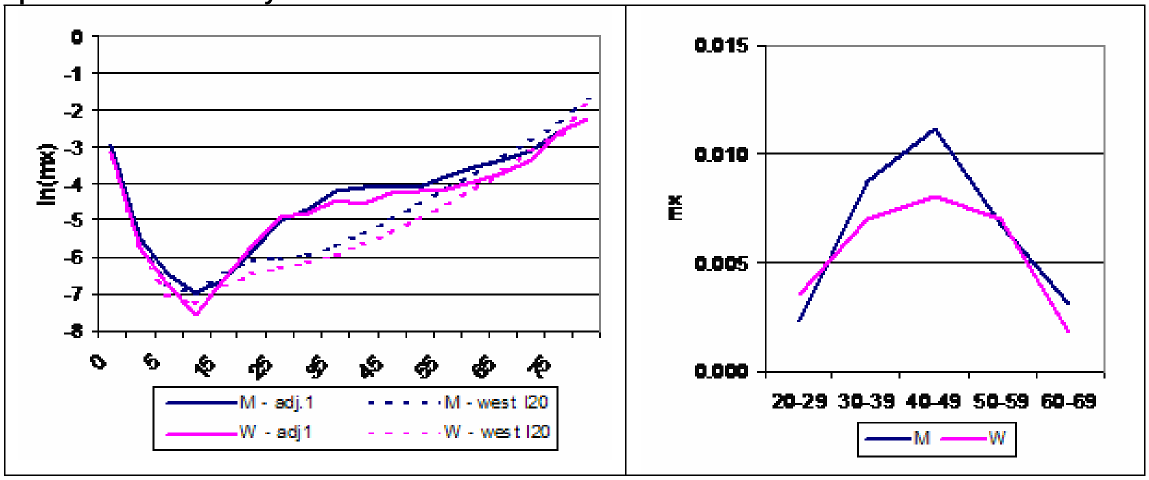
None of the definitive analyses described above have been completed. Below, we present some of the preliminary results.

Lay reports of causes of death indicate that despite a reluctance to label deaths explicitly as AIDS related, the community uses a few euphemisms that are consistently used to refer to AIDS deaths and that can be used for monitoring AIDS mortality. Most frequently mentioned lay diagnoses are *lung disease* and *cold*. Close to 90% of adult deaths attributed to these causes are de facto AIDS deaths, and together they account for 50-60% of the total number of AIDS deaths in the population. Less frequently mentioned are *diarrhea*, *TB*, *AIDS* itself, *shingles* and *mental or nerve problems*. Their positive predictive value is around 80% and together this group of diagnoses accounts for close to 10% of AIDS deaths. The specificity of most of these AIDS-indicative diagnoses is higher than 90%.

Extrapolations from these indicators for 2001 attribute between 60-70% of adult deaths (age 20-54) to AIDS and these results are corroborated by direct estimates of the share of AIDS attributable mortality based on verbal autopsy results.

An example of a comparison of a model and an empirical life table is given in figure 1. They illustrate the typical age pattern of adult AIDS mortality in a population that is heavily affected by the epidemic. In the final version of the paper we will generate estimates of changes in this pattern for the period ranging from 2001 up until the end of 2005.

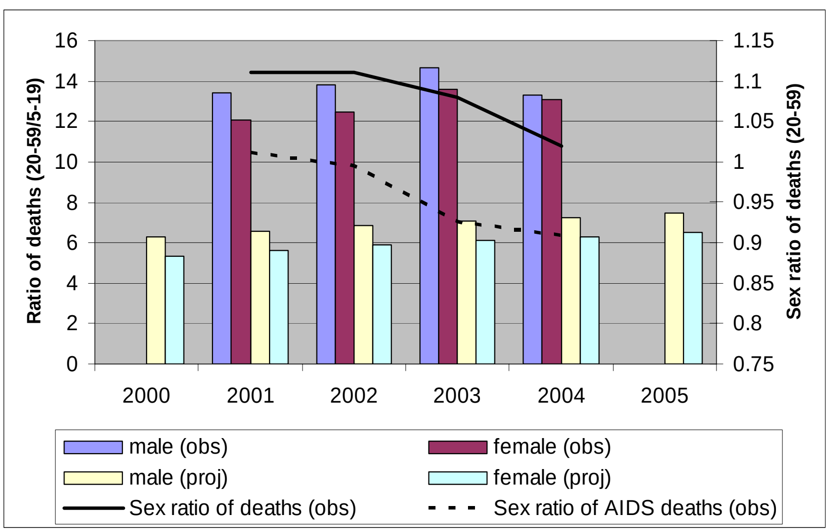
Figure 1. Left: comparison of empirical age and sex specific death rates for 2001 with those from the Coale-Demeny model west (level 20). Right: Estimates of age- and sex specific AIDS mortality rates



Our analyses of trends in AIDS mortality since the introduction of ART in mid 2003 are still very preliminary. Figure 2 should only be considered a primer, but is nonetheless suggestive of some crude tendencies. The figure illustrates trends in ratios of deaths among 20-59 year-olds to 5-19 year-olds by sex and calendar year. These age groups were selected on the basis that the upper age group (20 to 59 years) is most affected by AIDS, while the lower (5 to 19 years) will be little affected as half of infected children are expected to die within 24 months in the absence of ART(UNAIDS Reference Group 2002)[7]. Observed ratios are compared with AIDS-free projections from the 1994 census. Additional information displayed in the figure is the trend in the sex ratio of deaths as well as the estimated sex ratio of AIDS deaths (using the method based on the lay reports of causes of death).

Figure 2 illustrates 1) the high mortality impact of AIDS compared to AIDS free projections, 2) the reversal of AIDS mortality since the introduction of ART and 3) the greater improvement in male compared to female mortality in 2004. The decline in observed adult mortality in 2004 is a likely effect of the introduction of ART as it is difficult to explain by data quality issues or an implied tendency in the epidemiology of HIV. In a population where HIV prevalence has been increasing throughout most of the 1990s (MOH 2002), AIDS mortality in the absence of ART could be expected to increase at least until the middle of the decade. The reduction in adult deaths, however, appears more explicit among men than among women: the ratio of deaths declined from 14.67 to 13.30 for men and from 13.58 to 13.10 for women. The gender imbalance in the adult mortality decline is also visible in the sex ratio of deaths. That figure dropped from 1.11 to 1.02 between 2001 and 2004. Even though one could expect the ratio of male to female infections to decline in a maturing epidemic with predominantly heterosexual transmission, this is unlikely to explain the magnitude of the difference that is observed here. In 1994, the estimated male to female ratio of HIV infection was still close to unity (Fontanet et al. 1998).

Figure 2: Trends in ratios of deaths 20-54 vs 5-19 (observed vs. AIDS-free projections), and trends in sex ratios of deaths (all cause and AIDS specific)



Differential access to ART is the most likely factor driving the gender differences in the AIDS mortality trend as more men than women have enrolled in the fee based ART program in 2003 and 2004. Evidence that women experience more barriers to ART has also been identified in high-income settings (Gebo et al. 2005; McNaghten et al. 2003). Alternative or complementary explanations for the gender imbalance in AIDS mortality in the last year may include differences in ART adherence or lower effectiveness of the therapy. Studies in the United States and Canada have demonstrated poorer ART adherence among women (Kuyper et al. 2004; Berg et al. 2004), but the opposite (or inconclusive) results have been reached in studies among immigrants in Italy (Manfredi, Calza, and Chiodo 2004), in South Africa

[7] The rationale for using ratios of deaths is that they are not affected by underreporting in the burial surveillance as long as the underreporting is not age dependent. For trends in ratios of deaths to be affected by underreporting, the underreporting should not only vary by age but also over time and that is an unlikely scenario.

(Orrell, Bangsberg, Badri, and Wood 2003), and recently in Addis Ababa (Tadios 2005). The pharmacokinetics of ART may also differ between males and females (Kappelhoff et al. 2005), but evidence so far suggests a lower risk of clinical progression during ART among adherent women compared to men (Nicastri et al. 2005). The evidence for these alternatives is thus at best weak and it may much more simply be a matter of differential access between men and women. The recent initiative to provide free ART in Ethiopia may be sufficient to resolve the gender imbalance in the access to ART and AIDS mortality, but that conclusion awaits confirmation from the burial surveillance data.

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