HIV/AIDS-related mortality in Africa and Asia: evidence from INDEPTH health and demographic surveillance system sites

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ROSSIER, Clementine (Collab.)

Abstract
Background As the HIV/AIDS pandemic has evolved over recent decades, Africa has been the most affected region, even though a large proportion of HIV/AIDS deaths have not been documented at the individual level. Systematic application of verbal autopsy (VA) methods in defined populations provides an opportunity to assess the mortality burden of the pandemic from individual data. Objective To present standardised comparisons of HIV/AIDS-related mortality at sites across Africa and Asia, including closely related causes of death such as pulmonary tuberculosis (PTB) and pneumonia. Design Deaths related to HIV/AIDS were extracted from individual demographic and VA data from 22 INDEPTH sites across Africa and Asia. VA data were standardised to WHO 2012 standard causes of death assigned using the InterVA-4 model. Between-site comparisons of mortality rates were standardised using the INDEPTH 2013 standard population. Results The dataset covered a total of 10,773 deaths attributed to HIV/AIDS, observed over 12,204,043 person-years. HIV/AIDS-related mortality fractions and mortality rates varied widely across Africa and Asia, with [...]
INDEPTH NETWORK CAUSE-SPECIFIC MORTALITY

HIV/AIDS-related mortality in Africa and Asia: evidence from INDEPTH health and demographic surveillance system sites


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Background: As the HIV/AIDS pandemic has evolved over recent decades, Africa has been the most affected region, even though a large proportion of HIV/AIDS deaths have not been documented at the individual level. Systematic application of verbal autopsy (VA) methods in defined populations provides an opportunity to assess the mortality burden of the pandemic from individual data.

Objective: To present standardised comparisons of HIV/AIDS-related mortality at sites across Africa and Asia, including closely related causes of death such as pulmonary tuberculosis (PTB) and pneumonia.

Design: Deaths related to HIV/AIDS were extracted from individual demographic and VA data from 22 INDEPTH sites across Africa and Asia. VA data were standardised to WHO 2012 standard causes of death assigned using the InterVA-4 model. Between-site comparisons of mortality rates were standardised using the INDEPTH 2013 standard population.

Results: The dataset covered a total of 10,773 deaths attributed to HIV/AIDS, observed over 12,204,043 person-years. HIV/AIDS-related mortality fractions and mortality rates varied widely across Africa and Asia, with highest burdens in eastern and southern Africa, and lowest burdens in Asia. There was evidence of rapidly declining rates at the sites with the heaviest burdens. HIV/AIDS mortality was also strongly related to PTB mortality. On a country basis, there were strong similarities between HIV/AIDS mortality rates at INDEPTH sites and those derived from modelled estimates.

Conclusions: Measuring HIV/AIDS-related mortality continues to be a challenging issue, all the more so as anti-retroviral treatment programmes alleviate mortality risks. The congruence between these results and other estimates adds plausibility to both approaches. These data, covering some of the highest mortality observed during the pandemic, will be an important baseline for understanding the future decline of HIV/AIDS.

Keywords: HIV/AIDS; tuberculosis; Africa; Asia; Mortality; INDEPTH Network; Verbal Autopsy; InterVA

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T he human immunodeficiency virus (HIV) and the consequent acquired immune deficiency syndrome (AIDS) caused a globally devastating pandemic starting in the late twentieth century. This pandemic caused mortality of such a magnitude as to distort population age-sex distributions in the worst affected areas (1). Now with the advent and roll-out of effective treatment for case management, the situation is improving (2). However, because the pandemic most affected those areas of the world where reliable health data are scarce, there remain large uncertainties about measuring the impact of HIV/AIDS, with many assessments relying on modelled estimates (3). Thus, in reality, many millions of people attributed with HIV infection and/or AIDS mortality over the course of the pandemic were neither tested for the virus, nor had their deaths certified by physicians.

In the absence of laboratory testing and physician diagnosis, one way of determining the magnitude of HIV/AIDS-related mortality is by using verbal autopsy (VA), involving a structured interview with family or friends after a death (4). The interview material is then used to assign the cause of death. In many settings, particularly at earlier stages, physicians made such assessments of VA data. Recently, it has become more common to use computerised models to attribute cause of death, which are faster,
cheaper, and more consistent. Neither approach can be regarded as absolutely correct. Following a V A interview, assigning a death as due to HIV/AIDS is not entirely straightforward, because HIV-infected people may die of a variety of causes. As well as the wasting syndromes typical of AIDS deaths, other causes of death, including particularly pulmonary tuberculosis (PTB) and pneumonia, occur at higher rates and in different age groups among HIV-infected people.

In this paper, we present HIV/AIDS-specific mortality rates as determined by computer-interpreted V A from 22 INDEPTH Network Health and Demographic Surveillance Sites (HDSS) across Africa and Asia (5). These findings are complemented with the corresponding rates for PTB and pneumonia. Although these HDSSs are not designed to form a representative network, each one follows a geographically defined population longitudinally, systematically recording all death events and undertaking verbal autopsies on all deaths that occur. Our aim is to present the HIV/AIDS mortality patterns at each site, comparing these community-level findings with other estimated information on HIV/AIDS in Africa and Asia.

Methods
The overall INDEPTH dataset (6) from which these HIV/AIDS-specific analyses are drawn is described in detail elsewhere (7). The methods used are summarised in Box 1. Briefly, it documents 111,910 deaths in 12,204,043 person-years of observation across 22 sites. The Karonga site in Malawi did not contribute VAs for children.

**Fig. 1.** Map showing participating sites, with age–sex–time adjusted cause-specific mortality fractions and adjusted mortality rates for HIV/AIDS.

**Box 1.** Summary of methodology based on the detailed description in the introductory paper (7)

**Age–sex–time standardisation**
To avoid effects of differences and changes in age–sex structures of populations, mortality fractions and rates have been adjusted using the INDEPTH 2013 population standard (8). A weighting factor was calculated for each site, age group, sex, and year category in relation to the standard for the corresponding age group and sex, and incorporated into the overall dataset. This is referred to in this paper as age–sex–time standardisation in the contexts where it is used.

**Cause of death assignment**
The InterVA-4 (version 4.02) probabilistic model was used for all the cause of death assignments in the overall dataset (9). InterVA-4 is fully compliant with the WHO 2012 Verbal Autopsy standard and generates causes of death categorised by ICD-10 groups (10). The data reported here were collected before the WHO 2012 V A standard was available, but were transformed into the WHO 2012 and InterVA-4 format to optimise cross-site standardisation in cause of death attribution. For a small proportion of deaths, VA interviews were not successfully completed; a few others contained inadequate information to arrive at a cause of death. InterVA-4 assigns causes of death (maximum 3) with associated likelihoods; thus cases for which likely causes did not total to 100% were also assig-
ned a residual indeterminate component. This
served as a means of encapsulating uncertainty in
cause of death at the individual level within the
overall dataset, as well as accounting for 100% of
every death.

Overall dataset
The overall public-domain dataset (6) thus con-
tains between one and four records for each death,
with the sum of likelihoods for each individual
being unity. Each record includes a specific cause
of death, its likelihood and its age–sex–time
weighting.

The InterVA-4 ‘high’ HIV/AIDS setting was used for
sites in Kenya, Malawi, and South Africa. All other sites
used the ‘low’ setting; the ‘very low’ setting was not used.
The InterVA-4 guideline is that the ‘high’ setting is appro-
priate for an expected HIV/AIDS cause-specific mortality
fraction (CSMF) higher than about 1%, though it does not
result in any great dichotomisation of outputs; the clinical
equivalent is a physician’s knowledge that his/her current
case comes from a setting where HIV/AIDS is more or less
likely, irrespective of that current case’s particular symptoms.
The validity of the InterVA-4 model in assigning HIV/
AIDS as a cause of death in relation to HIV sero-status
has been extensively explored in conjunction with the
ALPHA Network (11), and found to be over 90% specific.

Sensitivity is more difficult to assess, since not all people
infected with HIV evidently die of AIDS. The same vali-
dation exercise pointed to large numbers of cases of PTB and
pneumonia as causes of death among the HIV-positive.

Deaths assigned to HIV/AIDS, and the closely related
causes of PTB and pneumonia, were extracted from the
overall dataset, with data on person-time ex-
posed by site, year, age, and sex. Each HDSS covers
a total population, rather than a sample, uncertainty
intervals are not shown.

For the sake of comparison with other estimates of HIV/
AIDS-related mortality, unadjusted data were extracted for
all sites for the period 2008–2012 (excluding data from the
Farafenni, The Gambia; Purworejo, Indonesia; and
FilaBavi, Vietnam sites which did not report for that period).
These data were grouped into three age bands
(0–14, 15–49, and 50 +) and aggregated by country,
to facilitate comparison with contemporaneous national
point estimates for 2010.

In this context, all of these data are secondary datasets
derived from primary data collected separately by each
participating site. In all cases, the primary data collection
was covered by site-level ethical approvals relating to
ongoing health and demographic surveillance in those
specific locations. No individual identity or household
location data were included in the secondary data and no
specific ethical approvals were required for these pooled
analyses.

Results
In the overall dataset, there were 10,455.4 deaths
attributed to HIV/AIDS (including fractions of 11,972
individual deaths), with a further 10,563.4 deaths attrib-
uted to acute respiratory infections (including pneumonia),
and 12,874.8 attributed to PTB.

The age–sex–time standardised CSMFs for HIV/AIDS
at each site are shown, together with the population-based
HIV/AIDS-specific mortality rate per 1,000 person-years,
in Fig. 1. In West African sites, HIV/AIDS CSMF ranged
from 2.10 to 8.00%, with HIV/AIDS-specific adjusted
mortality rates ranging from 0.16 to 0.77 per 1,000 person-
years. In eastern and southern Africa, except Ethiopia,
CSMFs were 9.81–18.85%, with rates from 0.65 to 3.09 per
1,000 person-years. In Asia, CSMFs were 0.15–3.83%,
with rates from 0.01 to 0.21 per 1,000 person-years.

Figure 2 shows HIV/AIDS mortality epidemic cur-
vves for the five sites where overall HIV/AIDS mortality
was at least 1 per 1,000 person-years. Apart from the
Agincourt, South Africa, site, for which a more or less
complete epidemic curve can be seen, the other sites
recorded mortality during a period of mainly declining
HIV/AIDS mortality.

Table 1 gives HIV/AIDS-specific mortality rates by age
group and site. During infancy, the highest HIV/AIDS-
specific mortality rate was reported from the Africa
Centre, South Africa (7.00 per 1,000 person-years),
contrasting with a zero rate from several Asian sites.

For the 1–4 age group, the Kisumu, Kenya, site recorded
the highest rate (5.40 per 1,000 person-years). In the 5–14
year age group, Asian sites recorded rates from 0 to 0.07
per 1,000 person-years, compared with African sites from
0.02 to 0.40 per 1,000 person-years. In adulthood, the
ranges across Asian sites for 15–49 years, 50–64 years,
and 65+ years were 0–0.23, 0.02–0.66, and 0–0.09,
respectively. Similarly for African sites, ranges were
0.08–3.65, 0.37–4.56, and 0–2.26, respectively.

Figure 3 shows the relationships between age–sex–time
standardised HIV/AIDS mortality rates and PTB mor-
tality rates for all 22 sites. Seven of the eight sites in Asia
had an HIV/AIDS rate below 0.1 per 1,000 person-years,
but PTB rates ranged from 0.11 to 0.75 per 1,000 person-
years. Conversely, six of the seven sites in eastern and
southern Africa had HIV/AIDS rates above 0.5 per 1,000
person-years, with PTB rates ranging from 0.52 to 4.96
per 1,000 person-years. The highest age–sex–time stan-
dardised HIV/AIDS mortality rate ratio was between
Kisumu, Kenya, and AMK, Bangladesh, at 343:1.

Figure 4 shows HIV/AIDS mortality rates for 15 sites
which had an overall HIV/AIDS-specific mortality rate
over 0.1 per 1,000 person-years, by age group, also
showing corresponding data for PTB and pneumonia.
Logarithmic scales have been used to visualise both high
and low levels of mortality while using the same scale for
each site.
Table 2 shows the INDEPTH results in comparison with national estimates from the UNAIDS Spectrum model (12) and Global Burden of Disease 2010 (13). Longitudinal INDEPTH data were aggregated over 2008–2012 (for the 19 sites reporting for that period) for the purposes of comparison with the Spectrum and Global Burden of Disease 2010 (GBD 2010) estimates, together with corresponding estimates for PTB.

Discussion

Against the background of extensive modelling approaches that have been applied to HIV/AIDS mortality, this dataset presents results from individually documented deaths at a range of sites across Africa and Asia. The expected huge differences in HIV/AIDS mortality rates between Africa and Asia were evident from these results, and, to a lesser extent, the substantial differences that occurred within the African continent. The good news is that HIV/AIDS deaths declined in recent years in all the sites with high mortality rates (Fig. 2), as the effects of prevention and treatment programmes took effect. The interpretation of findings at individual sites depends on local characteristics (14–35). Two sites, Ouagadougou in Burkina Faso and Nairobi in Kenya, followed urban populations. Bandarban in Bangladesh is located in a militarised frontier zone close to the Myanmar border, which may be associated with higher rates of HIV/AIDS mortality compared with other sites in Bangladesh.

The validity of VA cause of death assignment for HIV/AIDS is not straightforward. In these results, the similar and marked changes over time in the high mortality sites (Fig. 2) added veracity to the InterVA-4 outputs, since the model had no information about the progress of the epidemic over time. Similarly, the extremely low levels of HIV/AIDS-related death assigned as a cause in countries such as Bangladesh and India confirmed the specificity of the methods used. A previous assessment of InterVA-4 validity versus HIV sero-status showed high specificity, but sensitivity was unmeasurable since not all HIV-positive people go on to die from HIV/AIDS (11). However, the same study also showed high mortality rate ratios for PTB and pneumonia between HIV positive and negative cases. ICD-10 classification (36) suggests that almost all HIV-related deaths should be classified under the B20-B24 rubrics, but this is easier said than done in practice, either when using VA or when certifying a death, if there is no evidence of HIV status. In view of the apparently complex relationships between HIV/AIDS deaths and PTB deaths in different settings, as evidenced in Fig. 3, it is not simply a matter of adding together HIV/AIDS and PTB deaths across all settings. However, the total of what InterVA-4 assigns as HIV/AIDS and PTB deaths may provide a better approximation of the overall burden of HIV/AIDS-related mortality for at least the 15–49 year age group in high HIV settings. The question of HIV/AIDS-related mortality associated with pregnancy has also been a matter of debate (37). Another paper in this series analyses pregnancy-related mortality in detail, including the attribution of HIV/AIDS-related deaths between indirect maternal and incidental categories (38).

The WHO 2012 VA standard (39) includes an indicator relating to previous diagnosis of HIV, although the validation study suggested that this was seriously
Table 1. HIV/AIDS-specific deaths and mortality rates per 1,000 person-years, by age group and site, from 111,910 deaths in 12,204,043 person-years of observation across 22 sites

<table>
<thead>
<tr>
<th>Country: Site</th>
<th>Infant</th>
<th>1–4 years</th>
<th>5–14 years</th>
<th>15–49 years</th>
<th>50–64 years</th>
<th>65+ years</th>
</tr>
</thead>
<tbody>
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<td>Bangladesh: Matlab</td>
<td></td>
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<tr>
<td>Adjusted deaths</td>
<td>1.71</td>
<td>7.23</td>
<td>2.18</td>
<td>4.16</td>
<td>3.17</td>
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<td>0.04</td>
<td>0.01</td>
<td>0.00</td>
<td>0.02</td>
<td>0.00</td>
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<tr>
<td>Bangladesh: Bandarban</td>
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<tr>
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<td>7.02</td>
<td>3.89</td>
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<td>0.00</td>
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<td>0.00</td>
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<td>0.02</td>
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<td>0.13</td>
<td>0.29</td>
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under-reported in VA interviews (11). The WHO 2012 standard, and therefore InterVA-4, does not yet include any details of anti-retroviral therapy (ART), although that will become a more pressing issue as experience of mortality patterns among HIV positive individuals with long exposure to ART develops. It is as yet a relatively open question as to what the major causes of death among HIV-positive people might be after possible decades of ART.

There are other major pieces of work describing HIV/AIDS mortality patterns across Africa and Asia, but...
these largely relied on modelling estimates from whatever specific sources of data were available, and therefore carried large degrees of uncertainty given the sparse nature of the data from many settings. The two major sources of contemporaneous estimates for HIV/AIDS mortality come from the UNAIDS Spectrum model (12) and the GBD 2010 model (13). Although our purpose here is not to compare these two models with each other, it is worth noting that there are some major differences. For example, among the countries represented here, the estimates for Ethiopia vary three-fold.

Table 2 shows estimates of HIV/AIDS-related and PTB mortality rates for 12 countries according to Spectrum, GBD 2010, and InterVA-4, which in many cases were very similar, though with differences in places. It must be remembered that these comparisons were compromised by taking INDEPTH sites that are not designed to be nationally representative and putting their findings alongside modelled estimates that are intended to reflect national situations. In South Africa, it appeared that InterVA-4 assigned a substantial amount of HIV/AIDS mortality as PTB, which is perhaps unsurprising in that high-prevalence setting. InterVA-4 arrived at a substantially higher HIV/AIDS mortality estimate than Spectrum for Senegal, and vice-versa for India. There were also many similarities in PTB mortality rates, though differences were evident in Ghana, Kenya, and Senegal.

Similarly there were relatively few appreciable differences between GBD 2010 and InterVA-4 estimates. The differences may reflect local disparities in rates between sites and national populations, given that the relationships between symptoms and causes would not be expected to vary substantially between countries. It also has to be remembered that, although all these VAs have been processed in a standardised way using the WHO 2012 protocol, they were collected in the field in slightly different ways before 2012, and some observed differences may also reflect that. Overall, however, there was appreciable congruence in mortality rates between these various sources.

Conclusions
Measuring HIV/AIDS mortality continues to be a highly challenging area, particularly in Africa, where rates are high and data are often unavailable. This is the largest single systematic study that has applied common methodologies to HIV/AIDS mortality at the individual level across Africa and Asia, and it largely confirms the corresponding findings coming from modelled estimates. This mutually adds plausibility to both existing estimates and to these population-based findings. The challenges
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Conflict of interest and funding

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References


