Review of the definitions and assumptions for estimating AIDS deaths for the UNAIDS Reference Group on Estimates, Modelling and Projections

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Objectives:

- Review global data on excess non-AIDS death among people living with HIV (PLHIV) on antiretroviral therapy (ART) and not on ART (distinguishing these 2 subgroups)
- Review definitions and assumptions applied by groups reporting causes of death or the burden of HIV disease at national, regional and/or global levels

Overarching rationale

The UNAIDS HIV epidemiological estimates describe the scale and historic trends of HIV epidemics in countries around the world. They are used at global, regional, national, and sub-national level for advocacy, programme planning and impact assessments. The estimates are produced using mathematical models developed with guidance from the UNAIDS Reference Group on Estimates, Modelling and Projections (Reference Group).

Model outputs reported as "AIDS related deaths" currently represent **total excess mortality** among PLHIV, rather than distinguishing deaths as **AIDS-related** based on cause-of-death assessment*. This design was dictated by the source of data for determining modelled mortality rates among PLHIV on ART, which are calculated as total mortality among participants in clinical ART cohorts minus sex/age-matched total population mortality. In the Western and Central Europe and North America (WCENA) region, data from the ART Cohort Collaboration (ART-CC) indicates that in recent years, most excess mortality among PLHIV is due to non-AIDS causes. This raises two issues:

1. In countries with high quality case-reporting and vital registration data, UNAIDS models are calibrated so that modelled AIDS-related deaths fit to AIDS-attributed deaths reported through vital registration. However, if the definition model outputs representing 'excess mortality' among PLHIV are different from the definition of AIDS-related deaths recorded in vital registration, models may underestimate total epidemic sizes.
2. UNAIDS communicates the model-estimated deaths as 'AIDS-related deaths' and not as 'excess mortality among PLHIV', even though the latter is calculated by the models. This made little difference in early years of the epidemic, but over the past two decades, as antiretroviral treatment has reached high coverage, these two indicators have increasingly diverged, in all world regions.

The goal of the review is to summarise, globally and by world region and over time, evidence on the magnitude of differences between 'AIDS deaths' and 'excess mortality among PLHIV' and to assist the Reference Group to make recommendations to UNAIDS about clear definitions and communication around estimates of AIDS deaths.

* In countries where injecting drug use is an important source of transmission, there is an excess non-HIV mortality rate multiplier applied to the population of people with HIV who inject drugs (~x1.3). These deaths are not counted as AIDS deaths in the outputs.

Synopsis of methods

Review #1: Contacting various national, regional, and global organisations that report causes of death among PLHIV to gather definitions of AIDS-related mortality that are used by these organisations and compile these definitions.

Review #2: A rapid systematic review and meta-analysis of the percentage of overall mortality among PLHIV that is AIDS-related mortality – overall and stratified by world region. Trends by calendar year will also be analysed. Data will be gathered separately for PLHIV that are on and off ART, with all analyses stratified by ART status.

Review #3: A rapid systematic review to gather studies on PLHIV that capture data on both cause-specific mortality AND excess mortality among compared with a HIV-negative population.

Synopsis of findings

Review #1: Overall, responses and reports sent by the national, regional, and global organizations that were contacted regarding definitions of AIDS-related (or HIV-related) mortality, indicated that methods usually used specific International Classification of Disease (ICD) 10 codes to define AIDS-related mortality from the underlying cause of death. However, there was some variation in the ICD codes used, with some organisations (IHME and some cohorts) adjusting this information, for example, with reclassification of garbage codes given for the underlying cause of death, or taking into account other relevant information such as CD4 counts at time of death (the CoDe protocol). None of the organisations appeared to define AIDS-related mortality as excess mortality among PLHIV compared to the general population as Spectrum is currently doing.

Review #2: 78 studies captured data on the percentage of on ART mortality that is due to AIDS; 22 in Eastern and Southern Africa (ESA), 30 in Western and Central Europe and North America (WCENA), 19 in Asia-Pacific (AP), 3 in Latin America (LA), 2 in Western and Central Africa (WCA), 1 in the Caribbean, and 1 in Eastern Europe and Central Asia (EECA). 61,061 deaths among PLHIV on ART were included overall, with 25,805 (42%) classed as AIDS-related. When meta-analysing the percentages of deaths on ART due to AIDS, the adjusted percentage was 51% (95% confidence interval: 45-56%). In the ESA region, 61% (51-72%) of mortality was due to AIDS, whilst this figure was 65% (57-72%) in LA, 34% (28-39%) in WCENA, 46% (41-52%) in EECA, 76% (67-84%) in WCA, and 61% (51-70%) in AP. The percentage of deaths due to AIDS decreased over time when stratified by region and with national ART coverage percentages at the study mid-point.

25 studies had data regarding off ART mortality due to AIDS. These studies encompassed 7328 deaths, with 4218 (58%) being due to AIDS. The pooled percentage of off ART mortality captured by the studies (57% [95%CI: 44-70%]) varied from 79% (76-81%) in the LA region, 49% (27-72%) in WCENA, 56% (40-71%) in AP, 98% (95-99%) in the Caribbean, and 59% (46-71%) in ESA. However, these studies were often very small and there was uncertainty in whether they were actually capturing off ART mortality, or mortality for PLHIV who later started ART. In a sensitivity analysis restricting to 7 studies with a midpoint before 2000, the pooled estimate for off ART mortality due to AIDS was 79% (70-88%).

The confidence intervals of the pooled percentage of *on-ART* mortality due to AIDS overlapped Spectrum's estimates for each region for recent years. An exception was the WCA region with 76% (67-84%) vs 65% in Spectrum; this difference probably reflects that data from this region were from around 2000 when ART availability was still scarce. For off-ART mortality due to AIDS, there was less agreement between the pooled percentages and Spectrum's estimates , with no overlap for the AP, LA, and Caribbean regions, and some overlap for the ESA and WCENA regions.

Review #3: 8 studies captured data on excess mortality and AIDS-related mortality for PLHIV who were mostly on ART. All these studies were from high-income countries; 6 in WCENA, 2 in AP (Japan and South Korea). No data were found for PLHIV off ART. The total number of person-years included for PLHIV was 1,331,742, in which time there were 17,471 deaths, 7,721 (44%) due to AIDS. The pooled percentage of all-cause mortality due to AIDS from these studies was 43% (95%CI: 35-51%), whilst the pooled percentage of excess mortality among PLHIV who were mostly on ART was 53% (45-61%).

Recommendations

There was variation in how AIDS-mortality was defined by the different organisations in review #1 and by the studies found in reviews #2 and #3. The generalizability of this information for Spectrum's inputs/outputs is unclear. A possible route forward would be to send out a survey to representatives from all countries to clarify how they are defining AIDS-related mortality (e.g. just taking the ICD10 codes listed as underlying that HIV-related, or whether they are combining this with other data, or whether they're reclassifying some of these data). This information would more directly explain any over/underestimation of AIDS-related mortality between country-specific Spectrum estimates and country data. A definition of AIDS-related mortality for UNAIDS's use could also be determined to improve the between-country consistency in AIDS-related mortality information being provided to UNAIDS by country representatives. This should likely be ICD10 codes B20-B24, based on the World Health Organization's definition and the common denominator between the organizations captured in review #1. However, it should be noted that countries are taking different measures to clean these mortality data (e.g. reclassifying garbage codes) before this coding them and that these data vary in quality between countries. So, having a common definition of AIDS-related mortality may improve consistency, but issues will remain.

In review #3, the percentage of excess mortality among PLHIV that was AIDS-related was 53%, whilst the percentage of overall mortality in review #3 which was AIDS-related was 44%. For PLHIV on ART, UNAIDS models could potentially assume that 53% of excess mortality in WCENA, Japan, South Korea, and other high-income settings is due to AIDS-related causes. However, due to the lack of data captured for other regions, this percentage may not be generalisable to be used in models for other settings, including sub-Saharan Africa. The Spectrum and UNAIDS team should investigate potential adjustments to the model that would allow for a proportion of excess mortality to be specified as non-AIDS-related without worsening the fitting of other model parameters. For each region, there was good agreement between Spectrum's current estimates for the percentage of on ART mortality that is due to AIDS and the pooled percentages from review #2, perhaps indicating that an adjustment that left a higher percentage of excess mortality as AIDS-related would be preferable.

For mortality among PLHIV who are off ART, no data were identified on the percentage of excess mortality compared with the general population that was due to AIDS. Some data were available on the percentage of all mortality among PLHIV who are off ART that was due to AIDS, but the reliability of these data is uncertain. Using just the small amount of data from before 2000 perhaps improved the reliability of this estimate as PLHIV were less likely to subsequently start ART at that time. Therefore, in UNAIDS' models, continuing to refer to all excess mortality among PLHIV who are off ART, as AIDS-related is recommended until stronger evidence emerges that indicates otherwise.

Review #1: Definitions of AIDS-related mortality used by various organisations

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Rationale

For this review, I aimed to gather information on the definitions used for AIDS-related mortality by various national, and international organisations. This is so that any change to how AIDS-related mortality is defined in Spectrum can be considered regarding how this aligns with other organisations and the official World Health Organization definition. The purpose of this review is to understand how actual coding practices implemented by various organizations and research studies adhere to the WHO definition for AIDS deaths.

Methods

Representatives from various organisations were contacted. These were mostly suggested a priori by members of the UNAIDS Reference Group on Estimations, Modelling and Projections, although some were contacted upon suggestions from other organisations. This review contains information from those that responded with relevant documents/reports.

World Health Organization (WHO)

The WHO has produced guidelines for the measurement of HIV mortality measurement (1). Chapter 1 of that set of guidelines discusses how to obtain cause-of-death information for HIV/AIDS, mostly regarding International Classification of Disease (ICD) 10 codes related to HIV (B20-B24) (1) – listed in table 1.

For mortality among PLHIV, the WHO advises taking ICD information on the underlying cause of death. ICD10 rules specify that the underlying cause of death should be defined as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" (1). If the underlying ICD code is AIDS-related, then the death will be coded as an AIDS death. However, deciding on a single underlying cause of death is usually complicated and is often done via algorithms (1).

The WHO guidance document (1) states that *"Kaposi sarcoma, Burkitt lymphoma and any other malignant neoplasm of lymphoid, haematopoietic and related tissue, classifiable to C46.– or C81 to C96, should be considered to be a direct consequence of HIV, where this is reported. No such assumption should be made for other types of malignant neoplasm."*

It also states (1): *"Besides the exceptions mentioned below, any infectious disease classifiable to A00–B19, B25–B49, B58–B64, B99 or J12–J18 should be considered to be a direct consequence of reported HIV. Typhoid and paratyphoid fevers, other Salmonella infections, shigellosis (A01–A03) and TB (A15–A19) may be accepted as "due to" HIV disease, if so reported. In such cases, a code from the range B20–B24 would be selected. However, the following infectious and parasitic diseases should not be accepted as "due to" HIV (or any other disease or condition, including malignant neoplasms or immunosuppression):*

Exceptions: cholera (A00), botulism (A05.1), plague, tularaemia, anthrax, brucellosis (A20–A23), leptospirosis (A27), tetanus, diphtheria, whooping cough, scarlet fever, meningococcal disease (A33–A39), diseases due to Chlamydia psittaci (A70), rickettsioses (A75–A79), acute poliomyelitis (A80), Creutzfeldt–Jakob disease (A81.0), subacute sclerosing panencephalitis (A81.1), rabies, mosquito-borne viral encephalitis, tick-borne viral encephalitis, unspecified viral encephalitis (A82–A86), dengue haemorrhagic and other mosquito-borne viral fevers (A91–A92), yellow fever (A95), Junin and Machupo haemorrhagic fevers, Lassa fever (A96.0–A96.2), other viral haemorrhagic fevers (A98), smallpox, monkeypox, measles, rubella (B03–B06), acute hepatitis B and C (B16–B17.1), mumps (B26), malaria, leishmaniasis, trypanosomiasis, Chagas disease (B50–B57), sequelae of tuberculosis (B90), sequelae of poliomyelitis (B91), sequelae of leprosy (B92), sequelae of trachoma (B94.0), sequelae of viral encephalitis (B94.1), sequelae of viral hepatitis (B94.2)." (1)

Note that there are also HIV-related codes for "O98.7: HIV disease complicating pregnancy, childbirth and the puerperium", and "R75: Laboratory evidence of HIV".

Table 1: ICD10 codes B20-B24 relating to HIV (2).

B20: Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases
B20.0 HIV disease resulting in mycobacterial infection
HIV disease resulting in tuberculosis
B20.1 HIV disease resulting in other bacterial infections
B20.2 HIV disease resulting in cytomegaloviral disease
B20.3 HIV disease resulting in other viral infections
B20.4 HIV disease resulting in candidiasis
B20.5 HIV disease resulting in other mycoses
B20.6 HIV disease resulting in Pneumocystis jirovecii pneumonia
HIV disease resulting in Pneumocystis carinii pneumonia
B20.7 HIV disease resulting in multiple infections
B20.8 HIV disease resulting in other infectious and parasitic diseases
B20.9 HIV disease resulting in unspecified infectious or parasitic disease
HIV disease resulting in infection NOS
B21: Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms
B21.0 HIV disease resulting in Kaposi sarcoma
B21.1 HIV disease resulting in Burkitt lymphoma
B21.2 HIV disease resulting in other types of non-Hodgkin lymphoma
B21.3 HIV disease resulting in other malignant neoplasms of lymphoid, haematopoietic and related tissue
B21.7 HIV disease resulting in multiple malignant neoplasms
B21.8 HIV disease resulting in other malignant neoplasms
B21.9 HIV disease resulting in unspecified malignant neoplasm
B22: Human immunodeficiency virus [HIV] disease resulting in other specified diseases
B22.0 HIV disease resulting in encephalopathy
HIV dementia
B22.1 HIV disease resulting in lymphoid interstitial pneumonitis
B22.2 HIV disease resulting in wasting syndrome
HIV disease resulting in failure to thrive
Slim disease
B22.7 HIV disease resulting in multiple diseases classified elsewhere
B23: Human immunodeficiency virus [HIV] disease resulting in other conditions
B23.0 Acute HIV infection syndrome
B23.1 HIV disease resulting in (persistent) generalized lymphadenopathy
B23.2 HIV disease resulting in haematological and immunological abnormalities, not elsewhere classified
B23.8 HIV disease resulting in other specified conditions
B24: Unspecified human immunodeficiency virus [HIV] disease

The Institute for Health Metrics and Evaluation (IHME) – Global Burden of Disease (GBD) studies

GBD models use ICD9 and ICD10 information. For HIV/AIDS deaths, they include the ICD10 codes listed in the table above (B20-B24), as well C46-C469 (Kaposi sarcoma), D84.9 (Immunodeficiency, unspecified) (3)

Additionally, GBD analyses reclassify many immediate and intermediate causes of death or intermediate causes of death, which are often misclassified as the underlying cause of death. Immediate causes, intermediate causes or ill-defined causes of deaths are often referred to as "garbage codes" [5]. They describe four types of misclassification of HIV deaths (4):

"(1) incorrectly assigning intermediate causes or ill-defined causes as the underlying cause of death;
(2) assignment of HIV deaths to relevant garbage codes, such as unspecified immunodeficiency;
(3) allocation of HIV deaths to diseases that can mimic HIV infection (e.g. inflammatory bowel disease and some skin diseases);
(4) misassigning HIV deaths to other underlying causes of death, such as tuberculosis and meningitis."

They redistributed various HIV/AIDS-related garbage codes to HIV/AIDS and other underlying causes of death, based on comparisons with mortality rates for these codes with pre-AIDS epidemic data from 1980-1984 (*Acitonmycosis; Bartonellosis; Urogenital candidiasis; Candidiasis; Coccidioidomycosis; Histoplasmosis; Blastomycosis; Paracoccidioidomycosis; Sporotrichosis and chromomycosis; Aspergillosis; Zygomycosis; Toxoplasmosis; Pneumocystosis; psorospermiasis and sarcosporidiosis; Cryptococcosis; Chromoblastomycosis/nocardiosis; Mycoses/unspecified mycosis; cutaneous leishmaniasis; other mycobacterial infection; immunodeficiency – antibody, immunodeficiency – WBC; immunodeficiency – other; Kaposi's sarcoma*) (4).

They also redistributed All ill-defined code for causes of death "garbage codes" proportionately to HIV/AIDS and other underlying causes. They used a separate method to redistribute intermediate causes to HIV/AIDS, using analyses of data where multiple causes of death were available (underlying and other causes) to determine the fraction that should be assigned to HIV/AIDS (specific to location, year, age, and sex) and applying this to other countries within those GBD super-regions. These intermediate causes were: *Senility; Unspecified Infectious Diseases; Unspecified Viral Diseases; Pulmonary Elmbolism; Sepsis (Non-maternal and neonatal sepsis); Pneumonitis; Chronic respiratory failure; Osteomyelitis; Acute kidney failure; Anemia unspecified; Hepatic Failure; Fluid, Electrolyte, Acid Base Disorders; Intermediate cause for CNS; Cachexia; Peritonitis & Acute Abdomen; Acute Respiratory Failure; Shock, Cardiac Arrest, Coma; Pleurisy, Pyothorax* (4).

Some deaths were incorrectly assigned to other underlying causes. These were reassigned by examining the age patterns of these underlying causes in years/locations without HIV epidemics and identifying where the age patterns shifted in years with HIV epidemics. This was applied to these causes: *Paratyphoid fever; Other diarrheal diseases; Respiratory tuberculosis; Tuberculosis of nervous system; Tuberculosis of other organs; Tuberculosis of bones and joints; Tuberculosis of genitourinary system; Tuberculosis peripheral lymphadenopathy; Tuberculosis of intestines, peritoneum and mesenteric glands; Other unspecified infectious diseases; Other lower respiratory infections; Other sexually transmitted infections; Other neglected tropical diseases; Encephalitis; HIV/AIDS resulting in other diseases; HIV/AIDS - Drug-susceptible Tuberculosis; Malaria; Drug-susceptible tuberculosis; Cervical cancer; Other nutritional deficiences; Other endocrine, metabolic, blood, and immune disorders; Hyperthyroidism; Other neurological disorders; Multiple sclerosis; Idiopathic epilepsy; Influenza; Pneumococcal pneumonia; H influenzae type B pneumonia; Pancreatitis* (4).

South African Medical Research Council (MRC)

The South African MRC have recently released two reports for their National Cause-Of-Death Validation (NCODV) project; with the first based on verbal autopsy data (5), and the second from samples of medical records and forensic pathology records (6). They also produced an earlier publication, which described an approach to estimating AIDS deaths from existing vital registration data (7). They applied the ICD-10 coding rules mentioned previously in this document (pages 7-8), with a slight modification to consider Pneumocystis, even without mention of HIV, as being due to HIV. They also allocate Kaposi's sarcoma to HIV/AIDS due to the very low frequency of Kaposi's sarcoma in South Africans without HIV.

In the earlier publication (7), they noted that *"Several codes have been identified as HIV pseudonyms (B33, B45, B59, and D84) as they are used to code terms such as 'retroviral disease' and 'immune suppression' that appear on death notifications."* The methods section of that analysis states (7):

"The number of misclassified AIDS deaths was estimated as the difference between the source cause-specific registered deaths, corrected for under registration, and the estimated number of deaths from the source causes had there been no HIV. Statistically significant declines were observed for ill-defined natural causes, tuberculosis (TB), protein energy malnutrition, and other nutritional deficiencies and statistically significant increases for septicaemia, meningitis and encephalitis, and endocrine nutritional and blood disorders. Although protein energy malnutrition mortality rates decreased significantly in older ages, it was decided not to apply this trend to other age groups because of the specific cause of the condition in older age groups."

In their first report, "Section 3.7.4 Coding cause of death" states (5):

"All cause of death coding has been performed by the research team after field work had been completed and the data sets cleaned. The InterVA-5 tool has been used for automated selection of the most probable underlying cause of death, based on the responses to the verbal autopsy questions. This is based on the responses to the Verbal Autopsy interview and does not take the narrative into account. The list of causes is restricted to the 64 causes listed in the WHO 2016 VA cause of death list from the WHO 2016 VA instrument. This tool has included an innovative categorisation based on selected questions to provide information about the social and health circumstances of death. The COMCAT93 categories will assist in contextualizing the determinants of the death in addition to the medical conditions by identifying whether health systems issues, care seeking behavior, resources etc. contributed to the death. The verbal autopsy survey data was downloaded from Kobotools by the SAMRC research team and formatted for input into InterVA-5 before processing by InterVA-5.

ICD-10 coding of the multiple causes of death and the underlying causes of death from the medical certificates of cause of death produced by the doctor reviews of verbal autopsy interviews and narratives, was done using Iris automated software. The verbal autopsy doctor review data was downloaded from Kobotools by the SAMRC research team. From this data, the Access data files required for Iris were prepared for batch processing. The dictionary for medical terms (text) to ICD-10 codes developed for the Western Cape local mortality surveillance system was updated and used. Rejects were manually coded by two researchers and a Co-principal investigator who had training in ICD-10 coding."

In their second report, "Section 3.3.4 Coding cause of death" states (6):

"All COD coding was performed by the researchers using Iris automated software26 which codes the multiple causes of death to 4-digit ICD-10 codes and selects the underlying COD by applying the ICD

coding rules. After cleaning the data set with the doctors' medical certificates of COD based on their review of MRs, the initial batch processing in Iris yielded about 39% rejects. These rejects were mainly due to spelling errors, additional words (e.g., poorly controlled hypertension, HIV defaulted etc.; cancer, carcinoma, ca, Ca etc.), conditions not in the dictionary, etc. In order to resolve these issues, the rejects were divided into 3 lots and manually coded to identify the underlying COD using an updated dictionary with additional medical terms."

United States Centers for Disease Control and Prevention (US CDC)

The US CDC has produced various tools and reports regarding mortality among PLHIV, with the types of the mortality data reported, and the definitions used, also varying due to the use of a range of data sources/linkages capturing different types of information. In the US CDC's most recent HIV Surveillance Report (vol 34) (8), they report on deaths of any cause among PLHIV (definitions for the terms used in these reports are located here: https://www.cdc.gov/hiv/statistics/surveillance/terms.html), but not HIV/AIDS-related mortality. Two other sources of mortality data among PLHIV that do contain data on cause-specific mortality are the NCHHSTP ATLASPlus (https://www.cdc.gov/nchhstp/atlas/index.htm) and CDC WONDER (https://wonder.cdc.gov/).

ATLASTPlus is a query-able, searchable database which includes surveillance data for HIV (and other infectious diseases) in the United States, including mortality data from the National HIV Surveillance System (NHSS). The "PWH deaths" are all-cause mortality deaths among persons with HIV, whilst the AIDS deaths are defined as all deaths among persons who have ever received an AIDS diagnosis (regardless of whether they had the condition at time of death, or if it was the cause).

CDC WONDER is a query-able, searchable database for all mortality in the United States, with cause of death from the National Center for Health Statistics (NCHS). Both underlying causes of death and multiple causes of death are available. CDC WONDER contains data for deaths where HIV is listed as the cause of death, defined using ICD-10 codes for "HIV-related deaths" (B20-24) in line with the ICD10 coding rules for HIV. They note that some of these deaths may not be among persons with CD4<200, so there may not be a corresponding AIDS diagnosis in the strictest sense.

Other recent research by the US CDC includes a report on Deaths Among Persons with Diagnosed HIV Infection from 2010-2018 [REF]. In that report deaths with a nonmissing underlying cause were classified as HIV-related or non–HIV-related using ICD10 codes (B20-24, O98.7, and R75) (9).

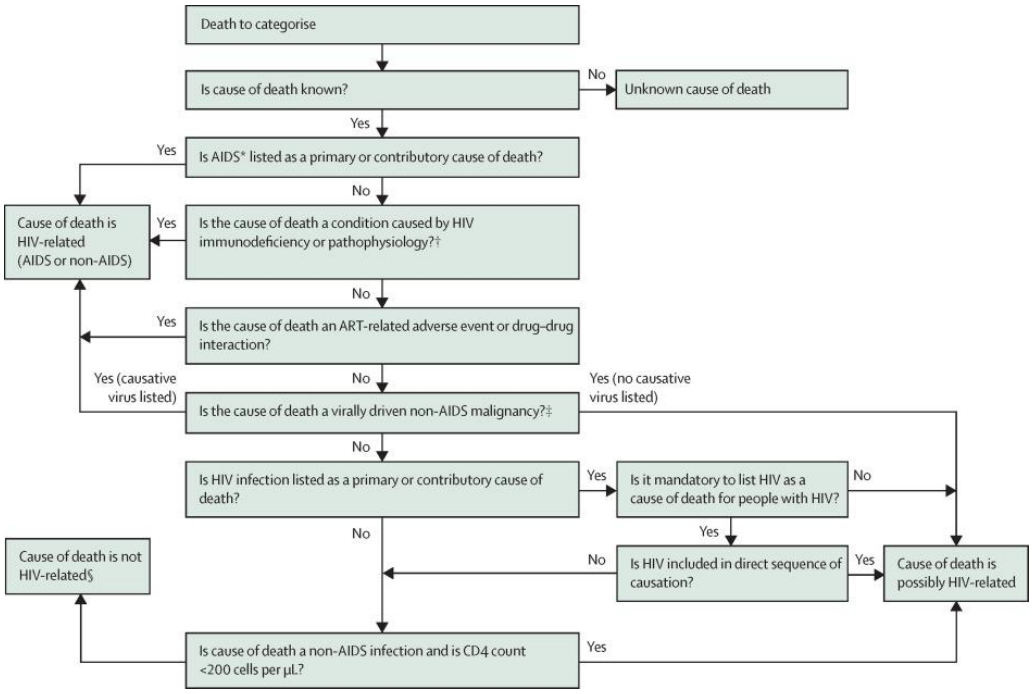
Additionally, they have produced slidesets on HIV mortality (10), with similar definitions for HIV-related mortality (HIV as the underlying cause using ICD10 information). Notably, these slidesets looked at mortality comparisons with the general population (i.e. excess mortality, but did not attribute all this excess mortality as AIDS-related) (10).

UK Health Security Agency (UK HSA)

Up to this point, the UK HSA (formerly Public Health England) has reported all-cause mortality in their reports on HIV, rather than splitting out AIDS-related mortality. However, in the future the UK HSA plans to start presenting HIV-related mortality based on the definitions in Croxford et al (11) that included a rapid review on how HIV-related mortality was defined:

"The literature review showed that most research focused on AIDS-related mortality with definitions for AIDS-defining conditions from the 1993 AIDS list of the US Centers for Disease Control and Prevention; WHO clinical stages 3 and 4; the International Classification of Diseases, 9th or 10th Revision (ICD-9 or ICD-10); or the Causes of Death in HIV (CoDe) protocol (12). Some studies developed customised definitions of AIDS-related mortality, incorporating factors such as time from AIDS illness to death and CD4 cell count. Several studies defined HIV-related deaths as those among people dying of AIDS-defining illnesses only or described deaths under the category HIV/AIDS. Few studies considered causes of HIV-associated mortality not related to AIDS. In studies describing HIV-related mortality or HIV-attributable mortality, HIV-related causes were defined by a specified set of ICD-10 (eg, B20–B24) or ICD-9 codes, or by custom criteria (eg, immunodeficiency-related disease such as bacterial pneumonia caused by Streptococcus pneumoniae and chronic diarrhoea). No studies considered suicide or substance misuse as HIV-related causes of death."

Figure 1: Determining whether a death can be considered HIV-related (taken from Croxford et al (11))



The papers notes that non-AIDS-defining virally driven malignancies considered to be HIV-related are Castleman disease, primary effusion lymphoma, anal cancer, penile cancer, vulval cancer, vaginal cancer, and oropharyngeal cancer, hepatocellular carcinoma, adult T-cell leukaemia or lymphoma, Hodgkin disease, nasopharyngeal carcinoma, laryngeal cancer, gastric cancer, and lymphoproliferative disorder (11). This is an expansion from the definition used by the World Health Organization.

Antiretroviral Therapy Cohort Collaboration (ART-CC)

The ART-CC is a collaboration of HIV cohorts from Western Europe and North America that combines data on adults with HIV who are on ART. The ART-CC has been coding causes of death among PLHIV on ART for many years using an amended version of the Coding Causes of Death in HIV (CoDe) Project methodology (12). Details of this process are listed, usually in the appendices, of various ART-CC publications (13-16).

Causes of death are classified into a single cause in the HIV Cohorts Data Exchange Protocol (HICDEP) format (https://hicdep.org/Wiki/v/10/pt/4/Table/104/FieldID/1321). Information on cause of death was recorded either as International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10), or free text. If ICD-9 or ICD-10 codes were available, causes of death were classified by a clinician and a computer algorithm. When ICD-9 or ICD-10 codes were not available, two clinicians independently classified each death. Disagreements between clinicians and/or computer-assigned codes were resolved via panel discussion.

Clinicians classified deaths using summary tables of patient data including ICD-9/ICD-10 codes or free text for cause of death, patient characteristics at ART initiation (age, sex, transmission risk group, AIDS-defining conditions, and HCV antibody status), use of ART prior to death, AIDS-defining conditions after starting ART, latest CD4 cell count (within 6 months of death). The process mostly revolves around the given underlying cause of death, but various rules are used that have been built up over the years to ascertain a cause in specific scenarios, particularly where there is conflicting or poorly-defined information. The rules for AIDS-related deaths are given below.

AIDS, AIDS infection, AIDS malignancy, and other infections

0. If patient started on ART in last 60 days and dies without any CD4 and no other data but death certificate says only HIV, call this AIDS.
1. "Low" CD4 count, which influences whether we code deaths as AIDS, is classified as <100 cells/mm3. If the CD4 is unknown but the patient has a recent (within 6 months) stage C disease, then the patient can be treated as having a "low" CD4 for the purposes of coding.
2. CoDe 01.1 ("AIDS: Infection") should be used if there was an AIDS-defining infection within the year prior to death, (regardless of CD4) if "HIV infection" is mentioned as most responsible or underlying cause of death.
3. Even if there was no AIDS-defining infection or AIDS-defining malignancy in the last year if there is a CD4<100 and HIV is given as both cause of death and underlying cause it will be coded as 01 ("AIDS").
4. If the patient was off therapy when last seen, and the CD4 count was low (< 100), then the death may be coded as 01 ("AIDS") even if the last available information was between 12 and 18 months ago.
5. If the cause of death is poorly defined, but there was an AIDS event within 2 months of death, this can be coded 01: AIDS.
6. If there is an ICD code of B218 ("HIV disease resulting in malignant neoplasm"), deaths should be coded as 01.2 ("AIDS: Malignancy") even in the absence of other supporting data (such as the recording of an AIDS event).
7. ICD codes of C82 to C85 (non-Hodgkin's lymphoma) should be coded as 01.2 ("AIDS: malignancy")
8. Deaths due to Invasive Cervical Cancer (ICC) or Kaposi's Sarcoma should be coded 01.2: AIDS malignancy.
9. When there is an ill-defined cause of death and CD4 > 100, but the patient was previously diagnosed with NHL this should be this should be coded 01.2: AIDS Malignancy.

10. If the ICD10 code gives an ill-defined cause of death (i.e. code R99) and the patient had TB, this should be coded as 01: AIDS, regardless of CD4 count. Additionally, if the TB was in the last year, this should be coded as 01.1: AIDS Infection.
11. Wasting disease should be classified as AIDS 01 (not AIDS infection 01.1).
12. Deaths due to Endocarditis and Myocarditis should be coded as 02 ("Infection") and sub classified as 02.1 if known to be bacterial.
13. Mycobacteria should be coded 01 "AIDS" in the absence of other reasons for death.
14. There is no need to use CoDe 02.2 ("Infection: others"). Just use CoDe 02 ("Infection")
15. CoDe 02.1 ("Infection: bacterial") should only be used if there is mention of a bacterial disease or of "sepsis" which is a term used almost exclusively for bacterial infections. Otherwise just use CoDe 02 ("Infection"). If cause of death is sepsis/septicaemia, code as 02.1 even if recent AIDS and/or low CD4
16. If only general HIV codes are available (i.e. B227, B203) and there is an absence of any other information or there was a high CD4 taken recently, then this cannot be coded as AIDS but should be coded as 92 Unknown.

Rules for patients with an ICD-10 B207 or B208 code ("HIV-disease resulting in multiple infections" and "HIV-disease resulting in other infectious and parasitic diseases")

1. If CD4 is low (<100) and the patient had pneumonia (unspecified), but there is no mention of sepsis, this should be coded as 01 ("AIDS")
2. If CD4 is unknown or 'high' and the patient had pneumonia (unspecified), but there is no mention of sepsis, this should be coded as 02 ("Infection").
3. If CD4 is low (<100) or unknown, and there is no mention of any cause of death other than HIV (B208 or B24 ("Unspecified HIV disease")), this should be coded as 01 ("AIDS")
4. For patients with a disagreement between CoDe 01 and 02, if CD4 is low (<100) and patient has 3 causes of death listed as B208, B24 and B218 ("HIV disease resulting in other malignant neoplasms") this should be coded 01 ("AIDS")

International epidemiology Databases to Evaluate AIDS (IeDEA)

IeDEA is a collaboration of HIV cohorts encompassing the Asia-Pacific, Southern Africa, West Africa, Central Africa, Latin America, and North America regions. A questionnaire was sent to regional representatives to gather information on what data on cause-of-death are available.

Asia-Pacific - There are four published Treat Asia HIV Observational Database (TAHOD) and Australian HIV Observational Database (AHOD) papers that present data on cause of death, including AIDS-related mortality (17-20). These papers used an amended version of the Coding Causes of Death in HIV (CoDe) project protocol to classify deaths (12). This takes into account of information recorded in the lead up to death that may not be included on the death certificate, such as recent CD4 cell counts or AIDS-defining events.

Southern Africa - Cause of death data are not collected as it is not within the IeDEA Data Exchange Standard framework. When performing linkage there is a cause of death variable, however, it is not as specific as to the disease/illness.

West Africa – No data are available.

East Africa - Targeted Cause-of-Death data available only for specific studies in sub-populations of the East Africa cohort. Five of 9 EA-IeDEA programs are providing some data on cause of death, albeit with many coded as “other” or “unknown”. There are a couple of programs which have fairly complete data especially on persons who are outreached. The method of ascertainment and quality of the data are not well described, and these data have not been published.

Central Africa - Cause of death data are not widely available for CA-IeDEA, has not been published, and is likely to be very incomplete.

CCASAnet/Latin America - Cause of Death currently being collected as part of “Registry Linkage” project among several participating countries (Argentina, Brazil, Chile, Honduras, Mexico, Peru) in the region; with analyses ongoing. AIDS-related mortality from registry-linkage studies in Latin America (CCASAnet) has been historically defined by any mention of HIV or AIDS defining events in death certification/vital status registry data (21, 22).

NA-ACCORD/North America - Cause of Death data from the National Death Index and other sources have been collected, and cohorts are busy updating linkages to these sources. There are no peer-reviewed NA-ACCORD publications on cause-specific mortality distributions.

Thai National HIV Database

In the Thai National HIV Database, these causes of death are classified as AIDS-related: tuberculosis, cryptococcosis, PCP, non-tuberculosis mycobacteria, mycoses, pneumonia, other infections, cancer (those included in the US CDC 1993 revised case definitions), wasting syndrome, and unspecified.

These causes are classified as non-AIDS-related: COVID-19, other infections, urogenital disease, hepatobiliary disease, pulmonary disease, cardiovascular disease, neurological disease, diabetes mellitus, hematologic disease, endocrine disease, other cancer, psychological disease/suicide, substance abuse, assault, poison, and accident/injury.

These causes are classified as uncertain cause of death: ill-defined old age, probable AIDS-related, undocumented AIDS-related, and uncertain.

Conclusions

Deaths among PLHIV can sometimes be thought of in four mutually-exclusive categories:

1) The deaths that would be expected in age- and sex-matched controls without HIV
2) "Excess deaths" among PLHIV that are not attributable to HIV (e.g. due to higher levels of substance use (23))
3) "Excess deaths" among PLHIV that are attributable to HIV, but which are not necessarily classified/coded as due to AIDS. This could include some viral non-AIDS-defining cancers, e.g. anal cancer (24).
4) "Excess deaths" among PLHIV that are due to AIDS

However, some mortality among PLHIV might be more indirectly caused by HIV through HIV causing sustained, raised levels of inflammation (both off and on ART), which leads to higher prevalence of comorbidities that are not considered HIV/AIDS-related, e.g. cardiovascular disease and some non-viral malignancies (25, 26). These deaths would likely be thought in the second category as the HIV is causing another condition, which then causes the mortality. To consider these deaths as HIV-related is similar to assuming all excess mortality (with the exception of some extra mortality, e.g. from injecting drug use) among PLHIV is attributed to HIV (distinct from AIDS).

Various definitions of AIDS-related mortality were found to have been used across the organisations that were contacted, including variation within organisations. ICD10 codes were mostly used with the general basis being to align with the WHO definitions, but the ICD10 codes selected for inclusion as AIDS-related mortality varied slightly across the organisations. The IHME performed exercises to reclassify ICD codes that may have been initially misclassified, but, after reclassification, the rules used were similar to the WHO's definition. The South African MRC included all Pneumocystis and Kaposi's Sarcoma deaths as being AIDS-related. For the US CDC, a range of definitions are used for AIDS-related mortality, with CDC WONDER using ICD10 codes (B20-24), and other research using codes (B20-B24, O98.7, and R75) – both roughly in line with the WHO's definition. However, for ATLASPlus AIDS deaths are defined as all deaths among persons who have ever received an AIDS diagnosis at any point, which is far from the WHO's definition. Going forward, the UK HSA is intending on using a definition of HIV-related mortality, with the explicit statement that this includes both AIDS and non-AIDS-related HIV mortality. The definition is overall roughly in line with what the WHO calls AIDS-related mortality, but their coding algorithm also gives a category of "possibly HIV-related", particularly related to non-AIDS-defining virally driven malignancies. The ART-CC HIV cohort collaboration uses the CoDe protocol to combine information related to HIV biomarkers or patient histories with the death certificate codes and, therefore, likely deviates somewhat with WHO definitions. A previous study of the Spanish CoRIS cohort (part of the ART-CC), compared just using ICD10 codes (i.e. the WHO definition) and the CoDe protocol, finding that just using the WHO ICD10 definition overestimates AIDS-related deaths (27). Within the IeDEA HIV cohort collaboration, there was variation in how AIDS-related mortality was defined for the different regions, with the CoDe protocol sometimes being used, whilst other analyses took mention of HIV or AIDS-defining events in the death certificate to indicate AIDS-mortality. The Thai National HIV database followed closely with the US CDC and WHO's definition, but also included a category for where it was uncertain whether mortality was due to AIDS. None of the organisations defined AIDS-related mortality as the difference in mortality between PLHIV and the general population as is currently done by UNAIDS using the excess mortality outputs from the Spectrum model. Of note, across the organisations, different terms were used to refer to (what is essentially) AIDS-related mortality, including HIV/AIDS-related mortality or just HIV-related mortality.

Review #2: To calculate the percentage of all mortality among PLHIV that is AIDS-related

Adam Trickey, Julie Ambia

Rationale

The aim of this review is to calculate the percentage of **all mortality** among PLHIV due to HIV/AIDS-related causes. Spectrum outputs AIDS-related mortality by calculating the excess mortality among PLHIV, compared with age- and sex-matched general population mortality (28). This may be specifying too large a proportion of all mortality as being AIDS-related – a previous review of studies up to 2015 found that in some regions the majority of deaths of PLHIV on ART were due to non-AIDS causes (29). That previous review found that in high-income countries the pooled percentage of mortality due to non-AIDS causes among PLHIV on ART was 53.0% (95% confidence interval: 43.6-62.3%), whilst this was 34.0% (20.3-49.1%) in "developing countries", and 18.5% (13.8-23.7%) in sub-Saharan Africa. The proportion of mortality due to AIDS likely differs by ART status, although there is a lack of data on this. This review aimed to quantify this **percentage of all mortality** separately for PLHIV on and off ART and by region.

Methods

Search strategy

The review used broad search terms to capture a wide range of studies reporting cause-specific mortality among PLHIV. The search was performed on 22/09/2023 in Embase (via OVID). The search terms were: (('AIDS' or 'HIV') and ('mortality' or 'death') and ('cause' or 'cause-specific') and ('ART' or 'HAART' or 'ARV' or 'antiretroviral')).

Studies were eligible to be included if the following criteria were met: 1) all included participants had HIV (or data on people that did and did not have HIV were stratified); 2) mortality data on PLHIV were stratified by ART status; 3) the study contains data on cause-specific mortality.

Studies were excluded that did not report on the percentage of mortality described as AIDS-related (or similar), or a way to calculate AIDS-related mortality from other available categories.

Exclude modelling studies, systematic reviews, and meta-analyses. Studies were also excluded if they contained fewer than <10 deaths overall, or they were in non-English language journals. Studies were excluded that specifically focus on a subgroup of people, such as children, pregnant women, intravenous drug abusers, and smokers.

After the initial inclusion/exclusion criteria were applied, the studies were re-reviewed to avoid duplication by publication type or by cohort. Where a study is available as both a conference presentation, pre-print, or a published manuscript, then the manuscript was selected. Pre-prints would be selected above conference presentations. If two conference presentations were available, then the most recent would be selected. Where two different studies were found from the same cohort, then the most recent study was selected. We had initially planned to remove studies from individual cohorts that participate in a cohort collaboration when a study from that cohort collaboration was also available, but this was not feasible due to a lack of clarity of reporting of the centres involved in many instances.

Extraction

For each study, we extracted the first author, country or countries of study, years of study, the source/cohort of data, the percentage of participants that were women, the median baseline age, and the definition of AIDS-related mortality. Data were stratified by ART status, and, where possible, across different follow-up periods (with the follow-up period start and end years noted) on: the number of PLHIV included, number of deaths, number of deaths due to AIDS-related mortality, number of deaths with missing (not unknown) causes of mortality, number of person-years, all-cause mortality rate, and the AIDS-related mortality rate. If any of these variables were unavailable, then there were noted as missing. For two studies (Kibuuka et al (30), Mocroft et al (31) and Tusch et al (32)) the countries included spanned two UNAIDS regions, but only had one country in one of those regions, so, for each, the region contributing multiple countries was instead specified. For Rodger et al (33) that contained multiple regions, the WCENA region that contained the most data was specified. Often, the median and interquartile range (IQR) age at baseline (whatever the study's definition of this was), was not available – sometimes as it was only reported for separate categories of a variable, sometimes as only the age at death was reported, or sometimes age was only reported in categories. If a median was unavailable, then a mean would be extracted instead (if available).

Recategorising causes of death as AIDS-related

For Chimbetete et al (34), Hodgkinson et al (35), Brites et al (36), Amuron et al (37), Bhowmik et al (38), Dao et al (39), Etard et al (40), Lawn et al (41), MacPherson et al (42), Namutebi et al (43), Otwombe et al (44), and Thinyane et al (45), we had to form our own categories of AIDS-related mortality from other sub-causes. For Chimbetete et al, AIDS, tuberculosis, and malignancies were classified as AIDS-related deaths, for Hodgkinson et al, deaths due to WHO stage 3 or 4 conditions were classified as AIDS-related, and for Brites et al, deaths due to malignancies, wasting syndrome, pneumonia, sepsis, and tuberculosis were classified as AIDS-related. Incorporating all deaths due to malignancies into AIDS-related mortality likely led to an overestimation of the percentage of deaths that were AIDS-related, as some would have been non-AIDS-defining malignancies. For Amuron et al, AIDS deaths were defined as diarrhoea, tuberculosis, acute febrile illness, poor feeding/starvation (wasting), anaemia, septicaemia, pneumonia, and Kaposi's Sarcoma. For Bhowmik et al, all types of reported mortality were classed as AIDS-related except drug induced hepatitis, cerebro-vascular accident, acute myocardial infarction, and unascertained deaths. For Dao et al, tuberculosis, diarrhoea, pneumonia, and meningitis were included as AIDS-related deaths. For Etard et al, all reported causes of death were classed as AIDS-related except for other deaths and those due to hepatitis. For MacPherson et al, all reported causes of death were classed as AIDS-related except hepatic failure, bladder carcinoma, endometrium carcinoma, obstetric, congestive cardiac failure, diabetes, renal failure, and upper gastrointestinal bleed. For Namutebi et al, tuberculosis, crytpo, ART toxicities, sepsis, diarrhoea, and lymphomas were counted as AIDS-related deaths. In Otwombe et al, all reported deaths were classified as AIDS-related except for unknown causes, cardiac failure, and epilepsy deaths, whilst in Thinyane et al, all were classed as AIDS-related except central nervous system mortality. For Concepcion et al, all reported causes of mortality were classified as AIDS-related except for cirrhosis and pulmonary emboli. In Sobhani et al, the number of AIDS-related deaths was calculated by subtracting those due to liver disease, cardiovascular causes, seizures, aspiration pneumonia, renal, hepatitis, and other causes.

Analysis and reporting

All analyses were carried out separately for data of PLHIV on and off ART. Data on the proportion of mortality among PLHIV that is AIDS-related was calculated by dividing the number of AIDS-related deaths by the denominator of the number of all deaths. These data were meta-analysed overall and stratified by UNAIDS region, through the metaprop command in Stata (random effects, weighting by the number of deaths). For Chao et al (46), the number of AIDS-related deaths was unavailable, so instead the proportion of the AIDS-related mortality rate over the all-cause mortality rate was calculated and multiplied by the number of all-cause deaths. For Kumar et al (47), the total number of deaths was not available, but was instead estimated from annual HIV mortality rates given in the paper by the adult population size from here: https://www.populationpyramid.net/barbados/2001/. Due to uncertainty about whether recent studies of PLHIV off ART would have remained off ART throughout follow-up, in a sensitivity analysis for off ART mortality, we restricted to studies with a midpoint before the year 2000.

The overall proportion of on ART mortality that is AIDS-related was also looked at stratifying by whether the study used the CoDe protocol or not, separately for the AP and WCENA regions. No studies in the ESA or WCA regions used CoDe and there were only three studies in total from the LA and EECA regions.

The proportion of mortality that is AIDS-related was plotted by calendar year (taking the mid-point between the study start and end years), with a trend line plotted and reported. For Brites et al (36), the study start and end years were unavailable, so the mid-year was estimated as 2016, as 2/3 of the studies published in 2019 had a mid-year of 2016. These plots of the percentage of mortality due to

AIDS by calendar year were also repeated stratifying by region, in regions with three or more data points.

Similarly, we plotted the proportion of mortality that is AIDS-related by the national ART coverage percentage at the study mid-year as a proxy for ART duration (assuming studies in places with higher ART coverage would have more PLHIV that had been on long-term ART). This analysis was performed separately for the study data of people on and off ART.

Meta-regressions were performed separately for on and off ART mortality to estimate the proportion of mortality due to AIDS in a variety of scenarios. The proportion and the corresponding standard errors for each study underwent logit transformations (ln(prop/(1-prop) for the proportion and SE/(prop*(1-prop)) for the standard error, so that estimates would be bounded between 0 and 1. These regression models contained coefficients for ART coverage, calendar year, use of CoDe protocol, and region (ESA/WCA, WCENA, or other).

Results

Of 4485 studies captured in the initial search, 105 were eligible for inclusion; 27 studies were removed, 6 were direct duplicates of the same analysis, and the remaining 21 were older manuscripts from cohorts where a newer manuscript was available. This left 78 studies remaining (table 2). Twenty-two studies were from Eastern and Southern Africa (ESA), 2 from Western and Central Africa (WCA), 30 from Western and Central Europe and North America (WCENA), 19 from l/.m,,Asia-Pacific (AP), 3 from Latin America (LA), 1 from the Caribbean, and 1 from Eastern Europe and Central Asia (EECA).

For the studies reporting a median or mean baseline age, this tended to be between 30 and 45 years of age (table 2). In the studies that reported it, the percentage of participants that were women ranged from 7% to 100%. The studies with the highest percentage of participants that were women tended to be from generalized epidemic settings. For 17/78 studies, the Cause of Death (CoDe) project protocol (12) (or variations thereof) were used to classify deaths as AIDS-related, whilst 16 just used ICD categories to classify these deaths (usually according to US CDC classifications), 2 used solely verbal autopsy, and 13 studies specified that death classification was decided by HIV physicians. For 21 studies, a combination of these methods were used or AIDS deaths were categorised from sub causes by ourselves, whilst for 9 there was little information available on how causes of death were decided and defined as AIDS-related.

On ART mortality

For the proportion of mortality on ART due to AIDS, 73 included studies had data available for on ART mortality, and one study (Price et al (48)) had data available for three follow-up periods (table 3). So, 75 data points with 61,061 deaths among PLHIV on ART were included overall, with 25,805 (42%) classed as AIDS-related. The percentage of on ART deaths classified as AIDS-related ranged from 3% in a study by Rodger et al using clinical trial data (33), to 97% in a study in Lesotho (45). When meta-analysing the proportions of deaths on ART due to AIDS, the overall percentage of mortality due to AIDS was 51% (95% confidence interval: 45-56%) (Figure 1). In the ESA region, 61% (51-72%) of mortality was due to AIDS, whilst this figure was 65% (57-72%) in LA, 34% (28-39%) in WCENA, 46% (41-52%) in EECA, 76% (67-84%) in WCA, and 61% (51-70%) in AP.

When looking at the adjusted proportions of death on ART due to AIDS stratified by use of the CoDe protocol, in the AP region, the pooled percentage among studies not using CoDe was 65% (56-75%) and 39% (33-45%) for those using CoDe. In the WCENA region, these percentages were 40% (30-44%) and 24% (16-31%), respectively.

Off ART mortality

Table 4 shows the data identified on the proportion of off ART mortality that is due to AIDS, with 25 studies included, providing 27 data points. The number of deaths in each study ranged from 17 to 2628, with 6/13 having fewer than 30 deaths. In total, 7328 deaths were included, 4218 (58%) due to AIDS. The percentage of off ART deaths classified as AIDS-related ranged from 5% in a study in New York City (Braunstein et al (49)) to 98% in a study in Barbados by Kumar et al (50). 9/27 studies reported fewer than 50% of deaths off ART as due to AIDS. Figure 2 shows the pooled percentage of off ART mortality in these studies was 57% [95%CI: 44-70%]). The pooled percentages varied from 79% (76-81%) in the LA region, 49% (27-72%) in WCENA, 56% (40-71%) in AP, 98% (95-99%) in the Caribbean, and 59% (46-71%) in ESA. In a sensitivity analysis restricting to 7 studies with a midpoint before 2000, the pooled estimate for off ART mortality due to AIDS was 79% (70-88%).

Comparing the pooled estimates with Spectrum's estimates

Table 5 presents Spectrum's regional estimates for the percentage of mortality due to AIDS for PLHIV on and off ART for the years 2000, 2004, 2008, 2012, 2016 and 2020 and compares this with the pooled random-effects estimates from this review. For on ART mortality, the confidence intervals of the pooled estimates match well with Spectrum's estimates for 2020, except for the WCA region 76% (67-84%) vs 65%, as data from this region were from around 2000 when ART availability was scarce.

For PLHIV off ART, there is more difference in the pooled estimate and Spectrum's estimates of the percentage of mortality due to AIDS. For AP the pooled prevalence is 56% (40-71%), which never overlaps with Spectrum's assumptions for 2000-2020 (89-93%), this is also the case for the LA region; 79% (76-81%) versus 83-92%. The same is true for the pooled prevalence from the Caribbean, but in the opposite direction: 98% (95-99%) compared with 84-92%. For ESA, Spectrum's estimates overlap with the pooled prevalence in recent years: 59% (46-71%); 71% in 2020. For WCENA, the very wide confidence intervals of the pooled estimate 49% (27-72%) mean that it overlaps Spectrum's estimates for 2020: 63%.

Trends by time and national ART coverage

Figure 3a shows there was little evidence that the proportions of deaths on ART due to AIDS decreased over time, with a coefficient of the trendline of -0.0033 (-0.0118 to 0.0052) per year, from a constant of 0.5510 in 1997. However, data availability over time depending on region. Figures 4a-c show these proportions of on ART mortality that are due to AIDS stratified by region – there was weak evidence of a decline over time in the AP region, from a constant of 0.7601 in 2002, with stronger evidence in the ESA and WCENA regions, from constants of 0.9076 in 2004 and 0.4361 in 1997, respectively.

There was evidence of a trend in the proportion of off-ART mortality due to AIDS by study midyear (trendline: -0.0174 [-0.0281 to -0.0067] per year, from a constant of 0.8822 in 1989) (Figure 3b). There was also no evidence of a trend in the proportion of off-ART mortality due to AIDS by study midyear when stratifying by region, except in the WCENA region (data not shown).

Figure 5a shows the proportion of deaths due to AIDS decreases with the national ART coverage in the study mid-year point for PLHIV on ART, whilst the evidence for a decrease for the off ART studies is similar (figure 5b). For those on ART, the per percentage point increase was -0.0048 (-0.0065 to -0.0030), from a constant of 0.7052 with 0% of PLHIV on ART. For those off ART, this was -0.0057 (-0.0085 to -0.0028) from a constant of 0.7674 with 0% of PLHIV on ART.

Meta regressions to estimate the proportion of mortality due to AIDS

Table 6 shows the coefficients from a meta-regression used to estimate the proportion of mortality due to AIDS, with an example calculation given. For on ART mortality, a setting in ESA or WCA with 90% ART coverage in 2020, where the CoDe protocol was not used, would have an estimated proportion of mortality due to AIDS of 0.43. For a setting in in the WCENA region, this would be 0.25, and for a setting elsewhere this would be 0.49.

For off ART mortality, the estimated proportion of mortality due to AIDS in a setting in ESA or WCA with 90% ART coverage in 2020 would be 0.66 (not using the CoDe protocol). The corresponding estimated proportions for settings in WCENA or other regions were 0.09 and 0.12, respectively, lower than the estimates for the proportion of on ART mortality due to AIDS.

Limitations

For the data regarding PLHIV both on and off ART, there were several limitations. The definitions of AIDS-related mortality differed between studies: some studies just took ICD values from death certificates at face value, whilst others (mostly those using the CoDe protocol) considered extra information, including recent CD4 counts. There is also a possibility that in some circumstances, AIDS is coded as the cause of death just because it is known by the clinician that the person had HIV, even if HIV was not the underlying cause (51). For some studies, there was no information on how AIDS-related mortality was defined. Therefore, some studies may be under-estimating the percentage of mortality due to AIDS, whilst others may be over-estimating it. For a few studies we had to form our own overarching definition of overall AIDS mortality from established subcategories of AIDS-related mortality. The studies included were very different as some were prospective cohorts and others were retrospective, which likely contributed to the high heterogeneity in the results. Also, the studies had different eligibility criteria regarding CD4 counts and ART regimens. Some studies were retrospective analyses of the causes of death in a vital/civil registry. There was only one study available from each of the EECA and Caribbean regions, so the evidence in these regions is very weak, and evidence is missing for other regions. We found fewer studies than expected, as many studies that had data on cause of death did not stratify by ART status. However, overall, there are quite a few studies available with the necessary information for on ART mortality.

The reliability of the included off-ART mortality data is very unclear. Far fewer studies were included than for on ART mortality. The overall percentage of mortality due to AIDS in the included studies was similar off ART and on ART (57% vs 51%), with a few studies having percentages of mortality due to AIDS that were far too low to be believable (e.g. 5% and 18%). The similarity in percentages of AIDS-mortality between people defined as “off ART” and “on ART” held across all regions. Over a quarter of the studies had data on fewer than 30 people off ART who died. The meta-regression used to estimate the proportion of off ART mortality due to AIDS does not give sensible results, with these proportions being very for recent years in high ART coverage settings: lower than the corresponding proportions for on ART mortality for the WCENA and other (non-ESA/WCA) regions. Overall, this highlights the unreliability of these off-ART mortality data. We cannot be sure if these studies actually captured people who were off ART throughout the study, or whether they were only off ART at a certain point and then started ART later on within the observation period. Whilst the converse is true for mortality among patients on ART, the issue is more problematic for “off ART” mortality. For the people defined as “on ART”, we at least know that they have been on ART at some point, and most would likely remain on ART as, globally, the vast majority of PLHIV on ART have suppressed viral loads (52). These findings likely do not reflect that a large proportion of the “on ART” AIDS-mortality could be among the minority of PLHIV who later stopped ART. For the PLHIV recorded as off ART at baseline (or another time-point), it is quite possible that the majority later started ART. This is further evidenced by off ART and on ART mortality both decreasing by the same amount with increasing ART coverage. Note that the Spectrum models contain an adjustment that reduces the proportion of off ART mortality that is due to AIDS in settings with high ART coverage. We performed a sensitivity analysis restricting the off ART mortality studies to those with midpoints before 2000 when ART coverage was much lower and unavailable in some regions; the pooled estimate in this sensitivity analysis was much higher: 79%.

Table 2: Characteristics of included studies

Author, year	Location	Start year	End year	Median age at baseline (IQR)	% Women	Cause of death info and AIDS-related mortality definition	AIDS mortality definition category
Abioye, 2023 (53)	Tanzania	2006	2009	37 (32-43)	68	HIV physicians	Physician
Albuquerque, 2017 (54)	Brazil	2007	2012	Mean: 39	38	Adapted Cause of Death (CoDe) project protocol	CoDe
Alejos, 2018 (55)	Multi-country Europe	2000	2014	36 (29-44)	28	Adapted Cause of Death (CoDe) project protocol	CoDe
Amuron, 2011 (37)	Jinja, Uganda	2005	2009	38 (NA)	71	Verbal autopsy, AIDS death classification done manually	Misc
Bhowmik, 2012 (38)	Kolkata, India	2005	2010	35 (15-75)	66	Medical records and verbal autopsy, AIDS death classification done manually	Misc
Bonnet, 2002 (56)	Bordeaux, France	1998	1999	43 (25-71)	29	CDC Classification of underlying cause	ICD
Borkowska, 2022 (57)	Tbilisi, Georgia	2012	2018	36 (28-45)	24	Cause of Death (CoDe) project protocol	CoDe
Braunstein, 2017 (49)	New York City, USA	2007	2013	NA	32	HIV-related ICD 9/10: B20-B24	ICD
Breger, 2020 (58)	Southern USA	1999	2014	39 (30-36)	27	ICD-10 and adapted Cause of Death (CoDe) project protocol	CoDe
Brites, 2019 (36)	Salvador, Brazil	UNK	UNK	Mean: 39	59	Not reported, AIDS death classification done manually	Misc
Chao, 2020 (46)	Eswatini	2014	2017	33 (NA)	62	Physician	Physician
Chen, 2017 (59)	Zhejiang, China	2006	2013	36 (26-43)	23	ICD-10 + AIDS death defined by WHO stage 3/4	Misc
Cheung, 2016* (60)	British Columbia, Canada	2001	2012	41 (33-49)	21	ICD10 categories: B20-B24	ICD
Chimbetete, 2020 (34)	Harare, Zimbabwe	2004	2017	33 (16-41)	62	Physician, AIDS classification done manually	Misc
Concepcion, 1996 (61)	Bronx, USA	1982	1995	39 (NA)	27	CDC Classification of underlying cause	ICD
Cowell, 2015 (62)	Connecticut, USA	1995	2011	45 (38-52)	35	CDC Classification of underlying cause, with extra classification of people with CD4 counts <50	Misc
Cox, 2016 (63)	Kampala, Uganda	2002	2012	36 (30-42)	58	Physician	Physician
Croxford, 2017 (64)	England and Wales	1997	2012	34 (28-41)	36	Death reports from HIV clinicians through routine surveillance and death auditing	CoDe
Croxford, 2019 (65)	London, UK	2016	2016	NA	23	Cause of Death (CoDe) project protocol	CoDe
Cuong, 2012 (66)	Quang Ninh Province, Vietnam	2007	2010	Mean: 32	29	Medical records and verbal autopsy	Misc
Dao, 2011 (39)	Lusaka, Zambia; Nairobi, Kenya	2005	2007	32 (28-36)	100	Medical records and verbal autopsy, AIDS death classification done manually	Misc
Duong, 2012 (67)	Multi-centre, Thailand	2001	2010	33 (29-38)	76	ICD 10	ICD
Etard, 2006 (40)	Dakar, Senegal	1998	2005	37 (31-43)	55	Medical records and verbal autopsy, AIDS death classification done manually	Misc
Feng, 2022 (68)	Xi'an, China	2010	2019	33 (27-44)	7	ICD10	ICD

Grinsztejn, 2013 (69)	Rio de Janeiro State, Brazil	1986	2009	35 (NA)	33	CoDe	CoDe
Halliday, 2016 (70)	Manchester, UK	2013	2015	NA	NA	Not reported	NA
Hessamfar-Bonarek, 2010 (71)	France	2005	2005	NA	24	ICD 10	ICD
Hodgkinson, 2020 (35)	Kakamega, Kenya	2004	2017	35 (30-42)	65	Not reported, AIDS death classification done manually	Misc
Jain, 2003 (72)	Texas, USA	1995	2000	39 (NA)	15	Physician	Physician
Jung, 2019 (19)	Multi-country (14) Asia-Pacific and Australasia	1999	2017	NA	25	Cause of Death (CoDe) project protocol	CoDe
Kibuuka, 2021 (30)	Kenya, Uganda, Tanzania, and Nigeria	2013	2020	39 (32-46)	58	Not reported	NA
Kim, 2013 (73)	New York City, USA	2004	2008	49 (NA)	28	CDC Classification of underlying cause	ICD
Kim, 2020 (74)	South Korea	2006	2016	36 (28-47)	7	Cause of Death (CoDe) project protocol	CoDe
Kiragga, 2019 (75)	Kampala, Uganda	2004	2014	36 (21-44)	69	Physician	Physician
Klakowicz, 2014 (76)	Vancouver, Canada	2007	2012	NA	35	Not reported	NA
Kumar, 2006 (47)	Barbados	1997	1999	NA	30	Physician	Physician
Lartey, 2015 (77)	Accra, Ghana	2007	2007	Mean: 40	52	CDC Classification of primary cause	ICD
Lawn, 2005 (41)	Cape Town, South Africa	2002	2005	33 (29-38)	74	Physician	Physician
Lee, 2013 (78)	Busan, South Korea	1998	2006	42 (35-49)	14	CDC Classification of underlying cause	ICD
Leone, 2011 (79)	Bergamo, Italy	1998	2009	Range: 25-44	21	ICD 10	ICD
MacPherson, 2009 (42)	Bushbuckridge district, South Africa	2005	2007	37 (31-45)	33	Physician or verbal autopsy, AIDS death classification done manually	Misc
Madut, 2020 (80)	Tanzania	2008	2009	Mean: 42	69	WHO verbal autopsy tool	Verbal autopsy
Martin, 2011 (81)	Alberta, Canada	1999	2005	39 (33-45)	33	ICD 9 & ICD 10	ICD
Martinez, 2007 (82)	Catalonia, Spain	1997	2004	40 (34-47)	22	Physician or verbal autopsy	Physician
Mocroft, 2013 (31)	33 European countries, Israel, and Argentina	2001	2011	40 (35-47)	27	CoDe	CoDe
Mollel, 2022 (83)	Kilombero and Ulanga, Tanzania	2005	2019	NA	65	Physician	Physician
Murphy, 2013* (84)	Five US cities	1994	2002	40 (NA)	100	Medical records, ICD 9, and verbal autopsy. AIDS deaths were defined as deaths due to AIDS-defining OIs and malignancies, and unspecific causes where CD4 was <200.	Misc
Namutebi, 2013 (43)	Kampala, Uganda	2011	2011	34 (28-40)	50	Physician, AIDS death classification done manually	Misc
Otwombe, 2013 (44)	Soweto, South Africa	2004	2010	36 (NA)	66	Physician or verbal autopsy, AIDS death classification done manually	Misc
Palella, 2011 (85)	12 HOPS sites, USA	1996	2007	39 (34-46)	15	Physician	Physician
Pang, 2018 (50)	Sichuan, China	2014	2015	Mean: 34	10	Cause of Death (CoDe) project protocol	CoDe

Park, 2022 (86)	Korea	2004	2018	NA	11	ICD10	ICD
Price, 2016 (48)	Malawi	2005	2014	NA	NA	Verbal autopsy	Verbal autopsy
Ressler, 2019 (87)	Colorado, USA	2013	2017	Mean: 52	16	Adapted Cause of Death (CoDe) project protocol	CoDe
Rodger, 2013 (33)	North America, South America, Europe, Asia, Australasia	2000	2006	43 (37-50)	20	CoDe	CoDe
Ronsholt, 2012 (88)	Copenhagen, Denmark	1997	2010	49 (43-52)	9	Physician	Physician
Sabin, 2006 (89)	United Kingdom	1998	2003	40 (18-70)	17	Not reported	NA
Salters, 2021 (90)	British Columbia, Canada	2007	2017	NA	29	ICD and lead author & physician	ICD
Sellier, 2020 (91)	Paris, France	2011	2015	NA	23	French mortality algorithm	CoDe
Seyler, 2003 (92)	Abidjan, Côte d'Ivoire	1996	1998	36 (30-40)	61	Event documentation committee	Misc
Shemtandulo, 2023 (93)	Tabora, Tanzania	2021	2022	40 (32-50)	50	Physician	Physician
Siraji, 2009 (94)	Southwestern Uganda	2008	2008	Mean: 36	42.9	Not reported	NA
Sobhani, 2007* (95)	Pune, India	2002	2003	Mean: 35	25.3	Not reported	NA
Tanuma, 2016 (96)	Hanoi, Vietnam	2007	2013	32 (NA)	37	Cause of Death (CoDe) project protocol	CoDe
Teja, 2007 (97)	Andhra Pradesh, India	1992	2005	43 (16-69)	24	AIDS death defined by WHO stage 3/4	Misc
Tepungipame, 2020 (98)	Kisangani, Democratic Republic of the Congo	2019	2020	Mean: 40	60	WHO case definition	Misc
Thao, 2015 (99)	Ho Chi Minh, Vietnam	2006	2011	32 (28-36)	19	Not reported	NA
Thinyane, 2013 (45)	Maseru, Lesotho	2010	2010	36 (32-42)	38	Not reported, AIDS death classification done manually	Misc
Trickey, 2023 (15)	17 European and North American cohorts	1996	2020	38 (31-47)	24	Adapted Cause of Death (CoDe) project protocol	CoDe
Tusch, 2023 (32)	17 cohorts across Europe and Australia	2012	2019	44 (36-51)	NA	Cause of Death (CoDe) project protocol	CoDe
Wada, 2014* (100)	10 sites, United States	1996	2010	41 (36-46)	60	AIDS-related if AIDS, an AIDS-defining illness, pneumonia or sepsis were listed as contributing causes	Misc
Walker, 2012 (101)	Zimbabwe and Uganda	2003	2004	36 (31-42)	65	Cause of death assigned by endpoint review committee	Misc
Wong, 2012 (102)	Tan Tock Seng, Singapore	2008	2010	47 (40-54)	9	CDC Classification of underlying cause (ICD 10)	ICD
Wood, 2003* (103)	British Columbia, Canada	1995	2001	41 (NA)	12	Physician	Physician
Wu, 2023 (104)	China	2017	2019	37 (28-52)	15	Not reported	NA
Yang, 2021 (105)	Zhumadian city in Henan Province, China	1995	2016	NA	48	ICD10	ICD
Yu, 2022 (106)	Dehong, Southwest China	2007	2016	36 (30-43)	40	Not reported	NA
Yue, 2022 (107)	Hunan province, China	2003	2018	NA	26	CD4 <200cells/μL or WHO stage 3/4	Misc

NA: Not available. *Murphy 2013 could be considered a duplicate of Wada 2014, as they both use data from the WIHS cohort, but Wada 2014 also had MACS data. Both Wood 2014 and Cheung 2016 contained data from the British Columbia Centre for Excellence, but Wood 2014 contained data for off ART mortality, whilst Cheung did not. Sobhani was included despite not all PWH being off ART, because the % on ART was so low.

Table 3: Proportions of mortality due to AIDS for PLHIV **on ART**

Study, pub year	Location	UNAIDS region	Study mid-year used	All-cause deaths (N with cause missing)	AIDS deaths	Proportion of all deaths due to AIDS
Abioye, 2023	Tanzania	ESA	2009	175	116	66%
Albuquerque, 2017	Brazil	LA	2011	43	32	74%
Alejos, 2018	Multi-country Europe	WCENA	2011	2774	1024	37%
Amuron, 2011	Jinja, Uganda	ESA	2007	197	120	61%
Bhowmik, 2012	Kolkata, India	AP	2008	56	45	80%
Bonnet, 2002	Bordeaux, France	WCENA	1999	74	32	44%
Borkowska, 2022	Tbilisi, Georgia	EECA	2017	301	139	46%
Braunstein, 2017	New York City, USA	WCENA	2012	11634	5165	44%
Breger, 2020	Southern USA	WCENA	2011	999	323	32%
Brites, 2019	Salvador, Brazil	LA	2016	76	49	64%
Chao, 2020	Eswatini	ESA	2017	49	44	89%
Chen, 2017	Zhejiang, China	AP	2012	356	245	69%
Cheung, 2016	British Columbia, Canada	WCENA	2010	1561	825	53%
Chimbetete, 2020	Harare, Zimbabwe	ESA	2014	504	266	53%
Cowell, 2015	Connecticut, USA	WCENA	2003	257	97	38%
Cox, 2016	Kampala, Uganda	ESA	2010	1028	848	82%
Croxford, 2017	England and Wales	WCENA	2009	2674	1190	45%
Croxford, 2019	London, UK	WCENA	2016	134	37	28%
Cuong, 2012	Quang Ninh Province, Vietnam	AP	2009	60	49	82%
Dao, 2011	Lusaka, Zambia; Nairobi, Kenya	ESA	2006	53	30	57%
Duong, 2012	Multi-centre, Thailand	AP	2006	50	30	60%
Etard, 2006	Dakar, Senegal	WCA	2002	93	72	77%
Feng, 2022	Xi'an, China	AP	2017	118	69	58%
Grinsztejn, 2013	Rio de Janeiro State, Brazil	LAC	1998	299	181	61%
Halliday, 2016	Manchester, UK	WCENA	2015	49	19	39%
Hessamfar-Bonarek, 2010	France	WCENA	2005	882	303	34%

Hodgkinson, 2020	Kakamega, Kenya	ESA	2014	750	316	42%
Jain, 2003	Texas, USA	WCENA	1998	42	15	36%
Jung, 2019	Multi-country (14) Asia-Pacific and Australasia	AP	2013	522	187	36%
Kibuuka, 2021	Kenya, Uganda, Tanzania, and Nigeria	ESA	2019	98	22	22%
Kim, 2013	New York City, USA	WCENA	2006	109	19	17%
Kim, 2020	South Korea	AP	2014	105	42	40%
Kiragga, 2019	Kampala, Uganda	ESA	2012	127	70	55%
Klakowicz, 2014	Vancouver, Canada	WCENA	2010	44	20	45%
Lartey, 2015	Accra, Ghana	ESA	2007	32	16	50%
Lawn, 2005	Cape Town, South Africa	ESA	2004	37	32	86%
Lee, 2013	Busan, South Korea	AP	2002	68	41	60%
Leone, 2011	Bergamo, Italy	WCENA	2004	116	48	41%
MacPherson, 2009	Bushbuckridge district, South Africa	ESA	2006	124	94	76%
Madut, 2020	Tanzania	ESA	2009	24	14	58%
Martin, 2011	Alberta, Canada	WCENA	2002	55	26	47%
Martinez, 2007	Catalonia, Spain	WCENA	2001	235	95	40%
Mocroft, 2013	33 European countries, Israel, and Argentina	WCENA	2006	237	53	22%
Mollel, 2022	Kilombero and Ulanga, Tanzania	ESA	2016	203	110	54%
Murphy, 2013	Five US cities	WCENA	1998	314	167	53%
Namutebi, 2013	Kampala, Uganda	ESA	2011	42	28	67%
Otwombe, 2013	Soweto, South Africa	ESA	2007	63	42	67%
Palella, 2011	12 HOPS sites, USA	WCENA	2002	318	131	41%
Pang, 2018	Sichuan, China	AP	2015	15	9	60%
Park, 2022	Korea	AP	2015	1322	881	67%
Price, 2016 (2005-2008)	Malawi	ESA	2008	37	31	84%
Price, 2016 (2008-2011)	Malawi	ESA	2011	63	51	81%
Price, 2016 (2011-2014)	Malawi	ESA	2014	60	46	77%
Ressler, 2019	Colorado, USA	WCENA	2016	118	27	23%
Rodger, 2013	North America, South America, Europe, Asia, Australasia	WCENA	2003	62	2	3%

Ronsholt, 2012	Copenhagen, Denmark	WCENA	2004	17	1	6%
Sabin, 2006	United Kingdom	WCENA	2001	64	32	50%
Salters, 2021	British Columbia (BC), Canada.	WCENA	2015	208	39	19%
Sellier, 2020	Paris, France	WCENA	2014	274	32	12%
Seyler, 2003	Abidjan, Côte d'Ivoire	WCA	1997	10	5	50%
Shemtandulo, 2023	Tabora, Tanzania	ESA	2022	1150	291	25%
Siraji, 2009	Southwestern, Uganda	ESA	2008	20	9	45%
Tanuma, 2016	Hanoi, Vietnam	AP	2012	45	19	42%
Tepungipame, 2020	Kisangani, Democratic Republic of the Congo	ESA	2019	328	75	23%
Thao, 2015	Ho Chi Minh, Vietnam	AP	2010	44	39	89%
Thinyane, 2013	Maseru, Lesotho	ESA	2010	35	34	97%
Trickey, 2023	17 European and North American cohorts	WCENA	2014	16,832	4203	25%
Tusch, 2023	17 cohorts across Europe and Australia	WCENA	2018	1700	169	10%
Wada, 2014	10 sites, United States	WCENA	2003	572	341	60%
Walker, 2012	Zimbabwe and Uganda	ESA	2004	179	102	57%
Wong, 2012	Tan Tock Seng, Singapore	AP	2009	49	23	47%
Wu, 2023	China	AP	2019	656	393	60%
Yang, 2021	Zhumadian city in Henan Province, China	AP	2011	3805	3,198	84%
Yu, 2022	Dehong, Southwest China	AP	2014	824	299	36%
Yue, 2022	Hunan province, China	AP	2015	4,411	2516	57%

Table 4: Proportions of mortality due to HIV/AIDS for PLHIV **off ART**

Study, pub year	Location	UNAIDS region	Study mid-year used	All-cause deaths	AIDS deaths	Proportion of all deaths due to AIDS
Albuquerque, 2017	Pernambuco, Brazil	LA	2009	272	200	74%
Bonnet, 2002	Bordeaux, France	WCENA	1999	33	20	61%
Braunstein, 2017	New York City, USA	WCENA	2012	376	18	5%
Chen, 2017	Zhejiang, China	AP	2012	1139	496	44%
Concepcion, 1996	Bronx, USA	WCENA	1989	113	109	96%
Cowell, 2015	Connecticut, USA	WCENA	2003	143	78	55%
Croxford, 2017	England and Wales	WCENA	2009	2628	1601	61%
Croxford, 2019	London, UK	WCENA	2016	72	13	18%
Grinsztejn, 2013	Rio de Janeiro State, Brazil	LAC	1998	568	458	81%
Hessamfar-Bonarek, 2010	France	WCENA	2005	131	63	48%
Jain, 2003	Texas, USA	WCENA	1998	46	26	57%
Kibuuka, 2021	Kenya, Uganda, Tanzania, and Nigeria	ESA	2019	24	8	33%
Kim, 2013	New York City, USA	WCENA	2006	99	19	19%
Kumar, 2006	Barbados	LAC	1998	222	218	98%
Lartey, 2015	Accra, Ghana	ESA	2007	189	101	53%
Lawn, 2005	Cape Town, South Africa	ESA	2004	31	26	84%
Pang, 2018	Sichuan, China	AP	2015	59	52	88%
Park, 2022	South Korea	AP	2015	347	104	30%
Price, 2016 (2005-2008)	Karonga, Malawi	ESA	2008	20	12	60%
Price, 2016 (2008-2011)	Karonga, Malawi	ESA	2011	18	9	50%
Price, 2016 (2011-2014)	Karonga, Malawi	ESA	2014	17	11	65%
Sellier, 2020	Paris, France	WCENA	2014	21	8	38%
Sobhani, 2007	Pune, India	AP	2003	172	112	65%
Teja, 2007	Andhra Pradesh, India	AP	1999	145	90	62%
Tepungipame, 2020	Kisangani, Democratic Republic of the Congo	ESA	2019	19	12	63%
Wong, 2012	Tan Tock Seng, Singapore	AP	2009	18	8	44%

Wood, 2003	British Columbia, Canada	WCENA	1998	406	346	85%

Table 5: Comparing Spectrum's regional estimates for the percentage of mortality due to AIDS for PLHIV on and off ART with the pooled estimates from this review

		UNAIDS estimates						Data from review	
Measure	**Region**	**2000**	**2004**	**2008**	**2012**	**2016**	**2020**	**Pooled estimate**	**Median mid-year**
% of deaths on ART due to AIDS*	Asia and the Pacific	83%	93%	84%	77%	74%	70%	61% (51-70%)	2012
	Caribbean	100%	83%	79%	70%	67%	61%	NA	NA
	Eastern and Southern Africa	87%	89%	82%	73%	69%	60%	61% (51-72%)	2017
	Eastern Europe and Central Asia	NA	63%	61%	54%	52%	43%	46% (41-52%)	2011
	Latin America	91%	87%	82%	77%	72%	61%	65% (57-72%)	2008
	Middle East and North Africa	96%	92%	87%	81%	80%	75%	NA	NA
	Western and Central Africa	NA	81%	79%	72%	67%	65%	76% (67-84%)	2000
	Western and Central Europe and North America	77%	69%	59%	52%	45%	37%	34% (28-39%)	2007
% of death off ART due to AIDS*	Asia and the Pacific	90%	93%	93%	92%	91%	89%	56% (40-71%)	2008
	Caribbean	92%	93%	91%	90%	89%	84%	98% (95-99%)	1998
	Eastern and Southern Africa	89%	91%	85%	80%	75%	71%	59% (46-71%)	2012
	Eastern Europe and Central Asia	88%	90%	89%	90%	89%	87%	NA	NA
	Latin America	92%	91%	90%	89%	87%	83%	79% (76-81%)	2004
	Middle East and North Africa	88%	89%	91%	92%	91%	89%	NA	NA
	Western and Central Africa	85%	87%	86%	84%	84%	79%	NA	NA
	Western and Central Europe and North America	90%	89%	88%	81%	70%	63%	49% (27-72%)	2004

NA: Not available as the denominator of number of people on ART in that region and year is estimated to be 0.

* Number of annual AIDS deaths (aged 15+) divided by the sum of this and the number of non-AIDS deaths in the HIV population (all ages) – calculated separately for PLHIV on and off ART, so different age groups are being combined and excess mortality for people who inject drugs is not included.

Table 6: Meta regression to estimate the proportion of mortality due to AIDS

On ART	**Coefficient**	**Lower 95%CI**	**Upper 95%CI**
Constant	1.208856	0.6508049	1.766908
ART coverage (%)	-0.0106809	-0.0238064	0.0024445
Years since 1997	-0.0122571	-0.0636273	0.0391131
CoDe used	-0.4818908	-0.9469689	-0.0168126
ESA or WCA region	-0.229935	-0.68662	0.22675
WCENA region	-1.048711	-1.608186	-0.4892371
Off ART	**Coefficient**	**Lower 95%CI**	**Upper 95%CI**
Constant	1.704681	0.5813049	2.828058
ART coverage (%)	-0.0265066	-0.0491098	-0.0039035
Years since 1989	-0.0426751	-0.1169518	0.0316015
CoDe used	1.196087	-0.0799548	2.472129
ESA or WCA region	2.677596	0.3861081	4.969085
WCENA region	-0.3041933	-2.133139	1.524753

CoDe: Causes of Death in HIV protocol

* An example calculation for the proportion of on ART mortality due to AIDS in a setting in ESA with 90% ART coverage in 2020, not using CoDe would be: (exp(1.208856 + (-.0106809*90) + (-.0122571*23) + (-.229935)))/(1+exp(1.208856 + (-.0106809*90) + (-.0122571*23) + (-.229935))) = 0.43

Figure 1: Meta-analysis of the proportion of **on ART** mortality (adjusted for unknown causes) that is due to AIDS

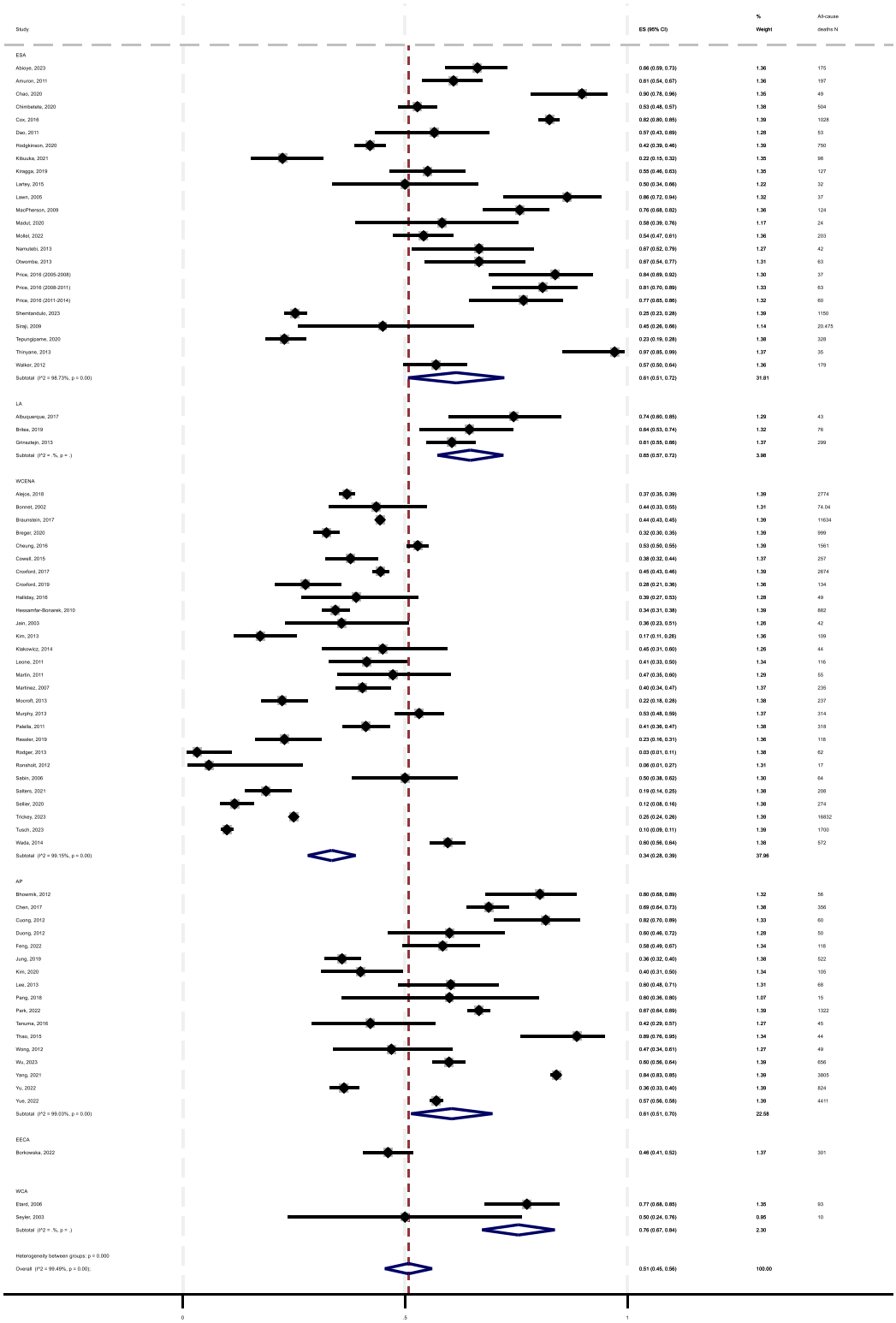


Figure 2: Meta-analysis of the proportion of **off ART** mortality (adjusted for unknown causes) that is due to AIDS

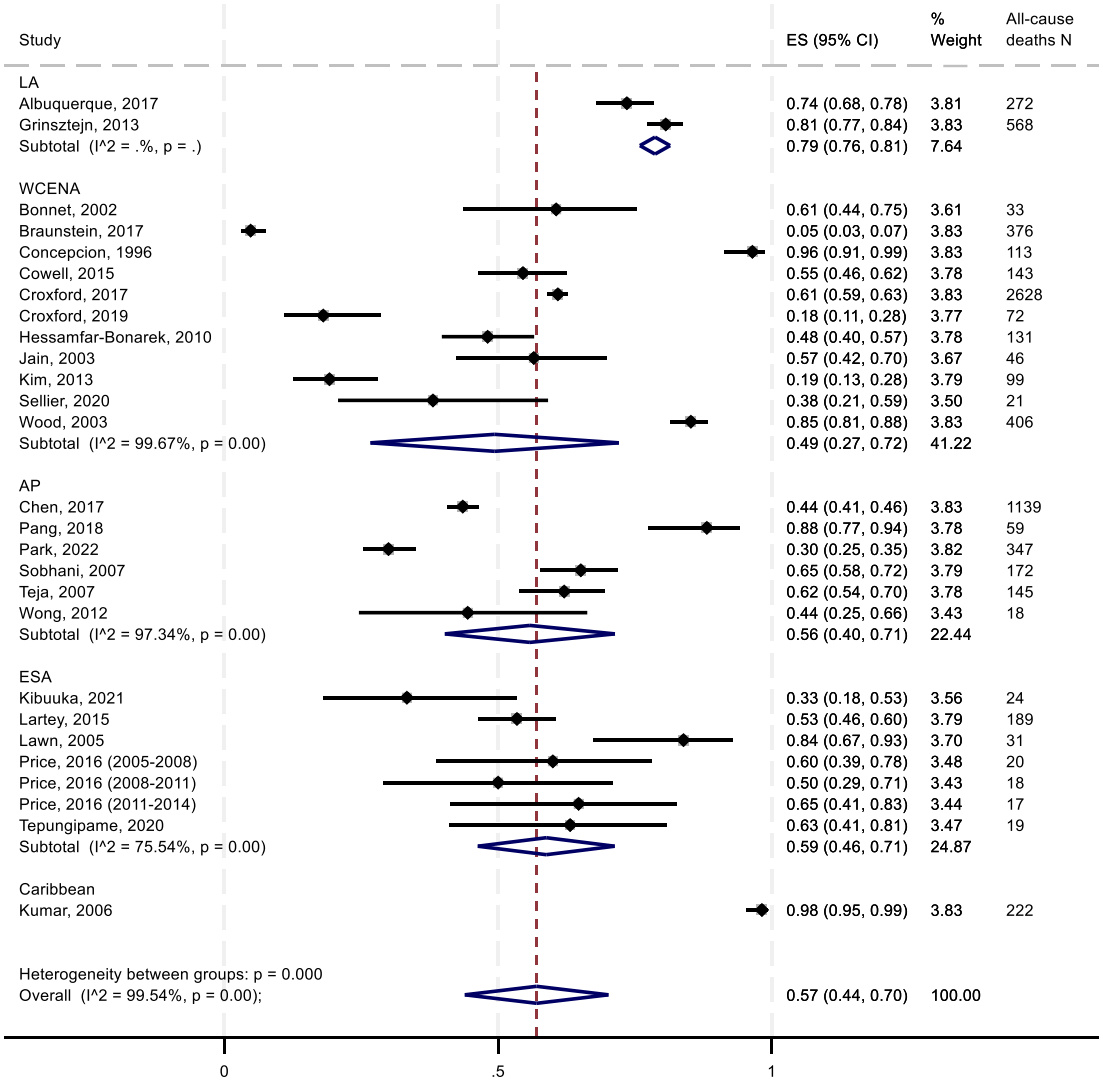
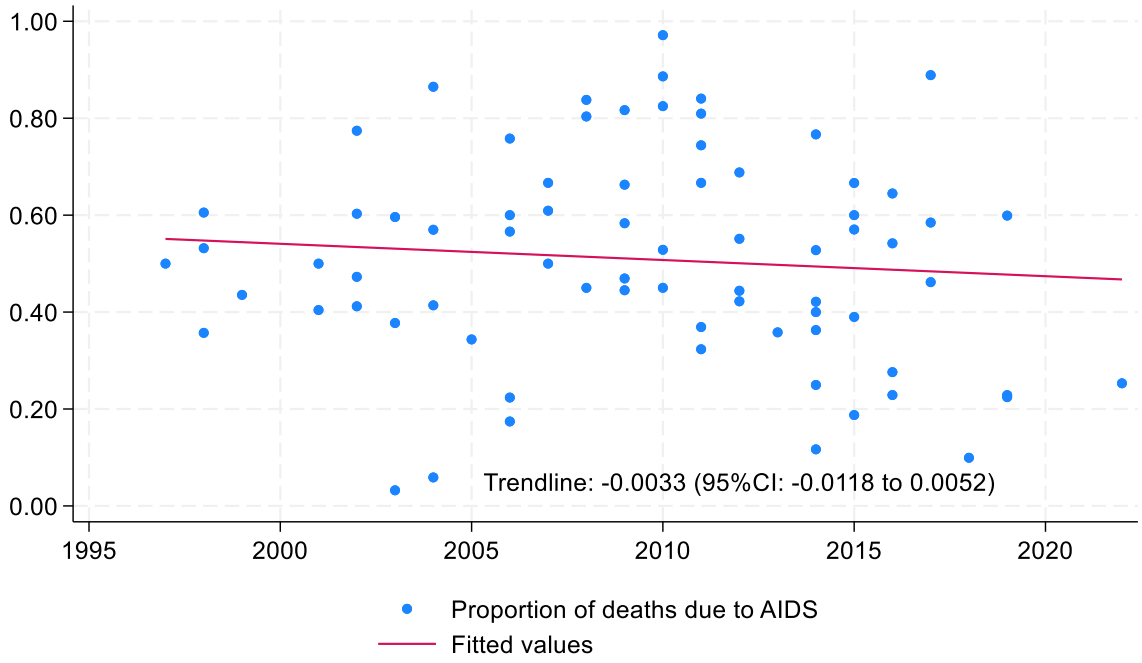


Figure 3a-b: Proportions of mortality due to AIDS over time a) on ART, and b) off ART

a) On ART



b) Off ART

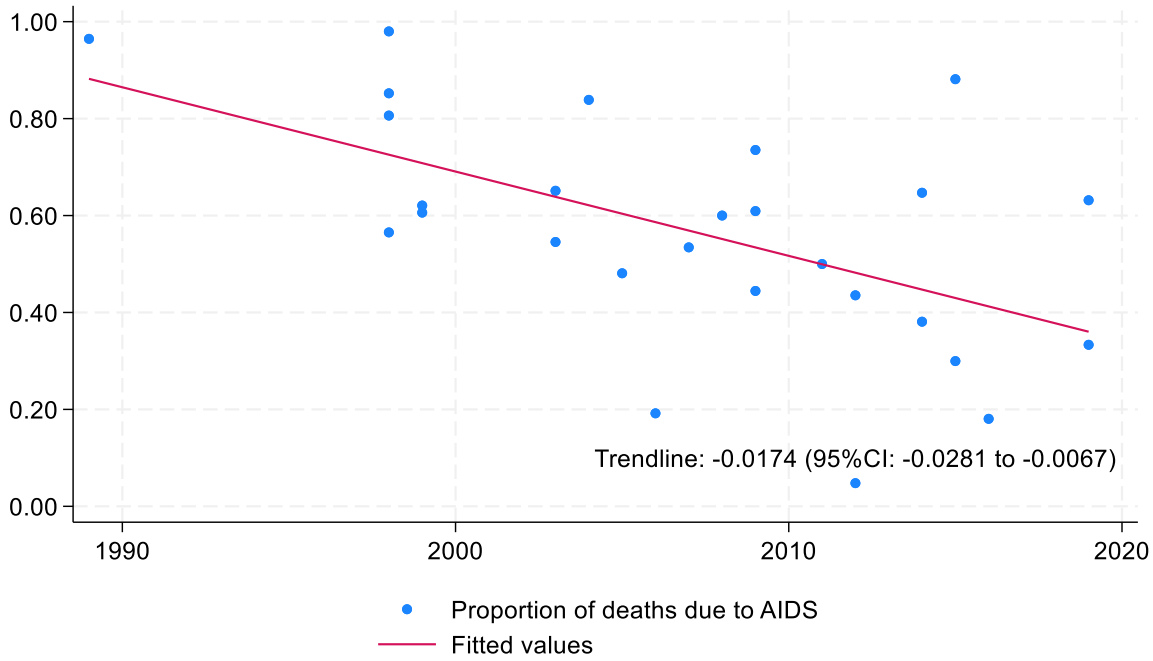
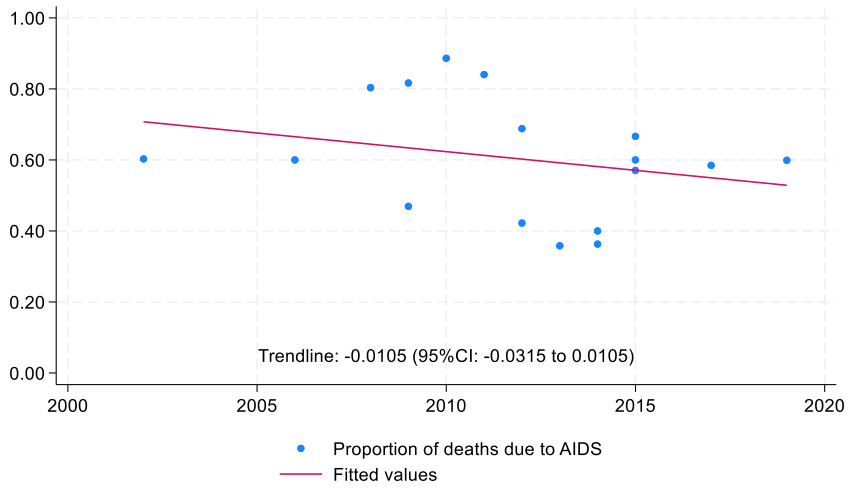
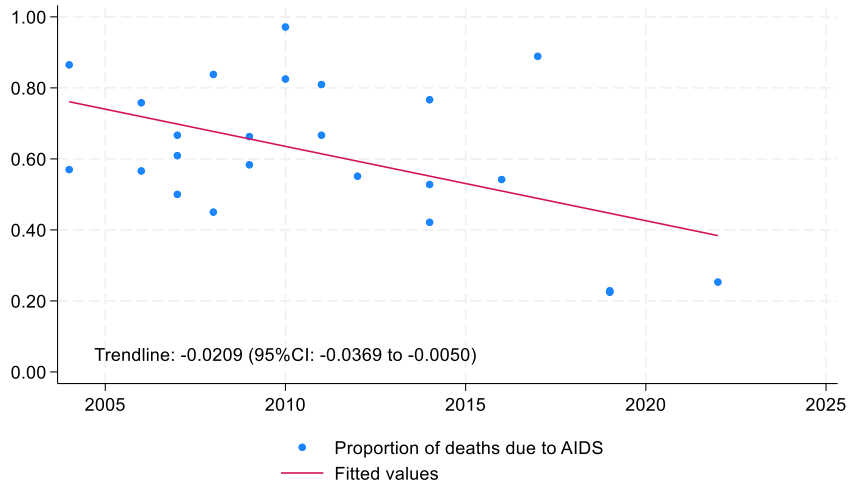


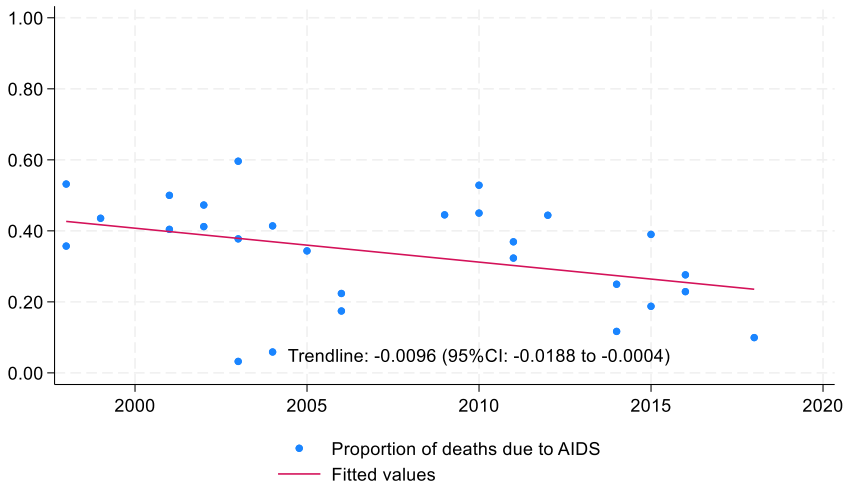
Figure 4a-c: Proportions of mortality due to AIDS over time on ART by region: a) Asia-Pacific, b) Eastern and Southern Africa, and c) Western and Central Europe and North America.



a)



b)

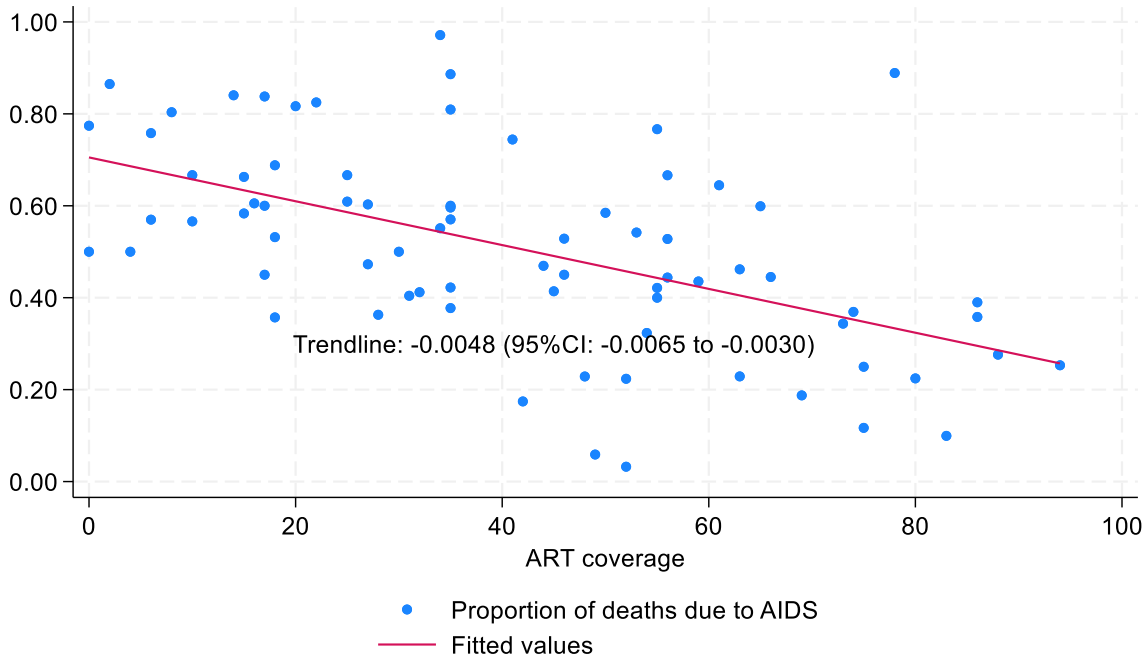


c)

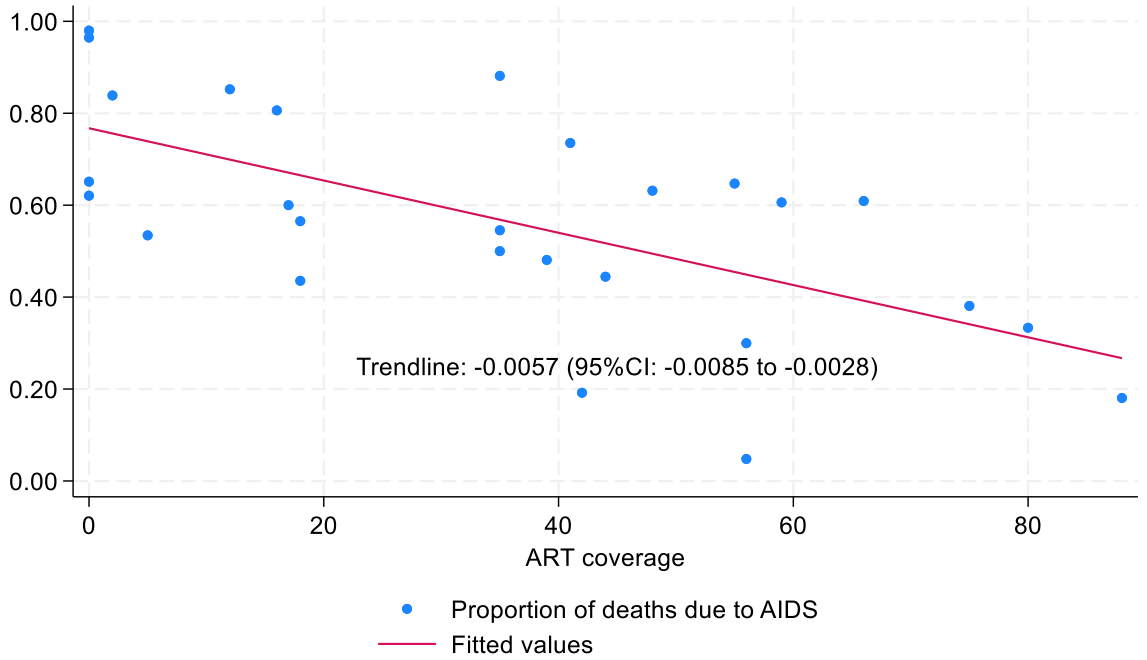
Note: No graphs were included for regions with very few data points.

Figure 5a-b: Proportions of mortality due to AIDS by national ART coverage for PLHIV a) on ART, and b) off ART

a) On ART



b) Off ART



Review #3: To calculate the percentage of excess mortality among PLHIV compared with the general population that is AIDS-related

Adam Trickey, Julie Ambia

Rationale

Whilst Review #2 aimed to calculate the percentage of **all mortality** among PLHIV that was due to HIV/AIDS-related causes, review #3 aimed to calculate the percentage of **excess mortality** among PLHIV due to HIV/AIDS-related causes. This is because Spectrum outputs excess mortality among PLHIV (relative to age- and sex-matched general population mortality), and currently labels that key output as AIDS-related mortality (28) after which UNAIDS and countries use this metric to evaluate progress toward (global, UNAIDS strategy and national program) targets for reducing AIDS mortality. However, recent analyses have indicated that, with changing distributions of causes of death since the scale-up from 1996 of ART, a sizeable percentage of this excess mortality among PLHIV may no longer be AIDS-related (108). This review aimed to quantify this **percentage of excess mortality associated with HIV,** separately for PLHIV on and off ART and by UNAIDS region.

Methods

Search strategy

This review used the same broad search terms as Review #2, but separate inclusion/exclusion criteria. The search was performed on 22/09/2023 in Embase (via OVID). The search terms were: (('AIDS' or 'HIV') and ('mortality' or 'death') and ('cause' or 'cause-specific') and ('ART' or 'HAART' or 'ARV' or 'antiretroviral')).

Studies were eligible to be included if the following criteria were met: 1) they contained data on PLHIV; 2) the study contained data on HIV/AIDS (or non-HIV/AIDS-related) cause-specific mortality rates among PLHIV; 3) the study contained age-matched/comparator all-cause mortality rates among people without HIV.

Studies were excluded if they were systematic reviews, meta-analyses, or modelling studies. Studies were also excluded if they contained fewer than <10 deaths overall, or they were in non-English language journals. Studies were excluded that specifically focus on a subgroup of people, such as children, pregnant women, intravenous drug abusers, and smokers. Additionally, studies were excluded that had only one type of cause-specific mortality, unless it was a broad category such as AIDS-related or non-AIDS related (e.g., exclude a study that only looks at cardiovascular mortality).

After the initial inclusion/exclusion criteria were applied, the studies were re-reviewed to avoid duplication by publication type or by cohort. Where a study is available as both a conference presentation, pre-print, or a published manuscript, then the manuscript was selected. Pre-prints would be selected above conference presentations. If two conference presentations were available, then the most recent would be selected. Where two different studies were found from the same cohort, then the most recent study was selected. If a study from an individual cohort that participates in a cohort collaboration, as well as a study from that cohort collaboration (with overlapping years of study) are both available, then the individual cohort study was excluded to avoid duplication of data. We also searched references of eligible studies, to identify other eligible studies not picked up by the initial search.

Extraction

For each study, we extracted the first author, country or countries of study, years of study, and the source/cohort of data, where applicable. Where possible, data were stratified across different follow-up periods and by ART status.

Within each study follow-up period, we extracted for PLHIV: Number of persons, number of deaths, number of deaths due to each reported type of cause-specific mortality, person-years, all-cause mortality rate, cause-specific mortality rates, excess mortality rate, definition of HIV/AIDS-related mortality, median baseline CD4 cell count, median baseline age, % female, % on ART. We had intended to stratify this by ART status if appropriate data were available. For people without HIV, we extracted: Number of persons, number of deaths, person-years, all-cause mortality rate, median baseline age, % female.

If a study reported an all-cause mortality rate among PLHIV and a standardised mortality ratio (SMR) compared with a general population/people without HIV, then an all-cause mortality rate for the general population would be calculated by dividing the rate among PLHIV by the SMR (e.g. 118 deaths per 10,000 person-years among PLHIV divided by an SMR of 5.7 = 20.7 deaths per 10,000 person-years). If studies reported the total number of deaths to PLHIV and the subset of deaths due to non-AIDS causes, then the remainder would be used as AIDS-related deaths.

In De Coninck et al (109), the number of cause-specific deaths was only given for non-AIDS cancer, cardiovascular disease (CVD) and violent deaths, so the remainder were assumed to be HIV/AIDS-related, although this is likely an overestimate.

Evidence synthesis

We reported the overall excess mortality rates among PLHIV versus the general population, the AIDS-related mortality rate among PLHIV, and the proportion of excess mortality that is made up of AIDS-mortality. As the number of "excess deaths" was not always available, this was calculated by dividing the number of deaths due to AIDS by the proportion of the excess mortality rate that was due to AIDS (e.g. 1268/0.29=4367). These data were meta-analysed through the metaprop command in Stata to calculate the pooled proportion of excess mortality due to AIDS. We repeated this to calculate the pooled proportion of all-cause mortality due to AIDS (random effects, weighting by the number of all deaths). Our intention was to report and calculate these proportions separately for PLHIV on and off ART and for different regions.

Meta-regression

A random-effects meta-regression was carried out through the metareg command in Stata (random effects, weighting by the number of excess deaths). The outcome was the proportion of excess mortality due to AIDS and the independent variables were national ART coverage at the study mid-year point (using UNAIDS data – some of which is confidential) and whether the Causes of Death in HIV (CoDe) protocol (12) was used to determine mortality due to HIV/AIDS. For the study by Karnite et al(110), we took 2009 as the study mid-year as this was the year that was used to calculate the SMRs with the general population, whilst the study start year was 1987 when the first case of HIV in Latvia was recorded, so the data would have been heavily right-skewed.

Results

Of 4485 studies identified by the initial search, 17 were eligible for inclusion. Searching through the references of the eligible studies resulted in two extra studies being identified: one from British Columbia, Canada (111) and one from Denmark (112) (N=19). Eleven studies were then removed, four from the Spanish CoRIS cohort(23, 113-115), two from the Danish HIV cohort(112, 116), and one from the PISCIS cohort(82) that are all part of the ART-CC, one poster that duplicated information from an included manuscript by Croxford et al (117), and three that were older studies from the same cohort/population as other eligible studies(118-120). After these removals, eight studies remained (table 7). All studies were from high-income countries where sex between men is the major mode of acquisition; 6/8 from the WCENA region, one from Japan, and one from South Korea. Due to a lack of data, no analyses were performed stratifying by region.

The percentage of PLHIV that were female was <40% in all studies (all but one studies reported percentage). The percentage of PLHIV on ART was not always available or clear. Only one study had all PLHIV on ART; no studies reported the data for PLHIV off ART. The definition of HIV/AIDS-related mortality and how this was captured varied between studies. Two studies used the CoDe protocol, one used a panel of physicians, and the other five taking the underlying cause ICD-10 information at face value without correction for misclassified causes of death or other information (e.g., recent CD4 cell counts). None of the included studies reported on cause-specific mortality in a manner that would allow the proportion of mortality due to AIDS to be adjusted to exclude deaths where data on the cause were entirely missing (distinct from unknown).

For two studies, the required data were available for multiple follow-up periods (table 8). The total number of person-years included for PLHIV was 1,331,742, in which time there were 17,471 deaths, for an overall mortality rate of 0.0131 per year. Of the 17,471 deaths, 7,721 were classified as HIV/AIDS-related, an overall AIDS-related mortality rate of 0.0058 per person-year, giving 44% of all-cause mortality that was due to HIV/AIDS – 43% (95% confidence interval: 35-51%) in the random effects meta-analysis. The all-cause and AIDS-related mortality rates varied from 0.0049 and 0.0007 in the 2012-2015 follow-up period in Trickey et al (where all PLHIV were on ART) (16), respectively to 0.0335 and 0.0214 in Fontela et al.'s 1999-2003 follow-up period (121). The lowest general population comparator mortality rate was 0.0015 in Nishijima et al, rising to 0.0086 in Eyawo et al (111).

The excess mortality rates comparing the PLHIV with the general population varied from 0.0021 in Trickey et al's 2012-2015 follow-up period to 0.0318 in Fontela et al's 1999-2003 follow-up period (16, 121). The proportion of the excess mortality that could be attributed to HIV/AIDS-related causes varied from 0.33 in Trickey et al (16) to 0.73 in Park et al (86). The meta-analysed proportion was 0.53 (95%CI: 0.45-0.61), which was the same as the unweighted mean. In both studies that reported multiple successive time periods, the excess mortality rate as well as the percentage of excess mortality attributed to AIDS decreased over time.

In the meta-regression for the proportion of excess mortality due to AIDS, the constant term was 0.8072 (95%CI: -0.1522, 1.6297), the coefficient for the percentage of PLHIV on ART was -0.0084 (95%CI: -0.0244, 0.0075), and the coefficient for the study using the CoDe protocol was -0.4603 (95%CI: -1.1431, 0.2225). An example of a calculation for a setting with 90% ART coverage, not using the CoDe protocol would be: (exp(0.8072 + (-0.0084*90)))/(1+exp(0.8072 + (-0.0084*90)))=0.51.

Limitations

There are several limitations regarding the extracted data. Firstly, no information available for sub-Saharan Africa or any low- or middle-income countries, so the generalisability of these results outside of Europe, North America, and high-income East Asian countries is unclear. All these studies were in settings where sex between men was the major route of transmission, so the applicability of these findings to Spectrum's excess non-AIDS mortality among injecting drug use-driven epidemics is also unclear. The definition of HIV/AIDS-related mortality and how this was captured varied between studies, which may mean that some studies are underestimating or overestimating HIV/AIDS-related mortality due to misclassified ICD codes. The reporting for most studies did not allow us to separate out the deaths where all data on cause of death were missing – distinct from deaths where data were available, but the cause was coded as unknown – which may have led to the proportion of deaths due to AIDS being under-estimated. Finally, the percentage of PLHIV on ART was not always available or was unclear, which may also affect the generalisability and interpretation of these findings for use as model parameters in ART-stratified population. Whilst most studies likely had high percentages of PLHIV on ART by the end of their follow-up (if not the start), just one study had all PLHIV on ART – the study with the lowest mortality rates.

Table 7: Characteristics of included studies

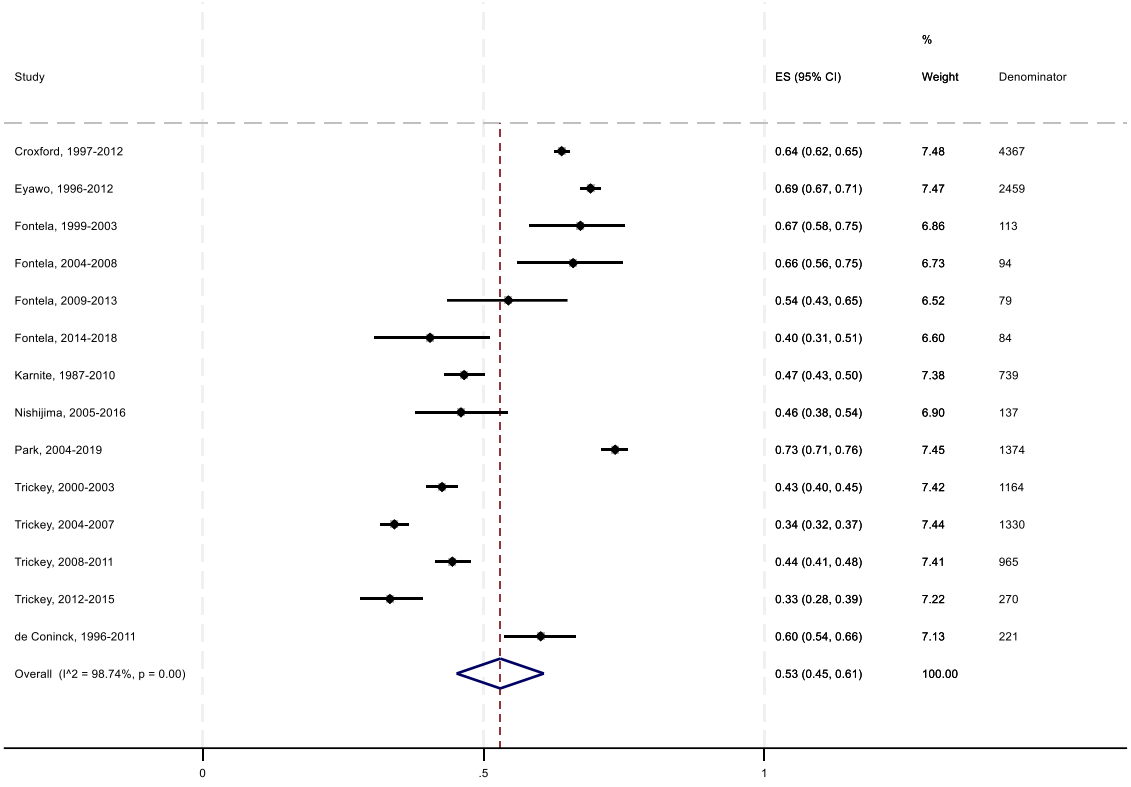
First author	Location	Years	Median baseline age	% female	% on ART	Comparison against gen-pop	AIDS-related mortality definition
Croxford (64)	England and Wales	1997-2012	34 (IQR: 28-41)	36%	66%	Age- and sex-matched general population mortality rates	Death reports from HIV clinicians through routine surveillance and death auditing
de Coninck (109)	Sweden	1996-2011	Mean: 37.6	36%	>56%	1:2 matching with HIV-negative people from population register by age, sex, and birth region	ICD9/ICD10. Only rates for non-AIDS cancer, CVD, and violent deaths given; the remainder were assumed to be AIDS-related
Eyawo (111)	British Columbia, Canada	1996-2012	38 (IQR: 32-46)	20%	74%	Direct comparison with a randomly sampled (age/sex-matched) HIV-negative control group in region who had personal health numbers	ICD9/ICD10 categories
Fontela (121)	Navarra, Spain	1999-2018	1999-2003: 37 (IQR: 34-41) 2014-2018: 47 (IQR: 40-52)	33%	1999-2003: 72% 2014-2018: 88%	Age- and sex-matched general population mortality rates	HIV-related ICD10s: B20-B24 and R75
Karnite (110)	Latvia	1987-2010	NA	NA	NA	Age-matched general population mortality rates	HIV-related ICD10s: B20-B24
Nishijima (122)	Tokyo, Japan	2005-2016	36 (IQR: 32-46)	8%	32% at enrolment	Age- and sex-matched general population mortality rates	Adapted Cause of Death (CoDe) project protocol
Park (86)	South Korea	2004-2019	Mean: 40.3	11%	91%	Age- and sex-matched general population mortality rates	ICD10 categories
Trickey (16)	Europe (Multi-country)	2000-2015	37 (IQR: 31-45)	27%	100%	Age-, sex-, and country-matched general population mortality rates	Adapted Cause of Death (CoDe) project protocol

Table 8: Extracted data on mortality rates

First author	Years	N	Deaths	AIDS deaths	Person years	All-cause mortality rate among PWH	AIDS mortality rate among PWH	All-cause mortality rate among gen-pop	Excess all-cause mortality rate vs gen-pop	AIDS mortality as % of Excess mortality	AIDS mortality as % of all-cause mortality
Croxford*	1997-2012	88994	5302	2791	448839	0.0118	0.0062	0.0021	0.0097	0.64	0.53
de Coninck	1996-2011	4066	275	133	24336	0.0113	0.0055	0.0022	0.0091	0.60	0.48
Fontela	1999-2003	839	119	76	3552	0.0335	0.0214	0.0016	0.0318	0.67	0.64
	2004-2008	881	101	62	3826	0.0264	0.0162	0.0002	0.0246	0.66	0.61
	2009-2013	964	89	43	4159	0.0214	0.0103	0.0024	0.0190	0.54	0.48
	2014-2018	1059	97	34	4686	0.0207	0.0073	0.0028	0.0179	0.41	0.35
Karnite	1987-2010	4888	738	344	31273	0.0236	0.0100	0.0021	0.0215	0.46	0.42
Nishijima	2005-2016	2797	165	63	18858	0.0088	0.0033	0.0015	0.0073	0.46	0.38
Park*	2004-2019	13919	1669	1009	97439	0.0171	0.0104	0.0030	0.0141	0.73	0.60
Trickey	2000-2003	35697	1380	496	94735	0.0151	0.0049	0.0036	0.0115	0.43	0.32
	2004-2007	54213	1700	454	153993	0.0118	0.0028	0.0036	0.0082	0.34	0.24
	2008-2011	72800	1725	429	207739	0.0082	0.0020	0.0037	0.0045	0.44	0.24
	2012-2015	64959	710	90	129317	0.0049	0.0007	0.0028	0.0021	0.33	0.14
Eyawo	1996-2012	13729	3401	1698	108990	0.0312	0.0156	0.0086	0.0226	0.69	0.50

* Included in review #2 – often studies were not eligible for review #2 due to not stratifying by ART status.

Figure 6: Meta-analysis of the proportion of excess mortality that is due to AIDS



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