Recommendations for defining preventable HIV-related mortality for public health monitoring in the era of "getting to zero": an expert consensus

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ABSTRACT

Background: “Getting to Zero”, reducing avoidable mortality due to HIV, is a commonly cited strategic aim.

Methods: Recommendations to define preventable HIV-related mortality for public health monitoring using death certificate data were agreed by experts.

Findings: Deaths among people positive for HIV should be categorised as: HIV-related, possibly HIV-related, not HIV-related, or unknown. “HIV-related” deaths should include those where the primary/contributory cause is listed as AIDS, a condition caused by HIV immunodeficiency/pathophysiology, a virally driven malignancy (with causative virus listed), or an antiretroviral treatment (ART)-related adverse reaction/drug-drug interaction. Deaths due to a virally driven malignancy without the causative virus listed should be categorised as “possibly HIV-related”. Deaths not categorised above with HIV listed as a primary/contributory cause should be initially categorised as “possibly HIV-related” and then reviewed nationally/locally to re-assign. Deaths due to a non-AIDS infection, where CD4 count within a year of death was <200 cell/μL, should be categorised as “possibly HIV-related”. All “HIV-related” and “possibly HIV-related” deaths should be considered “preventable” where: i) an individual was diagnosed with HIV late (<350 cells/μL) and either died from an AIDS-defining condition within 12 months of HIV diagnosis or died due to an AIDS-related malignancy diagnosed within 12 months of HIV or ii) an intervention/screening for a condition known to reduce the incidence of the HIV-related cause was not received. “HIV-related” and “possibly HIV-related” deaths should be considered “potentially preventable” where: i) cause of death was an ART-related adverse event/drug-drug interaction or ii) access/uptake of HIV care and/or ART was inadequate. Applying this definition to 2019 UK surveillance data, 30% of 644 deaths among people with HIV were “HIV-related”/“possibly HIV-related” and at least 63% of these were “preventable”/“potentially preventable.

Interpretation: Measuring preventable HIV-related mortality should become a standard approach and inform interventions to improve outcomes.

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UNSTRUCTURED SUMMARY

"Getting to Zero" - reducing mortality due to both HIV and avoidable deaths among people with HIV - is a commonly cited strategic aim. However, there are either no clear definitions attached to these aims, with regard to what constitutes HIV-related or preventable mortality, or their ambition is limited. This Viewpoint article presents consensus recommendations to define preventable HIV-related mortality for a pragmatic approach to public health monitoring using national surveillance data. These recommendations were informed by a comprehensive literature review and agreed by 43 international experts, including clinicians, public health professionals, researchers, commissioners and community representatives. Applying these recommendations to 2019 UK data, 30% of deaths among people with HIV were "HIV-related"/"possibly HIV-related" and at least 63% of these were "preventable"/"potentially preventable. The application of these recommendations by health authorities will ensure consistent monitoring of HIV elimination targets and allow for the identification of inequalities and areas for intervention.

BACKGROUND

Availability of antiretroviral therapy (ART) has resulted in a substantial decline in all-cause mortality among people with HIV and marked increases in life expectancy.[1-4] With the introduction of treatment, and as people live longer with HIV, there have been fewer deaths due to acquired immunodeficiency syndrome (AIDS) and an increasing proportion of deaths from non-AIDS-related conditions, including non-AIDS malignancies, cardiovascular disease (CVD), and liver disease.[1,2,5]

In the era of international HIV elimination goals, a number of governmental and non-governmental organisations have aims for "getting to zero", including reducing mortality due to HIV and/or AIDS and avoidable deaths among people living with HIV. The Joint United Nations Programme on HIV/AIDS (UNAIDS) calls for a reduction of AIDS-related deaths worldwide, likely to represent World Health Organization (WHO) stages three and four.[6] The Fast Track Cities Initiative (FTCI) seeks to "stop preventable HIV deaths".[7] However, there are either no clear definitions attached to these aims, with regard to what constitutes HIV-related or preventable mortality, or their ambition is limited. In particular, monitoring only deaths due to an AIDS-defining illness would miss many deaths attributable to HIV infection.

In this paper, we describe development of expert consensus recommendations to define preventable HIV-related mortality using national HIV surveillance data.

APPROACH

In 2020, a collaboration, led by FTCI London with the British HIV Association (BHIVA), the European AIDS Clinical Society (EACS), and the United Kingdom Health Security Agency (UKHSA) (formerly Public Health England), initiated a project to develop consensus recommendations for defining preventable HIV-related mortality to enable monitoring towards global targets and implementation of appropriate interventions to improve person-centred HIV care. The project included a rapid review scoping how preventable HIV-related mortality was defined in the literature, drafting of proposed recommendations to define preventable HIV-related mortality, an international expert review of these draft recommendations, a wider stakeholder discussion with consensus and piloting of the agreed recommendations against historical national HIV surveillance data from the UK.

Rapid literature review

A systematic approach was taken in rapidly reviewing the literature in March 2021 to scope how preventable, HIV-related death was being defined. The search terms and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram can be

found in Appendix 1 (pages 9-11), alongside all references (pages 1-8). Academic databases (Embase, Medline), theses (e-theses online service (EThOS), Networked Digital Library of Theses and Dissertations (NDLTD), Open Access Theses and Dissertations (OATD)), the UNAIDS website, WHOdatabase, and International AIDS Society, and AIDS conference abstracts were searched. Studies published from 2010 to 17 March 2021 in the English language presenting a measurable definition of mortality were reviewed (conference abstracts 2016-2020). A 2010 cut-off was used to capture relatively recent studies and reflect the WHO recommendations for a public health approach to ART, widening access with an increased threshold for prescription (<350 cells/μL), which impacted survival of people with HIV.[8] Studies of children (aged <15 years) were excluded. There were 10,385 de-duplicated search results of which 129 were included after full-text review.

The literature review revealed that most research focussed on "AIDS-related mortality" using the definitions for AIDS-defining conditions from either the 1993 Centers for Disease Control and Prevention (CDC) AIDS list,[9] WHO stages three and four, the International Classification of Diseases, Ninth or Tenth Revision (ICD-9 or ICD-10) codes or Causes of Death in HIV (CoDe) protocol.[10] Some studies developed customised definitions of "AIDS-related mortality", incorporating factors such as time from AIDS illness to death and CD4 cell count. There were several studies that defined HIV-related deaths as those among people dying of AIDS-defining illnesses only or described "HIV/AIDS" deaths. Few studies considered non-AIDS-related causes of HIV-associated mortality. Those that described "HIV-related mortality" or "HIV-attributable mortality" defined HIV-related with a specified set of ICD-10 (e.g. B20-B24) or ICD-9 codes or by custom criteria (e.g. immunodeficiency-related disease such as bacterial pneumonia caused by *Streptococcus pneumoniae*, chronic diarrhoea, etc.). There were no studies considering suicide or substance misuse as HIV-related causes of death. Studies describing preventable mortality among people with HIV were rare but generally authors considered deaths from AIDS, following late diagnosis and within a year of HIV diagnosis to be avoidable.

Based on these literature search findings, a team of public health professionals and an HIV clinician at the UKHSA drafted recommendations for defining preventable HIV-related mortality, which were then tested through expert panel review and stakeholder discussion.

Expert review of proposed recommendations

Findings from the rapid literature review and the draft recommendations were sent to a group of international experts for comment and the recommendations were amended based on initial feedback. In June 2021, the UKHSA hosted a wider stakeholder meeting to present and

discuss the updated definition recommendations. The meeting was attended by 43 international experts including specialist clinicians, public health professionals, researchers, and civil society representatives, who advocated for a pragmatic approach to monitoring preventable HIV-related deaths for public health purposes. A full list of stakeholders who contributed and their affiliations can be found in Appendix 2 (pages 12-14) . Through working group discussions and written communication following the meeting, a definition for monitoring was agreed upon, in the form of a series of recommendations.

RECOMMENDATIONS

This definition of preventable HIV-related mortality was devised for surveillance and public health monitoring purposes. As such, these recommendations should be applied to nationally reported data for deaths complemented with patient information on HIV testing, diagnosis, and care. Categorisation of deaths using this method will result in over- and under-reporting of some categories; however, this should subsequently be corrected as part of a more detailed national and/or local review where possible, using methodology such as the Causes of Death in HIV (CoDe) protocol.[10]

Recommendation 1: Deaths among people with HIV should be categorised as: (a) HIV-related, (b) possibly HIV-related, (c) not HIV-related, or (d) unknown cause of death.

Recommendation 2: Deaths among people with HIV should, for surveillance purposes, initially be categorised based on information on the death certificate. In some settings, there may be no death certificate or official cause of death reported. Where these data are systemically inadequate, it is recommended that WHO guidance is followed.[11] In a setting where information is routinely available, but cause is missing, cause of death should be recorded as “unknown”.

Recommendation 3: The definition applies only to those people who have tested positive for HIV. HIV diagnosis may (rarely) be made post-mortem. In high prevalence countries with inadequate data on HIV status of cases, it is recommended to apply WHO tools.[11]

Recommendation 4: Where an AIDS-defining illness (Appendix 3, page 15) is reported as a primary or contributory cause of death, the death should be categorised as “HIV-related [AIDS]”.

Recommendation 5: Where one of the listed conditions (Appendix 4, page 16 – adapted from Lucas et al.[12]) caused by HIV immunodeficiency or pathophysiology (e.g., HIV-related nephropathy or HIV-associated dementia) is recorded as a primary or contributory cause of death, the death should be categorised as “HIV-related”.

Recommendation 6: Where the primary or contributory cause of death is listed as an ART-related adverse reaction or drug-drug interaction, the death should be categorised as "HIV-related".

Recommendation 7: Where the primary or contributory cause of death is listed as a virally driven non-AIDS-related malignancy, the death should be categorised as specified in Table 1. Where the causative virus is listed as a contributory cause, the death can be considered as "HIV-related" and where the virus is not specifically mentioned, the death should be categorised as "possibly HIV-related" and further investigation into the clinical data and circumstances around the death may be required.

[TABLE 1]

Recommendation 8: Where HIV infection is listed as a cause or as contributing to the cause of death, the death should be categorised as "possibly HIV-related". Deaths in this category should be reviewed at either a national or local level (for example by applying the CoDe protocol[10]) to confirm they are "HIV-related" or to amend categorisation to "not HIV-related". Findings from local reviews should be fed back through national surveillance pathways. In countries where it is mandatory to include HIV infection on the death certificate, regardless of its contribution to the cause of death, this recommendation will need to be adapted locally and applied when HIV is included in the direct sequence of causation. This is likely to over-report HIV-related mortality at the national surveillance level, but this may be corrected to a degree when undergoing the subsequent review process where possible (e.g., CoDe[10]).

Recommendation 9: Table 2 shows how a number of causes of death should be categorised where HIV infection is not included as a primary or contributory cause on the death certificate.

[TABLE 2]

Recommendation 10: An "HIV-related" or "possibly HIV-related" death should be considered "preventable" where a person is diagnosed late (CD4<350 cells/μL) or very late (CD4<200 cells/μL) and:

- Dies within 12 months due to an AIDS-defining condition, or
- Dies due to an AIDS-related malignancy that occurred/was diagnosed concurrently with or in the first 12 months following the person's HIV diagnosis

Even if an individual has no identifiable missed opportunities for earlier HIV diagnosis, this recommendation recognises that people should be aware of their individual risks and we, as public health and other allied professionals, have an obligation to increase understanding

among communities as to where and how to access testing, either through the healthcare system or elsewhere.

The impact of a distant history of late diagnosis (in particular for malignancies) will be captured using the date of diagnosis and categorised in ranges of the time between late diagnosis and death (e.g., 1-4, 5-9, 10-19, ≥20 years), and hence considered "potentially preventable" for specific conditions, but a further investigation into the clinical data and circumstances around the death may be needed in order to determine if "preventable".

Recommendation 11: An "HIV-related" or "possibly HIV-related" death should be considered "potentially preventable" where the primary or contributory cause of death is listed as an ART-related adverse reaction or drug-drug interaction.

Recommendation 12: An "HIV-related" or "possibly HIV-related" death should be considered "potentially preventable" where access to, uptake of, or persistence with, HIV specialist care and/or ART was inadequate, including:

- HIV treatment was commenced more than three months after diagnosis and within one year of death.
- Viral load was not effectively suppressed in the three years prior to death (without evidence of stopping ART due to initiating palliative care). This would include people attending HIV services not receiving ART (including where ART not available) and people with periods of significant viraemia (>1,000 copies/mL on two or more occasions) in the three years prior to death. Three years was chosen as a pragmatic cut-off based on expert opinion. In low- and middle-income countries, a viral load ≤1,000 copies/mL defines treatment success (virological suppression), according to the WHO.[13]
- No evidence of accessing HIV treatment/care services within the three years prior to death.

Recommendation 13: An "HIV-related" or "possibly HIV-related" death should be considered "preventable" where an intervention for a condition known to reduce the incidence of the HIV-related condition that caused death was not received. Preventive interventions to be considered include vaccination for hepatitis B virus (HBV), hepatitis A virus, invasive pneumococcal disease, human papillomavirus (HPV), varicella, coronavirus disease 2019 (COVID-19), and influenza, as well as cytology for cervical cancer, screening for tuberculosis and/or cryptococcal antigen screening.[14-17] However, countries should adapt this list according to what is/was recommended and/or available at that time. Where the intervention or screening

was not available but the intervention reflected best practice or international guidelines at the relevant time, the death should be categorised as “potentially preventable”.

These recommendations have been presented as flow diagrams to aid in categorisation of deaths as HIV-related and/or preventable in Figure 1 and 2 below. Application of these recommendations to UK HIV surveillance data is described below and presented visually in Appendix 5 (pages 17-18).

[FIGURES 1 and 2]

APPLICATION USING UK DATA

In the UK, national HIV surveillance is the responsibility of the UKHSA. Data on people newly diagnosed with HIV and people receiving HIV care in England, Wales and Northern Ireland are reported by diagnosing laboratories and National Health Service (NHS) outpatient clinics. Data on people with HIV from Scotland are collected and submitted to the UKHSA by Public Health Scotland. Data on deaths among people with HIV (all-cause mortality) are received by the UKHSA either through direct reporting by clinicians annually, and/or through routine linkage of HIV surveillance data with the national death register held by the Office for National Statistics (ONS).

There were 644 deaths that occurred among people with HIV aged ≥15 years in the UK in 2019, reported to the UKHSA. Median age at death was 54 years (interquartile range: 47-63 years).

Of the 644, 116 people died of unknown causes (18%), with either no death certificate data available or with an unknown cause listed. Of the remaining 528 people, 104 died from an AIDS-defining illness, whose deaths were classified as “HIV-related [AIDS]” (16% of total). A further five people died from a condition caused by HIV immunodeficiency or pathophysiology, whose deaths were classified as “HIV-related [non-AIDS]” (1% of total). Of the remaining 419 people, 29 died from a virally driven malignancy; 11 had the causative virus listed on the death certificate and their deaths were thereby classified as “HIV-related [non-AIDS]” (2% of total) and 18 had no causative virus listed and their deaths were thereby classified as “possibly HIV-related” (3% of total). In 2019, no one was reported to have died from an ART-related adverse event or drug-drug interaction.

Of the remaining 390 people, 199 had HIV listed as a primary or contributory cause of death. These deaths were reviewed nationally by an HIV clinician, a pathologist, and an epidemiologist; it became evident that HIV was often included on the death certificate as an underlying condition (cause 2), alongside a range of other co-morbidities, many having no

obvious causative link to the death. HIV was assessed as being likely a contributory cause in a quarter of cases, resulting in 53 “possibly HIV-related” deaths (8% of total). It is important to note that in the UK, it is not mandatory to include HIV infection as a cause of death on the death certificate unless it contributes directly to the cause of death. Two people died from a non-AIDS infection with a CD4 count of <200 cells/µL within a year of death; these deaths were classified as “possibly HIV-related” (0·3% of total).

The deaths of the remaining 335 people were considered to be “not HIV-related” (52% of total). Overall, almost a third of deaths (30%) among people in the UK with HIV in 2019 were considered to be “HIV-related” (n=120) or “possibly HIV-related” (n=73).

Among the 193 deaths classified as “HIV-related” or “possibly HIV-related”, 26 (13%) were “preventable”, being among people who died from an AIDS-defining illness within 12 months of a late HIV diagnosis (CD4<350 cells/µL). Another 31 deaths (16%) were among people who died of an AIDS-defining illness more than 12 months after a late HIV diagnosis, which were considered “potentially preventable”. Of these, five people were diagnosed late one to four years prior to death, six people five to nine years prior, 15 people 10-19 years prior, and five people more than 20 years prior. We recommend further local clinical investigation into these deaths to gain additional insight into the individual circumstances and whether they were preventable. With regard to treatment and HIV care markers for the remaining 136 people, there were nine (5%) who started ART more than three months after diagnosis and within 12 months of death, 44 (23%) whose viral load was not effectively suppressed in the three years prior to death with periods of significant viraemia (>1,000 copies on two or more occasions) and 12 (6%) who were not in care and/or taking treatment in the three years prior to death, resulting in a further 65 “potentially preventable” deaths. Currently, national HIV surveillance data in the UK do not allow for assessment of the receipt of interventions and/or screening.

Overall, as a minimum based on these recommendations, 13% (26/193) of “HIV-related” and “possibly HIV-related” deaths among people with HIV in the UK in 2019 were “preventable” and a further 50% (96) were “potentially preventable”, representing 19% (122/644) of all deaths.

DISCUSSION

The expert, consensus recommendations for defining preventable HIV-related mortality presented here provide a pragmatic approach to the public health monitoring of progress towards international HIV mortality targets. Measuring preventable HIV-related mortality will allow for the identification of inequalities among subgroups of people with HIV and will provide insight into where along the HIV care pathway appropriate interventions could be targeted to

improve outcomes. It will also facilitate resource allocations for HIV programmes nationally. Review of local implementation of EACS HIV management guidelines and ECDC HIV testing guidelines may prove informative.[17,18]

It is important to acknowledge that application of these recommendations is reliant on the existence of robust national HIV surveillance systems, which not all countries will have. National public health agencies and institutions should strengthen their surveillance systems to ensure adequate capture of mortality data on people with HIV as well as data on HIV diagnosis and subsequent HIV care (e.g., viral load, CD4 counts, and ART uptake). The latest Dublin Declaration HIV monitoring data indicate that only 68% of the 50 European and Central Asian countries capture data on deaths among people with HIV through surveillance mechanisms; 80% were able to report data on both ART and viral loads among those diagnosed.[19]

In the UK, 30% of deaths among people with HIV occurring in 2019 were either “HIV-related” or “possibly HIV-related”; of these, at least 63% were “preventable” or “potentially preventable”. Overall, at least one in five deaths among people with HIV were HIV-related and preventable. Notably, one in six people with HIV died of an AIDS-defining illness in the era of effective treatment. Applying these recommendations to the UK data has set the baseline for tracking progress towards reaching zero preventable HIV-related deaths among people with HIV. However, further work is needed to improve reporting of intervention uptake and screening among people with HIV in the UK to further quantify preventable deaths; this information could be collected through existing enhanced national HIV surveillance mechanisms, such as the National HIV Mortality Review, a collaboration between the UKHSA and BHIVA.[20] We encourage other countries to consider applying this methodology to their national HIV surveillance data, adapting it where necessary.

The recommendations for defining preventable HIV-related mortality presented here rely on both accurate and timely death certificate data and reviews of deaths among people with HIV, both nationally and locally. For those deaths that require further investigation at a local level to better understand the circumstances leading up to death (i.e. through use of the CoDe protocol[10]), clear processes need to be in place to facilitate feedback of these local findings to national public health agencies. This will allow re-categorisation of deaths initially considered to be “potentially preventable” to either “preventable” or “not preventable” (i.e. do not meet the definition of “preventable”). Although it is important to note as described in Recommendation 13, that this will differ by country and health system. Conversely, national surveillance leads should feed back instances where HIV has been incorrectly included on the death certificate and ensure learnings for future completion. Having a robust feedback loop will become

particularly important as we move closer towards zero preventable HIV-related mortality, with increased scrutiny into each death among individuals with HIV. There is a need to ensure clinicians are adequately trained to accurately report causes of mortality on death certificates, to improve data quality and reliability.[21,22]

In conclusion, adoption of these expert-agreed recommendations for defining preventable HIV-related mortality should be considered by health authorities to monitor HIV elimination goals. International health bodies, including the UNAIDS, WHO, and ECDC, will need to continue to work with countries to improve collection of mortality data among people with HIV and data on HIV clinical care. Measuring preventable HIV-related mortality should inform stakeholders on how to improve outcomes for people living with HIV and identify areas for intervention.

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AUTHOR CONTRIBUTIONS

All authors were involved in development of the consensus definition, critically appraised the manuscript and approved its submission. SEC and AKS conceived this work. SEC led the study, carried out data analyses, drafted the manuscript, incorporated author comments, and was responsible for the final submitted version. VM and SEC carried out the literature review. VM extracted the HIV surveillance data for analysis, verified the data analysis, and designed the flow diagrams in Figures 1 and 2. AKS, SBL, RFM, and FAP categorised causes of death and reviewed the death certificate data. SBL led development of Appendix 4 (page 16).

DATA AVAILABILITY STATEMENT

No data are available. Patient-level data are collected by the UKHSA and stored on secure servers that can only be accessed by the relevant surveillance team at UKHSA. The principles for accessing, storing and sharing data are given in UKHSA's HIV and STI data sharing policy found here: https://www.gov.uk/government/publications/hiv-and-sti-data-sharing-policy.

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DECLARATIONS OF INTEREST

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Tables

Table 1: Virally driven non-AIDS related malignancies considered to be HIV-related

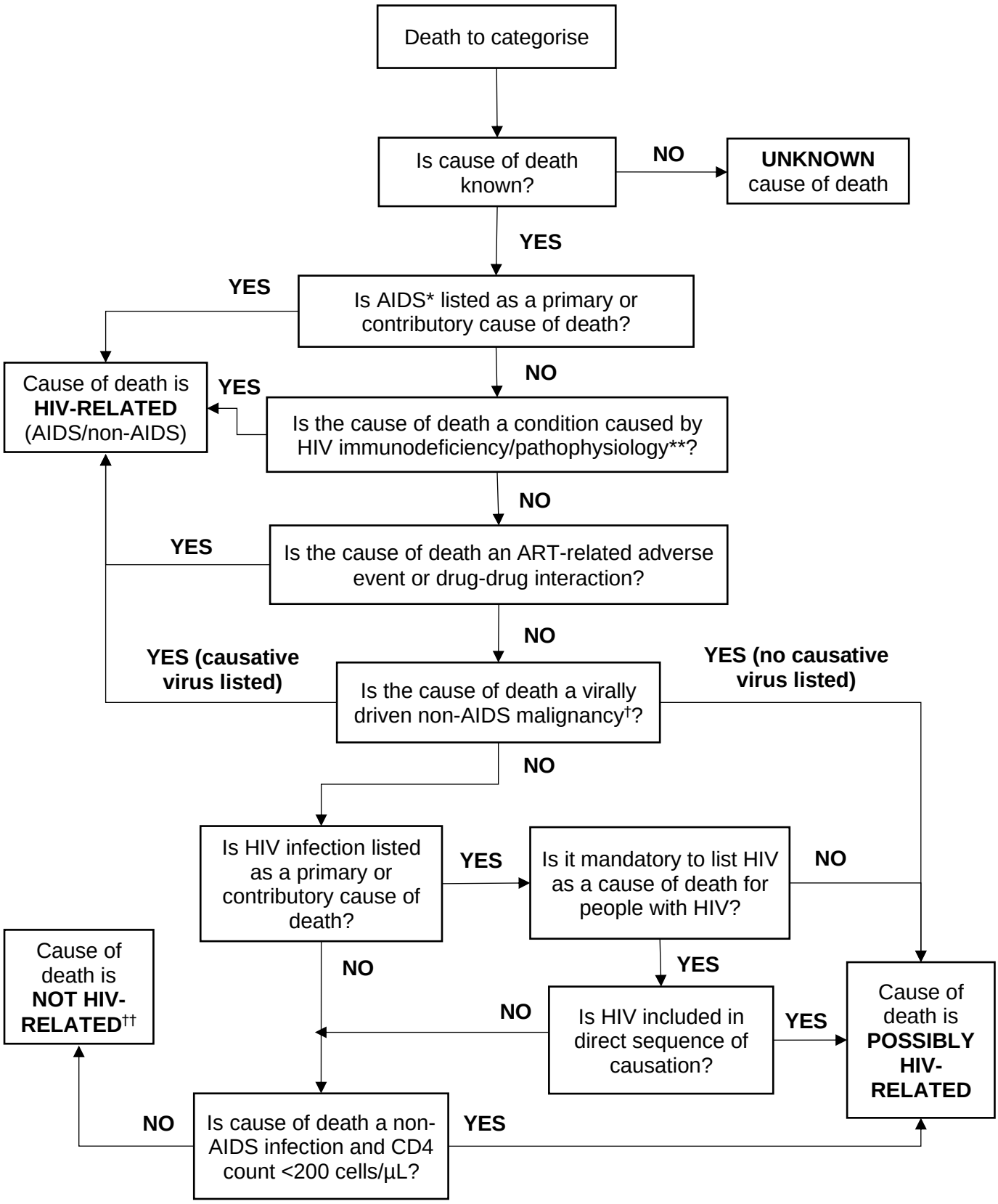
Virus	**Virally driven malignancy**
Human herpes virus 8	Castleman Disease Primary effusion lymphoma
Human papillomavirus (HPV)	Anal cancer Penile cancer Vulval cancer Vaginal cancer Oropharyngeal cancer
Hepatitis B virus (HBV) Hepatitis C virus (HCV)	Hepatocellular carcinoma
Human T-lymphotropic virus (HTLV)	Adult T-cell leukaemia/lymphoma
Epstein Barr virus	Hodgkin Disease Nasopharyngeal carcinoma Laryngeal cancer Gastric cancer Lymphoproliferative disorder (not lymphoma)

Table 2: Categories recommended where HIV is not included as a primary or contributory cause on the death certificate

Cause of death	**Category**	**Condition**
Non-AIDS infection	Possibly HIV-related	Among those with a last CD4 count within a year of death <200 cells/μL
Non-AIDS malignancy	Not HIV-related	Unless it is a virally driven non-AIDS-related malignancy listed in Table 1 (see Recommendation 7)
Conditions occurring more frequently in people living with HIV	Not HIV-related	
Co-morbidities (e.g., CVD, chronic obstructive pulmonary disease, etc.)	Not HIV-related	
Suicide, substance misuse, accident, mental health illness, homicide	Not HIV-related	

Figures

Figure 1: Determining whether a death can be considered HIV-related



* See Appendix 3 for a list of AIDS-defining conditions.
** See Appendix 4 for a list of conditions caused or worsened by HIV immunodeficiency/pathophysiology.
† See Table 1 for a list of virally driven malignancies.
††Includes other co-morbidities including conditions occurring more frequently in people living with HIV, suicide, substance misuse, and mental illness.

Figure 2: Determining whether an HIV-related or possibly HIV-related death was preventable