

Protocol

Coding Causes of Death in HIV

CoDe^{*}

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1. Background

A significant proportion of deaths in HIV-1 infected persons are now caused by non-AIDS events.¹⁻⁷ It is important to closely monitor the causes of death in this population in order to target interventions appropriately, should specific causes of death emerge or become predominant.⁷⁻¹⁰ It is possible that deaths from diseases related to an accelerated aging process will become more frequent. The same applies for causes of death related to co-infections (e.g. hepatitis) or other co-morbidities (e.g. sequelae of intravenous drug use). Furthermore, it is important to be able to evaluate the risk factors for such emerging diseases, including their possible relationship with immunodeficiency.

Until now there has not been a uniform classification system for causes of death in HIV patients. Studies have either created their own coding systems based on frequent and/or 'important' causes (e.g. rare but important adverse events such as lactic acidosis and pancreatitis), or have used ICD9 or ICD10 codes from death certificates. In many cases, the ICD system cannot be directly adapted to HIV infected persons. Many AIDS defining illnesses are poorly identified in the ICD system, and some diseases (e.g. CNS diseases) have a different aetiology in HIV patients and are therefore not covered by the ICD system, or at great risk of mis-classification.¹¹⁻¹³

There has generally been a lack of standardization of the extent and quality of the data on which the coding is based, and a central review process is rarely used. This has led to a wide variation in how the causes of death were coded and recorded, both within and between different studies.

In July 2004, a meeting was held in Copenhagen with the participation from executive committees of a large number of pivotal observational studies and clinical trials that routinely collect data on causes of death. At this meeting, it became clear that there was a need for a harmonization and standardization of the approach taken when collecting data on cause of death and when reviewing these deaths. As a result, the CoDe Project was initiated.

2. Pilot

Through an initial pilot phase, the CoDe case report form (CRF) and guidelines were tested widely at clinics taking part in the D:A:D Study and externally. The pilot included a total of 80 cases from more than 20 clinics. Reviewers appointed by the CoDe working group tested the review process. Subsequently, the CRF and guidelines were modified according to the experience, to ensure clarity of the guidelines and facilitate the collection of data and completion of the CRF. The CoDe methodology has been incorporated in the D:A:D collaboration [D:A:D manual.pdf](#)

3. Methods

The CoDe Project is a uniform coding system that can be applied to studies of individuals with HIV infection, including:

- a detailed data collection on the causes of death and contributing factors, and
- a centralised review process of the data collected.

The purpose of the data collection is to provide sufficient data for the reviewers' classification of the cause of death. Other variables (ethnicity, country, detailed ART history and more) are not a part of the CoDe data collection itself. If desired, this information can be combined with CoDe data collection, e.g. according to principles described by HICDEP ([HICDEP.pdf](#)).

For CoDe, the final coding of the causes of death is performed during the central review.

3.1 Data Collection

A key factor in the evaluation of the pathological processes leading to death is the amount and quality of information available for review. Thus, information that is collected on illnesses, risk factors, and injuries should be as complete as possible. The CoDe case report form (CRF) has been developed for this reason and it is anticipated that the information requested is readily available from the source documents.

The CRF contains the following sections:

- Section 1: Background demographics
- Section 2: Data sources available for the completion of the form
- Section 3: Risk factors
- Section 4: Co-morbidities
- Section 5: Cause of death
- Section 6: Post-Mortem/ Autopsy
- Section 7: ART and laboratory values prior to death
- Section 8: Adverse effects to any type of medical treatment

Guidelines for the completion of the CRF are available in Appendix C. The CRF should be completed by a physician or appointed health care staff, preferably a person with first-hand knowledge of the deceased. Importantly, due to the complexity of the conditions leading to death, preferably *Section 5* of the CRF should be completed by a clinician involved in managing the patient's care around the time of death.

3.2 Review

3.2.1 Purpose of Central Review

Coding of causes of death is a complicated process. The quantity and quality of the documentation that can be obtained varies greatly, and there are inherent uncertainties of the causality sequence of the conditions leading to or contributing to the fatal outcome. By conducting a central review based on a predefined algorithm, and with evaluation by 2 or more expert reviewers, it is anticipated that the reliability and reproducibility of the coding will be enhanced.

3.2.2 How to perform a Central Review

The central review should follow the CoDe guidelines and be performed independently by at least two qualified reviewers. If agreement can be reached immediately, the cause of death is established. If there is disagreement between the two reviewers, or both have coded the cause of death as unknown or unclassifiable, the specific case should be referred to one or more additional reviewers (in case of an organ or disease specific controversy, preferably a specialist within the relevant area should be consulted). The entire panel should work on reaching consensus. However, if this cannot be achieved, the case will either be classified according to majority decision, or by default be unclassifiable.

3.3 Implementation

3.3.1 Infrastructure and quality assurance

Each study implementing the CoDe methods for coding causes of death is responsible for organizing the infrastructure for the data-collection and subsequent review within the frames of the particular study, and for establishing a panel of reviewers. The quality of the information should be ensured by source verification during monitoring, performed by qualified health personnel not affiliated with the centre. Quality control of the database should be ensured by standard quality control measures as established by the individual study.

All cohorts included in the D:A:D Study have implemented CoDe for the collection of causes of death (please refer to the [D:A:D manual.pdf](#) for details of reporting and quality assurance).

3.3.2 Database specifications

CoDe is publicly available free of charge. If studies (outside of the D:A:D collaboration) wish for assistance in setting up the infrastructure for CoDe or to adapt the database specifications, please contact the CoDe coordinating office.

3.3.3 Ethics

It is the responsibility of each study implementing the CoDe methods to ensure that all necessary documents and approvals - according to local/national regulations - are obtained before initiating the data collection. If pertinent, the Medicines Agency and/or Data Surveillance Authorities should be notified.

3.3.4 Feedback

All users of the CoDe project are encouraged to provide feedback to the Coordinating Center. All comments can be sent by email to: code@cphiv.dk or faxed to the [Coordinating Center](#). These comments will provide valuable input when future modifications of the forms and protocol are implemented.

1 4. Organization

4.1 CoDe Working Group

The working group include the persons, who have been actively involved in developing the CoDe project ([Appendix A](#)). The working group will convene annually (by face-to-face meetings or teleconference), or when a critical mass of issues has been raised, to evaluate the progress of the study. The working group is the executive body of the CoDe project.

4.2 Coordinating Office

The coordinating office is located at CHIP, Rigshospitalet, Copenhagen University Hospital and University of Copenhagen, Faculty of Health Sciences.

The coordinating office:

- Contributes to the continued development of the CoDe methods
- Develops and maintains the database specifications
- Organizes teleconferences and meetings for the CoDe working group
- Makes the CoDe documents publicly available

5. Scientific use

Scientific material from studies which have implemented the CoDe methodology are encouraged. Permission is not required. Such material, however, should include acknowledgement of the CoDe methods by referring to the www.cphiv.dk/CoDe website in the methods section of the material. Copies of published articles using the CoDe methodology would be appreciated at the coordinating office.

6. Reference list

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Appendix A. CoDe Working Group

Appendix A. CoDe Working Group

Name	First name	Affiliation	City	Country
d'Arminio Monforte	Antonella	ICONA	Milan	Italy
Chene	Genevieve	Mortalité 2000; ART CC	Bordeaux	France
Davey	Richard	NIH	Washington	USA
De Wit	Stephane	St Pierre Brussels Cohort	Brussels	Belgium
De Wolf	Frank	ATHENA	Amsterdam	Netherlands
Egger	Matthias	ART CC	Bristol	United Kingdom
Ellefson	Michelle	CHIP; EuroSIDA	Copenhagen	Denmark
El-Sadr	Wafaa	CPCRA	New York	USA
Friis-Møller	Nina	CHIP; DAD	Copenhagen	Denmark
Holkmann Olsen	Christian	CHIP; EuroSIDA	Copenhagen	Denmark
Kirk	Ole	CHIP; EuroSIDA	Copenhagen	Denmark
Law	Matthew	AHOD	Sydney	Australia
Ledergerber	Bruno	SHCS	Zürich	Switzerland
Lewden	Charlotte	Mortalité 2000; ART CC	Bordeaux	France
Lundgren	Jens	CHIP; DAD	Copenhagen	Denmark
Mateu	Silvia	BASS	Barcelona	Spain
Mocroft	Amanda	Royal Free Hospital; EuroSIDA	London	United Kingdom
Peto	Tim	Oxford University; DART study	Oxford	United Kingdom
Phillips	Andrew	Royal Free; DAD; EuroSIDA	London	United Kingdom
Pradier	Christian	Nice Cohort	Nice	France
Reiss	Peter	ATHENA, AMC	Amsterdam	Netherlands
Rhame	Frank	ESPRIT	Minneapolis	USA
Sabin	Caroline	Royal Free; DAD	London	United Kingdom
Sterne	Jonathan	ART CC	Bristol	United Kingdom
Weber	Rainer	SHCS	Zürich	Switzerland
Åkerlund	Börje	HivBIVUS	Stockholm	Sweden

Appendix B. CoDe Case Report Form (CRF)

Cause of Death Form (CRF)

CoDe

*Study: _____

*Patient ID code: _____

*Date of death : ____ - ____ - ____
(dd/mm/yy eg 01-FEB-05)

Section 1 ♦ Background demographics

- * A. Year of birth (yyyy) ____ - ____ - ____ - ____
- B. Gender : ☐ male ☐ female
- C. Height (cm) : ____ - ____ - ____
- D. Weight (kg) : ____ - ____ - ____
(most recent before death)
- E. Date : ____ - ____ - ____
(dd-mm-yy; weight measured)

Section 2 ♦ What data sources were available for the completion of this form? (please mark all that apply)

- A. Hospital files ☐ Yes, complete ☐ Yes, incomplete ☐ No
- B. Outpatient clinic chart ☐ Yes, complete ☐ Yes, incomplete ☐ No
- C. Autopsy report ☐ Yes, complete ☐ Yes, incomplete ☐ No

If other, specify:

- D. Registry ☐
- E. Obituary ☐
- F. Patient's relatives or partner ☐
- G. Patient's medical provider ☐
- H. Nursing home ☐
- I. Other: _____

Section 3 ♦ Risk factors:

A. Ongoing risk factors in the year prior to death:

1. Cigarette smoking ☐ Yes ☐ No ☐ Unknown
2. Excessive alcohol consumption ☐ Yes ☐ No ☐ Unknown
3. Active illicit injecting drug use ☐ Yes ☐ No ☐ Unknown
4. Active illicit non-injecting drug use ☐ Yes ☐ No ☐ Unknown
5. Opiate substitution (methadone) ☐ Yes ☐ No ☐ Unknown

Section 4 ♦ Co-morbidities:

A. Ongoing chronic conditions:

1. Hypertension ☐ Yes ☐ No ☐ Unknown
2. Diabetes mellitus ☐ Yes ☐ No ☐ Unknown
3. Dyslipidemia ☐ Yes ☐ No ☐ Unknown

B. Prior cardiovascular disease

(myocardial infarction, stroke or invasive cardiovascular procedure)

☐ Yes ☐ No ☐ Unknown

C. History of depression

☐ Yes ☐ No ☐ Unknown

D. History of psychosis

☐ Yes ☐ No ☐ Unknown

E. Liver disease:

1. Chronic elevation of liver transaminases ☐ Yes ☐ No ☐ Unknown
2. Chronic HBV infection ☐ Yes ☐ No ☐ Unknown
3. Chronic HCV infection ☐ Yes ☐ No ☐ Unknown
4. HDV infection ☐ Yes ☐ No ☐ Unknown
5. History of previous liver decompensation ☐ Yes ☐ No ☐ Unknown
6. Clinical signs of liver failure in the 4 weeks before death ☐ Yes ☐ No ☐ Unknown
7. Liver histology available (ever) ☐ Yes ☐ No ☐ Unknown

If Yes, please indicate: the date of most recent biopsy ____ - ____ - ____ the stage of fibrosis (0-4): ☐

(dd-mm-yy eg 01-FEB-05)

* Please note that if any of the mandatory fields remain empty the CRF will not be registered

Cause of Death Form

CoDe

*Study: _____

*Patient ID code: _____

Section 5 ♦ Cause of death

A. Was the death sudden? ☐ Yes ☐ No ☐ Unknown

B. Was the death unexpected? ☐ Yes ☐ No ☐ Unknown

C. Please complete the table below by recording all illnesses and conditions (acute and chronic) or injuries that the patient had at the time of death.

	Illness / Condition / Injury (text)	Date of onset dd/mm/yy (eg 01-FEB-05)	Certainty of diagnosis ^a		
			Definite	Likely	Possible
1.		____-____-____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.		____-____-____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.		____-____-____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.		____-____-____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.		____-____-____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.		____-____-____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.		____-____-____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.		____-____-____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.		____-____-____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

^aCertainty of Diagnosis: Definite = 95-100% certainty, Likely = 80-95% certainty, Possible = 50-80% certainty

* D. Brief narrative of the sequence of events leading to death (please include means of diagnosis of illnesses):

E. In summary, the causal relation between the conditions leading to death was (complete this section with the corresponding number from table C above):

1. Condition that directly caused death (immediate cause): _____

2. Due to or as a consequence of: _____

3. Due to or as a consequence of: _____

4. Condition that initiated the train of morbid events (the underlying condition): _____

* Please note that if any of the mandatory fields remain empty the CRF will not be registered

CoDe

*Patient ID code: _____

☐ Yes ☐ No ☐ Unknown☐ Yes, with the agent: _____ ☐ No ☐ Unknown[illegible]**C. Laboratory values** (please complete all fields where data is available)

Laboratory values	Time	Value	Unit	Date dd/mm/yy (eg 01-FEB-05)
CD4+ cell count	1. Most recent prior to last stopping ART		Cells/mm ³	___ - ___ - - - -
	2. Most recent prior to death		Cells/mm ³	___ - ___ - - - -
HIV RNA	1. Most recent at time of stopping ART		Copies/mL	___ - ___ - - - -
	2. Most recent prior to death		Copies/mL	___ - ___ - - - -
Haemoglobin	Most recent prior to death		/	___ - ___ - - - -

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Cause of Death Form

CoDe

*Study: _____

*Patient ID code: _____

Section 8 ♦ Adverse effects to any type of medical treatment:

A. Was the death considered to be related to a medical treatment? ☐ Yes ☐ No ☐ Possibly

B. The suspected relation was to: ☐ Antiretroviral treatment ☐ Other medical treatment

Please provide a brief narrative of the suspected association including the name of the medication and the date of starting:

Please refer to the 'CoDe instructions' for definitions and guidelines for the completion of this form

Completed by: Name (in print): _____

Position : ☐ Physician ☐ Nurse ☐ Other (describe) : _____

Directly involved in the medical care of the patient around the time of death? ☐ Yes ☐ No

Date (dd/mmm/yy): ____ - ____ - ____

Signature: _____

* Please note that if any of the mandatory fields remain empty the CRF will not be registered

Appendix C. Guidelines for completion of the CoDe CRF



Instructions for the completion of the CoDe Cause of Death form

General: Please complete the form by marking the appropriate box with an 'X', by completing a numeric field, or by completing information on day, month and year for date-variables. If information is unknown, mark the appropriate box or write 'NA' (not available). For information on dates, if the day is unknown, write 'NA-mm-year', if the month is unknown, write 'NA-NA-year', if the day, month and year are unknown, write 'NA-NA-NA'. Complete text fields as indicated in the form. Include copies of source documentation where indicated; the source documents should be anonymized (erase patient name) and labelled with Study name and Patient ID on each page.

Heading: **Study and patient ID.** Complete the specific study name (cohort or trial) and Patient ID code at the top of each page of the CRF. The patient's date of death should be recorded on the first page only.

Section 1: **Background demographics.** Please record most recent measurements of height or weight and the corresponding date. In case there is no information at all on height or weight, please complete the relevant item by 'NA'.

Section 2: **Data source.** If several sources of information were available, please include all. For hospital files and outpatient clinic charts: If the files are **complete** and contains the relevant information describing the events leading to death, the sources should be recorded as '**complete**'. If the files are intact, but does not contain the relevant information the records should be coded as '**incomplete**' (e.g. if the patient was admitted elsewhere with the terminal condition, and a copy of this file from a different hospital is unavailable).

Section 3: **Risk factors**
Risk factors in the year prior to death: Please note that information is requested for presence of cigarette smoking, excessive alcohol consumption (definition listed below), active illicit drug use and opiate substitution *within the last year*.

If data are not available, or information not provided in the source documents, please indicate 'unknown' (rather than leaving blank).

Definition:

Section 3.1 Cigarette smoking: regular cigarette smoking more than 3 days a week, *or* any mentioning of cigarette smoking in the source documents.

Section 3.2 Excessive alcohol consumption: More than 35 alcohol units per week (or 5 units per day), *or* any mentioning of ongoing excessive alcohol use in the source documents. (one unit of alcohol corresponds to 125ml of wine; 300ml of beer; or 20ml of spirits. This equates to approximately 12g of beer or wine; or 6g of spirits).

Section 4: **Co-morbidities**
For conditions listed in section 4, presence *at any time point* should be marked with 'Yes'. If data are not available, or information not provided in the source documents, please indicate 'unknown' (rather than leaving blank). The presence or absence of all listed risk factors should be completed using the definitions provided below.

Definitions:

Section 4.A.1 Hypertension: Systolic blood-pressure ≥ 140 mmHG or diastolic blood pressure ≥ 90 mmHg, or any mentioning of arterial hypertension or anti-hypertensive medication in the source documents.



Instructions for the completion of the CoDe Cause of Death form

Section 4.A.2 Diabetes Mellitus:

- Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL), or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL), or
- Two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test, or
- any mention of anti-diabetic therapy in the source documents.

Section 4.A.3 Dyslipidemia: Serum-total cholesterol ≥ 6.2 mmol/L (240 mg/dL), LDL cholesterol ≥ 4.2 mmol/L (160 mg/dL) or HDL cholesterol ≤ 0.9 mmol/L (35 mg/dL), or fasting triglycerides ≥ 2.3 mmol/L (200 mg/dL), or any mentioning of lipid lowering medication.

Section 4.B Prior cardiovascular disease: Prior myocardial infarction (NSTEMI or STEMI), stroke (cerebral infarction or haemorrhage, or subarachnoidal haemorrhage), or invasive cardiovascular procedure (coronary artery stenting or by-pass operation, carotid artery endarterectomy).

Section 4.C History of depression:

Any mentioning in the source documents of depressive episode(s), incl. bipolar (hypomania/mania plus depression) disorders.

Section 4.D History of psychosis:

Any mentioning in the source documents of psychotic episode(s), incl. schizophrenia, schizoaffective or delusional disorders.

Section 4.E.1 Chronic elevation of liver transaminases: Elevated transaminases (AST (S-GOT) or ALT (S-GPT)) for more than 6 consecutive months.

Section 4.E.2 Chronic hepatitis B: The presence of HBsAg in the serum for at least 6 months.

Section 4.E.3 Chronic hepatitis C: Anti-HCV and/or HCV RNA positive (excluding those who have a positive anti-HCV, but are HCV RNA negative).

Section 4.E.4 Hepatitis D: Persistent high anti-HDV titer (IgM or IgG), HDV antigen in the liver, and/or HDV RNA in serum or liver.

Section 4.E.6 Clinical signs of liver failure including decompensated liver cirrhosis: Failure of biochemical synthesis (incl. hypo-albuminemia and/or low coagulation factors); ascites, variceal bleeding, hepatorenal syndrome, or hepatic encephalopathy with coma.

Section 4.E.7 Date of most recent liver biopsy (if ever): ***If the day, month, or year is unknown, write 'NA' (not available).***

Stage of liver fibrosis:

0 = no fibrosis, 1 = mild fibrosis, 2 = moderate fibrosis, 3 = severe fibrosis, including bridging fibrosis, 4 = cirrhosis.

Section 5:

Cause of death.

- **Was the death sudden?:** Acute death with no known ongoing terminal illness
- **Was the death unexpected?:** Not anticipated based on knowledge of the patients physical and psychological health status and risk factors

Examples given:

- A. *Sudden and unexpected:* Patient perceived to be in good health is found dead at home
- B. *Sudden and expected:* Patient with active ongoing illicit intravenous drug use dies from overdose
- C. *Not sudden and unexpected:* Patient with known ongoing severe illness dies unexpectedly from an unrelated illness or from unexpected complications to the patients underlying disease



Instructions for the completion of the CoDe Cause of Death form

Complete the table by recording ***all*** illnesses and conditions (acute and chronic) or injuries that the patient had at the time of death, and indicate the certainty of diagnosis for each illness/condition:

Definite (95-100% certainty)

For the diagnosis to be *definite*, there should be confirmation based on:

- Neoplasms: Histopathology (autopsy or biopsy)
- Infections: Direct microscopy, culture or PCR
- Other: Histopathology (autopsy or biopsy)

Likely (80-95%)

For the diagnosis to be *likely*, there should be confirmation based on:

- Clinical history and supporting evidence by imaging and/or laboratory markers

Possible (50-80%)

For the diagnosis to be *possible*, there should be confirmation based on:

- Clinical history, signs and symptoms

For each illness/condition, please also record the ***date of onset*** (the time of first diagnosis of clinical disease). The illnesses and conditions should be listed chronologically with the most recent and acute conditions in the top, and older and chronic conditions listed in the end.

For each illness/condition, please indicate if it was acute or chronic. For chronic conditions with exacerbations, please record information relevant to cause(s) of death in the *brief narrative* section. The dates should be recorded as dd/mm/yy for day, month and year. If the day, month, or year is unknown, write NA (not available).

Brief narrative: Please describe the sequence of events leading to death. Please include details related to the diagnostic confirmation of the causative conditions.

Summary of the narrative:

Please complete the summary by introducing in each line the appropriate *number* (from the above table) for each cause of death (immediate, contributing, underlying).

Please use the following definitions for the categorisation of the causes of death in the summary:

- ***Immediate cause of death:*** The disease(s) or injury directly leading to death.
- ***Contributing cause of death:*** The disease(s) or injury, which contributed to a fatal outcome.
- ***Underlying cause of death:*** The disease or injury, which initiated the train of morbid events leading directly or indirectly to death, or the circumstance of the accident or violence, which produced the fatal injury.

Only one cause should be entered on each line (by entering the appropriate *number* (1-9) from table C in the same section).

The first line (immediate cause of death) must always have an entry. If the condition in the first line resulted from a contributory or underlying condition, put this condition on the next line, and so on, until the full sequence is reported. *Always* enter the underlying cause of death on the lowest used line.

The terminal event (for example, cardiac arrest or respiratory arrest) should not be listed as the underlying cause of death. If a mechanism of death seems most appropriate to you for 'the immediate cause', then you must always list its origin(s) on the line(s) below it (for example, cardiac arrest due to coronary artery atherosclerosis or cardiac arrest due to blunt impact to chest). If an organ system failure such as congestive heart failure, hepatic failure, renal failure, or respiratory failure is listed as a cause of death, always report the aetiology of the organ system failure on the line(s) below (for example, renal failure due to Type I diabetes mellitus).



Instructions for the completion of the CoDe Cause of Death form

When indicating neoplasms as a cause of death, include the following: 1) primary site or that the primary site is unknown, 2) benign or malignant, 3) cell type or that the cell type is unknown, 4) grade of neoplasm, and 5) part or lobe of organ affected. (For example, a primary well-differentiated squamous cell carcinoma, lung, left upper lobe.)

Always report the fatal injury (for example, stab wound of chest), the trauma (for example, transection of subclavian vein), and impairment of function (for example, air embolism).

If two or more possible sequences resulted in death, or if two conditions seem to have added together, report this in the narrative.

A listing of the conditions that are AIDS defining (CDC stage C) is included in the Appendix.

Section 6: ***Post-mortem/ Autopsy.***

Please provide a brief summary of the findings from the autopsy report, and describe for each organ system whether pathology was identified and its characteristics. Please also include a copy of the full report. If the autopsy findings differ from the clinical history, please make a note in the *comments* section.

Section 7: ***ART and laboratory values.***

Definitions:

ART: any licensed antiretroviral drug (not necessarily HAART).

Please complete the table with laboratory values of CD4 count and HIV RNA for:

- 1) the most recent measurement prior to last stopping ART, and
- 2) the most recent prior to death (if different to the above)
 - a. if there was no CD4 count available between the time of stopping ART and death, please write 'NA' (not available)

For Haemoglobin, please record the most recent measurement prior to death. In the field next to the value, please record the units (either mmol/L, g/dL or g/L).

The dates should be recorded as dd/mm/yy for day, month and year. If the day, month, or year is unknown, write NA (not available).

Section 8: ***Adverse effects.***

Adverse effect: An unwanted response to a medicine (side effect; adverse event).

Please indicate if the cause of death was considered to be related to a medical treatment (acute or late onset) or not. If the relation is suspected with 50-80% certainty, indicate it as 'possibly'.

Indicate if the suspected relation was to antiretroviral treatment or other medical treatment, and provide in the *comments* section a brief narrative of the suspected association including the generic name of the medication, type of adverse effect and the date of its onset.

The dates should be recorded as dd/mm/yy for day, month and year. If the day, month, or year is unknown, write NA (not available).

Signature:

Please print your name, position, and professional relationship to the patient (whether you were directly involved in the medical care of the patient around the time of death).



Appendix.

AIDS defining illnesses: Modified CDC Category C 1993 Definition

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- CMV disease (other than liver, spleen, or nodes)
- CMV retinitis
- Encephalopathy, HIV-related (including AIDS Dementia Complex)
- Herpes simplex, chronic ulcers (> 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi's sarcoma (mucocutaneous or visceral)
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of the CNS
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- M. tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent bacterial (2 documented episodes within 1 year of each other)
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent (2 documented episodes within 1 year of each other)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV (weight loss (over 10% of baseline) with no other cause, and 30 days or more of either diarrhoea or weakness with fever)

Additions to CDC Definition

- Aspergillosis, invasive
- Bartonellosis
- Chagas disease (American trypanosomiasis) of the CNS
- Herpes zoster, multi-dermatomal (≥ 10 lesions in a non-contiguous site)
- Leishmaniasis, visceral (kala-azar)
- Lymphoma, non-Hodgkin's, all cell types
- Microsporidiosis (> 1 month's duration)
- Nocardiosis
- Penicillium marneffii, disseminated
- Pneumocystis carinii, extrapulmonary
- Rhodococcus equi disease

*Please note that Hodgkin's Lymphoma is now classified as a "non-AIDS defining malignancy"

Appendix D. Review Form

Review Form

CoDe

Study: _____

CoDe Event ID: _____

Date of death : ____ - ____ - ____
(dd/mm/yy eg 01-FEB-05)

Section 1 ♦ Underlying cause of death and conditions contributing to death

(Please refer to the table on page 2)

Cause of death	Illness/Condition/ Injury (text)	CoDe (01-92)	Certainty:		
			Definitely	Likely	Possibly
Immediate (Mandatory)	ICD10 code (optional) ____ . ____		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Contributing (If applicable)			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Contributing (If applicable)			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Contributing (If applicable)			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Contributing (If applicable)			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Underlying (Mandatory)	ICD10 code (optional) ____ . ____		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments:

Section 2 ♦ Death related to immunodeficiency?

Was the underlying or contributing cause of death a CDC C disease or Hodgkin's Lymphoma?

☐ Yes ☐ No ☐ Unknown*If No,*by applying the CoDe guidelines on the next page, do you consider the death to be related to immunodeficiency?
(Please refer to the algorithm on page 2)☐ Yes, definitively

Comments _____

☐ Yes, likely☐ Yes, possibly☐ No, assumed not☐ No, definitely not**Completed by :** Name (Signature) : _____**Date** (dd/mm/yy eg 01-FEB-05): ____ - ____ - ____ **Initials:** _____

For internal use only: Reviewer ID _____ Date _____

Reviewer Reference Page

CoDe

Section 1 Instructions:

The CoDe system: All of the causes should be coded by using the CoDe codes provided in the below listing. Note that the system is separated in three sections, where the first section including more specific causes takes priority over the second, which again takes priority over the third section:

Code	Description	Code	Description
01	AIDS (ongoing active disease)	13	Chronic obstructive lung disease
	01.1 Infection	14	Liver failure (other than 03, 03.1, 03.2)
	01.2 Malignancy	15	Renal failure
02	Infection (other than 01.1)	16	Accident or other violent death (not suicide)
	02.1 Bacterial	17	Suicide
	02.1.1 Bacterial with sepsis	18	Euthanasia
	02.2 Others	19	Substance abuse (active)
	02.2.1 Other with sepsis		19.1 Chronic Alcohol abuse
	02.3 Unknown aetiology		19.2 Chronic intravenous drug-use
	02.3.1 Unknown with sepsis		19.3 Acute intoxication (indicate agent)
03	Chronic viral hepatitis (progression of / complication to)	If the cause of death can't be specifically classified, general classification can be used:	
	03.1 HCV	20	Haematological disease (other causes)
	03.1.1 HCV with cirrhosis	21	Endocrine disease (other causes)
	03.1.2 HCV with liver failure	22	Psychiatric disease (other causes)
	03.2 HBV	23	CNS disease (other causes)
	03.2.1 HBV with cirrhosis	24	Heart or vascular (other causes)
	03.2.2 HBV with liver failure	25	Respiratory disease (other causes)
04	Malignancy (other than 01.2 and 03, 03.1, 03.2)	26	Digestive system disease (other causes)
05	Diabetes Mellitus (complication to)	27	Skin and motor system disease (other causes)
06	Pancreatitis	28	Urogenital disease (other causes)
07	Lactic acidosis	29	Obstetric complications
08	MI or other ischemic heart disease	30	Congenital disorders
	08.1 AMI		
	08.1.1 Definitive AMI (Dundee 1)		
	08.1.2 Possible AMI (Dundee 2/9)		
	08.2 Other ischemic heart disease		
09	Stroke	If the cause of death is unclassifiable, use:	
10	Gastro-intestinal haemorrhage (if chosen, specify underlying cause)	90	Other causes (provide details in Section 1)
11	Primary pulmonary hypertension	91	Unclassifiable causes
12	Lung embolus	92	Unknown

- **Immediate cause of death:** The disease(s) or injury directly leading to death.
- **Contributing cause of death:** The disease(s) or injury, which contributed to a fatal outcome.
- **Underlying cause of death:** The disease or injury, which initiated the train of morbid events leading directly or indirectly to death, or the circumstance of the accident or violence, which produced the fatal injury.

Please note:

Hodgkin's Lymphoma is now classified as a Non-AIDS defining malignancy.

Death reason 8 (MI or other ischemic heart disease) has been subdivided based on use of the WHO Monica Dundee score, and a sudden cardiac death category has been included and an external cardiologist will be supervising the coding of such events.

Reviewer Reference Page

CoDe

Section 2 Instructions:

*Please evaluate the relatedness of the death with immunodeficiency by using the below algorithm. The CD4 counts that should be taken into consideration are the CD4 count prior to last stopping ART, and the most recent prior to death. The former (CD4 count at last stopping ART) should be weighed the highest.

<i>CD4 counts prior to death</i>	<i>CD4 < 50 cells/μL</i>	<i>CD4 50-199 cells/μL</i>	<i>CD4 \geq 200 cells/μL</i>
Sudden	Possibly immunodeficiency-related	Assumed not immunodeficiency-related	Assumed not immunodeficiency-related
Not sudden	Likely immunodeficiency- related	Possibly immunodeficiency-related	Assumed not immunodeficiency-related

'Yes, definitely': underlying or contributing cause of death a CDC C disease or Hodgkin's lymphoma

'Yes, likely', 'Yes, possibly' or 'Assumed not': see table above

'No, definitely not': the underlying, contributing and immediate causes of death are of such a nature that it is inconceivable that the person died of causes related to immunodeficiency.

Appendix E. Instructions for Review

Review Instructions



Instructions for the review of the 'CoDe' Cause of Death form

The review of causes of death in the CoDe project should be based on a synthesis of the information provided in the CoDe Case Reporting Form. The review should result in a specific coding of the cause(s) of death (underlying, contributing and/or immediate) as well as coding of relatedness to immunodeficiency. For each of these, the reviewer should also indicate the degree of certainty by which the code is made, as the intention is to reduce the classification category of unknown, but at the same time allow for sensitivity analysis depending on degree of certainty.

Each case is reviewed by at least two reviewers.

General:

Please complete page one of the form by marking the appropriate box with an 'X', by completing a numeric field, or by completing text fields as indicated in the form. Page 2 is provided only for reference and does not need to be submitted.

Section 1: ***Underlying cause of death and conditions contributing to death***

Please complete the table by recording the name of the illness/condition/injury and the corresponding CoDe category for the:

- Immediate cause of death: The disease(s) or injury directly leading to death.
- Contributing cause of death: The disease(s) or injury, which contributed to a fatal outcome.
- Underlying cause of death: The disease or injury, which initiated the train of morbid events leading directly or indirectly to death, or the circumstance of the accident or violence, which produced the fatal injury.

Only one cause should be entered in each row of the table. The first row (immediate cause of death) must *always* have an entry. If the condition in the first row resulted from a contributory or underlying condition, put this condition on the next row, and so on, until the full sequence is reported. Always enter the underlying cause of death in the lowest row. If the underlying cause of death is the same as the immediate cause of death, please reintroduce the code (but not necessary to reintroduce the text under 'Illness/Condition/Injury')

The CoDe algorithm:

For all causes of death (underlying, contributing and/or immediate), but in particular for the underlying cause, the coder should attempt to allocate this in to one of the specific CoDe categories (1-19; please refer to the categories listed in the table in the review form). Only when the coder is unable to code the cause of death in categories 1-19 with a degree of certainty of more than 50% (see below), should he/she use the next level in the algorithm (general categories 20-30). Only if the cause of death cannot be classified in any of these, the categories 90-92 should be used.

For the immediate and the underlying causes of death - ICD10 codes (optional):

If the reviewer wants to include a more precise code describing the specific disease entity, this can be recorded in the column labelled 'ICD10'. To facilitate the lookup of specific codes, this tool at CDC may be useful (please specify ICD10 in top)

<http://wonder.cdc.gov/wonder/cgi-bin/asp/ICDFinder.asp?finder=icd9> .

Review Instructions



Instructions for the review of the 'CoDe' Cause of Death form

Certainty:

In addition to the codes, the *certainty* of the coding should also be indicated. The certainty should be indicated on a scale from 0% to 100% (comparable to a visual analogue scale). If the reviewer is less than 50% sure then the next "level" of the coding scheme should be used.

If two or more possible sequences appear to have resulted in death, or if two conditions seem to have added together, please describe this under comments.

Section 2: ***Death related to immunodeficiency?***

Please evaluate the relatedness of the death with immunodeficiency by using the below algorithm. The CD4 count(s) that should be taken in to consideration are the CD4 count prior to last stopping ART, and the most recent prior to death (CoDe CRF section 6). The former (*the CD4 count at last stopping ART*) should be weighed the highest.

Death related to immunodeficiency?

- ***'Yes, definitely'***: underlying or contributing cause of death a CDC C disease or Hodgkin's lymphoma
- ***'Yes, likely', 'Yes, possibly' or 'Assumed not'*** : see table below
- ***'No, definitely not'***: the underlying, contributing and immediate causes of death are of such a nature that it is inconceivable that the person died of causes related to immunodeficiency.

<i>CD4 count(s) prior to death</i>	<i>CD4 < 50 cells/μL</i>	<i>CD4 50-199 cells/μL</i>	<i>CD4 \geq 200 cells/μL</i>
<i>Sudden</i>	Possibly immunodeficiency-related	Assumed not immunodeficiency-related	Assumed not immunodeficiency-related
<i>Not sudden</i>	Likely immunodeficiency-related	Possibly immunodeficiency-related	Assumed not immunodeficiency-related

Review Instructions



Instructions for the review of the 'CoDe' Cause of Death form

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- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi's sarcoma (mucocutaneous or visceral)
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of the CNS
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- M. tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent bacterial (2 documented episodes within 1 year of each other)
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent (2 documented episodes within 1 year of each other)
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- Pneumocystis carinii, extrapulmonary
- Rhodococcus equi disease

***Please note that Hodgkin's Lymphoma is now classified as a Non-AIDS defining malignancy.**