

# Manual of Operations

# MOOP

## Data Collection on Adverse Events of Anti-HIV Drugs

# D:A:D

**Version of MOOP: Version 1.3\***

(\* Differs from Version 1.2 due to the introduction of a new data-collection on causes of death, CoDe, and the inclusion of D:A:D Cohort II)

**Updated: February 2005**

**Participating cohort studies:**

EuroSIDA, (20 European countries); Swiss HIV Cohort Study, (Switzerland);  
ICONA, (Italy); ATHENA Cohort, (The Netherlands);  
CPCRA, (USA); Nice Cohort, (France); Aquitaine Cohort, (France);  
HivBivus, (Sweden); BASS Cohort, (Spain);  
Australian HIV Cohort, (Australia); Brussels St.Pierre Cohort (Belgium)

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- \* Version 1.3 differs from version 1.2 due to the introduction of a new data-collection on causes of death, CoDe, and the inclusion of D:A:D Cohort II

The following Sections have been revised:

Section 3

- Description of checking charts (prior section 9) included
- CoDe included ( 3.8 - replacing fatal case checking charts)

Section 6

- CoDe methods applied for the data collection on causes of death

Section 7.3

- Cohort monitoring changed to once every other year

## Table of contents

<b>1</b>	<b>Presentation/Introduction.....</b>	<b>4</b>
1.1	Abbreviations .....	5
1.2	Contact information for the study coordinating office (CHIP) .....	5
<b>2</b>	<b>Data Collection.....</b>	<b>6</b>
2.1	Data Management .....	6
2.2	Basic Data Collection.....	6
<b>3</b>	<b>Guidelines for Completion of Forms .....</b>	<b>7</b>
3.0	Guidelines for Completion of Enrolment Forms .....	7
3.1	Guidelines for Completion of Follow-up Forms .....	7
3.2	Guidelines for Completion of the Event Form .....	8
3.3	Guidelines for Completion of Event Checking Charts .....	9
3.4	Event Checking Chart for Cases of Myocardial Infarction (MI) .....	9
3.5	Event Checking Chart for Cases of Stroke .....	10
3.6	Event Checking Chart for Invasive Cardiovascular Procedures.....	11
3.7	Event Checking Chart for Cases of Diabetes Mellitus.....	11
3.8	CoDe Case Report for Fatal Cases .....	11
3.9	Route of Communication .....	12
<b>4</b>	<b>Case definitions .....</b>	<b>12</b>
4.1	Definitive Myocardial Infarction (MI).....	13
4.2	Possible Acute MI .....	13
4.3	Possible Coronary Death .....	13
4.4	Fatal Case with Insufficient Data .....	13
4.5	Stroke .....	17
4.6	Diabetes Mellitus .....	18
<b>5</b>	<b>Reasons for discontinuation of antiretroviral treatment .....</b>	<b>18</b>
<b>6</b>	<b>Causes of death.....</b>	<b>19</b>
<b>7</b>	<b>Monitoring.....</b>	<b>20</b>
7.1	Site Monitoring .....	20
7.2	Source Data Verification .....	21
7.3	Cohort Monitoring .....	21
<b>8</b>	<b>Regulatory requirements.....</b>	<b>21</b>
	<b>APPENDIX A – Lists of Medication</b>	
	<b>APPENDIX B – Forms</b>	
	<b>APPENDIX C – Monitoring Report and Monitor Log</b>	
	<b>APPENDIX D – Training Material</b>	
	<b>APPENDIX E – Patient Informed Consent</b>	

## 1 Presentation/Introduction

The cohort study: **D**ata Collection on **A**dverse events of Anti-HIV **D**rugs (D:A:D) is a data collection study for HIV-infected patients under active follow up.

11 cohorts across the world are participating and the study has enrolled more than 23.000 patients in Cohort I from December 1999 to April 2001 and an additional 12.000 patients were enrolled in Cohort II from May 2001 to February 2004.

The study period has been extended and is projected to last at least until 2006.

The purpose of the study is to evaluate the long-term side effects of antiretroviral therapy by looking at the incidence of myocardial infarction among HIV/AIDS patients. This is to investigate the possible association between the development of cardiovascular diseases and treatment with antiretroviral drugs.

A milestone of the DAD study was the identification of an increased risk of myocardial infarction with increasing duration of combination antiretroviral therapy (NEJM, 2003;349(21); 1993-2003 ). As the D:A:D study continues to accumulate follow-up time, our ability to describe the exact nature of the relationship between combination antiretroviral therapy and cardiovascular disease, and to describe the extent to which this relationship can be explained by metabolic changes, will increase.

The data collection includes information on conventional risk factors and previous diseases such as myocardial infarction, stroke, diabetes mellitus, hereditary tendency, smoking, fat redistribution etc.

In each of the participating cohorts, the data collection takes place at least every 8 months. Data is computerised by each cohort and subsequently merged in a database in Copenhagen.

Support for the study is given by the Oversight Committee for The Evaluation of Metabolic Complications of HAART, and several pharmaceutical companies producing antiretroviral drugs contribute financially.

The study coordinating office (SCO), Copenhagen HIV Programme, has the overall responsibility for the conduct of the study. However, the study is supervised by a Steering Committee represented by each cohort.

The SCO has established guidelines and instructions for the conduct of the study. This quality assurance is implemented in the D:A:D protocol and operationalised in this Manual Of Operations (MOOP).

The D:A:D study coordinating office  
Copenhagen HIV Programme (CHIP)

## 1.1 Abbreviations

CHIP	Copenhagen HIV Programme
CK	Creatinine Kinase
CK-MB	Creatinine Kinase - Myocardial Bound
CoDe	<u>C</u> oding <u>C</u> auses of <u>D</u> eath in HIV
CSF	Cerebro-spinal Fluid
DAD	<u>D</u> ata Collection on <u>A</u> dverse events of Anti-HIV <u>D</u> rugs
ECG	Electrocardiogram
HAART	<u>H</u> ighly <u>A</u> ctive <u>A</u> ntiretroviral <u>T</u> herapy
LDH	Lactate Dehydrogenase
MOOP	Manual of Operations
PTCA	Percutaneous Transluminal Coronary Angioplasty / Stent
SAH	Sub-arachnoidal haemorrhage
SCO	Study Coordinating Office
SOP	Standard Operating Procedure
TIA	Transient Ischemic Attack
WBC	White Blood Cells

## 1.2 Contact information for the study coordinating office (CHIP)

Address: D:A:D Coordinating Centre  
Copenhagen HIV Programme,  
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Office hours are Monday to Friday from 08.30 – 15.00.  
Outside these hours, an answering machine is available.

## 2 Data Collection

The principal investigator at each site is responsible for the data collection for the D:A:D study including completion of case report forms. However, the responsibility of filling in the case report forms can be delegated to other study personnel (e.g. study nurses). When the case report forms are being completed, please ensure that data are entered correctly in accordance with procedures already implemented by the cohort and of the highest possible standard.

### 2.1 Data Management

Data for the D:A:D study are collected at each site by study personnel filling in the case report forms (follow-up forms) at least every 8 months in addition to the already existing data collection in the cohorts (for details see [section 2.2](#)). Subsequently, data are submitted to the respective cohort coordinating office and computerised. At this point, data are transported electronically by each cohort to the SCO in Copenhagen. A data manager affiliated with the SCO is responsible for merging all data into a central database to which there is limited access in order to uphold data safety and confidentiality.

A standard operating procedure (SOP) has been developed for the management of the data, detailing the data format and the procedures for electronic transfer. This SOP is available at the Cohort Coordinating Center and at [www.cphiv.dk](http://www.cphiv.dk).

Throughout the study, the quality of the data is assessed by site and cohort monitoring to ensure a valid data collection ([see section 7](#)).

### 2.2 Basic data collection

The data collection for the D:A:D study includes all items specified in the case report forms. In addition, it is required that all participating cohorts have the ability to provide supplementary data that includes the following:

- Gender
- Race (if available)
- Mode of infection
- Documented HIV antibody test
- Weight (at least once annually)
- Height
- Complete antiretroviral treatment (date of initiation, date of discontinuation, reason for discontinuation (a list of reasons for discontinuation can be found in [section 5](#)))
- Information on disease specific prophylaxis against *Pneumocystis carinii* (*jiroveci*) pneumonia, *Toxoplasmosis* and *Mycobacterium avium* complex.
- Opportunistic infections
- CD4 cell count/ plasma HIV viral load (>3 measurements per year)
- HIV related events (CDC group C)
- Death (*novel data-collection on specific causes of death – please refer to [section 6](#) and to the [CoDe Protocol](#)*)

### 3 Guidelines for completion of forms

#### 3.0 Guidelines for completion of enrolment forms

(Note: enrolment has been completed for DAD Cohort I and II as of July 2004)

##### ITEM 1: Diseases/procedures ever diagnosed/performed

Please check carefully whether the patient has ever experienced one or more of the diseases referred to. If the patient has been diagnosed with the same disease at several occasions, please write the date the disease was first diagnosed. This does also imply the performance of procedures.

Diseases occurred before enrolment to the DAD study do not have to fulfil the detailed case definitions (however, very important during follow up) – diagnoses and procedures made previously are accepted. Please note that stroke covers cerebral infarction *and* cerebral haemorrhagia.

The answer no covers: the disease /procedure has never been diagnosed/performed. The information should be obtained from patient interview and/or review of the patient record. The box unknown should *only* be ticked if data are missing in the patient record or in cases of uncertainty (unable to interpret data).

ITEMS 2-8 on the enrolment form are the same as for the Follow-up form. Please see section 3.1, [Guidelines for completion of follow-up forms](#).

#### 3.1 Guidelines for completion of follow-up forms

The following contains information and clarification of the items in the follow-up form, the event form, and the event checking charts. Of note, most cohorts have incorporated the follow-up form in their standard data collection forms. Thus the order of the items listed below may be different depending on the cohort.

The information should be obtained from patient interview and/or review of the patient record. The answer 'no' means the disease /procedure has never been diagnosed/performed. The box unknown should *only* be ticked if data are missing in the patient record or in cases of uncertainty (unable to interpret data).

##### ITEM 1: Diseases/procedures diagnosed/performed since last follow up

Please find case definitions in [Section 4](#). Note that these diagnoses should only be applied when patients fulfil these criteria. In cases of doubt, please contact the study coordinating office (SCO). If one of the diseases has occurred or one of the surgical procedures listed has been performed since last follow up, a standardised event form must be submitted to the study coordinating office "real time" ([Section 3.2/Appendix B](#)).

##### ITEM 2: Myocardial infarction or stroke experienced by first-degree relatives

The data collection only includes myocardial infarction or stroke experienced by first-degree relatives *before* the age of 50 years.

Please note that stroke covers cerebral infarction *and* cerebral haemorrhage.

**ITEM 3: Blood samples**

Preferably, the blood tests (serum total cholesterol, serum HDL cholesterol and serum triglycerides) are collected when the patients are fasting. If there is any doubt at the time of blood drawn, please leave the box 'fasting' empty.

**ITEM 4: Blood pressure**

Please enter the systolic and diastolic blood pressure last measured. The unit for blood pressure measurement is mmHg.

**ITEM 5: Ongoing treatment**

Drugs within the different groups (anti-platelets, ACE inhibitors, other antihypertensive agents, lipid lowering agents, insulin or derivatives hereof, oral antidiabetic agents and anabolic steroids/appetite stimulants) are specified.

Please find medication lists in appendix A. Medications that are not listed in the MOOP will not be a part of the data collection.

**ITEM 6: Cigarette smoking**

For this study, the definition of a regular cigarette smoker is a person who smokes cigarettes at least every other day (more than 3 days a week).

Only cigarette smokers are of interest. If someone smokes cigars or a pipe, please answer 'no' to this question.

**ITEM 7+8: Fat redistribution**

The assessment of development of fat redistribution is based on evidence of fat accumulation or loss of fat by physician's examination *and* patient's confirmation hereof.

**Indication of dates in the follow-up forms**

*If the month is unknown, please write 07 and the year in the box. If the year is unknown a code is not requested, please leave the box empty.*

*For the event form: Exact date is required.*

**3.2 Guidelines for completion of the event form**

The event form is of great importance for the initial reporting of the study endpoints. The reporting is the responsibility of the investigator at each site, with reference to the individual cohort coordinating office.

The study coordinating office should be notified as soon as possible after the event has occurred ("real time") and no later than 8 weeks after occurrence.

The initial event form should be followed by a more detailed report provided in the **event checking charts** (please see [sections 3.3-3.8](#)). This more detailed report may replace the event form (if all documentation is available within the specified period of 8 weeks). Alternatively, the event checking chart should follow the initial event form and be sent to the SCO as soon as possible.

Please fill in all centre, cohort and patient identifiers at the top of the page.

**ITEM 1**

If a patient qualifies for one of the described endpoints, please start by identifying the reason for the completion of the form under item 1. For precise case definitions, see [section 4](#). If in doubt of whether an event qualifies for recording, please contact the coordinating centre.

**ITEM 2**

Record the features associated with this event. Record briefly the symptoms leading to diagnosis. If a coronary event occurs, please describe both enzymes and ECG.

**ITEM 3**

Provide a brief narrative description of the event and give a short summary of the patient history leading to the event.

Please sign and date the event form before faxing directly to the D:A:D study coordinating office at +45 36 47 33 40 and provide the cohort coordinating office with a copy of the form.

### 3.3 Guidelines for completion of event checking charts

The event checking charts include data necessary for the validation of the study endpoints. The event checking charts may be used as the initial reporting form (i.e. replacing the event form) or may be used for collection of additional information on already reported events.

**All event checking charts:**

Page header: Please fill in all centre, cohort and patient identifiers at the top of the page.

Page footer: Sign and date the form before sending it to the D:A:D study coordinating office. The cohort coordinating office should keep a copy of the form. (Refer to instructions regarding 'Route of communication - event checking charts', [section 3.9](#)).

### 3.4 Event checking chart for cases of myocardial infarction (MI)

To be completed for patients who have experienced a myocardial infarction (definitive or possible, fatal<sup>1</sup> and non-fatal cases)

**ITEM 1 - ECG's**

Please complete with the numbers of included ECG's which are dated:

- prior to the MI,
- at the time of MI (within hours/days of onset), and
- after the MI

Ensure that all ECG's are marked with pt ID code, ECG velocity, date and time.

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<sup>1</sup> For fatal cases, please also complete the 'CoDe reporting form'

**ITEM 2 - Serology**

Please record sequence and/or peak-values of measurements performed within 72 hours of the MI. For iso-enzyme peak-values and sequence of corresponding enzymes: CK and CK-MB, LDH-1 and LDH-2 are required.

For Troponin T and/or I the peak-value is sufficient, although the sequence is desired.

**ITEM 3 - Summary**

Provide a brief narrative description of the event including information on duration and nature of the symptoms. Indicate whether the symptoms were typical ([see section 4.1](#))

**3.5 Event checking chart for cases of stroke**

To be completed for patients who have experienced a stroke<sup>1</sup>.

**ITEM 1 – Type of stroke**

Please complete whether the stroke has been identified as being due to: Haemorrhage, infarction, sub-arachnoidal haemorrhage (SAH), or clinical stroke where the pathogenesis remains unknown.

**ITEM 2 – Means of diagnosis**

Record:

- Findings from the clinical examination
- Describe whether the neurological deficits are focal and/or global
- Include an estimate of the duration of the symptoms<sup>2</sup>

**ITEM 3 – Examination of Cerebrospinal Fluid (CSF)**

Indicate whether examination of cerebrospinal fluid has been conducted and provide a description of the findings (i.e. information on pleocytosis (white blood cells in CSF), xantochromi, CSF-protein and CSF-glucose).

**ITEM 4 – Other etiology**

Indicate whether the patient was diagnosed with other CNS pathology in association with the stroke, including evidence of space occupying lesions or evidence of CNS infection.

**ITEM 5 – Underlying medical condition**

Indicate whether the patient suffered from any medical condition known to be associated with increased risk of stroke (e.g. atrial flutter/fibrillation, hypertension)

**ITEM 6 – Previous history of neurological disorder**

Indicate whether the patient has a history of neurological disorder, HIV-related or not, and provide a brief description of the condition.

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<sup>2</sup> Duration of less than 24 hours followed by complete remission of symptoms implies that the cerebral lesion was a 'Transient Ischemic Attack' – this diagnosis does not qualify as a stroke

### 3.6 Event checking chart for Invasive cardiovascular procedures

#### ITEM 1 – Type of invasive cardiovascular procedure

Please complete if the patient has ever undergone a procedure of:  
*Coronary artery by-pass grafting, Coronary angioplasty/stenting (PTCA), or Carotid endarterectomy.*

#### ITEM 2

Indicate whether the procedure was associated with an MI<sup>3</sup> and if the procedure was conducted as acute intervention during acute MI or complicated by an MI.

#### ITEM 3

Indicate whether the procedure was complicated by stroke<sup>4</sup>

#### ITEM 4

Indicate whether copies of original source documents from the hospital record have been included in the report.

### 3.7 Event checking chart for cases of Diabetes Mellitus

To be completed for patients who have developed diabetes.

#### ITEM 1 – Blood sugar measurements

For the diagnosis of diabetes mellitus two elevated fasting blood sugar measurements are required (ADA definition: Fasting plasma-glucose >7 mmol/L (126 mg/dL) measured on two independent occasions [[Section 4.6](#)]).

#### ITEM 2 – Other medical therapy

Indicate if there is evidence that the diabetes is precipitated by other medical therapy (other than ART), e.g. therapy with corticosteroids, pentamidine or other.

#### ITEM 3 - Pancreatitis

Based on hospital records, is there a current or previous medical history of pancreatitis (acute or chronic)?

### 3.8 Event checking chart for fatal cases

This has been replaced by the CoDe (Coding Causes of Death in HIV) Case reporting form (CRF). The route of communication for the CoDe CRF is the same as for the event checking charts. For details, please refer to the [CoDe Protocol](#).

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<sup>3</sup> If yes, complete checking chart for cases of MI

<sup>4</sup> If yes, complete checking chart for cases of stroke

### 3.9 Route of communication – Event checking charts

Each cohort is in charge of the route of communication for event forms and event checking charts within the cohort. It is the choice of the individual cohort whether to use the above route of communication, or to make the event checking charts available to the investigators at the sites. The event checking charts may substitute the original event forms as primary reporting documents. What remains imperative is that the initial reporting of an event to the cohort coordinating office is not delayed.

1. The **event form** is sent from the site to the local cohort coordinating center. A copy is kept at the site.
2. The cohort coordinating office reviews the information provided in the event form and completes the **event checking chart** by corresponding with the investigator at the site.
3. The **event form** and the **event checking chart** are both forwarded to the study coordinating office in Copenhagen along with copies of original documents from the medical record where required, e.g. ecg's. All identifying information should be erased from these hospital documents and the study patient ID-code inserted. Copies of the event form and the checking chart are kept at the cohort coordinating office.
4. The study coordinator reviews the forms for completeness and may request additional information if necessary. (The answers provided, including additional source documentation, are forwarded to the Study coordinating office).
5. The cohort coordinating center finally uses the event checking chart for source data verification of the event during monitoring visits to the site. It should be recorded in the monitoring reports that source data verification has been done. Any additional information that appears from the monitoring procedure is added to the event checking chart, and the chart is marked to indicate that monitoring was done. The completed chart is forwarded to the Study coordinating office (a copy is kept at the cohort coordinating center).

## 4 Case definitions

In case of uncertainty of whether a patient fulfils the diagnostic criteria, please contact the D:A:D coordinating centre for clarification.

Case definitions of MI applicable to the D:A:D study have been prepared on the basis of the manual for the MONICA study (coronary event registration data component – website: <http://www.ktl.fi/publications/monica/manual/>), a study concerning coronary/stroke events and the characteristics hereof.

#### **4.1 Definitive myocardial infarction (MI)**

- i) definitive\* electrocardiogram (ECG),
- ii) symptoms\* together with probable\* ECG and abnormal enzymes (or troponine)\*,
- iii) typical symptoms\*, abnormal enzymes\* and ischaemic/non-codable/not available\* ECG, or
- iv) fatal cases with naked-eye appearance of fresh MI and/or recent coronary occlusion found at necropsy.

#### **4.2 Possible acute MI**

Living patients with typical symptoms\* whose ECG\* and enzymes\* do not place them as myocardial infarction and in whom there is no conclusive evidence for another diagnosis for the attack.

#### **4.3 Possible coronary death**

Fatal cases where there is no conclusive evidence for another cause of death, clinically or at autopsy:

- a) with symptoms\* (typical, atypical or inadequately described), or
- b) history of previous chronic heart disease (definitive/possible MI, coronary insufficiency or angina pectoris in the absence of significant valvular disease or cardiomyopathy), or
- c) evidence of chronic coronary occlusion or stenosis or old myocardial scarring at necropsy.

#### **4.4 Fatal case with insufficient data**

Fatal case with no autopsy, no history of typical or atypical or inadequately described symptoms\*, no previous history of chronic ischaemic heart disease, and no other diagnosis.

\*See the next 2 pages for definitions

Table 1. Definitions of myocardial infarction (please refer to the text for details).

	<b>ECG</b>	<b>Cardiac enzymes</b>	<b>Symptoms</b>	<b>Comment</b>
<b><i>Definite myocardial infarction</i></b>				
i)	ECG typical	-	-	-
ii)	ECG probable	<i>and</i> Enzymes elevated	<i>and</i> Symptoms typical, atypical or not interpretable	-
iii)	ECG ischaemic, uncodable or not available	<i>and</i> Enzymes elevated	<i>and</i> Symptoms typical	-
iv)	-	-	-	Fatal cases with MI/ recent coronary occlusion found at autopsy
<b><i>Possible myocardial infarction for living patients</i></b>				
	-	-	Symptoms typical	-
<b><i>Possible coronary death</i></b>				
i)	-	-	Symptoms typical, atypical or inadequately described	<i>and</i> No evidence for other cause of death
ii)	-	-	-	Fatal cases with a history of previous chronic heart disease
iii)	-	-	-	Fatal cases with evidence of heart disease at autopsy
<b><i>Fatal cases with insufficient data</i></b>				
	-	-	-	No autopsy, no history of symptoms, no previous history of chronic ischaemic heart disease, and no other diagnosis

**ECG changes\***

*ECG typical*, evolution of ECG from normal to highly pathological:

- a) Development of Q waves: Progression of Q codes from no Q to a diagnostic Q is sufficient. Progression from no Q to an equivocal Q or from equivocal Q to a diagnostic Q must be accompanied by deterioration in the ST segment or the T wave. Any of these types of progression must be accompanied by a T wave progression on  $\geq 3$  records, or
- b) Evolution of an injury current which last more than one day: An ST segment elevation lasting more than one day and T wave progression on  $\geq 3$  records.

*ECG probable*, evolution of ECG from normal to slightly pathological or from slightly pathological to highly pathological:

Evolution of depolarisation changes:

- a) no major ST segment depression in one ECG record and another record with a major ST segment depression.
- b) no ST segment elevation in one ECG record and another record with an ST segment elevation.
- c) no major T wave inversion in one record and another record with a major T wave inversion.

*ECG ischaemic*, corresponding ECG abnormalities without evolution.

*ECG uncodable*: uncodable for technical reasons or because of the presence of suppression codes (suppress most other codes, please refer to the MONICA Manual for details: third degree A-V block, persistent Wolff-Parkinson White Pattern, artificial pacemaker, complete left bundle branch block, complete right bundle branch block, intraventricular block, ventricular fibrillation and asystole, idioventricular rhythm, and supraventricular tachycardia above 140/minute).

**Cardiac enzymes elevated**

The enzymes include creatine phosphokinase (CK) (and the MB isoenzyme of CK), lactic dehydrogenase, cardiac-specific troponin T and cardiac-specific troponin I. Documentation of increases in amino-transferases is also accepted.

**Symptoms typical**

Symptoms are typical when chest pain is present and characterised by:

- oppressive thoracic pain/ angina pectoris (any synonym for pain is acceptable such as "pressure", "discomfort", "ache")
- duration of more than 20 minutes, and
- no definite non-cardiac, or cardiac non-atherosclerotic cause.

**Symptoms atypical**

Symptoms should be coded as 'atypical' if the symptoms were not typical but there was one or more of the following conditions present:

- atypical pain
- acute left ventricular failure
- shock
- syncope

**AND** the absence of cardiac disease other than ischaemic heart disease

**AND** no definite non-cardiac or cardiac non-atherosclerotic cause.

*(Note: acute left ventricular failure, shock or syncope, do not convert otherwise typical symptoms into atypical ones.)*

Atypical pain would be pain recorded as of short duration or intermittent with each bout lasting for less than 20 minutes, or pain at an unusual site (upper abdomen, arms, jaw, neck).

Acute left ventricular failure means that diagnosis was made clinically or that the patient became severely breathless suddenly. Chronic heart failure or breathlessness getting worse over several days would not qualify.

*\*Diagnostic criteria: Q waves- any Q wave in precordial leads V2 , V3 or V4 is diagnostic (unless there is axis rotation in precordial leads). Equivocal Q wave is a wide and deep Q-wave in leads III, aVR or V1 combined with no Q waves in all other leads. In all other leads a Q wave is abnormal if it is: 1) >0.04 sec in duration (i.e., one small square) or 2) at least one quarter the height of the R wave in the same QRS complex (except for lead aVL where it should be at least one half).*

*ST deviation: in the normal ECG, ST depression should not exceed 1mm in leads I, II III, aVF and V and elevation should not exceed 2 mm in the same leads*

## 4.5 Stroke

Rapidly developed clinical signs of focal or global disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than a cardiovascular origin. Secondary stroke caused by trauma should be excluded.

The differentiation between infarction and haemorrhage should be based on results of cerebral scanning or necropsy. In case of uncertainty (results not interpretable, or test not performed), please indicate so on the event form.

*Global disturbance:* this applies to patients with subarachnoid haemorrhage or deep coma but excluding coma of systemic vascular origin such as shock, Stokes-Adams syndrome or hypertensive encephalopathy.

*Definitive focal signs:*

- Unilateral or bilateral motor impairment (including dyscoordination)
- Unilateral or bilateral sensory impairment
- Aphasia/dysphasia (non-fluent speech)
- Hemianopia (half-sided impairment of visual fields)
- Diplopia
- Forced gaze (conjugate deviation)
- Dysphagia of acute onset
- Apraxia of acute onset
- Ataxia of acute onset
- Perception deficit of acute onset.

Not acceptable as sole evidence of focal dysfunction

- Dizziness, vertigo
- Localised headache
- Blurred vision of both eyes
- Dysarthria (slurred speech)
- Impaired cognitive function (including confusion)
- Impaired consciousness
- Seizures

(Although strokes can present themselves in this way, these signs are not specific and therefore, cannot be accepted as definite evidence for stroke.)

## 4.6 Diabetes mellitus

For a definite diagnosis, the definition used in the D:A:D Study is based on the ADA criteria (*Diabetes Care* 20:1183–1197, 1997):

- Fasting plasma glucose > 7.0 mmol/L (126 mg/dL)

The measurement of elevated plasma glucose should be repeated at least on two consecutive independent occasions (different dates), without interim normal plasma glucose levels.

In the absence of information on fasting plasma glucose levels, please describe whether the diagnosis was based on:

- Symptoms of diabetes plus random blood glucose concentration > 11.1 mmol/L (200mg/dL), or
- Two-hour plasma glucose > 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test, or
- The diagnosis has been made elsewhere, and the patient has received dietary advice or has been started on anti-diabetic therapy (please include information on generic drug name).

## 5 Reasons for discontinuation of antiretroviral treatment

A list of reasons for discontinuation of anti-retroviral treatment which includes the most frequent reasons experienced by physicians and patients. Please, if possible, indicate which of the statements listed below best explain the reason for discontinuation of antiretroviral treatment:

- ❖ Treatment failure (i.e. virological, immunological, and /or clinical failure)
- ❖ Abnormal fat redistribution
- ❖ Concern of cardiovascular disease
  - Dyslipidaemia
  - Cardiovascular disease
- ❖ Hypersensitivity reaction
- ❖ Toxicity, predominantly from abdomen/G-I tract
  - Toxicity – GI tract
  - Toxicity – Liver
  - Toxicity – Pancreas
- ❖ Toxicity, predominantly from nervous system
- ❖ Toxicity, predominantly from kidneys
- ❖ Toxicity, predominantly from endocrine system
  - Diabetes
- ❖ Haematological toxicity (incl. anemia)
- ❖ Hyperlactatemia / lactic acidosis
- ❖ Toxicity, not mentioned above
- ❖ Toxicity, any
- ❖ Pregnancy related
- ❖ Availability of more effective treatment (not specifically failure or side effect related)
- ❖ Structured Treatment Interruption (STI)
- ❖ Patient's wish/ decision
- ❖ Physician's decision
- ❖ Other causes, not specified above
- ❖ Unknown

## 6 Causes of death

After the endorsement by all cohorts in D:A:D of the new project on Coding of Death in HIV patients (the CoDe project), the collection on causes of death in D:A:D has changed. The causes of death that are being collected routinely at follow-up are listed below. In addition to this, and for all causes of death occurring after January 1<sup>st</sup> 2005, a CoDe CRF should be completed (please refer to the [CoDe Protocol](#))

- Acute Myocardial Infarction or Stroke<sup>5</sup>
- Other cardiovascular diseases<sup>6</sup>
- Symptoms caused by mitochondrial toxicity (lactic acidosis, liver failure, etc.)
- Complications due to diabetes mellitus<sup>7</sup>
- Pancreatitis
- Complications due to hepatitis
- HIV-related
- Suicide
- Drug Overdose
- Other
- Unknown, Fatal case with no information

---

<sup>5</sup> If yes, complete checking chart for cases of MI or stroke

<sup>6</sup> Complete event form if necessary

<sup>7</sup> Complete event form if necessary

## 7 Monitoring

### 7.1 Site monitoring

The quality assurance for the D:A:D study includes monitoring. Each participating cohort appoints a monitor, who is not in any way associated with the particular site in the cohort.

The monitoring must be performed at regular visits to all sites *at least once annually* to ensure that the data collection live up to the highest possible standards and expected reliability. This in accordance with the site questionnaire participating investigators have signed before enrolment of patients, indicating their anticipated performance regarding data collection for the D:A:D study including event reporting.

#### **Requirements for site monitoring:**

- training of site personnel planned and coordinated by the respective cohort study coordinator (training materials available in Appendix D).
- availability of study documents - protocol and MOOP - must be ensured.
- depending on the regulatory system, the authorities in some countries may require a signed patient information and informed consent form for each patient participating in a cohort study. If that is the case, the monitor must verify that all enrolled patients have signed the informed consent form.
- at site visits a random review of at least 10% of all patients participating in the study must be performed by the monitor. The cohort is responsible for selection of patients for review, however 100% of the records of patients who have died or experienced an event/developed signs of cardiovascular must be reviewed.
- if the monitor becomes aware of a missed event the requirement for review increases to 25% of all the patients at the particular site. This should be indicated in the monitoring report.
- at each visit the monitor must ensure that a complete and up-to-date patient identification log is available. This to uniquely identify the patient's record within the cohort.
- completion of a monitoring report on the outcome of monitor visits are mandatory for all visits. The report must contain specific information on the requirements mentioned above. A standardised monitoring report (Appendix C) has been made in order to attain homogeneous reporting but reports with similar contents are accepted, if preferred by the respective cohort.
- The reports must be submitted to the cohort and subsequently forwarded to the study coordinating office by fax within a month after the site visits have taken place.
- the monitor log must be signed at each monitor visit.

## 7.2 Source data verification

The monitor must have direct access to all subject files/records, laboratory reports and other relevant source data to ensure correct data entry in the case report forms and to verify the data collection.

Source data verification is undertaken at the regular monitoring visits during the D:A:D study as a quality assurance.

Source data verification is required for **items 1, 3, 4 and 5 on the enrolment and follow-up forms.**

Full cooperation by the investigator and other study personnel is expected. All records must be available for monitoring.

## 7.3 Cohort monitoring

In addition to site monitoring the cohort coordinating offices across the world will be monitored by the study coordinating office in Copenhagen at regular intervals. This quality assurance is performed in accordance with the requirements of participating cohorts outlined in the [DAD Protocol](#).

## 8 Regulatory requirements

It is the responsibility of each participating site to ensure that all necessary documents and approvals - according to local/national regulations - are obtained before enrolling patients in the study. If applicable notify the Medicines Agency and/or Data Surveillance Authorities.

Some countries may require patient informed consent before enrolment - for this purpose, please find a sample provided in [Appendix E](#).

**APPENDIX A – Lists of medication**

**APPENDIX B – Forms**

**APPENDIX C – monitoring report and monitor log**

**APPENDIX D – Training material**

**APPENDIX E – Patient Informed Consent**

## Appendix A

### Lists of medication

#### **Platelet Aggregation Inhibitors**

Clopidogrel Bisulfate, Ticlopidine Hcl, Acetyl Salicylate(low), Dipyridamole, Trifusal

#### **ACE inhibitors**

*Hypotensives, Ace Blocking Type:* Benazepril Hcl, Captopril, Enalapril Maleate, Enalaprilat Dihydrate, Fosinopril Sodium, Lisinopril, Moexipril Hcl, Perindopril, Perindopril Erbumine, Quinapril Hcl, Ramipril, Trandolapril, Zofenopril

*Hypotensives,angiotensin Receptor Antagonist:* Candesartan Cilexetil, Eprosartan Mesylate, Irbesartan, Losartan Potassium, Telmisartan, Valsartan

#### **Other antihypertensive agents**

*Alpha-Adrenergic Blocking Agents:* Phentolamine Mesylate

*Alpha/Beta-Adrenergic Blocking Agents:* Carvedilol, Labetalol Hcl

*Beta-Adrenergic Blocking Agents:* Acebutolol Hcl, Atenolol, Betaxolol Hcl, Bisoprolol Fumarate, Carteolol Hcl, Celiprolol, Metoprolol, Fumarate, Metoprolol Succinate, Metoprolol Tartrate, Nadolol, Nebivolol, Penbutolol Sulfate, Pindolol, Propranolol Hcl, Sotalol, Timolol Maleate

*Calcium Channel Blocking Agents:* Amlodipine Besylate, Diltiazem Hcl, Diltiazem Malate, Felodipine, Isradipine, Mibefradil Di-Hcl , Nicardipine, Nifedipine, Nisoldipinel, Verapamil Hcl

*Hypotensives,ganglionic Blockers:* Mecamylamine Hcl, Hypotensives,miscellaneous:  
Pargyline Hcl

*Hypotensives,sympatholytic:* Alseroxylon, Bethanidine Sulfate, Clonidine Hcl, Debrisoquine Sulfate, Deserpidine, Guanabenz Acetate, Guanadrel Sulfate, Guanethidine Sulfate, Guanfacine Hcl, Lofexidine Hcl, Methoserpidine, Methyldopa, Moxonidine, Rauwolfia Serpentina, Rescinnamine, Reserpine, Rilmenidine Phosphate, Tolonidine Nitrate

*Hypotensives,vasodilators:* Doxazosin Mesylate, Hydralazine Hcl, Minoxidil, Prazosin Hcl, Terazosin Hcl

*Loop Diuretics:* Bumetanide, Ethacrynic Acid, Furosemide, Torsemide

*Potassium Sparing Diuretics:* Amiloride Hcl, Spironolactone, Triamterene

*Thiazide and related Diuretics:* Bendroflumethiazide, Benzthiazide, Chlorothiazide, Chlorthalidone, Cyclothiazide, Hydrochlorothiazide, Hydroflumethiazide, Indapamide, Methyclothiazide, Metolazone, Polythiazide, Quinethazone, Trichlormethiazide

**Lipid lowering agents**

*Bile Salt Sequestrants:* Cholestyramine, Colestipol Hcl, Cholestyramine/Aspartame, Cholestyramine/Sucrose

*Lipotropics:* Atorvastatin Calcium, Bezafibrate, Cerivastatin Sodium, Clofibrate, Clofibrate Magnesium, Dextrothyroxine Sodium, Ezetimibe, Fenofibrate, Fluvastatin Sodium, Gemfibrozil, Lovastatin, Pravastatin Sodium, Probucol, Simvastatin

**Oral antidiabetic agents**

*Sulfonylureas:* Acetohexamide, Carbutamide, Chlorpropamide, Glibenclamid, Glibornuride, Gliclazide, Glimepiride, Glipizide, Gliquidone, Glisoxepide, Glyburide, Glyburide Micronized, Tolazamide, Tolbutamide

*Non-Sulfonylureas:* Acarbose, Guar Gum, Metformin Ch-Phenoxyacetate, Metformin Hcl, Metformin Pamoate, Miglitol, Nateglinide, Phenformin Hcl, Pioglitazone, Repaglinide, Rosiglitazone

**Insulin and derivatives hereof**

Insulin Isophane, Insulin Lente, Insulin Lispro, Insulin Nph, Insulin Protamine Zn, Insulin R, Insulin Zinc

**Anabolic steroids and appetite stimulants**

*Anabolic steroids:* Nandrolone, Oxandrolone, Oxymetholone, Stanozolol, Testosterone

*Miscellaneous:* megestrol acetate, drabinol

## APPENDIX B – Forms

- Enrolment
- Follow-up
- Event Form
- Checking Charts
  - Myocardial Infarction
  - Stroke
  - Invasive CVD Procedures
  - Diabetes
- CoDe Form

Patient identification code \_\_\_\_\_ Date of completion (dd/mm/yy) \_\_\_\_\_

Completed by \_\_\_\_\_

**1. Have any of the following diseases/procedures ever been diagnosed/performed:**

- a) Myocardial infarction  Yes  No  Unknown If yes, date of diagnosis (mm/yy): \_\_\_\_\_
- b) Stroke  Yes  No  Unknown If yes, date of diagnosis (mm/yy): \_\_\_\_\_
- c) Diabetes mellitus  Yes  No  Unknown If yes, date of diagnosis (mm/yy): \_\_\_\_\_
- d) Coronary artery by-pass grafting  Yes  No  Unknown If yes, date of procedure (mm/yy): \_\_\_\_\_
- e) Coronary angioplasty/stenting  Yes  No  Unknown If yes, date of procedure (mm/yy): \_\_\_\_\_
- f) Carotid endarterectomy  Yes  No  Unknown If yes, date of procedure (mm/yy): \_\_\_\_\_

**2. Have any first degree relatives (genetic mother, father, brother, sister) experienced myocardial infarction or stroke before the age of 50 years:**  Yes  No  Unknown

**3. Most recently measured:**

	Not done	Fasting	Value	Unit	Date of measurement (mm/yy)
Serum total cholesterol	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____
Serum HDL cholesterol	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____
Serum triglycerides	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____

**4. Systolic and diastolic blood pressure**  Not done  Value  \_\_\_\_\_/\_\_\_\_\_  
Date of measurement (mm/yy) \_\_\_\_\_

**5. Ongoing treatment**

- |                                    |  |   |  |
|------------------------------------|--|---|--|
|                                    | On treatment   |   | On treatment   |
| a) Anti platelets                  | <input type="checkbox"/> Yes <input type="checkbox"/> No | e) Oral antidiabetic agents               | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| b) ACE inhibitors                  | <input type="checkbox"/> Yes <input type="checkbox"/> No | f) Insulin or derivatives hereof          | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| c) Antihypertensive agents, others | <input type="checkbox"/> Yes <input type="checkbox"/> No | g) Anabolic steroids/ appetite stimulants | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| d) Lipid lowering agents           | <input type="checkbox"/> Yes <input type="checkbox"/> No |   |  |

**6. Is the patient currently a cigarette smoker**  Yes  No  Unknown  
If NO - has he/she ever smoked cigarettes  Yes  No  Unknown

**7. Is the patient experiencing loss of fat from extremities, buttocks or face?**  Yes  No

**8. Is the patient experiencing accumulation of fat in abdomen, neck, breasts or other defined location?**  Yes  No

Patient identification code \_\_\_\_\_ Date of completion (dd/mm/yy) \_\_\_\_\_

Completed by \_\_\_\_\_

**1. Have any of the following disease(s)/procedures been diagnosed/performed since D.A.D enrolment/ last follow-up:**

- a) Myocardial infarction (definitive/possible)  Yes  No If yes, date of diagnosis (mm/yy): \_\_\_\_\_
- b) Stroke  Yes  No If yes, date of diagnosis (mm/yy): \_\_\_\_\_
- c) Diabetes mellitus  Yes  No If yes, date of diagnosis (mm/yy): \_\_\_\_\_
- d) Coronary artery by-pass grafting  Yes  No If yes, date of procedure (mm/yy): \_\_\_\_\_
- e) Coronary angioplasty/stenting  Yes  No If yes, date of procedure (mm/yy): \_\_\_\_\_
- f) Carotid endarterectomy  Yes  No If yes, date of procedure (mm/yy): \_\_\_\_\_

**2. Have any first degree relatives (genetic mother, father, brother, sister) experienced myocardial infarction or stroke before the age of 50 years?** Yes  No  Unknown**3. Most recently measured:**

	Not done	Fasting	Value	Unit	Date of measurement (mm/yy)
Serum total cholesterol	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____
Serum HDL cholesterol	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____
Serum triglycerides	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____

**4. Systolic and diastolic blood pressure**  Not done  Value \_\_\_\_\_/\_\_\_\_\_  Date of measurement (dd/mm/yy) \_\_\_\_\_

**5. Ongoing treatment at time of this follow-up**

	On treatment at current visit (Y=Yes, N=No, U=Unknown)	Start date (dd/mm/yy)	Stop date (dd/mm/yy)
a) Anti-platelets	<input type="checkbox"/>	_____	_____
b) ACE inhibitors	<input type="checkbox"/>	_____	_____
c) Antihypertensive agents, others	<input type="checkbox"/>	_____	_____
d) Lipid lowering agents	<input type="checkbox"/>	_____	_____
e) Oral antidiabetic agents	<input type="checkbox"/>	_____	_____
f) Insulin or derivatives hereof	<input type="checkbox"/>	_____	_____
g) Anabolic steroids/appetite stimulants	<input type="checkbox"/>	_____	_____

**6. Is the patient currently a cigarette smoker**  Yes  No  Unknown**7. Is the patient experiencing loss of fat from extremities, buttocks or face?**  Yes  No**8. Is the patient experiencing accumulation of fat in abdomen, neck, breasts or other defined location?**  Yes  No







# DAD

## Event Checking Chart

### Cases of invasive cardiovascular procedures

Name of centre and cohort \_\_\_\_\_

Patient ID code: \_\_\_\_\_ Gender: \_\_\_\_\_

Year of birth (yyyy): \_\_\_\_\_ Date of event (dd/mm/yy): \_\_\_\_\_

---

1. Which invasive cardiovascular procedure has been conducted?

- Coronary artery by-pass grafting
- Coronary angioplasty/stenting
- Carotid endarterectomy

2. Was the procedure conducted in relation to a myocardial infarction?

- no
- yes - acute intervention during MI
- yes - the procedure was complicated by an MI
- yes - after MI

(if yes, complete checking chart for cases of MI)

3. Was the procedure complicated by stroke?

- no
- yes (if yes, complete checking chart for stroke)

4. Have copies of original documents from the hospital record been collected?  
(Description of the procedure, coronary-arteriography, ecg's etc.)

yes, the following: \_\_\_\_\_

\_\_\_\_\_

no, will be forwarded later

no, can not be obtained because: \_\_\_\_\_

\_\_\_\_\_

---

All available information regarding this event has been collected,

Signature: \_\_\_\_\_ the Study Coordinating Office, Date: \_\_\_\_\_ ( dd/mm/yyyy)

Monitored at site by: \_\_\_\_\_ Date: \_\_\_\_\_  
Print Name Signature dd/mm/yyyy

Please return this form to the DAD study coordinating office incl. ecg's & copies of other relevant documents from the medical record (made anonymous and labelled with the patients ID-code) by air-mail and keep a copy of the chart at the cohort coordinating office.



## Event Checking Chart Cases of Diabetes Mellitus

Name of centre and cohort \_\_\_\_\_

Patient ID code: \_\_\_\_\_ Gender: \_\_\_\_\_

Year of birth (yyyy): \_\_\_\_\_ Date of event (dd/mm/yy): \_\_\_\_\_

---

1. Has diabetes been diagnosed by repeated elevated fasting plasma glucose? yes  no

If yes, please indicate measurements on independent dates:

date: / /	fasting plasma glucose:	unit:
date: / /	fasting plasma glucose:	unit:

if no, how was diabetes diagnosed?: \_\_\_\_\_

---

2. Did the patient receive any medical treatment, other than ART, that could have precipitated diabetes? yes  no

if yes, which therapy (please indicate drug by generic name)? : \_\_\_\_\_

---

3. Any current or previous medical history of pancreatitis? Yes  No  Unknown

All available information regarding this event has been collected,

Signature: \_\_\_\_\_ the Study Coordinating Office, Date: \_\_\_\_\_ ( dd/mm/yyyy)

Monitored at site by: \_\_\_\_\_ Date: \_\_\_\_\_  
Print Name Signature dd/mm/yyyy

Please return this form to the DAD study coordinating office incl. copies of relevant documents from the medical record (made anonymous and labelled with the patients ID-code) by air-mail and keep a copy of the chart at the cohort coordinating office.

# Cause of Death Form (CRF)



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
- D. Registry  Yes  No
- E. Obituary  Yes  No
- F. Patient's relatives or partner  Yes  No
- G. Patient's medical provider  Yes  No
- H. Nursing home  Yes  No
- I. Other  Yes, describe \_\_\_\_\_  No

## Section 3 ♦ Risk factors: (please mark all that apply)

### 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: (please mark all that apply)

### 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)

# Cause of Death Form

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/mmm/yy (eg 01-FEB-05)	Certainty of diagnosis*		
			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"/>

\*Certainty 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):

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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. Due to, or as a consequence of (the underlying condition): \_\_\_\_\_

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

# Cause of Death Form

Study: \_\_\_\_\_

Patient ID code: \_\_\_\_\_

# CoDe

## Section 6 ♦ Post-mortem / Autopsy:

**A. Has autopsy been performed:**

Yes       No       Unknown

*If Yes, did the autopsy reveal any pathology in (please mark all that apply):*

1. CNS       Yes, describe: \_\_\_\_\_  No       Unknown
2. Respiratory organs       Yes, describe: \_\_\_\_\_  No       Unknown
3. Cardiovascular system       Yes, describe: \_\_\_\_\_  No       Unknown
4. Gastro-intestinal (incl.liver)       Yes, describe: \_\_\_\_\_  No       Unknown
5. Uro-genital       Yes, describe: \_\_\_\_\_  No       Unknown
6. Muscular-skeletal       Yes, describe: \_\_\_\_\_  No       Unknown
7. Endocrine glands       Yes, describe: \_\_\_\_\_  No       Unknown
8. Did the autopsy reveal any evidence of intoxication:

Yes, with the agent: \_\_\_\_\_  No       Unknown

Please provide a brief summary of the findings from the autopsy report (please also include a copy of the full report):

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## Section 7 ♦ ART and laboratory values prior to death

**A. Please indicate when and if the patient first initiated ART (in months before death):**

1 month before     3 months before     6 months before     More than 6 months before     Never Received

**B. Did the patient receive ART at the time of death?**  Yes     No

o *If No*, Date of stopping \_\_\_ - \_\_\_ - \_\_\_ (dd/mmm/yy eg 01-FEB-05)

**C. Laboratory values** (please complete all fields where data is available)

Laboratory values	Time	Value	Unit	Date dd/mmm/yy (eg 01-FEB-05)
CD4+ cell count	1. Most recent prior to last stopping ART		Cells/mm <sup>3</sup>	___ - ___ - ___
	2. Most recent prior to death		Cells/mm <sup>3</sup>	___ - ___ - ___
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		/	___ - ___ - ___

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

# Cause of Death Form



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

*If yes, please specify which one(s)?*

Antiretroviral therapy:	Date of first initiation: dd-mmm-yy (eg 01-FEB-05)	Certainty of relationship to drug*		
		Highly	Likely	Possible
	___ - ___ - ___	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	___ - ___ - ___	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	___ - ___ - ___	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	___ - ___ - ___	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Other medication:</b>				
	___ - ___ - ___	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	___ - ___ - ___	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	___ - ___ - ___	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	___ - ___ - ___	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

\***Highly** suspected (95-100% certainty); **Likely** (80-95%); **Possible** (50-80%)

Please provide a brief narrative of the suspected association

---



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

## **APPENDIX C – Monitoring report and monitor log**

**Name of cohort**

---

**Name of site**

**Site no.**

---

**Principle investigator**

---

**Date of visit**

---

(tick box and please write comment no. referring to the comments page)

	<b>Yes</b>	<b>No</b>	<b>Comment No.</b>
Protocol / MOOP available	<input type="checkbox"/>	<input type="checkbox"/>	
Patient information/informed consent (if needed)	<input type="checkbox"/>	<input type="checkbox"/>	
Monitor log	<input type="checkbox"/>	<input type="checkbox"/>	
Training of site personnel	<input type="checkbox"/>	<input type="checkbox"/>	
Source data available	<input type="checkbox"/>	<input type="checkbox"/>	
Accurate patient identification list/patient log	<input type="checkbox"/>	<input type="checkbox"/>	
10% source data verification*	<input type="checkbox"/>	<input type="checkbox"/>	
25% source data verification**	<input type="checkbox"/>	<input type="checkbox"/>	

(Requirements for Source data verification are specified in the MOOP in section 7.2)

\*Please find enclosed a list for documentation of reviewed records

\*\*If any missed events, 25% source data verification is required

This report consists of \_\_\_\_\_ pages.

---

**Completed by** (signature of monitor)

**Date**

---

**Reviewed by** (signature of cohort coordinator)

**Date**







# Monitor log

Cohort : \_\_\_\_\_ Country : \_\_\_\_\_

Investigator: \_\_\_\_\_ Site code: \_\_\_\_\_

Hospital: \_\_\_\_\_

Date of visit (dd/mm/yy)	Signature of monitor	Purpose of visit	Signature of site representative

## APPENDIX E – Patient Informed Consent

### Patient information

*A draft patient information and informed consent to be adjusted as required by each centre/country/cohort*

#### Introduction

You are asked to participate in a study being undertaken at your hospital

.....  
The title of the study is " Data on Adverse Events of Anti-HIV Drugs" (D:A:D), a multinational study following more than 35.000 patients across Europe, Australia and USA.

#### Purpose of the study

The purpose of the study is to collect data on HIV-infected patients to evaluate whether there is correlation between development of a cardiovascular disease and antiretroviral treatment - an evaluation of long-term side effects. The data collection will take place at least every 8 months and is projected to last for two years. The data are results of routine blood tests, information on diseases such as myocardial infarction, stroke and diabetes mellitus, hereditary tendency and smoking status. In case of death, information on the cause of death is collected. The data will be obtained from your medical record, and no additional blood samples or visits at your clinic are required. **Organisation**

The study coordinating office is Copenhagen HIV Programme, Denmark, and the Steering Committee represented by ..... (cohort) will supervise the conduct of the study.

The study has been approved by the independent local ethics committee

Support for the study is given by the Steering Committee for The Evaluation of Metabolic Complications of HAART, and a number of pharmaceutical companies producing anti-retroviral drugs contribute financially.

#### Confidentiality

Only doctors, nurses and personnel authorised by government agencies will have access to your records. This is necessary to make sure that the trial is performed according to the highest possible standards.

Results from this study will be analysed and may be published in medical journals but your identity will not be revealed. No information containing your name will be allowed off the hospital premises and your personal records will be identifiable only by a code.

Your participation is voluntary and you can withdraw your consent at any time without any influence on your future treatment/hospital care.

## **Patient informed consent**

The full nature of the D:A:D study has been explained to me.

I have read the patient information sheet and have been given the opportunity to ask questions and these have been answered to my satisfaction.

It has been explained to me that in case of my death, my next of kin may be approached for a medical release form.\*

It has been explained that I can withdraw my consent at any time for any reason.

It has also been explained to me that authorised personnel may review my record but that identifiable information under no circumstances will be made publicly available.

### **I consent to enter the above mentioned study**

Name \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

### **Investigator**

Name of doctor \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

\*Optional; can be included if local standards require.