



Guidelines for completion of the 3 New Endpoints in the D:A:D Study:

**Non-AIDS Defining Cancer
Chronic Liver Disease
End-stage Renal Disease**

Version 1.1: 23 March 2010

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In version 1.1 the Guidelines have been updated due to changes made in the Non-AIDS Defining Cancer and the End-Stage Renal Disease event forms



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Background for the 3 New Endpoints:

The D:A:D study has expanded the protocol to include 3 new *non-fatal* endpoints: Non-AIDS Defining Cancer, Chronic Liver Disease, and End-Stage Renal Disease.

Thus far, the D:A:D study has collected information on these disease entities only based on information on causes of death (CoDe).

However, to better assess the possible association of cART treatment with the risk of different organ diseases and cancer, the data-collection is at this stage expanded to also include the non-fatal outcomes.

Non-AIDS Defining Cancer

More than 60 % of all deaths in HIV positive persons receiving combination Anti-Retroviral Treatment (cART) are from causes other than AIDS (1-7). In the D:A:D study covering the period from 1999-2007 12% of all deaths in persons on cART were due to non-AIDS defining cancer. Several studies have suggested higher rates of a number of non-AIDS defining cancers in HIV-infected individuals as compared with the background population, in particular in immunodeficient stages (8-10).

The primary objective of the D:A:D sub-study on non-AIDS defining cancers is to assess the possible relationship between exposure to cART and risk of cancers (overall and according to most prevalent types). Secondary objectives include an assessment of the possible associations between immunodeficiency and the risk of non-AIDS-defining cancers.

Chronic Liver Disease

Untreated HIV, as well as several other immunodeficiency disorders, can lead to acceleration of the liver disease seen in patients chronically infected with either hepatitis B or hepatitis C virus (11-16). The D:A:D study has previously found that longer exposure to cART is associated with a slight increase in the risk of liver mortality.

As the number of patients co-infected with hepatitis B virus and hepatitis C virus is large, it is important to further explore if continued exposure to cART may ultimately lead to significant progression of liver failure. With longer follow-up and the inclusion of non-fatal outcomes of liver disease, the study will in the future be able to investigate whether clinically significant treatment-associated liver disease occur.

End-stage Renal Disease

Several drugs that are used to treat HIV and its' complications are nephro-toxic. Some of these drugs may exert acute and completely reversible impairment of renal function, but effects of long-term exposure have not been properly explored. Some recent studies suggest that exposure to some of these drugs may lead to permanent impairment of kidney function in some patient subgroups.

The CRFs are available online at:

<http://www.cphiv.dk/DAD/StudyDocuments/tabid/112/Default.aspx>

Please contact the D:A:D Coordinating Office at: www.cphiv.dk or call at + 45 35 45 57 57 if you have questions or would like hard copies mailed to you.

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1.0 Guidelines for completion of Non-AIDS-Defining-Cancer CRF

To be completed for patients who have been diagnosed with a malignant disease (other than AIDS defining cancer: Non-Hodgkin's lymphoma, Kaposi's sarcoma or invasive cervical cancer; **or** basal or squamous cell skin cancer).

HEADING: The date of first diagnosis is the day, month and year the tumor was diagnosed for the first time by a recognized medical practitioner, whether clinically or microscopically confirmed. If there is a relapse in the same primary location or dissemination from the same primary cancer, a new CRF does not need to be completed.

ITEM 1 Diagnosis

Please provide the specific type and the primary location of the cancer and if available the ICD-10 or ICD-9code in the spaces provided in the CRF.

ITEM 2 Stage at diagnosis

Please tick the appropriate box (only one box) for the stage of the cancer at the time of diagnosis.

ITEM 3 Histology/cytology

Please indicate whether a pathology report is available after a biopsy.

If yes: please indicate whether copies of original source data have been included and give a brief summary of the report in English in the space provided.

If no or unknown: please complete item 4.

ITEM 4 If the diagnosis is not confirmed by histology/cytology please mark by which means the cancer was diagnosed and specify in the space provided.

ITEM 5 Prior history of chemo-and/or radiotherapy for a malignant disease

Please indicate in the appropriate boxes whether the patient has received chemo- and/or radiation therapy in the past or not. If yes, please indicate what kind of therapy the patient received and the year of therapy.

Case definition of Non-AIDS Defining Cancer

- A. Diagnosis of cancer (*other than: AIDS defining (non-Hodgkin's lymphoma, Kaposi's sarcoma or invasive cervical cancer); and basal and squamous cell skin cancers*) in a pathology report that established the diagnosis
- B. Diagnosis of cancer (*other than: AIDS defining (non-Hodgkin's lymphoma, Kaposi's sarcoma, or invasive cervical cancer); and basal and squamous cell skin cancers*) in a hospital discharge summary or consultation note from the hospitalization or clinic visit during which the diagnosis was established
- C. In the absence of **A** or **B**: Strong suspicion of cancer supported by (i) evidence from radiological or other imaging technique, (ii) or biochemical assay
- D. In the absence of **A**, **B** or **C**: Strong suspicion of cancer by visual inspection (e.g. skin metastasis, suspected malignant melanoma, tissue growth resembling cancer visualized during endoscopy/anoscopy) not explained by other known conditions.

Confirmed: A or B

Probable: C

Possible: D

Event Checking Chart**Cases of Non-AIDS-Defining Cancers**

Name of centre and cohort _____

Patient ID code: _____ Gender: Male Female

Year of birth (yyyy): _____ Date of first diagnosis (dd/mm/yy): _____

1. DiagnosisPlease complete this form if the patient has been diagnosed with a malignant disease
(excluding AIDS defining cancers, and basal and squamous cell skin cancers)Primary location (if known): _____ (e.g. lung); unknown - please provide specific type: _____
(e.g. adenocarcinoma, osteosarcoma, leukemia)

If available, please include the: ICD-10 _____, or ICD-9 code _____

2. Stage (spread) at diagnosis (Tick one only):

- Localized (growth within the organ of origin)
 Disseminated (spread to tissue outside the organ of origin, incl to regional lymph nodes)
 Unknown

3. Histology/cytology

Is a pathology report (or summary hereof) available?

 Yes, full report Summary of report No Unknown

If 'no' or 'unknown', please complete Question 4

If yes, please include a copy of the full report (and provide a brief summary in English):

4. If the diagnosis is not confirmed by histology/cytology, is the diagnosis based on

(Tick all that apply and 1 at a minimum):

- I. Radiology or other imaging technique (cancer suggestive findings)
 II. Biochemical assay (elevated markers of cancerous growth (e.g. prostate specific antigen, alpha-fetoprotein, cancer cell markers))
 III. Strong suspicion of cancer by clinical inspection (skin metastasis, suspected malignant melanoma, suspected cancerous growth visualized during endoscopy/anoscopy)
 IV. Other

Of those marked above, please specify: _____

5. Has the patient previously received chemo- and/or radiation therapy for a malignant disease?Yes , no , unknown If yes, please tick off the appropriate box: chemotherapy , radiation , year of treatment: _____

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

Monitored at site by: _____ Date: _____

Print Name

Signature

dd/mm/yyyy

2.0 Guidelines for completion of Chronic Liver Disease CRF

HEADING: The date of event is the day, month and year the first time the patient developed one of the clinical signs of liver failure listed under **item 1** or the day, month and year the patient had a liver transplantation performed.

ITEM 1 – Definition of endpoint

Please complete the CRF **the first time** the patient develops one of the clinical signs of liver failure listed in the CRF **or** if the patient has undergone a liver transplant

ITEM 2- Diagnosis

Please provide the specific diagnosis of the patient's liver disease in the space provided in the form. If available, please include the ICD-10 or ICD-9 code

ITEM 3- Co-morbidities and risk factors

Please mark if the patient has been diagnosed with:

- **Chronic hepatitis B virus (HBV)**
Chronic hepatitis B is inflammation of the liver that lasts at least 6 months
- **Chronic hepatitis C virus (HCV).**
Chronic hepatitis C is inflammation of the liver that lasts at least 6 months
- **Current or past alcohol abuse**
Alcohol abuse definitions: **For men:** An intake of > 25 alcohol-containing units a week
For women: An intake of > 20 alcohol-containing units a week

ITEM 4- Documentation of presence of cirrhosis

Please indicate whether a liver biopsy or a fibroscan has been performed. If **yes** please indicate in the space provided the date of the most recent biopsy/fibroscan and the Metavir stage of fibrosis (F0-F4: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa, F3, numerous septa without cirrhosis; F4, cirrhosis). Please indicate whether copies of original source data have been included and give a brief summary of the report in English in the space provided.

Case definition of Chronic Liver Disease

- A.1** Clinical symptoms of end-stage liver failure in patients with chronic liver disease, based on the diagnosis documented in a clinical note of either
 - (i) bleeding from gastric or esophageal varices
 - (ii) hepatic encephalopathy stage III or IV
 - (iii) hepatorenal syndrome
- A. 2** liver transplantation documented in a clinical note
- B.** Pathology report or fibro-scan report documenting severe liver fibrosis or cirrhosis (Metavir F3 or F4 or fibroscan liver stiffness \geq 8 kPa)

Confirmed: A1 and B; or A2 **Probable:** A1

Event Checking Chart

Cases of Chronic Liver Disease- Severe Clinical Manifestations

Name of centre and cohort _____

Patient ID code: _____ Gender: Male Female

Year of birth (yyyy): _____ Date of Event in Question 1 (dd/mm/yy): _____

1. Definition of endpoint

Please complete this form if the patient has developed one of the following clinical signs of **liver failure** for the first time:

bleeding from gastric or esophageal varices (endoscopy verified)

hepatic encephalopathy stage III or IV (pre-coma or coma)

hepatorenal syndrome (acute renal failure in patient with existing severe chronic liver disease)

or,

the patient has undergone liver transplantation

2. Diagnosis

Please provide the specific diagnosis of the patients liver disease: _____

If available, please include the ICD-10 _____ or ICD-9 code _____

3. Co-morbidities and risk factors

Is the patient known with:

Chronic HCV? Yes No Unknown

Chronic HBV? Yes No Unknown

Current or past alcohol abuse? Yes No Unknown

4. Documentation of presence of cirrhosis

A. Has liver biopsy been performed? Yes No Unknown

B. Has fibroscan of the liver been performed? Yes No Unknown

If **Yes** to A or B, please indicate:

the date of most recent biopsy/ fibroscan (dd/mm/yy) ___ ___ - ___ ___ - ___ ___ and

Metavir stage of fibrosis (F0-F4): |__|

Please include a copy of the full report (and please provide a brief summary in English):

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

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

3.0 Guidelines for completion of End-stage Renal Disease CRF

HEADING: The date of event is the day, month and year when the patient for the first time initiated permanent haemodialysis or peritoneal dialysis **or** the date the patient had a kidney transplantation performed.

ITEM 1- Definition of endpoint

Please complete the CRF **the first time** the patient has initiated permanent (expected to last at least 3 months) haemodialysis or peritoneal dialysis **or** if the patient has undergone kidney transplantation.

ITEM 2 – Diagnosis and categories of renal disease

Please indicate the category that best applies to characterize the patient's renal disease. All of the listed diseases are diagnosed by a histology result, **except for** polycystic kidney disease.

If the specific diagnosis of the patient's kidney disease and the ICD-10 or ICD-9 code are available, please record this data in the space provided in the CRF.

ITEM 3- Histology

Please indicate whether a kidney biopsy has been performed. If **yes** please indicate whether copies of original source data have been included and give a brief summary of the report in English in the space provided.

Case definition of End-stage Renal Disease

- A. Hemodialysis or peritoneal dialysis expected to last at least three months documented in a clinical note
- B. A kidney transplant, documented in a clinical note

Confirmed: A or B

Probable: Not applicable

**Event Checking Chart
Cases of End Stage Renal Disease (ESRD)**

Name of centre and cohort _____

Patient ID code: _____ Gender: Male FemaleYear of birth (yyyy): _____ Date of Event (dd/mm/yy): _____
(date of events listed in question 1)**1. Definition of endpoint**For the patient with **chronic renal disease**, please complete this form **the first time** the patient has initiated permanent (expected to last at least 3 months) dialysis: haemodialysis peritoneal dialysis,**or** the patient has undergone kidney transplantation**2. Diagnosis and categories of renal disease**Please indicate which category applies best for the characterization of the patients' renal disease (*tick one or more as appropriate*):

Chronic renal failure, with underlying etiology

 HIV associated nephropathy glomerulonephritis interstitial nephritis polycystic kidney disease hereditary / congenital vascular diabetic nephropathy systemic disease other unknown**If available, please provide the specific diagnosis of the patients' kidney disease: _____ and please include the ICD-10 _____ or ICD-9 code**

3. HistologyHas kidney biopsy been performed? Yes No Unknown**If yes, please include a copy of the full report (and please provide a brief summary in English):**_____

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

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