CHIP COPENHAGEN HIV PROGRAMME

“Data Collection on Adverse Events of Anti-HIV Drugs”

The D:A:D Study

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Background

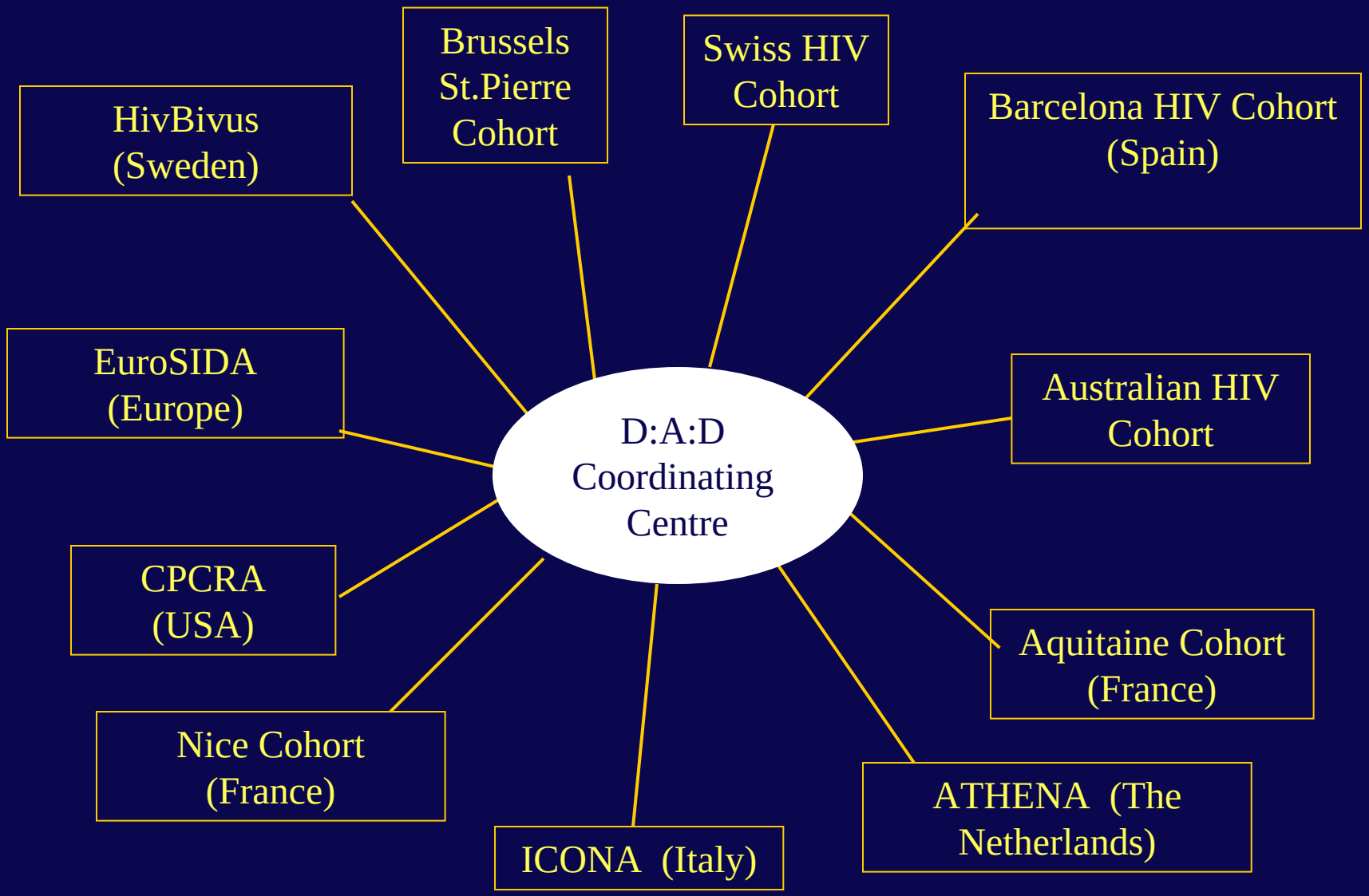
- Combination ART (cART) widely introduced in the Europe in 1996
- cART is associated with dyslipidaemia, insulin resistance, abnormal body fat distribution
- Several case reports in 1998/1999 indicated pre-mature atherosclerosis and risk of myocardial infarction in young HIV+ patients exposed to cART
- cART is not able to eradicate the HIV, hence treatment is lifelong

The Need for D:A:D

- February 1999, EMEA/Committee for Medicinal Products for Human Use (CHMP) – Industry
- Oversight Committee for the Evaluation of the Metabolic Complications of Highly Active Antiretroviral Therapy
- A collaborative committee with representation from academic institutions, EMEA, FDA, the patient community, and all pharmaceutical companies with licensed anti-HIV drugs in the U.S. market: Abbott, Agouron, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Pfizer, and Hoffmann–LaRoche

The Need for D:A:D

- Initiated in 1999 as part of EMEA initiative, The D:A:D Study aims to assess whether exposure to cART is associated with an increased risk of myocardial infarction (MI)
- Established to ensure corporate responsibility in researching the long-term effects of antiretroviral therapy



N=23,000+ in 2000
N= 35,000+in 2005
N= 49,000+ in 2009

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Why looking at adverse effects in observational studies

- All cohorts were pre-existing
- Potential for detecting long term and rare adverse events (Events are few; large sample size needed)
  - Which would be missed in Randomised Clinical Trials (RCT) due to limited number of patients and follow-up
- Potential for detecting adverse reactions in a ’real life setting’
  - patients exposed not selected as in RCTs

Design

- Prospective follow-up
  - Accumulated ~ 200,000 PYFU (in Autumn 2009)
- Centrally validated end-points
- Observational design
  - No control group
  - No conclusions on causality can be drawn, only associations
  - Subject to bias
    - Carefully conducted statistically analysis can reduce this

D:A:D ‘old’ [original] events

Primary:

- Myocardial Infarction (MI)

Other Endpoints:

- Stroke
- Invasive Cardiovascular procedures
- Diabetes
- Death (all causes – now CoDe)

- All events are reported ‘real time’ to the DAD Study Coordinating Office at CHIP
- Reimbursement of 200 US$ per form

- Event reporting forms at: www.cphiv.dk

D:A:D

- The data collection for DAD takes place at least every 8 months
- Each cohort gathers and computerises its data; subsequently it is merged in a database in Copenhagen.
- Core data is information on incident cases of cardiovascular disease, which are reported immediately to the local cohort coordinating office by fax, using the event reporting forms
- The data collection also includes information on risk factors for cardiovascular disease

D:A:D characteristsics

- Hypothesis driven
- Sufficient power
- Primary model and sensitivity analysis
  - assess robustness of primary model
  - understand biological plausibility
  - awareness on limitations
- External review from end-points experts
- Cohort collaboration with participating cohorts agreeing to a common research agenda where a need for collaboration is *essential* in order to have the questions answered

D:A:D Organisation Structure

- Originally a Consortium of eight Pharmaceutical Companies (working through a Contract Research Organisation-PRISM Event Management)
- PRISM contracts with the DAD Coordinating Centre to undertake a sponsored Study entitled: “Data Collection on Adverse Events of Anti-HIV Drugs”, “The D:A:D Study”
- The Site Principal Investigator for each cohort is affiliated with the Copenhagen HIV Programme (the “D:A:D Protocol Coordinating Centre”) and on the Steering Committee

D:A:D Ownership and Access to Data

D:A:D Steering Committee

- Scientific independence
- Rights to Primary trial data
- Agrees to engage best effort if the Oversight committee requests additional data analyses pursuant to an obligation under statute or to a statutory, regulatory or governmental body
- Oversight Committee representation on the D:A:D Steering Committee (participating in all teleconferences and annual face-to-face meeting)

Process around Publications from D:A:D

The D:A:D study Steering Committee may freely publish and disseminate the results of the research findings relating to their involvement in the Study

The Investigators will provide the “Oversight Committee” with a copy of any proposed abstract or manuscript prior to submission for publication

Reasonable consideration will be given to comments from the “Oversight Committee” members to abstracts and manuscripts

The “Institution” or Site Principal Investigator will allow the “Oversight Committee” at least 5 working days for review of abstracts and 15 working days for review of manuscripts

From and after the date 24 months following completion of the Study, neither the “Institution” nor Site Principal Investigator will be required to provide a proposed publication to the “Oversight Committee” for its prior review, provided no confidential information owned by the “Oversight Committee” is disclosed

The Need for D:A:D

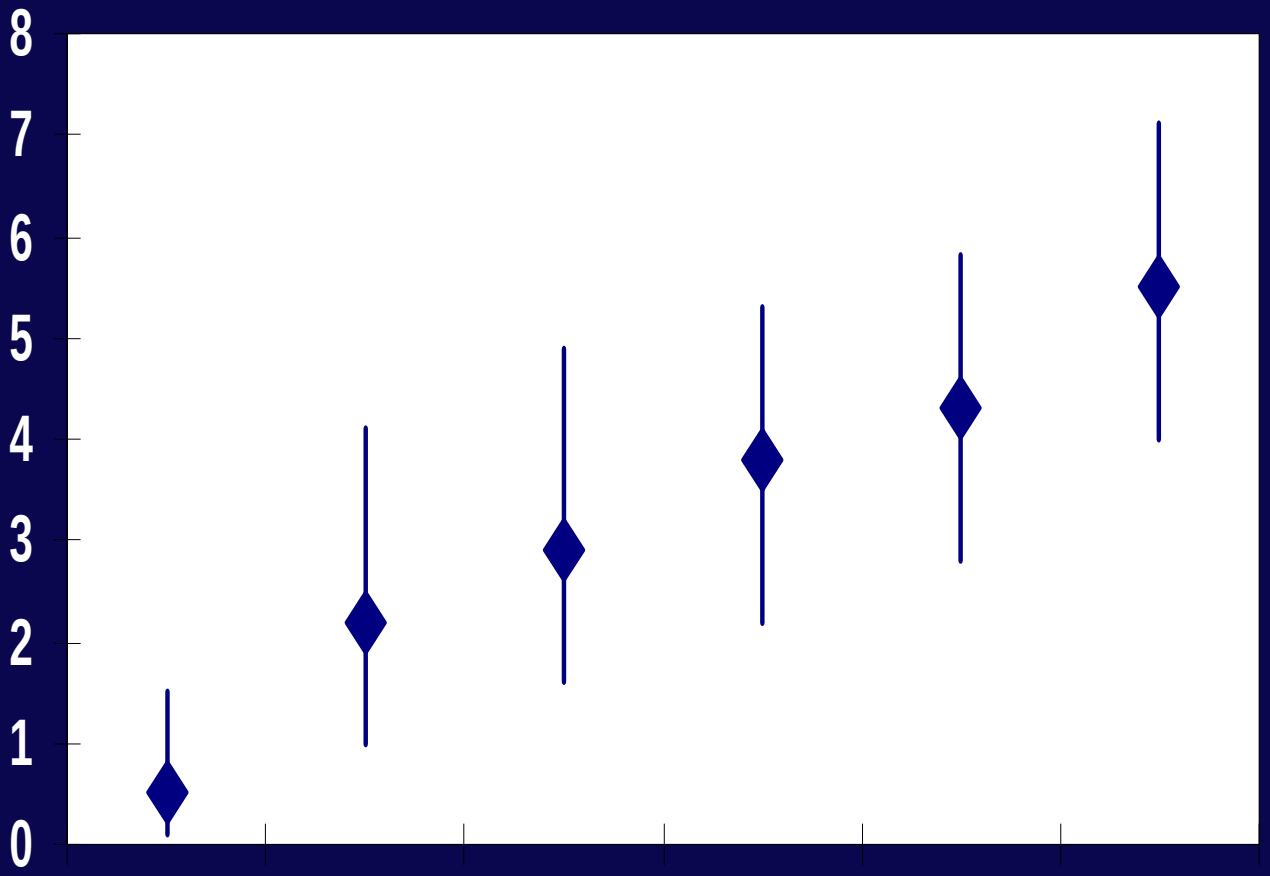
19 publications in peer-reviewed journals since 2003 including:

Combination Antiretroviral Therapy and the Risk of Myocardial Infarction, *N Engl J Med*. 2003; 349(21): 1993-2003.

Class of Antiretroviral Drugs and the Risk of Myocardial Infarction. *Engl J Med*. 2007; 356: 1723-35

Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study, *Lancet.* 2008; 371(9622): 1417-26.

MI by CART exposure



Years on CART	None	<1	1-2	2-3	3-4	>4	Total
No. MIs	3	9	14	22	31	47	126
No. PY	5,714	4,140	4,801	5,847	7,220	8,477	36,199

D:A:D
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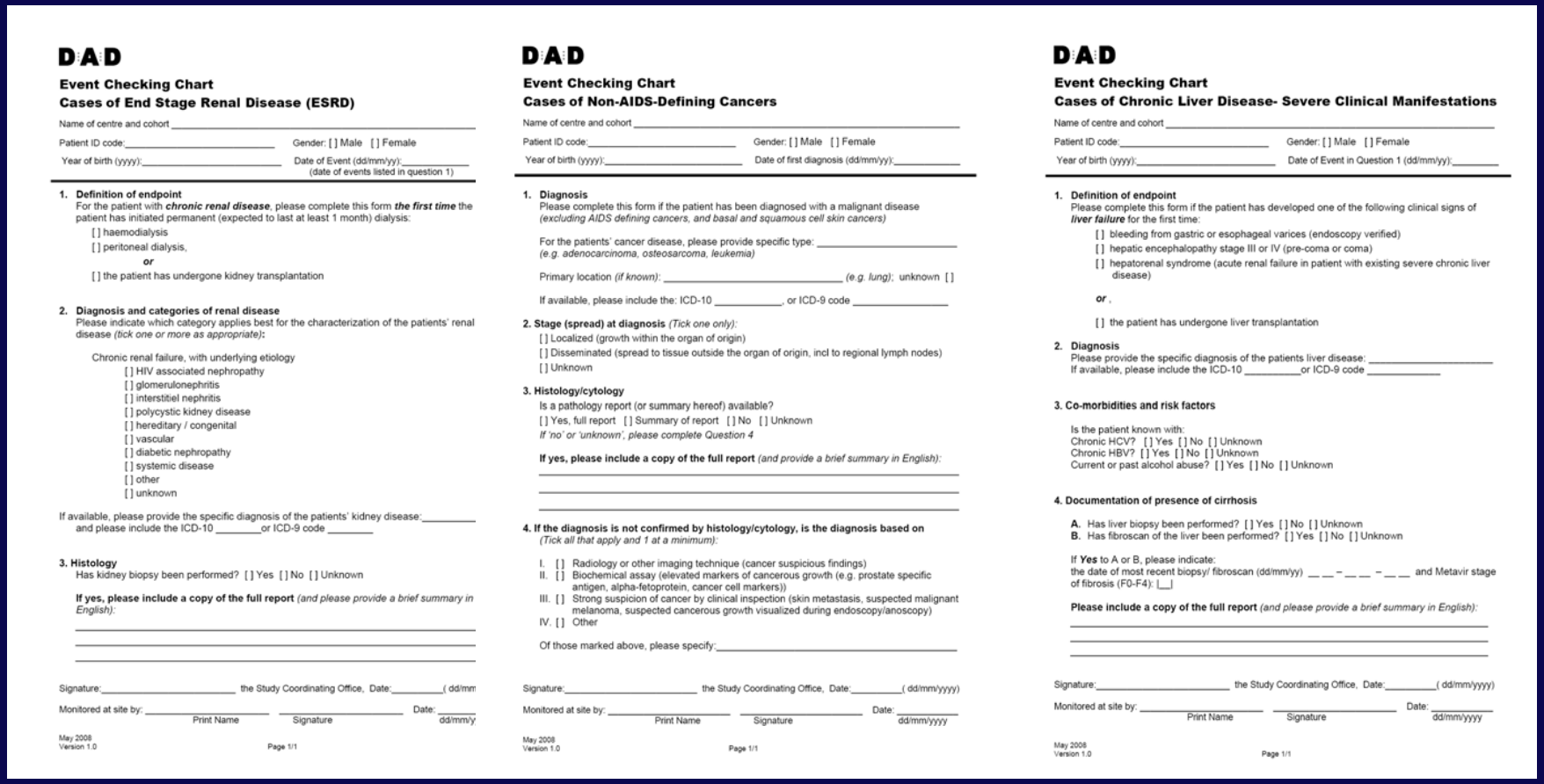
N. Engl. J. Med. 2003;349(21); 1993-2003

In 2008 expanded due to success and increasing concern around the following: **Non-AIDS Defining Cancers, Chronic Liver Disease, End-stage Renal Disease**



D:A:D

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

Name of centre and cohort _____

Patient ID code:_____ Gender: [ ] Male [ ] Female

Year 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 1 month) 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
[ ] interstitiel 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. **Histology**
Has 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

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

May 2008
Version 1.0
Page 1/1

D:A: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. **Diagnosis**
Please complete this form if the patient has been diagnosed with a malignant disease *(excluding AIDS defining cancers, and basal and squamous cell skin cancers)*

For the patients' cancer disease, please provide specific type: _____
(e.g. adenocarcinoma, osteosarcoma, leukemia)

Primary location *(if known)*: _____ *(e.g. lung)*; unknown [ ]

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 suspicious 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:_____

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

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

May 2008
Version 1.0
Page 1/1

D:A:D

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

May 2008
Version 1.0
Page 1/1

Conclusions

- Challenges:
  - Inherent ’issues’ due to study design
- Lessons learned:
  - Scientific independence
  - Transparency and clear and formal organisation with a contract –research-organisation
  - Dedicated participation from Priciple Investigators involved
  - Feed-back and communication with the patient community
  - Scientific questions with (immediate) clinical impact
- Added value:
  - National cohorts – National guidelines
  - EACS (European AIDS Clinical Society) guidelines
  - Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents