D:A:D

The Data Collection on Adverse events of Anti-HIV Drugs

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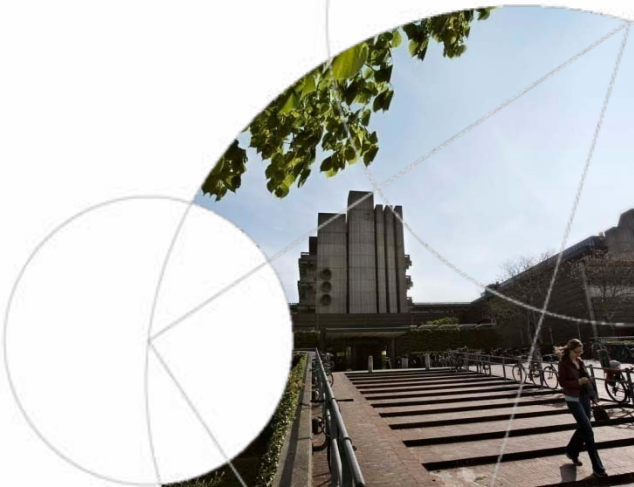


The Need for D:A:D

- 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

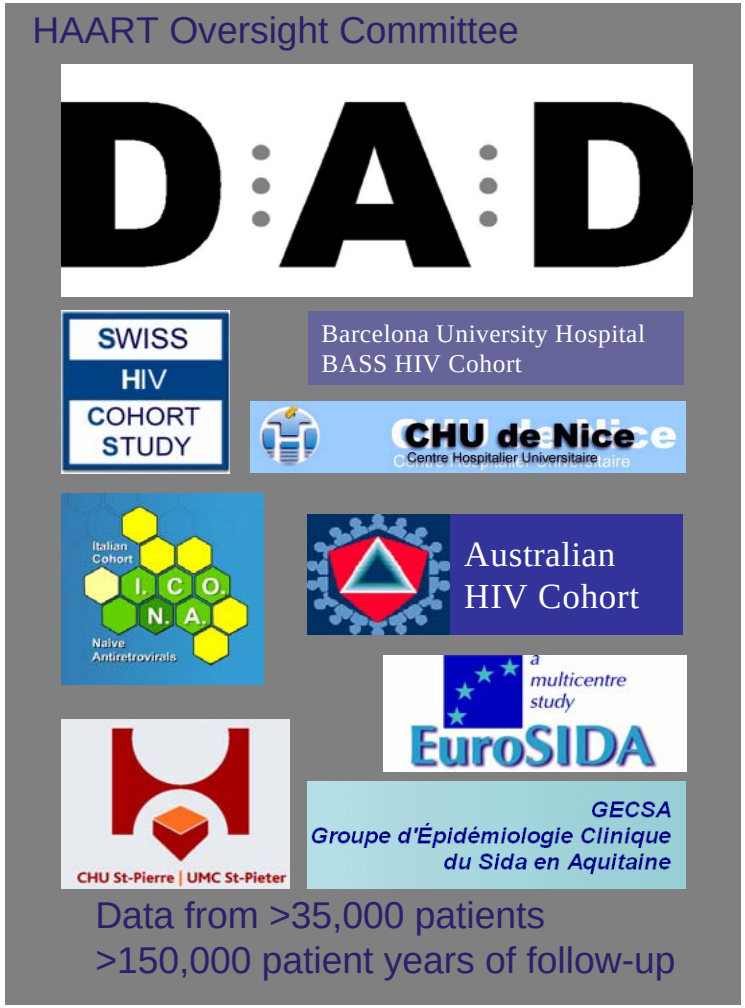
The Need for D:A:D

- Established to ensure corporate responsibility in researching the long-term effects of antiretroviral therapy
- 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
- Events are few; large sample size needed

DAD study

- A prospective multi-cohort study of HIV-infected persons under active follow up
- The purpose of the study is to assess the incidence of myocardial infarction among HIV/AIDS patients who are receiving anti-retroviral therapy
- 11 cohorts worldwide participate
- 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

Those Involved:



The Need for D:A:D

- Initially identified events as: **MI, Stroke, Invasive Cardiovascular Procedure, Death, Diabetes**
- **17 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.

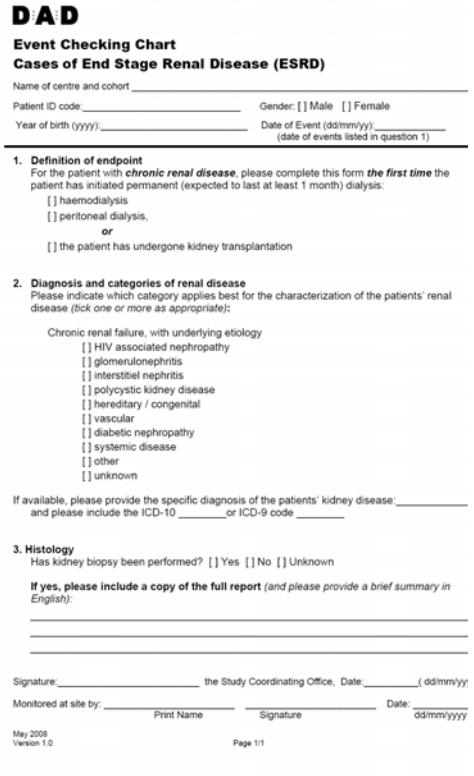
Engl J Med. 2007; 356: 1723-35

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.

The Need for D:A:D

- Last year 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/yy

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

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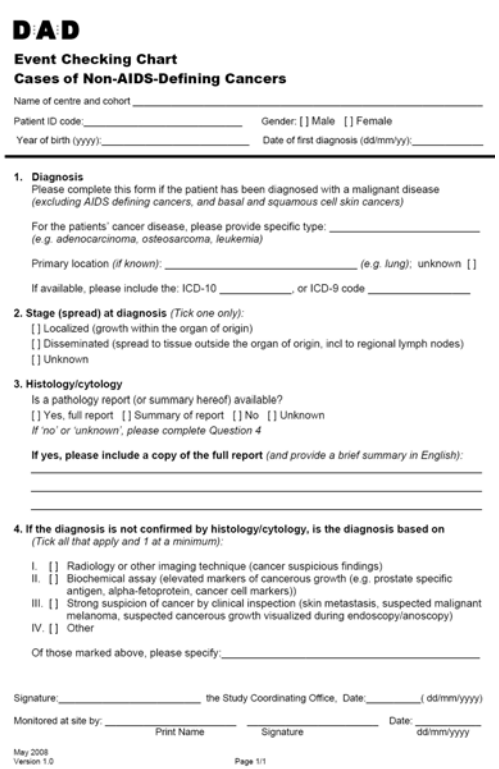

D:A:D

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

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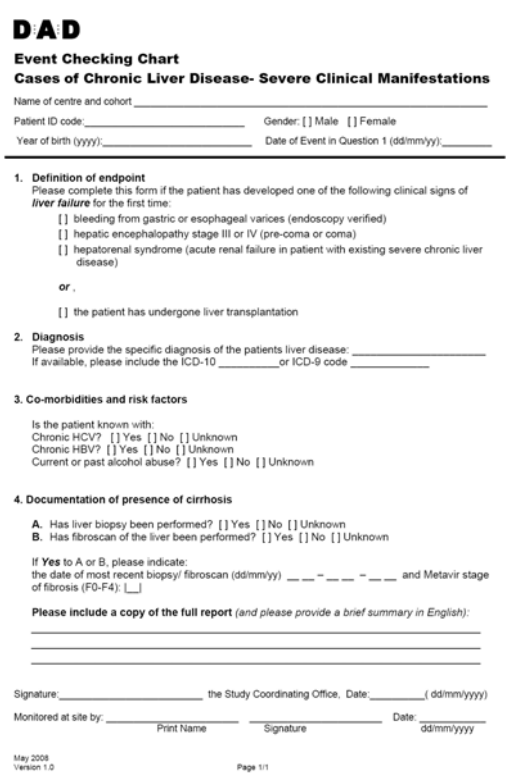

D:A:D

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

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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 "Institution" or 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.