



2006/07

REPORT

CHIP

COPENHAGEN HIV PROGRAMME

The main part of this report covers activities that have taken place in 2006 and 2007. No report was issued in 2005 and therefore publications and presentations for 2005 have also been included here.
All reports can be downloaded at the CHIP web page: www.cphiv.dk

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FROM THE CHAIRMAN OF THE BOARD

CHIP was formed to do high-quality research with the ultimate aim of improving evidence-based interventions that improve the health of people suffering from infectious diseases in general and from HIV in particular. To maintain a dynamic evolution of a research group two sets of accomplishments need to be strived for: (i) the reporting of results from research that has impact and possibly causes paradigm shifts; (ii) initiation of new research projects to ensure that the research portfolio remains contemporary.

The most striking but also unexpected achievement from 2005-2007 was the premature termination of the SMART study¹ (p 17). This study was expected to carry on until 2012, but at a memorable study executive committee meeting in January 2006, we decided to halt the study per advise from the independent data-safety-and-monitoring-board. The research question SMART posed was whether it was necessary to continuously use antiretroviral therapy for the remaining of an infected person's life once the therapy had commenced. The alternative being to use this therapy intermittently as long as the immune function remained above levels where current guidelines indicate it should be commenced in the first place. The data, however, that was revealed in January 2006 convincingly showed that continuous use clearly out-competed intermittent use. Less

surprisingly, intermittent use was associated with excess risk of opportunistic diseases – the halt mark diseases of HIV. However, what completely stunned us was that organ diseases not traditionally thought to be affected by HIV and the associated immunodeficiency, were also seen at an increased rate from using antiretroviral therapy intermittently. The results suggested that HIV-related factors would accelerate the course of disease for pathologies as diverse as liver impairment secondary to co-infection with chronic hepatitis viruses (B and especially C), cardiovascular diseases, kidney diseases and perhaps even cancers. That was surprising and unexpected, as also highlighted in the accompanying editorial when we published the main findings in New England Journal of Medicine² later on in 2006.

What was rewarding was the fact that the D:A:D study (p. 11) had already in 2005 found out that impairment of the immune-function may accelerate the risk of dying from these different causes³. However, as the D:A:D study was observational in nature, we were not certain – until the SMART findings were disclosed – that immunodeficiency was indeed causally related to the increased risk.

The SMART study included more than 5,000 patients followed for 1½ year on average. As a consequence,

¹The SMART study: Strategies for Management of Anti-Retroviral Therapy. A large, long-term, randomized trial comparing two antiretroviral treatment strategies.

²Writing Group: WM El-Sadr, JD Lundgren, JD Neaton, F Gordin, D Abrams, RC Arduino, A Babiker, W Burman, N Clumeck, CJ Cohen, D Cohn, D Cooper, S Emery, G Fätkenheuer, B Gazzard, B Grund, J Hoy, K Klingman, M Losso, N Markowitz, J Neuhaus, AN Phillips, and C Rappoport. CD4+ Count-Guided Interruption of Antiretroviral Treatment. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. N Engl J Med 2006; 355(22): 2283-2296

³Writing committee: R Weber, CA Sabin, N Friis-Møller, P Reiss, WM. El-Sadr, O Kirk, F Dabis, MG Law, C Pradier, S De Wit, B Åkerlund, G Calvo, A d'Arminio Monforte, M Rickenbach, B Ledergerber, AN Phillips, and JD Lundgren Liver-related deaths among persons infected with the human immunodeficiency virus: The D:A:D Study. Arch Intern Med. 2006;166:1632-1641

an enormous amount of data and biological samples have been collected. It will take several years to completely digest this large repository, but some key findings have already emerged (see p. 17) – e.g. HIV activates fibrinogenesis (reflected in increased levels of d-dimers) and depletes HDL-cholesterol.

Based on this data, we were able to formulate - in an editorial comment in British Medical Journal in January 2007⁴ - a provocative new research question: Is use of antiretroviral therapy earlier in the course of the chronic HIV infection as indicated in current guidelines, able to reduce - not only rare opportunistic diseases - but also these various types of organ diseases. This study – called START - will start by end of 2007.

New exciting studies have been initiated. Just to mention a few: We reported in New England Journal of Medicine in April 2007⁵ that the signal –reported in 2003 - of increased risk of myocardial infarction associated with longer exposure to antiretroviral therapy, was confined to the class of drugs “protease inhibitors” and not to the other class of drugs “non-nucleoside reverse transcriptase inhibitors”. It has been questioned whether antiretroviral therapy is able to completely normalise the immune function; however, in a report from EuroSIDA in the Lancet in July 2007⁶ we reported that it appears

possible although it takes many years for patients who start therapy late in the course of the chronic HIV infection.

The research productivity – quantified as cumulative number of impact factors of the journal in which each article is published – has fluctuated around 100 per year in this decade.

Although CHIP has a particular interest in HIV, we are interested in research related to all types of infectious diseases. CHIP has several infectious disease specialists and has trained many younger physicians on their way to becoming infectious disease specialists. One area of long-standing interest is bacterial meningitis, where persons affiliated with CHIP have co-authored publications in the last decade (see p. 32). However, management of infectious diseases at the intensive care units is another long-standing area of interest. We are privileged to now coordinate a randomised trial assessing a plasma marker supposedly specifically indicating ongoing bacterial infections in patients admitted to the intensive care unit – the marker “procalcitonin”. The research question is whether daily measurement of procalcitonin will lead to optimisation of diagnostic workup and more rational use of antibiotic therapy resulting in improved chance of surviving. Currently, 20-30% of patients admitted to intensive care units die. The study – called PASS (p. 20) – is currently

⁴ AN Phillips, BG Gazzard, N Clumeck, MH Losso, JD Lundgren When should antiretroviral therapy for HIV be started? Editorial. *BMJ* 2007;334:76-78

⁵ Writing committee: N Friis-Møller, P Reiss, CA Sabin, R Weber, A D’Arminio Monforte, W El-Sadr, R Thiebaut, S de Wit, O Kirk, E Fontas, MG Law, A Phillips, JD Lundgren on behalf of the D:A:D Study Group. Class of Antiretroviral Drugs and the Risk of Myocardial Infarction. *N Engl J Med.* 2007 April 26;356:1723-35

⁶ A Mocroft, AN Phillips, J Gatell, B Ledergerber, M Fisher, N Clumeck, M Losso, A Lazzarin, JD Lundgren for the EuroSIDA Study Group. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. *Lancet.* 2007 July 19 online. *Lancet.* 2007 Aug 4;370(9585):407-13



The Panum Institute

recruiting. An additional bonus from implementing PASS is that 7 intensive care units across Denmark have agreed to team up in a unique and unprecedented collaboration that will be able to continue to formulate and perform research also when PASS has been completed.

Research requires skilled researchers able to form independent thoughts. However, modern research efforts require teamwork, not only when formulating research questions but also when conducting research. CHIP has been fortunate to be able to attract some brilliant minds who unselfishly have ensured that our research programme has successfully moved forward. At CHIP we are 37 full-time employees and this number has been stable in the last couple of years. We are also fortunate to participate in multiple international collaborations, enabling us to work with equally minded people from all parts of the world (p. 6). It is not possible to fully quantify the number of colleagues linked up in these various international collaborative networks, but it is in the thousands.

A well-functioning research group also requires support from peers. Mentoring is important, irrespective of seniority. Mentoring comes from interacting with colleagues you do research with, and this is very true for the research CHIP is involved in. However, there is also a need for a more external perspective. CHIP has profited from good advice of-

fered by many, including professors *Hans Bisgaard, Nils Brünner, Henry Masur, Brian Gazzard, and Ian Weller.*

By November 2007, CHIP will move to new locations at the Faculty for Health Sciences, University of Copenhagen – the Panum Institute. We will miss Hvidovre Hospital that has hosted some of us from more than two decades, but the move is the right thing for CHIP. We look forward to becoming more integrated in functions taking place in the institution which hosts us, and look forward to working with colleagues at the Institute of International Health, Immunology and Microbiology, The Copenhagen School for Global Health being one area. Additionally, we will extend collaboration to and work with the section on viral diseases and the department of clinical microbiology and the department of infectious diseases at the State Hospital – Rigshospitalet – located in close proximity to the Panum Institute.

What will the future bring? Well, the ongoing projects will keep us busy for some time to come. However, as an additional component, we will focus on translation of research results on optimal care of patients infected with HIV to the resource-limited settings of the world, where most HIV-infected persons live. In this respect, we look forward to strengthening our collaboration with the World Health Organisation.

INTERNATIONAL COLLABORATION

CHIP was formed in order to engage in international collaborations. HIV is an international crisis and requires international collaboration. There are simply too many patients affected to merely focus on what can be done within a small country like Denmark.

What are the incentives to engage in international research collaborations for an academic research group like CHIP? Firstly, the collaboration will by necessity identify other investigators in other countries who are equally interested to engage. This is a special “breed” of colleagues who in most part are energetic, dynamic and usually are among the best qualified in the countries where they work. The collaboration has to consist of such people, as it is this dynamic interchange that drives the research process. Secondly, the topic for research has to be state-of-the-art and complex in nature – why else bother? Once these two criteria are fulfilled (and maintained), this opens up the possibility of attracting funds for the research.

Attracting research funds to international collaborations is not an easy task. Agreement on a budget and how to distribute it among the partners requires trust and open discussions within the consortium. However, the hardest thing is to identify a financial sponsor. The sponsor has to be philanthropic – and the only thing the collaboration can guarantee is that it will cost money. Seldom – and particularly so in international collaboration - is there a chance that an invention will be made as a consequence of the research being conducted which can be patented and subsequently generate funds. Rather, the research is usually benefiting “the common good of mankind”. Probably needless to say, but the competitions for such funds is fierce.

CHIP has survived since its inception on attracting funds to create and continue international collaborations.

EuroSIDA (p.14) has been funded by the European Commission since 1990, and on 1st March 2006 secured funding under Framework Programme 6 until February 2010.

D:A:D (p. 11) has been supported by the oversight committee for metabolic complications – an international syndicate of pharmaceutical companies, regulatory authorities, patient advocacy groups and academia – since 1999. Funding is currently secured until end of 2009, but we hope to be able to continue the study at least for an additional 3 years.

“International Network for Strategic Initiatives in Global HIV Trials” (INSIGHT) was funded on 1st July 2006 by the National Institutes of Allergy and Infectious Diseases, National Institutes of Health for a five-year period. INSIGHT is responsible for conducting the SMART (p. 17), ESPRIT (p. 24), STALWART (p. 25) and START (p. 4) studies. CHIP serves as one of four international coordinating centres.

New collaborations have been formed in the last couple of years:

“The Network of European AIDS Treatment” (NEAT) was funded by the European Commission in October 2006 for a 4-year period. A total of 37 partners constitute NEAT of which CHIP is one. CHIP serves as convener on the task of “ARV [Antiretroviral] toxicity, complications of HIV infections” within the research work package and co-chairs the work package on EU networking.

“The Collaboration of Observational HIV Epidemiological Research Europe” (COHERE) was formed in 2005 and served to unite HIV observational research groups across Europe in collaborative efforts requiring merger of data from multiple observational research groups. In total, more than 200,000 HIV-infected persons are followed in the 33 cohorts that have joined in COHERE, mostly adult patients but with a large constituency of HIV-infected children and pregnant women. COHERE has so far received funds from “Agence Nationale de Recherches sur le SIDA” (ANRS), the Dutch HIV Monitoring Foundation, and The Augustinus Foundation, Denmark and will be part of the bid by EuroCORD (see below) to the European Commission Framework Programme 7 application in 2009. CHIP together with the University of Bordeaux serves as the core coordinating structure of COHERE.

EuroCORD was formed in 2005 and is an administrative umbrella organisation among research programmes funded by the European Commission. A total of four concerted actions (CA) were funded via Framework Programme 6 from 1st March 2006 for 4 years (CASCADE, EuroHIVResistance, EuroSIDA & PENTA). COHERE was included as a fifth member. As per agreement with the European Commission, EuroCORD will respond to calls for proposals to be released in 2009 allowing for the possibility of continuing HIV Observational Research from 2010 under the Framework Programme 7 once Framework Programme 6 funds run out by February 2010. Additionally, EuroCORD will serve as secretariat for the International Workshop for HIV Observational Research from 2009 onwards.

“capACity building and Training in HIV/Aids Treatment and management across Europe” (ACTIVATE) will create and pilot training curricula on HIV/AIDS treatment and management within the four CA that constitute the core of EuroCORD. ACTIVATE was funded by the Directorate Generale SANCO within the European commission for 3 years.

In addition to these internal research collaborations, CHIP has engaged in collaboration with the **World Health Organisation (WHO)** on various levels since 2004. CHIP has served as a moderator and collaborated with the WHO Pharmacovigilance group at the Geneva Head Quarters, and the WHO Monitoring Centre in Uppsala (headed by Prof. Ralph Edwards) on organising WHO’s “Training course for the Introduction of Pharmacovigilance into HIV/AIDS Programmes” (September 2004 in Pretoria, South Africa and September 2006 in Barbados). CHIP continues to serve a consulting role on HIV drug-safety with the WHO Monitoring Centre in Uppsala. Per request from the WHO prequalification programme, CHIP served as coordinator for the development of template text on drug efficacy and safety for use as product inserts by companies producing generic HIV drugs. CHIP has also served as consultant to the HIV department at the Geneva HQ on modelling outcome of HIV and recommendations on 2nd line antiretroviral therapy in resource limiting settings. Additionally, CHIP has interacted with the HIV department at WHO-Europe on discussions on aspects of management of persons in the eastern region of Europe. There are ongoing discussions on whether to further these collaborations by making CHIP a WHO Collaborative Centre – negotiations that may take some time to complete.

HIV in Europe 2007: Working together for optimal testing and earlier care

University of Copenhagen (represented by CHIP) and AIDS action Europe with technical assistance from WHO Europe have come together to organise a pan-European conference entitled “HIV in Europe 2007: Working together for optimal testing and earlier care” in anticipation of World AIDS Day 2007.

For the first time, key pan-European HIV stakeholders including advocates, clinicians and public health professionals as well as policy-makers are convening to debate and take action in addressing critical issues around HIV testing and care in a European setting.

In an unprecedented collaboration, HIV stakeholders will agree to a common understanding on the role of HIV testing and counselling in optimising diagnosis and the need for earlier care, and agree on concrete actions to move us forward in Europe. The ultimate aim is to improve patient outcomes, reduce HIV-related morbidity and mortality for those infected, and decrease HIV incidence across the region.

The conference is planned in Brussels for the 26th and 27th of November 2007.

MONITORING

CHIP has an extensive monitoring and quality assurance system in place that ensures that investigator driven studies collect high quality data and establish good research practices during the complete research process from data collection to publication of data.

With research sites in most European countries including Eastern Europe, CHIP provides qualified monitoring in accordance with “Good Clinical Practise” (GCP) guidelines in various geographical and cultural settings making the composition of the monitoring group essential.

CHIP clinical monitors are employed based on clinical experience, knowledge of HIV medicine and language skills, which means that the monitors for the most part master the local language in the countries where they are responsible for our monitoring activities. If the group does not have the language skills needed for a specific country, translators are consulted.

Furthermore, local monitors at national coordinating centres affiliated with CHIP are employed in countries with multiple research sites, including Germany and Spain.

Within the INSIGHT network CHIP serves as one out of four international coordinating centres (ICC). Besides the Copenhagen ICC, the coordinating centres are located in London, Washington and Sydney. The ICCs, the statistical data and management center (SDMC) in Minnesota and representatives of the study sponsors work closely together to ensure the best possible quality of monitoring and uniformity between the ICCs.

CHIP is responsible for the implementation and monitoring of large international randomised clinical phase II and III trials, e.g. the ESPRIT study (p. 24), the SILCAAT study (p. 25), the SMART study (p. 17) and the STALWART study (p. 25).

In addition, the cohort studies - EuroSIDA and DAD - are monitored annually for data quality and end-point validation.

The main activities in the monitoring group in 2006/2007, in addition to the ongoing monitoring of the ESPRIT and SILCAAT studies, have been the implementation of the STALWART study in our region and the closure of the SMART study.

The STALWART study, a phase II IL-2 study, involves investigators in Germany, Poland, Portugal and Spain, and many resources and efforts have been spent opening STALWART sites. A large component of this has been translating new European regulatory requirements, as described below, into standard of operating procedures (SOP), the implementation of a new pharmacovigilance reporting system and ensuring proper proficiency testing programmes at each of the laboratories at the participating sites.

The SMART study officially closed on 11 July 2007 for patient follow-up and therefore closing procedures, including data cleaning, are the main focus until 31 December 2007.

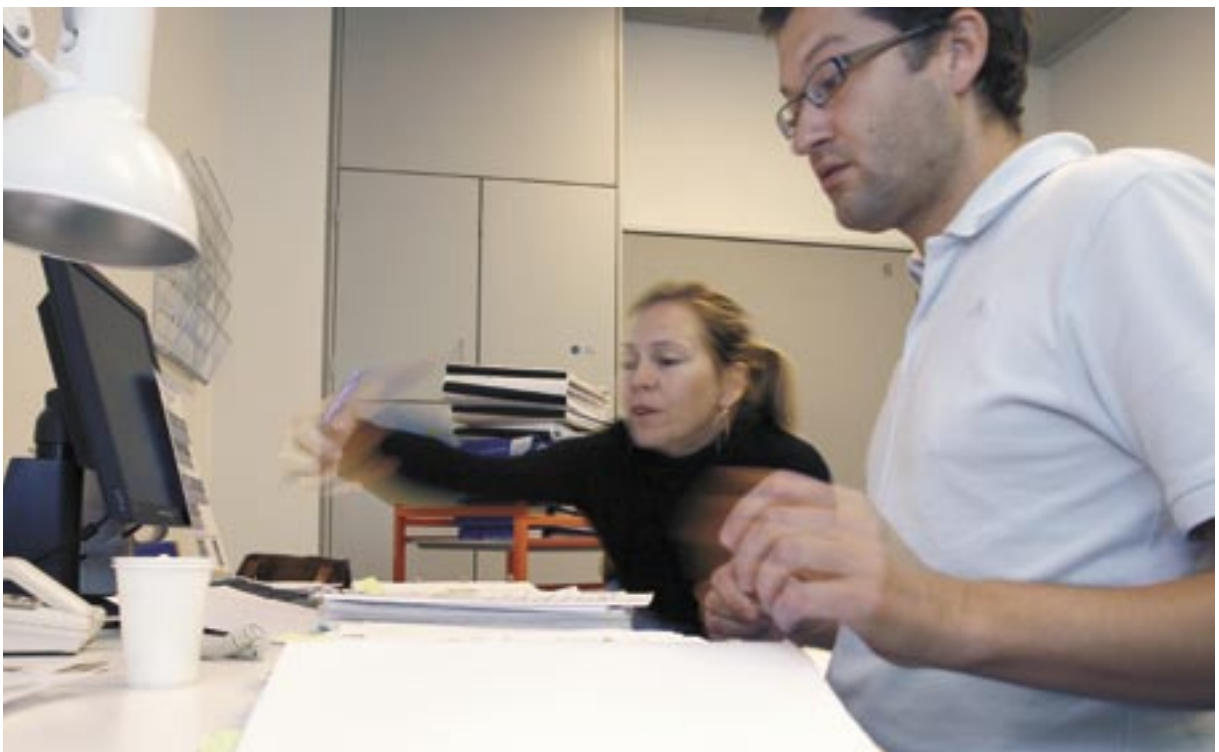
In addition to the HIV/AIDS studies, the monitoring group also monitors the PASS Study; a randomised, single-blinded, multicenter trial to investigate if clinical management guided by daily standardised

Procalcitonin measurements can reduce the mortality in critically ill patients (p.20). At the moment the group is preparing for the first interim analysis in the autumn of 2007.

The monitors are not only responsible for data monitoring, protocol training and protocol adherence. Also obtaining regulatory approvals are part of their area of expertise. Due to the implementation of EU Directive 2001/20/EC, it has become increasingly more challenging to obtain approval for a clinical study in Europe. Investigators need highly specialised study staff to be able to meet the regulatory requirements related to clinical studies. Numerous

study documents must be prepared for submission to the local authorities regulating the research, and CHIP provides the assistance and expertise to obtain the necessary approvals in close collaboration with study staff at the research sites.

Less experienced sites are supported by us in building up the infrastructure and expertise needed to comply with European and international study requirements. This way new sites can become involved in research within the clinical trial network or the observational studies addressing important research questions on how to optimise treatment for HIV and AIDS.



OBSERVATIONAL STUDIES

D:A:D

Scientific purpose

The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) is a prospective multi-cohort study of HIV-infected persons under active follow up. The main objective of the study is to assess the incidence of myocardial infarction and other cardiovascular disease endpoints in HIV-infected persons, and to investigate whether treatment with antiretroviral drugs is associated with development of cardiovascular disease as a late onset adverse effect.

Description

11 cohorts worldwide participate with a total current enrolment of more than 33,389 patients from 212 clinics in 21 countries in Europe, Argentina, USA and Australia. The original study population of 23,437 patients was enrolled from December 1999 to April 2001, and is referred to as D:A:D Cohort I; an additional 10,021 patients were enrolled in D:A:D Cohort II throughout the Spring of 2004. As of February 1st 2006, the patients in Cohort I have contributed more than 111,000 person-years (PY) of follow-up, and 26,139 PY were available from Cohort II.

On average patients are seen in the clinics every 3 months and specific data collection for D:A:D takes place at least every 8 months. Each cohort gathers and computerises its data; subsequently they are merged in a database in Copenhagen.

Organisation

The coordinating office at CHIP is staffed by the principal investigator, the study coordinators and

the central data-manager. It has the overall responsibility, including the coordination, collection and cleaning of data, review and query of events, and the preparation of draft research papers.

The coordinating office organises Steering Committee meetings with representation from each cohort, the lead statistician, EMEA, patient community and industry representatives. The SC approves all analytic proposals prior to their execution and has the overall responsibility for the scientific conduct of the study.

Results

In 2005-2006, the study presented numerous novel analyses. Key analyses from the study were presented at the 13th CROI, 2006 (figure 1⁷), exploring the association of cumulative exposure to protease inhibitors and non-nucleoside reverse-transcriptase inhibitors with the risk of myocardial infarction (MI). These analyses found increased exposure to protease inhibitors to be associated with an increased risk of myocardial infarction. No evidence of such an association for non-nucleoside reverse-transcriptase inhibitors was observed (however, the number of person-years of observation for exposure to this class of drug was less than that for exposure to protease inhibitors). The observed effect of protease inhibitors may be in part a consequence of the effects of these agents on serum lipid profiles. In our study, the relative rate of myocardial infarction was 1.16 per year of exposure to protease inhibitors, which corresponds to a doubling of the risk over a

⁷ Friis-Møller N, Reiss P, El-Sadr W et al. [abstract 144] Exposure to PIs and NNRTIs and risk of Myocardial Infarction (MI): Results from the D:A:D Study. 13th Conference on Retroviruses and Opportunistic Infections, Denver. 2006

5-year period of exposure. The magnitude of this association is similar to the increment in risk attributable to diabetes mellitus or cigarette smoking and is greater than that associated with a family history of cardiovascular disease. Whether this effect translates into an important additional absolute risk in a person depends on his or her pre-existing cardiovascular-disease risk profile.

A comparison of predicted versus observed rates of MI was published in *HIV Medicine*⁸. This study used the Anderson Framingham equation⁹ to predict the rate of MI, and compared these rates to the ones observed. These analyses showed that the observed rate of MI in the D:A:D study was of a similar magnitude to, or slightly higher than, that predicted by the Framingham risk equation, whereas the underestimation was greater for a European prediction model. Predicted and observed rates of MI - according to duration of cART (combination antiretroviral therapy) - increased in parallel, suggesting that cART-induced changes in conventional CVD (cardiovascular disease) risk factors in part explain the association.

Data on changes in CVD risk factors over calendar time were presented at the 12th CROI, 2005¹⁰. This study found that, overall, the CVD risk factor profile of patients in D:A:D had worsened over time, with an increase in the proportion of patients at high risk of CVD. However, after controlling for these changes, and for increased exposure to cART, the risk of MI had decreased over the years, possibly as a result of improved targeting of interventions to those at high risk (e.g. use of lipid-lowering drugs) or because of changes in the choice of cART.

A study exploring risk factors for hypertension was published in *Antiviral Therapy*¹¹. This project found that elevated blood pressure in HIV-infected persons was associated with conventional risk factors for hypertension. Antiretroviral drugs had no independent harmful effect on blood pressure changes or the development of hypertension.

The D:A:D study also presented novel findings on predictors of causes of death¹². A central finding was that deaths from causes generally thought to be non-AIDS-related were more likely to occur in persons with lower rather than higher CD4 counts. De-

⁸ Law MG, Friis-Møller N, El-Sadr WM et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med* 2006; 7(4):218-230.

⁹ Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991; 121(1 Pt 2):293-298

¹⁰ Sabin C, Morfeldt L, Friis-Møller N et al. [abstract #866] Changes over time in antiretroviral therapy (ART) use and risk factors for cardiovascular disease (CVD) in the D:A:D study. 12th Conference on Retroviruses and Opportunistic Infections, Boston . 25-2-2005.

¹¹ Thiebaut R, El-Sadr WM, Friis-Møller N et al. Predictors of hypertension and changes of blood pressure in HIV-infected patients. *Antivir Ther* 2005; 10(7):811-823

¹² Weber R, Friis-Møller N, Sabin C et al. [abstract K-188] HIV and Non-HIV-related deaths and their relationship to immunodeficiency; the D:A:D study. 12th Conference on Retroviruses and Opportunistic Infections, Boston . 24-2-2005.

¹³ Weber R, Sabin CA, Friis-Møller N et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med* 2006; 166(15):1632-1641.

¹⁴ de Wit S, Sabin C, Weber R et al. Relationship between use of stavudine and diabetes mellitus. 8th International Congress on Drug Therapy in HIV Infection, November 2006, Glasgow, Scotland . 2006.

¹⁵ Van der Valk M, Friis-Møller N, Sabin C et al. Effect of interventions to improve dyslipidaemia. 8th International Congress on Drug Therapy in HIV Infection, November 2006, Glasgow, Scotland . 2006

¹⁶ Worm S, Sabin C, El-Sadr W et al. The Metabolic Syndrome at baseline in the D:A:D Study. 8th International Congress on Drug Therapy in HIV Infection, November 2006, Glasgow, Scotland . 2006.

ath from liver disease (LRD) was the most frequent non-AIDS-related cause of death in the D:A:D Study. Further specific analyses of LRD were published in Archives of Internal Medicine in 2006¹³, which found that the risks for LRD included age, transmission group, HCV and HBV infection. Furthermore, a strong association between immunodeficiency (CD4 cell count) and increased risk of LRD was observed, which was independent of other factors including hepatitis (figure 2).

Other analyses from the study presented in 2006, include the assessment of predictors of diabetes¹⁴, the evaluation of effect of various interventions to improve ART induced dyslipidaemia¹⁵, and the evaluation of the presence and predictors of the metabolic syndrome in the D:A:D Study¹⁶.

The future

The study is projected to continue at least until 2008, and provide more than 180,000 person-years of data.

The D:A:D study continues to follow patients prospectively, focusing on monitoring the risk of cardiovascular disease, its association with more extended exposure to cART, and its relationship to the specific drug classes used. A central research area is to explore the underlying mechanisms for the risk of MI with combination antiretroviral therapy. Furthermore, the study has accrued substantial information on causes of death, and future analyses will further explore predictors of death from AIDS- and non-AIDS related causes. All cohorts taking part in the D:A:D collaboration have implemented the standardised coding from the CoDe Project (p. 28), which will assist the evaluation of causes of death.

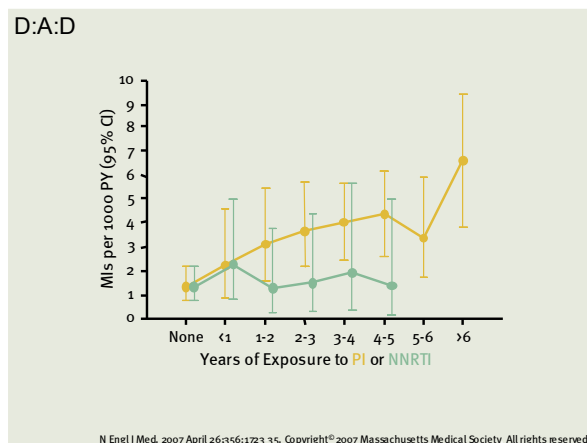


Figure 1

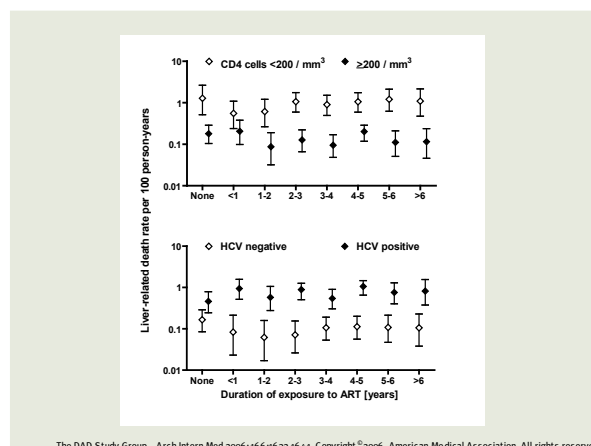


Figure 2. Rates of liver-related deaths per 100 person years by duration of combination antiretroviral therapy (cART), stratified by CD4 cell count (A) and hepatitis C virus (HCV) status (B).



Scientific purpose

The primary objective of the EuroSIDA study is to prospectively study demographic, clinical, therapeutic, virological and laboratory data from persons infected with HIV across Europe in order to determine the long-term virological, immunological and clinical outcome.

The EuroSIDA study group has now been working on this study for 13 years and has several notable accomplishments to date, including the publication of over 80 papers in peer-reviewed journals (including the New England Journal of Medicine and the Lancet among others). The focus of EuroSIDA has naturally changed over this period, which demonstrates an eagerness to be flexible, dynamic, and focus on contemporary issues.

Study Overview (status as of December 2006)	
Patients enrolled	14,200
Number of countries	31
Number of clinics	93
Total Person-years of follow-up	59,652
CD4 cell measurements	268,563
Viral load measurements	223,099
Plasma samples collected	44,464

The study is headed by a 12-member steering committee, elected by the EuroSIDA investigators. The coordination of the study is carried out at CHIP.

There have been over 20 articles published in peer-reviewed journals in the last two years and they covered topics such as treatment failure and discontinuation, evolution of resistance, ART interruption and disease progression, and the effects of ART on kidney function. In July, 2007 EuroSIDA had its fourth publication accepted in the Lancet related to normalisation of CD4 counts in patients with HIV and maximal virological suppression on cART.

The EuroSIDA study group continued in 2006 to participate in and further initiate international inter-cohort collaborations to address issues which cannot readily be answered within the EuroSIDA study itself. Such collaborations include the D:A:D Study, COHERE, the ART Cohort Collaboration, and the PLATO collaboration.

In 2006, these collaborations resulted in three publications in peer-reviewed journals. They included topics from the D:A:D Study such as liver related deaths in HIV patients (published in Arch Intern Med) and the use of the Framingham Equation to predict MI risk in HIV (published in HIV Medicine). Additionally, the ART Cohort Collaboration published a collaborative analysis of HIV treatment responses in The Lancet. These collaborations have been very fruitful and are likely to be even more important in the coming years.

Finally, EuroSIDA has presented 13 abstracts at major international HIV conferences in over the last two years covering a variety of topics dealing with the key issues mentioned below.



1996



2006



The EuroSIDA study has expanded considerably since 1996 and now includes 93 centres in over 30 countries. As the maps show, the greatest expansion has been in Eastern Europe.

The future

Late in 2006, EuroSIDA received notification that it had received European Union funding to continue the study activities. In addition to collection of data and plasma, other key issues to be analysed within the future include: Hepatitis B and C co-infection, Association between virological resistance and clinical outcome, The epidemic in the eastern part of Europe, and, Long-term and rare toxicity of antiretroviral therapy.

The foundation of the EuroSIDA study is the data provided by the 93 participating clinics. Over the last 10 years, many dedicated people have completed follow-up forms in a timely and accurate manner to allow the study to provide updated information on clinical practice in HIV clinics in Europe. The rate of loss-to-follow-up continues to be very low – less than 5% per year.

In addition to the high data quality, the active participation of many EuroSIDA investigators in specific scientific projects is another cornerstone of the study, making this multi-national cohort study a true team effort of European clinicians.

Plasma repository

The number of plasma samples in the EuroSIDA repository continues to grow and remains a cornerstone for virological analyses. To this extent, it is of extreme importance to have a large plasma repository to allow for selection of samples drawn within a narrow time interval from a given event of interest such as changes of antiretroviral therapy or virological failure. In 2006 we collected 4,300 samples, bringing the total number of samples in the repository to 44,464.

The collection of samples and the analyses thereof will be a very important part of the EuroSIDA study in the coming years – including HIV resistance, hepatitis B and C serology/virology and pharmacokinetic analyses.

The HIV sequencing of plasma samples for EuroSIDA projects carried out in 2006 was done by the virological laboratory in Badalona, Spain headed by *Bonaventura Clotet* and *Lidia Ruiz*.

As a supplement, data is also collected for resistance testing performed locally on patients participating in EuroSIDA. Data from these two data sources allows for analyses of the influence of resistance mutations on the patients' clinical prognosis.

The Hepatitis workpackage of EuroSIDA is carried out by the laboratories of Dr. *Vincent Soriano* in Madrid, Spain and Dr. *Bernd Kupfer* in Bonn, Germany. *Jürgen Rockstroh* is the Principal Investigator. *David Burger* is the PI of the Pharmacokinetics workpackage and is located in Nijmegen, The Netherlands.

Enrolment status

The EuroSIDA study has recruited sites over the last 8 years in Eastern Europe and has recently included new clinics in Belarus and Russia.

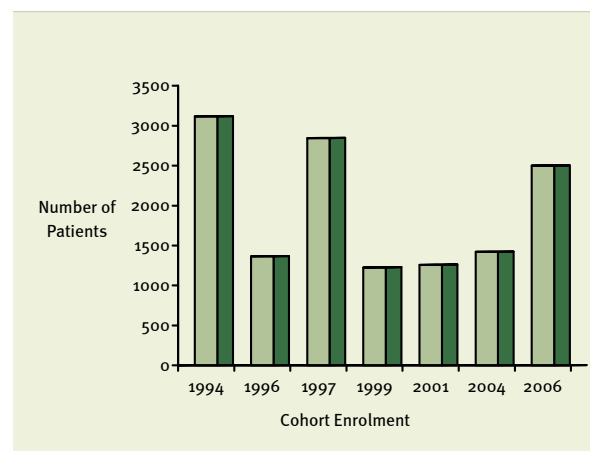


Figure 1. The study has enrolled seven cohorts of adult patients, with another 2,500 patients scheduled for enrolment in late 2007. The last cohort of 2,500 patients enrolled included 1,250 at existing and new clinics in Eastern Europe. As follow-up accumulates, this will allow for more detailed analyses of issues especially relevant for Eastern Europe.

RANDOMISED CLINICAL TRIALS

TREATMENT STRATEGY TRIALS



The “Strategies for Management of Antiretroviral Therapy” (SMART) study compared how well two strategies of using antiretroviral therapy (ART) could keep patients alive without experiencing serious diseases. The two strategies were:

- The “viral suppression” (VS) strategy complied with current treatment guidelines, and stipulated that ART was to be used at all times to maximally suppress HIV replication, irrespective of the cost of doing so, in terms of allowing the virus to become resistant to the medication.
- The “drug conservation” (DC) strategy, where ART was used intermittently to maintain the CD4+ lymphocyte cell count above thresholds where ART would be indicated in patients who had not yet commenced it – namely >200 cells/ μl . This strategy was believed to be potentially important, as ART is not eradicated and hence should be continued for life. At the same time, it was feared that the benefits of ART would gradually decline over time. Furthermore, colleagues in resource-limited settings – struggling with having sufficient amount of medication to all in need – were curious whether the same amount of therapy could be stretched. As it turned out, patients randomised to the DC strategy only had use of ART $1/3$ of the time, so three times as many patients could be treated, had the strategy been shown to be effective.

A total of 5,472 patients from 318 hospital clinics in 33 countries on all inhabited continents of the world were enrolled in the study. This makes the SMART study the largest global effort to ad-

dress a strategic question in relation to using ART. This global effort reflected that – at the time - the research question posed by SMART was important and relevant to a very large constituency of colleagues. That the study came to a definitive answer much sooner than anticipated, was a tribute to the network and the patients who participated, and will shape the discussion on how best to use ART for several decades to come.

An independent data safety and monitoring board (DSMB) followed the progress of the study. We were aware that at their last regular meeting in November 2005, additional analyses were requested, but the exact nature of what they were discussing was of course not disclosed. This is how such studies should be conducted – those who design and conduct the study must be unaware (“blinded”) of the intermediary results. However, when the study executive committee met to discuss other business at a memorable meeting in Sydney, Australia in January 2006, the “bomb exploded”. We were made aware that the data-safety-and-monitoring-board felt that we should become unblinded to the results. Unblinded is a major and non-reversible process – those who see the results can no longer be involved in the study. However, we fully agreed to follow the board’s recommendations and within 24 hours additional recruitment into the study was halted and a letter was disseminated to all clinics recommending all patients in the DC-group to be placed on ART. Multiple health- and patient-based web sites also informed on the content of the recommendations, and a rare medical alert was released on the Pubmed website. The findings were reported to the medical community at a medical conference in early February 2006.

The reasons for all this are depicted in table 1. Not only was there an increased risk of contracting opportunistic diseases in patients randomised to follow the DC strategy, but the risk of dying from non-AIDS related causes and contracting cardiovascular, kidney and liver disease also increased in this group of patients. The latter finding was the most surprising. We had hoped that these diseases would be seen less frequently in the DC group, and that this would balance out a possible slight excessive risk of opportunistic diseases from not using ART; ART was thought to only protect against AIDS. But clearly we – and the whole research community - were wrong. HIV is more harmful to the body than what was previously anticipated.

A major effort was launched in order to try to understand exactly why these surprising findings had emerged. It will take several years to complete, but some important observations have been made:

Contrary to some sceptic investigators' beliefs, the excess risk of opportunistic diseases in the DC arm was not only seen in patients with a history of severe immunodeficiency – as a matter of fact the harm was comparable irrespective of prior nadir CD4+ lymphocyte cell count.

Conversely, the highest degree of harm was observed in patients already on ART and having the maximal benefits hereof – i.e. those who had high CD4+ counts and no detectable HIV-RNA in their blood.

However, the harm seen in these patients if they were randomised to the DC strategy was not explained by “rapid droppers” – i.e. patients whose CD4+ lymphocyte cell counts dropped quickly over weeks or months. The harm continued also after several months and years after adhering to the DC strategy.

More detailed analyses suggested that current guidelines on when to start ART are probably too conservative. Allowing the CD4+ lymphocyte cell count to drop to 200 cells/ μ L does indeed increase the risk of opportunistic diseases. 350 cells/ μ L is a much safer threshold for starting ART. This confirmed results from an analysis from the EuroSIDA cohort conducted without knowledge of the SMART results¹⁷, table 1.

However, had the CD4+ lymphocyte cell count threshold for commencing ART in the DC group been elevated to 350 cells/ μ L, the harm would likely have persisted. HIV may impair immune function in other ways than those that can be determined by measuring the CD4+ lymphocyte cell count in peripheral blood.

What this impairment of immune function is, remains to be identified. However, in 2007 some important leads have been discovered. Preliminary analyses suggest that fibrinogenesis (a part of the clotting process) was activated in SMART patients interrupting ART by following the DC strategy. A

¹⁷ CD4+ Count-Guided Interruption of Antiretroviral Treatment. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. Writing Group: WM El-Sadr, JD Lundgren, JD Neaton, F Gordin, D Abrams, RC Arduino, A Babiker, W Burman, N Clumeck, CJ Cohen, D Cohn, D Cooper, S Emery, G Fätkenheuer, B Gazzard, B Grund, J Hoy, K Klingman, M Losso, N Markowitz, J Neuhaus, AN Phillips, and C Rappoport. *N Engl J Med* 2006; 355(22): 2283-2296

SMART Primary and Supportive Endpoint Results

	DC Group		VS Group		HR (DC/VS)	P-value
	N	Rate	N	Rate	[95% CI]	
OD or death (primary endpoint)	120	3.3	47	1.3	2.6 [1.9, 3.7]	<0.001
CVD, Renal, Liver	65	1.8	39	1.1	1.7 [1.1, 2.5]	0.009
- CVD	48	1.3	31	0.8	1.6 [1.0, 2.5]	0.05
- Renal	9	0.2	2	0.1	4.5 [1.0, 20.9]	0.05
- Liver	10	0.3	7	0.2	1.4 [0.6, 3.8]	0.46

Table 1

surrogate of fibrinogenesis – d-dimer levels – increases within the first month of stopping ART, and a case control study assessing d-dimer levels just before clinical events took place suggests that it continues to increase in those that subsequently become harmed from the DC strategy. Clearly, this is only the first peak in trying to understand the harm observed in the DC group in SMART, but it is so surprising (the 2nd big surprise in SMART), that it will be extremely interesting to continue this line

of research and more fully come to understand the inflammatory pathways that are activated. Think, for example if we were able to identify a subgroup of patients who are particularly harmed by the DC strategy. If this subgroup can be identified early, and the harm thus prevented, the remaining patients may perhaps safely use the DC strategy? More fundamentally, how viral diseases such as HIV interact with the immune system and why d-dimer levels are particularly affected by this virus is very intriguing.

THE PROCALCITONIN AND SURVIVAL STUDY: PASS

Scientific purpose

The Procalcitonin And Survival Study (PASS) is designed to investigate if daily Procalcitonin measurements and timely and appropriate response to abnormal Procalcitonin values can reduce mortality for critically ill patients.

Additionally, the study, will show if it is possible to reduce the frequency of sepsis complications, the quantity of antimicrobial chemotherapy used, and the length of the ICU (Intensive Care Unit) stay.

Description

Bacterial infection is a major cause of mortality in the ICU. The initial diagnosis of bacterial infection and the monitoring of the antimicrobial treatment effect is complicated in ICU patients, since: 1) symptoms, 2) clinical signs and 3) the traditionally most used biomarkers of infection are often affected from other causes than infection. Additionally, these parameters often give information regarding the infection status with a significant time delay. Delay of relevant antibiotics and antimicrobial surgery in bacterially infected ICU patients carries a high and increasing mortality rate.

Procalcitonin is a marker of bacterial infection which has been demonstrated to increase shortly after the release of bacterial products to the blood stream, and it has been shown that blood levels of procalcitonin start a relevant decrease within 24 hours

of when bacterial infection is controlled. We have shown that an increase in the procalcitonin level for just 24 hours in ICU patients is an independent predictor of mortality with a corresponding hazard ratio of 1.8 in patients with a 24 hour procalcitonin increase, compared to a decreasing procalcitonin level.

The hypothesis in the PASS-study is that by controlling procalcitonin increases by means of intensifying antimicrobial diagnostics and therapy, when procalcitonin levels increase, infection-related mortality can be reduced.

The PASS-Study is a randomised, single-blinded, multicentre interventional study with a 28-day mortality primary endpoint. The study has a calculated sample size of 1,000 critically ill patients and it refers to ICH-GCP rules and guidelines. All relevant authorities, including the regional ethics committee, have approved it. The study is registered at the US National Institutes of Health register-site (www.clinicaltrials.gov)

The PASS-Study is coordinated by Copenhagen HIV Programme, and Department of Clinical Microbiology 445, Copenhagen University Hospital, Hvidovre. Eight ICUs in Denmark participate and the database and biobank that will be formed by the PASS-study will be used for investigating multiple purposes regarding the treatment of critically ill patients.

Achievements in 2005-7

- A. Protocol approved by ethics committee, data-controlling authorities
- B. Establishment of Steering Committee and PASS-study-group
- C. Establishment of the Procalcitonin bio-analysis in the Department of Clinical Microbiology, Hvidovre Hospital and Department of Clinical Biochemistry, Århus University Hospital, Skejby, including 365 days/ year real-time analysis
- D. Establishment of 365 day/year transport of bio-material from recruiting sites to laboratories.
- E. Study initiation and recruitment at eight major intensive care units in Denmark
- F. 297 subjects included in the study (Sept. 2007)
- G. Oral presentations of the PASS-study at 3 international congresses and at numerous occasions in Denmark
- H. 2 publications in international peer-reviewed journals (1 letter + 1 review)

The future

Major aims for the PASS-Study the following year:

- A. Further consolidation of the study group
- B. Increase in inclusion rate at the sites that recruit less patients
- C. Maintenance of the high inclusion rate at the best performing sites
- D. Interim analyses performed at 500 and 750 patients included
- E. Total inclusion of the 1,000 patients before the end of 2008
- F. Conclusion of the primary study aim (following total inclusion)
- G. Start of publication and presentation of the main results in international forums
- H. Start of specific design of sub-studies on the database, the serum-bio-bank and the DNA-bank

ROYAL FREE HOSPITAL (RFH) STUDIES

CHIP has a long-standing working relation with the HIV clinic and the statistical department at the Royal Free Hospital (RFH), London. This collaboration continued through 2007 and includes 3 clinical trials, which are all in agreement with the overall purpose of CHIP: to perform clinically relevant HIV research. The role of CHIP in all three studies is primarily as contributor to the protocol development, protocol implementation and coordination of the trials.

BI SWITCH

Scientific purpose

All drugs can result in toxicities; however, these may vary widely even within the same class of drugs. The purpose of the BI Switch study has been to assess the effects of changing from one drug (efavirenz) in one drug class (non-nucleoside reverse transcriptase inhibitors) to another drug within the same drug class (nevirapine) in HIV-1 infected individuals receiving highly active antiretroviral therapy (HAART), having a viral load < 50 copies/ml, and experiencing CNS toxicity. The follow-up period was 24 weeks.

Description

BI Switch was a randomised, open-label, single UK centre pilot study.

Results and the future

The trial was completed in 2005. Overall 31 patients were enrolled. CHIP has finalised a study report, and study data were presented at the Eighth International Congress on Drug Therapy in HIV Infection, Glasgow, 2006 (abstract P59). Currently, a study manuscript is under preparation.

ALCAR

Scientific purpose

One important condition in HIV is the development of distal symmetric polyneuropathy (DSP), which may either be caused by the HIV infection itself, the treatment or a combination of the two. The purpose of ALCAR is to evaluate the safety and efficacy of acetyl L-carnitine (ALCAR) over 48 weeks in combination with antiretroviral therapy for the prevention of DSP and lipid abnormalities in treatment naïve HIV infected individuals.

Description

ALCAR is a randomised, double blinded; placebo controlled pilot study performed at sites in Austria and the UK.

Results and the future

The trial was completed in 2006 with a total enrolment of 43 patients. CHIP has finalised the study report and currently study data are under analysis and are intended for submission for presentation at an international conference in 2008.

NRTI SPARING

Scientific purpose

All drugs can result in toxicities but these vary between drugs and drug classes. Similarly the potency of drugs varies between drugs and drug classes. The current treatment guidelines recommend the use of 3 drugs from two drug classes as first-line treatment.

Description

The NRTI sparing study is an open-label pilot study, carried out at two UK sites. The study will assess the efficacy, safety, tolerability and pharmacokinetics over 48 weeks of a two-drug, two-class regimen (lopinavir/ritonavir plus nevirapine) not including drugs from the most commonly used (and recommended) drug class (nucleoside reverse transcriptase inhibitors) in adult HIV-1 infected individuals naïve to the study drugs and without any mutations in HIV-1 RNA to these drugs.

Results and the future

The recruitment to the study was completed in October 2006 with a total enrolment of 41 patients. The last follow-up visit is expected to be in December 2007.

Four protocol stipulated interim analyses have been performed. These analyses have all been evaluated by the study's Data Safety Monitoring Board (DSMB). The DSMB has concluded, "no changes to the study conduct as outlined in the protocol or premature stopping of the study is warranted based on safety or efficacy data presented in the interim report".



Royal Free Hospital



Scientific purpose

Potent antiretroviral drug combinations have consistently been shown to result in prolonged survival and less HIV-associated morbidity. The target of these drugs is the suppression of the HIV replication. An additional strategy for the management of HIV could be to stimulate the recovery of the immune function. Two long-term, large-scale studies are currently investigating an immunological response by selectively raising the CD4+ lymphocyte count rather than targeting the virus. The studies investigate this approach by assessing the effects of subcutaneous recombinant interleukin-2 (sc rIL-2) and no sc rIL-2 on HIV disease progression and death over a long-term follow-up period in patients who are taking combination antiretroviral therapy (cART).

The following two studies were designed to investigate the effects of sc rIL-2 in patients with a continuum of low CD4+ lymphocyte counts (the SILCAAT study) and medium to high CD4+ lymphocyte counts (the ESPRIT study).

A third study investigates the use of sc rIL-2 on patients who are either treatment naïve or have not received anti-HIV therapy within one year prior to randomization (the STALWART study).

Preliminary results suggest that IL-2 with cART has a significant advantage over cART alone, but the future use of IL-2 as part of a standard therapy can only be determined when in-depth analyses of the ongoing studies have been completed.

Description

The study is a phase III, randomised, open-label, multi-centre study involving 255 sites in 25 countries on 6 continents - and with 4,150 patients recruited, it is the largest randomised treatment study in HIV research to date. CHIP is one of four International Coordinating Centres (ICCs) and coordinates the study specifically in Austria, Belgium, Germany, Poland, Portugal, Spain, and the Scandinavian countries with 982 patients under management.

Achievements (2005-2007) and the future

Regular investigator meetings have taken place at international conferences, e.g. CROI, IAS, and EACS. One of the main topics was the new rIL-2 re-cycling proposal, an effort to have patients in the rIL-2 arm (who are currently not at their CD4+ goal and without medical contraindication towards rIL-2) continue using rIL-2 also towards the end of the study to maintain a difference in CD4+ count between the two study groups hence ensuring a successful conduct of the study. The main obstacle related with rIL-2 use seems to be toxicities. Various prophylaxis and symptom relief medications are being used to limit toxicities to the extent possible.

The most recent Data Safety and Monitoring Board (DSMB) meeting took place in November 2006. After reviewing safety and efficacy data from all sites the DSMB concluded that “no consideration of early stopping based on safety or efficacy is indicated.” The ESPRIT study will continue without change of conduct. The required number of events (320) is expected to occur by the end of 2008, at which time the study is expected to close.



Description

The study is a phase III, randomised, open-label, multi-centre study involving 1,971 patients from 129 sites in 11 countries on 5 continents. Like in ESPRIT the role of CHIP in SILCAAT is to be one of four ICCs coordinating the sites in Belgium, Germany and Spain with overall 418 patients randomised.

Achievements (2005-2007) and the future

In the transition from a company-based study (by Chiron, now Novartis) to a study conducted by INSIGHT (p. 6) in 2003, participating sites have been registered to the new version of the protocol that has a data collection and end point reporting very similar to that of ESPRIT data collection and endpoint reporting are very similar to that of ESPRIT, and most patients participating in the study have re-consented to the new protocol version.

Regular investigator meetings have taken place throughout the year at international conferences, and a joint rIL-2 re-cycling proposal, as described under the ESPRIT study, has been undertaken.

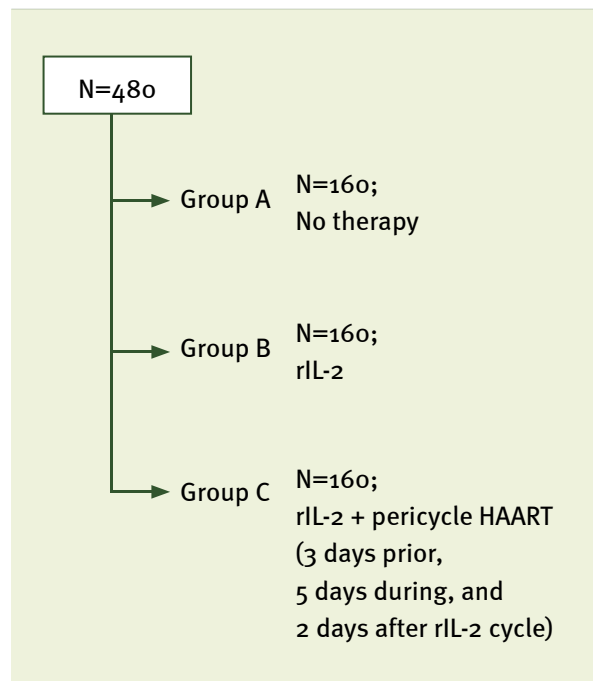
SILCAAT was evaluated at the most recent DSMB meeting in November 2006. The conclusions were the same as for ESPRIT that “no consideration of early stopping based on safety or efficacy is indicated”. SILCAAT continues without change of conduct. The overall required number of events (300) is expected to occur within the next 1-2 years, at which time the study is expected to close.



Description

The study is a phase II, randomised, open-label, multi-centre study. The purpose of STALWART is to compare the effects of sc rIL-2 administered with and without concomitant pericycle highly active antiretroviral therapy (HAART) to no therapy in patients with HIV-1 infection and CD4+ T lymphocyte count ≥ 300 cells/mm³. Pericycle HAART is given only for a few days before, during and after each 5-days IL-2 cycle.

Study randomisation (1:1:1) within strata defined by clinical site:



The hypothesis being tested is that intervention at an early stage of HIV infection with intermittent sc rIL-2 therapy either alone or with pericycle HAART can maintain or increase CD4+ T cell counts as compared to controls that receive neither antiretroviral therapy nor rIL-2.

Like in ESPRIT and SILCAAT, the Copenhagen ICC is responsible for coordinating sites in Germany, Poland, Portugal and Spain.

Achievements in 2005-2007 and the future

STALWART opened in September 2005 and enrolled the first participant in December 2005. Overall, about 480 people will be enrolled around the world of which 122 are expected to come from the Copenhagen region. Participants will be followed until a common closing date, which will be 12 months after the last patient, is randomised. As per August 2007, 35 out of 56 sites have been opened for patient enrolment and 153 participants have been randomised.

A Data and Safety Monitoring Board (DSMB) meeting took place in November 2006. After carefully reviewing comparative safety and efficacy data from all participating sites, the DSMB concluded that there are no concerns arising from either efficacy or safety data warranting a change in the conduct of STALWART at the present time. The next data review will take place end of 2007.

Results

If rIL-2 is shown to be clinically effective in either or both of the two ongoing phase III studies ESPRIT and SILCAAT, rIL-2 could serve an important role as part of standard therapy. The results of STALWART as a phase II study evaluating the safety and immunologic and virologic effects of rIL-2 in asymptomatic, treatment naïve HIV-infected patients will nicely complement these two trials and our knowledge on how best to use rIL-2 in HIV-infected patients and its potential as an antiretroviral-sparing agent.



PROJECTS

THE CoDe ("CODING OF DEATH IN HIV") PROJECT

Background

The CoDe project was initiated in 2004 based on the realisation that there was a need to harmonise and standardise the approach taken when collecting data and reviewing the causes of death in HIV-1 infected patients. This has become increasingly necessary as a significant proportion of deaths in HIV-1 infected people are now caused by non-AIDS events, many AIDS defining illnesses are poorly identified in the ICD system, and some diseases (e.g. CNS diseases) have a different aetiology in HIV patients and are therefore not covered by the ICD system, or at great risk of mis-classification.

Scientific purpose

The purposes of the CoDe project are:

- 1) The development of an algorithm to classify deaths of HIV-infected persons.
- 2) Creating a surveillance system for emerging trends in the causes of deaths based on this consensus algorithm.

Methods

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

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

The purpose of the data collection is to provide sufficient data for the reviewers' classification of the cause of death. The review of causes of death in the CoDe project should be based on a synthesis of the information provided in the CoDe Case Reporting Form. The review should result in a specific coding

of the cause(s) of death (underlying, contributing and/or immediate) as well as coding of relatedness to immunodeficiency. For each of these, the reviewer should also indicate the degree of certainty by which the code is made, as the intention is to reduce the classification category of "unknown", but at the same time allow for sensitivity analyses depending on degree of certainty. Each case is reviewed by at least two reviewers (figure 1).

Pilot

The methodology and pilot of CoDe were presented at the 10th European AIDS Conference in Dublin, November 2005. In the CoDe pilot of 60 cases, an eventual 100% agreement on the underlying cause of death and 90% on immunodeficiency relatedness was achieved between reviewers. Uniform data collection forms were successfully utilised to obtain detailed information on the deaths from the site clinicians. Providing specific guidelines enabled the reviewers to arrive at consensus regarding underlying cause of death and whether it was related to immunosuppression.

Implementation

As of December 2006, a total of 1069 Case Reporting Forms had been received and entered into the central CoDe database, and two independent reviewers had coded 131 of these.

Setup

The CoDe working group include the persons who have been actively involved in developing the project (www.cphiv.dk, click "CoDe" menu). The working group is the executive body of the CoDe project.

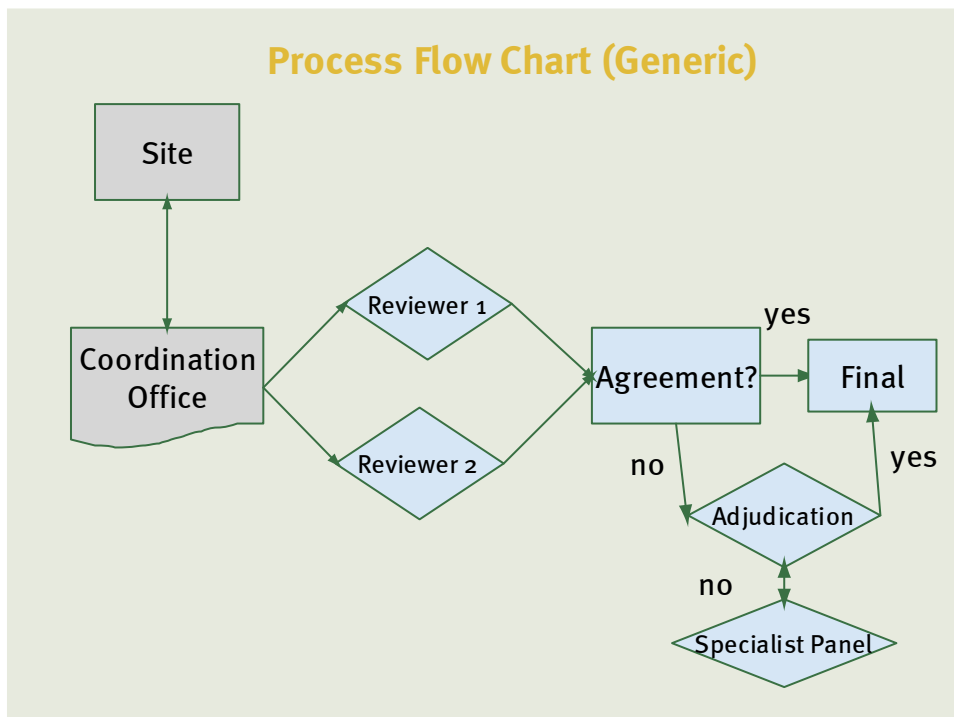


Figure 1

CHIP's role

The coordinating office is located at CHIP. The coordinating office:

- Contributes to the continued development of the CoDe methods
- Develops and maintains the database specifications
- Organises tele-conferences and meetings for the CoDe working group
- Makes the CoDe study documents publicly available

Evaluation and feed-back

CoDe is publicly available free of charge. Following the experience and evaluation of the CoDe pilot, this method has been implemented widely in HIV cohorts, and will be the subject of continuous evaluation.

If studies wish assistance in setting up the infrastructure for CoDe, or to adapt the database specifications, please contact the CoDe coordinating office (code@cphiv.dk).

COHERE (COLLABORATION OF OBSERVATIONAL HIV EPIDEMIOLOGICAL RESEARCH EUROPE)

COHERE (Collaboration of Observational HIV Epidemiological Research Europe) is a cohort collaboration structure that was created in 2005. The mission of COHERE is to conduct epidemiological research on the prognosis and outcome of HIV-infected people from across Europe including pregnant women, children, and adults.

The research will focus on scientific questions requiring a large sample size of patients, which the contributing cohorts cannot answer individually and which do not overlap with existing collaborations between participating COHERE cohorts. COHERE currently receives funding from ANRS (Agence nationale de recherches sur le sida et les hépatites virales), France; HIV Monitoring Foundation, The Netherlands; The Augustinus Foundation, Denmark and the Swiss Bridge Award 2006, Switzerland. A process is ongoing to secure future funding from ANRC, The European Commission and MRC (Medical Research Council) for both the core functions in COHERE but also for specific projects.

The pilot project in COHERE was headed by *Caroline Sabin* and aimed to investigate the response to combination Antiretroviral Therapy (cART) for variation across ages. The data merger was performed by the two coordination centres in COHERE in close collaboration with the data managers in each of the participating cohorts. The regional coordination center (RCC) in Bordeaux covering all Western cohorts (n=13), defined as England, France, Spain and a cross-European cohort (CASCADE) and the Eastern cohorts RCC, coordinated by CHIP, covering

any cohorts in the remaining countries.

The inclusion criteria defined that the patients should have been treatment naïve until starting highly active antiviral therapy (HAART) defined as 3 drugs combined in the treatment regimen and the this treatment should be initiated after the 1st of January 1998. The merger was done on data from 30 cohorts, included data on 69,456 patients which had 420,784 treatment periods recorded, 1,389,442 CD4 cell counts made and for which 893,280 HIV-RNA measurements had been performed. After final assessment of completeness and quality of the data on 49,921 individuals (29% female, 39% of non-European origin) were included into the analysis. Patients age ranged from 0-87 yrs, with 223 (0.5%), 184 (0.4%), 219 (0.4%) and 201 (0.4%) in the four youngest age groups of 0-1, 2-5, 6-12, 13-17, respectively and 2693 (5.4%), 1656 (3.3%) and 1613 (3.2%) in the three oldest age groups 50-54, 55-59, >60, respectively.

A quite unique data set for which the results from the analysis was presented on a poster at 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, February 2007.

Currently a group headed by *Matthias Egger* is in the process of investigating HIV-related lymphomas in the era of Highly Active Antiretroviral Therapy and *Andrew Philips* is heading a group, which will investigate incidence, prevalence and outcome of extensive virological failure in patients with HIV (PLATO II).

HIV/TB PROJECT

Tuberculosis (TB) is the most frequent coinfection among HIV-infected patients worldwide. Use of combination antiretroviral therapy (cART) may significantly influence the clinical presentation, management and prognosis for HIV-infected patients coinfecting with *Mycobacterium tuberculosis*, as well as the incidence of this disease. Furthermore, there may be major regional diversities across Europe in these clinical issues related to TB. Clinicians still face several unresolved issues related to the optimal management of TB in the HIV-infected patient. These include the clinical approach to interactions between HIV and TB therapies, the overlapping toxicity between these treatments, and the role of prophylaxis against TB. The best time to initiate cART and TB therapy in relation to each other, particularly in patients with advanced HIV infection, remains a clinical dilemma because of the concern regarding potential immune reconstitution inflammatory syndrome (IRIS).

Therefore, a multi-cohort collaboration has been established entitled “Co-infection with *Mycobacterium tuberculosis* among HIV-infected patients in Europe” (HIV/TB project). This is a prospective multi-cohort study. The overall goal of this project is to establish a cohort of HIV- and TB-coinfecting patients and based on this to describe and analyse possible regional diversity in the clinical management and outcome of HIV/TB patients across Europe.

HIV/TB project is unique in being a large multi-national collaboration including clinical sites in most of Europe with a substantial contribution from Eastern Europe and also sites in Argentina.

Collaborators across Europe have been identified, a study protocol and study materials (including Case Report Form (CRF)) have been developed and the project was initiated during the summer of 2006.

Project Status

As of September 2007, more than 900 patients have been identified (table) and data on patient characteristics as well as data on treatment and outcome thereof have been collected and are currently being keyed in Copenhagen. Data collection and data validation will continue in the coming months, and site visits have been performed to ensure correct completion of the forms.

Region	Enrolled Patients with HIV and TB
Eastern Europe	629
Western Europe	182
Argentina	149
Total	960

It has been very reassuring to see investigators from across Europe and Argentina contribute to this study, and to see that this probably most vulnerable and time-consuming part of the project has been successful.

The number of patients identified exceeds the 700 patients stipulated in the study protocol, and the substantial contribution from Eastern Europe provides a strong basis for the analysis.

Future of the project

The first results from the study will be presented in the beginning of 2008.

EXPERIMENTAL AND CLINICAL RESEARCH IN PNEUMOCOCCAL MENINGITIS

Background

The decision to initiate meningitis research - both clinical and experimental - was made in 1995. A collaboration between Statens Serum Institut (SSI), The Department of Infectious Diseases, University Hospital Hvidovre, and CHIP was the driving force, encouraged by results obtained in the late 1980's and 1990's suggesting that the host response to invasive microbial pathogens was in itself contributing to the decimal outcome of severe infections despite relevant and efficient antimicrobial chemotherapy.

Experimental research

The experimental research was initially conducted in a rabbit model of bacterial meningitis and later on extended to the rat model of bacterial meningi-

tis. These complementary models primarily differ with respect to research aim where rabbits are used to delineate the kinetics of the infectious and inflammatory process in short term studies (up till 24 hours after infection), and rats are used in more extensive studies of clinical disease, disease outcome and injury to the brain, middle- and inner ear.

Clinical research

The clinical research is based on the national reporting of Invasive pneumococcal infections to SSI and samples of CSF from patients suspected of having CNS infections admitted to the Department of Infectious Diseases at Hvidovre Hospital.

Clinical studies have intentionally succeeded the experimental work in order to try out experimental findings.

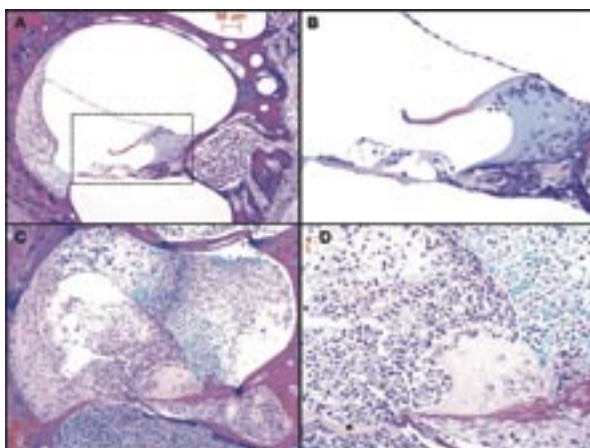


Figure 1. Sections through the inner ear of a rat (the cochlea). A) is from a normal uninfected rat and the organ of Corti (the primary site for perception of sound with hair cells) is shown enlarged in B). C) and D) is from a rat with meningitis where the channels around the organ of corti are completely obstructed with leukocytes (Dark purple cells) and pneumococci (bright blue strings interposed between leukocytes). Furthermore the Organ of Corti appears bright and necrotic without any remaining hair cells and thus capacity to perceive sound. (PAS-Alcian blue staining, Brandt et al. 2006).

Results

Our scientific results have provided significant insight into the mechanisms of disease leading to immune activation, neuronal injury and death:

- 1) CSF leukocyte influx is significantly influenced by the local intracranial production of IL-8, degree of septicaemia and the pneumococcal serotype^{18, 19, 20, 21}.
- 2) Limiting systemic leukocyte activation results in attenuated leukocyte accumulation in the CSF. Intracranial cytokine production is decreased at the expense of increased septicaemia and mortality^{22, 23, 24}.
- 3) Increasing the peripheral cellular immune response also reduces CSF leukocyte accumulation. Decreased bacteraemia and therefore decreased re-entry of bacteria from the bloodstream to the CSF suggests improved infection control leading to controlled leukocyte accumulation^{25, 26}. Increasing the antibacterial leukocyte capacity improves overall di-

sease outcome, at the expense of increased damage to areas with direct leukocyte-neuronal interaction as the inner ear (cochlea)²⁷.

- 4) Septicaemia - suggested in most cases to be the origin of meningitis - determines to a great extent the course of the local infection as well as its outcome.

Limiting bacteraemia therefore leads to improved survival and outcome²⁸.

- 5) The duality of meningitis with respect to the cause of poor outcome and sequelae - systemic versus local - and host versus bug has recently been further elucidated.

Brain injury appears to result from the local meningeal infectious process whereas septicaemia determines the severity of clinical disease. Septicaemia contributes significantly to the breakdown of the blood-brain-barrier and development of hydrocephalus²⁹.

¹⁸ Ostergaard C, Yieng-Kow RV, Larsen CG, Mukaida N, Matsushima K, Benfield T et al. Treatment with a monoclonal antibody to IL-8 attenuates the pleocytosis in experimental pneumococcal meningitis in rabbits when given intravenously, but not intracisternally. *Clin Exp Immunol* 2000; 122(2):207-211.

¹⁹ Ostergaard C, Brandt C, Konradsen HB, Samuelsson S. Differences in survival, brain damage, and cerebrospinal fluid cytokine kinetics due to meningitis caused by 3 different *Streptococcus pneumoniae* serotypes: evaluation in humans and in 2 experimental models. *J Infect Dis* 2004; 190(7):1212-1220.

²⁰ Ostergaard C, O'reilly T, Brandt C, Frimodt-Moller N, Lundgren JD. The Influence of the blood bacterial load on the meningeal inflammatory response in *Streptococcus pneumoniae* meningitis. *BMC Infect Dis* 2006; 6(1):78.

²¹ Ostergaard C, Benfield TL, Sellebjerg F, Kronborg G, Lohse N, Lundgren JD. Interleukin-8 in cerebrospinal fluid from patients with septic and aseptic meningitis. *Eur J Clin Microbiol Infect Dis* 1996; 15(2):166-169.

²² Ostergaard C, Yieng-Kow RV, Benfield T, Frimodt-Moller N, Espersen F, Lundgren JD. Inhibition of leukocyte entry into the brain by the selectin blocker fucoidin decreases interleukin-1 (IL-1) levels but increases IL-8 levels in cerebrospinal fluid during experimental pneumococcal meningitis in rabbits. *Infect Immun* 2000; 68(6):3153-3157.

²³ Brandt CT, Lundgren JD, Frimodt-Moller N et al. Blocking of leukocyte accumulation in the cerebrospinal fluid augments bacteremia and increases lethality in experimental pneumococcal meningitis. *J Neuroimmunol* 2005; 166(1-2):126-131.

²⁴ Ostergaard C, Johansen JS, Benfield T, Price PA, Lundgren JD. YKL-40 is elevated in cerebrospinal fluid from patients with purulent meningitis. *Clin Diagn Lab Immunol* 2002; 9(3):598-604.

The future

Recent incorporation of in-vivo imaging techniques (MRI) into our experimental research has provided the opportunity to perform studies where multiple parameters all closely related to the pathophysiology of meningitis (brain oedema, break down of the vascular blood-brain-barrier, focal brain injury, degree of inflammation and hydrocephalus) can be obtained in conjunction with standard clinical,

biochemical and microbiological data. These data collected from the same subject on several occasions allow for interpretation of physiological interrelationships and a reduction in the number of subjects needed.

Future research will incorporate this multidisciplinary approach in the study of viral CNS infections – studies of pathophysiology, disease sequelae and treatment.

²⁵ Ostergaard C, Benfield T, Gesser B et al. Pretreatment with granulocyte colony-stimulating factor attenuates the inflammatory response but not the bacterial load in cerebrospinal fluid during experimental pneumococcal meningitis in rabbits. *Infect Immun* 1999; 67(7):3430-3436.

²⁶ Brandt CT, Lundgren JD, Lund SP et al. Attenuation of the bacterial load in blood by pretreatment with granulocyte-colony-stimulating factor protects rats from fatal outcome and brain damage during *Streptococcus pneumoniae* meningitis. *Infect Immun* 2004; 72(8):4647-4653.

²⁷ Brandt CT, Caye-Thomasen P, Lund SP et al. Hearing loss and cochlear damage in experimental pneumococcal meningitis, with special reference to the role of neutrophil granulocytes. *Neurobiol Dis* 2006; 23(2):300-311.

²⁸ Brandt CT, Frimodt-Moller N, Lundgren JD et al. Evaluation of anti-pneumococcal capsular antibodies as adjunctive therapy in experimental pneumococcal meningitis. *J Antimicrob Chemother* 2006; 58(6):1291-1294

²⁹ Brandt CT, Holm D., Liptrot M et al. Impact of bacteremia on the pathogenesis of experimental pneumococcal meningitis. *J Infect Dis*. In press.



ORGANISATION

ORGANISATION

CHIP has a solid organisation shaped to support its activities. Besides being a strong scientific group, CHIP has a relatively large, but dynamic operational and administrative staff to secure the efficient implementation and coordination of sites, regulatory work, data capture and data entry, as well as monitoring and quality assurance.

The scientific data analysis and interpretation of findings are the important and valuable outcomes of CHIPs activities, corresponding to the tip of the iceberg. The below labour-intensive operational activities, like the biannual follow-up of more than 14,000 patients in EuroSIDA distributed between 93 sites in 33 countries, the merger of data comprising more than 150,000 patient years of follow-up in D:A:D, and the coordination of activities in more than a handful of large randomised controlled trials form the rest of the iceberg.

The structure of CHIP has been consolidated in the recent times. The coordinators from the operational functions of CHIP have been delegated the responsibility for operational and administrative personnel in their functions and have formed a management coordination group. The scientific staff is represented in the management group by *Ole Kirk*. This structure secures the necessary coordination and high level of information. The single functions have their group meetings to disseminate information, discuss and share experiences and bring up new ideas.

Location

CHIP is primarily located at the Panum Institute, Building 21.1 with laboratory facility just above in 21.2 and freezer-bay located nearby, all at the Faculty of Health Sciences at University of Copenhagen, Denmark.

In addition, personnel are funded in collaborating groups:

- Statisticians working from Royal Free & University College Medical School, Department of Primary Care & Population Sciences, London, (UK)
- Monitors working from the Clinical Trials Unit (UASP), Hospital Clínic Barcelona, Spain
- Monitor working out of Zentrum der Inneren Medizin, J. W. Goethe University Hospital, Frankfurt, Germany.

Scientific Group

Besides *Jens Lundgren*, the scientific group comprises a number of long-term involved researchers with part time positions as Clinical Research Associates. *Nina Friis-Møller* is primarily responsible for CHIP's D:A:D activities, but also involved in CoDe development, *Ole Kirk* is primarily responsible for the EuroSIDA and TB activities, *Ulrik Bak Dragsted* advises on IL-2 studies and Royal Free activities and *Daniela Gey* is responsible physician related to the NIH studies. In addition, CHIP houses five PhD students. *Signe Westring Worm* is deeply involved in D:A:D data and focuses, apart from the daily D:A:D activities, on metabolic complications to HIV and anti-retroviral therapy. *Daria Podlekareva* has developed a HIV-TB study protocol and is engaged in collaboration not only with HIV clinics but also TB-clinics

mainly in Eastern Europe. *Lars Peters* recently joined the group with a long-lasting experience in hepatitis and focuses on HIV-hepatitis co-infection and diagnostic markers using both data from EuroSIDA and the SMART study. *Jens-Ulrik Jensen* has coordinated the efforts to develop the PASS protocol and initiate the randomised trial to investigate the diagnostic value of the plasma marker, procalcitonin, supposed to specifically indicate on-going bacteraemia in patients admitted to the intensive care units. *Justyna Kowalska*, engaged as of November 1st, 2007, will work with a project implying a substantial amount of statistics, developing models to evaluate risk and benefits of treatments based on clinical endpoints. In 2006/7 CHIP housed *Christian Brandt* for half a year, giving him an opportunity to finalise his innovative and labour intense PhD thesis on bacterial meningitis using his own validated rat model. Also *Christian Holkmann Olsen* is currently working on the last details of his PhD thesis focused on development and testing of the CoDe system.

Statistical Group

The statistical group that has been linked to CHIP for many years work out of the Royal Free & University College Medical School in London. Prof. *Andrew Phillips* heads the group and is involved in the INSIGHT Executive Committee, Senior statistician *Amanda Mocroft's* primary responsibility is EuroSIDA assisted by *Alessandro Cozzi-Lepri*, PhD and the PhD students *Wendy Bannister*, *Zoe Fox* and *Joanne Reekie*. Prof. *Caroline A. Sabin* is dedicated to D:A:D.

The Monitoring Group

Karoline B. Jensen is coordinator for CHIPs largest group of 10 in-house monitors; *Birgitte Gram Jensen*, *Charlotte Matthews*, *Heidi M. Juncher-Benzon*, *Jorunn Tverland*, *Liselotte Borup*, *Mary Pearson*, *Per O. Jansson*, *Bitten Aagaard*, *Mie Kofoed-Djursner*, *Søren Stentoft Reilev*. The skills and activities of the group are described in detail in the theme article on monitoring at p. 9.

In more than one sense the monitors have been productive – three monitors have been or are currently enjoying their maternity leave. To cover for the monitors on leave we have been very lucky to find and engage three new monitors, *Bitten*, *Mie* and *Søren* – already integrated and highly productive in the spirit of CHIP. Also our out of the country monitor staff has developed. In Germany *Klaus Tillmann* and *Ulrike Knust* are hard working and in daily contact with Copenhagen. In Spain the monitor group now comprise three dedicated monitors *Sara Varea*, *Núria Ramos* and *David Garcia*. *Daniela Gey*, our Clinical Trial Manager, is a valuable support for the RCT activities.

The Cohort Group

The operational activities of the cohort group are coordinated by *Michelle Ellefson* assisted by *Ulla Hjørnholm* and *Annemette Borch* as well as a number of student staff taking care of data forms logistic and quality assurance. In a decade *Ingerlise Gjørup* was synonymous with EuroSIDA and as *Ingerlise* retired in February 2007 we had to reorganise the acti-



vities – no one would be able to cover what *Ingerlise* managed due to her many years of experience and creator of the history: *Annemette's* main function is to secure flow of forms and monitoring visits, *Ulla* assists the many EuroSIDA sites with regulatory issues and secures the flow of CoDe forms and reviews, *Bjørn Lyngsøe* is responsible for the cohort accounting. The daily work in the cohort group is the most complex in CHIP: besides the operational staff it involves most of the scientists; the data-managers, data entry and bioinformatics staff; CHIP's statistical group at Royal Free Hospital in London; as well as investigators, partners and other collaborators form the many cohort collaborations.

The IT and Bioinformatics Group

Jesper Kjær, who recently achieved his MSc in Bioinformatics based on an innovative, high quality thesis, coordinates the activities of the group. Besides managing the EuroSIDA database and securing the mergers of data from D:A:D, COHERE and CoDe the function is responsible for the many administrative databases and tools as well as for the functionality of the web-based portals and tools covering the activities of the whole of CHIP. *Leif Høj* has recently joined CHIP to strengthen the bioinformatic profile of the group. *Dennis Kristensen* is our main web interface programmer, *Allen Sawitz* manages D:A:D mergers, and a large staff of keyers take care of data entry, scanning and quality assurance. The group also administers the flow of samples to and from the repository.

Secretariat

Karen Skov Hansen coordinates the secretariat function. *Marianne Jeppesen* assists the monitoring

group with travel arrangements, courier, systems and shipment. *Peer Aagaard* primarily 'manages' *Jens Lundgren* and translation tasks as well as guest and temporary staff housing and permits. Also cross function projects is managed by the secretariat.

Finance and laboratory

Helle Bo Duus and *Bjørn Lyngsøe* secure the daily accounting and the long term follow-up and reporting of financial and contractual obligations. *Helle* also administers personnel files and acts as a work environment and safety officer.

The laboratory function secures the overview and handling of the more than 90,000 samples in the research repository, mainly EuroSIDA samples, but also manages the logistics and coordination of collection of samples from the randomised controlled trials and the safe shipment of the samples to the US-based repository for these trials. In the near future when CHIP is relocated at Panum, the laboratory function will be developed to support the needs of our PhD students. First focus will be securing analysis capabilities related to the hepatitis co-infection project. The finance and lab functions are staff functions to the Director of Administration.

Management

Jens Lundgren, Director, and *Jesper Grarup*, Director of Administration currently form the management of CHIP. The intention is to expand the management by engaging a senior scientist as Scientific Director to focus on the development of CHIPs scientific function and thereby taking over some of Jens' responsibilities. *Jesper Grarup* entered the group in March 2006, replacing *David Mollerup*. *Jesper* had worked ten years as a veterinary practitioner in small animal



hospital practice which resulted in the development of an allergy, and a shift to more than 10 years in the pharmaceutical industry with responsibility for the clinical development of human drugs. *Jesper* has a hands-on experience with most of the tasks currently ongoing in CHIP and makes a nice administrative match to *Jens'* scientific responsibilities.

The activities of CHIP will indisputably shift a little, as we are proud to announce that the University of Copenhagen has granted *Jens Lundgren* the professorship of Viral Diseases. *Jens* will, besides CHIP, take the post as chief physician and consultant in Viral Diseases at Rigshospitalet.

CHIP will be located at the Faculty of Health Sciences under the Institute of International Health, Immunology and Microbiology (ISIM) at the Panum Institute – ISIM being also the Institute where the professorship is anchored. We are all looking forward to the many new possibilities for collaboration that open by the relocation of CHIP.

EACS

CHIP is actively involved in the European AIDS Clinical Society medical exchange programme for young HIV physicians. In 2005 *Justyna Kowalska* from Poland stayed at CHIP for three months as part of the exchange programme and she has now been granted a position as Clinical Research Associate in order to complete a PhD thesis focusing on risks and benefits of specific antiretroviral regimens vis-à-vis different clinical endpoints. During 2006 we had *Ivan Zhyltsou* from Belarus staying and experiencing a cultural chock, but giving all of us a more thorough understanding of the conditions for

HIV treatment and research in Belarus. Currently *Elena Kozorov* from Belarus is visiting as part of the programme.

PhD Students

CHIP currently houses five PhD students and supports two additional PhDs at The Royal Free in London. The PhD activities are described under Organisation, see p. 36.

Master of bioinformatics

Jesper Kjær has completed his studies parallel to his full-time position as manager of his group. *Jesper* and his thesis co-worker, *Leif Høj* has used resistance data from HIV-infected patients combined with biochemical knowledge of enzyme molecule structure of main drug groups to develop a computer based model to predict the phenotypic susceptibility of the drug classes. We will utilise *Jesper* and *Leif's* skills in bioinformatics and model development, increasing the aspect of data interpretation in CHIPs projects.

Funding

CHIP is entirely dependent on external project-specific funding. The past year and a half has been very busy as some of the major grants have been up for refunding.

EU

CHIP as coordinator succeeded in obtaining refunding of EuroSIDA until spring 2010 and is already engaged in a networking with three other funded coordinating actions within the sixth Framework Program (EuroCORD) in order to respond in common to a call for proposals to continue EU-funded acti-



vities after 2010. CHIP is involved as partner in two additional EU projects, **ACTIVATE** and **NEAT** – and is currently contributing to two Seventh Framework Program applications.

NIH

The NIH grant application process has been troublesome. In July 2006 CHIP was granted a role as International Coordinating Centre (ICC) in the **INSIGHT** network application. The research activities to fill the network were applied for in the form of Clinical Trial Unit applications from the four ICCs of the **INSIGHT** network. For many reasons, of which political reasons contribute substantially, none of the CTU applications were granted. Instead the network was asked to come up with a proposal for a **When-to-start-study** in acknowledgement of **INSIGHT** being the only network capable of conducting such a study. The **START** study was preliminary granted 10 million USD in early summer 2007 to be used for an initial study phase over two years. Additional funding will depend on interim analysis and recalculation of sample size. The funding of the

already initiated studies will continue as planned until completion of the trials (**SMART** by the end of 2007, **Esprit** and **SILCAAT** in 2008 – early 2009).

Pharmaceutical Industry

The EuroSIDA grant does not cover all proposed activities and therefore industry funding for the analytical work related to resistance mutations, toxicities and co-infections is a valuable contribution to the activities. Sponsorship agreements are only entered into if the scientific question to be investigated under the agreement is found to be scientifically sound and valuable for patient safety and treatment as evaluated by the Scientific Steering Committee. The resulting reports are often used for regulatory submission as response to requests from the regulatory authorities.

Also **D:A:D** was funded by the **HAART Oversight Committee** for an additional period. The Oversight Committee was originally formed on a requests from **EMEA** which follows the **D:A:D** results and continued funding closely.

FINANCIAL CONTRIBUTORS

Study	Public	Private
EuroSIDA	EU Commision	Boehringer-Ingelheim Bristol-Myers Squibb Gilead Sciences GlaxoSmithKline Merck & Co Inc Pfizer Inc Tibotec
D:A:D	The Oversight Committee for The Evaluation of Metabolic Complications of HAART EMA FDA	Abbott Laboratorie Boehringer-Ingelheim Bristol-Myers Squibb Gilead Sciences GlaxoSmithKline Merck & Co Inc Pfizer Inc Roche Pharmaceuticals
Esprit	NIH	
SILCAAT	NIH	
STALWART	NIH	
SMART	NIH	
INSIGHT network	NIH	
PASS	Danish Research Council	Lundbeck Foundation A.P. Møller og hustru Chastine Mærks Mc-Kinney Møllers Foundation Toyota Foundation B.R.A.H.M.S.-Diagnostica GmbH
COHERE	ANRS, Agence nationale de recherches sur le SIDA Dutch HIV Monitoring Foundation	Augustinus Foundation
NEAT	EU Commission	
ACTIVATE	EU Commission	
EUROCORD		IWHOD
ALCAR	Royal Free Hospital	
NRTI-sparring	Royal Free Hospital	

ACKNOWLEDGEMENTS

Key persons left the group in the past year. First of all, *David Mollerup* wanted to pursue new challenges in the Danish Cancer Society after many years of engaged work where he contributed to the development of the monitoring function and CHIP in general – we highly appreciate *David's* achievements and his social skills, which leave a pleasant memory. Also many thanks to *Anne Fau* known to many as a skilled and hard working monitor with a good sense of humour, and *Annette Fischer* our dedicated and well structured lab technician, as well as *Kell Greibe* our administrative coordinator and *Esther Aragon* our dedicated Spanish monitor for many years. Likewise we would like to thank *Lena Hansen* our lab technician, whom we have shared with the department of infectious diseases for many years. *Lena* approaches her retirement and we are glad that *Lena* accepted to spend her last months staying at Hvidovre Hospital finalising analyses for CHIP. *Ingerlise Gjørup* retired on February 1st 2006 after more than 40 years engagement at Hvidovre

University Hospital. Thereby an era ended for CHIP. *Ingerlise* worked with *Jens* even before CHIP was formed and EuroSIDA still was 'AIDS in Europe'. *Ingerlise* has been the stable element throughout all the years and her knowledge 'database' is impossible to replace. We are very grateful for the many years of *Ingerlise's* loyal service and not least her friendly but direct follow-up on pending issues that contributed to the success of EuroSIDA. Remarkable is also *Ingerlise's* concern and care for EuroSIDA and the well-being of CHIP – we highly appreciate that. *Ingerlise*, many thanks and all the best in your busy life in retirement.

The Board of Directors continues to provide constructive guidance and ask challenging questions to secure our focus on the 'core business' and a constant development of the group. Three external members of the Board, Prof. *Nils Brünner*, Prof. *Hans Bisgaard* and Mr. *Michael Nord* are acknowledged with appreciation.

AWARDS

As of June 1st 2007 *Jens Lundgren* was announced co-chief editor of HIV Medicine together with *Brian Gazzard*. *Jens Lundgren* was awarded membership of the

American Society of Clinical Investigation, honorary membership of the International Association of Physicians in AIDS Care (IAPAC) and the Polish AIDS Society in 2005.

PRESENTATIONS

2007

9th Intl Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, Sydney July 2007

Oral presentation

- 1 Does diabetes mellitus (DM) confer an equivalent risk of coronary heart disease (CHD) to pre-existing CHD in HIV-positive individuals? SW Worm, S De Wit, R Weber, CA Sabin, P Reiss, W El-Sadr, A D'Arminio Monforte, O Kirk, E Fontas, F Dabis, MG Law, JD Lundgren and N Friis-Møller on behalf of the D:A:D study group. Abstract No 0-09

XVI International HIV Drug Resistance Workshop, Barbados, June 2007

Poster Presentations

1. Prediction of phenotypic susceptibility to the three major HIV drug classes from physicochemical properties of the primary enzymatic structure using artificial neural networks (ANNs). J Kjær, L Høj, Z Fox and JD Lundgren
2. Association between Resistance and CD₄ Count Change in Patients on ART with Ongoing Viraemia. ZV Fox, AM Geretti, B Clotet, A Cozzi-Lepri, T Hill, H Green, CA Sabin, B Ledergerber, JD Lundgren and AN Phillips for the UK Collaborative Group on HIV Drug Resistance, EuroSIDA and UK CHIC Studies
3. Rate of accumulation of thymidine analogue mutations in patients left on virologically failing regimens containing zidovudine or stavudine. A Cozzi-Lepri, AN Phillips, J Martinez-Picado, A d'Arminio Monforte, C Katlama, A-B Eg Hansen, A Horban, J Bruun, B Clotet and J Lundgren for the EuroSIDA Study Group
4. Proof-of-Principle Evaluation of Predictive Performance for Therapy Outcome of Baseline Estimated Fitness and Genetic Barrier towards Resistance in a Clinical Cohort of HIV-1 Treated Patients. K Deforche, A Cozzi-Lepri, K Theys, B Clotet, R Camacho, J Kjaer, K Van Laethem, AN Phillips, Y Moreau, JD Lundgren and A-M Vandamme for the EuroSIDA Study Group.

5th European HIV Drug Resistance Workshop, Cascais, March, 2007

Poster Presentation

1. Prediction of phenotypic susceptibility to seven protease inhibitors from chemical and structural descriptors of the protease gene's amino acid sequence using artificial neural networks. J Kjær, L Høj, Z Fox and JD Lundgren

14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, February 2007

Oral presentation

1. HIV-induced immunodeficiency and risk of fatal AIDS-defining and Non-AIDS-defining malignancies: Results from the D:A:D Study Group. A D'Arminio Monforte, D Abrams C Pradier R Weber, F Bonnet, S De Wit, N Friis-Møller, A Phillips, C Sabin, JD Lundgren, and the D:A:D Study Group. Abstract No. 84

Poster Presentation

- 1 Predicting the risk of coronary heart disease (CHD) in HIV-infected patients: The D:A:D CHD risk equation. N Friis-Møller, R Thiébaud, P Reiss, W El-Sadr, R Weber, A d'Arminio Monforte, E Fontas, SW Worm, O Kirk, A Phillips, CA Sabin, JD Lundgren, M Law, and the D:A:D Study Group.
2. Presence of the metabolic syndrome (MS) is not a better predictor of cardiovascular disease (CVD) than the sum of its components; Data from the D:A:D study. SW Worm, CA Sabin, P Reiss, W El-Sadr, A D'Arminio Monforte, C Pradier, R Thiebaut, M Law, M Rickenback, S de Wit, JD Lundgren, N Friis-Møller and the D:A:D Study Group
3. Underutilization of recommended interventions for prevention of cardiovascular (CV) disease in HIV-infected patients with established CV disease or diabetes. CA Sabin, R Weber, F Dabis, P Reiss, S de Wit, W El-Sadr, A D'Arminio Monforte, M Law, O Kirk, SW Worm, N Friis-Møller, JD Lundgren, and the D:A:D Study Group

4. Detection of chronic renal failure (CRF) among HIV-patients within the EuroSIDA Study. A Mocroft, O Kirk, J Gatell, P Reiss, P Gargalianos, K Zilmer, M Beniowski, JP Viard, S Staszewski, JD Lundgren for the EuroSIDA Study Group
5. Normalisation of CD4 count in HIV-infected patients with maximal virological suppression (<50 copies/ml) taking combination antiretroviral therapy. A Mocroft, AN Phillips, J Gatell, B Ledergerber, M Fisher, N Clumeck, M Losso, A Lazzarin, G Fätkenheuer, JD Lundgren for the EuroSIDA Study Group
6. Predicted risk of coronary heart disease (CHD) with Tipranavir exposure compared to conventional PI in the RESIST trial. N Friis-Møller, M Kraft, H Valdez, D Hall, and JD Lundgren

2006

The 8th International Congress on Drug Therapy in HIV Infection, Glasgow, November 2006

Oral Presentations

1. Relationship between use of stavudine and diabetes mellitus. S. de Wit, CA Sabin, R Weber, SW Worm, P Reiss, R Thiebaut, W El-Sadr, A d'Arminio Monforte, E Fontas, MG Law, AN Phillips, N Friis-Møller, JD Lundgren for the DAD Study Group
2. Effect of interventions to improve dyslipidaemia. M de Valk, N Friis-Møller, CA Sabin, F Dabis, A d'Arminio Monforte, R Weber, S Worm, W El-Sadr, S de Wit, C Pradier, O Kirk, M Law, AN Phillips, JD Lundgren, P Reiss for the DAD Study Group
3. Final safety and efficacy analysis of a randomised pilot study evaluating early versus late switch from efavirenz to nevirapine as part of HAART: the BI Switch Study. M Youle, U B Dragsted, D Podlekareva, C Smith, A Carroll, F Turner, M Johnson

Poster Presentations

1. Comparison of single and boosted-protease-inhibitor (PI) versus non-nucleoside reverse transcriptase inhibitor (NNRTI) containing regimens in previously antiretroviral naïve patients. A Mocroft, O Kirk, A Horban, N Clumeck, HJ Stellbrink, A d'Arminio, K Zilmer, J Gatell, AN Phillips, JD Lundgren for the EuroSIDA Study Group
2. Abacavir hypersensitivity reaction in EuroSIDA. W Bannister, N Friis-Møller, A Mocroft, JP Viard, J van Lunzen, O Kirk, P Gargalianos, D Banhegyi, A Chiesi, J Lundgren for the EuroSIDA Study Group
3. The Metabolic Syndrome at baseline in the D:A:D Study. S Worm, C Sabin, W El-Sadr, P Reiss, A Monforte, M Rickenbach, R Thiebaut, S de Wit, E Fontas, M Law, O Kirk, J Lundgren, N Friis-Møller for the DAD Study

The XVI International AIDS Conference, Toronto, August 2006

Oral Presentations

1. Progression of HIV-related disease or death (POD) in the randomised SMART study: why was the risk of POD greater in the CD4 guided ((re)-initiate ART at CD4<250 cells/μL) drug conservation (DC) vs the virological suppression (VS) arm? Jens D. Lundgren on behalf of the SMART Study Group
2. Risk of discontinuation of nevirapine due to toxicities in antiretroviral naïve and experienced patients with high and low CD4 counts. A Mocroft, J Rockstroh, J Gasiorowski, F Antunes, G Panos, A d'Arminio Monforte, A Rakhmanova, AN Phillips, JD Lundgren for the EuroSIDA Study Group
3. All naïve patients are not equal: when and how to start HAART. JD Lundgren

Poster Presentations

1. The ability of four genotypic resistance algorithms for predicting HIV-RNA responses 4-24 weeks after initiating a boosted PI-containing regimen. Z Fox, J Kjær, AN Phillips, L Ruiz, B Clotet, S Staszewski, C Holkmann Olsen, A Horban, B Ledergerber, JD Lundgren for the EuroSIDA Study Group
2. Genotypic resistance profile before initiation of cART and association with virological and clinical outcome in EuroSIDA. WP Bannister, AN Phillips, B Clotet, P Reiss, B Ledergerber, A Lazzarin, C Katlama, A Cozzi-Lepri, L Ruiz, JD Lundgren for the EuroSIDA Study Group
3. Short term clinical disease progression in HIV-1 positive patients taking combination antiretroviral therapy: The EuroSIDA risk-score. A Mocroft, B Ledergerber, K Zilmer, O Kirk, B Hirschel, JP Viard, P Reiss, P Francioli, A Lazzarin, L Machala, AN Phillips, JD Lundgren for the EuroSIDA study and the Swiss HIV Cohort study.

4th European Drug Resistance Workshop, Monte Carlo, March 2006

Poster Presentations

1. The ability of four genotypic resistance algorithms to predict HIV-RNA responses to boosted PI-containing regimens after 4 and 12 weeks follow-up. Z Fox, M Gisslen, B Gazzard, J Kjær, H Nielsen, M Youle, I Cassetti, AN Phillips, UB Dragsted, and JD Lundgren on behalf of the MaxCmin1, MaxCmin2 and COLATE trial Groups

13th Conference on Retroviruses and Opportunistic Infections, Denver, February 2006

Oral presentation

1. Exposure to PI and NNRTI and risk of myocardial infarction: Results from the D:A:D Study. N Friis-Møller, P Reiss, W El-Sadr, A d'Arminio Monforte, R Thiebaut, S De Wit,

R Weber, E Fontas, M Law, A Phillips, O Kirk, CA Sabin, JD Lundgren, and the D:A:D Study Group

Poster Presentations

1. Mutation at reverse transcriptase codon 214 is antagonist to thymidine analogue mutations type 2 profiles and predicts virological response to thymidine analogue-containing cART regimens only if TAM type 1 profiles concomitantly detected. A Cozzi-Lepri, L Ruiz, F Ceccherini-Silberstein, A Mocroft, A Phillips, J Gatell, B Ledergerber, P Reiss, B Clotet, JD Lundgren and the EuroSIDA Study Group
2. Factors associated with the development of opportunistic infections in HIV-1-infected adults with high CD4 cell counts in the EuroSIDA study. D Podlekareva, U Dragsted, A Mocroft, B Ledergerber, M Beniowski, A Lazzarin, J Weber, N Clumeck, A Phillips, JD Lundgren and the EuroSIDA Study Group
3. Exposure to antiretroviral therapy and the risk of liver-related death: Is there an association? Results from the D:A:D Study. R Weber, C Sabin, N Friis-Møller, A d'Arminio Monforte, P Reiss, W El-Sadr, F Dabis, M Law, C Pradier, S De Wit, O Kirk, A Phillips, JD. Lundgren; On behalf of the D:A:D Study Group

2005

10th European AIDS Conference/EACS, Dublin, November 2005

Poster Presentations

1. Liver-related Deaths among HIV-infected Persons; Data from the D:A:D Study. R Weber, N Friis-Møller, CA Sabin, P Reiss, A d'Arminio Monforte, F Dabis, W El-Sadr, S De Wit, L Morfeldt, MG Law, C Pradier, G Calvo, O Kirk, AN Phillips, JD Lundgren on behalf of the D:A:D Study Group
2. Comparison of resistance profiles between patients starting nevirapine and efavirenz in EuroSIDA. W Bannister, L Ruiz, B Ledergerber, A Cozzi-Lepri, O Kirk, S Staszewski, C Loveday, B Clotet, A Phillips, J Lundgren for the EuroSIDA Study Group
3. Evolution of drug resistance in HIV infected patients remaining on a virologically failing cART regimen. A Cozzi-Lepri, AN Phillips, L Ruiz, B Clotet, C Loveday, J Kjaer, N Clumeck, L Viksna, F Antunes, L Machala and JD Lundgren.
4. Pilot of the CoDe (Coding of Death) project - a standardized approach to code causes of death in HIV infected individuals. CH Olsen, N Friis-Møller, A d'Arminio Monforte, G Chene, R Davey, S De Wit, F De Wolf, M Egger, M Ellefson, W El-Sadr, O Kirk, M Law, B Ledergerber, C Lewden, S Mateu, A Mocroft, T Peto, A Phillips, C Pradier, P Reiss, F Rhame, C Sabin, J Sterne, R Weber, B Åkerlund, JD Lundgren, for the CoDe Working Group.

Oral presentations

1. Use of antimycotic therapy is an independent risk factor for HIV-disease progression among patients with a CD4 count above 200/ μ L in the era of combination antiretroviral therapy. D Podlekareva, A Mocroft, P Reiss, P Aldins, C Katlama, B Ledergerber, HJ Stellbrink, AD Monforte, O Kirk, JD Lundgren
2. Is there an association between the endpoints in trials of virological efficacy and clinical long-term prognosis? O Kirk, A Mocroft, P Reiss, B Ledergerber, B Knysz, G Fätkenheuer, S Chaplinskas, JM Gatell, A Phillips, JD Lundgren for the EuroSIDA Study Group
3. Clinical progression according to HIV drug resistance accumulated on antiretroviral therapy in EuroSIDA. A Cozzi-Lepri, A Phillips, A Mocroft, O Kirk, L Ruiz and JD Lundgren.
4. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? The EuroSIDA study. JD Lundgren, A Mocroft, V Soriano, J Röchstroh, P Reiss, O Kirk, S de Wit, JM Gatell, B Clotet, A Phillips

3rd IAS Conference on HIV Pathogenesis and Treatment,

Rio de Janeiro, July 2005

1. Rates of viral suppression and regimen change according to initial HAAR regimen. A collaborative analysis of 12 prospective cohort studies. R Hogg, J Lundgren, D Costagliola, A d'Arminio Monforte, B Ledergerber, F de Wolf, G Fusco, S Staszewski, G Chene, A Phillips, J Gil, N Schmeisser, M May, J Sterne, M Egger.
2. Impact of Lamivudine (3TC) on the risk of liver related death (LRD) in 2,041 HBsAg and HIV-positive individuals. Results of an intercohort analysis. M Puoti, A Cozzi-Lepri, G Parainfo, J Lundgren, M Rickenback, I Suarez-Lozano, M Winnock, A Gervais, J Gill, J Rockstroh, C Mussini, A Castagna, A De Luca, A d'Arminio Monforte.
3. Risk factors for new onset diabetes mellitus (DM) in HIV patients. C Sabin, N Friis-Møller, P Reiss, R Weber, A d'Arminio Monforte, F Dabis, W El-Sadr, S de Wit, S Mateu, O Kirk, C Pradier, L Morfeldt, M Law, J Lundgren.

3rd European Resistance Conference, Athens, March 2005

1. The COLATE trial: comparison of the evolutionary distance for protease and reverse transcriptase sequences. J Kjaer
2. How to read viral load in patients with virus variants that you can not suppress. J Lundgren

**12th Conference on Retroviruses and Opportunistic Infections,
Boston, February 2005**

Poster Presentations

1. Changes over time in antiretroviral therapy (ART) use and risk factors for cardiovascular disease (CVD) in the D:A:D study. C Sabin, L Morfeldt, N Friis-Møller, M Rickenbach, P Reiss, A d'Arminio Monforte, C Pradier, O Kirk, G Calvo, M Law, P Mercié, W El-Sadr, S De Wit, JD Lundgren on behalf of the D:A:D Study Group
2. HIV and Non-HIV-related deaths and their relationship to immunodeficiency; the D:A:D study. R Weber, N Friis-Møller, C Sabin, P Reiss, A d'Arminio Monforte, F Dabis, W El-Sadr, S De Wit, L Morfeldt, MG Law, C Pradier, G Calvo, C Holkmann Olsen, AN Phillips, JD Lundgren on behalf of the D:A:D Study Group
5. Risk of AIDS and death at given HIV-RNA and CD₄ count level, according to specific antiretroviral drugs in the CART regimen. C Holkmann-Olsen¹, J Gatell, B Ledergerber, C Katlama, N Friis-Møller, J Weber, A Horban, S Staszewski, J Lundgren, A Phillips, and EuroSIDA
6. HIV-1 subtypes and virological response to HAART in Europe. W Bannister, L Ruiz, C Loveday, S Vella, K Zilmer, D Podlekareva, B Knysz, A Phillips, J Lundgren, A Mocroft and the EuroSIDA Study Group

7. Thymidine analogue mutation profiles: factors associated with acquiring specific profiles and their impact on virological response to therapy. A Cozzi-Lepri, L Ruiz, C Loveday, A Phillips, B Clotet, P Reiss, J Lundgren, and EuroSIDA Study Group
8. A Comparison of Risk of Treatment Limiting Adverse Events in HCV-co-infected vs Non-co-infected persons with HIV in EuroSIDA. JD Lundgren, J Rockstroh, V Soriano, B Ledergerber, O Kirk, E Vinogradova, P Reiss, C Katlama, A Blaxhult, A Mocroft, and EuroSIDA Study Group

Oral presentations

1. Cardiovascular outcomes in HIV infection. JD Lundgren et al
2. Relationship between prolonged exposure to combination antiretroviral therapy (cART) and myocardial infarction (MI): effect of sex, age and lipid changes. W El-Sadr, P Reiss, S De Wit, A d'Armino Monforte, R Thiebaut, L Morfeldt, R Weber, C Pradier, G Calvo, MG Law, O Kirk, C Sabin, N Friis-Møller JD Lundgren on behalf of the D:A:D Study Group
3. Mortality Rates According to Initial HAART Regimen: A Collaborative Analysis of 12 Prospective Cohort Studies. R Hogg, J Lundgren, D Costagliola, A Monforte, B Ledergerber, F de Wolf, G Fusco, S Staszewski, G Chêne, A Phillips, J Gill, J Rockstroh, M May, J Sterne, M Egger, and ART Cohort Collaboration

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2007

1. **When should antiretroviral therapy for HIV be started?** AN Phillips, BG Gazzard, N Clumeck, MH Losso, JD Lundgren. Editorial. *BMJ* 2007;334:76-78.
2. **Interruption of combination antiretroviral therapy and risk of clinical disease progression to AIDS or death.** C Holkmann Olsen, A Mocroft, O Kirk, S Vella, A Blaxhult, N Clumeck, M Fisher, C Katlama, AN Phillips and JD Lundgren for the EuroSIDA study group. *HIV Med.* 2007;8:96-104.
3. **Class of Antiretroviral Drugs and the Risk of Myocardial Infarction.** Writing committee: N Friis-Møller, P Reiss, CA Sabin, R Weber, A D'Arminio Monforte, W El-Sadr, R Thiebaut, S de Wit, O Kirk, E Fontas, MG Law, A Phillips, JD Lundgren on behalf of the D:A:D study group. *N Engl J Med.* 2007 April 26;356:1723-35.
4. **Evolution of drug resistance in HIV infected patients remaining on a virologically failing cART regimen.** A Cozzi-Lepri, AN Phillips, L Ruiz, B Clotet, C Loveday, J Kjær, H Mens, N Clumeck, L Viksna, F Antunes, L Machala, JD Lundgren. *AIDS.* 2007 Mar 30;21(6):731-32.
5. **Chronic renal failure among HIV-1-infected patients.** A Mocroft, O Kirk, J Gatell, P Reiss, P Gargalianos, K Zilmer, M Beniowski, J-P Viard, S Staszewski, and JD Lundgren for the EuroSIDA study group. *AIDS.* 2007 May 31, 21(9):1119-1127.
6. **Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. The Antiretroviral Therapy (ART) Cohort Collaboration.** Writing committee: M May, JAC Sterne, C Sabin, D Costagliola, AC Justice, R Thiebaut, J Gil, A Phillips, P Reiss, R Hogg, B Ledergerber, A d'Arminio Monforte, N Schmeisser, S Staszewski, M Egger. *AIDS.* 2007 May 31, 21(9):1185-1197.
7. **Primary Pneumocystis infection in infants hospitalized with acute respiratory tract infection.** H Larsen, M-L von Linstow, B Lundgren, B Høgh, H Westh, JD Lundgren. *Emerg Infect Dis.* 2007 Jan;13(1):66-72.
8. **Predictors of CD4 count change over 8 months of follow up in HIV-1-infected patients with a CD4 count \geq 300 cells/microl who were assigned to 7.5 MIU interleukin-2.** The ESPRIT Research Group; Z Fox, F Antunes, R Davey, B Gazzard, N Klimas, A Labriola, M Losso, JD Neaton, AN Phillips, K Ruxrungtham, S Staszewski, L Weiss, JD Lundgren. *HIV Med.* 2007 Mar;8(2):112-23.
9. **Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study.** A Mocroft, AN Phillips, J Gatell, B Ledergerber, M Fisher, N Clumeck, M Losso, A Lazzarin, JD Lundgren for the EuroSIDA Study Group. *Lancet.* 2007 July 19, online. *Lancet.* 2007 Aug 4;370(9585):407-13.
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12. **Risk of discontinuation of nevirapine due to toxicities in antiretroviral naive and experienced HIV-infected patients with high and low CD4 counts.** A Mocroft, S Staszewski, R Weber, J Gatell, J Rockstroh, J Gasiorowski, G Panos, A d'Arminio Monforte, A Rakhmanova, AN Phillips, JD Lundgren *Antiviral Ther.* 2007;12(3):325-33.
13. **Current haemoglobin levels are more predictive of disease progression than haemoglobin measured at baseline in patients receiving antiretroviral treatment for HIV-1 infection.** JD Kowalska, A Mocroft, A Blaxhult, R Colebunders, J van Lunzen, D Podlekareva, A-BE Hansen, L Machala, I Yust and T Benfield for the EuroSIDA Study Group. *AIDS Res Hum Ret.* 2007; 23 (10): 1183-1188

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 17. **Pharmacokinetics from two randomised trials evaluating the safety and efficacy of indinavir, saquinavir and lopinavir in combination with low-dose ritonavir: The MaxCmin 1 & 2 Trials.** US Justesen, Z Fox, C Pedersen, P Cahn, J Gerstoft, N Clumeck, M Losso, B Peters, N Obel, A Castagna, UB Dragsted, and JD Lundgren on behalf of the MaxCmin 1 & 2 Trial groups. *Basic Clin Pharmacol Toxicol*. (In press)
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1. **The Use of the Framingham Equation to Predict Myocardial Infarctions in HIV-infected Patients: Comparison with Observed Events in the D:A:D Study.** MG Law, N Friis-Møller, WM El-Sadr, R Weber, P Reiss, A d'Arminio Monforte, R Thiébaud, L Morfeldt, S De Wit, C Pradier, G Calvo, O Kirk, CA Sabin, AN Phillips, and JD Lundgren for the D:A:D Study Group. *HIV Med*. 2006;7:218-230.
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 6. **Virological and immunological outcomes at 3 years after starting antiretroviral therapy with regimens containing non-nucleoside reverse transcriptase inhibitor, protease inhibitor, or both in INITIO: open-label randomised trial.** Writing committee: P Yeni, DA Cooper, J-P Aboulker, AG Babiker D Carey, JH Darbyshire, M Florida, P-M Girard, RL Goodall, MH Hooker, A Mijch, V Meiffredy, B Salzberger for the INITIO trial coordinating committee. *Lancet*. 2006; 368:287-98
 7. **Factors associated with development of opportunistic infections in HIV-1 infected adults with high CD4 cell counts: a EuroSIDA study.** D Podlekareva, A Mocroft, UB Dragsted, B Ledergerber, M Beniowski, A Lazzarin, J Weber, N Clumeck, N Vetter, A Phillips, and JD Lundgren for the EuroSIDA Study Group. *J Infect Dis*. 2006 Sep 1; 194(5):633-41.
 8. **Impact of lamivudine on the risk of liver-related death in 2,041 HBsAg- and HIV-positive individuals: results from an inter-cohort analysis.** M Puoti, A Cozzi-Lepri, C Arici C, NF Moller, JD Lundgren, B Ledergerber, M Rickenbach, I Suarez-Lozano, M Garrido, F Dabis, M Winnock, L Milazzo, A Gervais, F Raffi, J Gill, J Rockstroh, N Ourishi, C Mussini, A Castagna, A De Luca, A Monforte; HBV-HIV International Intercohort Study Group. *Antivir Ther*. 2006;11(5):567-74.
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- the ESPRIT and SILCAAT Research Groups. *HIV Clin Trials*. 2006;7(3):125-141.
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 15. **Limited but increasing use of treatment for hepatitis C across Europe in patients coinfectd with HIV and hepatitis C.** A Mocroft, J Rockstroh, V Soriano, O Kirk, J-P Viard, S Caplinskas, J Gasiorowski, A Chiesi, AN Phillips, JD Lundgren for the EuroSIDA Study. *Scand J Inf Dis*. 2006;38:1092-1097.
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 19. **Comparison of single and boosted protease inhibitor versus nonnucleoside reverse transcriptase inhibitor-containing cART regimens in antiretroviral-naïve patients starting cART after January 1, 2000.** A Mocroft, A Horban, N Clumeck, HJ Stellbrink, A d'Arminio Monforte, K Zilmer, O Kirk, J Gatell, AN Phillips, and JD Lundgren for the EuroSIDA Study Group. *HIV Clin Trials*. 2006;7(6):271-284.
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 5. **Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients.** A Alberti, N Clumeck, S Collins, W Gerlich, J Lundgren, G Palù, P Reiss, R Thiebaut, O Weiland, Y Yazdanpanah, S Zeuzem (The ECC Jury). *J Hepatol*. 2005 May;42(5):615-2.
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- in patients with HIV.** A Mocroft, C Oancea, J van Lunzen, P Vanhems, D Banhegyi, A Chiesi, E Vinogradova, S Maayan, AN Phillips and J Lundgren. *Am J Gastroenterol.* 2005 Jul;100(7):1446-54.
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 17. **A randomised trial to evaluate lopinavir/ritonavir versus saquinavir/ritonavir in HIV-1 infected subjects. The Max-Cmin2 trial.** UB Dragsted, J Gerstoft, M Youle, Z Fox, M Losso, J Benetucci, DT Jayawwera, A Rieger, JN Bruun, A Castagna, B Gazzard, S Walmsley, A Hill, and JD Lundgren for the Max-Cmin2 trial group. *Antivir Ther.* 2005;10(6):735-43.



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