Welcome from the DEAN

The Faculty of Health Sciences is glad that CHIP has settled in at the Faculty and actively contributes to fulfilment of the Faculty's vision that is characterised by:

- Excellent research.
- Attractive research-based study programmes in a stimulating study environment.
- Communication, internationalisation and innovation in an open, visible interaction and collaboration for the benefit of the community.
- An inspiring workplace and an active team player in developing Copenhagen as an international metropolis of science.

We regard the international research effort and the dynamic atmosphere of CHIP as an asset and a perfect match with our vision. Further, we acknowledge that CHIP on top of the research work has been able to develop the Master of HIV to be initiated in September 2010. This adds further to the scope of our newly established "Copenhagen School of Global Health" and strengthens the platform for future research and education in global health.
CHIP's external communication is impressive as is the record of published results in international journals.
We congratulate CHIP with the achievements and have great expectations for the years to come.

Ulla Wewer,
Dean, Professor,
DMSc

From the Director

2009 was another exciting year for CHIP. It was a year of planned transition as well as some unexpected scientific challenges.

Several large projects that we had focused on for years came to their natural completion – and some long-awaited definitive answers were provided on whether interleukin 2 (IL-2) in HIV (p. 12) and the use of procalcitonin (PCT) to guide antibacterial therapy in the intensive care unit (p. 14) are of clinical benefit. On both accounts, the answer was no.

Jens D. Lundgren, MD, DMSc

Some view these findings as disappointing. I do not share that view. Research is a repetitive process of formulating and testing hypotheses. If you know the answer to a given hypothesis before the research is completed, it is at best problematic and most likely a waste of time and resources to conduct the research. In particular, in clinical research, where randomised controlled trials are used to address the hypothesis, you have to be open to the possibility that each of the strategies examined have equal chance of success; if not, it is not ethical to conduct the randomised controlled trial in the first place.

There is contemporary sense in our society that things have to move quickly. At CHIP, we want to follow this trend while maintaining CHIP's vision that the activities we focus on aim to improve the care of persons suffering from infectious diseases, including HIV. We understand that being thorough and moving quickly may not always be compatible. Sometimes advances in patient care come quickly. Most often however, they come in incremental steps that require hard work, commitment, and time. Both of the research projects mentioned above are good examples of this. IL-2 was first given to AIDS patients 25 years ago – and the rationale debated ever since – as has the utility of PCT in sepsis diagnosis and management for the last 15 years. We are proud to have contributed to both questions.

D:A:D (p. 18) implemented plans for expansion during 2009. The study now includes 50,000 HIV-infected persons and the number of different diseases captured has increased as well. D:A:D is internationally recognised as the leading study to detect emerging and clinically important adverse effects from continued exposure to antiretroviral therapy. The EuroSIDA study remains a major contributor to the D:A:D collaboration (p. 19). This study is now one of several cohort studies in the EuroCoord consortium - http://www.eurocoord.net/ - which combines all HIV observational studies across Europe.

An unexpected scientific challenge of 2009 was the handling of the 2009 influenza A (H1N1)v pandemic – also called the swine flu. The world prepared itself for an influenza pandemic associated with a significantly higher degree of mortality than was experienced. The exercise however demonstrated what was required as preparation plans for the next influenza pandemic. The two FLU studies that the INSIGHT network implemented (p. 10) in great haste

have had a pivotal role in determining that it is simply not sufficient to have surveillance systems in operation that can tract transmission of the infection. In order to calibrate the response, we also need to be able to quantify what harm the infection may cause to those infected.

Dissemination of original research remains the best marker to evaluate the productivity of the core activity of CHIP. It is not a perfect marker, as acceptance of papers in medical journals contains a certain degree of unpredictability, but evaluation of time trends gives a reasonable, unbiased view. The research productivity within CHIP remains acceptable with an average impact factor of 8.99 per publication for journals in which the research has been published during the first decade of this millennium including 2009 (p. 52).

An area that CHIP will continue to focus on is education on the clinical handling of infectious diseases. CHIP contributed with research & mentorship to the successful defence of 3 Ph.D theses and one doctoral dissertation in 2009 (p. 37). Additionally, in 2009, the Danish Accreditation authority (ACE) approved the Master of HIV education – we look forward to opening the first modul in September 2010.

The information technology function of CHIP transited in 2009 from primarily focusing on providing support to CHIP projects, to also engaging in collaborations with the World Health Organisation to develop an IT platform for global collection and analyses of data on antiretroviral resistance. In 2010 – among other projects – the IT function will spearhead a portal for the dissemination of up-to-date data and educational material related to adverse drug reactions from the use of antiretroviral drugs in HIV.

Research requires skilled and dedicated investigators and a good infrastructure – both of which require financial resources. CHIP has benefitted since its inception more than 10 years ago on grants and donations from international research foundations and institutions, such as the European Commission and the National Institutes of Health. CHIP became a partner of several Framework Programme (FP) 7 programmes during 2009, and trust that even more funding will come from this source in 2010. In parallel, we aim to expand focus on domestic sources of funding in 2010, as CHIP can't continue to survive on the grace of international good will without substantial local commitment.

It will be interesting to see what CHIP looks like at the end of this decade. Being still entirely dependent on external funding, we do not have the luxury of planning far in advance, but the vision is clear: our competitiveness for attracting international research funds is and will remain our key asset.

Finally, I would like to thank all colleagues working at or collaborating with CHIP. As you know, CHIP would be nothing without you. It is the intention of CHIP to provide a platform and foster an environment for skilled persons to collaborate and exchange. Finally, my appreciation also goes to the leadership of the State University Hospital (Rigshospitalet) and the University of Copenhagen for your support and for hosting CHIP.

From the Director of Administration

The past year has established the broader scope of CHIP in the organisation. The strong scientific efforts in clinical and observational trials has been further developed by increasing the number of DAD patients by 16,500 and adding new event types – and by setting up two new Influenza H1N1v studies with unprecedented speed. A challenge to the organisation that has been met with engagement and a "Yes we can" attitude.

Jesper Grarup, DVM

Importantly, CHIP's clinical core activity has been complemented with efforts to secure earlier testing and care in the form of the Indicator Disease project (see HIV in Europe section) and planning of efforts to document the transmission of disease in subjects with well-suppressed viral load. Not least, the development and successful accreditation of the Master of HIV education has been a demanding experience for CHIP and a large step in to the new scope of dissemination of the scientific results of the research. Likewise, the first real e-Learning module developed by CHIP was introduced in 2009. The joint effort of four research networks to develop the EuroCoord application was coordinated by CHIP and has had a major impact on the activity level of the organisation.

The IT and bioinformatics function at CHIP is vital for all other functions. Databases, websites and web tools, information sharing and software applications all need to function in order for CHIP to deliver. In the recent years the IT function has developed and added resources over and above the operational and support functions;the IT group managed to seek their own grants e.g. to deliver a modular resistance database system to WHO and has enhanced the data merger tools and the bioinformatics profile as well as the ability to develop e-newsletters and web-tools.

To cope with the complexity inherent with new activities, the quality management system has been reviewed and updated to fit the challenges.

We are lucky that we have managed to attract many skilled new staff members in the past year and thereby been able to shape the organisation to meet the many new challenges that come with the broader scope of research CHIP initiated in 2009. Jens' new, full-time personal assistant, Mette Brandt Madsen, was thrown into compiling the new EACS guidelines and concurred the challenge. The monitoring group welcomed Marie Louise Jakobsen without whom the PASS study would not have been completed so fast and successfully. For The HIV in Europe coordination, Dorte Raben came in, hitting the ground running and the regulatory aspects of clinical trials and the e-Learning project has benefitted from Ellen Moseholm Larsen's structured approach. The engaging of Casper Frederiksen, who quickly illustrated the fylogenetic relations of the influenza virus, secured the focus on bioinformatics. Nanna Lange was the long-missed link between IT and the other functions at CHIP; she has a strong IT and web profile and at the same time, a good sense for evaluating and establishing client requirements. Tina Bruun has worked with Jens for over 10 years in the clinic and now, as she has recently joined the team at CHIP as coordinator of transmission risk activities, we all can appreciate why Jens has been dependant on her for so many years.

The Master of HIV is in the capable hands of Maiken Mansfeld, who has the enormous challenge of coordinating the different modules and securing the professional marketing of the education. Thankfully, Charlotte Matthews returns from maternity leave in March to collaborate on the Master's coordination with Maiken.

Randomised Clinical Trials

CHIP
COPENHAGEN HIV PROGRAMME

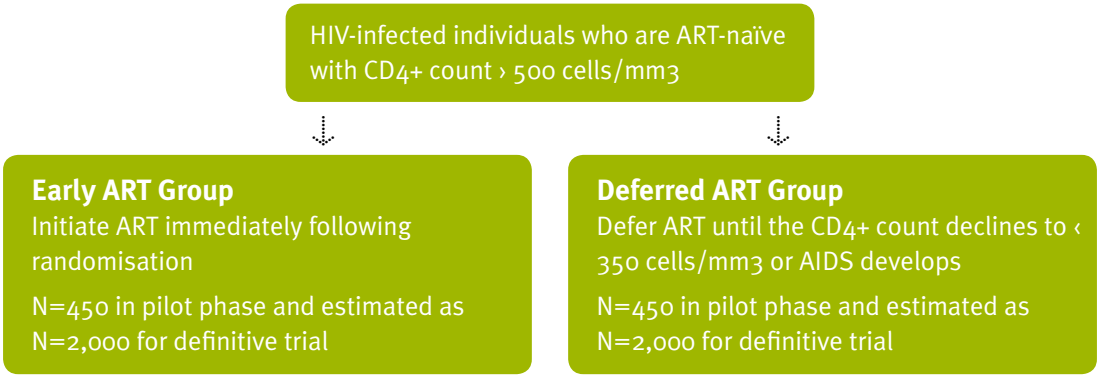
START

Description and study objective

START is an international randomised trial comparing early antiretroviral therapy (ART) vs. deferred ART. The purpose of START (Strategic Timing of AntiRetroviral Therapy) is to determine whether the immediate initiation of ART in HIV-1 infected persons who are antiretroviral naïve with a CD4+ lymphocyte count above 500 cells/mm3 is superior in terms of reducing the occurrence of serious morbidity and mortality, compared to deferral of ART until the CD4+ lymphocyte count declines below 350 cells/mm3, as most of the current guidelines recommend.

START will proceed in two phases: 1) a pilot phase and 2) a definitive phase. In the initial phase, START will enroll 900 participants from 22 countries in the Americas, Europe, Africa, the Middle East, and Australia. If the first phase is successful, enrolment will expand to approximately 4,000 participants. The entire study is expected to take about 6 years.

START Schematic



The pilot phase started in early 2009 with the first patient randomised in April. To enroll in START, most sites require access to the central drug repository, which is expected to open end of 2009/early 2010. Successful completion of the pilot phase requires enrolment of at least 900 participants in 1 year by 70 designated sites supported by the main study funder, Division of AIDS (DAIDS). Additional sites, funded by organizations other than DAIDS, will also participate in the pilot and definitive phase.

Substudies

There are 5 START Substudies (Informed Consent, Neurology, Genomics, Arterial Elasticity and Pulmonary Substudy) that either did or are about to start at a subset of sites. Other Substudies (e.g. a substudy on bone density and transmission risk behaviour) are in the planning phase and may be launched during 2010.

START

Accomplishments in 2009 and START at the Copenhagen ICC

As one of four International Coordinating Centres (ICCs) within the INSIGHT network, CHIP is responsible for implementation and conduct of START across European countries. For the pilot phase, this includes 27 sites from 6 countries (Belgium, Denmark, Finland, Germany, Poland and Spain). Additional countries and sites are expected in the definitive phase. External funding in our region, provided through a grant from the German Federal Ministry of Education and Research *(Bundesministerium für Bildung und Forschung, BMBF)*, will support START with funding for 16 German sites.

Extensive preparations for this worldwide project have continued throughout 2009. A main focus was the finalization of the clinical trial agreements (CTA) with the pharmaceutical companies providing ART within START. In the Copenhagen region, all 16 DAIDS funded sites have been registered and trained. They are either open and enrolling or awaiting opening of the European central drug repository.

FLU 002 and 003

Description and study objective
In order to better understand the emerging pandemic caused by the new influenza A (H1N1v), the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) decided in early August 2009 to conduct two observational studies that will describe the outcome of patients who seek medical care for influenza-like illness (FLU 002) and who are hospitalized with severe or complicated influenza A (FLU 003). Both studies are funded by the U.S. National Institutes of Health.

This challenging task fits nicely within INSIGHT's mission to define optimal strategies for the management of HIV and other infectious diseases through a global clinical research network. INSIGHT is ideally suited to conduct the two FLU studies due to its wide geographic distribution, its ability to quickly collect and analyse data from large patient populations and move biological material quickly across borders for central analysis. These studies of pandemic influenza A (H1N1)v represent INSIGHT's first global investigations of infectious disease other than those caused by HIV.

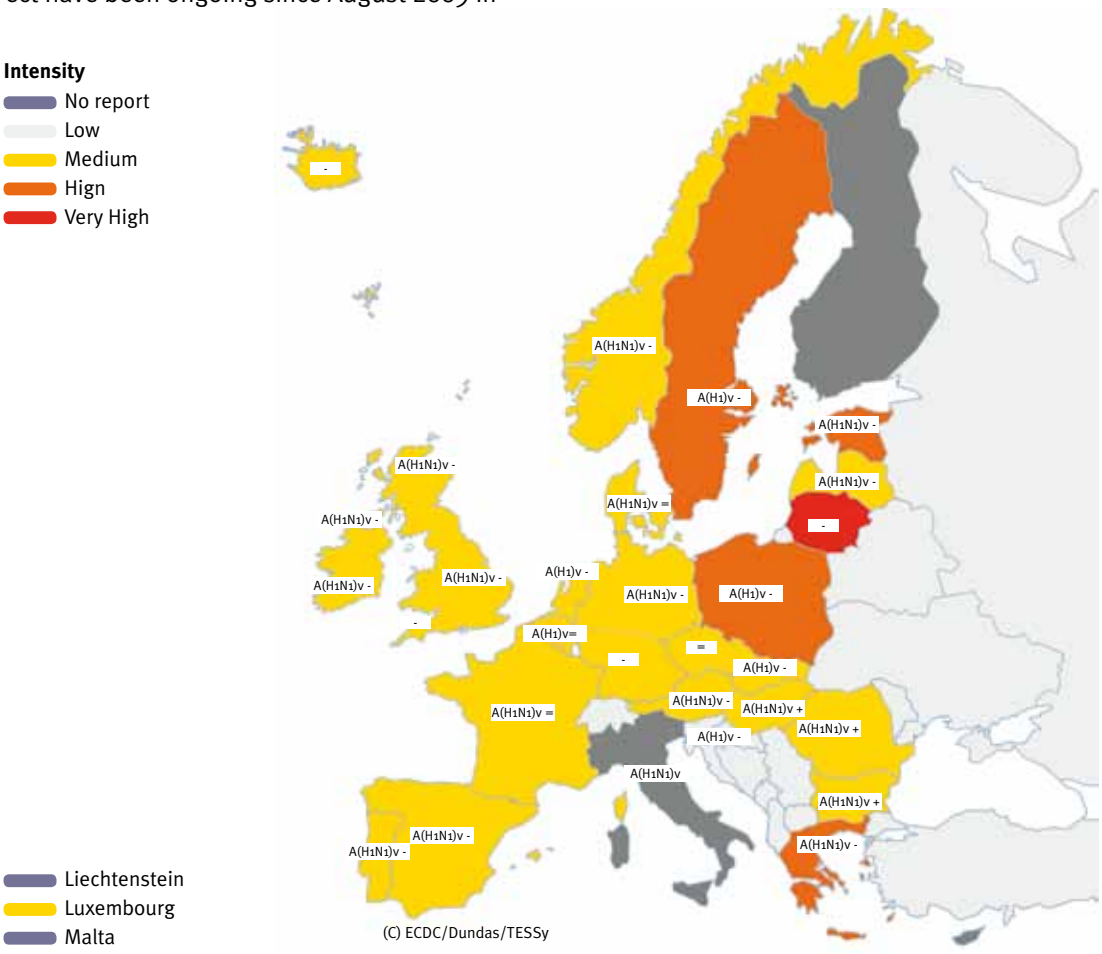
Close to 100 geographically dispersed sites in 20 countries worldwide are represented in FLU. Depending on how the pandemic unfolds, 5,000 patients will be enrolled in FLU 002 and 1,000 in FLU 003. Their clinical course will be described over a follow-up period of 14 and 60 days respectively. Both studies will store specimens to characterize the virus, to assess antiviral resistance and to study biomarkers that predict severity of infection and characteristics of the virus. The planned data collection will provide timely information to better inform patient management, to guide policy and guidelines within geographically diverse populations and to design future studies.

Accomplishments in 2009 and FLU at the Copenhagen ICC

CHIP, serving as one of four International Co-ordinating Centres (ICCs) within the INSIGHT network, is responsible for implementation and conduct of the FLU studies at 28 sites across 10 European countries: Austria, Belgium, Denmark, Estonia, Germany, Lithuania, Norway, Poland, Portugal and Spain.

Extensive preparations for this worldwide project have been ongoing since August 2009 in a very short time frame and the first patients were enrolled already in early October 2009. Within most European countries, the H1N1v Influenza epidemic reached its peak in late 2009 and the sites from the Copenhagen region are actively enrolling patients.

For more information about this and other trials conducted by INSIGHT, please visit the INSIGHT website at www.insight-trials.org.



*A type/subtype is reported as dominant when ›40% of all samples are positive for the type/subtype.

Legend:			
Low	No influenza activity or influenza at baseline levels	-	Decreasing clinical activity
Medium	Usual levels of influenza activity	+	Increasing clinical activity
High	Higher than usual levels of influenza activity	=	Stable clinical activity
Very high	Particularly severe levels of influenza activity	A(H1)v	Type A, Subtype H1v
		A(H1N1)v	Type A, Subtype H1N1v

Interleukin-2 Studies

Description and scientific purpose
ESPRIT and SILCAAT: two long term, large scale phase III, randomised, open-label, multi-centre studies that aimed to evaluate the clinical effects of subcutaneous (sc) interleukin 2 (IL-2 Group) plus antiretroviral therapy (ART) versus ART alone (Control Group) on the development of opportunistic disease or death (from any cause) in HIV-infected patients with ≥ 300 and 50-299 CD4+ cell counts, respectively. Publications containing summaries of these findings are listed at the end of this report (p 50).

STALWART, an international phase II, multi-centre, open-label, randomised controlled trial investigated 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 randomisation. A paper containing the results of the STALWART trial has been accepted for publication and will be made publically available in early 2010.

Below is an overview of the activities on study close out and extended follow-up that took place during 2009.

Study close out (ESPRIT and SILCAAT)
Clarifying whether administration of IL-2 provides clinical protection in HIV-infected populations started more than a decade ago and more than 6000 study participants were enrolled in the ESPRIT and SILCAAT studies. The studies closed to patient follow-up concurrently on 15 November 2008 after the required number of events had occurred. The INSIGHT network (www.insight-trials.org), QOPEC (Quality Oversight and Performance Evaluation Committee), the four ICCs and all ESPRIT and SILCAAT sites worldwide were simultaneously conducting the study closeout procedures. CHIP was coordinating that process for more than 40 sites in 9 countries within Europe.

A tremendous amount of data was cleaned and sample shipment took place worldwide. The site de-registration process was completed by 31 May 2009 where all 255 ESPRIT sites and 125 SILCAAT sites around the world were officially de-registered. The unblinding of data of both studies took place at a closed meeting in Buenos Aires in January 2009 and study results were presented shortly thereafter at the Conference on Retroviruses and Opportunistic Infections (CROI) and published in October 2009 (N Engl J Med. 2009 Oct 15;361(16):1548-59).

Extended follow-up (STALWART)
After the ESPRIT and SILCAAT studies showed that IL-2 produces a rise in CD4+ cell counts but that these higher CD4+ cell counts do not protect patients from opportunistic infections or death, all further STALWART IL-2 cycles were cancelled and data were unblinded and shared with the STALWART team and patients. In order to continue safety and other assessments, STALWART patients are being followed for an extended follow-up period. During 2009 the transition for this extended follow-up took place at 36 sites worldwide.

PASS

The Procalcitonin And Survival Study (PASS) – A 1,200 patient randomized trial to investigate whether antimicrobial interventions guided by daily measurements of biomarker procalcitonin can improve survival in patients in the intensive care unit (ICU).

Bacterial infections highly influence the mortality rate and the rate of organ failure in ICU patients, and appropriate initial treatment and subsequent relevant adjustments in the treatment can be challenging. Procalcitonin (PCT) is a biomarker of ongoing bacterial infection. The effect of procalcitonin-guided antimicrobial interventions in critically ill patients remains unclear.

Patients were randomly assigned within the first 24 hours of admission to the intensive care unit (ICU) to either an antimicrobial therapy guided by daily PCT measurements or by standard of care (SOC). PCT levels were measured daily and revealed to ICU staff only for persons in the PCT-group. The protocol mandated intervention in the PCT-group in persons with elevated levels of PCT using a pre-specified algorithm. Primary end point was death from any cause within 28 days. Of the 1,200 participants randomized, 604 were allocated to the PCT-group and 596 to the SOC-group and baseline characteristics were comparable in the groups. As expected, broad-spectrum antimicrobials were used more frequently in the PCT group than in the SOC group. Within

28 days after randomization, 190 (31.5%) persons in the PCT-group died vs. 191 (32.0%) in the SOC-group (relative risk 0.99 [0.92-1.07]). The number of follow-up days with mono- or multi organ failure was higher in the PCT group (p<0.0001); most pronounced for respiratory failure (days on mechanical ventilation: 3207 vs. 2501, p<0.0001), and length of ICU stay was longer in the PCT arm (6 vs. 5 days, p=0.004).

PCT guided use of antimicrobial interventions did not improve survival in persons admitted to the ICU and the duration of organ failure was prolonged using this strategy (see figure above).

STATUS: The study was completed on the 30th of June 2009 and the primary results have been presented at the Infectious Diseases Society of America Meeting, Philadelphia, USA in late October 2009.

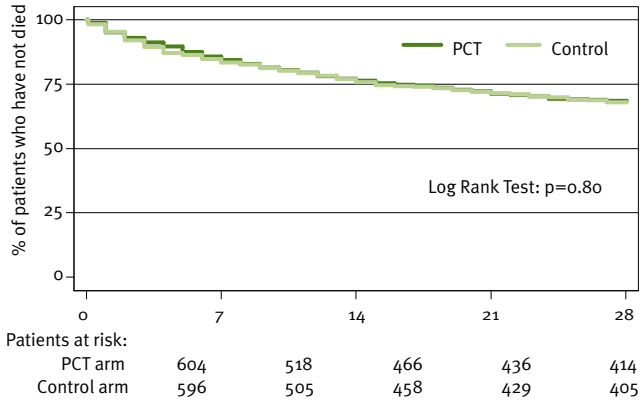
ClinicalTrials.gov identifier: NCT00271752.

Coordinating Centre & Sponsor: Copenhagen HIV Programme, Faculty of Health Sciences, University of Copenhagen

Clinical Centres: Intensive Care Units at the following University Hospitals: Hvidovre, Glostrup, Herlev, Gentofte, Hillerød, Roskilde, Skejby and Århus.

Microbiological Centre: Department of Clinical Microbiology, University Hospital of Copenhagen, Hvidovre.

Kaplan-Meier: Time to death (28 days follow-up)



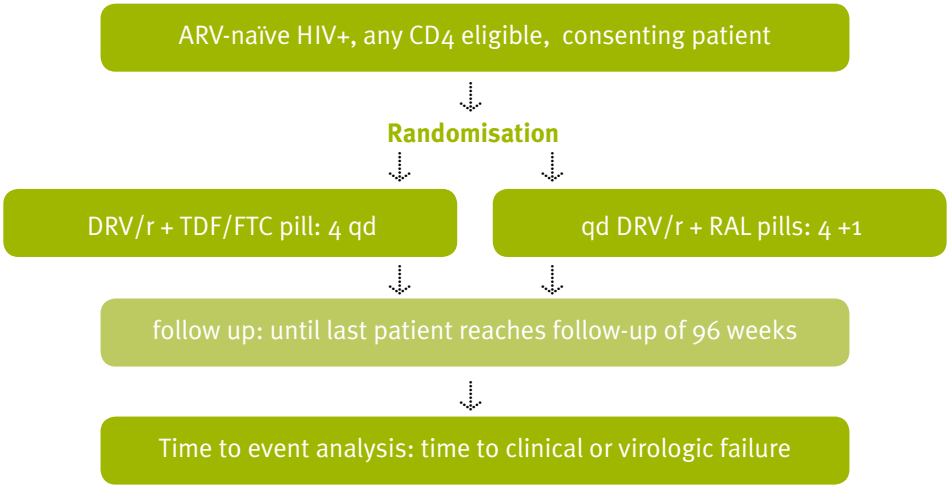
NEAT

Description and study objective

NEAT (European AIDS Treatment Network) is an EU funded initiative with 41 partner institutions of which CHIP is one. NEAT's mission is to strengthen European HIV clinical research capacity by building a clinical and laboratory network for HIV therapeutics. NEAT will promote transnational clinical research from proof of concept to phase III-IV strategic effectiveness trials with direct involvement of 41 core partners from 16 countries and over 350 affiliated centres with established set-up for international clinical studies.

NEAT 001 / ANRS 143 - the first trial launched by NEAT - is a phase III, multicentre open-label randomised trial comparing the efficacy and safety of two first line regimens in HIV-1-infected antiretroviral naïve subjects over at least 96 weeks: darunavir (DRV)/ritonavir (r) + tenofovir (TDF)/emtricitabine (FTC) vs. DRV/r + raltegravir (RAL). The study's primary objective is to assess the non-inferiority of DRV/r + RAL compared to DRV/r + TDF/FTC.

NEAT Schematic



NEAT will enroll a total of 800 participants at 96 sites from 16 countries within Europe. The entire study is expected to last a minimum of 96 weeks with enrolment planned to start in 2010. In addition, a number of ancillary studies and sub-studies are planned within this first NEAT trial funded by the EU and ANRS.

Accomplishments in 2009 and NEAT at the Copenhagen CTU

As one of four Clinical Trial Units (CTU) within the NEAT network, CHIP is responsible for the implementation and conduct of the trial at 22 sites from 7 European countries (Austria, Belgium, Denmark, Germany, Poland, Portugal and Sweden).

Extensive preparations for this European project have been ongoing throughout 2009 including the release of protocol version 1.0 in October 2009, set up of trial logistics, negotiations with pharmaceutical companies providing study drug and preparations for submission to Ethics Committees and Competent Authorities.

Observational Studies

CHIP
COPENHAGEN HIV PROGRAMME

D:A:D

Study Objectives

The D:A:D (the Data Collection on Adverse events of Anti-HIV Drugs) is a prospective multicohort study of HIV-infected persons under active follow-up. The main objective of the study is to assess the incidence of myocardial infarction (MI) 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.

At a glance

Study Overview (status as of October 2009)	
Patients enrolled	49,782
Number of clinics	212
CD4 count measurements	961,488
Total Person-years of follow-up	199,790
Triglycerides measurements	479,278
Centrally validated endpoints, MIs	668

2009 in review

The D:A:D study expanded with the inclusion of more than 16,000 patients and initiated the collection of new end-points: non-AIDS defining cancers, chronic liver disease and end-stage kidney disease for central validation at the D:A:D coordinating centre at CHIP. There were 3 articles published in peer-reviewed journals; 2 articles accepted for publication; and 3 submitted. They covered topics such as the risk of MI assessed in 13 individual anti-HIV drugs; the metabolic syndrome and risk of MI; the association between modifiable risk factors and specific causes of death amongst HIV-infected; and Diabetes mellitus (DM), pre-existing coronary heart disease (CHD) and the risk of subsequent CHD events in HIV-infected patients.

Additionally the study group had 2 oral presentations and 2 posters at international conferences in 2009. Please visit www.cphiv.dk/dad/ to view the entire presentation or publication details.

What's next?

Due to the large size of the D:A:D study, the study will have the potential of exploring possible relationships with drug exposure and rare outcomes such as end-stage kidney disease and chronic liver disease in the years to come . From 2009 and onwards the study will focus on the associations with long-term drug exposure and long-term complications in particular non-AIDS defining cancers. Additionally the D:A:D study will assess the relationship with immunodeficiency and non-fatal cancer outcomes.

EuroSIDA

Study Objectives

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.

At a glance

Study Overview (status as of October 2009)	
Patients enrolled	16,505
Number of countries	35
Number of clinics	103
Total Person-years of follow-up	84,069
CD4 cell measurements	357,312
Viral load measurements	300,639
Plasma samples collected	69,106

2009 in review

The EuroSIDA study group celebrated their 15th anniversary in 2009. A total of 126 articles have published in peer-reviewed journals so far, of which 9 were published in 2009. These articles covered topics such as hepatitis C, HIV virology and pharmacokinetics as well as issues addressed in cohort collaboration (ART-CC, COHERE, D:A:D). Additionally the study group had 8 oral presentations and 8 posters at international conferences in 2009. Please visit www.cphiv.dk/EuroSIDA/ to view the entire presentation or publication details. The study includes 16,500 patients (table) of which approximately 4,000 are from Eastern Europe, thus putting the study in a unique position of analysing regional differences in HIV epidemiology and HIV management across Europe.

What's next?

In November, EuroSIDA together with CASCADE, PENTA and COHERE submitted an application for the EuroCoord Network of Excellence to the European Commission. The application involved over 300 centres and clinics and will involve both new and existing science areas within each of the networks as well as a process of further integrating and harmonising observational research in HIV.

a multicentre study
EuroSIDA

The EuroSIDA study group

The multi-centre study group on EuroSIDA (national coordinators in parenthesis).

Argentina: (M Losso), C Elias, Hospital JM Ramos Mejia, Buenos Aires. **Austria:** (N Vetter), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck. **Belarus:** (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; O Suetnov, Regional AIDS Centre, Svetlogorsk. **Belgium:** (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent. **Bosnia-Herzegovina:** (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo. **Bulgaria:** (K Kostov), Infectious Diseases Hospital, Sofia. **Croatia:** (J Begovac), University Hospital of Infectious Diseases, Zagreb. **Czech Republic:** (L Machala), H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. **Denmark:** (J Nielsen), G Kronborg,T Benfield, M Larsen, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense, L Oestergaard, Skejby Hospital, Aarhus. **Estonia:** (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. **Finland:** (M Ristola), Helsinki University Central Hospital, Helsinki. **France:** (C Katlama), Hôpital de la Pitié-Salpétière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; JM Livrozet, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, D Neau, Unité INSERM, Bordeaux. **Germany:** (J Rockstroh), Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; S Staszewski, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. 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L. 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Virology group: B Clotet, R Paredes(Central Coordinators) plus ad hoc virologists from participating sites in the EuroSIDA Study.

Steering Committee: F Antunes, B Clotet, D Duiculescu, J Gatell, B Gazzard, A Horban, A Karlsson, C Katlama, B Ledergerber (Chair), A D'Arminio Montforte, A Phillips, A Rakhmanova, P Reiss (Vice-Chair), J Rockstroh

Coordinating Centre Staff: J Lundgren (project leader), O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, J Kjær, L Peters, J Reekie, J Kowalska

Statement of Funding:
Primary support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773) and the 6th Framework (LSHP-CT-2006-018632) programs. Support in 2009 also included unrestricted grants by Bristol-Myers Squibb, GlaxoSmithKline, Roche, Gilead, Pfizer, Merck and Co., Tibotec and Boehringer-Ingelheim. The participation of centres from Switzerland was supported by a grant from the Swiss Federal Office for Education and Science.

Updated 20 October 2009

Projects

CHIP
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The CoDe ("Coding of Death in HIV") Project

Scientific purpose

The CoDe project was initiated out of the 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 persons 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 are at great risk of mis-classification. 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, as well as a centralised review process of the data collected.

The project is currently being implemented in the D:A:D study and the methodology was also used by the HIV/TB Project. In addition, the CoDe coding system has been applied within the INSIGHT group collaborative work for SMART, ESPRIT and SILCAAT and The Antiretroviral Therapy Cohort Collaboration (ART-CC). See below for references.

Methods

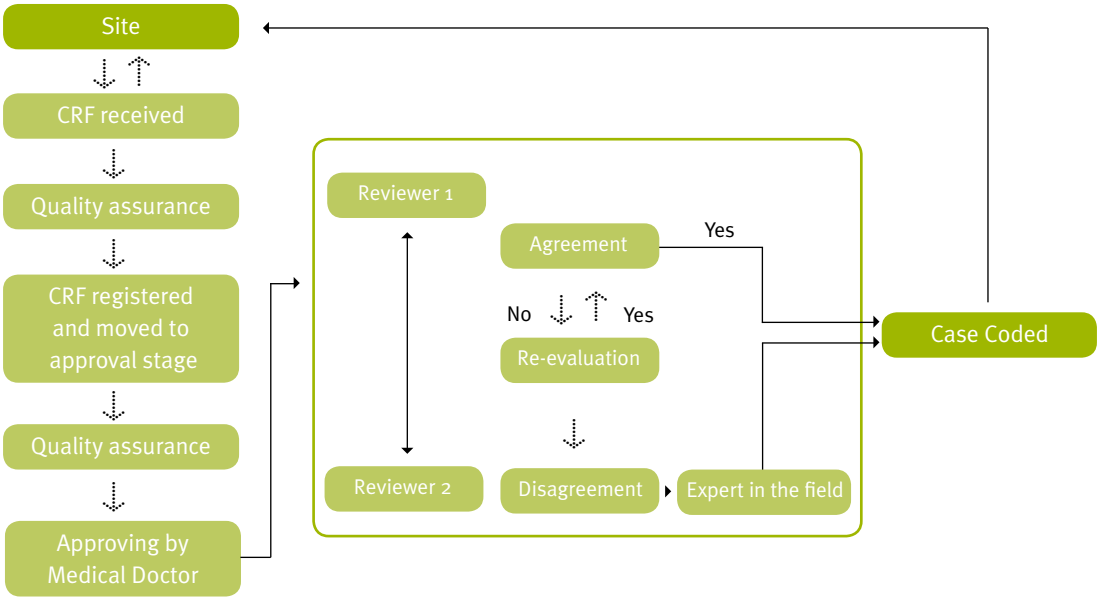
CoDe is a uniform coding system that can be applied to studies of individuals with HIV infection, including:

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

All study documents, CRFs, and other material are free to use and accessible online at www.cphiv.dk/CoDe.

Status

A CoDe Working Group meeting was held in March 2009 in Lisbon in order to evaluate the project and look at current areas of research focus. Based on the collected data and experience gained from the project, the group discussed how to move forward in 2010 and outlined the project's research priorities.



Implementation

CHIP is the coordinating office for implementing the CoDe project within the D:A:D study as well as coordinating and testing the overall methodology. They are responsible for the overall coordination of the project and the review process.

As of October 2009, a total of 1823 CRFs have been registered in the central CoDe database, of these approximately 360 in 2009. Nearly two-thirds of these cases have gone through the review process and have received a final classification of death as well as a classification of whether they were related to immunedeficiency.

Currently CoDe project's reviewers group consists of 31 senior physicians being actively involved in HIV patients' care and representing all European regions (http://www.cphiv.dk/CoDe.aspx)

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HIV/TB 2009

The project entitled "Co-infection with Mycobacterium tuberculosis among HIV-infected patients in Europe" or HIV/TB project, initiated by CHIP in 2006, is currently the largest international cohort of HIV-infected patients diagnosed with active tuberculosis. It currently includes 1075 HIV/TB patients from Eastern and Western Europe and Argentina.

- Eastern Europe (EE): Belarus, Latvia, Romania, Russia, Ukraine (582 patients).
- Central/Northern Europe (CNE): France, Denmark, Switzerland, United Kingdom (168 patients)
- Southern Europe (SE): Italy and Spain (210 patients)
- Argentina (115 patients)

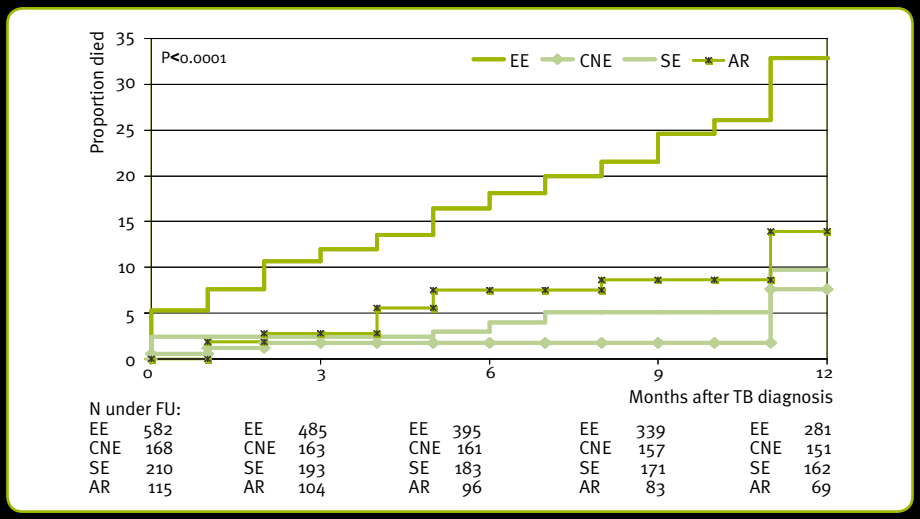
The primary aims of the project are to analyse regional diversity in patients' characteristics and management of HIV/TB patients across Europe and Argentina and to assess risk factors associated with death in these patients.

These important questions are addressed in the manuscript "Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina" which has recently been published in AIDS (AIDS 2009, 23:2485–2495). The most striking finding is that HIV/TB patients in EE, compared to those in the other regions, were at 3-5-fold increased risk of death within the first year after diagnosis of TB. At the same time, a higher proportion of patients from this region was infected with mycobacteria strains resistant to main TB drugs, and significantly lower proportion of patients were receiving combination antiretroviral therapy (cART).

During 2009, we extended the follow-up time to up to 2 years after TB diagnosis. Detailed analysis of causes of death and resistance patterns, which is currently ongoing, will help to better understand the substantial differences in mortality across regions.

In 2010, we plan to establish a prospective study, which will further contribute to a better understanding of various complicated clinical issues related to the HIV/TB coinfection.

Figure: Cumulative probability of death within 1 year of TB diagnosis in HIV-infected patients according to the region of residence



EuroCoord

In November, a three-year process advanced to a new phase with the submission of the EuroCoord Network of Excellence (NoE) application to the EU in response to their call for proposals under the 7th Framework. The proposed NoE has been formed by unifying 4 separate projects into one organisational structure, while at the same time allowing them to maintain autonomy in the areas necessary to ensure their continued success and productivity. The application has over 300 affiliated centres and investigators and has been developed with the goal and intention of ensuring the collaborative nature of European HIV observational research.

The daily business of EuroCoord will continue over the coming months while the application is under review. This will include:

EuroCoord CHAIN
The EU has funded EuroCoord to do a resistance project through CHAIN. This project will markedly increase the number of individuals with available information as compared to what each cohort or collaboration would be able to achieve. Additionally, it will allow us to answer important scientific questions that require data from large numbers because resistance profile and/or the outcome of interest is rare.

ACTIVATE

EuroCoord is also collaboratively implementing the ACTIVATE project. ACTIVATE (cap**AC**ity building and **T**raining in h**IV**/**A**ids **T**reatment and management across **E**urope) was awarded for 3 years (2007-2010) by DG SANCO. In October 2009, CHIP organised a training in Minsk, Belarus as a follow-up to the course in 2008. This course included 52 participants from 15 countries. Topics included Managing Resistance, Epidimiology and Statistics, HIV in Pregnancy, and Managing HBV and HCV co-infections and were presented by experts from both Eastern and Western Europe.

IWHOD (International Workshop on HIV Observational Databases)

In 2009, EuroCoord, in partnership with the scientific committee (SC) of the IWHOD, took over the organisation and administration of the cohort workshop.

The cohort workshop involves cohorts from Europe, Australia, North America and resource limited countries. The presented data at this workshop is not made public, thereby allowing for discussion of work-in-progress. The 2009 workshop was a two-day program held in Lisbon and included representation of 56 cohorts. Of the 171 abstracts submitted, 109 were presented.

COHERE (Collaboration of Observational HIV Epidemiological Research Europe)

Established in 2005, COHERE is a cohort collaboration which focuses on scientific questions requiring a large sample size of patients which the contributing cohorts cannot answer individually and which do not overlap with existing COHERE collaborations.

CHIP acts as one of two regional data management and coordinating centres for COHERE. In 2009, COHERE formalised the relationship with EuroCoord and is now one of the founding networks applying for the Network of Excellence funding under the European Commission.

Three publications were accepted during 2009; 2 in HIV-related non-hodgkins lymphoma and one looking at triple class virologic failure. A full list of COHERE publications and presentations from 2009 are available on page 50 of this report.

Indicator Disease-guided Testing

Progress towards optimal testing and earlier care - Indicator disease guided testing
An average of 1out of three Europeans infected with HIV remain unaware of their infection. Of those that are diagnosed, 50% are diagnosed very late in the course of their disease and long after they should have started treatment. Undiagnosed HIV results in poorer prognosis for the individual and increased transmission risk. Cost effectiveness analyses suggests cost savings if a population with a HIV prevalence of 1% or more are tested although this rate may be as low as 0.1%. However, there is very little – if any - evidence on HIV prevalence for various conditions and diseases in specific and easy to identify sections of society.

The concept of indicator disease guided testing was initiated at the HIV in Europe 2007 Conference. In the pilot phase of the project launched in May 2009, eight indicator diseases have been identified to assess HIV prevalence. These include patients presenting for care with::

(1) a sexually transmitted disease (including gonorrhoea, syphilis and other ulcerative genital conditions and chlamydia),
(2) malignant lymphoma, irrespective of type,
(3) cervical or anal dysplasia or cancer,
(4) herpes zoster in a person younger than 65 years,
(5) Hepatitis B or C virus infection (acute or chronic – and irrespective of time of diagnosis relative to time of survey),
(6) ongoing mononucleosis-like illness,
(7) unexplained leukocytopenia or thrombocytopenia lasting at least 4 weeks,
(8) seborrheic dermatitis / exanthema.

The study is coordinated by CHIP and enrolment of the 7500 patients started in 2009. Participating countries include: Austria; Belarus; Belgium; Bosnia; Croatia; Denmark; Germany; Italy; Netherlands; Poland; Spain; Sweden; UK; and Ukraine. The first phase is expected to be complete by mid 2010, where after an evaluation will inform the development of the second phase of the study.

HIV in Europe
Working Together for Optimal Testing and Earlier Care

HIV in Europe 2009 Stockholm

The HIV in Europe Conference, held under the auspices of the Swedish Presidency of the European Union on 2-3 November 2009 at the Nobel Forum in Stockholm, Sweden, gathered key European constituencies to discuss the prevailing obstacles to testing and present concrete results derived from the initiative. In 2009, CHIP took on the role as coordinating centre of the HIV in Europe initiative and coordinated the organisation of the conference in Stockholm.

Aims of Stockholm Conference:

- Identify and implement a definition of late presentation: an individual presenting with a CD4 count below 350 or with an AIDS diagnosis
- Discuss ways to estimate the number of infected not yet diagnosed population
- Criminalisation project, which aims at compiling a stigma index to gain more precise data on the extent of stigma across Europe and its impact on decisions about testing and treatment uptake

The conference was well attended with 36 civil society representatives, 34 researchers/health professionals, 22 policy makers and 9 industry sponsors from 25 countries (15 EU, 10 outside EU). Results of the ongoing projects will be published in 2010 and presented at international conferences and via the HIV in Europe website www.hiveurope.eu.

The PARTNER Study

Partner on **ART**: **N**ew **E**valuation of Transmission **R**isk

There is increasingly strong evidence that virally suppressive ART reduces infectiousness of people with HIV through sex. However, precise estimates of this risk of transmission from unprotected intercourse when the infected person is on ART with a most recent plasma viral load ‹50 copies/mL are not available, particularly for men who have sex with men (MSM). It is extremely important that more precise estimates are obtained, both for counselling purposes, and for investigations into the potential prevention effects of a policy of expanding ART coverage to be offered to all people with diagnosed HIV.

In 2009, Royal Free Hospital in London and CHIP began working together on a study on HIV transmission risk. The aim of the study is to precisely estimate the rate of transmission of HIV to an ongoing unprotected sex partner in persons with current plasma viral load ‹50 copies/mL on ART, and to assess factors associated with transmission of HIV to an ongoing unprotected sex partner. The study, coordinated at CHIP by Tina Bruun, will be launched as a European collaborative study and will include approximately 1650 participants.

PARTNER

Teaching and Outreach

CHIP
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Teaching and Outreach

CHIP has developed markedly in the past year, reflecting the University environment we are now a part of but also reflecting our wish to contribute to disseminating and applying the scientific results we have generated.

PhD students

CHIP strives to maintain a critical mass of PhD students and clinical assistants associated with the ongoing research activities – mainly related to EuroSIDA and D:A:D. It is important for the large projects to have engaged and dynamic younger researchers attached to expand the points of view, but equally important for PhD students to be involved directly and gain a thorough understanding of the day-to-day business of large research projects and an experience of working in a large network of international researchers. Also the direct involvement with the statistical group at Royal Free and the PhD students there is mutually inspiring. Currently, Lars Peters, Justyna Kowalska, Daria Podlekareva, and Caspar da Cunha-Bang are PhD students located at CHIP. Joanne Reekie and Alim Kamara are PhD students located at Royal Free Hospital, London. Within the last year Daria Podlekareva, Signe Westring Worm, and Jens-Ulrik Jensen successfully defended their PhD theses (p. 37). Christian Brandt received his doctoral as well in 2009.

Master Students

CHIP has supervised 2 Master students over 2009.

”Notification of Suspected Unexpected Serious Adverse Reactions according to the EU-Directive 2001/20/EC - a descriptive analysis of the legislation and the requirements in a European context based on publicly available data and a survey” was a thesis project conducted by Ellen Moseholm Larsen as part of the Master in Health Science education at the University of Copenhagen. The work underlying this thesis has been completed in the first half of 2009 in collaboration with Copenhagen HIV Programme (CHIP), under the supervision of Jesper Grarup and Ole Kirk.

”Understanding factors relating to HIV drug adherence in Viet Tiep Outpatient Clinic for

Transplantation Database

Following bone marrow or solid organ transplantation, treatment with immunosuppressive drugs, used to prevent rejection, renders patients susceptible to several opportunistic infections. Among these, post-transplant cytomegalovirus-infection is a potentially serious complication with risk of progression to CMV-disease associated with increased morbidity and mortality and reduced graft survival.

In a collaborative project between CHIP and Rigshospitalet, a prospective transplantation database and biobank will be established over consecutive patients receiving transplants. The project is a quality assurance and safety tool, which will evaluate the risks and associations of developing viral infections among transplant patients in order to optimise treatment. This project will be lead by Caspar da Cunha-Bang.

HIV infected people in Haiphong, Vietnam" was a thesis project conducted by Dinh Thi Mai Huong as part of the Master in International Health education at the University of Copenhagen. This thesis has been completed in collaboration with Copenhagen HIV Programme (CHIP), under the supervision of Lars Peters, Ole Kirk, and Jens Lundgren.

Internal education sessions

For the past few years, Daniela Gey has been the driver of the very popular programme for the weekly internal education sessions for CHIP staff members. Many subjects and teachers with closer or more remote relation to CHIP have willingly contributed.

Danish Institute for Study Abroad (DIS)

Lars Peters, Ulrik Bak Dragsted, Signe Worm and others from CHIP have been active in teaching at DIS (affiliated with Copenhagen University). Lars is the coordinator on the "A Biomedical Exploration of HIV and AIDS" course that ran in the Spring and Fall. This course included an overview of understanding of the complexity of HIV/ AIDS from a biological and medical perspective. The course also included biological characterisation of HIV (virology, immunology and epidemiology), and medical and clinical aspects of HIV/AIDS (development of HIV infection, opportunistic infections, treatments, complications and co-infections). The course featured distinguished guest lecturers from CHIP, including Nina Friis-Møller, Daria Podlekareva and Tina Bruun. Additionally, Lars, Ulrik, and Signe taught a short and intensive summer course on HIV/AIDS.

Master of HIV

In April 2009 CHIP resubmitted an application for accreditation for a one-year Masters programme of HIV. The Master of HIV was thereafter accredited in September 2009.

Starting in September 2010, under the Copenhagen School of Global Health and in close collaboration of the Master of International Health and Disaster Management, the Master of HIV is the first ever Masters Programme that focuses on both clinical and organisational management of HIV, and with a possibility of laboratory training. The Master is open to both people with a clinical (e.g. nurses, doctors) or an operational background (e.g. health programme managers, health care advisors) in the field of HIV.

While the focus of the Masters' is on HIV, due to the complex interplay between HIV, other diseases and their management teaching is generic and cross-disciplinary. This makes the Masters education applicable to people in a multitude of working positions.

A long history with EACS (European AIDS Clinical Society)
EACS produces the European Guidelines for treatment of HIV infected adults in Europe. So far the treatment guidelines have been translated from English into 13 additional languages. The first HIV treatment guidelines were published in Aids, Volume 17, Supplement 2 June 2003. A pocket version was first distributed at the 10th European AIDS Conference / EACS in Dublin in 2005. The guidelines are regularly updated by our teams of specialists. Over 7000 copies of the updated and extended guidelines (Version 5) were published during the 12th European AIDS Conference in Cologne.

The EACS Medical Exchange Programme enables doctors from Europe and from developing countries to benefit from a 4 month or 1 year exchange to one of the EACS European centres. CHIP has hosted EACS scholars since 2003 and welcomed Alexey Kruk for a one-year stay in 2009. Alexey has been working closely with the group at CHIP and within only 4 months of starting, had an oral presetation at EACS in Cologne. The presentation, entitled "Tuberculosis (TB) among HIV-1 infected patients across Europe: change over time and risk factors" was based on data from the EuroSIDA study.

A former EACS scholar from 2008, Csaba Kosa, also had an oral presentation at the EACS conference in Cologne entitled "Survival and prognostic factors for patients with non-AIDS defining malignancies (NADM)"

e-Learning Course "The practical approach to GCP"

As a task related to the training workpackage of the NEAT Network of Excellence, CHIP has developed a comprehensive e-Learning course – it has been important for CHIP to develop this as an add-on to the many on-line GCP training options. Thus, the course contains our experiences and practical hints, which, we anticipate, will help guide investigators to an easier GCP compliance.

We hope the e-Learning course will help the more inexperienced researchers initiate and conduct randomised clinical studies. The primary focus of the e-Learning course is to provide the participants with

Knowledge and understanding of current requirements
Tools to facilitate study procedures such as obtaining regulatory approvals and conduct of the study in general, including reporting of valid study results
CHIP's experiences as an international study-coordinating center

Aim

The e-Learning course is based on Good Clinical Practice (GCP) guidelines and the EU Clinical Trials Directive (Directive 2001/20/EC). The e-Learning course reflects CHIP's knowledge and experiences, as knowledge sharing is an important aim of CHIP. Thus, the E-Learning course is meant as a practical approach to GCP and a supplement to the existing GCP e-Learning courses.

The "Practical Approach to GCP" e-Learning course is divided into 5 modules:

1. The Regulatory Module
2. The Protocol and Study Participant Info module
3. The Safety and Drug module
4. The Study Conduct module
5. The Quality Management module

The E-learning course can be accessed at www.cphiv.dk

Dissertations

CHIP
COPENHAGEN HIV PROGRAMME

HIV and Cardiovascular Disease – Contribution of Metabolic Components and Drugs

Summary of Ph.D thesis defended successfully 29 January 2009
Signe Westring Worm, MD, Ph.D

The thesis is based on the three original papers published in peer-reviewed journals and in addition a review, available on the internet, is included.

The introduction of combination antiretroviral therapy (cART) in 1996 has dramatically improved the survival of HIV-infected individuals and significantly reduced HIV-related morbidity and mortality. However, this efficient treatment is associated with metabolic side effects; and a high prevalence of potential CVD risk factors have been reported. The clustering of many of the metabolic side effect associated with the use of cART, has striking similarities to the metabolic syndrome (MS), a term used to describe a clustering of risk factors for cardiovascular disease (CVD). Recent studies has shown an association between exposure to cART and a risk of myocardial infarction (MI), but also HIV per se has a yet not completely understood role for the risk of CVD.

Concepts for the management of CVD in the general population needs validation amongst HIV- infected individuals, before the concepts or entities can be adapted in to daily clinical care. The analysis of the MS, recognised as a CVD risk enhancer by the NCEP guidelines, is such an entity. This PhD thesis discussed the importance of identifying all CVD risk factors, and not only the risk factors in the MS definition, as we found a strong association between an increasing number of the risk factors in HIV-infected patients and an increased CVD risk. The presence of the MS in HIV-infected individuals did not appear to increase the CVD risk over and above that conferred by the components of the syndrome separately. The identification of one CVD risk factor should immediately lead the physician to search for other CVD risk factors as an increasing number of risk components is strongly associated with a risk of CVD. Another concept discussed was the 'DM as a CHD risk equivalent'. We compared the impact of development of DM to the impact of pre-existing CHD for the future risk for CHD. We found DM to be an important and independent risk factor for CHD in HIV-infected populations, but it does not appear to confer the same risk as pre-existing CHD. We have evidence to suggest that DM is becoming an increasing problem among those infected with HIV, and we have recently reported an increase of DM among patients under follow-up from 3.8% in 1999/2000 to 5.2% in 2005/6.

Regardless of whether diabetic patients have a risk of CHD identical to that of patients with prior CHD, the absolute risk of CHD in this subgroup of patients remains high. Thus, we suggest that targets for interventions among HIV-infected individuals should be based on the entire risk factor profile rather than just the presence or absence of DM. And, it is still of great importance to screen for this modifiable risk factor and to intervene against the development of DM. The thesis has further discussed that not all of the risk associated with cART can be directly explained through classical metabolic mechanisms. Although thymidine analogues from the NRTI drug class have been associated with the development of IR, DM and dyslipedemia, these were not associated with an excess risk of MI. Unexpectedly, we found abacavir, a drug with no reported metabolic side effect, significantly associated with an increased risk of MI. Guidelines on treatment of the HIV-infection have already notified the signal between abacavir and MI, but requires

additional confirmation of our findings. Further investigations are initiated to explore the biological explanation for the association between abacavir and MI, especially focusing upon the importance of inflammation amongst HIV-infected individuals.

Dynamic Use of Biomarker Procalcitonin in the Intensive Care Unit

Summary of Ph.D thesis defended successfully 24 August 2009

Jens-Ulrik Jensen, MD, Ph.D

Bacterial infection remains a major cause of mortality in patients who are admitted to the intensive care unit. Diagnosis and monitoring of effects of antibacterial treatment is particularly complicated in these critically ill patients, since infections may not clinically present typically, difficulties in separating colonisation from invasive infection, patients may suffer from multiple pathologies and receive medication affecting the usual parameters to assess the treatment response. Additionally, the established biomarkers, namely C-reactive protein and white blood cell count have several limitations in these patients, because of their slow elimination kinetics and a low specificity for bacterial infection. Therefore, a need for novel methods to diagnose bacterial infections and monitor the response to antibacterial chemotherapy would be desirable. Unfortunately, results regarding the biomarkers of infection investigated so far are diverging; this is also true for the most investigated biomarker of infection, Procalcitonin.

The aim of this Ph.D. was to investigate the prognostic power of Procalcitonin measurements and, most importantly, the ability of PCT-guided antimicrobial therapy in improving survival and other outcome parameters in ICU patients. Core elements in this approach were to: 1) study outcome endpoints other than sepsis or other clinical diagnoses, 2) as a diagnostic and treatment monitoring biomarker of ongoing bacterial infection with daily sequential measurements, to investigate the potentially useful information from changes in levels of the biomarker over time after admission to ICU, 3) to apply the randomised controlled intervention methodology to assess whether procalcitonin-guided antibiotic use can reduce mortality in critically sick patients.

Paper I is an original article of 472 ICU patients and 3,642 PCT measurements, sampled on all days of the ICU admission. The main result was that one single day of PCT increase in the ICU, was an independent predictor of mortality (based on at least two measurements), and conversely, that the level of PCT at admission, was not a predictor of mortality. The hazard ratio for death, for patients who had at least one day of PCT-increase was 1.8 [95% CI 1.4-2.4]. It was also found, that increases in white blood cells or C-reactive protein were not predictors of mortality.

Paper II is the protocol for the PASS trial, a 1,200 patient randomized interventional trial, which has been developed in part on the basis of the results of paper I. Along side paper II, the data from the open reports from the so far performed interim analyzes are included. To preserve the integrity of the study, outcome data from the study remained blinded until the study had been completed (after the PhD defence). The results from the trial were later presented at the Infectious Disease Society of America meeting, Oct 28th – Nov 1st 2009, Philadelphia, USA.

Difference in HIV Care Across Europe with Focus on Tuberculosis and Other Opportunistic Infections

Summary of Ph.D thesis defended successfully 8 December 2009
Daria N. Podlekareva, MD, Ph.D

This PhD thesis is based on three original manuscripts and a review manuscript of the results from the EuroSIDA study.

One of the goals of this PhD was to determine risk factors associated with development of opportunistic infections (OIs) at relatively high CD4 cell count. The strongest predictors for that were current CD4 cell count and use of cART. However, the main finding was that irrespective of a significant increase in CD4 cell count, the risk of developing OIs was non-negligible. Thus, this study contributed to the accumulating evidence on earlier (vs. deferred) cART initiation, when immune function is yet not severely compromised, in order to prevent disease progression as early as possible. Some OIs (i.e. tuberculosis) can develop at any spectrum of immunodeficiency. HIV/TB co-infection provides major challenges for clinicians due to composed pathogenetic mechanisms, treatment complexity and drug-drug interaction. The situation with HIV/TB epidemic in Eastern Europe (EE) is of particular concern due to the high prevalence of TB in the general population, fast growing HIV epidemic and overlapping risk groups for acquiring both diseases (i.e. injection drug users). Therefore a major focus of this research was on HIV-epidemic in EE and HIV/TB co-infection in particular. An independent international HIV/TB project, addressing clinical and epidemiological aspects of this co-infection has been developed and initiated in 2006. The database now consists of 1075 HIV-infected patients from Europe and Argentina diagnosed with active TB between 2004 and 2006.

Profound regional differences in clinical prognosis after TB diagnosis, in particular a 3-5-fold higher one-year mortality rate in EE compared with Western Europe and Argentina were found. This study highlights the concern of a low use of cART in EE compared with the other parts of Europe and Argentina and high prevalence of multi drug resistant (MDR)-TB in this region. It also emphasises the increasing problem of the HIV/TB epidemic throughout Europe and addresses not only clinical, but also public health issues related to the HIV/TB co-infection.

Further, EuroSIDA is the first clinical study to document a pronounced regional difference in patients' characteristics across Europe. Our data emphasises a more recent HIV epidemic in EE: 50% of the HIV-infected population have a history of injection drug use and are co-infected with hepatitis C. A low usage of cART in HIV-infected patients in EE was also documented.

One of the reasons for low usage of cART and high mortality rate of HIV/TB co-infected patients in EE could be a suboptimal management of these patients. Compliance with current HIV-guidelines (when to start cART, what regimen to use, frequency of laboratory monitoring) and ability to maintain maximum virological suppression were assessed and compared across the European regions using the EuroSIDA database. The analysis showed, that a high proportion of EE patients with low CD4 cell count had not initiated cART, and among patients who had initiated cART, their ability to maintain maximal virological suppression

was considerably lower when compared to patients from the rest of the Europe. In addition, the HIV-RNA and CD4 cell counts of patients in this region are less frequently monitored than in other regions. Countries from Northern Europe archived the best results in terms of virological response to cART and results of this region can be used to benchmark HIV-care.

Thus, this study introduces a benchmark of HIV care and a set of health care indicators, which can be used for assessment of clinical management of HIV-infected patients. It can be further adjusted and implemented elsewhere. The new knowledge obtained during the current PhD project is applicable for the enhancement of surveillance efforts and the establishment of targeted interventions in the specific regions and population groups, and for specific diseases. This may help to identify patients in greatest need and ultimately improve the clinical management of these patients and thereby also their prognosis.

Experimental studies of Pneumococcal Meningitis

Summary of doctoral thesis defended successfully 27 November 2009

Christian T Brandt, MD, DMSc

This thesis summarizes experimental meningitis research conducted at Statens Serum Institut in collaboration with the Copenhagen HIV programme and the Danish Research Centre for Magnetic Resonance between 2001 and 2007. Previous experimental studies had shown that the host inflammatory response in invasive infections contributed significantly to an extremely poor outcome despite initiation of efficient antimicrobial chemotherapy. Consequently, we aimed to investigate and clarify how the course of disease in pneumococcal meningitis was modulated by local meningeal inflammation and concomitant systemic infection and inflammation. Experimental studies were based on the development of a rat model of pneumococcal meningitis, refined and optimized to closely resemble the human disease, mimicking disease severity, outcome, focal- and global brain injury and brain pathophysiology. These endpoints were evaluated by the development of a clinical score system, definition of outcomes and measurement of hearing loss by oto-acoustic emission. The investigation of invitro and invivo brain pathology with histology and MRI revealed an injury pattern similar to that found clinically.

Additionally, MRI enabled the study of parameters closely related to the cerebral pathophysiology of meningitis (brain oedema, blood brain barrier permeability, focal brain injury and hydrocephalus). Modulation of the inflammatory host response was achieved by initiation of treatment prior to infection: 1) G-CSF treatment increased the peripheral availability of leukocytes, 2) Selectin blocker fucoidin attenuated meningeal leukocyte accumulation and 3) A serotype specific Ab augmented systemic pneumococcal phagocytosis. The studies revealed a dual role of the inflammatory response in pneumococcal meningitis. Whilst focal brain injury appeared to result from local meningeal infectious processes, clinical disease severity and outcome appeared determined by systemic infection. Furthermore,

systemic disease contributed significantly to BBB permeability and brain ventricle expansion. Ventricle expansion was also associated with clinical appearance. An augmented systemic host response limited pneumococcal bacteraemia and protected from fatal outcome, but did not reduce occurrence of focal brain injury. Thus, our findings suggest that meningitis sequelae arise from local disease complications whereas fatal outcome is accelerated by systemic infection. Understanding of the relationship and interplay between septicaemia, ICP, ventricle expansion and brain edema could help optimize the treatment of these disease complications by, for example, improved systemic infection control.

New therapeutic approaches to improve survival and neurological outcome from pneumococcal meningitis may be achieved through identification of the pathogen factors that initiate and prolong extensive systemic and local inflammation. Investigation of genomic differences and protein expression between pneumococcal serotypes or between identical serotypes with different virulence are considered crucial to this progress. Future progress may also be achieved by disease prevention with pneumococcal vaccines. Randomized trials of treatment strategies including bacteriostatic agents, antioxidants or more specific anti-inflammatory agents are realistic possibilities in the near future.

Acknowledgements

Karen Skov Hansen left CHIP to follow her inner entrepreneur and settle with her own business. Karen worked hard and professionalised many of the complicated processes related to adhering to regulatory requirements in clinical trials. Without Karen's kind but firm hand, many posters and abstracts would never have met their deadlines. We are happy that we can still utilise Karen's skills regarding translation and graphical work – although we would have preferred it could have been within the frames of CHIP.

After 7 years as DAD data-manager Allen Sawitz is now enjoying his life as a pensioner. In a professional and friendly fashion Allen has managed to get all of the cohort data-managers to work together throughout the annual mergers, secured a very high quality of data and in addition, high levels of commitment from all involved – many thanks.

Clinical monitor, Søren Stentoft Reilev unfortunately had to relocate his family to the isle of Funen. We owe Søren a major part of the honour for being able to finalise the PASS study with unprecedented speed and we are glad that we have the opportunity to work with Søren as a monitor for the TAExaCOP trial where CHIP is doing the data management and scientific advisement.

Awards

Signe Westring Worm
PhD Student of the Year, Panum Institute, University of Copenhagen
Danish Research Council Post-doctorate grant

Daria Podlekareva
World AIDS Day promoted article by LWW Partnerships: 'Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina', published in AIDS.

Jens-Ulrik Jensen
The Danish Freemasons Scientific Award 2009, dedicated to research within mild induced hypothermia of critically ill patients with severe sepsis and septic shock
Region Hovedstadens Forskningsfond Grant

Laboratory

CHIP also houses laboratory facilities and secures a biobank of samples. Shipments for analysis and securing the repository are the responsibility of Ruth Kjærgaard for the clini cal trials and Annette Fischer for the observational studies.

Funding

CHIP is entirely dependent on external project-specific funding; only Jens' university position and a one-time contribution to the marketing of the master education are funded by the University.

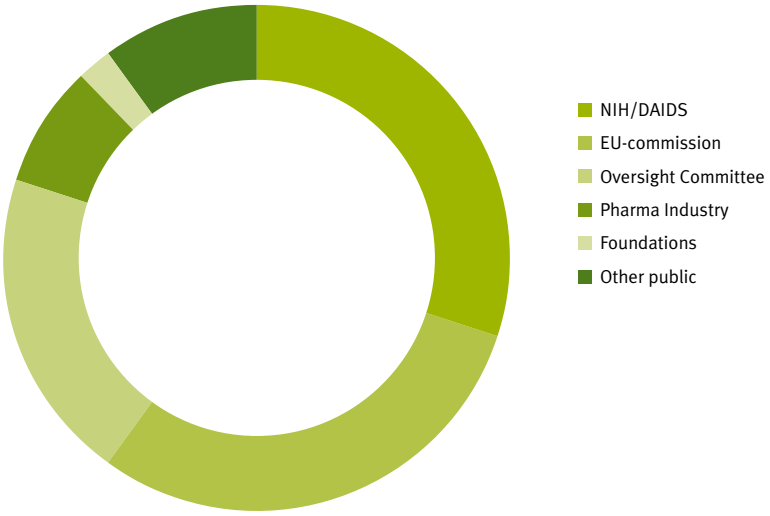
EU

CHIP as coordinator is completing the last year of funding for EuroSIDA in February 2010. The continued funding will be under the umbrella of EuroCoord (see specific section). CHIP is involved as a partner in four additional EU projects ACTIVATE, CHAIN, NEAT and the WHO project, Monitoring Medicines.

NIH

CHIP receives limited network funding as International Coordinating Centre in the INSIGHT Network. The START study was granted 10 million USD in early summer 2007 to be used for an initial study phase over two years. Due to massive delay caused by the NIH objection to act as sponsor based on responsibilities imposed by the Clinical Trials EU Directive, the initiation of START has been delayed substantially, and further complicated due to contract negotiations with the pharmaceutical companies supplying the study drug.

CHIP funding



Pharmaceutical Industry

It is important to notice that CHIP is not involved in clinical trials with pharmaceutical companies as sponsors; the studies conducted or coordinated at CHIP being regulatory registration studies or phase IV post marketing studies.
It is important for us that the activities of CHIP are driven by an academic research agenda supported by public funding and that CHIP is a strictly non-profit research organization working solely for the benefit of patients by conducting high quality science. We emphasize that the private co-funding we raise is encouraged by and in line with the policies of our public sponsors.

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 if the scientific question to be investigated under the agreement is found 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.

The D:A:D study was funded by the HAART Oversight Committee for an additional period including merger 13 in 2012. The prolonged funding also includes a major increase in the type of events collected by adding chronic liver disease, end-stage kidney disease and non-AIDS defining cancers. Likewise, an additional cohort of 16,000 patients was included. The Oversight Committee originally was formed based on requests from EMEA that follow closely the D:A:D results and continued funding.

Together with the University of Bordeaux, CHIP is administering the activities of the legal entity established to take care of the International Workshop on HIV Observational Databases (IWHOD). The 'HIV in Europe' initiative is coordinated by CHIP and is a cross-European and multidisciplinary initiative working for optimal testing and earlier care for HIV in Europe (p. 28) A number of pharmaceutical companies sponsor the initiative (please see table on page 46) but the activities and oversight are governed by an academic steering committee without industry representation.

Financial contributors current year

Study/activity	Public	Private
EuroSIDA	EU Commission	Gilead Sciences Merck & Co Inc Pfizer Inc Tibotec
D:A:D	The Oversight Committee for The Evaluation of Metabolic Disorders of HAART EMEA FDA	Abbott Laboratorie Boehringer-Ingelheim Pharmaceuticals Inc Bristol-Myers Squibb Gilead Sciences GlaxoSmithKline Merck & Co Inc Pfizer Inc Roche Pharmaceuticals Tibotec
INSIGHT network	NIH	
INSIGHT START	Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), Australian National Health and Medical Research Council (NHMRC); Bundesministerium fur Bildung und Forschung (BMBF), Division of Clinical Research, NIAID, NIH; National Institute for Mental Health (NIMH), NIH; National Institute of Neurological Disorders and Stroke (NINDS), NIH; National Cancer Institute (NCI), NIH; European AIDS Treatment Network (NEAT); Department of Bioethics, NHI, Clinical Center	
INSIGHT FLU	NIAID, NIH	
PASS	Danish Research Council	B.R.A.H.M.S.-Diagnostica GmbH
COHERE	ANRS, Agence nationale de recherches sur le sida Dutch HIV Monitoring Foundation	
NEAT	EU Commission	
ACTIVATE	EU Commission	
EUROCOORD-CHAIN	EU Commission	Gilead Sciences
IWHOD	NIH Office of AIDS Research NEAT ANRS, Agence nationale de recherches sur le sida	Boehringer-Ingelheim Gilead Sciences GlaxoSmithKline Pfizer Inc Roche Pharmaceuticals Tibotec
HIV in Europe	AIDS Action Europe European AIDS Treatment Group (EATG) University of Copenhagen	Abbott Laboratorie Boehringer-Ingelheim Bristol-Myers Squibb Gilead Sciences GlaxoSmithKline Merck & Co Inc Schering-Plough Swedish Research Council Tibotec
Milky Way project	EDCTP HIVCENER, Frankfurt UCL, London CHIP, Copenhagen	
Pharmacovigilance for ARTs		Bill & Melinda Gates Foundation

Publications

CHIP
COPENHAGEN HIV PROGRAMME

During 2009, a total of 31 articles were published or accepted for publication in peer-reviewed journals. Scientific articles are one of the main-outcomes for CHIP as an organisation, and the articles published in 2009 derive from a variety of projects and nicely illustrate the diversity of the projects CHIP is involved in.

1 Absence of a relation between efavirenz plasma concentrations and toxicity-driven efavirenz discontinuations in EuroSIDA. M van Luin, WP Bannister, A Mocroft, P Reiss, G Di Perri, G Peytavin, J Molto, A Karlson, A Castagna, M Beniowski, JD Lundgren, DM Burger; the EuroSIDA study group
Antiviral Therapy. 2009;14(1):75-83.

2 Use of risk equations for predicting disease progression in HIV infection. A Mocroft, JD Lundgren.
Clin Infect Dis. editorial

3 Procalcitonin monitoring in trauma intensive care patients: how helpful is it? JU Jensen, JD Lundgren.
Critical Care Medicine 2009 Jun;37(6):2093-4.

4 Hepatitis C Virus (HCV) Coinfection Does Not Influence the CD4 Cell Recovery in HIV-1 Infected Patients with Maximum Virologic Suppression. L Peters, A Mocroft, V Soriano, J Rockstroh, P Aldins, M Losso, L Valerio, P Reiss, B Ledergerber, J Lundgren, for the EuroSIDA Study Group.
JAIDS. (in press)

5 Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. When to Start Consortium, J A Sterne, M May, D Costagliola, F De Wolf, A N Phillips, R Harris, M J Funk, R Geskus, J Gill, F Dabis, J M Miró, A Justice, B Ledergerber, G Fätkenheuer, R Hogg, A D'Arminio Monforte, M Saag, C Smith, S Staszewski, M Egger, S R Cole.
Lancet. 2009 Apr 18;373(9672):1352-63.Epub 2009 Apr 8.

6 Major breakthroughs in the medical treatment of HIV infection.O Kirk, J Gerstoft, JD Lundgren, N Obel.
Ugeskr Laeger. 2009 Mar 2;171(10):787-789.

7 Diabetes mellitus, preexisting coronary heart disease, and the risk of subsequent coronary heart disease events in patients infected with human immunodeficiency virus: the DATA Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study). SW Worm, S De Wit, R Weber, CA Sabin, P Reiss, W El-Sadr, AD Monforte, O Kirk, E Fontas, F Dabis, MG Law, JD Lundgren, N Friis-Møller.
Circulation. 2009 Feb 17;119(6):805-11. Epub 2009 Feb 2.

8 Presence of the metabolic syndrome is not a better predictor of cardiovascular disease than the sum of its components in HIV-infected individuals: data collection on adverse events of anti-HIV drugs (D:A:D study). SW Worm, CA Sabin, P Reiss, W El-Sadr, A Monforte, C Pradier, R Thiebaut, M Law, M Richenbach, S De Wit, JD Lundgren, N Friis-Møller.
Diabetes Care. 2009 Mar;32(3):474-80. Epub 2008 Dec 3.

9 Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. A M Kesselring, F W Wit, C A Sabin, J D Lundgren, J Gill, J Gatell, A Rauch, J S Montaner, F de Wolf, P Reiss, A Mocroft.
AIDS. 2009 Aug 24, 23 (13): 1689-99.

10 The ART Cohort Collaboration: Variable impact on mortality of AIDS defining events diagnosed during combination antiretroviral therapy: Not all AIDS Defining Conditions are Created Equal. Writing committee: Mocroft, A., Sterne, J., Egger, M., May, M., Grabar, S., Furrer, H., Sabin, C., Fatkenheuer, G., Justice, A., Reiss, P., d'Arminio Monforte, A., Gill, J., Hogg, R., Bonnet, F., Kitahata, M., Staszewski, S., Casabona, J., Harris, R. and Saag, M. Clin Infect Dis. 2009 Apr 15;48(8):1138-51.

11 Activation and Coagulation Biomarkers are Independent Predictors of the Development of Opportunistic Disease in Patients with HIV Infection. Rodger AJ, Fox Z, Lundgren JD, Kuller LH, Boesecke C, Gey D, Skoutelis A, Goetz MB, Phillips AN; the INSIGHT Strategies for Management of Antiretroviral Therapy (SMART) Study Group.
J Infect Dis. 2009 Sep 15;200(6):973-983.

12 Rate of Accumulation of Thymidine Analogue Mutations in Patients Continuing to Receive Virologically Failing Regimens Containing Zidovudine or Stavudine: Implications for Antiretroviral Therapy Programs in Resource-Limited Settings. Cozzi-Lepri A, Phillips AN, Martinez-Picado J, d'Arminio Monforte A, Katlama C, Hansen AB, Horban A, Bruun J, Clotet B, Lundgren JD; EuroSIDA Study Group.
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14 Risk of virus transmission from well-treated patients with HIV? Gerstoft J, Mathiesen L, Lundgren JD, Nielsen HI, Pedersen C, Obel N, Laursen A. Ugeskr Laeger. 2009 Mar 23;171(13):1085.

15 Uncertainty as to whether the use of antiretroviral therapy for persons recently infected with HIV has a favorable risk-to-benefit ratio. Lundgren JD, Phillips AN, Neaton J.
Clin Infect Dis. 2009 Apr 15;48(8):1162; author reply 1162-3.

16 Interruption of antiretroviral therapy is associated with increased plasma cystatin C. Mocroft A, Wyatt C, Szczech L, Neuhaus J, El-Sadr W, Tracy R, Kuller L, Shlipak M, Angus B, Klinker H, Ross M; INSIGHT SMART Study Group.
AIDS. 2009 Jan 2;23(1):71-82.

17 History of viral suppression on cART as a predictor of virological failure after a treatment change. J Reekie, A Mocroft, B Ledergerber, M Beniowski, B Clotet, J van Lunzen, A Chiesi, C Pradier, L Machala, J D Lundgren on behalf of the EuroSIDA Study Group.
HIV Medicine (in press).

18 High prevalence of the metabolic syndrome in HIV-infected patients: impact of different definitions of the metabolic syndrome. SW Worm, N Friis-Møller, M Bruyand, A D'Arminio Monforte, M Rickenbach, P Reiss, W El-Sadr, A Phillips, J Lundgren, C Sabin, for the DAD Study Group.
AIDS. 2010 Jan 28, 24(3): 427-35. Epub ahead of print 30 nov 2007.

19 Estimated average annual rate of change of CD4 counts in patients on combination antiretroviral therapy. A Mocroft, AN Phillips, B Ledergerber, C Smith, JR Bogner, K Lacombe, A Wiercinska-Drapalo, P Reiss, O Kirk, JD Lundgren for the EuroSIDA Study group.
Antiviral Therapy (accepted for publication).

20 Predictors of hepatitis B virus (HBV) genotype and viremia in HIV-infected patients with chronic hepatitis B in Europe. V Soriano, A Mocroft, L Peters, J Rockstroh, F Antunes, N Kirkby, S de Wit, A d'Arminio Monforte, R Flisiak, and J Lundgren on behalf of EuroSIDA.
Journal of Antimicrobial Chemotherapy (accepted for publication).

21 Markers of inflammation, coagulation and renal function are elevated in adults with HIV infection. J Neuhaus, et al.
J Infect Dis; in press

22 Risk of all-cause mortality associated with non-fatal AIDS and serious non-AIDS events among adults infected with HIV. J Neuhaus, et al.
AIDS; in press

23 Relative risk of death in the SMART study. B Grund, J Neuhaus, A Phillips; INSIGHT SMART Study Group.
Lancet Infect Dis. 2009 Dec;9(12):724-5.

24 Lipoprotein particle subclasses, cardiovascular disease and HIV infection. DA Duprez, LH Kuller, R Tracy, J Otvos, DA Cooper, J Hoy, J Neuhaus, NI Paton, N Friis-Møller, F Lampe, AP Liappis, JD Neaton for the INSIGHT SMART Study Group.
Atherosclerosis 2009; doi:10.1016/j.atherosclerosis.2009.05.001 (epub first).

25 Prognosis of HIV-associated non-Hodgkin lymphoma in patients starting combination antiretroviral therapy. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group.
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26 Triple class virologic failure in HIV-infected patients on antiretroviral therapy for up to 10 years. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group.
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27 Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina. Podlekareva DN, Mocroft A, Post FA, Riekstina V, Miro JM, Furrer H, Bruyand M, Panteleev AM, Rakhmanova AG, Girardi E, Losso MH, Toibaro JJ, Caylá J, Miller RF, Obel N, Skrahina A, Chentsova N, Lundgren JD, Kirk O; HIV/TB Study Writing Group.
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J Infect Dis. 2009 Dec 29 (Epub ahead of print).

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N Engl J Med. 2009 Oct 15;361(16):1548-59.

30 Incidence and risk factors of HIV-related non-Hodgkin lymphoma in the era of combination antiretroviral therapy: European multi-cohort study. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group.
Antiviral Ther. 2009; 14(8):1065-74.

31 Implementing the number needed to harm in clinical practice: risk of myocardial infarction in HIV-1-infected patients treated with abacavir. JD Kowalska, O Kirk, A Mocroft, L Høj, N Friis-Møller, P Reiss, I Weller, JD Lundgren.
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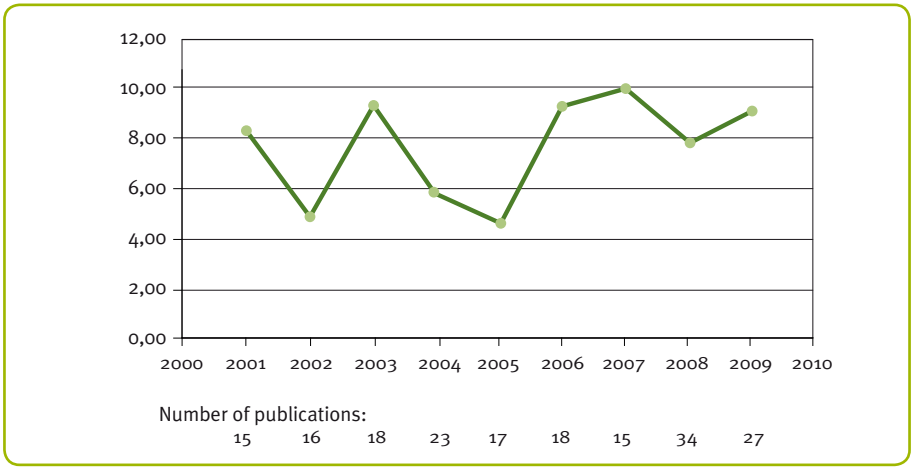
Average Impact Factor based on single publications



Presentations 2009

CHIP
COPENHAGEN HIV PROGRAMME

EACS Conference
11-14 November 2009 Cologne

Plenary Session

Earlier Recognition of HIV: A Pressing Need
Prof. Jens Lundgren, MD DMSc. Co-chair "HIV IN EUROPE Initiative" steering committee. University of Copenhagen & State University Hospital, Denmark

Oral

1 Estimating AIDS and non-AIDS related deaths for patients with missing death data in the EuroSIDA cohort Justyna D. Kowalska, Amanda Mocroft, Bruno Ledergerber, Robert Colebunders, Mattie Ristola, Josip Begovac, Helen Sambatakou, Court Pedersen, Jens D. Lundgren, Ole Kirk

2 Improvements in mortality between 2002-2007 across Europe : Differences between regions of Europe A Mocroft, B Gazzard, A Karlsson, I Karpov, S D Wit, J v Lunzen, C Katlama, K Zilmer, O Kirk, JD Lundgren on behalf of the EuroSIDA study group.

3 Tuberculosis (TB) among HIV-1 infected patients across Europe: change over time and risk factors Alexej Kruk, Wendy Bannister, Daria Podlekareva, Nelly Chensova, Aza Rakhmanova, Andrzej Horban, Pere Domingo, Jens D Lundgren, Amanda Mocroft, Ole Kirk, for the EuroSIDA Study Group.

4 Survival and prognostic factors for patients with non-AIDS defining malignancies (NADM) Csaba Kosa, Joanne Reekie, Johannes Bogner, Pierre-Marie Girard, Gerd Fätkenheuer, Antonio Chiesi, Martin Fisher, Frederik Neess-Engsig, Amanda Mocroft, Ole Kirk

5 Has the uptake of treatment for chronic hepatitis C virus infection (CHC) in HIV-positive patients in Europe changed over time? A. Mocroft, M. Vogel, M. Beniowski, C. Pradier, M. Battegay, D. Jevtovic, V. Soriano, L. Peters, J. Lundgren,J.K. Rockstroh, for the EuroSIDA Study Group.

6 Health Care Index (HCI) and Outcome following a diagnosis of tuberculosis (TB) O Kirk, A Mocroft, DN Podlekareva, FA Post, V Riekstina, JM Miro, H Furrer, M Bruyand, AM Panteleev, AG Rakhmanova, E Girardi, MH Losso, JJ Toibaro, J Caylá, RF Miller, N Obel, A Skrahina, N Chentsova, JD Lundgren, for the HIV/TB study group.

7 Epidemiological and virological characteristics of chronic HBV infection in HIV-positive patients in Europe from 1994 - 2006. Martin Vogel, Amanda Mocroft, Lars Peters, Francisco Antunes, Nikolai Kirkby, Stephane De Wit, Antonella d'Arminio Monforte, Robert Flisiak, Jürgen K. Rockstroh, Vincent Soriano for the EuroSIDA Study Group.

8 CD4 count, viral suppression, prophylaxis and the risk of primary pneumocystis pneumonia in the cart era - the Collaboration of Observational HIV Epidemiological Research Europe (COHERE). Amanda Mocroft, Jose M. Miro, Hansjakob Furrer, for the Opportunistic Infections Working Group.

9 Mortality rates of elderly HIV-infected adults treated with antiretroviral are closer to general population than in younger patients. Charlotte Lewden on behalf of COHERE.

Posters

1 Dialysis and renal transplantation in HIV-infected patients: a European survey in 2008 A Mocroft, JC Trullas, F Cofan, J Tourret, A Moreno, C Isnard, C Fux, C Katlama, P Reiss, J Lundgren, JM Gatell, O Kirk, JM Miro and the EuroSIDA Investigators.

2 Predictors of having a resistance test following confirmed viral load (VL) failure of cART. ZV Fox, AN Phillips, A Cozzi-Lepri, A d'Arminio Monforte, A Karlsson, A Mocroft, G Kronborg, J Kjaer, B Clotet and JD Lundgren for the EuroSIDA study group.

3 Prevalence of HIV-1 drug resistance over calendar time in EuroSIDA patients receiving antiretroviral

therapyWendy Bannister, Alessandro Cozzi-Lepri, Jesper Kjær, Bonaventura Clotet, Adriano Lazzarin, Jean-Paul Viard, Gitte Kronborg, Dan Duiculescu, Marek Beniowski, Ladislav Machala and Andrew Phillips.

4 Presence of drug resistance during the course of treatment in patients who developed virological failure to the three original classes of antiretroviral drug. Frank de Wolf on behalf of COHERE.

5 Viral load outcome after virologic failure of the three original antiretroviral drug classes in 2000-2007. Dominique Costagliola on behalf of COHERE.

6 HIV-related Hodgkin lymphoma in the era of HAART: incidence and survival in a European mulit-cohort study. Julia Bohlius on behalf of COHERE.

47th Annual Meeting of the Infectious Diseases Society of America, Philadelphia, October 2009

Oral

1 Can sequential procalcitonin or neopterin measurements help improve survival in the ICU? J Jensen, B Lundgren, J D Lundgren.

2 Efficacy and safety of Procalcitonin (PCT) guided antimicrobial chemotherapy (AMC) in the intensive care unit (ICU): Final results from a ransomised controlled trial of 1,200 patients. J Jensen, L Hein, M Bestle, K Thornberg, J Løken, M Steensen, Z Fox, H Tousi, P Søe-Jensen, J Kjær, A Ø Lauritsen, D Strange, P L Petersen, N Reiter, S Hestad, K Thormar, M H Andersen, T Mohr, P Fjeldborg, K M Larsen, N Drenck, C Østergaard, B Lundgren, J Grarup, J Lundgren.

Poster

1 Post-transplant CMV infection (CMVI): Therapeutic and immunological risk factors. C da Cunha-Bang, S Sørensen, M Iversen, H Sengeløv, J Hillingsø, S Mortensen, Z Fox, J Lundgren, The Herpes Virus Transplantation Study Group at the State University Hospital (Rigshospitalet), State University Hospital & Univeristy of Copenhagen, Denmark.

Frontiers of Retrovirology: Complex retroviruses, retroelements and their hosts, Montpellier, September 2009

Poster

1 A Bioinformatic Approach to Indentify New Potential Resistance Relevant Amino Acid Substitution (AAS) in HIV-1 Protease. CM Frederiksen, J Kjær, A Cozzi-Lepri, Z Fox and JD Lundgren.

5th European Conference on Clinical and Social Research on AIDS and Drugs, Vilnius, April 2009

Poster

1 A regioinal comparison of the mode of HIV-1 transmission in patients enrolled in the EuroSIDA study. J Tverland, J Reekie, M C Paulsen, A Mocroft, A Vassilenko, V Uzdaviniene, N Zakharova, N Chentcova, M Ellefson, O Kirk for EuroSIDA. Poster 72 KB

7th European Drug Resistance Workshop, Stockholm, March 2009

Poster

1 Predictors of having a resistance test following at least one episode of viral load (VL) failure of cART: data from EuroSIDA. ZV Fox, AN Phillips, A Cozzi-Lepri, A d'Arminio Monforte, A Karlsson, A Mocroft, G Kronborg, J Kjaer, B Clotet and JD Lundgren for EuroSIDA.

16th Conference on Retroviruses and Opportunistic Infections, Montreal, February 2009

Oral

1Risk of myocardial infarction (MI) in those exposed to specific antiretroviral drugs (ARVs) from the protease (PI), non-nucleoside reverse transcriptase (NNRTI) and nucleos(t)ide reverse transcriptase inhibitor (NRTI) drug classes: the D:A:D Study. JD Lundgren, P Reiss, S W Worm, W El-Sadr, S DeWit, R Weber, A d'Arminio Monforte, O Kirk, E Fontas, F Dabis, M G Law, N Friis-Møller, A N Phillips, C Sabin, on behalf of the D:A:D study group.

2 High hepatitis C viremia is associated with an increased risk for mortality in HIV/Hepatitis C virus coinfected individuals. J Rockstroh, L Peters, V Soriano, P Reiss, A d'Arminio Monforte, M Beniowski, M Losso, O Kirk, B Kupfer, A Mocroft on behalf of the EuroSIDA Study Group.

3 Association between modifiable and non-modifiable risk factors and specific causes of death in the HAART era: Results from the D:A:D study. C Smith, R Weber, S Worm, A Phillips, R Thiebaut, N Friis-Møller, C Pradier, O Kirk, A d'Arminio Monforte, W El Sadr, P Reiss, J Lundgren, C Sabin on behalf of the D:A:D Study Group.

4 Effect of Interleukin-2 on Clinical Outcomes in Patients with a CD4+ Cell Count of 300/mm3: Primary Results of the ESPRIT Study. Marcelo Losso.

5 Effect of Interleukin-2 on Clinical Outcomes in Patients with CD4+ Cell Count 50 to 299/mm3: Primary Results of the SILCAAT Study.
Yves Levy and SILCAAT Sci Committee.

Posters

1 Hyaluronic Acid as a Prognostic Marker of Hepatic Coma and Liver-related Death in HIV/Viral Hepatitis Coinfected Patients. L Peters, A Mocroft, V Soriano, J Rockstroh, B Ledergerber, A Karlsson, B Knysz, C Pradier, K Zimler, JD Lundgren for the EuroSIDA study group.

2 Mutation A376S in the RT connection domain is associated with an increased risk of virological failure to nevirapine- based therapy in NNRTI-naïve HIV-infected subjects in the EuroSIDA Study. R Parades, W Bannister, A Cozzi-Lepri, C Pou, R Bellido, J Bogner, P Gargalianos, D Bánhegyi, B Clotet, JD Lundgren and the EuroSIDA study group.

3 Serious Fatal and Non Fatal Non-AIDS Defining Illnesses (non-ADI) in Europe. A. Mocroft, P Reiss, J Gasiorowski, B Ledergerber, A Chiesi, J Gatell, A Rakhmanova, MA Johnson, O Kirk, JD Lundgren for the EuroSIDA study group.

4 Relationship between Current Level of Immunodeficiency and Non-AIDS malignancies. J Reekie, A Mocroft, F Engsis, A d'Arminio Monforte, A Wiercinska-Drapalo, P Domingo, F Antunes, N Clumeck, O Kirk, JD Lundgren for the EuroSIDA study group.

5 Interruption of Antiretroviral Therapy and Changes in Hyaluronic Acid as Marker of Liver Fibrosis Progression in SMART Viral Hepatitis Coinfected Participants and Matched Controls. L Peters, J Neuhaus, A Mocroft, V Soriano, J Rockstroh, G Dore, M Puoti, E Tedaldi, B Clotet, B Kupfer, JD Lundgren, MB Klein for the INSIGHT SMART Study Group.

6 Risk of extensive triple class virologic failure of the three original antiretroviral drug classes among people followed from therapy initiation with NNRTI or ritonavir-boosted PI regimens. R Lodwick on behalf of the PLATO II project team of COHERE.

7 Impact of cART on Incidence and Prognosis of HIV-1-associated Non-Hodgkin-Lymphoma - European Multi-Cohort Study. J Bohlius, M Egger, on behalf of the COHERE study group.

8 Antiretroviral Therapy (ART) Reinitiation and Hepatitis B Virus (HBV) Rebound among HIV – HBV Coinfected Patients following ART interruption in the SMART Study. V. Soriano.

9 Does Treatment Interruption within the SMART trial lead to changes in hepatitis C virus load in HIV-/HCV-coinfected patients? J Rockstroh.

10 Does Activation of Inflammatory and Coagulation Pathways Independently Predict the Development of Opportunistic Disease in Patients with HIV Infection? A Rodger.