European Network of HIV/AIDS Cohort Studies to Coordinate at European and International Level Clinical Research on HIV/AIDS

Final Report Summary - EUROCOORD (European Network of HIV/AIDS Cohort Studies to Coordinate at European and International Level Clinical Research on HIV/AIDS)

Executive Summary:
More than 2.2 million people are currently living with the Human Immunodeficiency Virus (HIV) in Europe and an estimated 35 million people worldwide are HIV positive. HIV is currently the sixth leading cause of death globally and halting the spread of HIV/AIDS remains one of the eight UN Millennium Development Goals. Although significant advances have been made in HIV management and treatment leading to considerable reductions in morbidity and mortality, many challenges remain.
The European Network of HIV/AIDS Cohort Studies to Coordinate at European and International Level Clinical Research on HIV/AIDS (EuroCoord) has been at the forefront of HIV/AIDS research by bringing together some of the biggest HIV cohorts and collaboration (CASCADE, COHERE, EuroSIDA and PENTA) within Europe.

The overarching aim of EuroCoord is to use the scientific strengths of each collaboration to ensure that the best, most competitive research is performed. Such a large, integrated network has allowed a common virtual database to be established, which currently has access to data from over 350,000 HIV-infected individuals across the European continent, and beyond, both male and female, from neonates to geriatric populations, infected through sex between men, sex between men and women, injecting drug use, nosocomially and from mother to child, with and without co-infection with hepatitis viruses, of different ethnic and socio-economic backgrounds, from indigenous and migrant populations, in settings with varying levels of access to care and laboratory techniques. Our multidisciplinary research has thus allowed us to address key areas of HIV research aimed at improving the management and life of HIV-infected individuals, whilst allowing us to explore differences within sub-groups.

EuroCoord has issued over 120 publications in peer-reviewed journals in the past five years and has played a central role in contributing evidence for national and international treatment guidelines, wherever possible, by developing papers and reports on characteristics of the European HIV positive population, pathogenesis of HIV, co-infection, impact of management strategies and treatment of sub groups of patients as well as prediction models. EuroCoord has also been involved in building training courses and learning tools for researchers across Europe and has developed processes for data harmonisation with the HIV Cohorts Data Exchange Protocol (HICDEP).

EuroCoord is in a position to mobilise European HIV cohort research, bringing it within one truly pan-European network of cohort studies with a strong and increasing presence in the Central- and Eastern European region. The structure of our network, maintaining autonomy within each individual network but within one common research platform, has ensured that the most competitive science is performed whilst allowing us to pool our expertise and resources to undertake new initiatives within an integrated collaborative structure.

**Project Context and Objectives:**

More than 2.2 million people are currently living with HIV in Europe and an estimated 35 million people worldwide are HIV positive. HIV is currently the sixth leading cause of death globally and halting the spread of HIV/AIDS remains one of the eight UN Millennium Development Goals. Although significant advances have been made in HIV management and treatment leading to considerable reductions in morbidity and mortality, many challenges remain which are now compounded by an altered economic climate. Persistent epidemic areas particularly in Eastern Europe, co-infections, inequalities in access to healthcare and an ageing population highlight the need for a continued collaborative approach. European scientists have been key players in HIV research, directly contributing to advances in treatment, enriching the knowledge base as well as monitoring the epidemic.

The main objective of EuroCoord is to bring together the biggest European HIV cohorts and collaborations from over 100 research institutions and to exploit the strengths of each participating collaborations to ensure that the best, most competitive research is performed. The main advantage of this collaborative method of working is the formation of a common virtual database, which currently has access to data from over 300,000 HIV positive individuals across the European continent, and beyond, both male and female, from neonates to geriatric populations, infected through sex between men, sex between men and women,
injecting drug use, nosocomially and from mother to child, with and without co-infection with hepatitis viruses, of different ethnic and socio-economic backgrounds, from indigenous and migrant populations, in settings with varying levels of access to care and laboratory techniques. The biggest of its kind globally, this dataset is used by EuroCoord researchers to definitively answer questions that could not be reliably addressed through single studies alone.

The work of EuroCoord is organised into several work packages, all of which are interrelated and unified through the Scientific Oversight Group and the management work package. The training, Scientific Oversight and Data Management work packages represent the cross-network activities which aim to ensure sufficient complementarities, added value and assimilation across EuroCoord including the new science areas of TB, Migrant Health and Modelling.

Through collaborative work and partnership EuroCoord aims to continue to contribute evidence for treatment guidelines, wherever possible, and to develop papers and reports on characteristics of the European HIV positive population, pathogenesis of HIV, impact of management strategies and treatment of sub groups of patients as well as prediction models.

Building research capabilities for researchers across Europe is an important objective. EuroCoord aims to improve research skills including statistical techniques to allow researchers to undertake observational research of the highest calibre, and to provide basic and updated laboratory and clinical training to aid the management of HIV-infected people. This will be achieved through the development of online resources, residential courses, PhD and short term staff exchange. Engagement with patients groups and the community is also part of this objectives and initiatives such as newsletters and a workshop will be undertaken.

The overall coherence and maintenance of the scientific agenda of EuroCoord is a priority and several specialist groups will be formed to aid the scientific development of the network and prevent potential overlap in the following areas: pharmacology, immunology/HIV-virology, methodology, vertically infected children to adults, monitoring and resource issues and improving the management of hepatitis co-infection.

EuroCoord will expand on the standardisation efforts on how best to conduct clinical research. Working under the EuroCoord umbrella it is essential to create and disseminate standardised methods and protocols effectively, allowing the process of data collection to be harmonised. An objective of EuroCoord is to create a common platform to facilitate the merging of data from multiple HIV cohorts. This will be achieved by the development of an HIV Cohorts Data Exchange Protocol (HICDEP). Cross-network mergers using the HICDEP format will be performed for different projects and studies and a data inventory will be created to allow for feasibility assessment of new scientific projects.

EuroCoord’s multidisciplinary research aims to improve the management and life of HIV-infected people whilst allowing us to explore differences within sub-groups. The overall common vision for the scientific aspects for EuroCoord can be categorised under the broader headings of: Characterising HIV positive populations in Europe; Understanding pathogenesis; Uptake of and response to therapy; Implications of long-term infection and exposure to treatment; Implications of specific management strategies; Improving the management of hepatitis co-infection; Tuberculosis among HIV positive people; HIV and AIDS in migrant populations in Europe; Modelling the HIV positive population in Europe.

An important objective for EuroCoord is to describe the characteristics of the HIV epidemic in Central and Eastern Europe and to contribute to capacity building in the region by involving a number of new clinical sites in EuroCoord. Given that access to treatment is not equally distributed across Europe, being particularly deficient in many of the recent member states of the Union, it is imperative that the scope of surveillance includes and is expanded in Central & Eastern Europe. Difficulties faced in those regions
include those involved with establishing and maintaining public health campaigns to diminish further transmission, creating and establishing infrastructure providing access to combination antiretroviral therapy (cART), and monitoring the response to treatment. The necessary effort and cost to European governments to respond to these challenges in the years to come will be significant.

A greater insight into host, including genetic, and viral determinants of disease progression and control, is of immense importance for forming the basis for monitoring patients to support clinical decision-making. Our work in this area will focus on viral dynamics, HIV resistance and an increased understanding of biomarkers in HIV infection.

Combination ART has dramatically improved the outcome for individuals who live in countries with appropriate access to treatment. cART is expensive and access to care and hence response to treatment varies tremendously across the European continent. Our work in this area will focus on describing uptake and response to ART and the comparison of response to treatment in different patient populations.

The World Health Organisation has highlighted the urgent need to strengthen cART pharmacovigilance, and new European Union legislation prioritises the importance of measures to monitor long-term adverse drug reactions. Non-AIDS defining events, including malignancies and end stage organ disease now occur more commonly, and are associated with significantly higher mortality than AIDS-related events. Our work in this area will focus on the extent of treatment exhaustion and its implication, toxicities associated with antiretroviral therapy and long-term outcomes.

Improving patient management has a large impact on improving patient care. Our work in this area will focus on strategies for management in different patient groups and how best to measure patient care. Migration has had an impact on the spread of Tuberculosis (TB) particularly since the 1980s, when migration levels have been at their highest, particularly since migration patterns mostly involve the flow of people from high to low TB incidence regions. Our work aims to improve the management of TB-HIV infected individuals, and gain a greater understanding of the healthcare needs of HIV infected migrant populations in Europe. This work will also be complemented by a comprehensive overview of the HIV epidemic in Europe with plausible estimates of current and future total HIV burden.

HIV within migrant populations, largely (but not exclusively) from Sub-Saharan Africa, is increasingly a feature across all of Europe. Migrant populations are a heterogeneous group and comparatively little research currently addresses HIV in these populations. Furthermore, migrant populations often experience inequalities in health and health outcomes, including HIV. Our overall aim is to prevent HIV infection and improve diagnosis and prognosis of migrant populations living with HIV in Europe, by providing evidence to support policy and intervention development at European level.

In order to provide comprehensive information on the HIV infected population in any given European country, we also plan to develop a new stochastic computer simulation model, via the SSOPHIE (Stochastic Simulation of Outcomes of People with HIV in Europe) project that can be used for the purpose of reconstructing and projecting the status of HIV infected individuals in a given country. EuroCoord offers a unique environment for the cross-pollination of ideas through interaction between clinicians, basic and translational scientists, epidemiologists, sociologists, economists and patients. Its unique approach has changed the paradigm of HIV collaboration and will continue to ensure that Europe remains at the vanguard of HIV research.

Project Results:
Over the past 5 years, EuroCoord has mobilised European HIV cohort research, bringing together the biggest cohort collaborations (EuroSIDA, CASCADE, COHERE and PENTA) within one truly pan-
European network of cohort studies succeeding in increasing its presence in the Central and Eastern European region.

A great number of projects and studies have taken place under the EuroCoord umbrella aiming to improve the management and life of HIV-infected people. Through collaborative work and partnership EuroCoord has contributed evidence for treatment guidelines, wherever possible, and published a great number of papers and reports on the characteristics of the European HIV positive population, the pathogenesis of HIV, the impact of management strategies and treatment of sub groups of patients as well as prediction models.

Management of EuroCoord

The EuroCoord Network of Excellence operates under a well-established management structure composed of the Council of Partners, the Executive Board, the External Advisory Board and the Secretariat. This structure has allowed the Network to facilitate innovative cross-network research and ensured scientific dialogue and communication across all networks and partner institutions over the 5 year period. Part of this structure is the Secretariat which has ensured the timely production of annual reports and monitored any changes to the consortium over time. The Secretariat has also ensured internal and external communications and dissemination of research outputs through the EuroCoord website.

Training and outreach

Building research capabilities for researchers part of the EuroCoord Network has been an important goal on EuroCoord’s agenda. Over the course of the EuroCoord funding period, we have built on work currently carried out by partners to organise integrated multidisciplinary training for HIV clinicians and researchers in Europe, with dissemination of expertise, knowledge transfer and learning. Under the framework of the existing partnership between PENTA and the European Society for Paediatric Infectious Diseases a training programme (Tr@inforPed HIV) aimed at healthcare professionals caring for HIV infected children was delivered from 2011-15. The training programme uses a combination of interactive training and online course discussion, and an annual residential course in Rome. The online material has been translated into French, Spanish and Russian. In collaboration with UNICEF, 6 residential training courses have been delivered (2 in Russia, 2 in Ukraine, 1 each in Georgia and Uzbekistan), each proceeded by online training. Two further training courses in Russia have been developed, as well as ongoing clinical and research links in the region. Several other training courses have taken place namely on statistical methodology and phylogenetics.

In addition to these residential training courses, seven free online training modules have been completed accessible via the EuroCoord website. These modules have focused on highly relevant research topics like “Good clinical practice”, “Introduction to cohort studies”, “CoDe: Coding of Causes of Death”, “Improving data quality”, “How to write a manuscript”, and finally “Engagement with the patient community”.

The International Workshop on HIV Observational Databases (IWHOD), a small workshop with a particular focus on observation HIV research methodology has been organised by EuroCoord. This workshop has grown in popularity, receiving an increasing number of high quality abstracts each year. With respect to outreach, two main activities were undertaken: the production and distribution of the EuroCoord Digest, a newsletter highlighting recently published research for the general public, and the organisation of The EuroCoord-European AIDS Treatment Group Joint Workshop in 2015.

Data management

Within cohort collaborations, information held by individual HIV cohorts are combined to address scientific questions that cannot be answered by any individual study alone. This pooling of information is only possible if HIV cohorts collect similar data which can be shared in a format which is easily understood and
interpreted by others, and which can be efficiently combined. HICDEP – the HIV Cohorts Data Exchange Protocol – provides a data structure for HIV studies to facilitate data sharing and cohort collaborations. Over the last five years, EuroCoord has worked to develop HICDEP to meet the challenges of the evolving HIV field. Extensive work has been done to harmonise data items in this period including addition of fields and tables on, for example, HIV-infected children, pregnancy, ethnicity, non-AIDS clinical events including cancers, diagnostic procedures, causes of death, transition from paediatric to adult care, socioeconomic items, and study site location. HICDEP is regularly updated in response to specific issues raised by researchers, methodologists and statisticians via the public wiki (at hicdep.org) and in discussion with data managers within EuroCoord and other groups such as IeDEA (the International epidemiologic Databases to Evaluate AIDS).

Annual releases of new HICDEP versions over the last five years have summarised each year’s progress, and helped to ensure that the data standard continues to be current and relevant to the needs of future HIV cohort collaborations. Using the HICDEP has enable EuroCoord to bring together data from over 40 cohorts of HIV-infected people residing in Europe, representing over 357,000 HIV-positive persons, and over 2 million person-years of follow-up.

In order to guide the development of HICDEP, a data inventory survey was implemented, completed by EuroCoord cohorts to indicate relevant meta information about the available data, methods of data collection and procedures for quality assurance in the cohorts. The survey results have been updated annually and the results are available for researchers within EuroCoord to assess the feasibility of planned collaborative analyses.

A third data platform, the Distributed Data Management tool (DDM), is used by cohorts to create data extractions from their databases and automatically conduct quality assurance checks. The DDM was released and used in the 2013 data mergers between the following cohort collaborations COHERE, CASCADE and ART-CC, and made publicly available at http://www.hiv-ddm.net/. The tool has provided an easier way for data managers to contribute to more than one collaboration. Data mergers between COHERE and CASCADE have taken place annually, with data pooled to address a wide range of scientific questions including timing of treatment initiation, predictors of clinical and immunological response and management of HIV co-infections.

Scientific achievements

EuroCoord’s multidisciplinary research aims to improve the management and life of HIV-infected people. The main scientific achievements for EuroCoord can be categorised under the following broader headings:

Characterising HIV positive populations in Europe

Knowledge of the characteristics of the infected population is crucial to the development and evaluation of appropriate healthcare interventions, resource planning and allocation and to limit the spread of the epidemic. Our work in this area has focused on facilitating the identification of early infection, reducing the burden on health care resources from patients who present late, and characterising the different populations infected with HIV.

Eastern Europe (EE) has been the scene of a rapid increase in both the number of new HIV and AIDS diagnoses in the recent years. Detecting early infection is crucial to help develop prevention policies and directing service provision. Under EuroCoord, work has been undertaken to estimate HIV incidence and to characterise those newly infected in three EE countries namely Estonia, Poland and Ukraine. An avidity assay has been identified and validated to differentiate recent from long-standing HIV infection and was introduced to routine surveillance in each country. Samples of newly diagnosed HIV positive people were collected and tested with the assay which has enabled to identify those with recent HIV infection and
provide estimates of HIV incidence for each three countries. In Ukraine, enhanced surveillance to characterise those at risk of HIV, and estimate HIV incidence within the capital city of Ukraine, Kiev was conducted over a two year period. Results indicated that men who have sex with men (MSM) and persons who inject drugs (PWID) are disproportionately affected by HIV, with risks to sexual partners of PWID. Of particular interest were the MSM, with one in four MSM newly diagnosed with HIV and one in three recently-infected. The study showed that people were comfortable with disclosing their risk through a self-completed questionnaire completed by the attendee using a handheld electronic tablet. As a result, these findings suggest that previous numbers for MSM within Kiev are underestimated due to none disclosure, highlighting the importance of work to minimise stigmas and discrimination. Incidence estimates for the period April 2013 – March 2014 were similar to those reported within the USA, at 21.5 per 100,000 population, with alarmingly high incidence rates for MSM. Methods for estimating incidence suggest that only 29 of the estimated 466 new infections for that year were diagnosed, resulting in a high number of people newly-infected remaining undiagnosed, who may well be participating in high-risk behaviour increasing the risk of further onward transmission. Phylogenetics analysis revealed high levels of local transmission and bridging between risk groups.

In Estonia, the study included 325 newly diagnosed HIV-positive people, conferred at the Estonian HIV Reference Laboratory. Preliminary results showed that the majority of newly diagnosed were being diagnosed within the Estonian capital, Tallinn, and tested because they had symptoms or high risk behavior. A high proportion (30%) of them was classified as having been recently infected and HIV incidence was estimated at 1.42% during 2013 corresponding to 1528 new infections. These results suggest that HIV incidence in Estonia is higher than expected from the diagnosis rate and from the previous similar studies from other countries highlighting the urgent need for better testing policy and healthcare interventions.

In Poland, there were 1094 new diagnoses reported to the national surveillance system in 2013 including 251 diagnoses made through the voluntary council testing network, which provided remaining serum samples for incidence testing. The overall incidence was estimated at 4 - 7.6 per 100,000 population, with the highest estimates for individuals aged between 25-34. Very high incidence was found in both MSM and PWID.

The evolving HIV epidemic among pregnant women and children, including the more recent and accelerating epidemic in EE has been closely monitored and described within EuroCoord. A major achievement has been the development of the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) which currently involves 22 paediatric and pregnancy cohorts from 17 countries. EPPICC has also contributed to a global paediatric HIV cohort collaboration (Collaborative Initiative for Paediatric HIV Education and Research (CIPHER)) which has pooled data on >160,000 HIV-infected children to address key questions on the epidemiology of perinatally HIV-infected adolescents globally and the durability of first line therapy. Other EPPICC work has involved bespoke cohort studies of children living with HIV, including a new cohort in Ukraine (>1000 patients) and a cohort of children, adolescents and youth living with HIV/Hepatitis C (HCV) co-infection from across Europe.

In addition, the EPPICC network conducted a detailed online survey of our paediatric and adult cohorts across 16 countries represented in EuroCoord, to assess the number of perinatally HIV infected children/adolescents receiving care and the number transferring to adult HIV care. The study found that the perinatally HIV infected population in the European Union/European Economic area is larger than previously reported at over 8,000 patients, compared to previous estimates of ~5000 cases reported by the ECDC and the World Health Organisation (WHO), which suggests underreporting in some national
surveillance systems. Importantly, a number of countries are working towards linking paediatric and adult cohort databases to enable continued follow up of perinatally infected patients in adulthood.

An analysis by the European Collaborative Study Group in EuroCoord conducted in the Ukraine explored differences in clinical status, mother-to-child-transmission (MTCT) and its prevention and pregnancy outcomes between HIV-infected pregnant injecting drug users (IDUs) and non-IDUs. More than 6000 mother-child pairs were included in the analysis which found that IDUs had worse clinical status, poorer access to prevention to MTCT prophylaxis and cART, more adverse pregnancy outcomes and higher risk of MTCT than non-IDU women. However, there were some important successes identified, including an increasing proportion of IDUs who were aware of their HIV status before pregnancy, a declining proportion receiving no prevention to MTCT prophylaxis and substantially lower MTCT risk in recent years regardless of IDU status. These data support the need to provide comprehensive care to female IDUs, including harm reduction, family planning and HIV treatment as well as provision of antenatal care and prevention to MTCT, with an emphasis on improving timely access.

As combination antiretroviral therapy (cART) works best if it is initiated when people still have a relatively high CD4 count, it is important for people to know they are HIV positive as soon as possible after they become infected. Early diagnosis also reduces the risk of onward HIV transmission. However, many people are still diagnosed at a fairly advanced stage of the disease. They have been termed “late presenters”. One of the key achievements has been the standardisation of the definition of late presentation and the characterisation of this population by region and over time. In collaboration with the European Centre for Disease Control (ECDC) and the HIV in Europe Initiative, trends in late presentation were reported between 2000 and 2013 based on data merged in EuroCoord. While late presentation with HIV infection has decreased in recent years; it remains an important issue across Europe and in all groups of people at risk of HIV infection. As individuals presenting late have a poorer clinical outcomes, particularly in the first and second year after diagnosis compared to non-late presenters, this research has important public health implication.

As part of EuroCoord, EuroSIDA has achieved its original objective with a total of 6200 people enrolled in the study during this time period, and over the years a total of 5475 have been recruited in EE.

Understanding pathogenesis

A greater insight into the impact of host genetic, viral, socio-economic and geographical origin determinants on disease progression and control is of immense importance for forming the basis for monitoring patients to support clinical decision-making. Our work in this area has focused on viral dynamics, HIV resistance and an increased understanding of biomarkers in HIV infection.

Through CASCADE, EuroCoord has provided insight into the clinical implications of HIV viral tropism to cellular co-receptors (CCR5 (R5), CXCR4 (X4)) in the body by assessing whether HIV disease progression differs in HIV positive people harbouring a X4-tropic virus versus a R5-tropic virus at the time of seroconversion. Samples from 1387 HIV-infected people were analysed and viral tropism was determined. Results showed that individuals harbouring X4-tropic virus compared to R5 had similar CD4 and viral load levels at seroconversion but had faster decline in CD4 cell count up to 30 months of follow-up and also tended to have shorter time to treatment initiation.

Host genetic variations may be at play when trying to explain inter-individual differences in HIV disease progression. Human exome sequencing (i.e. targeting the ~1.5% of the genome that is protein coding) is an attractive approach to comprehensively test common and rare polymorphisms or single nuclear polymorphism (SNP) for disease association. We conducted a study in which we sequenced the exomes of HIV infected people from the extremes of the phenotype distribution namely HIV controllers and rapid
progressors to assess the impact of protein altering mutations on HIV outcome. Preliminary results indicate that the top SNP associated with HIV control is rs1055827 located on chromosome 6.

EuroCoord has also contributed to the study of the epidemiology of rare events such as the spontaneous control of HIV infection, a phenomenon that occurs in approximately 1% of those infected and remains poorly understood. Developing a better understanding of “HIV Controllers” (HIC) ability to control HIV infection may contribute to the development of immune therapies or an HIV vaccine. One thousand and seventy-five HIC have been identified among a sample of 111,070 eligible HIV-infected people (0.97%). Among this sample, 88 lost control (8.2%), 296 initiated antiretroviral therapy (ART, 27.5%) and 13 died during control (1.2%). Forty two percent of HICs were still HIC 15 years after HIV diagnosis; viral blips were a major predictor of loss of control. This is the largest European Registry of Long Term Non Progressors to date, enabling further genetic, immunologic and virologic studies.

As the proportion of HIV positive people living into old age, research into non-AIDS events in this population has become of interest. EuroSIDA in EuroCoord has established several studies to investigate and describe biological markers prior to the development of clinical events using the plasma repository. One particular area of interest is biomarkers for specific malignancies. One study investigated the validity of applying the commonly used cut off of prostate specific antigen (PSA) $\geq 4.0 \, \mu g/L$ as a clinical indicator for men at risk of prostate cancer. Findings indicated that PSA is highly predictive of prostate cancer in HIV-positive men, an association which was detectable more than 5 years prior to diagnosis, however the commonly used PSA $> 4 \, \text{ng/mL}$ to indicate high prostate cancer risk was not sensitive enough in our study, and the lower cut-off of PSA $> 1.5 \, \text{ng/mL}$ warrants consideration.

Another nested case control study investigating the link between Epstein-Barr virus and several markers of B-cell activation and inflammation in the time leading up to non-hodgkin and hodgkin lymphoma development in HIV-positive people is currently underway. The results may identify non-invasive plasma markers which have potential to be used a clinical setting to identify HIV-positive people at high risk of lymphoma and to inform individualised care.

Previous studies have demonstrated that low vitamin D levels are associated with inflammation, HIV disease progression and death. Serial plasma samples were utilised to investigate the prognostic value of vitamin D for AIDS, non-AIDS-defining events and death, and its association with markers of inflammation and immune deficiency. Results showed a two-fold higher vitamin D level reduced the likelihood of death by more than half. Vitamin D levels were lower shortly before death in HIV positive people, which may be related to activation of the immune system and inflammation.

Whilst current studies from sub-Saharan African (SSA) countries are limited, there are conflicting results on whether HIV disease progression is different in persons living in these countries and the impact of socio-economic factors. EuroCoord researchers have sought to investigate whether HIV treatment guidelines, based on cohorts from Europe and North America, are applicable to African populations. Data from European and sub-Saharan African (SSA) seroconverter cohorts were used to estimate and compare CD4 cell loss ART-naïve and AIDS-free individuals, time from seroconversion to AIDS, death and ART initiation. Estimates between Europeans, Africans in Europe, and Africans in SSA were compared. Despite initially lower CD4 levels and slower CD4 decline in African cohorts, there was little difference in survival among African and European cohorts. Current guidelines for ART initiation appear appropriate to African populations.

Another study examined differences by geographical origin (GO) in time from HIV seroconversion to AIDS, death, and initiation of cART. Using CASCADE in EuroCoord data, the GO included were western countries, North Africa and Middle East, sub-Saharan Africa, Latin America, and Asia. No differences
were found by GO in risks of AIDS and death, although seroconverters from North Africa and Middle East and sub-Saharan Africa appeared to have lower mortality than western countries. Chances of initiating cART differed by GO: seroconverters from sub-Saharan Africa were more likely to initiate cART than western countries, but not after adjustment for CD4 at seroconversion. In settings with universal access to healthcare, GO does not play a major role in HIV disease progression.

Uptake of and response to therapy

Combination ART has dramatically improved the outcome for individuals who live in countries with appropriate access to treatment. cART is expensive and access to care and hence response to treatment varies tremendously across the European continent. Our work in this area will focus on describing uptake and response to ART and the comparison of response to treatment in different patient populations.

To further understand and provide guidance for improving upon the poorer health outcomes among HIV infected people from EE compared to Western Europe (WE), a clinic survey that covered different aspects of HIV clinical care among EuroSIDA clinics was conducted. The survey demonstrated that compared with clinics in WE, more clinics in EE deferred ART in asymptomatic patients for longer, and significantly fewer clinics in the East provided resistance testing before initiating ART or upon ART failure. Clinics in EE were also less likely to offer hepatitis B (HBV) vaccination, have access to new HCV drugs and integrate Tuberculosis (TB) and HIV treatment.

Side effects, poor absorption, drug interactions and drug resistance are all reasons why an HIV positive person may switch to another HIV regimen. The question ‘when is it best to switch regimen’ remains relevant both in the resource rich and resource limited settings. Through EuroCoord, we have tried to address this question. Preliminary results of a study showed that the risk of drug resistance mutation accumulation was 2-fold higher if ART regimen is not changed upon occurrence of viral resistance compared to an immediate regimen switch.

Regarding the use of specific ART strategies, because of the existence of very effective and well tolerated regimens the focus is now on regimen simplifications in people with suppressed viral load. Little research has been done on the efficacy/tolerability of un-boosted atazanavir (ATV400) with abacavir/lamivudine (ABC/3TC) as a switch strategy in clinical practice. Our results showed that a switch to ATV400 + ABC/3TC in selected subjects with suppressed viremia was associated with relatively low rates of viral failure and discontinuation due to adverse events. Criteria about how to best select people that might benefit from this switching strategy were also provided.

In 2009, a meta-analysis merging together data from several randomised clinical trials of regimens containing raltegravir (RAL) showed that after the initial two months of follow-up, cancers became more common in RAL users than in people receiving the comparator regimens, raising concerns about RAL users’ safety profiles. A carefully conducted analysis comparing people using RAL with a control group of people using other concomitant regimens not containing RAL showed that, at the time of starting these regimens baseline individuals in the RAL cohort tended to have more co-morbidities than those in the control group. However, once these differences were taken into account, there was no difference in the risk of malignancy or in survival among RAL-exposed individuals compared to those starting control cART regimens.

The trend towards starting treatment at higher CD4 counts, brings into focus potential issues around HIV drug resistance. The EuroCoord-CHAIN project looked at the effects of transmitted drug resistance (TDR) – resistance that has been transmitted to an HIV positive person who has not yet started treatment (treatment naïve). It found that patients with TDR were more likely to fail treatment if they had received at least one drug to which the virus had lost susceptibility. The study also found that treatment with a drug
classified even with low-level resistance is associated with a significantly higher risk of treatment failure, emphasising the need for at least three fully-active drugs in the first-line regimen and underlining the need for drug resistance testing in all treatment-naïve patients.

Most HIV infected people see the amount of virus in their blood decrease and their CD4 cell count increase in the first six months after starting therapy. However, there is no consensus as to what constitutes a “normal/optimal” immunologic response to therapy. To allow clinicians to monitor their patients’ early immunologic response after treatment initiation leading to a viral control, reference curves for increases in CD4 cell count after the initiation of a cART in HIV-1 infected naïve people were established. Using data from EuroCoord, a total of 28,992 people were included in this analysis. The main reasons for variations in CD4 cell count at 6 months were the AIDS stage at cART initiation and the baseline CD4 cell count. Authors concluded that a CD4 cell count increase of at least 100 cells/mL is generally required for people to stay ‘on track’ (ie. in the same percentile as when they start), with slightly higher gains required to stay on track for those starting with CD4 cell counts in the higher percentiles. These findings will soon be published in HIV Medicine accompanied by an online tool made available to clinicians.

Implications of long-term infection and exposure to treatment

Non-AIDS defining events, including malignancies and end stage organ disease now occur more commonly, and are associated with significantly higher mortality than AIDS-related events. Our work in this area will focus on the extent of treatment exhaustion and its implication, toxicities associated with antiretroviral therapy and long-term outcomes.

With ART, perinatally HIV-infected children are surviving into adolescence and young adulthood for the first time, and those in EPPICCC cohorts are some of the oldest survivors globally. Key questions are arising over the long term outcomes of ART in children and adolescents and how this may be optimised in the future. EPPICCC was one of the first large cohorts to assess long term outcomes of children who initiated treatments during infancy (age<12 months) and showed that low morbidity and mortality and good long-term immune and virological response was achieved. One of the key questions examined was the durability of first line treatment. We showed that one-in-five children switched to second-line therapy at 5 years of treatment, and children who initiated treatment at older ages or on nevirapine-based first line regimens were at risk of more rapid switch to second line treatment. Further detailed analyses are ongoing investigating the long term mortality, AIDS and serious non-AIDS events and immune and virological response.

Within EPPICCC, we have devised and implemented a comprehensive model of pharmacovigilance of antiretroviral therapy (ART) in paediatric HIV. To date, seven antiretroviral drugs (abacavir, atazanavir, combivir, darunavir, etvirine, fosamprenavir, tenofovir) have been studied within this model, and the studies have generally observed low rates of short and long term toxicities in children and adolescents. Low CD4 count and/or a high viral load are associated with greater risks of clinical disease, including both the occurrence of AIDS and non-AIDS events. However, it is unknown whether the relationship between those at high or low risk of clinical disease varies with age, over time or in regions of Europe. Our study results showed that the difference in risk between those at high and low risk was widest for non-AIDS events for those aged <30 years suggesting other factors become more important than HIV control as people age, including the effect of age on morbidity and mortality itself. The difference was increasing over time for AIDS and non-AIDS suggesting improvements in care for those at low risk and better management required for those at high risk. There were also some regional differences, with the difference between those at low and high risk largest for non-AIDS events in Central East and East regions and lowest in North and Central Western Europe reflecting differences in patient management and underlying
socioeconomic differences.

As part of EuroCoord, The European Paediatric HIV and Lipodystrophy Study Group estimated the prevalence and risk factors for lipodystrophy syndrome, characterised as body fat abnormality and/or metabolic disturbances in HIV infected children and adolescents. The study found that half the children and adolescents who had accumulated long treatment durations included in this study had lipodystrophy syndrome which underlines the importance of continued surveillance of children treated with ART.

Implications of specific management strategies

Improving patient management has a large impact on improving patient care. Our work in this area will focus on strategies for management in different patient groups and how best to measure patient care. EuroSIDA in EuroCoord has worked on identifying a core set of quality of care indicators that may be used for benchmarking HIV care and management across Europe. Results comparing various HIV-RNA based quality of care indicators as well as data comparing country-specific HIV-RNA suppression rates were presented.

In Ukraine, we assessed how the WHO Option B strategy resulted in tripling the use of cART in pregnancy between 2008 and 2010, with substantial decline in MTCT; however, we identified socio-economic disparities in access to optimal care. With increasing exposure of infants to ART in utero, safety issues have a growing importance. EPPICC analyses showed that combination neonatal prophylaxis is not associated with an increase in haematological toxicity compared with one-drug prophylaxis, but our work has added to the literature indicating an association between preterm delivery and use of cART in pregnancy.

In Western Europe, the UNAIDS target of MTCT rates of <2% by 2015 has been met. Factors behind this decline were explored, including the growing proportion of women conceiving whilst on fully suppressive ART and earlier start of ART in pregnancy in women not yet on treatment. As prevention to MTCT strategies in Europe have evolved, we have assessed the extent to which “real world” practices follow policy, identifying missed opportunities for prevention relating to use of ART and/or prophylaxis, mode of delivery and other factors. We showed that some babies remain at higher risk of HIV infection, including those whose mothers inject drugs, or who start ART too late, or have problems adhering to ART.

Through the PENTA trials network, EuroCoord’s focus has been towards strategic trials addressing key clinical questions relating to the management, treatment and long-term outcomes of vertically HIV-infected children and young people in Europe. These aims address questions that are central to clinical practice and improving public health.

The importance of questions relevant for older HIV-infected children and adolescents reflects both the decreasing number of HIV-infected infants born to HIV-infected women because of effective prevention of mother to child transmission as well as the increasing number of young people surviving into adolescence and adulthood in well-resourced and middle-income countries. Adherence to medication is a major issue during adolescence. Therefore PENTA prioritised trials to evaluate the efficacy and acceptability of simplified approaches to taking antiretroviral therapy:

PENTA 16 (BREATHER) investigated weekend breaks off efavirenz-based treatment for HIV-infected younger children, adolescents and youth (age 8-24 years) who had achieved viral suppression. Young people expressed the desire to lead more normal social lives at weekends (eg “sleepovers”; socialising without need to carry medication etc.). This study capitalised on the long-lasting properties of efavirenz and showed that over a relatively short period 5 days ART with a 2-day weekend break can keep the virus level as low as when ART is taken every day. Young people interviewed in a social science substudy enjoyed the freedom of not taking medication at weekends and experiencing fewer side effects from the
medication, however they also stressed the need for support in adjusting to such a new pattern of taking medication.

The PENTA 11 trial evaluated CD4-guided ART planned treatment interruptions (PTIs) compared with continuous therapy in children with chronic HIV infection. Children continued to be followed after the trial to evaluate whether the treatment interruptions caused any longer-term damage. At 2 years after the trial no difference was seen in information processing speed, sustained attention, short-term memory and quality of life functioning between the 2 groups. By the end of the planned 5 year follow-up no clinical, immunological or virological consequences of treatment interruptions were observed.

The PENTA 18 trial (KONCERT) investigated simplification to once-daily versus twice-daily dosing of the protease inhibitor, ritonavir-boosted lopinavir, in children/adolescents. This drug is the only ritonavir-boosted fixed dose combination tablet formulation available for older children and is important as ritonavir liquid is very unpalatable and the only ritonavir tablet available is large. Lopinavir/ritonavir is already licensed once-daily in adults. In contrast the KONCERT trial showed that once-daily dosing was not non-inferior virologically in children/adolescents, possibly because of more variable pharmacokinetics. The results do not support routine use of once daily lopinavir/ritonavir. However, lack of safety concerns or development of resistance do suggest that once daily dosing could be used in selected, adherent children, with close viral load monitoring. Both children and carers reported a preference for once daily dosing.

Bone toxicity, renal impairment, lipodystrophy and also costs are a major long-term concern since HIV-infected children receive ARTs throughout childhood, and the most commonly used “backbone” treatment is with nucleoside reverse transcriptase inhibitors (NRTIs) which have the most potential problems.

The PENTA network was extended over the period of EuroCoord and strengthened with the inclusion of Uganda and Ukraine in the BREATHER trial; South Africa, Zimbabwe and Mexico have also submitted approvals for the forthcoming ODYSSEY and SMILE trials.

Improving the management of hepatitis co-infection
A significant proportion of persons infected with HIV are co-infected with hepatitis B or C viruses which presents an additional complication for patient management and a potentially more serious outcome for those who are co-infected.

Using data from HIV infected people with known date of HIV seroconversion (CASCADE), we aimed to establish whether the relative timing of both HIV and HCV infections in MSM has an impact on progression. MSM who had not started HIV-therapy, known as ART-naïve were included. Preliminary results showed that the moment of acquiring HCV infection relative to HIV (e.g. acquiring HCV after 2 years of HIV infection), does not have an impact on the immunological response or the evolution of HIV viral load (HIV RNA) over time. However, HCV itself, irrespective of the moment of acquiring HCV relative to HIV, does have an impact on the immunological response during the first two years following HCV infection; HIV-positive MSM who acquire HCV, have a lower CD4 cell count the first two years of an HIV/HCV-coinfection than matched HIV-positive MSM without HCV.

We also have documented a high risk of both primary HCV infection and HCV re-infection among PWID and MSM. These findings underline the need for maintaining focus on preventive measures to reduce injecting drug use, sharing of contaminated needles and unprotected sex, but also that clinicians should be vigilant to identify patients with recent HCV infection and provide counselling to minimise the risk of
onwards transmission and consider the need for HCV treatment.

HIV/HCV co-infected people have many competing risk factors for early death, and an understanding of the spectrum of causes of death is therefore important in order to develop strategies for improving survival of this population. We have shown that among HIV/HCV co-infected patients around a quarter of all deaths are liver-related, but striking regional differences in causes of death were observed, with AIDS and non-liver-related death dominating in EE whereas rates of liver-related death still remained low compared with other European regions. In a subsequent study we developed a risk score for liver-related death that is easy for clinicians to use and could serve as an important tool for prioritising patients for HCV treatment. The risk score derived has been validated in an independent patient group through collaboration with the Swiss HIV Cohort Study.

Under EuroSIDA in EuroCoord, a new cohort consisting of HIV/HCV co-infected patients was launched in 2014 and has enrolled over more than 3,700 new patients. This new cohort has resulted in the opening of seven new EuroSIDA sites since July 2014. Five of the seven new sites are opened in EE. A total of 74 centres from 31 countries are participating in cohort 10 (14 Central and EE countries).

Most infected children living in EE and Central Asia are from socially vulnerable families, with many living in institutions, are at high risk of co-infection. EPPICC’s work has involved bespoke cohort studies of children living with HIV, including a new cohort in Ukraine (>1000 patients) and a cohort of children, adolescents and youth living with HIV/HCV co-infection from across Europe.

Tuberculosis among HIV positive people
The TB:HIV Study in EuroCoord is the first international, prospective, cohort study of adult HIV-positive people co-infected with TB across Europe and Latin America. The study collects data on patients from 62 TB and HIV clinics from 19 countries and has been conducted over the past five years (2011-2015). By the end of 2013, 1413 patients had been enrolled into the study, each of them being followed-up for two years. An additional 123 TB/HIV co-infected children were included into a paediatric sub-study of the TB:HIV study.

As part of the TB:HIV study, a survey of the clinics involved was conducted in 2013 which investigated the organisation and delivery of HIV and TB health care and potential differences between treatment centres in EE and WE. The main results from this survey showed that HIV and TB treatment are less often integrated at the same clinic in EE compared to WE, availability of the anti-TB drug rifabutin and second- and third-line anti-TB drugs was lower in EE, and opioid substitution therapy for IDUs was available at fewer centres in EE compared with WE.

In 2014, data from HIV/TB co-infected people enrolled into the study, namely data from the time when they were diagnosed with their TB disease were presented. Significantly more HIV/TB co-infected people from WE compared to EE had a definite TB diagnosis and received ART for their HIV disease. Furthermore, a very high proportion of HIV/TB co-infected people from EE (40%) were diagnosed with multidrug-resistant TB (defined as resistance against two of the most potent-acting anti-TB drugs). Among those who had an anti-TB drug susceptibility test available, only 66% of patients in EE received treatment with the sufficient number of active anti-TB drugs (which is a minimum three) compared to 90-96% in the other study regions. Many HIV/TB co-infected people in EE received inadequate treatment regimens for their TB disease which is known to fuel further amplification of anti-TB drug resistance.

In 2015, data on 12 months’ outcome for the HIV/TB co-infected people included in the study were
Almost one-third of HIV/TB co-infected people in EE had died within the first year after they started anti-TB treatment compared to 5%-11% in the other regions. When considering other factors that might play a role in their survival, HIV/TB co-infected people receiving care in EE still had a ¾ fold increased risk of dying within the first year after the TB diagnosis compared with those followed in WE & Latin America. Other factors that were associated with death included inadequate anti-TB treatment, absence of drug susceptibility testing, severe immunosuppression due to untreated HIV disease and disseminated TB disease. Furthermore, significantly fewer HIV/TB co-infected people received ART at 12 months after TB diagnosis in EE compared to the other regions despite treatment initiation being recommended for all patients by every international guideline.

Recently, outcome for individuals with fully susceptible TB included in the HIV:TB study were also reported. Even for the included in the HIV/TB co-infected people who would be expected to respond to standard anti-TB therapy, there were significant differences across Europe, with HIV/TB co-infected people in EE having significantly poorer outcome compared with their counterparts followed in Latin America or WE. These findings suggest that other and yet unidentified factors may be important in explaining the poorer outcome for HIV/TB co-infected people in EE.

A large proportion of HIV/TB co-infected people enrolled into the study (844/1413) originate from the EE countries, the study’s main focus area. The number of HIV/TB co-infected people has been rapidly increasing in this region over the past years. The situation is further complicated by the world’s highest prevalence of multidrug-resistant TB and the even more difficult to treat extensively drug resistant TB (XDR-TB) in EE. The true extent of the problem concerning HIV/TB co-infected patients, including data on anti-TB drug resistance, is presumably underestimated as surveillance is generally limited, and EE is a region from where scientific data remain scarce.

The analyses from the study clearly demonstrate the obvious need for improved TB diagnostics including increased resistance testing for anti-TB drugs and treatment for both TB and HIV. Further, integration of TB and HIV clinics in EE along with increased social support including offering opioid substitution therapy would improve retention in care thereby improving the overall outcome of HIV/TB co-infected people. Altogether, we have shown that HIV/TB co-infected people are indeed suboptimally managed in EE, and moreover we have tried to identify modifiable factors associated with poor disease outcome.

Data collection is almost completed for the HIV:TB study, and several scientific projects are currently being carried out. This will provide more detailed information on patients such as what is the optimal management of these patients with respect to treatment changes in relation to results of TB drug susceptibility testing results, response to HIV therapy, and occurrence of immune reconstitution syndrome.

HIV and AIDS in migrant populations in Europe

The overall aim regarding “Migrant Health” has been to prevent HIV infection as well as to improve diagnosis and prognosis of migrant populations living with HIV in Europe by providing evidence to support policy development at European level. We have successfully achieved this goal by conducting the two de novo aMASE (advancing Migrant Access to health Services in Europe) clinical and community electronic surveys in Belgium, France, Germany, Greece, Italy, The Netherlands, Portugal, Spain, Switzerland and United Kingdom and by harmonising and analysing the information on geographical origin across all 24
European cohorts within 11 European countries in the COHERE dataset. We have actively engaged with European AIDS Treatment Group (EATG) and ECDC, and collaborated with other parties within EuroCoord’s framework.

In the aMASE clinical survey at total of 2218 HIV-positive migrants were interviewed within 57 clinics across 9 European countries using computer assisted tools and pooled clinical and biomarker data to complement self-reported information. In the web-based aMASE community study at total of 1637 migrants living in Europe were reached, the majority of whom were not living with HIV. Both surveys were made available in 14 languages and have considerable content overlap to allow for comparison. This work was done in close collaboration with EATG who partnered with our researchers to deliver an innovative project to include and engage migrant communities affected by HIV in the study.

Results of the aMASE project show that 30% of HIV-positive migrants report having difficulties accessing health care and that of those accessing health care services in the 2 years prior to their diagnosis, 61% were not offered HIV tests, highlighting missed opportunities for HIV testing. These findings suggest that services that migrants access most – emergency care and family doctors – should routinely offer HIV testing. Definite or probable post-migration HIV acquisition was highest among MSM (72%) than heterosexuals (38%) and among people from Western (72%), Central (58%), Eastern-Europe (58%) and Latin-America (68%), where proportions of MSM were higher, than among Sub-Saharan Africans (SSA) (32%). Pre-migration HIV acquisition was highest among SSA (20%). The aMASE community survey found that 8.5% of respondents did not know that AIDS is caused by a virus called HIV. Nearly three quarters (73%) of those who answered the survey had tested for HIV and of those nearly one in five (19%) were living with HIV. Among those not living with HIV who had tested over half (58%) had tested in the past two years. Those who had not tested at all reported not doing so because they did not consider themselves to be at risk (80%).

Additional analyses looking at mortality in male and female migrants living with HIV in Western Europe was also undertaken. These analyses included 123,344 men and 45,877 women followed-up in 24 cohorts from 11 European countries of which 20.7% and 50.7% were migrants, respectively. Globally, migrants had lower mortality rate than native populations but mortality varied depending on geographical origin, sex and transmission category. In additional analyses, immunological and virological responses to cART in WE have been shown to vary by geographical origin and sex; migrants from Sub-Saharan Africa started at lower CD4-cell counts which remained lower overtime. We also report progressively earlier cART initiation in native and migrant populations following efforts to increase prompt diagnosis and treatment. However, the inequality gap for migrant populations is still observed, supporting the need of intensified efforts targeting these groups.

Modelling the HIV positive population in Europe

HIV infection can potentially take years to be diagnosed because symptoms at the time of infection don’t always arise. This makes it difficult to assess from routine surveillance data the total number of people who live with HIV in a given setting. An important aim of EuroCoord was to develop such a method which provides comprehensive information on HIV-infected populations in European countries.

The SSOPHIE (Stochastic Simulation of Outcomes of People with HIV in Europe) project relies on a mathematical model of HIV infection and the progression of antiretroviral therapy. In the first instance, we used an already existing model and updated various parameters and assumptions based on new data and analyses. The factors associated with the viral load rise and CD4 count decline in people who have not yet initiated ART were then investigated and results showed that amongst ART-naïve individuals, viral load continues to increase over time and more quickly in those who are older.
The method developed to produce HIV estimates is based on a computationally intensive statistical approach known as approximate Bayesian computation. It involves creating a huge number of different populations using computer simulation and choosing the ones that most closely resemble the real population. By replicating the HIV-positive population of interest, it is possible to infer the size of an infected population and its characteristics. Developing this method has been the main part of the SSOPHIE project. The method was first piloted to data on MSM in the UK and also to hypothetical data to assess how well the method worked for different scenarios in terms of data availability. The method has also been applied to data from the Netherlands, Spain, Estonia and Sweden.

This newly developed method involves fitting the model to surveillance data from a given country. The SSOPHIE project has therefore continued to work closely with colleagues from the ECDC who manage HIV surveillance within Europe.

Finally an implementation plan was developed for applying the method to generate best estimates together with a range in which the estimates are thought to plausibly lie within. The plan details the course of action and necessary resources if the method were to be used more widely, i.e. for a number of different European countries.

Potential Impact:
Since the start of EuroCoord over 120 publications have been published and 103 conference abstracts presented. EuroCoord results are disseminated mainly through the EuroCoord website www.eurocoord.net which includes a list of all our publications. Significant publications are showcased with an accompanying news story and the most recent findings are summarised in an annual article to show support to the World AIDS Day campaign. Progress from across EuroCoord is also summarised in the form of e-newsletters circulated to various stakeholders. Two briefing papers were produced to highlight the importance of cohorts in informing public health policy and highlighting some of EuroCoord’s work in HIV research in Europe.

With respect to outreach, two main activities were undertaken: the production and distribution of the EuroCoord Digest, a newsletter highlighting recently published research for the general public, and the organisation of The EuroCoord-European AIDS Treatment Group Joint Workshop in 2015.

Two issues of the “EuroCoord Digest”, a newsletter highlighting recently published academic journal articles for a lay public, were published in May and December 2015. The EuroCoord Digest has been widely disseminated via the European AIDS Treatment Group (EATG) and the EuroCoord networks.

Secondly, a Community Outreach Workshop, sponsored jointly by EuroCoord and EATG, was held 8-9 November 2015 in Brussels. The aim of the event was to improve the wider HIV community’s understanding of observational epidemiology in HIV and its impact on care and clinical practice. Representatives from the European Community Advisory Board (ECAB), a high-level scientific platform that brings together delegates from European and international institutions to address key science and policy issues related to HIV and HIV co-infections, attended this event. The Workshop was well-received. It fostered dialogue between prominent community representatives and EuroCoord researchers which will inform the next chapter of observational research on HIV in Europe.

To support the development of data management and analytical skills, an example dataset of HIV natural history was made publically available for educational purposes on the HIV Cohorts Data Exchange Protocol (HICDEP.org) online platform in 2014. This includes data for 1000 patients on viral load, CD4 cell count, clinical events and combination antiretroviral therapy (cART) in 7 HICDEP-structured tables. The data was simulated from the HIV Synthesis model which is an individual-based stochastic model.
generating data on the course of HIV infection from patients in the UK from 1980 up until 2010, and kindly provided by the EuroCoord modelling group. Throughout the five year duration of EuroCoord, numerous presentations on the subject of data harmonisation have been made at workshops and meetings. The group provided a response to the National Institutes of Health Request for Information: Input on Information Resources for Data-Related Standards Widely Used in Biomedical Science, and have supported the International Epidemiologic Databases to Evaluate AIDS (IeDEA) in their recently successful application to BD2K to extend the IeDEA Data Standard and harmonize this with HICDEP. This harmonisation of the two data standards will facilitate collaborations between the IeDEA network and cohorts within EuroCoord in the future. A high number of publications and presentation have arisen from EuroCoord scientific achievements and they have been directly or indirectly informing HIV treatment guidelines and policies. Detecting early infection in Estonia, Poland and Ukraine has allowed to assess the extent of the epidemics in these countries and helped identify groups more at risk of infection which will inform targeted prevention strategies and direct service provision. Our work on HIV late presenters has provided a much-needed evidence base for policy makers involved in HIV control programmes. HIV testing strategies that encourage early testing in all populations at risk, that ensure timely referrals, and that improve retention in care are required to further reduce the incidence of late presentation with HIV infection in Europe. With the EPPICC in EuroCoord network we have been able to enable continued follow up of perinatally infected patients in adulthood by linking paediatric and adult cohort databases. In the Ukraine a study aiming to assess how the World Health Organisation Option B strategy resulted in a tripling of cART use in pregnancy between 2008 and 2010, with substantial decline in mother-to-child-transmission (MTCT); however, we identified socio-economic disparities in access to optimal care. With increasing exposure of infants to ART in utero, safety issues have a growing importance. Results from these activities have been presented at international scientific conferences and training courses attended by the clinical and scientific community and at meetings/workshops of activist groups and of policy makers, including the World Health Organisation. We have published peer-reviewed journals, written reports for the European Medicines Agency and disseminated findings via public websites. Our activities have provided evidence to support, and are cited in, international clinical guidelines. Within EuroCoord, several PENTA trials were undertaken to evaluate the efficacy and acceptability of simplified approaches to taking ART for children and adolescents infected with HIV. Results from these trials and their importance for young HIV infected people have been disseminated to the participants both through written and pictorial information designed by youth advocates and through group meetings to explain the results and discuss their relevance and generalisability. Results of these trials have been presented at international scientific conferences, national investigators meetings and training courses attended by the clinical and scientific community and at meetings/workshops of activist groups and of policy makers, including the World Health Organisation. We have published in peer-reviewed journals and disseminated findings via public websites. Data from the KONCERT trial investigating the simplification to once-daily versus twice-daily dosing of the protease inhibitor, ritonavir-boosted lopinavir, in children/adolescents have been submitted to the Food and Drug Administration and our activities have provided evidence to support, and are cited in, national and international clinical guidelines. Several publications have reported on a diverse area of topics such as cause of death, HIV drug resistance, vitamin D insufficiency and the associated risk of clinical disease progression and all-cause mortality, and non-AIDS diseases. Several papers have also reported on the difference between HIV-
positive persons in Eastern and Western Europe and regional differences in management of HIV across Europe. Benchmarking was introduced as a research area and there is a continuing effort to identifying a core set of quality of care indicators that may be used for benchmarking HIV care and management across Europe. Through EuroSIDA, EuroCoord has contributed significantly to the surveillance of disease trends in the prognosis for HIV-positive individuals.

Several COHERE studies have added key evidence to this long-running debate and, together with evidence from clinical trials (START, TEMPRANO), have informed current European guidelines recommending the immediate initiation of ART irrespective of CD4 cell count levels. Work on HIV control has enabled to create the European Registry of Long Term Non Progressors to date, enabling further genetic, immunologic and virologic studies.

Results of the HIV:TB study are novel and document the public health emergency currently happening in Eastern Europe among this vulnerable population. The study collects a combination of clinical and laboratory data on HIV/TB co-infected people, which provides a unique (and rarely reported) opportunity to investigate management and outcome and adds to the already existing surveillance data provided by the World Health Organisation and the European Centres for Disease Prevention and Control. The study has shed light on which public health interventions are needed in order to reduce mortality and improve the overall situation for the patients. The results will provide a better in-depth understanding of the situation concerning TB/HIV co-infected people, which will ultimately lead to a better prognosis for them.

The aMASE Study in EuroCoord is the first multinational study which specifically samples migrants from across the globe living in Europe. It has demonstrated the importance of post-migration HIV acquisition and the need for improved primary prevention for migrant communities. It also highlights how HIV prevention initiatives need to function within a context of low risk perception and the importance of developing trans-national approaches to HIV prevention and care. Through close collaboration with the European Centre for Disease Prevention and Control and EATG we have maximized the dissemination of our results to a wide audience. Not only have we produced scientific reports but have disseminated our work through webs, social media, videos and lay reports. Through the analysis of existing cohort data and the new data generated by the aMASE surveys, EuroCoord helps provide the evidence policy-makers and HIV programme managers require to develop more effective HIV testing, prevention and care initiatives for migrant communities, and in so doing improve the health of the whole population.

The SSOPHIE (Stochastic Simulation of Outcomes of People with HIV in Europe) project in EuroCoord has developed a method that has the potential to be used across Europe and elsewhere, by providing in-depth information about HIV-positive populations, which would be unavailable otherwise. These estimates are very important in terms of informing public health decisions and may impact issues relating to prevention, diagnosis and treatment of HIV. Working with the European Centre for Disease Prevention and Control has given the opportunity to present this work at their annual “HIV/Sexually transmitted infections” surveillance meetings where national-level surveillance experts and epidemiologists convene from many European countries.

List of Websites:

www.eurocoord.net