Research Update

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CLINICAL INVESTIGATION

Developing a multidisciplinary network for clinical research on HIV infection: the EuroCoord experience

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Frank de Wolf*[1,2], Caroline Sabin[3], Ole Kirk[4,5], Claire Thorne[6], Genevieve Chene[7] & Kholoud Porter[8]

[1]Stichting HIV Monitoring, Academic Medical Center, Amsterdam, the Netherlands
[2]Imperial College, London, UK
[3]University College London, London, UK
[4]Copenhagen HIV Programme, University of Copenhagen, Denmark
[5]Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark
[6]Institute of Child Health, University College London, London, UK
[7]Université Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, F-33000 Bordeaux, France
[8]Medical Research Council Clinical Trials Unit, London, UK
*Author for correspondence:
E-mail: info@EuroCoord.net

Over the past 15 years, European cohorts and collaborations have played a key role in developing our understanding of HIV progression and the effects of antiretroviral therapy, enabling European expertise to contribute directly to the advances in patient diagnosis and management worldwide, and providing a continued surveillance mechanism for detection of emerging problems at a European level. These collaborations now form the foundation of EuroCoord, a Network of Excellence, recently funded by the European Commission's 7th Framework Program for Health Research. EuroCoord currently comprises studies that jointly contain longitudinal data from almost 270,000 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 coinfection 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. Through a multidisciplinary approach, EuroCoord's overall aim is to address key areas of longitudinal HIV research aimed at improving the management and life of HIV-positive individuals, whilst allowing us to explore differences within subgroups.

Keywords: antiretroviral therapy • cohort collaboration • Europe • hepatitis • HIV • migrants • modeling • pediatric • pregnant women • seroconverters • TB

There are currently over 2.2 million people living with HIV across Europe, with an estimated 100,000 newly infected in 2009 alone [101]. Combination antiretroviral therapy (cART) has dramatically improved the outcome for those who are able to access it [1–3]. However, despite improvements in life expectancy in western Europe and other industrialized countries [4,5], it is generally still not comparable to that seen in the HIV-negative population [6–9]. cART is not a cure and, once initiated, anti-HIV drugs have to be taken for life. Given the potential for therapy failure due to difficulties with adherence, the emergence of resistance [10] and the development of adverse drug reactions as a result of long-term antiretroviral exposure [11], disease progression on treatment remains highly variable and requires continual monitoring. In addition, there could be changes in the circulating virus that may impact on the rate of disease progression and response to treatment [12,13].

Access to HIV treatment and care varies tremendously across the European continent. cART remains expensive (over €5000 per patient per year) [14] and is not universally and continuously available to all HIV-positive individuals in every country. Even when available, the essential tools for patient management, such as CD4 monitoring and viral load and resistance testing, are not necessarily accessible. With the challenges compounded by an epidemic of multidrug-resistant TB in some areas [15] and high rates of hepatitis B and C [16,17], the efforts made to date to

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improve patients' outcomes in western Europe need to be sustained and expanded to encompass all European citizens.

Europe has a particularly strong heritage of conducting well-designed cohort studies that follow (usually) large groups of HIV-positive people over many years [18–25]. These cohorts have been pivotal in contributing to HIV treatment guidelines and aiding clinical management. They complement clinical trials as they raise questions that may then be answered by trials and provide a resource for trial design. They also contribute to the assessment of long-term outcomes of therapy, which is important given the relatively short duration of follow-up in most clinical trials. As new HIV drugs are introduced and management practices change, it is only through the follow-up of HIV cohorts that we are able to continually assess risk factors for success and failure, the likely impact of such changes on the HIV population and the introduction and consequences of changes in the virus itself.

Recently funded through the European Commission's 7th Framework Program for a 5-year period, EuroCoord is a Network of Excellence (NoE) of four major European cohorts and collaborations:

- PENTA, a program of clinical trials and cohort studies, including the European Pregnancy and Pediatric HIV Cohort Collaboration, among HIV-positive children and pregnant women;
- CASCADE, a collaboration of 28 cohorts of adults with known dates of HIV seroconversion, providing a major source of information, particularly on HIV natural history;
- EuroSIDA, a cohort study of HIV-positive adults from >100 clinics in 33 countries across Europe;
- COHERE, a relatively new collaboration of 36 cohorts and collaborations of HIV-positive individuals, including adults, children and mother–child pairs.

Together, these cohorts and collaborations contribute data from almost 270,000 HIV-positive individuals across Europe. EuroCoord includes 23 partner institutions from 16 countries (Figure 1A) and >100 collaborating centers (Figure 1B), enabling EuroCoord to provide a truly European perspective. Its main aim is to exploit the scientific strengths that exist within each of the networks and to identify any complementarities between the research objectives of each, to enable investigators to enhance the research that is conducted, thus providing added value.

The purpose of this paper is to provide an overview of the development of EuroCoord, highlighting key achievements of its founding networks and its future scientific aims.

Key achievements

The four networks that make up EuroCoord have published extensively over the past 15 years. Study findings have been incorporated into national and international treatment guidelines. As well as the research highlighted in this section, the networks have included a program of training and staff exchange.

PENTA's contributions to pediatric HIV knowledge include the results of the PENPACT 1 trial, run in collaboration with Pediatric AIDS Clinical Trials Group/International Maternal Pediatric Adolescent AIDS Clinical Trials Group, which demonstrated no difference in viral response when comparing children starting protease inhibitor treatment with those on non-nucleoside reverse transcriptase inhibitor-based regimens and that the timing of switch to second-line treatment does not affect long-term viral load [26]. Other research helping to optimize treatment of HIV-positive children has included investigation of planned treatment interruptions (PENTA 11 trial), which is now in 5-year long-term follow-up, together with ongoing immunology and neurodevelopmental studies. Pharmacokinetic studies contributing to licensing new indications for antiretroviral drugs for children are also a key activity. Research within the network has also contributed to a greater understanding of rates, risks and prevention of mother-to-child transmission of HIV in the cART era, including changes in mode of delivery, adverse effects of cART use in pregnancy and investigation of the emerging HIV epidemic in eastern Europe.

CASCADE has enhanced knowledge of the natural history of HIV, allowing patient outcomes to be improved. Some of its contributions have been: providing survival expectations and describing the extent to which these have changed following the availability of therapy and changes in patient management [27–29], providing clinicians with estimates of their patients' risk of developing AIDS and of dying given their age and current routine laboratory measurements [30], establishing that clinicians do not need to take account of their patients' rate of CD4 cell decline when considering whether to initiate therapy [31], defining expected levels of CD4 cell count and HIV viral load by time since infection [32,33] and emphasizing the continuing importance of HIV as an underlying condition even in supposedly non-HIV related causes [34]. Recently, CASCADE has quantified the likely risk of AIDS and death for individuals not initiating therapy at CD4 levels higher than currently recommended by guidelines, relative to individuals initiating therapy at these levels [35].

EuroSIDA is a prospective cohort study initiated in 1994 of more than 16,000 adult patients in 103 hospitals from 33 European countries (16 from eastern Europe) plus Israel and Argentina. Using direct data

Figure 1. EuroCoord Collaboration. Location and number of **(A)** partner institutions and **(B)** collaborating centers.

collection based on comprehensive standardized clinical record forms, the study has the flexibility to introduce new questions over time, where new issues arise and the ability to rapidly collect data from clinics to address such issues in a standardized way across Europe. The study also includes a plasma repository, currently containing approximately 70,000 specimens, which enables combining laboratory research (HIV drug resistance and hepatitis B and C coinfection) with the extensive clinical database [36–38]. The network centers on fostering excellence in research, sharing expertise and know-how and providing answers to clinically relevant key questions in HIV infection, such as: examining the efficacy of therapy and the factors that limit this [1,39–44], detecting current and emerging late onset adverse events among patients on cART [45,46], continuing the surveillance of HIV in clinics across Europe describing temporal changes and regional differences in parameters of overall health status and access to cART [18,47–50].

COHERE is a collaboration of 35 cohorts that started in 2005 with seed funding from the French National Agency for Research on AIDS and Viral Hepatitis, the Dutch HIV Monitoring Foundation and the Danish Augustinus Foundation. So far, its main contribution has been to epidemiological research on the prognosis and outcome of HIV-positive people at all ages from across Europe. The research conducted focuses on scientific questions requiring a large sample size of patients, which the contributing cohorts cannot answer individually and that do not overlap with existing collaborations between participating COHERE cohorts. Contributions have been made to knowledge on age-dependent variation in the response to cART [51], the occurrence, risk factors and prognosis of non-Hodgkin lymphoma and Hodgkin's disease in the cART era [52–54], the incidence and clinical outcomes of triple-class virologic failure in patients on long-term cART [55,56], the use of pneumocystis prophylaxis in the era of cART [57], and life expectancy in cART-treated patients over time [58].

EuroCoord structure

The EuroCoord network is structured into a series of workpackages (Figure 2). Briefly, it is overseen through a management workpackage, three cross-network workpackages (training and outreach, scientific oversight and data management), eight network-specific workpackages and three new areas of joint research (TB, migrant health and HIV modeling). These 15 workpackages are key to the success of EuroCoord. While the cross-network workpackages ensure that management of the four networks is streamlined, the network-specific workpackages allow the four networks, each of which serves a very different purpose, to remain as separate entities.

Cross-network activities

The main objective of the training workpackage is to build on the extensive ongoing program of training within the network, as well as training activities that exist through other EU-funded projects, such as NEAT and CHAIN, to augment and update the skills of health professionals and researchers. These include clinical-management skills as well as those relating to epidemiological and statistical methodology, an area that is very well represented within EuroCoord institutions.

The scientific oversight workpackage has the remit of overseeing and co-coordinating the ongoing scientific work across the NoE in order to ensure that EuroCoord is able to maximize the value of the research that is conducted. Central to the success of this workpackage is the creation of specialist subgroups to cover areas of common interest; current groups include those considering pharmacokinetics and pharmacology, immunology and virology, statistical methodology, and hepatitis coinfection. The creation of these subgroups is flexible and subgroups will be created and disbanded according to the scientific questions. In addition, other key aims of this workpackage are to facilitate translation of any research outputs into policy; for example, through links with the European AIDS Clinical Society and the International AIDS Society and to develop collaborations with other research networks. Importantly, this workpackage also acts as the face of EuroCoord, to communicate the outputs of the network to the scientific community and the wider public.

The data management workpackage aims to harmonize data collection across the EuroCoord network. Currently, similar information is collected across the four networks and this workpackage will develop shared data formats, standard operating procedures and protocols, which will ensure that these common data items are collected in a standard format, thus permitting easy sharing of data. Use of the HIV Cohorts Data Exchange Protocol, a protocol developed jointly between the participating networks [59] and already widely used when aggregating datasets, will be extended. A public website has been created to disseminate the ongoing work and to take input from both members of the network and other interested parties [102].

Network-specific activities

EuroCoord's ultimate research aim is to improve the management and life of HIV-positive individuals. Investigators aim to do this by conducting research in order to address key questions within the following broad areas.

Characterizing HIV-positive populations in Europe

Knowledge of the characteristics of the HIV-positive population and how this is changing over time is crucial

to the development and evaluation of appropriate healthcare interventions, resource planning and allocation, and to limit the spread of the epidemic. Work in this area, particularly in central and eastern Europe, will focus on facilitating the identification of early infection, reducing the burden on healthcare resources from patients who present late and characterizing the different populations who have HIV.

Understanding pathogenesis

A greater insight into host (including genetic) and viral determinants of disease progression and control is of immense importance for forming the basis of patient monitoring in order to support clinical decision making. Increases in knowledge of pathogenesis can also help provide insights into vaccine development, particularly for therapeutic vaccines, which is an active area of research for the pharmaceutical industry. Work in this area will focus on viral dynamics, HIV resistance and an increased understanding of biomarkers in HIV infection.

Uptake of & response to therapy

The high cost of cART means that access to care, and hence response to treatment, varies tremendously across the European continent. However, progress is encouraging, with a 36% increase between 2008 and 2009 in numbers of people receiving treatment and with 93% of HIV-positive pregnant women on treatment to prevent mother-to-child transmission [103]. Work in this area will focus on describing uptake and response to cART and the comparison of response to treatment in different patient populations.

Implications of long-term infection & exposure to therapy

The WHO has highlighted the urgent need to strengthen cART pharmacovigilance [104] and new EU legislation prioritizes the importance of measures to monitor long-term adverse drug reactions [60]. 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 [61–64]. Work in this area will focus on the extent of treatment exhaustion and its implication, toxicities associated with antiretroviral therapy and long-term outcomes.

Implications of specific management strategies

Improving patient management is key to improving patient care and hence outcomes. Work in this area will focus on strategies for management of different patient groups, including individuals with extensive drug resistance and children/adolescents and how best to measure patient care.

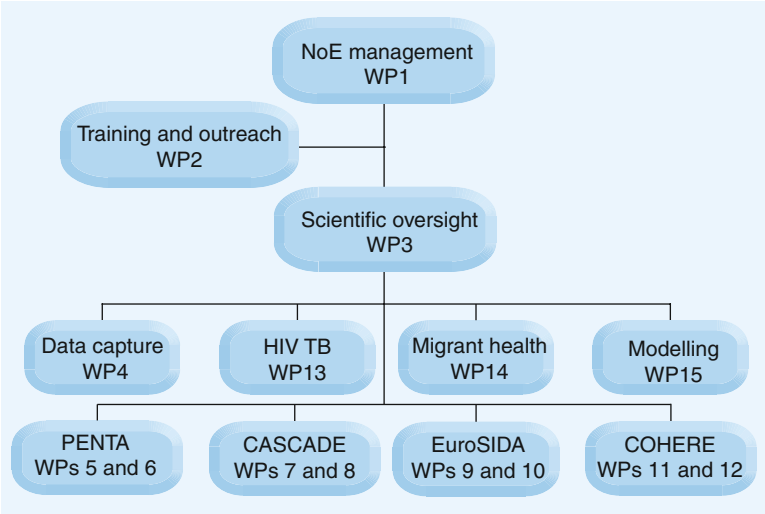

Figure 2. EuroCoord workpackage structure.
NoE: Network of Excellence.

Whilst management strategies and treatment guidelines are frequently updated, there is currently no consistent measure for quality of care and how it relates to clinical outcome. An objective of EuroCoord is to establish a benchmark for quality of care by considering the adequacy of treatment and the impact on morbidity and mortality within centers, countries and regions.

Improving the management of hepatitis coinfection

A significant proportion of HIV-positive persons are coinfected with hepatitis B or C viruses, which presents an additional complication for patient management and potentially a more serious outcome for those who are coinfected. EuroCoord aims to assess the consequences of hepatitis C virus infection on HIV disease and the outcome of patients on anti-hepatitis C virus therapy. As new anti-hepatitis C virus medications are introduced, their uptake in European clinics will be tracked and the outcomes of patients prescribed them will be monitored.

New areas of joint research

A particularly exciting feature of the network is the development of three new programs of research into HIV and TB, HIV and migrants and modeling the HIV epidemic. Migration has had an impact on the spread of both HIV and TB, particularly since the 1980s, when migration levels have been at their highest, especially since migration patterns mostly involve the flow of people from high to low HIV and TB incidence regions.

EuroCoord aims to improve the management of TB–HIV-positive individuals and gain a greater understanding of the healthcare needs of HIV-positive 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.

The WHO estimates that a third of the world's population is infected with TB and [105], although countries in the WHO European region account for only 5% of all TB cases, 12 of the 14 countries most affected by multidrug-resistant TB are in this region. This has resulted in these countries having TB incidence rates comparable to those in Africa and the region's overall treatment success rate being the same as that in Africa. Furthermore, while TB rates have decreased in most of western Europe over the past 10 years, rates have increased in eastern Europe. Besides, TB is a leading killer among HIV-positive people with mortality rates of approximately five per 100,000 in the general population in central Europe and more than ten per 100,000 in eastern Europe. EuroCoord's wide spectrum of research into HIV and TB will include studies of the incidence and prognosis of TB and temporal changes to these, the effects of anti-TB therapy and prophylaxis, the impact of TB on the management of HIV and the identification of risk factors for the development of immune reconstitution inflammatory syndrome.

HIV within migrant populations, largely (but not exclusively) from sub-Saharan Africa, is increasingly a feature across Europe. Migrant populations are a heterogeneous group and comparatively little research currently addresses HIV in these populations [65]. Furthermore, migrant populations often experience inequalities in health and health outcomes, including HIV. Whilst a proportion of HIV infection in migrants is first diagnosed in their host country, acquisition is often assumed to have occurred premigration. However, there is evidence that HIV is being increasingly acquired post-migration [66]. A key aim of EuroCoord is to provide evidence to support policy and intervention development that will prevent HIV infection and improve diagnosis and prognosis for migrant populations living with HIV in Europe.

The success of UNAIDS in highlighting HIV as a global issue has been due in part to the modeling work that has produced estimates of numbers of people living with HIV, of those in need of treatment, of orphans and so forth in every country. It has been learnt that it is useful to produce best estimates, with suitable plausibility limits, even for countries where data are poor and there is much uncertainty, in order to be able to build up a global picture. The process of producing such estimates and compiling them into a regular report can help with providing an impetus for countries to upgrade their surveillance data and hence improve estimates, which in turn are vital for evaluating the impact of prevention, treatment and care programs. UNAIDS estimates of the number of people with HIV, largely based on prevalence surveys, are produced for European countries [101]. However, in order to be best placed to ensure the issues of prevention, diagnosis and treatment of HIV remain on the political agenda in Europe, estimates are required that describe not only the number of people living with diagnosed and undiagnosed HIV infection, but also a breakdown of important aspects of the status of those infected (e.g., CD4 count, distribution of the undiagnosed, number/proportion on cART, number with triple-class failure/resistance and number of infected women who become pregnant) according to diagnosis status. Although the field is in its infancy, early stochastic computer-simulation models of HIV progression and the effect of cART have been developed that have the potential to produce such estimates. These models are based heavily on data derived from European HIV cohort studies. A new stochastic computer-simulation model will be developed that can be used for the purpose of reconstructing and projecting the status of HIV-positive individuals in a given country.

Future perspective

Over the next 5 years it is the intention of the EuroCoord NoE to strengthen HIV cohort research across Europe, in both adults and children. By taking a truly multidisciplinary approach, and by combining datasets of such large size, EuroCoord will be in the unique position of being able to address key areas of research that will improve the management and lives of those with HIV. Much of this research would not be possible within individual cohorts or countries due to the small size of some of the cohorts. Finally, utilization of a common research platform will permit the most complementary, collaborative and competitive science to be undertaken.

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Executive summary

Background

- European clinical cohorts and cohort collaborations have played a key role in developing our understanding of HIV progression and the effects of antiretroviral therapy.
- EuroCoord is a network of excellence established by four HIV cohorts and collaborations within Europe:
  - PENTA, a program of trials and cohort studies conducted among HIV-positive children and pregnant women;
  - CASCADE, a collaboration of 28 cohorts of adults with known dates of HIV seroconversion, providing a major source of information on HIV natural history in particular;
  - EuroSIDA, a cohort study of HIV-positive adults from >100 clinics in 33 countries across Europe;
  - COHERE, a collaboration of 36 cohorts and collaborations of HIV-positive individuals, including adults, children and mother–child pairs.
- The four networks that make up EuroCoord have published extensively over the past 15 years on a broad variety of studies ranging from the natural history of HIV, to the effect of timely introduction of combination antiretroviral therapy, the risks of resistance to antiretroviral drugs and the risks of comorbidity in the treated population. Study findings have been incorporated into national and international treatment guidelines. As well as the research, the networks have included a program of training and staff exchange.

Structure

- From January 2011, EuroCoord is funded for 5 years by the European Commission's 7th Framework Program for Health Research.
- EuroCoord currently comprises studies that jointly contain longitudinal data from almost 270,000 HIV-positive individuals from all-risk groups across the European continent and beyond.
- EuroCoord is structured into a series of workpackages, which are key to its success. It is conducted through a management workpackage, three cross-network workpackages (training and outreach, scientific oversight and data management), eight network-specific workpackages and three new areas of joint research (TB, migrant health and HIV modeling). While the cross-network workpackages ensure that management of the four networks is streamlined, the network-specific workpackages allow the four networks, each of which serves a very different purpose, to remain as separate entities.

Overall aim

- Through a multidisciplinary approach, EuroCoord's overall aim is to address key areas of longitudinal HIV research aimed at improving the management and lives of HIV-positive individuals, whilst allowing explorations of differences within subgroups to be conducted.

Key research aims

- To improve the management and lives of HIV-positive individuals, by:
  - Characterizing and modeling HIV-positive populations in Europe;
  - Improving understanding of pathogenesis;
  - Documenting uptake of and response to therapy;
  - Evaluating implications of long-term HIV infection and antiretroviral therapy exposure;
  - Assessing implications of specific management strategies;
  - Analyzing effects and improving management of hepatitis and TB coinfection.
- To develop and implement novel methodology, research platforms and technologies.
- To establish training programs to improve clinical management and research skills.

New EuroCoord research

- HIV and TB:
  - Monitor incidence, long-term prognosis and temporal changes;
  - Effects of anti-TB therapy and prophylaxis;
  - Impact on management of HIV;
  - Risk factors for immune reconstitution inflammatory syndrome.
- HIV and migrants
  - Determination of likely country of acquisition;
  - Identify barriers to prevention, testing and treatment;
  - Key HIV outcomes and relationship with country of habitation.
- Modeling
  - Develop stochastic computer-simulation model to provide Europe-wide consensus estimates for rates of diagnosis, treatment usage, resistance, pregnancy, AIDS/death and so forth.

Future perspective

- EuroCoord will strengthen European HIV cohort research, by bringing it within a single pan-European network of cohort studies, exploiting the scientific strength of each participating network and building on complementarities between them.
- Through utilization of a common research platform, EuroCoord will permit the most complementary, collaborative and competitive science to be undertaken.

EuroCoord appendix

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Geneviève Chêne, University Bordeaux Segalen, France; Dominique Costagliola, Institut National de la Santé et de la Recherche Médicale, France; Julia Del Amo, Instituto de Salud Carlos III, Spain; Carlo Giaquinto, Fondazione PENTA, Italy; Di Gibb (Scientific Coordinator April 2012–June 2013), Medical Research Council, UK; Jesper Grarup, Københavns Universitet, Denmark; Ole Kirk, Københavns Universitet, Denmark; Bruno Ledergerber, University of Zurich, Switzerland; Laurence Meyer, Institut National de la Santé et de la Recherche Médicale, France; Alex Panteleev, St. Petersburg City AIDS Centre, Russian Federation; Andrew Phillips, University College London, UK; Kholoud Porter (Executive Board Chair January 2011–March 2012), Medical Research Council, UK; Caroline Sabin (Scientific Coordinator January 2011–March 2012), University College London, UK; Claire Thorne (Executive Board Chair Elect April 2012–June 2013), University College London, UK; Stephen Welch, Fondazione PENTA, UK.

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†Ex-officio members.

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