

The EuroSIDA study: 25 years' scientific achievements

Running title: The EuroSIDA study

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Abstract:

The EuroSIDA study was founded in 1994, and follows adult people living with HIV (PLHIV) in 100 collaborating clinics across 35 countries covering all European regions, Israel and Argentina. The study aims to study the long-term virological, immunological and clinical outcome of PLHIV, and to monitor temporal changes and regional differences in outcomes across Europe. Annually collected data includes basic demographic characteristics, information on AIDS- and non-AIDS-related clinical events, details about antiretroviral therapy (ART), hepatitis C treatment and other medications, in addition to a range of laboratory values. The summer 2016 dataset held data from a total of 23,071 individuals contributing with 174,481 person-years of follow-up, while EuroSIDA's unique plasma repository held over 160,000 samples. Over the past 25 years, close to 300 articles have been published in peer-reviewed journals (h-index 52), covering a range of scientific focus areas, including monitoring of clinical and virological outcomes, uptake, efficacy and adverse events to ART, influence of hepatitis coinfection, variation in the quality of HIV care and management across settings and regions, and biomarker research. Recognizing that there remain unresolved issues in the clinical care and management of PLHIV in Europe, EuroSIDA was one of the cohorts to found the RESPOND cohort consortium on infectious diseases in 2017. In celebration of the EuroSIDA study's 25th anniversary, this article aims to summarize key scientific findings and outline current and future scientific focus areas.

Introduction

The EuroSIDA study was founded in 1994 with the aims of studying the long-term virological, immunological and clinical outcomes for HIV-1 infected individuals, and of assessing the impact of antiretroviral drugs on the outcomes of people living with HIV (PLHIV) across Europe. The past two decades have seen dramatic changes to the HIV epidemic in Europe, but many issues on the clinical care and management of HIV remain unresolved. EuroSIDA has aimed to stay at the forefront of answering the questions most meaningful to the clinical care of PLHIV for the past 25 years. This has demanded a dynamic research agenda within a flexible cohort structure. Thus, while the main objectives of the study remain the same as in 1994, EuroSIDA has continuously reevaluated the scientific scope of the study, as well as the data needed to answer key scientific questions, and the objectives of the study have broadened to four major themes: monitoring the efficacy of antiretroviral therapy (ART), monitoring current or emerging late onset adverse events to ART, monitoring temporal changes and regional differences in HIV care and management across Europe, and monitoring the uptake and outcome of hepatitis C (HCV) therapy, particularly direct acting antivirals (DAAs). In celebration of the EuroSIDA study's 25th anniversary, this article aims to summarize key scientific findings and outline current and future scientific focus areas.

Sites and participants

EuroSIDA currently has 100 participating clinics across 35 countries, each clinic headed by a principal investigator. The principal investigator is responsible for enrolling participants, collecting and reporting data, seeking and maintaining ethical approval, and for obtaining informed consent from all participants, according to local regulations. Any principal investigator is also eligible for the EuroSIDA Steering Committee, which is elected by the EuroSIDA study group for a five-year period. The EuroSIDA Coordinating Center is located at CHIP (Centre of Excellence for Health, Immunity and Infections) at Rigshospitalet, Copenhagen, Denmark.

As of June 2016 EuroSIDA held data from 23,071 participants contributing with 174,481 person years of follow-up (PYFU). Characteristics of EuroSIDA participants with ongoing follow-up are given in table 1. Participants are HIV-1

positive individuals aged 16 years or older, who have a planned appointment at the collaborating clinic. The first two cohorts included only participants with a CD4 cell count of less than 500 cells/ μ L in the previous 4 months before enrolment, but this inclusion criterion was dropped with the third cohort due to introduction of combination ART. People are consented and enrolled consecutively from each clinic during time-limited enrolment waves and thus both people diagnosed with HIV recently and decades ago may be included. The consecutive enrolment aims to ensure that no participant is excluded due to concern of irregular follow-up or included based on treatment status.

EuroSIDA began recruiting participants in 1994, and to ensure that EuroSIDA remains representative of the current HIV population, new cohorts have been enrolled with regular intervals, coming to a total 10 enrolment waves over 23 years (figure 1). EuroSIDA seeks to include centers from across Europe, ensuring that all European geographic regions are well represented in the study. The first participants from Central Europe were recruited in 1999 when collaborating sites from the Czech Republic, Hungary and Poland joined. The network has since expanded to include most countries from Central Europe and also many countries in the former Soviet Union. The latest enrolment wave included an additional 4,000 HIV/HCV coinfecting individuals, and ran from 2014 to 2016.

Data collection

EuroSIDA is a non-interventional study which only collects data from participants' routine clinic visits. Until 2016, data was collected at enrolment and thereafter twice annually. To adapt to the clinical reality that many PLHIV now have less frequent clinic visits than when the study was initiated, data collection was reduced to once annually from autumn 2016 and onward.

Table 2 outlines data collected in EuroSIDA. This includes basic demographic characteristics, laboratory values, information on ART, and information about treatment related to cardiovascular diseases. Dates of diagnosis of all AIDS-defining illnesses are recorded, using the 1993 Centers for Disease Control and Prevention clinical criteria [1]. Since 1998, information about adverse events has been collected, according to the Data Collection on Adverse events

of Anti-HIV Drugs (D:A:D) definitions [2], and detailed information about the cause of death is collected using the Coding of Death (CoDe) algorithm [3]. EuroSIDA started collecting more detailed data on anti-HCV treatment in the summer of 2014, and further, an adverse events form is completed for all participants who discontinue an anti-HCV treatment regimen earlier than scheduled due to toxicity or intolerance. In addition to data, most centers collect plasma samples twice annually as part of the routine clinical management.

By autumn 2014 EuroSIDA transitioned from collecting data on paper forms to using the electronic case report system, REDCap [4]. Alternatively, sites may transfer data electronically using the HICDEP format [5,6]. Throughout the study, the backbone of the EuroSIDA data collection has remained similar to that of the first data collection. However, the forms undergo regular revision, and questions have been added to or removed from the forms as specific research questions have arisen; e.g. serum-creatinine was included in the form as concerns of renal toxicity arose. In addition to the standard data collection, individual surveys have been conducted to address specific questions (table 2).

With the autumn 2016 data collection, a modular data collection was introduced. The modular data collection means that a set of core values is collected for all patients in a core module, while other data is collected only for a relevant subset of patients, allowing sites and participants to opt in or out of specific modules. For example, data related specifically to HCV (including liver-specific laboratory values, anti-HCV treatment etc.) is only requested for HIV/HCV co-infected participants.

Quality assurance:

To ensure correct selection of participants and verification of collected data, an extensive quality assurance program has been in place since EuroSIDA was initiated. Monitoring previously included on-site visits to all participating centers. However, as the study has evolved, new processes have been formulated to adapt to new requirements of the study. Thus, since 2017 EuroSIDA has transitioned to centralized monitoring, building on the risk-based

monitoring used in clinical trials [7]. The monitoring includes regular data checks, queries, central validation of events, and random event monitoring performed by investigators on-site, which ensures that EuroSIDA retains a high data quality. If a collaborating clinic continuously delivers poor data or continuously does not deliver data, that site may become inactivated from EuroSIDA, as described in the participation criteria, available online <https://chip.dk/Studies/EuroSIDA/Study-documents>. A site may also choose to discontinue its engagement in EuroSIDA.

Loss to follow-up:

The annual loss-to-follow-up (LTFU) rate (defined as no CD4 cell count measurement, HIV-RNA measurement or clinic visit for 365 days or more) has been relatively low throughout the study. Analyses performed in 2008 found that the incidence of LTFU within EuroSIDA was 3.72/100 PYFU, but varied substantially across countries [8]. In an attempt to minimize LTFU, clinics are queried if a participant has no recorded visit for more than one year, and again after 2 and 5 years.

Findings to date

The EuroSIDA study group has published close to 300 articles in peer-reviewed journals (h-index 52) since 1997, on its own and in collaboration with other cohorts, if larger data sets have been required. A complete list of publications may be found on the EuroSIDA website: <http://www.chip.dk/eurosidea>. Some major focus areas for publications are summarized below.

Temporal trends and regional differences in the clinical course of HIV:

EuroSIDA was among the first studies to report on the dramatic declines in mortality following the introduction of new, potent antiretroviral regimens in the mid-1990's [9]. Studies published in 2000 and 2003 showed continued declines in mortality and AIDS-defining illnesses following the introduction of combination ART [10,11]. EuroSIDA continues the surveillance of trends in the prognosis for PLHIV, and has published several articles regarding cause-

specific mortality [12], AIDS and non-AIDS related mortality [13–15], as well as short-term clinical disease progression [16,17]. In recent years, EuroSIDA has focused on regional differences in outcomes, and has shown significant variability in mortality rates across regions of Europe, Israel and Argentina [18].

Uptake, efficacy of and adverse events to ART:

Monitoring the usage and efficacy of ART is central to EuroSIDA's work, alongside surveillance of long-term adverse events [19]. EuroSIDA started to collect data on adverse events in 1998 and information on non-AIDS events have been routinely collected since 2001. In 1999, EuroSIDA was a founding partner of the D:A:D study together with nine other cohorts (<http://www.chip.dk/Studies/DAD/About>). This cohort collaboration has reported extensively on long-term adverse events to ART, including in particular cardiovascular disease [20,21]. EuroSIDA was among the first to demonstrate an increased incidence of chronic kidney disease with increasing exposure to tenofovir disoproxil fumarate (TDF), and also found an increased risk of chronic kidney disease in association with the use of either ritonavir-boosted atazanavir or lopinavir or unboosted atazanavir [22]. This work was later carried on in the D:A:D study with EuroSIDA as an important contributor. A recent study found an increased incidence of bone fractures among people ever exposed to TDF [23]. Other EuroSIDA work has included assessment of long-term efficacy of ART and predictors of virological success and failure [24,25], in addition to monitoring resistance across Europe, e.g. demonstrating geographical and temporal differences in resistance testing strategies and in detected drug resistance [26].

Surveillance of AIDS and non-AIDS events and opportunistic infections:

With follow-up accumulating since 1994, EuroSIDA has a unique opportunity to monitor trends in AIDS- and non-AIDS events, including cancers and organ-specific end stage diseases. EuroSIDA contributed evidence to suggest that pneumocystis pneumonia (PCP) prophylaxis as well as chemoprophylaxis for other common opportunistic infections could be safely discontinued in persons on ART with a sustained CD4 cell count above 200 cells/uL [27,28]. Further, EuroSIDA has published a number of articles exploring the influence of viral load and CD4 counts on the development

of clinical events, suggesting that AIDS, non-AIDS and death rates are strongly influenced by the immunological and virological status, but vary minimally by ART-regimen for a given CD4 cell count and viral load [15,29,30]. Recent years have seen an increased focus on non-AIDS-related diseases as the HIV population ages. Two recent studies showed that the relative importance of factors other than those related to optimal HIV control (e.g. biological age and smoking), increases with increasing age in the development of non-AIDS-related clinical events, respectively cancers [31,32].

Assessing the influence of hepatitis co-infection:

An important focus area for EuroSIDA is hepatitis research, with a particular focus on HCV co-infection [33–36]. One study found that around 1/4 deaths among HCV treatment-naïve individuals were attributable to HCV infection [33]. With the introduction of DAAs against HCV, EuroSIDA decided to enroll 4000 HIV/HCV co-infected individuals in 2014-2016, bringing the total number of HIV/HCV co-infected participants to forty-six percent (46.3%, n = 5,706) of the people under active follow-up. Thus, EuroSIDA follows one of the largest cohorts of HIV/HCV co-infected patients in the world. In total, around a quarter of all HIV/HCV co-infected individuals in EuroSIDA received anti-HCV treatment between 1998-2010, with an increasing trend over time and marked regional differences in the uptake of anti-HCV therapy across Europe [37]. Ongoing work aims to establish the continuum of HCV care, to monitor short-term and long-term uptake, efficacy, and adverse events to DAAs across Europe, and to monitor long-term risk of liver disease and other clinical outcomes [38,39].

Regional differences in the quality of HIV care and management:

EuroSIDA is the only cohort of PLHIV that includes participants from all European geographical regions, including countries from the eastern part of Europe (figure 2). Recruitment of participants from this region started in 1999, and EuroSIDA has been at the forefront of showing the now well-known regional differences in the HIV-epidemic across Europe, with a continued poorer outcome for individuals in Eastern Europe [18,40,41]. Such findings have led to an increased focus on benchmarking quality of care [42]. Recent studies explored variation in ART coverage and

virological suppression across countries of Europe, and across risk groups, and demonstrated substantial regional variation with particularly low levels of ART-coverage and virological suppression in Eastern Europe, and among people infected by injection drug use [43,44]. Results from a clinic survey showed differences in HIV care and management across Europe, and it is possible that such differences may contribute to the observed poorer clinical outcomes in Eastern Europe [45]. Other quality of care work has looked at the optimal frequency of viral load monitoring [46]. Benchmarking and quality of care research remains a focus area for EuroSIDA, and work is ongoing to triangulate different data sources and to strengthen the cohort structure in Eastern Europe.

Biomarker research and using the EuroSIDA plasma repository:

EuroSIDA's large plasma repository contains in excess of 160,000 prospectively collected plasma samples from a majority of EuroSIDA clinics since the initiation of the study. The potential of this unique biobank is demonstrated by the diversity of the studies performed using samples from the repository: EuroSIDA investigators were among the first to show that hyaluronic acid strongly predicted the 5-year risk of liver-related events among people with HIV and chronic HBV and/or HCV [47]. Another study explored the role of resistance mutations in subsequent risk of virological failure to first line non-nucleoside reverse transcriptase inhibitor-based ART, identifying a novel mechanism for nevirapine resistance [48]. Current research draws on the repository to identify biomarkers predictive of clinical endpoints. Specifically this has yielded publications estimating the optimal cut-off for prostate specific antigen to predict prostate cancer among PLHIV [49], and exploring the role of B-cell dysfunction in developing lymphomas [50]. The plasma repository is likely to play an even bigger part in future research, allowing investigators to explore the natural history of a wide array of diseases and their underlying pathophysiology.

Public health impact

EuroSIDA strives to make clinically relevant research, and several findings have made their way into treatment guidelines (including interruption of chemoprophylaxis for opportunistic infections). EuroSIDA has provided an up-to-date picture of clinical practice in HIV clinics across Europe over the past 25 years, which has helped to inform

public health experts and target programmatic responses. Of particular importance, EuroSIDA has been a pioneer in establishing HIV research in Central and Eastern Europe and was among the first to show regional disparities and the burden of HCV- and TB-coinfection in Eastern Europe. Results from EuroSIDA have thus contributed to attracting political and public attention to the situation in Eastern Europe. Furthermore, strong collaborations with policy makers such as the European Centre for Disease Prevention and Control (ECDC), have supported research utilization in health care policy.

Strengths and limitations

The size and geographical distribution of the EuroSIDA study are among its major strengths, and EuroSIDA is the only cohort of PLHIV that includes participants from all European geographical regions, including Eastern Europe. Thus, EuroSIDA has a unique opportunity of analyzing the HIV epidemic in this region. The standardized data collection allows for comparing high quality data from collaborating sites in 35 countries, and the consistent collection of core data throughout the study's existence allows for monitoring temporal trends.

A limitation of the study is that data collected by nature is limited and reflects the availability of data as well as the steering committee expert opinion on which variables are most essential to collect. On the other hand, the clinical experts ensure a clinically driven research agenda, and the flexibility of the data collection allows that emerging questions may be addressed promptly. Clinics in EuroSIDA are not selected at random, and participating sites are primarily urban clinics, many of which are university-affiliated [45]. Also, while being instrumental to addressing questions related to coinfection with viral hepatitis, the decision to include only HIV/HCV coinfecting people in the latest enrolment wave may affect the generalizability of our findings to the whole HIV-positive population. On the other hand, this makes the cohort fit to address questions about one of the largest health threats affecting PLHIV today.

Lessons learned

While some of EuroSIDA's limitations (e.g. the risk of selection bias, missing data, unmeasured confounding) are inherent to cohort research and cannot completely be avoided, some lessons for a strong cohort design have been learned.

Firstly, an international research collaboration of clinicians allows for combining clinical hypothesis-driven research with experience on the various public health challenges across Europe and facilitates a quick dissemination of knowledge into clinical practice. EuroSIDA's continuous expansion into new countries highlights the value of international knowledge sharing in addressing public health issues and establishing best practices. While EuroSIDA thus keeps a clinically driven research agenda, patient-centeredness and patient-involvement rightly plays a bigger part in health-care and research today than when EuroSIDA was founded, and it is evident that co-creation and a close involvement of patients should be central in any future cohort study.

In order to address the representativeness of the cohort, future studies may benefit from collecting information such as a typology of the participating clinics in addition to the size and demographic characteristics of cohort participants relative to all PLHIV followed at each clinic. Information about the number of people approached and reasons for accepting or refusing to participate would further help to address representativeness and describe the cohort population. The fact that EuroSIDA participants may be included at different stages of their HIV infection may be a strength in that it allows inclusion of a representative sample of people followed at each participating clinic, but may also be a limitation in that differences in disease stages may affect clinical outcomes, treatment and management. This highlights the importance of considering the effects of inclusion and exclusion criteria. Further, future cohorts may wish to make additional efforts to ensure adequate representation of marginalized groups that may not access testing and care. Finally, the transition to electronic data collection allowed us to introduce data entry rules that have made it possible to discriminate incomplete reporting from missing data due to other reasons. This previously was not possible and has helped to minimize missing data.

EuroSIDA: The next 25 years?

EuroSIDA's diverse research agenda over the past 25 years illustrates the ability of cohorts to provide real-life data that may be used by decision-makers and generate new hypotheses, as well as providing a significant contribution to clinical treatment guidelines. Cohort studies can provide long-term follow-up and clinical outcomes of a sample of the affected population, rather than the laboratory endpoints and short term outcomes that are often used in clinical trials. As the clinical treatment and management of HIV has improved, the relative importance of such long-term data has increased. Questions related to the prevention among those at risk of acquiring HIV, monitoring the safety and efficacy of pre exposure prophylaxis (PrEP), assessing the role of coinfections and comorbidities, and identifying drivers of inequalities in health are examples of questions not readily addressed in clinical trials, but which may be addressed in cohort studies. Recognizing that HIV remains a significant public health problem, EuroSIDA entered RESPOND as a founding partner. RESPOND, the International Cohort Consortium of Infectious Diseases (<https://www.chip.dk/Studies/RESPOND>), strives to continue 25 years of academic collaboration in HIV cohort studies and which includes many of the cohorts previously contributing to collaborations such as the D:A:D study, ART-CC and COHERE. The aim of RESPOND is to build an innovative, flexible and dynamic cohort consortium for the study of infectious diseases, including HIV and people at risk for HIV, as a generic structure for facilitating multi stakeholder involvement. Within RESPOND, EuroSIDA will continue to address unmet, innovative research questions that can only be met within a multi-cohort structure. There is a wide portfolio of research questions ongoing in research under three core themes: public health, outcomes with ART, and hepatitis. The modular data collection in RESPOND allows additional research modules to be added, as new research questions arise.

Collaboration

More information about the study is available on EuroSIDA's website: <http://www.chip.dk/Ongoing-Studies/EuroSIDA/About>. Any investigator or external collaborator may submit a research proposal, which goes through feasibility checks and is reviewed by the steering committee before it may be carried out. Investigators must

seek their own funding for specific research projects. Information on how to submit a research proposal is available online: <http://www.chip.dk/Studies/EuroSIDA/Submit-research-concept>.

Conclusions and future perspectives

For the past 25 years, the EuroSIDA study has been instrumental in providing knowledge about HIV and AIDS in Europe. EuroSIDA strives to continue generating science to improve outcomes for PLHIV. Current focus areas roughly fall into the following categories: i) hepatitis co-infection, ii) tuberculosis co-infection, iii) biomarkers of cancer and clinical outcomes, and iv) quality of care and public health issues. In addition, EuroSIDA continues to have a specific focus on the HIV-epidemic in the eastern part of Europe and in expanding the network into countries with poor or no existing HIV surveillance. With the key role in the cohort collaboration, RESPOND, EuroSIDA aims to continue to be at the forefront of HIV observational research in the coming years.

Competing interests:

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References:

- 1 Centers for Disease Control and Prevention (CDC). 1993 Revised classification system for HIV infection and expanded surveillance case definition definition for AIDS among adolescents and adults. Morb Mortal Wkly report Recomm reports 1993; 41:i-19.
- 2 Friis-Møller N, Weber R, Reiss P, Thiébaud R, Kirk O, d'Arminio Monforte A et al. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. AIDS. 2003 May 23;17(8):1179-93.
- 3 Kowalska JD, Friis-Møller N, Kirk O, Bannister W, Mocroft A, Sabin C, et al. The Coding Causes of Death in HIV

- (CoDe) Project Initial Results and Evaluation of Methodology. *Epidemiology* 2011; 22:516–523.
- 4 Research Electronic Data Capture. <https://chip-crf.info/redcap/> (accessed 24th Nov 2018)
- 5 HIV Cohorts Data Exchange Protocol. <http://hicdep.org/> (accessed 24th Nov 2018)
- 6 <https://www.chip.dk/Studies/EuroSIDA/Study-documents> (accessed 24th Nov 2018)
- 7 U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring. August 2013.
- 8 Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A, Chentsova N, et al. Loss to follow-up in an international, multicentre observational study. *HIV Med* 2008; 9:261–269.
- 9 Mocroft A, Vella S, Benfield T, Chiesi a, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* 1998; 352:1725–1730.
- 10 Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, et al. AIDS across Europe, 1994-98: the EuroSIDA study. *Lancet* 2000 Jul 22;356(9226):291-6.
- 11 Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, Monforte a d’Arminio, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 2003 Jul 5;362(9377):22-9.
- 12 Mocroft A, Brettle R, Kirk O, Blaxhult a, Parkin JM, Antunes F, et al. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. *AIDS* 2002; 16:1663–71.
- 13 Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, et al. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. *J Acquir Immune Defic Syndr* 2010; 55:262–70.
- 14 Reekie J, Gatell JM, Yust I, Bakowska E, Rakhmanova A, Losso M, et al. Fatal and nonfatal AIDS and non-AIDS events in HIV-1-positive individuals with high CD4 cell counts according to viral load strata. *AIDS* 2011; 25:2259–68.
- 15 Mocroft A, Phillips AN, Gatell J, Horban A, Ledergerber B, Zilmer K, et al. CD4 cell count and viral load-specific rates of AIDS, non-AIDS and deaths according to current antiretroviral use. *AIDS* 2013; 27:907–18.
- 16 Lundgren JD, Mocroft A, Gatell JM, Ledergerber B, D’Arminio Monforte A, Hermans P, et al. A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the

- EuroSIDA study. *J Infect Dis* 2002; 185:178–87.
- 17 Mocroft A, Ledergerber B, Zilmer K, Kirk O, Hirschel B, Viard J-P, et al. Short-term clinical disease progression in HIV-1-positive patients taking combination antiretroviral therapy: the EuroSIDA risk-score. *AIDS* 2007; 21:1867–75.
- 18 Reekie J, Kowalska JD, Karpov I, Rockstroh J, Karlsson A, Rakhmanova A, et al. Regional differences in AIDS and non-AIDS related mortality in HIV-positive individuals across Europe and Argentina: the EuroSIDA study. *PLoS One* 2012; 7:e41673.
- 19 Podlekareva D, Grint D, Karpov I, Vassilenko A, Rakmanova A, Mansinho K, et al. Changing utilization of Stavudine (d4T) in HIV-positive people in 2006-2013 in the EuroSIDA study. *HIV Med* 2015; 16:533–543.
- 20 The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group, Friis-Møller N, Reiss P, Sabin CA, Weber R, El-sadr W, et al. Class of Antiretroviral Drugs and the Risk of Myocardial Infarction. 2007; 356:1723–1735.
- 21 The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination Antiretroviral Therapy and the Risk of Myocardial Infarction. *N Engl J Med* 2003; 349:1993–2003.
- 22 Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. *AIDS* 2010; 24:1667–1678.
- 23 Borges ÁH, Hoy J, Florence E, Sedlacek D, Stellbrink HJ, Uzdaviniene V, et al. Antiretrovirals, Fractures, and Osteonecrosis in a Large International HIV Cohort. *Clin Infect Dis* 2017; 64:1413–1421.
- 24 Reekie J, Mocroft a, Ledergerber B, Beniowski M, Clotet B, van Lunzen J, et al. History of viral suppression on combination antiretroviral therapy as a predictor of virological failure after a treatment change. *HIV Med* 2010; 11:469–78.
- 25 Paredes R, Mocroft A, Kirk O, Lazzarin A, Barton SE, van Lunzen J, et al. Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study. *Arch Intern Med* 2000; 160:1123–32.
- 26 Schultze A, Phillips AN, Paredes R, Battegay M, Rockstroh JK, Machala L, et al. HIV resistance testing and

- detected drug resistance in Europe. *AIDS* 2015; 29:1379–1389.
- 27 Weverling GJ, Mocroft A, Ledergerber B, Kirk O, Gonzales-Lahoz J, d'Arminio Monforte A, et al. Discontinuation of *Pneumocystis carinii* Pneumonia Prophylaxis After Start of Highly Active Antiretroviral Therapy in HIV-1 infection. *Lancet* 1999 Apr 17;353(9161):1293-8.
- 28 Kirk O, Reiss P, Uberti-Foppa C, Bickel M, Gerstoft J, Pradier C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med* 2002; 137:239–250.
- 29 Olsen CH, Gatell J, Ledergerber B, Katlama C, Friis-Møller N, Weber J, et al. Risk of AIDS and death at given HIV-RNA and CD4 cell count, in relation to specific antiretroviral drugs in the regimen. *AIDS* 2005; 19:319–330.
- 30 Mocroft A, Furrer HJ, Miro JM, Reiss P, Mussini C, Kirk O, et al. The incidence of AIDS-defining illnesses at a current CD4 count \geq 200 cells/ μ L in the post-combination antiretroviral therapy era. *Clin Infect Dis* 2013; 57:1038–47.
- 31 Shepherd L, Borges H, Ledergerber B, Domingo P, Castagna A, Rockstroh J, et al. Infection-related and -unrelated malignancies, HIV and the aging population. *HIV Med* 2016; 17:590–600.
- 32 Mocroft A, Laut K, Reiss P, Gatell J, Ormaasen V, Cavassini M, et al. Where is the greatest impact of uncontrolled HIV infection on AIDS and non-AIDS events in HIV? *AIDS*. 2018 Jan 14;32(2):205-215.
- 33 Peters L, Mocroft A, Lundgren J, Grint D, Kirk O, Rockstroh J. HIV and hepatitis C co-infection in Europe, Israel and Argentina: a EuroSIDA perspective. *BMC Infect Dis* 2014; 14:S13.
- 34 Rockstroh J, Mocroft a, Soriano V, Tural C, Losso M, Horban a, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. *J Infect Dis* 2005; Sep 15;192(6):992-1002.
- 35 Rockstroh JK, Peters L, Grint D, Soriano V, Reiss P, Monforte ADA, et al. Does hepatitis C viremia or genotype predict the risk of mortality in individuals co-infected with HIV? *J Hepatol* 2013; 59:213–220.
- 36 Soriano V, Mocroft A, Rockstroh J, Ledergerber B, Knysz B, Chaplinskas S, et al. Spontaneous viral clearance,

- viral load, and genotype distribution of hepatitis C virus (HCV) in HIV-infected patients with anti-HCV antibodies in Europe. *J Infect Dis* 2008 Nov 1;198(9):1337-44..
- 37 Grint D, Peters L, Schwarze-Zander C, Beniowski M, Pradier C, Battegay M, et al. Temporal changes and regional differences in treatment uptake of hepatitis C therapy in EuroSIDA. *HIV Med* 2013; 14:614–23.
- 38 Peters L. , Laut K, Resnati C, Del Campo S, Leen C, Falconer K, et al. Uptake of hepatitis C virus treatment in HIV/hepatitis C virus-coinfected patients across Europe in the era of direct-acting antivirals. *AIDS* 2018 Sep 10; 32(14):1995-2004.
- 39 Amele S, Peters L, Lundgren. The hepatitis C continuum of care among HIV-infected individuals in EuroSIDA. 16th European AIDS Conference Milan, Oct 25-27, 2017. Abstract PS9/1.
- 40 Bannister WP, Kirk O, Gatell JM, Knysz B, Viard J-P, Mens H, et al. Regional changes over time in initial virologic response rates to combination antiretroviral therapy across Europe. *J Acquir Immune Defic Syndr* 2006; 42:229–37.
- 41 Podlekareva D, Bannister W, Mocroft A, Abrosimova L, Karpov I, Lundgren JD, et al. The EuroSIDA study: Regional differences in the HIV-1 epidemic and treatment response to antiretroviral therapy among HIV-infected patients across Europe--a review of published results. *Cent Eur J Public Health* 2008; 16:99–105.
- 42 Podlekareva DN, Reekie J, Mocroft A, Losso M, Rakhmanova AG, Bakowska E, et al. Benchmarking HIV health care: from individual patient care to health care evaluation. An example from the EuroSIDA study. *BMC Infect Dis* 2012; 12:229.
- 43 Laut K, Shepherd L, Gottfredsson M, Sedlacek D, Knysz B, Begovac J, et al. Persistent disparities in antiretroviral treatment (ART) coverage and virological suppression across Europe, 2004 to 2015. *Euro Surveill.* 2018 May;23(21)
- 44 Laut K, Shepherd L, Gottfredsson M, Sedlacek D, Knysz B, Begovac J, et al. Variation in antiretroviral treatment (ART) coverage and virological suppression among three HIV key populations. *AIDS* 2018 Nov 28;32(18):2807-2819.
- 45 Lazarus J V., Laut KG, Safreed-Harmon K, Peters L, Johnson M, Fätkenheuer G, et al. Disparities in HIV clinic

- care across Europe: findings from the EuroSIDA clinic survey. *BMC Infect Dis* 2016; 16:335.
- 46 Reekie J, Mocroft A, Sambatakou H, Machala L, Chiesi A, van Lunzen J, et al. Does less frequent routine monitoring of patients on a stable, fully suppressed cART regimen lead to an increased risk of treatment failure? *AIDS* 2008; 22:2381–2390.
- 47 Peters L, Mocroft A, Soriano V, Rockstroh J, Rauch A, Karlsson A, et al. Hyaluronic Acid Levels Predict Risk of Hepatic Encephalopathy and Liver-Related Death in HIV/Viral Hepatitis Coinfected Patients. *PLoS One* 2013 May 27;8(5):e64283.
- 48 Paredes R, Puertas MC, Bannister W, Kistic M, Cozzi-Lepri A, Pou C, et al. A376s in the connection subdomain of HIV-1 reverse transcriptase confers increased risk of virological failure to nevirapine therapy. *J Infect Dis* 2011; 204:741–752.
- 49 Shepherd L, Borges ÁH, Ravn L, Harvey R, Bower M, Grulich A, et al. Predictive value of prostate specific antigen in a European HIV-positive cohort: does one size fit all? *Antivir Ther* 2016; 21:529–534.
- 50 Shepherd LC, Borges ÁH, Harvey R, Bower M, Grulich A, Silverberg MJ, et al. The extent of B-cell activation and dysfunction preceding lymphoma development in HIV-positive people. *HIV Med* 2018 Feb; 19(2):90-101.
- 51 Mocroft A, Reiss P, Rakhmanova A, Banhegyi D, Phillips AN, De Wit S, et al. A survey of ATRIPLA use in clinical practice as first-line therapy in HIV-positive persons in Europe. *Infection* 2014; 42:757–762.
- 52 Peters L, Mocroft A, Soriano V, Rockstroh JK, Kirkby N, Reiss P, et al. High rate of hepatitis C virus (HCV) recurrence in HIV-infected individuals with spontaneous HCV RNA clearance. *HIV Med* 2014; 15:615–620.
- 53 Viard J-P, Souberbielle J-C, Kirk O, Reekie J, Knysz B, Losso M, et al. Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study. *AIDS* 2011; 25:1305–1315.
- 54 Shepherd L, Souberbielle J-C, Bastard J-P, Fellahi S, Capeau J, Reekie J, et al. Prognostic value of vitamin D level for all-cause mortality, and association with inflammatory markers, in HIV-infected persons. *J Infect Dis* 2014; 210:234–43.
- 55 Grint D, Peters L, Rockstroh JK, de Wit S, Mitsura VM, Knysz B, et al. Increased incidence of antiretroviral

drug discontinuation among patients with viremic hepatitis C virus coinfection and high hyaluronic acid, a marker of liver fibrosis. *AIDS* 2014 Feb 20;28(4):577-87.

56 Soriano V, Grint D, D' A, Monforte A, Horban A, Leen C, et al. Hepatitis delta in HIV-infected individuals in Europe. *AIDS*. 2011 Oct 23;25(16):1987-92.

57 Trullas JC, Mocroft A, Cofan F, Tourret J, Moreno A, Bagnis CI, et al. Dialysis and renal transplantation in HIV-infected patients: a European survey. *J Acquir Immune Defic Syndr* 2010; 55:582–589.