







The EuroSIDA study: 25 years of scientific achievements

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The EuroSIDA study was initiated 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 outcomes of PLHIV and to monitor temporal changes and regional differences in outcomes across Europe. Annually collected data include basic demographic characteristics, information on AIDS- and non-AIDS-related clinical events, and details about antiretroviral therapy (ART), hepatitis C treatment and other medications, in addition to a range of laboratory values. The summer 2016 data set held data from a total of 23 071 individuals contributing 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, ART uptake, efficacy and adverse events, the influence of hepatitis virus 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 International Cohort Consortium of Infectious Disease (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.

Keywords: AIDS, cohort studies, Europe, HIV, surveillance

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Introduction

The EuroSIDA study was initiated in 1994 with the aims of studying the long-term virological, immunological and clinical outcomes of 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 in the HIV epidemic in Europe, but many issues regarding the clinical care and management of PLHIV 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 re-evaluated 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 associated with ART, monitoring temporal changes and regional differences in HIV care and management across Europe, and monitoring the uptake and outcomes of hepatitis C virus (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 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 5-year period. The EuroSIDA Coordinating Center is located at the Centre of Excellence for Health, Immunity and Infections (CHIP) at Rigshospitalet, Copenhagen, Denmark.

As of June 2016, EuroSIDA held data from 23 071 participants contributing to 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 < 500 cells/ μ L in the previous

4 months before enrolment, but this inclusion criterion was dropped with the third cohort as a consequence of the introduction of combination ART. People provide consent and are enrolled consecutively at each clinic during time-limited enrolment waves, and, thus, both people diagnosed with HIV infection recently and those diagnosed decades ago may be included. The consecutive enrolment aims to ensure that no participant is excluded because of concerns about 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-infected population, new cohorts have been enrolled at regular intervals, with a total 10 enrolment waves over 23 years (Fig. 1). EuroSIDA seeks to include centres from across Europe, ensuring that all European geographical 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 study. 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 4000 HIV/HCV-coinfected individuals and ran from 2014 to 2016.

Data collection

EuroSIDA is a noninterventional study, which only collects data from participants' routine clinic visits. Until 2016, data were 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 onwards.

Table 2 outlines data collected in EuroSIDA. These data include 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 because of toxicity or intolerance. In addition to data, most centres collect plasma samples twice annually as part of routine clinical management.

Table 1 Characteristics of EuroSIDA participants under ongoing follow-up as per 1 January 2016

	All	Western Europe	Southern Europe including Israel/Argentina	Northern Europe	East Central Europe	Eastern Europe
Number under follow-up at 1 January 2016 (% of total)	12 327 (100)	2955 (24)	3258 (26)	2473 (20)	1853 (15)	1788 (15)
Number of clinics included	100	24	21	22	16	17
Sex [n (% of all)]						
Male	8993 (73.0)	2281 (77.2)	2362 (72.5)	1968 (79.6)	1365 (73.7)	1017 (56.9)
Female	3334 (27.0)	674 (22.8)	896 (27.5)	505 (20.4)	488 (26.3)	771 (43.1)
Current age (years) [median (IQR)]	50 (42–56)	53 (47–59)	51 (45–56)	53 (47–59)	44 (38–51)	38 (34–43)
HIV transmission category [n (% of all)]						
MSM	4493 (36.4)	1309 (44.3)	1032 (31.7)	1352 (54.7)	719 (38.8)	81 (4.5)
IDU	3351 (27.2)	515 (17.4)	1065 (32.7)	364 (14.7)	526 (28.4)	881 (49.3)
Heterosexual	3615 (29.3)	795 (26.9)	961 (29.5)	622 (25.2)	462 (24.9)	775 (43.3)
Other/unknown	868 (7.0)	336 (11.4)	200 (6.1)	135 (5.5)	146 (7.9)	51 (2.9)
Ethnic origin white [n (% of all)]	10 650 (86.4)	2251 (76.2)	2961 (90.9)	1823 (73.7)	1838 (99.2)	1777 (99.4)
Time since HIV diagnosis (years) [median (IQR)]	16.6 (10.1–23.1)	19.9 (13.0–24.5)	19.6 (12.0–24.8)	20.1 (13.7–25.2)	12.8 (7.9–18.1)	9.6 (5.4–13.6)
Time on ART (years) [median (IQR)]	13.3 (7.0–19.1)	17.0 (9.5–20.2)	16.3 (8.2–20.0)	16.9 (9.8–19.9)	10.4 (5.9–15.3)	5.5 (3.2–8.3)
Date of enrolment in EuroSIDA						
Month/year [median (IQR)]	06/08 (11/01–04/14)	07/08 (03/99–03/12)	03/08 (05/99–09/14)	12/05 (03/97–05/12)	07/08 (10/02–05/12)	04/12 (04/08–10/14)
CD4 count nadir (cells/ μ L) [median (IQR)]	218 (105–354)	188 (63–320)	248 (129–402)	200 (96–331)	242 (129–370)	210 (115–324)
CD4 count at enrolment (cells/ μ L) [median (IQR)]	410 (258–604)	421 (252–628)	435 (273–655)	380 (240–570)	412 (277–580)	395 (251–562)
On ART at 1 January 2016 [n (% of all)] [†]						
Yes	11 741 (95.2)	2896 (98.0)	3177 (97.5)	2406 (97.3)	1766 (95.3)	1496 (83.7)
No	586 (4.8)	59 (2.0)	81 (2.5)	67 (2.7)	87 (4.7)	292 (16.3)
HIV RNA at enrolment [n (% of all)] [‡]						
< 500 copies/mL	7181 (69.0)	1961 (75.7)	1919 (71.3)	1384 (69.2)	1171 (69.7)	746 (51.4)
\geq 500 copies/mL	3233 (31.0)	628 (24.3)	774 (28.7)	617 (30.8)	508 (30.3)	706 (48.6)
HIV RNA at 1 January 2016 [n (% of all)] [‡]						
< 500 copies/mL	11 383 (93.9)	2864 (98.1)	3075 (96.1)	2404 (98.0)	1722 (93.4)	1318 (77.1)
\geq 500 copies/mL	742 (6.1)	56 (1.9)	125 (3.9)	48 (2.0)	121 (6.6)	392 (22.9)
Previous AIDS diagnosis at 1 January 2016 [n (% of all)]						
Yes	3308 (26.8)	899 (30.4)	865 (26.6)	658 (26.6)	452 (24.4)	434 (24.3)
No	9019 (73.2)	2056 (69.6)	2393 (73.5)	1815 (73.4)	1401 (75.6)	1354 (75.7)
HCV status [n (%)]						
Anti-HCV negative	6403 (51.9)	1641 (55.5)	1613 (49.5)	1611 (65.1)	1022 (55.2)	516 (28.9)
Anti-HCV positive	5706 (46.3)	1269 (42.9)	1597 (49.0)	815 (33.0)	812 (43.8)	1213 (67.8)
Unknown	218 (1.8)	45 (1.5)	48 (1.5)	47 (1.9)	19 (1.0)	59 (3.3)
People with \geq 1 plasma sample [n (% of all)]	7767 (63.0)	2056 (69.6)	1627 (49.9)	2009 (81.2)	1635 (88.2)	449 (25.1)

Enrolment is in the EuroSIDA study. Regions are as defined in Fig 2.

[†]ART, antiretroviral therapy; HCV, hepatitis C virus; IDU, injecting drug use; IQR, interquartile range; MSM, men who have sex with men.[‡]ART is defined as taking any ART regimen, regardless of the number of antiretroviral drugs.[§]HIV RNA among those with an available measurement.

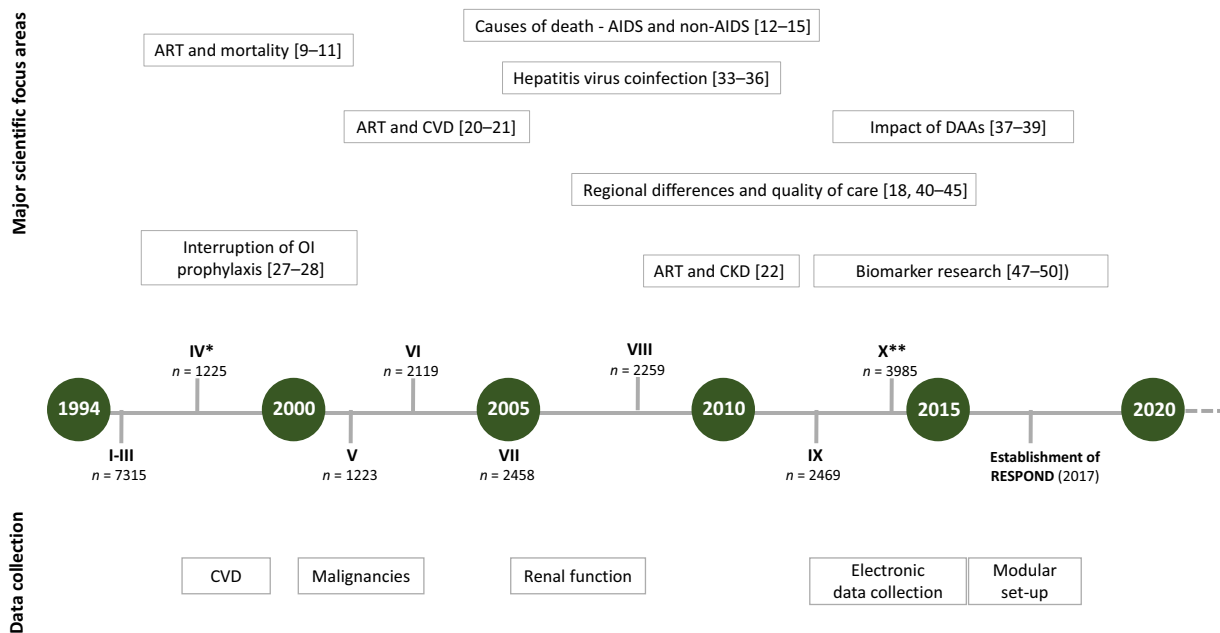


Fig. 1 The EuroSIDA study – scientific achievements, cohorts and data collection. Cohorts (enrolment waves) are indicated by roman numerals I–X. ART, antiretroviral therapy; CKD, chronic kidney disease; CVD, cardiovascular disease; DAA, direct-acting antiretroviral; HCV, hepatitis C virus; OI, opportunistic infection; RESPOND, The International Cohort Consortium of Infectious Disease. *Inclusion of first sites in Eastern Europe. **Inclusion of only HIV/HCV-coinfected people.

In autumn 2014, EuroSIDA transitioned from collecting data on paper forms to using the electronic case report system Research Electronic Data Capture [4]. Alternatively, sites may transfer data electronically using the HIV Cohorts Data Exchange Protocol 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; for example, serum creatinine was included in the form as concerns about 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, modular data collection was introduced. Modular data collection means that a set of core values is collected for all patients in a core module, while other data are 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.) are only requested for HIV/HCV-coinfected participants.

Quality assurance

To ensure correct selection of participants and verification of collected data, an extensive quality assurance

programme has been in place since EuroSIDA was initiated. Monitoring previously included on-site visits to all participating centres. 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 high data quality. If a collaborating clinic continuously delivers poor data or continuously does not deliver data, the participation of that site in EuroSIDA may be halted, 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].

Table 2 Data available in EuroSIDA

Demographics and basic clinical information	Date of birth [†]
	Sex [†]
	Country of origin [†]
	Ethnicity [†]
	Date first seen at department [†]
	Date of most recent clinic visit
	Date of first positive HIV-1 Ab test [†]
	If known, date of last negative HIV-1 Ab test [†]
	Mode of HIV infection [†]
	Mode of HCV infection [§]
	Body weight
	Height [†]
	Blood pressure
	Smoking status
Alcohol abuse [‡]	
Injecting drug use [‡]	
Pregnancy and mother-to-child transmission [‡]	
Laboratory values	HIV RNA
	CD4 cell count
	CD8 cell count ^{††}
	Haemoglobin [‡]
	Serum creatinine
	Platelets
	Alanine transaminase
	Aspartate transaminase
	Albumin
	Bilirubin
	INR [‡]
	Total cholesterol
	HDL cholesterol
	LDL cholesterol
	Serum triglycerides
	HbA1c
	Plasma glucose
	Urine dipstick
	HBV surface antigen
	HBV DNA, HBV surface antibody, HBV core antibody (IgG), HBV core antibody (total: IgM + IgG) [¶]
	Anti-HCV IgG
	HCV RNA
	HCV genotype and subtype
Parathyroid hormone [¶]	
Prostate-specific antigen [¶]	
Other tests	Resistance test
	Plasma samples
	HLA B*5701 ^{††}
	Bone mass density ^{††}
Antiretroviral therapy	Fibroscan [§]
	Liver biopsy
	CT and/or ultrasound of abdomen/liver performed? [§]
	Start and stop dates
Treatment related to risk of cardiovascular disease	Reason for discontinuation
	Adherence to antiretroviral therapy [¶]
	Hypersensitivity reactions and liver toxicity to integrase inhibitors ^{‡‡}
	Start and stop dates of antihypertensives, ACE inhibitors, insulin or derivatives thereof, oral antidiabetic agents, antiplatelets, statins, fibrates and lipid-lowering agents (not further specified)

Table 2 (Continued)

Treatment of HCV infection	Start and stop dates [§]
	Start and stop dosages [§]
Other medical treatment	Discontinuation of anti-HCV treatment before scheduled, and reason for discontinuation [§]
	Adherence to anti-HCV treatment [§]
	Adverse events associated with anti-HCV treatment and outcomes of adverse events [§]
	Opiate substitution therapy [¶]
	Antipsychotic therapy [¶]
	Antidepressant drugs [¶]
	Benzodiazepines [¶]
	Vitamin D [¶]
	Bisphosphonates [¶]
	Treatment against infections (including primary prophylaxis) [¶]
Clinical events and adverse events associated with antiretrovirals	All AIDS-defining events (according to the CDC 1993 definition) [1]
	AIDS- and non-AIDS-defining malignancies
	Cause of death
	Cardiovascular events (myocardial infarction and invasive coronary procedure)
	Diabetes mellitus
	End-stage renal disease
	End-stage liver disease
	Fractures
	Avascular necrosis [¶]
	Pancreatitis [¶]
Plasma samples	Lipodystrophy [¶]
	Plasma samples collected twice annually from majority of clinics
Selected specific surveys and laboratory measurements	EuroSIDA clinic survey [45]
	Centrally tested prostate-specific antigen [49]
	Survey of ATRIPLA use as first-line therapy [51]
	Centrally tested HCV RNA and HCV genotype [36,52]
	Centrally tested vitamin D levels [53,54]
	Centrally tested hyaluronic acid [47,55]
	Centrally tested hepatitis delta virus [56]
	Centrally tested resistance [48]
	Survey of dialysis and renal transplantation [57]

Ab, antibody; ACE, Angiotensin Converting Enzyme; CDC, Centers for Disease Control and Prevention; CT, computed tomography; HbA1c, Hemoglobin A1c; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; HLA, human leucocyte antigen; INR, International Normalised Ratio; LDL, low-density lipoprotein; IgG, immunoglobulin G; IgM, immunoglobulin M.

[†]Collected only at enrolment in EuroSIDA.

[‡]Collected for all at enrolment in EuroSIDA, and thereafter only for HIV/HCV-coinfected participants.

[§]From data set 44 (2016) and thereafter collected for HIV/HCV-coinfected participants only.

[¶]Not collected after data set 44 (2016).

^{††}Collected since data set 45 (2017).

^{‡‡}Collected since data set 43 (2015).

In an attempt to minimize LTFU, clinics are queried if a participant has had no recorded visit for > 1 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/euro sida>). Some major focus areas for publications are summarized below.

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

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-1990s [9]. Studies published in 2000 and 2003 showed continued declines in mortality and the rates of 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], and 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].

ART uptake, efficacy and adverse events

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-related events has 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 associated with ART, including in particular cardiovascular disease [20,21]. EuroSIDA was among the first studies 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 the

long-term efficacy of ART and predictors of virological success and failure [24,25], in addition to monitoring resistance across Europe, for example demonstrating geographical and temporal differences in resistance testing strategies and in detected drug resistance [26].

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

With follow-up accumulating since 1994, EuroSIDA has a unique opportunity to monitor trends in AIDS- and non-AIDS-related 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 > 200 cells/ μ L [27,28]. Further, EuroSIDA has published a number of articles exploring the influence of viral load and CD4 count on the development of clinical events, suggesting that the rates of AIDS- and non-AIDS-related events and death are strongly influenced by 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-infected population ages. Two recent studies showed that, with increasing age, risk factors other than those related to optimal HIV control (e.g. biological age and smoking) become relatively more important in terms of developing non-AIDS-related clinical events and cancers, respectively [31,32].

Assessing the influence of hepatitis virus coinfection

An important focus area for EuroSIDA is hepatitis research, with a particular focus on HCV coinfection [33–36]. One study found that around a quarter of 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-coinfecting individuals in 2014–2016, bringing the total percentage of HIV/HCV-coinfecting participants to 46.3% ($n = 5706$) of the people under active follow-up. Thus, EuroSIDA follows one of the largest cohorts of HIV/HCV-coinfecting patients in the world. In total, around a quarter of all HIV/HCV-coinfecting individuals in EuroSIDA received anti-HCV treatment between 1998 and 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

and efficacy of DAAs and associated adverse events across Europe, and to monitor the 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 (Fig. 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 injecting drug use

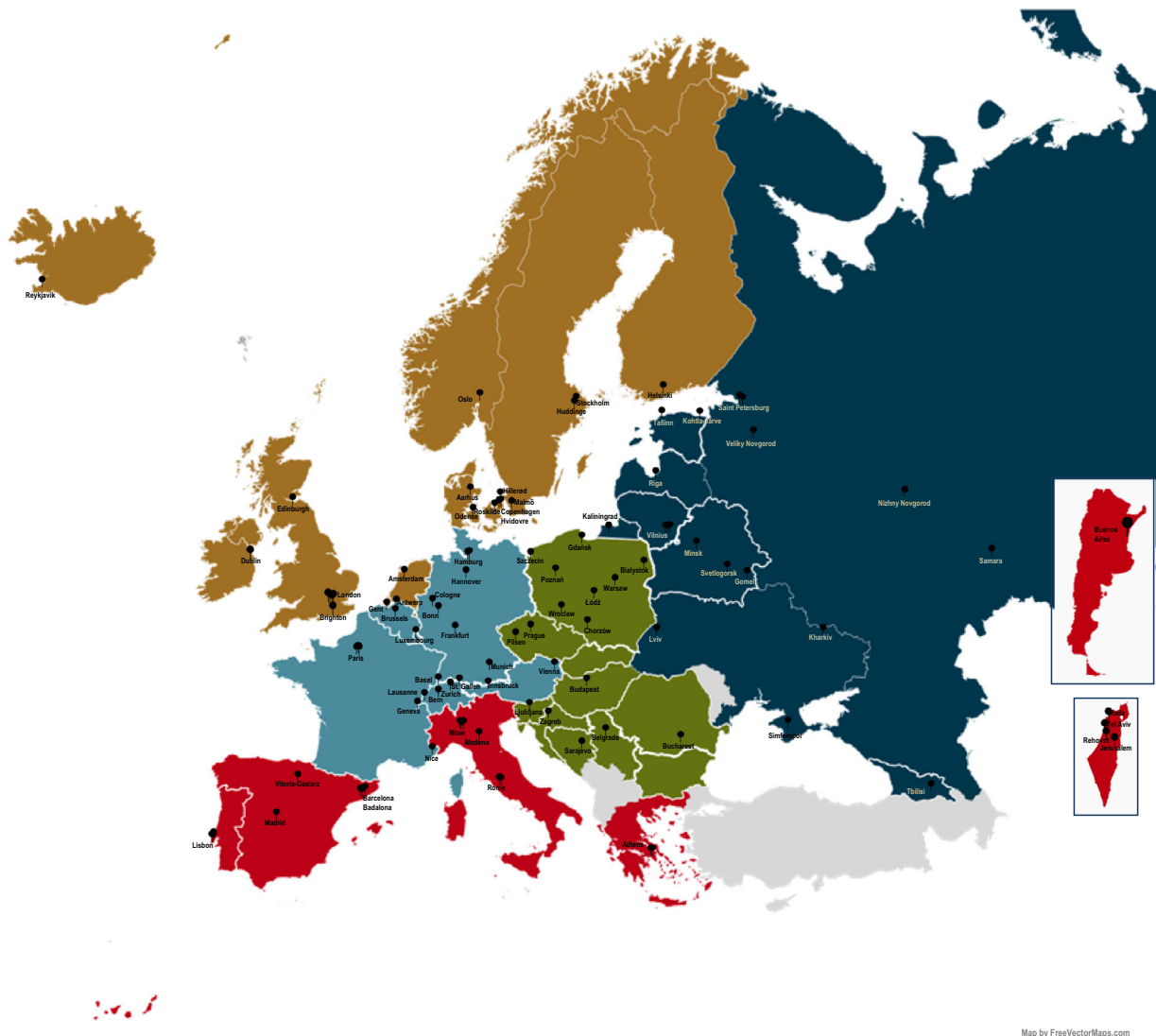


Fig. 2 Map of current EuroSIDA clinics, countries and regions. Countries are grouped into the following regions: *Western Europe* (light blue): Austria, Belgium, France, Germany, Luxembourg and Switzerland. *Southern Europe* (red): Argentina, Greece, Israel, Italy, Portugal and Spain. *Northern Europe* (brown): Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the UK. *East Central Europe* (green): Bosnia-Herzegovina, Croatia, the Czech Republic, Hungary, Poland, Romania, Serbia and Slovenia. *Eastern Europe* (dark blue): Belarus, Estonia, Georgia, Latvia, Lithuania, Russia and Ukraine. An up-to-date list of the EuroSIDA study group may be found on the website: <http://www.hiv.dk/Studies/EuroSIDA/Study-group>

[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 remain 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 infections [47]. Another study explored the role of resistance mutations in subsequent risk of virological failure on first-line nonnucleoside 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 the development of 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 carry out 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 studies to show regional disparities and the burden of HCV and tuberculosis coinfections 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 to analyse the HIV epidemic in this region. The standardized data collection allows comparison of high-quality data from collaborating sites in 35 countries, and the consistent collection of core data throughout the study's existence allows monitoring of temporal trends.

A limitation of the study is that the data collected by their nature are limited and reflect the availability of data as well as the steering committee expert opinion on which variables are most important to collect. However, the clinical experts ensure a clinically driven research agenda, and the flexibility of the data collection allows emerging questions to 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 hepatitis virus, the decision to include only HIV/HCV-coinfected people in the latest enrolment wave may affect the generalizability of our findings to the whole HIV-positive population. However, this makes the cohort fit for addressing 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 and unmeasured confounding) are inherent to cohort research and cannot be completely avoided, some lessons regarding strong cohort design have been learned.

Firstly, an international research collaboration of clinicians allows clinical hypothesis-driven research to be combined with experience of the various public health challenges across Europe and facilitates 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 maintains a clinically driven research

agenda, patient-centredness and patient involvement rightly play a bigger part in health care and research today than when EuroSIDA was initiated, and it is evident that co-creation and 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 number and demographic characteristics of cohort participants relative to all PLHIV followed at each clinic. Information about the number of people approached and reasons for agreeing 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 cohort studies 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 data missing for 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 making 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 infection have improved, the relative importance of such long-term data has increased. Questions related to preventing infection 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 infection 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-infected cohort studies and includes many of the cohorts previously contributing to collaborations such as the D:A:D study, The Antiretroviral Therapy Cohort Collaboration (ART-CC) and The Collaboration of Observational HIV Epidemiological Research in Europe (COHERE). The aim of RESPOND is to build an innovative, flexible and dynamic cohort consortium for the study of infectious diseases, including people with and at risk of HIV infection, as a generic structure for facilitating multi-stakeholder involvement. Within RESPOND, EuroSIDA will continue to address innovative and unresolved research questions that can only be addressed within a multi-cohort structure. There is currently a wide portfolio of research questions being examined 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: (1) hepatitis virus coinfection, (2) tuberculosis coinfection, (3) biomarkers of cancer and clinical outcomes, and (4) 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 a key role in the cohort collaboration RESPOND, EuroSIDA aims to continue to be at the forefront of HIV observational research in the coming years.

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