# Protocol for EuroSIDA

## A study in the RESPOND Consortium

**EuroSIDA**

**Clinical and virological outcomes for European people living with HIV**

**ClinicalTrials.gov Identifier: NCT02699736**

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## PROTOCOL SUMMARY

**Full title:** EuroSIDA - Clinical and virological outcomes for European people living with HIV

**Short title:** EuroSIDA

**Summary**: There are currently over 2 million people living with HIV across Europe. The epidemic continues to intensify in the Eastern European region where prevalence of HIV will continue to increase in the years to come. There are significant problems with the management of this public health crisis. Available antiretroviral therapy (ART) – although extremely effective - does not eradicate HIV and hence has to be continued for life. Other limitations are the development of HIV drug resistance, adverse effects of treatment, and the requirement for strict adherence. Despite these limitations, the widespread use of potent ART has resulted in a dramatic decrease in HIV-related mortality across Europe. As the incidence of AIDS has declined, the relative importance of co-morbidities and co-infections, such as chronic viral hepatitis and TB, has increased. A large proportion of people living with HIV are co-infected with hepatitis C virus (HCV), and liver-related death is now the second most common cause of death after AIDS in this population. With the introduction of more potent and better tolerated oral direct acting antivirals (DAAs) against HCV, major changes in the management and outcome HCV co-infection is anticipated in the coming years. However due to the high cost of DAAs, access to the treatment could vary substantially across Europe.

EuroSIDA has over 100 participating clinical centres across 35 European countries, Israel and Argentina across 6 geographical regions: South Europe, Central Europe, North-West Europe, Central Eastern Europe, Easter Europe and Argentina. The study includes more than 22,000 consecutively enrolled people living with HIV – one quarter from the eastern region – and of these approximately 14,000 persons are currently under active follow-up in the EuroSIDA study. New cohorts of patients are enrolled every 2-3 years to ensure all regions of Europe where the epidemic is prevalent are represented so the study will give timely information on the clinical presentation and outcome of treatment for people living with HIV. To be at the forefront of investigating the benefits and adverse effects of the HCV treatment in co-infected persons, EuroSIDA enrolled a new cohort (cohort 10) between 2014 and 2016, that exclusively consisted of 4000 persons living with HIV positive for antibodies against HCV. In 2019, EuroSIDA will enrol cohort 11 of approximately 2000 HIV-1 positive individuals.

All centers participating in EuroSIDA collect data at enrollment of new participants and hereafter follow-up patient data once a year and most centers collect plasma samples and send to the repository at the coordinating center. Enrolment and follow-up data are extracted from the participants records by staff at the sites and transferred via manual data keying or electronic data transfer. Clinical event data (except AIDS other than AIDS defining malignancies) will be collected in real-time on RESPOND event forms.

EuroSIDA is part of the multi-center study RESPOND International Cohort Consortium of Infectious Diseases. RESPOND is an innovative, flexible and dynamic cohort consortium for the study of infectious diseases, including HIV, built as a generic structure for facilitating multi stakeholder involvement. In RESPOND all collected data is part of a common data repository or ‘data lake’, which is stored in a database located at CHIP, Rigshospitalet, Copenhagen, Denmark. Data collection in RESPOND is modular with a core data collection module onto which additional modules/studies can be added. Pseudonymised patient data can be entered manually via an online secure platform or be electronically transferred from existing local, regional or national data structures to the data lake.

**Study start date**: The EuroSIDA study has been running since 1994 with ongoing enrolment of new cohorts of patients every 2-3 years.

# 1. STUDY BACKGROUND AND RATIONALE

## 1.1 Background

Implementation of new therapeutic strategies in routine clinical management is usually based on randomised controlled trials (RCTs). It has been increasingly difficult to evaluate the longer-term virological outcome of antiretroviral treatment (ART), since standard of care (and thus the control arm) is changing rapidly. This is primarily due to the continued emergence of new potent agents. The evaluation of the clinical benefit of these agents has further been complicated by the fact that the overwhelming majority of RCT's are designed with laboratory endpoints, which allow for the execution of trials with a relatively short duration (usually 48 weeks). However, laboratory endpoints are only surrogate markers for clinical outcome and are unlikely to capture all the relevant information occurring by use of ART, such as how ART affects the course of coexisting diseases (e.g. hepatitis B and/or C) or rare or late-onset drug induced toxicities, nor will they provide information on HIV-associated diseases that are less influenced by immune recovery (e.g. malignant lymphomas).

Further, controlled trials usually have stringent inclusion and exclusion criteria, and the results from such trials may not necessarily be applicable to all groups of individuals subsequently treated. For example, injecting drug users are rare participants in phase I-III trials but constitute 40% or more of all persons living with HIV in Europe today. Lastly, pharmaceutical companies run most trials and information for publication is potentially selective. They may concentrate on virological efficacy in a highly committed small group of homogenous participants, rather than the population effect of a new regimen in a very diverse patient group who will undoubtedly have different patterns of adherence and tolerability to those in a clinical trial.

Although viral hepatitis C (HCV) treatment is limited in duration and the infection potentially curable, there are many similarities between the above described limitations of RCTs of ART in persons living with HIV and the RCTs investigating treatment against HCV. Older individuals with advanced fibrosis, co-morbidities and ongoing substance abuse are often excluded from these trials. The efficacy and adverse effects of treatment are therefore usually less favourable in patients treated outside clinical trials. Furthermore, successful HCV treatment is defined as being HCV-RNA negative 12 weeks after end-of-treatment (a sustained virologic response, SVR). Hence, after achievement of an SVR, the person remains at risk of liver-related death, although the risk is lower than without treatment. In addition, HCV re-infection and competing risk of death could further off-set the benefit of HCV therapy.

Assessment of long-term clinical outcome from treatment of HIV-1 and co-infections such as chronic viral hepatitis is therefore of major importance to the patient community, health care providers, public health officials and other stakeholders. Data from RCTs using e.g. 48 weeks of follow-up only provides a snapshot of which benefits (or lack of such) the patient may potentially experience from a therapy. Such trials highlight the potential short-term efficacy of regimens in terms of virological outcome, while observational studies can provide key data on long-term clinical outcome.

The primary supplement to the RCTs – to provide insight into the efficacy and safety of drug interventions - are well-designed prospective observational cohort studies such as EuroSIDA. Such studies lack the ability to definitively detect causal relationships, where RCTs are required to ensure an unbiased result. However, cohort studies can provide long-term follow-up on a large

representative sample of persons followed in clinics. This provides information for immediate use by decision-makers; it also generates hypotheses on topics where considerable uncertainties exist. Where appropriate, these questions can then be tested in controlled trials. The prolonged EuroSIDA study will continue to be one of the few cohort studies that can provide extended long-term follow-up of patients, and thus help to complement findings from RCTs, as discussed above.

## 1.2 EuroSIDA – the history

The EuroSIDA study is a prospective observational cohort study that was started in 1994. Over 300 investigators from over 100 clinics in 35 European countries, Israel and Argentina conduct the study. Since 1994 10 cohorts have been added to EuroSIDA: Cohort I=3115; Cohort II=1364; Cohort III=2837; Cohort IV=1225; Cohort V=1223; Cohort VI=2118; Cohort VII=2458, Cohort VIII=2254, Cohort IX=2500, and Cohort X= 4000. Cohort 11 intending to enrol 2000 new individuals is planned to start end of 2019. The current number of enrolled participants exceeds 22,000 of which 14,000 are currently under active follow-up in the EuroSIDA study.

The format of the forms used for enrolment and follow-up in the EuroSIDA study, have remained similar since the start of EuroSIDA in 1994, although new questions and details have been added as appropriate, and some have been removed if they were no longer relevant.

The study is the largest pan-European cohort study and few studies of a comparable design are available on a global scale. Historically, EuroSIDA has been crucial in reporting key changes in the HIV epidemic, such as the dramatic changes in morbidity and mortality when cART was first introduced. As new anti-HCV treatment has been introduced to HIV/HCV co-infected persons, it is important for EuroSIDA to remain in the forefront of investigating the treatment benefits and adverse effects. The already existing large EuroSIDA database will continue to be updated once a year to ensure that analyses are performed on the most recent dataset.

The long list of peer reviewed publications from the EuroSIDA study – in total more than 280 publications – is strong proof of the impact of this research that is driven by these academic investigators and is an important supplement to the many publications that come out of pharmaceutical company sponsored research.

## 1.3 Study objectives

EuroSIDA's primary objective is to prospectively study clinical, therapeutic, demographic, virological and laboratory data as well as plasma from people living with HIV across Europe to determine the long-term virological, immunological and clinical outcome in a large cohort of consecutive enrolled study participants. The specific objectives, falling into four main categories, are as follows:

- To assess the factors associated with the clinical, immunological and virological course of HIV infection and HIV-related co-infections and co-morbidities
- To detect current or emerging late onset adverse events among persons on ART
- To continue surveillance of HIV in clinics around Europe to describe temporal changes and regional difference
- To investigate the long-term clinical outcomes of common co-infections and co-morbidities and the impact of treatment

## 1.4 EuroSIDA in RESPOND

EuroSIDA is a founding partner and major stakeholder of the RESPOND International Cohort

Consortium of Infectious Diseases Cohort Consortium, which is an investigator-initiated multi-center collaboration lunched in 2017. EuroSIDA continue its activities as a separate cohort with its own research agenda and Steering Committee but contribute pseudonymized data towards RESPOND.

The aim of RESPOND is to build an innovative, flexible and dynamic cohort consortium for the study of infectious diseases, including HIV, as a generic structure for facilitating multi stakeholder involvement. In RESPOND all contributed data is part of a common data repository or 'data lake', which is stored in a central database. However, the data collection itself is project-based or modular, with specific studies consisting of targeted data collection for subgroups of participants. A participant can therefore be part of several specific studies in RESPOND. All sites/centres will collect data to one or more specific studies depending on their participant inclusion. The common data repository allows for important cross-cutting research across modules and studies, with important synergies, and costs savings in terms of data collection.

For most participants in RESPOND core data is collected for the following categories: Demography and basic clinical information; Relevant virological and immunological information; Laboratory information regarding organ function and biomarkers for metabolic illness, Coinfection incl genotype and relevant paraclinical information; and ART information.

EuroSIDA is represented in the RESPOND Executive Committee as well as in the RESPOND Scientific Steering Committee and in the various scientific interest groups set up for each study into which EuroSIDA provides data.

# 2. METHODOLOGY

## 2.1 Study design

EuroSIDA is a multi-center prospective observational cohort study. The over 100 clinics participate in EuroSIDA are referred to as sites or centres and receive a unique centre number. New cohorts of patients are enrolled every 2-3 years.

All centers participating in EuroSIDA collect data at enrollment of new participants and hereafter follow-up patient data once a year. Enrolment and follow-up data are extracted from the participants records by staff at the sites. Most centers collect plasma samples and send to the repository at the coordinating center. Clinical event data (except AIDS other than AIDS defining malignancies) will be collected in real-time on RESPOND event forms.

All submitted data is part of the RESPOND common data repository or 'data lake', which is stored in a databaseat CHIP, Rigshospitalet in Copenhagen. The statistical centre for EuroSIDA is based at University College London, UK, which works closely with CHIP in Copenhagen.

All study documents, including details and procedures for the completion of FU forms, study status, newsletters, scientific publications and presentations are available online and are updated continuously at www.chip.dk

## 2.2 Enrolment

In cohort 1-9, consecutive patients living with HIV-1 were enrolled. For cohorts 1-3, eligible persons were those who had had a CD4 cell count <500 cells/mm$^3$ during the previous 4 months. The CD4 cell count restriction was removed for subsequent cohorts. In cohort 10, the centers enrolled consecutive people living with HIV-1 (regardless of CD4 cell count and ART status) who are positive for antibodies against HCV (regardless of HCV-RNA status, fibrosis stage and prior HCV therapy), and not already enrolled in EuroSIDA until the predefined number of participants was reached. Participants do not need to receive ART in order to participate in the EuroSIDA

study.
In EuroSIDA cohort 11, which will start enrolling patients from October 2019, inclusion criteria will align with the enrolment criteria in the RESPOND Outcomes Study.

## 2.3 Data items collected

- Demography and basic information: Date of birth, gender, country of origin, ethnicity, height, weight, date of first HIV-1 positive test and mode of HIV-1 transmission.

- Laboratory data: Relevant routine virological and immunological data for characterization of the HIV infection, hepatitis B+ C and other relevant co-infections, as well as routine laboratory data that describe the function of the bone marrow, kidneys and liver. Biomarkers of metabolic disease.

- Medical treatment: All HIV medicine, including start- and stop dates and reason for discontinuation. Medical treatment related to co-infections and co-morbidities.

- Clinical events: AIDS, myocardial infarction, stroke, invasive cardiovascular procedures, kidney failure, liver failure, cancer, bone fractures, cause of death.

- Data on frequency and outcome of pregnancy

- Plasma samples

## 2.4 Data collection

All centers participating in EuroSIDA collect data at enrollment of new participants and hereafter follow-up patient data once a year and most centers collect plasma samples and send to the repository at the coordinating center. Clinical event data (except AIDS other than AIDS defining malignancies) will be collected in real-time on RESPOND event forms.

Enrolment and follow-up data are extracted from the participants records by staff at the sites and transferred via manual data keying or electronic data transfer. Manual data keying is performed in electronic case report forms (e-CRFs) using the secure online browser-based Research Electronic Data Capture tool (REDCap). Electronic data capture entails extraction from local electronic databases and submission through the RESPOND Electronic Submission Tool (REST). Electronic data is submitted in the HICDEP (HIV Cohorts Data Exchange Protocol) format.

## 2.5 Study monitoring of data quality

Data quality has been a top priority for the EuroSIDA study since its initiation. Historically, the EuroSIDA study has utilized annual on-site monitoring visits in order to verify data quality and provide on-site re-training when needed. As the study has evolved, new processes have been formulated to adapt to new requirements of the study. The EuroSIDA study currently undergoes extensive quality assurance procedures and has six quality assurance (QA) processes in place

1. Data quality checks/rules in REDCap that automatically detects and notifies when a user has entered in data erroneously, i.e. units measured beyond set limitations, etc.
2. Query lists that detect missing data and/or data that need further clarification or correction
3. Data cleaning
4. 100% form assessment on Event forms by Medical Personal
5. On site monitoring
6. The RESPOND Electronic Submission Tool (REST) used by sites submitting data electronically generates a report of errors and the data are not submitted before the investigator decides to do so, making it possible to correct errors before submitting data

# 3. DATA ANALYSIS METHODS

## 3.1 Sample size determination

The large numbers of participants included in EuroSIDA ensures enough power to study smaller subgroups of persons, such as individuals with specific drug regimens, individuals in different regions of Europe, women, ethnic minorities, people who inject drugs and men who have sex with men, etc. However, for some of the objectives, such as detection of late onset adverse events, power will still be limited and extended follow-up and/or joint analyses with other cohorts will be required, as already done on several occasions.

Two additional key parameters have been taken into account when estimating the sample size. The combined annual loss-to-follow-up and death rate has been reasonably low and stable. If either loss to follow up or death rates increase the number of new patients to be enrolled in future cohorts will be increased correspondingly to ensure a stable participant number. Importantly, extensive activities will focus on ensuring that the lost-to-follow-up rate remains low.

As the EuroSIDA study is an observational research study, it is not possible to determine a pre-defined sample size based on a power calculation on the basis of one primary objective outcome. For each concrete research proposal submitted, the EuroSIDA Steering Committee carefully evaluates the amount and quality of the date available to answer the question to ensure enough sample size.

## 3.2 Data analysis

Our objectives fall into two broad categories:
1) Factors associated with course of HIV infection and HIV-related co-infections and co-morbidities
2) Monitoring of trends over time and regional differences in various important aspects and therapy of HIV infection and HIV/HCV co-infection:

Regarding category 1: Broadly, the analytical methods for addressing the objectives in this category will consist of logistic regression or standard survival analysis techniques. The main time to event endpoints consist of time to development of a new AIDS defining disease (or death), reaching viral load less than 400 (or 50) copies /mL, time to virological failure (the time to two consecutive viral load values > 400 copies/mL at least 6 months from the start of the regimen or, if restricted to those achieving a viral load < 50 copies/mL, the time to rebound above 400 copies/ml), and CD4 count increasing to > 400 /$mm^3$ (i.e. in the normal range for HIV-negative people) or a suitable proportional (e.g., 50% increase in CD4 count after starting treatment) or absolute (e.g. 100 cells/$mm^3$ increase) increase. In general, time is measured from the date of starting a drug regimen.

Binary endpoints will include whether the first viral load measurement in the period 6-12 months from the start of the regimen is > 400 copies/mL or not, treating those with missing viral load in this period either as > 400 copies/ml (i.e. failure) or excluding these persons from the analysis. The advantage such endpoints have over time to event endpoints are that they are less sensitive to frequency of viral load measures. Similar endpoints can be defined for CD4 count responses. There are several issues and complications which need to be carefully addressed in analysis including: left truncation where individuals started a given therapy before entry into EuroSIDA; whether only one or two consecutive values above or below a threshold are required to define occurrence of an event; the use of different viral load assays in different clinical sites; definition of loss-to-follow-up and the associated right-censoring strategy; among others. The statistical analysis team has extensive experience during the past years of the study in recognising these

types of issues and in attempting to deal with them in practical ways.

*Regarding category 2:* Objectives in this category principally involve monitoring temporal changes. These include monitoring of incidence rates of AIDS diseases or deaths in regular time intervals and prevalence of various conditions (e.g. viral load < 400 copies/mL, CD4 count < 50/mm$^3$, etc) at regular time points, by including all participants under follow-up at each time point. Multivariable Poisson or Cox regression models will be used to assess the degree to which trends over time in death rates, for example, can be explained by changes in use of newer treatment regimens or other factors. Similarly, multivariable logistic regression methods (i.e. for the binary dependent variable of viral load < 400 copies/mL or not) will be used to try to understand why prevalence of viral load < 400 copies/mL, for example, changes over time. We will also monitor trends in responses to antiretroviral therapy in people starting treatment for the first time. Here viral load response will be measured according to the approaches mentioned above. Many of the issues mentioned above for category 1 also apply to several of these analyses.

### 3.3 Possible limitations

As for observational studies in general, possible limitations of the EuroSIDA study include unmeasured confounding and confounding by indication. Variables may be missing from some participants which may introduce bias and loss of statistical power.

## 4. STUDY SUBJECTS

### 4.1 Study population

The EuroSIDA study population are people living with HIV-1 above the age of 18 years in the proportions in which they are represented in the participating clinics regardless of gender, ethnic background, sexual orientation, political opinion, religious or philosophical conviction.

The continual addition of new cohorts will ensure that participants in EuroSIDA remain broadly representative of those seen regularly in clinics around Europe.

As part of the routine analysis performed gender issues are investigated to assess any new developments related to this. Women make up approximately 26% of the participants in the EuroSIDA study, thus the study is in a strong position to study whether clinical issues are equally relevant to women as men. Pregnant women may participate in the study as there is no interference with their treatment or pregnancy by participation in EuroSIDA.

### 4.2 Inclusion criteria

Valid from cohort 11 enrolment 2019, the following applies:

HIV-1 positive persons ≥18 years of age, not already enrolled in EuroSIDA, are eligible for inclusion. Participants should be enrolled consecutively in one of the following two groups:

1. Participants who have started integrase inhibitor (INSTI) based antiretroviral therapy (ART) after 1/1/2012 and have a CD4 cell count and HIV-RNA available in the 12 months prior to starting INSTI or within 3 months after starting INSTI

2. If participants have not started INSTI, they should be included providing they have a CD4/HIV-RNA in the 12 months prior to baseline or within 3 months after baseline.

   Baseline for participants who have not started INSTI based ART is defined as the date

the patient is first seen in your clinic after 1/1/2012. If the patient was first seen at your clinic before 1/1/2012, the baseline will be set at 1/1/2012.
Thus, the baseline cannot be earlier than 1/1/2012. Persons do not need to have started ART to be included.

Furthermore, participants should

- Have a signed Informed Consent for EuroSIDA
- Have a signed informed consent for the RESPOND consortium and data repository, if required by local/national legislation in order to have data in the common data repository.

### 4.3 Exclusion criteria

- Persons under 18 years of age
- Persons receiving INSTI before 1/1/2012

## 5. RISK FOR PARTICIPANTS

No ethical, safety or other issues related to EC-policy regulated areas have been identified within this study.

Participation in the EuroSIDA study does not include any risk for participants. The study does not intervene with the clinical management of the participants and it does not test any drugs. Participants remain under the guidance and treatment of their personal physician and treatment will not be influenced by the study.

## 6. Biological materials

### 6.1 Sample collection

Most participating centres collect plasma samples for the EuroSIDA study. A sample of 2 x 1 ml plasma is collected once a year from the participants simultaneously with samples collected for the routine clinical management. Samples are frozen and stored at the centre for later shipment to the repository at the coordinating centre.

It is the responsibility of the investigator (to be assisted by the courier service and the coordinating centre) to ensure that all study samples for international transport are appropriately handled, packed and shipped.

For detailed instructions regarding the collection, labelling, processing and shipment of these samples, please see the EuroSIDA instructions at https://www.chip.dk/Studies/EuroSIDA/Study-documents .

### 6.2 Repository/Biobank

Collected plasma samples are shipped to the coordinating centre at Rigshospitalet, Denmark, and stored in secure holding facilities at - 80° Celsius. Access to these samples and any analysis performed are the responsibility of the EuroSIDA Steering Committee (SC). Samples will only be used for scientific research as described and will be stored for the duration of the study in accordance with The Danish Data Protection Agency's approval. Samples will be destroyed the latest on 31st December 2045 in accordance with current legal and ethical requirements.

# 7. Personal data handling and approvals

## 7.1 Confidentiality of study participants

The confidentiality of all study participants will be protected in accordance with GCP Guidelines and national regulations.

Participants in the EuroSIDA study are de-identified and assigned a unique 7-digit PID number at the sites where they are enrolled. The de-coding list is held by the individual site in a safe location.

All study data is marked with this 7-digit PID number. Date of birth is collected as date, month and year of birth, and no unique person identifiers are present on data submitted to the coordinating centre. All data (hardcopies, computerised and samples) at the coordinating centre are stored and protected in accordance with current regulatory laws and approved by The Danish Data Protection Agency (DK: Datatilsynet, approval no. 2012-58-0004, RH-2018-15, I-Suite nr.: 6140)

The Principal Investigators and staff at the EuroSIDA centres will keep any information and data related to the EuroSIDA study provided by the coordinating centre, and all data and records generated in the course of conducting the study, confidential and will not use the information, data, or records for any purpose other than conducting the study.

Every reasonable step will be taken to protect the privacy of participant health information and to prevent misuse of this information. The participant records (paper/digital) may be seen by institutional Review Boards (IRBs) or Ethic Committees (ECs) who review the study to make sure it is ethically acceptable and by research staff and study monitors, and their designees.

## 7.2 Regulatory approvals

It is the responsibility of each participating clinical research site to ensure that all necessary documents and approvals are obtained according to local and/or national regulations before any study related activities are performed.

The Principal Investigator (PI) at each centre is responsible for obtaining and maintaining this/these approval(s) at all times during the conduct of the study as stipulated in the site contract.

## 7.3 Data handling

RegionH, the entity where CHIP is based, is the data protection officer (DPO) for the EuroSIDA study and are following General Data Protection Regulation (GDPR) in Europe.
As EuroSIDA researchers physically are located at different European universities and hospitals, datasets containing information from the participants´ medical records and their biologic samples might be analysed at other locations than the EuroSIDA coordinating centre provided that this remains within the appropriate ethics, regulatory and data protection approvals. All EuroSIDA data is annually sent to the Statistical Center at UCL, London, for statistical analysis.

Participants will in the Informed Consent forms be informed about the above conditions.

## 7.4 Duration of Study/Termination of contract

Completion of the Study will be on the 31st December 2030 or upon a situation where there are insufficient funds to continue the EuroSIDA Study. At any time before the completion it can be agreed to prolong the study past the original date of completion.

Upon completion of the EuroSIDA study, the following activities must be conducted by the PI, as appropriate:

- Return of all related study data to the coordinating centre

- Data clarifications and/or resolutions
- Review of centre study records for completeness
- Shipment of stored samples to the repository at the coordinating centre

CHIP may for any reason terminate contracts with a Site within 30 days of written termination notice. Upon receipt of a termination notice Site shall cease any work not deemed necessary by CHIP.

If such actions are taken, selected members of the SC and/or the coordinating centre will discuss this with the PI (including the reasons for taking such action) at that time. The PI will inform their local/regional/national regulatory authorities and Ethics Committee (as appropriate) of the suspension or termination of the study and the reason(s) for the action.

### 7.5 Records retention
Following the closure of the EuroSIDA study, the PI at the EuroSIDA centres will maintain a copy of all site study records in a safe and secure location. CHIP will inform the investigator of the time period for retaining these records.

## 8. Study Administration and Economy

### 8.1 Study Group and SC
The EuroSIDA study is investigator-initiated and over 300 investigators participate in the EuroSIDA Study Group. In countries with several sites participating in EuroSIDA a national coordinator has been appointed.

The Study Group elects the members for the EuroSIDA Steering Committee (SC) which governs the study. The SC has 17 members elected for a 5-year period, and representation is sought for all six geographical regions covered by EuroSIDA (South Europe, Central Europe, North-West Europe, Central Eastern Europe, Easter Europe and Argentina). The SC elects a chair. The SC meets face-to-face once a year and by teleconferences every other month. Final approval of projects, research proposals and publications is made by the EuroSIDA SC.

### 8.2 Sponsor and coordinating center
The study sponsor and coordinator is CHIP, which is an independent research institution at the Department of Infectious Diseases at Rigshospitalet, Copenhagen, Denmark.

### 8.3 Funders
EuroSIDA has received funding from ViiV Healthcare LLC (1.247.500€), Janssen Scientific Affairs, Janssen R&D (187.500€), Bristol-Myers Squibb Company (450.000€), Merck Sharp & Dohme Corp (240.000€), Gilead Sciences (268.000€) and the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement n˚ 260694 (3.750.000€). The participation of centres from Switzerland has been supported by The Swiss National Science Foundation (Grant 148522). The study is also supported by the International Cohort Consortium of Infectious Disease (RESPOND).

### 8.4 Site Reimbursement
Clinics participating in the EuroSIDA study will be reimbursed for enrolment and follow up data collection for each participant, event forms and sending samples. Site reimbursement will be to the hospital/research account.

# 9. Recruitment and Informed Content

## 9.1 Recruitment

Eligible participants at a participating site will be asked to participate in the EuroSIDA study and in the RESPOND consortium data lake.

The PI or his/her designee will inform the participants of all aspects pertaining to his/her participation in the EuroSIDA study and in RESPOND.

## 9.2 Informed Consent Procedure

When Patient Informed Consent is required by the local and/or national Ethics Committees, this will be obtained from each patient before any study related procedure is performed.

In accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) – Good Clinical Practice Guidelines the following procedure for obtaining Informed Consent will be followed:

- The participant will prior to study start be informed verbally by a doctor or study nurse about the study and receive written information about the study, if required by the national local ethical committee
- The participant will have the opportunity to ask questions
- The participant will be informed that participation is voluntary and that he/she can withdraw his/her consent at any time without any consequence for his/her treatment or future relationship to the clinic/hospital.
- If required by the national or local ethical committee the patient must sign the Patient Informed Consent form before any study related activities can begin

# 10. Remuneration and benefits

No remuneration will be paid to the participants. There are no direct benefits to the participants. However, the benefit of conducting observational research including research on stored samples includes advancing scientific understanding of HIV infection and other co-infections and co-morbidities and their complications; this knowledge guides international and European treatment recommendations to the benefit of people living with HIV or AIDS.

# 11. Publication

Findings from this study, positive, negative or inconclusive, are intended to be published as multi-centre publication(s) in accordance with the ICMJE- guidelines in peer-reviewed journals and/or presented at medical conferences (‘Publication’). Multi-centre Research proposals will be submitted and reviewed under the oversight of the EuroSIDA Steering committee. Final approval of projects will be made by the EuroSIDA Steering Committee.

The EuroSIDA study group will appear in an appendix in all published manuscripts. Copyrights concerning Publication of the study remain with the authors of the Publication, regardless of any other provisions regarding intellectual property rights.

The EuroSIDA Newsletter that is sent out to all EuroSIDA Investigators four times a year via e-mail. All publications and presentations will be listed on the CHIP webpage, www.chip.dk

## 12. Ethical considerations

The study will be conducted according to the Declaration of Helsinki in its current version, the requirements of Good Clinical Practice (GCP) as defined in current EU GCP Directive, Human Subject Protection and Data Protection Acts or with the local law and regulation, whichever affords greater protection of human subjects.

## 13. List of selected EuroSIDA publications

*For a complete listing of publications directly emanating from the EuroSIDA study, please see www.chip.dk*

1. Discontinuation of Secondary Prophylaxis against Pneumocystis carinii Pneumonia in Patients with HIV Infection Who Have a Response to Antiretroviral Therapy. Ledergerber B, Mocroft A, Reiss P, Furrer H, Kirk O, Bickel M, Uberti-Foppa C, Pradier C, d'Arminio Monforte A, Schneider MME, and Lundgren JD, for eight European Study Groups. N Engl J Med 2001;344(3):168-74.

2. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, Costagliola D, D'Arminio Monforte A, de Wolf F, Reiss P, Lundgren JD, Justice AC, Staszewski S, Leport C, Hogg RS, Sabin CA, Gill MJ, Salzberger B, Sterne JA; ART Cohort Collaboration. Lancet. 2002;360:119-29

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