A Standardized Algorithm for Determining the Underlying Cause of Death in HIV Infection as AIDS or non-AIDS Related: Results from the EuroSIDA Study

Justyna D. Kowalska,[1] Amanda Mocroft,[2] Bruno Ledergerber,[3] Eric Florence,[4] Matti Ristola,[5] Josip Begovac,[6] Helen Sambatakou,[7] Court Pedersen,[8] Jens D. Lundgren,[1,9] and Ole Kirk[1,9]; for the EuroSIDA Study Group*

[1]Copenhagen HIV Programme, University of Copenhagen, Denmark; [2]University College London Medical School, Royal Free Campus, London, United Kingdom; [3]Division of Infectious Diseases and Hospital Epidemiology, University Hospital, University of Zürich, Zürich, Switzerland; [4]Institute of Tropical Medicine, Medical Service, Antwerp, Belgium; [5]Helsinki University Central Hospital, Helsinki, Finland; [6]University Hospital of Infectious Diseases, Zagreb, Croatia; [7]Ippokration General Hospital, University of Athens, Athens, Greece; [8]Odense Universitetshospital, Odense, Denmark; [9]Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark

Objectives: Analyzing changes in causes of death over time is essential for understanding the emerging trends in HIV population mortality, yet data on cause of death are often missing. This poses analytic limitations, as does the changing approach in data collection by longitudinal studies, which are a natural consequence of an increased awareness and knowledge in the field. To monitor and analyze changes in mortality over time, we have explored this issue within the EuroSIDA study and propose a standardized protocol unifying data collected and allowing for classification of all deaths as AIDS or non-AIDS related, including events with missing cause of death. **Methods:** Several classifications of the underlying cause of death as AIDS or non-AIDS related within the EuroSIDA study were compared: central classification (CC-reference group) based on an externally standardised method (the CoDe procedures), local cohort classification (LCC) as reported by the site investigator, and 4 algorithms (ALG) created based on survival times after specific AIDS events. **Results:** A total of 2,783 deaths occurred, 540 CoDe forms were collected, and 488 were used to evaluate agreements. The agreement between CC and LCC was substantial ($\kappa = 0.7$) and the agreement between CC and ALG was moderate ($\kappa < 0.6$). Consequently, a stepwise algorithm was derived prioritizing CC over LCC and, in patients with no information available, best-fit ALG. Using this algorithm, 1,332 (47.9%) deaths were classified as AIDS and 1,451 (52.1%) as non-AIDS related. **Conclusions:** Our proposed stepwise algorithm for classifying deaths provides a valuable tool for future research, however validation in another setting is warranted.
Key words: *AIDS, cause of death, CoDe project, HIV, mortality, non-AIDS event*

HIV-positive persons remain at a higher risk of death compared with HIV-negative persons with similar characteristics.[1-5] Analyzing changes in the underlying causes of death has become a priority in clinical HIV research. A relative increase in non-AIDS-related deaths has been shown by many observational studies, including non-AIDS-defining malignancies, liver disease, and cardiovascular disease-related deaths.[6-8] Moreover, a link between immunodeficiency and specific non-AIDS-related morbidity and mortality

*Members of the EuroSIDA Study Group are listed in the Acknowledgments.

Address for correspondence: Justyna D. Kowalska, Copenhagen HIV Programme, University of Copenhagen, Faculty of Health Sciences, The Panum Institute/Building 21.1, Blegdamsvej 3B, DK-2200 Copenhagen, Denmark; e-mail: jko@cphiv.dk

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has been observed.[9,10] Therefore the focus has changed in reporting and assessing the causes of death, and data collection has expanded.[11] Additionally, with the increasing role of observational studies in providing information on antiretroviral treatment efficacy and long-term toxicities,[12] there are urgent needs for cohort collaboration and standardization of the process of determining the cause of death. The Coding of Death in HIV (CoDe) Project was launched in 2004 in response to these needs; it introduced a system of external evaluation of causes of death in HIV patients along with a standardization of quantity and quality of data collected for such assessment.[13,14] EuroSIDA, among others studies, has adopted the methodology.[2,15] One remaining area of concern is the lack of a standardized approach for unifying data that has been collected before CoDe introduction and the determination of the cause of death in patients with missing information regarding the sequence of events leading to death.

The aim of this study therefore was to use information from EuroSIDA to develop and apply a standardized protocol for unifying data from different sources in order to classify all deaths as AIDS or non-AIDS related, including events with an unknown cause of death.

PATIENTS AND METHODS

EuroSIDA is a prospective, observational study of 16,597 HIV-1-infected patients at 103 centers across Europe, Israel, and Argentina; further details have been reported elsewhere.[16] Data are collected prospectively at clinical sites and are extracted and sent to the coordinating center at 6-month intervals. For patients who died, the date and cause of death (19 predefined causes plus free text fields) are reported by the site investigator (see forms at www.cphiv.dk). Since 2004, a 4-page CoDe case report form (CRF), to be completed for each fatal case, collects information on demographics, risk factors, and co-morbidities (the status in the last year before death), autopsy results, antiretroviral therapy, most recent laboratory results, and narration on death circumstances. Cause of death is determined by conducting a central review based on the data collected on the form.[13]

All patients in the EuroSIDA study who died before August 2008 were included in this analysis. The underlying cause of death was defined as the disease or injury that initiated the train of morbid events leading directly to death or the circumstances of the accident or violence that produced the fatal injury. Deaths that occurred as a result of the morbid trend started by the AIDS event were classified as AIDS related. Three methods of identifying underlying cause of death were used (**Figure 1**).

1. Patients with CoDe CRFs had cause of death evaluated by a coordinating center clinician according to the CoDe project principles[13] and were assigned an underlying cause of death (AIDS or non-AIDS) (central classification); they served as a reference group. All AIDS-defining conditions were classified according to the clinical criteria from the Centers for Disease Control and Prevention (CDC). The clinician reviewing the forms was blinded to the local cohort classification.
2. For the local cohort classification, information provided by site investigators in the EuroSIDA CRF was centrally reviewed by a clinician and was classified as AIDS or non-AIDS related.
3. Algorithms were created whereby underlying cause of death was determined as AIDS or non-AIDS related based on the clinical AIDS events diagnosed prior to death. If there was no AIDS diagnosis prior to death, the event was considered non-AIDS related. The death was defined as AIDS related if the time from the AIDS event to death was lower than the median (or upper quartile) time based on studies from before the widespread introduction of combination antiretroviral therapy (cART)[17,18] (**Table 2**) and was defined as non-AIDS otherwise. For individual AIDS events where the survival time was not reported (pulmonary tuberculosis, cervical cancer, recurrent pneumonia), a threshold of 12 or 17 months was used.[19] Four algorithms were created:

    - algorithm 1 – AIDS-related death if the survival time was lower than the upper quartile of the survival time for the specific disease and lower or equal to 17

months where the specific survival time was unknown
- algorithm 2 – using median survival time and 17 months where it was unknown
- algorithm 3 – using median survival time and 12 months where it was unknown
- algorithm 4 – using upper quartile of the specific survival time and 12 months where it was unknown

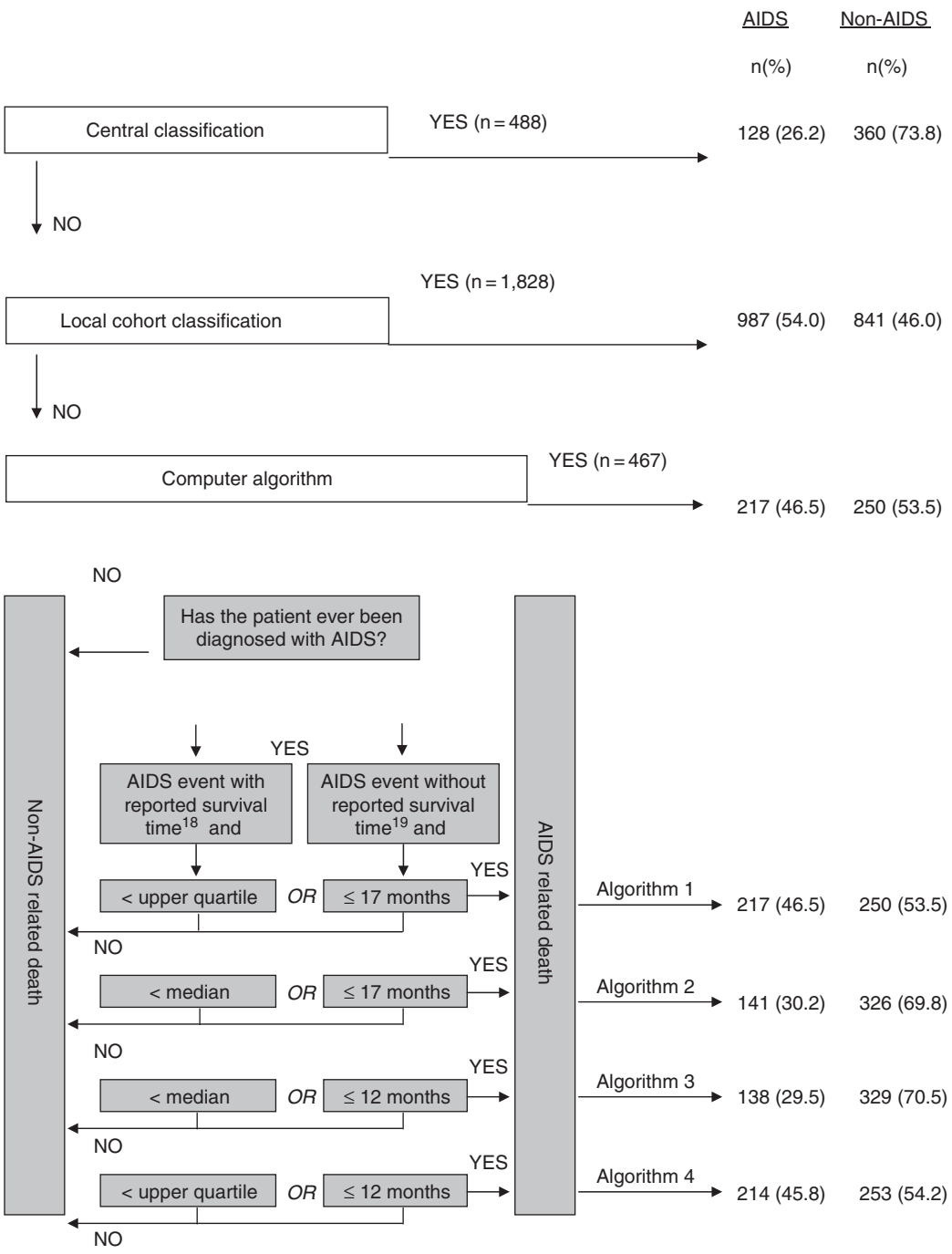

Figure 1. The 3-step algorithm for assigning death as AIDS or non-AIDS related in the EuroSIDA study.

Table 1. The agreement between different methods of classifying death as AIDS or non-AIDS related

Method of identifying the underlying cause of death	AIDS death by central classification n (%)	Non-AIDS death by central classification n (%)	Sensitivity,[a] %	Specificity,[a] %	Kappa (95% CI)
Local cohort classification					
AIDS death	94 (19.3)	20 (4.1)	73.4	94.4	0.70 (0.60-0.80)
Non-AIDS death	34 (7.0)	340 (69.6)			
Algorithm 1					
AIDS death	85 (17.4)	33 (6.8)	66.4	90.8	0.59 (0.50-0.67)
Non-AIDS death	43 (8.8)	327 (67.0)			
Algorithm 2					
AIDS death	65 (13.3)	27 (5.5)	50.8	92.5	0.48 (0.38-0.58)
Non-AIDS death	63 (12.9)	333 (68.2)			
Algorithm 3					
AIDS death	63 (12.9)	25 (5.1)	49.2	93.0	0.47 (0.38-0.56)
Non-AIDS death	65 (13.3)	335 (68.7)			
Algorithm 4					
AIDS death	83 (17.0)	31 (6.4)	64.8	91.4	0.58 (0.50-0.67)
Non-AIDS death	45 (9.2)	329 (67.4)			

Note: Analysis includes only 488 patients with central classification available and does not include events classified as "unknown." **Kappa agreement interpretation:** 0-0.2 slight, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 substantial, and 0.81-1 almost perfect agreement.[20] **Algorithm 1** uses survival time upper quartile for the specific disease (**Table 2**) and 17 months where it was unknown. **Algorithm 2** uses survival median time and 17 months where it was unknown. **Algorithm 3** uses survival median time and 12 months where it was unknown. **Algorithm 4** using survival time upper quartile and 12 months where it was unknown.

[a]Sensitivity measures the proportion of AIDS-related deaths that are correctly identified as such and specificity measures the proportion of non-AIDS-related death that are correctly identified.

For example, if the last AIDS event was Kaposi sarcoma, where the median survival time was reported as 15 (interquartile range [IQR], 7-26) months, death was classified as AIDS related if the patient survived less than 26 months after the diagnosis using algorithm 1 and 4 or 15 months using algorithm 2 and 3. If the patient survived 26 months or longer and 15 months or longer, respectively, the death was coded as non-AIDS related.

Kappa agreements were used to compare central classification (reference group) with local cohort classification and all computerized algorithms.[20] Statistical analyses were performed using SAS (Version 9.1; Statistical Analysis Software, Cary, North Carolina, USA).

RESULTS

In total, 2,783 deaths occurred between May 1994 and the end of August 2008; 540 deaths had a CoDe CRF available, and 52 of these deaths were classified as "unknown." Therefore, 488 events had a definite central classification and were eligible for evaluation of agreement using different classification systems. Of these, 276 (56.6%) patients had at some point had an AIDS event and most frequent AIDS diagnoses prior to death were AIDS-related infection (66.3%), AIDS-defining cancer (18.5%), and HIV wasting (10.9%). Date of diagnosis was available for all AIDS events. The median time between last AIDS diagnosis and death was 24.7 (IQR. 3.4-90.0) months. The median death date was July 2005 (IQR, July 2004 - August 2008). There were 128 (26.2%) deaths classified as AIDS related by central classification and 114 (23.4%) by local cohort classification. The distribution of AIDS-related deaths were 118 (24.2%), 92 (18.9%), 88 (18.0%), and 114 (23.4%) for algorithms 1, 2, 3, and 4, respectively. The details for agreements between central classification, local cohort classification,

Table 2. Time span used for algorithms determining the underlying cause of death as AIDS or non-AIDS related based on the survival time from last clinical AIDS events diagnosed prior to death

Last AIDS event diagnosed before death	Median (IQR)[a]	Algorithm 1	Algorithm 2	Algorithm 3	Algorithm 4
	Survival time in months				
Progressive multifocal leukoencephalopathy	2 (1-5)	5	2	2	5
Malignant lymphoma	3 (1-8)	8	3	3	8
AIDS dementia complex	4 (1-12)	12	4	4	12
Cytomegalovirus end organ disease (other than retinitis)	4 (0-12)	12	4	4	12
Mycobacterium avium, extrapulmonary infection	4 (2-12)	12	4	4	12
Other mycobacterium, extrapulmonary infection	5 (1-11)	11	5	5	11
Candidiasis, pulmonary	5 (1-11)	11	5	5	11
Cytomegalovirus retinitis	6 (3-13)	13	6	6	13
Cryptococcosis	6 (1-15)	15	6	6	15
Cryptosporidiosis	6 (2-16)	16	6	6	16
CNS toxoplasmosis	8 (3-17)	17	8	8	17
HIV wasting syndrome	8 (2-20)	20	8	8	20
Salmonella septicaemia	10 (4-20)	20	10	10	20
Herpes simplex infection, not skin	10 (2-21)	21	10	10	21
Oesophageal candidiasis	12 (5-23)	23	12	12	23
Herpes simplex ulceration	12 (5-23)	23	12	12	23
Pneumocystis jiroveci pneumonia	14 (5-25)	25	14	14	25
Kaposi sarcoma	15 (7-26)	26	15	15	26
Tuberculosis, extrapulmonary	19 (7-37)	37	19	19	37
Other AIDS-defining diagnosis	12 or 17	17	17	12	12

[a]From Mocroft et al.[18]

and each computerized algorithm are presented in **Table 1**. The best agreement was between central and local cohort classification ($\kappa = 0.70$). For all 4 computerized algorithms, the agreement with central classification was moderate ($\kappa < 0.60$); the highest agreement was for algorithm 1 ($\kappa = 0.59$), which also had highest sensitivity for AIDS-related death. Algorithms 1 and 3, allowing longer survival after AIDS event to still classify death as AIDS related, showed higher sensitivity; and algorithms 2 and 3, allowing shorter time, showed higher specificity.

For sensitivity analysis, we investigated the agreement between all death cases with available local classification and algorithms 1 through 4. There were 2,248 deaths available; agreement between local classification and algorithms 1, 2, 3, and 4 was 0.51 (95% CI, 0.47-0.54), 0.43 (0.39-0.47), 0.43 (0.40-0.47), and 0.51 (0.47-0.54), respectively. Additionally we tested one additional algorithm using shorter survival time after specific AIDS event to quality death as AIDS related (lower quartile survival time); the agreement with central classification was $\kappa = 0.33$ (0.23-0.42); sensitivity was 31% and specificity was 95%.

Based on these results, a stepwise algorithm (**Figure 1**) was identified for classifying cause of death, which prioritized central classification over local cohort classification; for patients with no information from these first 2 sources, algorithm 1 was used. This stepwise algorithm was applied to all 2,783 deaths in EuroSIDA. More than half (1,575) of these deaths occurred before 1999, 677 from 1999 to 2004, and 531 from 2004 onwards. The majority of cases from the first 2 calendar periods were available from local cohort classification (80.2% and 74.7%, respectively), which changed to 76.8% available from central classification after 2004. The proportion of unknown cases steadily decreased over time, from 19.8% before 1999 to 11.9% after 2004. Overall, central classification was

available for 488 (17.5%) deaths, and 128 (26.2%) deaths were classified as AIDS related; local cohort classification was available for an additional 1,828 (65.7%) deaths, classifying 987 (54.0%) as AIDS related. In 1,516 (82.9%) of these cases, AIDS event was diagnosed with a median of 4.0 (IQR, 1.0-15.0) months before death. The median death date for this group was October 1996 (IQR, June 1995 - January 2000). Algorithm 1 was applied in the remaining 467 (16.8%) deaths, classifying 217 (46.5%) as AIDS related. In 345 (73.9%) of these cases, AIDS event was diagnosed with median 10.0 (IQR, 4.0-25.5) months before death; median death date was September 1996 (IQR, May 1995 - November 1999).

In total, 1,332 (47.9%) deaths were classified as AIDS related and 1,451 (52.1%) as non-AIDS related (**Figure 1**).

DISCUSSION

As patients with HIV experience a much wider range of co-morbidities and causes of death, it is becoming increasingly important to develop a standardized approach for unifying information collected on causes of death, enabling cross-study comparisons and trends over time to be monitored more easily. Using a range of routinely collected data, we have developed an algorithm that will allow the underlying cause of death to be determined as AIDS or non-AIDS related for all patients.

After 2004 when the CoDe project was introduced,[13] information on death and its contributory factors have been collected in parallel on both the EuroSIDA and CoDe CRF. The overall coverage for CoDe CRFs in the recent years is 95%. Information collected according to the CoDe principles and protocol is assumed to be of the highest quality, delivering an endpoint with reproducibility and accuracy necessary for scientific research and validated externally. On the contrary, information collected on the EuroSIDA form contains only the final investigators' judgment on the underlying cause of death, which might be based on unique personal experience or center-specific practices (eg, consulting only patients co-infected with tuberculosis) and influenced by parallel completion of death certificate.[21] The stepwise algorithm reflects these differences between central and local classification.

Our algorithm applies mainly to cases with unknown cause of death, including deaths from early in the cohort's history as well more recent deaths, where only limited information is available. This subset of patients varies from the one used for algorithm standardization, with more patients progressed in the course of HIV infection and different availability and quality of antiretroviral treatment. For that reason, we chose to use the information on survival time for specific AIDS events that has been reported for the early part of the epidemic in Europe, when patients were not on cART.[18] We believe these data better reflect the natural history of disease progression, as an AIDS event is a valid marker for ineffective treatment.[22,23] It is also worth noting that the majority of unknown causes of death in our study arise from this specific period of time when there was considerably less focus on collecting information on cause of death.

The algorithm we propose uses just one element from the patient's history, namely an AIDS event, and could be made considerably more complicated by incorporating other information, such as non-AIDS morbidity or CD4 count, to achieve better accuracy in predicting whether a death was AIDS or non-AIDS related. However non-AIDS events are a heterogeneous group of diseases for which survival in the HIV-infected population and causal relation with prior AIDS events has not yet been sufficiently studied. Therefore there is no reliable and precise information on which to base the algorithm's assumptions. On the contrary, AIDS morbidity is well studied, and prognosis for survival after any possible AIDS event is documented by many publications.

In addition to simplicity, our algorithm is based on AIDS events that have been collected and quality assured throughout the whole follow-up period. In contrast, detailed information on non-AIDS events and risk factors has been introduced later in the epidemic and the extent of the data collected has changed over time. Introducing more complex computerized algorithms would result, in our opinion, in increasing specificity for a small group of deaths with the cost of lowering sensitivity for the majority of events.

Of note, the CD4 cell count is not part of the suggested algorithm; this enables future analyses of associations between specific cause of death and level of immunodeficiency. It is also worth noting that the algorithms have been developed in the EuroSIDA cohort and for the specific research needs of this study. They may serve as a useful tool in other cohorts and for other research purposes,

yet their validity needs to be re-evaluated in another setting and we would welcome such an opportunity.

AIDS-related death should not be considered the same as HIV-related death, the latter being a wider definition including deaths caused by conditions related to HIV infection but not necessarily AIDS defining (eg, immune reconstitution syndrome). We believe our classification should serve as the first step in identifying HIV-related deaths. Further work in this important area is ongoing.

Detailed causes of death are not lost in the stepwise algorithm, but they are available for a smaller subset of patients. With improving survival of HIV-infected patients, death became a rare endpoint. This has resulted in a major limitation for most analyses investigating trends over time, especially when looking into exposure to specific risk factors or antiretroviral treatment. For such analyses, classification of AIDS- and non-AIDS-related deaths still remains a valid approach.

The clear advantage and purpose for developing and applying our proposed stepwise algorithm is that it would make causes of death available for all deaths within our cohort and they could be classified as AIDS or non-AIDS related, including those with limited information. This would allow for a better understanding of why HIV-positive people are dying and the factors associated with AIDS- and non-AIDS-related mortality. Ultimately, this may lead to further improvements in clinical management and treatment of HIV-positive patients.

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The EuroSIDA Study Group (national coordinators)

Argentina: (M Losso), C Elias, Hospital JM Ramos Mejia, Buenos Aires. **Austria:** (N Vetter) Pulmologisches Zentrum der Stadt Wien, Vienna; (R Zangerle) Medical University Innsbruck, Innsbruck. **Belarus:** (I Karpov), A Vassilenko, Belarus State Medical University, Minsk; VM Mitsura, Gomel State Medical University, Gomel; O Suetnov, Regional AIDS Centre, Svetlogorsk. **Belgium:** (N Clumeck) S De Wit, B Poll, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp; (L Vandekerckhove) University Ziekenhuis Gent, Gent. **Bosnia:** (V Hadziosmanovic) Klinicki Centar Univerziteta Sarajevo, Sarajevo. **Bulgaria:** K Kostov, Infectious Diseases Hospital, Sofia. **Croatia:** J Begovac, University Hospital of Infectious Diseases, Zagreb. **Czech Republic:** (L Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. **Denmark:** (J Nielsen) G Kronborg,T Benfield, M Larsen, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense, L Oestergaard, Skejby Hospital, Aarhus. **Estonia:** (K Zilmer) West-Tallinn Central Hospital, Tallinn, Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. **Finland:** (M Ristola), Helsinki University Central Hospital, Helsinki. **France:** (C Katlama) Hôpital de la Pitié-Salpétière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; JM Livrozet, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, D Neau, Unité INSERM, Bordeaux. **Germany: (**J Rockstroh) Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; S Staszewski, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. **Greece:** (J Kosmidis) P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital; H Sambatakou, Ippokration Genereal Hospital, Athens. **Hungary:** (D Banhegyi) Szent Lásló Hospital, Budapest. **Ireland:** (F Mulcahy) St. James's Hospital, Dublin. **Israel:** (I Yust) D Turner,

M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa; S Maayan, Hadassah University Hospital, Jerusalem. **Italy:** (A Chiesi) Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, M Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, F Iacomi, P Narciso, C Vlassi, M Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan; A d'Arminio Monforte, Istituto Di Clinica Malattie Infettive e Tropicale, Milan. **Latvia:** (B Rozentale) P Aldins, Infectology Centre of Latvia, Riga. **Lithuania:** (S Chaplinskas) Lithuanian AIDS Centre, Vilnius. **Luxembourg:** (R Hemmer), T Staub, Centre Hospitalier, Luxembourg. **Netherlands:** (P Reiss) Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. **Norway:** (J Bruun) A Maeland, V Ormaasen, Ullevål Hospital, Oslo. **Poland:** (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, R Flisiak, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk; E Jablonowska, E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz. **Portugal:** (F Antunes) E Valadas, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. **Romania:** (D Duiculescu) Spitalul de Boli Infectioase si Tropicale; Dr. Victor Babes, Bucarest. **Russia:** (A Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; E Vinogradova, St Petersburg AIDS Centre, St Peterburg; S Buzunova, Novgorod Centre for AIDS, Novgorod. **Serbia:** (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. **Slovakia:** (M Mokráš) D Staneková, Dérer Hospital, Bratislava. **Slovenia:** (J Tomazic) University Clinical Centre Ljubljana, Ljubljana. **Spain:** (J González-Lahoz) V Soriano, L Martin-Carbonero, P Labarga, Hospital Carlos III, Madrid; (S Moreno) Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona. **Sweden:** (A Karlsson), Karolinska University Hospital, Stockholm; PO Persson, Karolinska University Hospital, Huddinge; L Flamholc, Malmö University Hospital, Malmö. **Switzerland:** (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel. **Ukraine:** (E Kravchenko) N Chentsova, Kiev Centre for AIDS, Kiev; (G Kutsyna) Luhansk AIDS Center, Luhansk; (S Servitskiy), Odessa Region AIDS Center, Odessa; (S Antoniak) Kiev; (M Krasnov) Kharkov State Medical University, Kharkov. **United Kingdom:** (S Barton) St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College London Medical School, London (University College Campus); A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew's Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

Virology group: B Clotet, R Paredes(Central Coordinators) plus ad hoc virologists from participating sites in the EuroSIDA Study. **Steering Committee:** F Antunes, B Clotet, D Duiculescu, J Gatell, B Gazzard, A Horban, A Karlsson, C Katlama, B Ledergerber (Chair), A D'Arminio Montforte, A Phillips, A Rakhmanova, P Reiss (Vice-Chair), J Rockstroh. **Coordinating Centre Staff:** J Lundgren (project leader), O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, J Kjær, L Peters, J Reekie, J Kowalska.

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