a multicentre study

EuroSIDA

Estimating AIDS and non-AIDS related deaths for patients with missing death data

Kowalska JD, Mocroft A, Ledergerber B, Colebunders R, Ristola M, Begovac J, Sambatakou H, Pedersen C, Lundgren JD and Kirk O
for the EuroSIDA study group

12th EACS Conference
November 12, 2009

Background

- Qualifying causes of death for HIV-infected patients is a complex procedure (diverse reasons for death, incomplete data on circumstances)
- The CoDe project aims to standardise the data collection on causes of death on developed CRFs
- There is no standard approach for observational studies on how to evaluate causes of death when information about the circumstances of death is missing

Aim

- To explore and compare different methods for evaluating the cause of death as AIDS related (ARD) or non-AIDS related (non-ARD)
- To develop computerized algorithms estimating the cause of death based on patients' AIDS event history
- To apply the algorithms in all EuroSIDA fatal cases (use for further analysis)

Methods

All fatal cases in the EuroSIDA cohort with available CoDe CRF

Medical doctor evaluation

Cause of death classification

Computerized algorithms

Cause of death estimation

Methods

All fatal cases in the EuroSIDA cohort with available CoDe CRF

Medical doctor evaluation

Cause of death classification

Computerized algorithms

Cause of death estimation

Central classification
(CoDe CRF)
(reference group)

Methods

All fatal cases in the EuroSIDA cohort with available CoDe CRF

Medical doctor evaluation

Cause of death classification

Computerized algorithms

Cause of death estimation

Central classification
(CoDe CRF)
(reference group)

Local cohort classification
(EuroSIDA CRF)

Methods

All fatal cases in the EuroSIDA cohort with available CoDe CRF

Medical doctor evaluation

Cause of death classification

Central classification
(CoDe CRF)
(reference group)

Local cohort classification
(EuroSIDA CRF)

Computerized algorithms

Cause of death estimation

No AIDS event in patients history

Non-ARD

Methods

All fatal cases in the EuroSIDA cohort with available CoDe CRF

Medical doctor evaluation

Cause of death classification

Central classification
(CoDe CRF)
(reference group)

Local cohort classification
(EuroSIDA CRF)

Computerized algorithms

Cause of death estimation

No AIDS event in patients history

Non-ARD

If death occurs within specified timeframes after AIDS event the cause was estimated as AIDS related (ARD)

AIDS event **ARD**

Methods

All fatal cases in the EuroSIDA cohort with available CoDe CRF

Medical doctor evaluation

Cause of death classification

Central classification
(CoDe CRF)
(reference group)

Local cohort classification
(EuroSIDA CRF)

Computerized algorithms

Cause of death estimation

No AIDS event in patients history

If death occurs within specified timeframes after AIDS event the cause was estimated as AIDS related (ARD)

Otherwise as not AIDS related (non-ARD)

Methods

All fatal cases in the EuroSIDA cohort with available CoDe CRF

Medical doctor evaluation

Cause of death classification

Central classification
(CoDe CRF)
(reference group)

Local cohort classification
(EuroSIDA CRF)

Computerized algorithms

Cause of death estimation

No AIDS event in patients history

Non-ARD

If death occure within specified timeframes after AIDS event the cause was estimated as AIDS related (ARD)

AIDS event ARD

Otherwise as not AIDS related (non-ARD)

AIDS event Non-ARD

EuroSIDA

Methods

All fatal cases in the EuroSIDA cohort with available CoDe CRF

Medical doctor evaluation

Cause of death classification

Central classification
(CoDe CRF)
(reference group)

Local cohort classification
(EuroSIDA CRF)

Computerized algorithms

Cause of death estimation

No AIDS event in patients history

Non-ARD

If death occure within specified timeframes after AIDS event the cause was estimated as AIDS related (ARD)

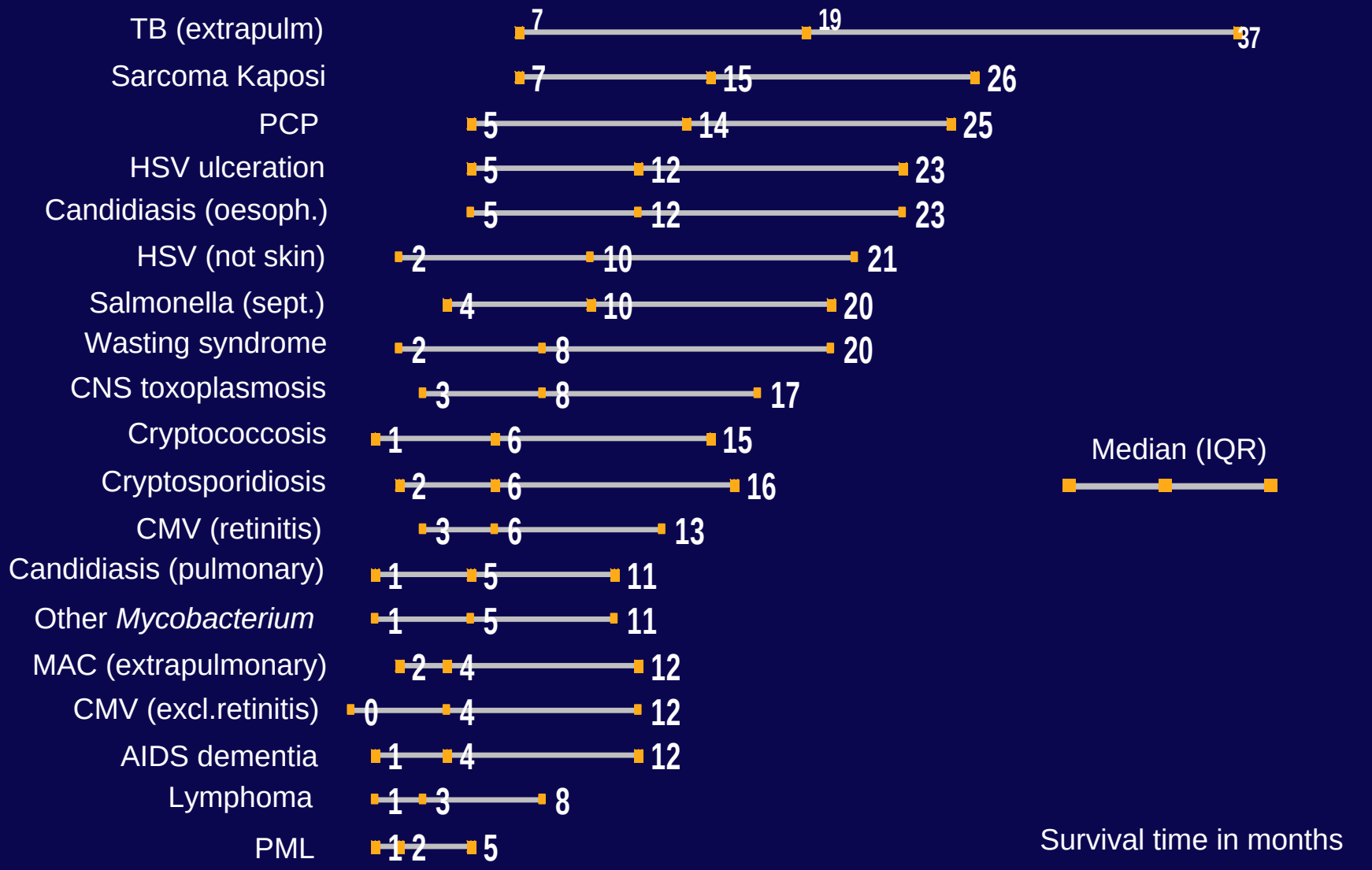
AIDS event ARD

Otherwise as not AIDS related (non-ARD)

AIDS event Non-ARD

EuroSIDA

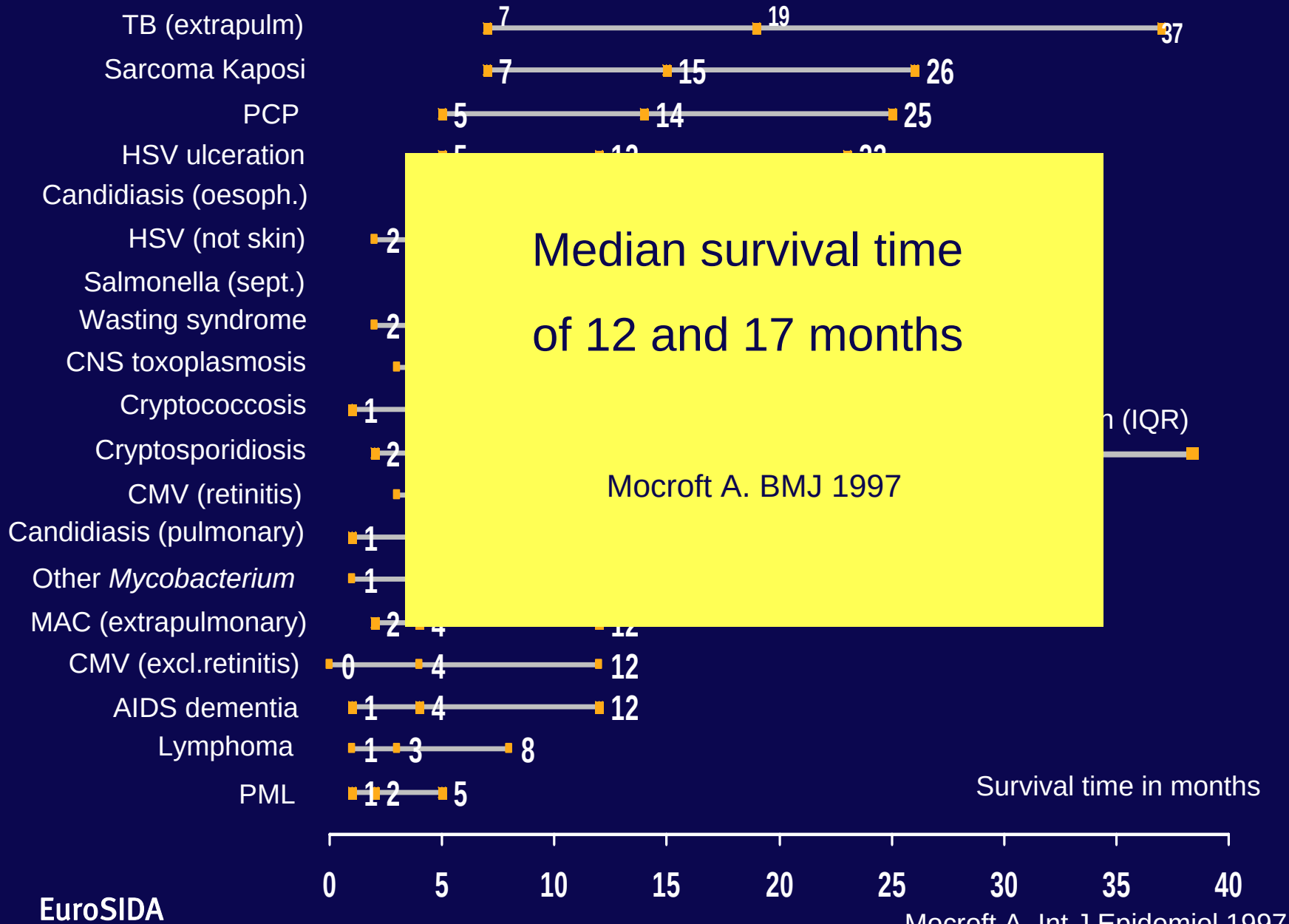
Defining timeframes for estimating ARD and non-ARD



EuroSIDA

Mocroft A. Int J Epidemiol 1997

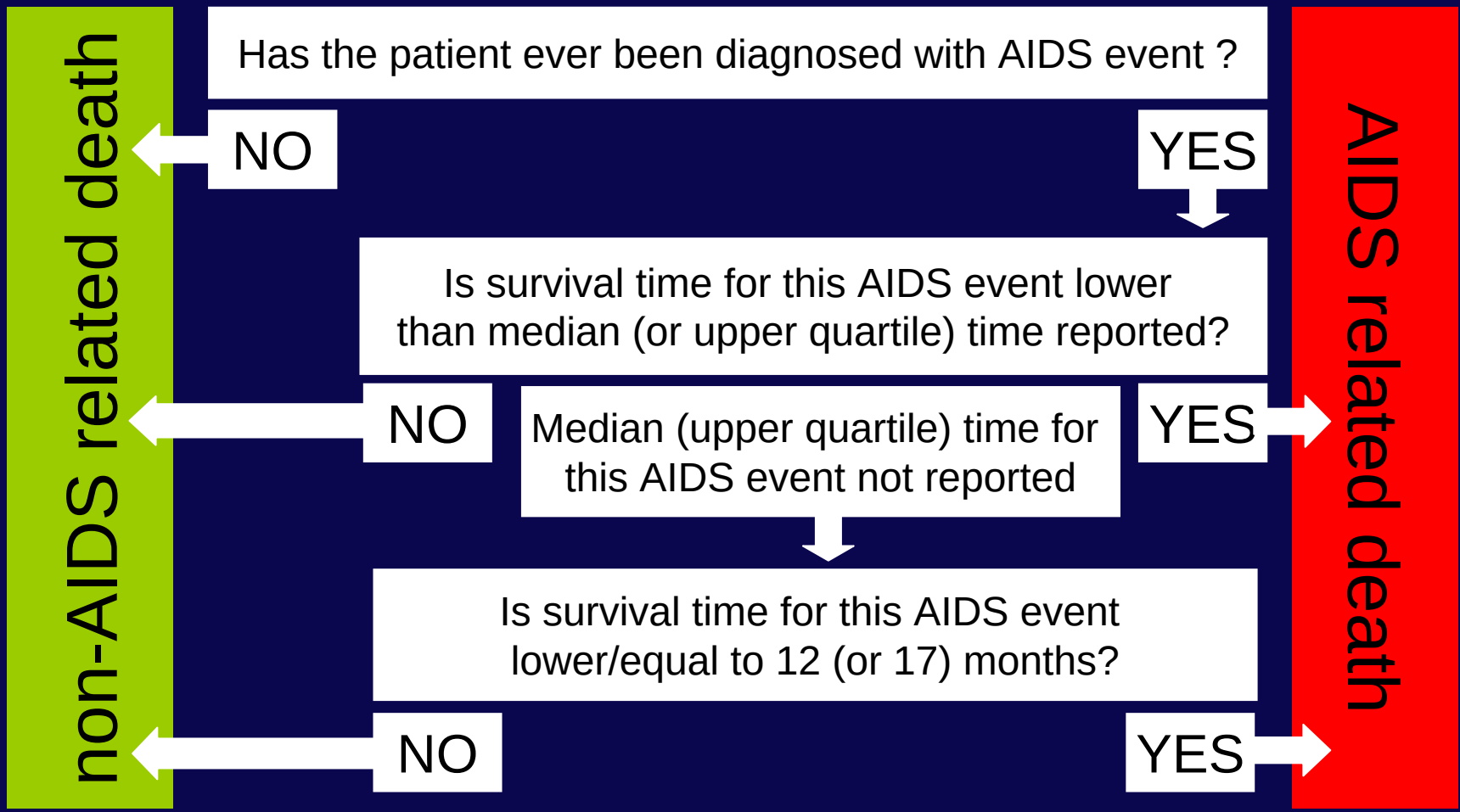
Defining timeframes for estimating ARD and non-ARD



EuroSIDA

Mocroft A. Int J Epidemiol 1997

Flow chart for computerized algorithms



Results

- 2783 fatal cases occurred in the EuroSIDA cohort between May 1994 and August 2008
- 540 EuroSIDA fatal cases had CoDe CRF available
- In 52 (9.6%) cases cause of death was unknown; 488 deaths were included in this analysis
- All 488 fatal cases occurred after year 2000 (83.6% after year 2004)
- 212 (43.4%) of these patients were never diagnosed with AIDS defining event before death

Results
Agreements between different evaluations

		ARD	Non-ARD	Total	Kappa (95% CI)
Central classification		128 (26.2)	360 (73.8)	488 (100)	
EuroSIDA	ARD	94 (19.3)	20 (4.1)	114 (23.4)	0.70 (0.60-0.80)
	Non-ARD	34 (7.0)	340 (69.6)	374 (76.6)	

Results
Agreements between different evaluations

		ARD	Non-ARD	Total	Kappa (95% CI)
Central classification		128 (26.2)	360 (73.8)	488 (100)	
EuroSIDA	ARD	94 (19.3)	20 (4.1)	114 (23.4)	0.70 (0.60-0.80)
	Non-ARD	34 (7.0)	340 (69.6)	374 (76.6)	
Algorithm 1	ARD	85 (17.4)	33 (6.8)	118 (24.2)	0.59 (0.50-0.67)
Upper Q + 17	Non-ARD	43 (8.8)	327 (67.0)	370 (75.8)	

Results
Agreements between different evaluations

		ARD	Non-ARD	Total	Kappa (95% CI)
Central classification		128 (26.2)	360 (73.8)	488 (100)	
EuroSIDA	ARD	94 (19.3)	20 (4.1)	114 (23.4)	0.70 (0.60-0.80)
	Non-ARD	34 (7.0)	340 (69.6)	374 (76.6)	
Algorithm 1	ARD	85 (17.4)	33 (6.8)	118 (24.2)	0.59 (0.50-0.67)
Upper Q + 17	Non-ARD	43 (8.8)	327 (67.0)	370 (75.8)	
Algorithm 2	ARD	65 (13.3)	27 (5.5)	92 (18.9)	0.48 (0.38-0.58)
Median + 17	Non-ARD	63 (12.9)	333 (68.2)	396 (81.1)	

Results
Agreements between different evaluations

		ARD	Non-ARD	Total	Kappa (95% CI)
Central classification		128 (26.2)	360 (73.8)	488 (100)	
EuroSIDA	ARD	94 (19.3)	20 (4.1)	114 (23.4)	0.70 (0.60-0.80)
	Non-ARD	34 (7.0)	340 (69.6)	374 (76.6)	
Algorithm 1	ARD	85 (17.4)	33 (6.8)	118 (24.2)	0.59 (0.50-0.67)
Upper Q + 17	Non-ARD	43 (8.8)	327 (67.0)	370 (75.8)	
Algorithm 2	ARD	65 (13.3)	27 (5.5)	92 (18.9)	0.48 (0.38-0.58)
Median + 17	Non-ARD	63 (12.9)	333 (68.2)	396 (81.1)	
Algorithm 3	ARD	63 (12.9)	25 (5.1)	88 (18.0)	0.47 (0.38-0.56)
Median + 12	Non-ARD	65 (13.3)	335 (68.7)	400 (82.0)	

Results
Agreements between different evaluations

		ARD	Non-ARD	Total	Kappa (95% CI)
Central classification		128 (26.2)	360 (73.8)	488 (100)	
EuroSIDA	ARD	94 (19.3)	20 (4.1)	114 (23.4)	0.70 (0.60-0.80)
	Non-ARD	34 (7.0)	340 (69.6)	374 (76.6)	
Algorithm 1	ARD	85 (17.4)	33 (6.8)	118 (24.2)	0.59 (0.50-0.67)
Upper Q + 17	Non-ARD	43 (8.8)	327 (67.0)	370 (75.8)	
Algorithm 2	ARD	65 (13.3)	27 (5.5)	92 (18.9)	0.48 (0.38-0.58)
Median + 17	Non-ARD	63 (12.9)	333 (68.2)	396 (81.1)	
Algorithm 3	ARD	63 (12.9)	25 (5.1)	88 (18.0)	0.47 (0.38-0.56)
Median + 12	Non-ARD	65 (13.3)	335 (68.7)	400 (82.0)	
Algorithm 4	ARD	83 (17.0)	31 (6.4)	114 (23.4)	0.58 (0.50-0.67)
Upper Q + 12	Non-ARD	45 (9.2)	329 (67.4)	374 (76.6)	

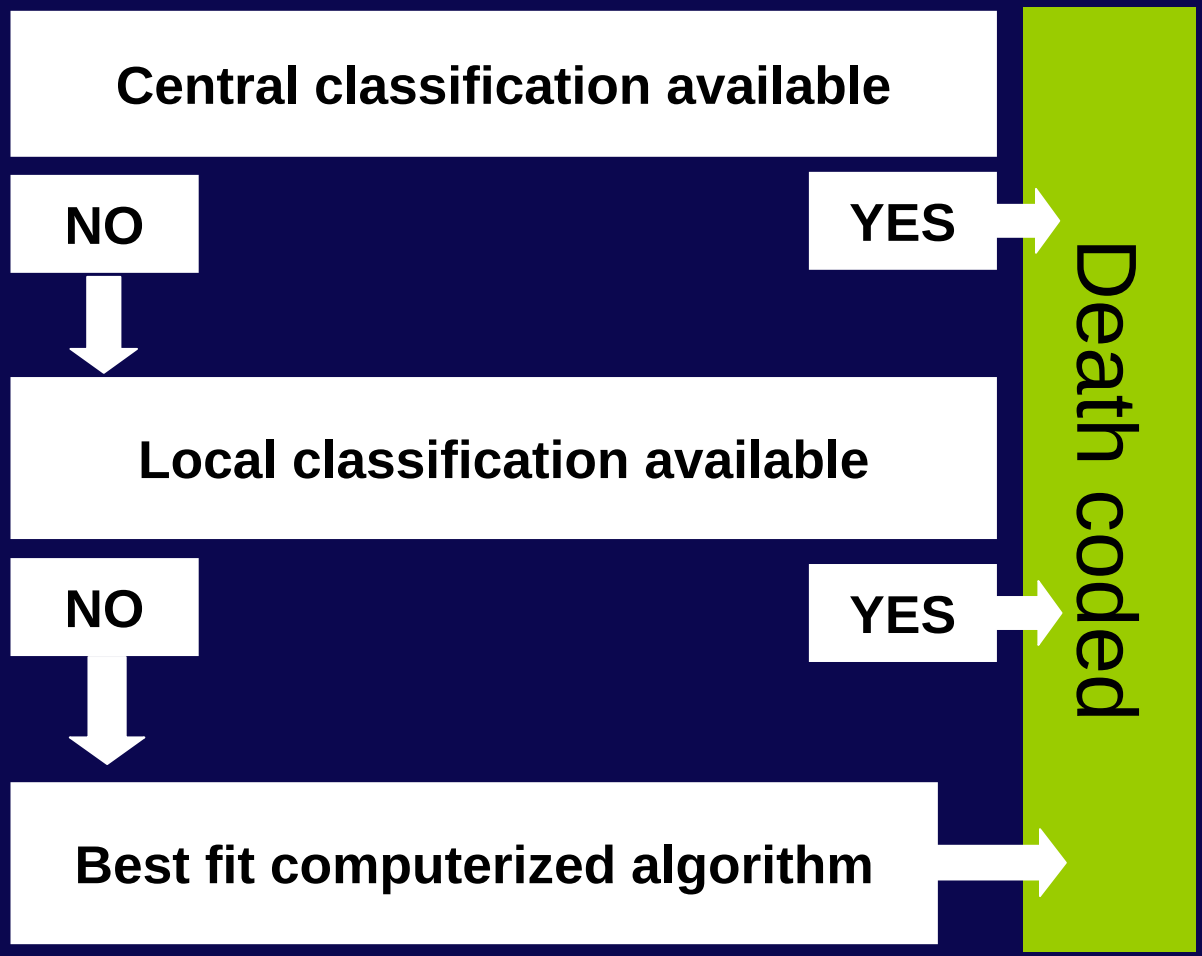
Results
Agreements between different evaluations

		ARD	Non-ARD	Total	Kappa (95% CI)
Central classification		128 (26.2)	360 (73.8)	488 (100)	
EuroSIDA	ARD	94 (19.3)	20 (4.1)	114 (23.4)	0.70 (0.60-0.80)
	Non-ARD	34 (7.0)	340 (69.6)	374 (76.6)	
Algorithm 1	ARD	85 (17.4)	33 (6.8)	118 (24.2)	0.59 (0.50-0.67)
Upper Q + 17	Non-ARD	43 (8.8)	327 (67.0)	370 (75.8)	
Algorithm 2	ARD	65 (13.3)	27 (5.5)	92 (18.9)	0.48 (0.38-0.58)
Median + 17	Non-ARD	63 (12.9)	333 (68.2)	396 (81.1)	
Algorithm 3	ARD	63 (12.9)	25 (5.1)	88 (18.0)	0.47 (0.38-0.56)
Median + 12	Non-ARD	65 (13.3)	335 (68.7)	400 (82.0)	
Algorithm 4	ARD	83 (17.0)	31 (6.4)	114 (23.4)	0.58 (0.50-0.67)
Upper Q + 12	Non-ARD	45 (9.2)	329 (67.4)	374 (76.6)	

Kappa agreements interpretation by Landis JR:

< 0 no agreement	0.4 – 0.59 moderate
0 - 0.19 poor	0.6 – 0.79 substantial
0.2 - 0.39 fair	0.8 – 1 almost perfect

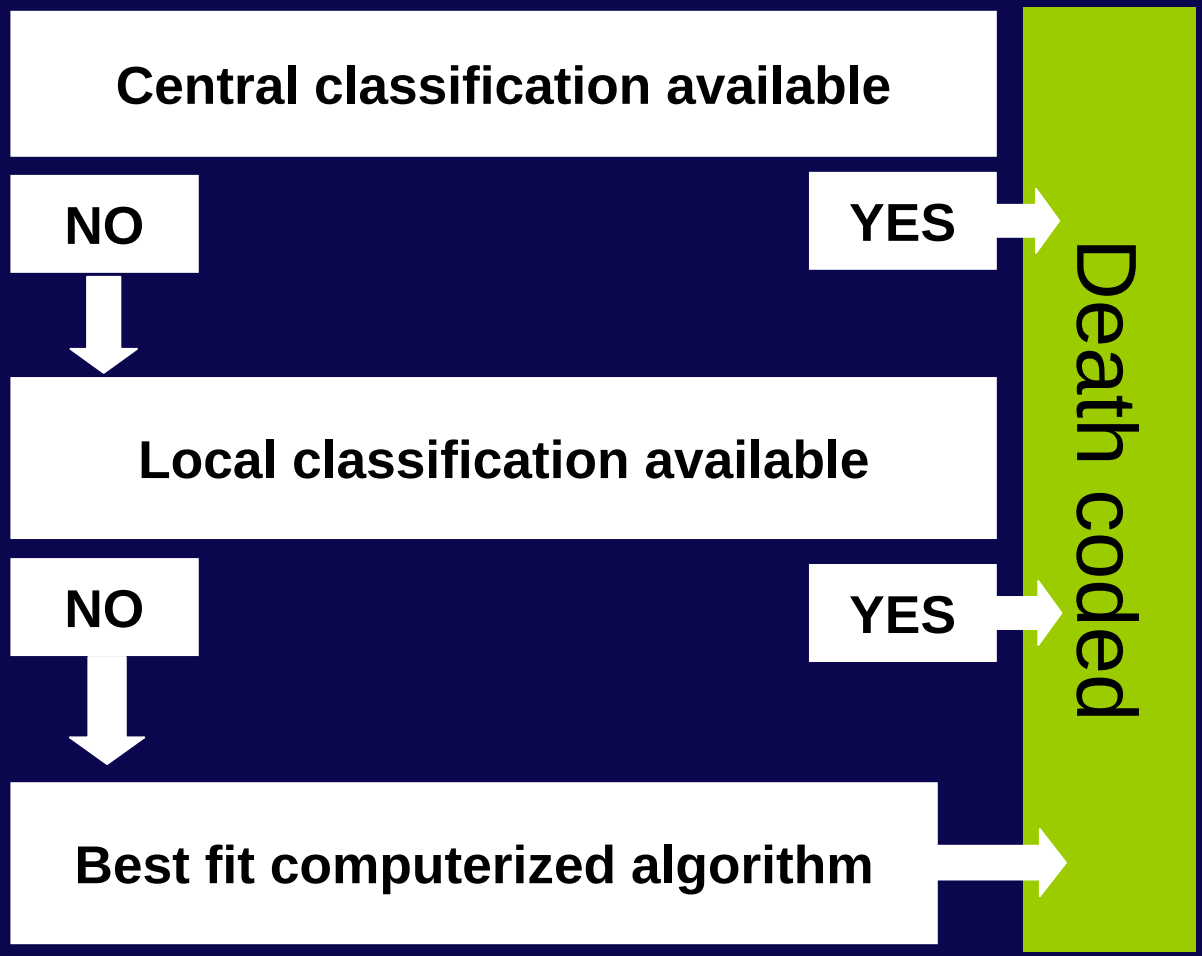
3-step algorithm for assigning deaths as AIDS related or not



EuroSIDA

*36.4% occurred before year 1996

3-step algorithm for assigning deaths as AIDS related or not

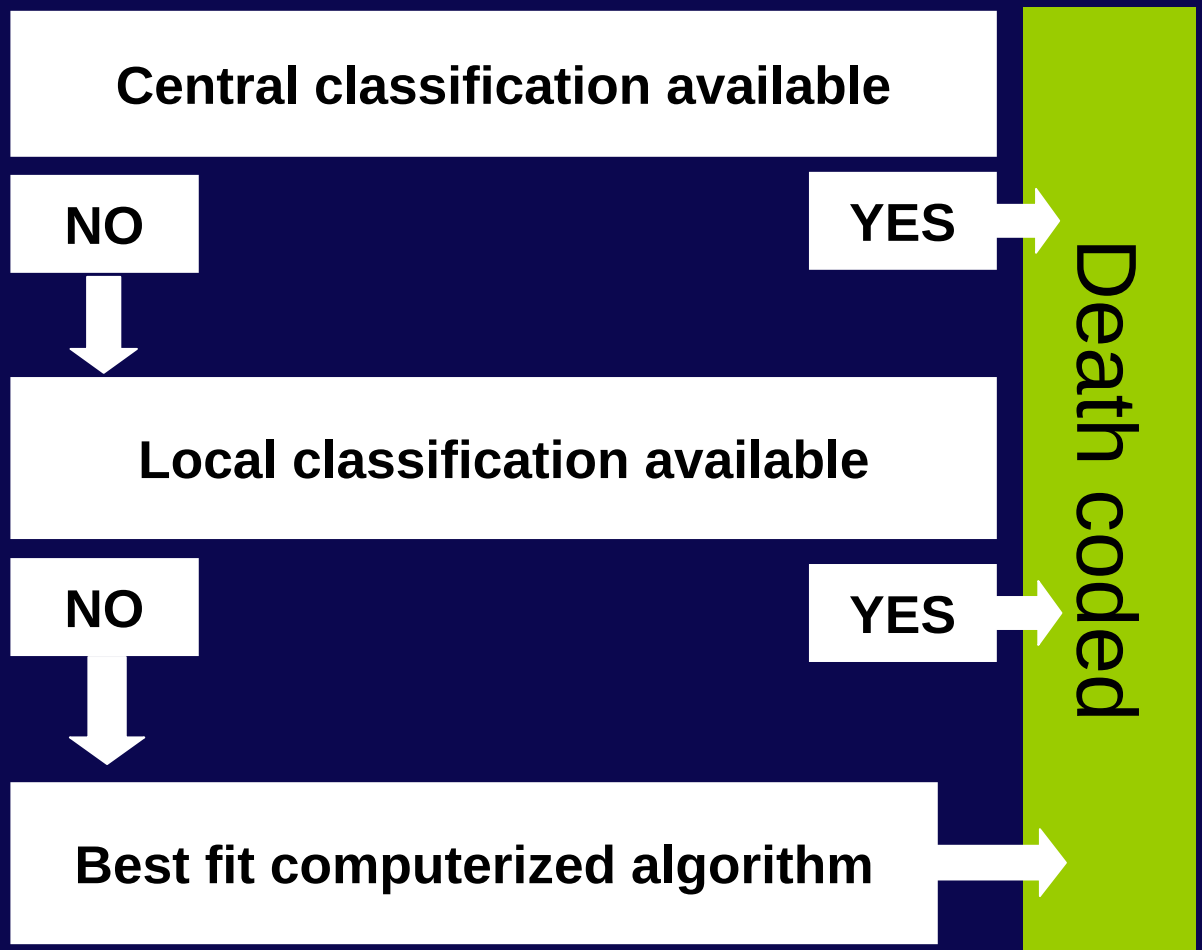


	All cases n (column%)	ARD n (row%)	Non-ARD n (row%)
Central classification available	488 (17.5)	128 (26.2)	360 (73.8)
Local classification available	1828 (65.7)	987 (54.0)	841 (46.0)
Best fit computerized algorithm	467* (16.8)	217 (46.5)	250 (53.5)

EuroSIDA

*36.4% occurred before year 1996

3-step algorithm for assigning deaths as AIDS related or not



	All cases n (column%)	ARD n (row%)	Non-ARD n (row%)
Central classification available	488 (17.5)	128 (26.2)	360 (73.8)
Local classification available	1828 (65.7)	987 (54.0)	841 (46.0)
Best fit computerized algorithm	467* (16.8)	217 (46.5)	250 (53.5)
	2783 (100)	1451 (52.1)	1332 (47.9)

EuroSIDA

*36.4% occurred before year 1996

Conclusions

- The computerized algorithms may serve as a useful tool in estimating cause of death for events with missing information
- Central and local classification should take priority serving as a gold standard
- The 3-step algorithm allows to analyse all deaths including those with unknown cause
- Proposed 3-step algorithm will be further validated in an independent cohort

Perspectives

- Investigating causes of death in HIV patients is crucial for understanding patterns of mortality in this population
- This should start with differentiating AIDS from non-AIDS related deaths
- Analysing further non-AIDS related deaths would help in understanding the risk and benefit of antiretroviral treatment

The EuroSIDA Study Group

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

Thank you