a multicentre study

EuroSIDA

Has the uptake of treatment for chronic hepatitis C infection in Europe changed over time?

A Mocroft, M Vogel, M Beniowski, C Pradier, M Battegay, D Jevtovic, V Soriano, L Peters, JD Lundgren, JK Rockstroh
for the EuroSIDA study group

Introduction

- With improvements in cART, liver related disease has become leading cause of death in HIV / HCV coinfected persons[1]
- Current HCV treatment guidelines[2] suggest all HIV / HCV coinfected persons (↑ liver enzymes, HCVRNA+ and >F1 fibrosis) should be considered for treatment
- Typically, only 10-20% of patients start therapy[3-5]

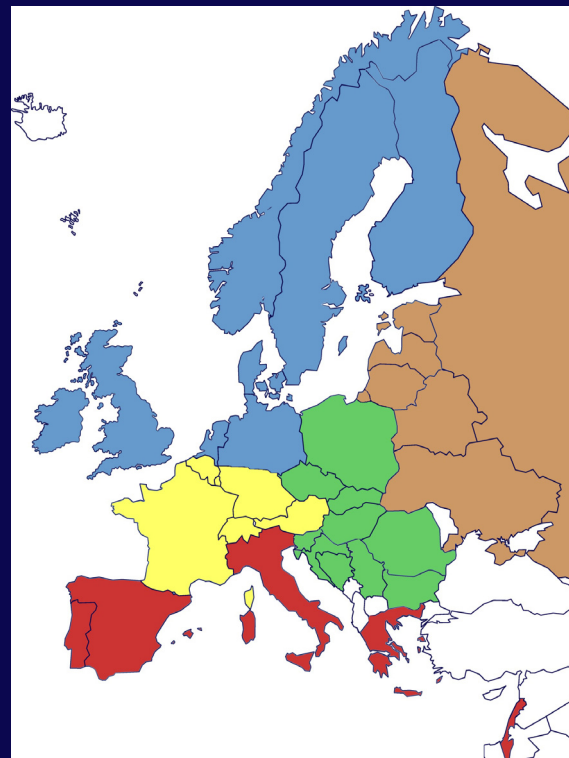
[1]Weber et al, Arch Int Med 2006;66:1632. [2]Rockstroh et al, HIV Med 2008;9:82. [3]Rauch et al, JAIDS 2005;38:238. [4]Mocroft et al, Scand J Infect Dis 2006;38:1092. [5]Zinkernagel et al, Antivir Ther 2006;11:131.

Aims

- To determine treatment uptake for chronic HCV within EuroSIDA study and the factors associated with treatment uptake
- Investigate the impact of anti-HCV treatment on clinical outcomes

The EuroSIDA study

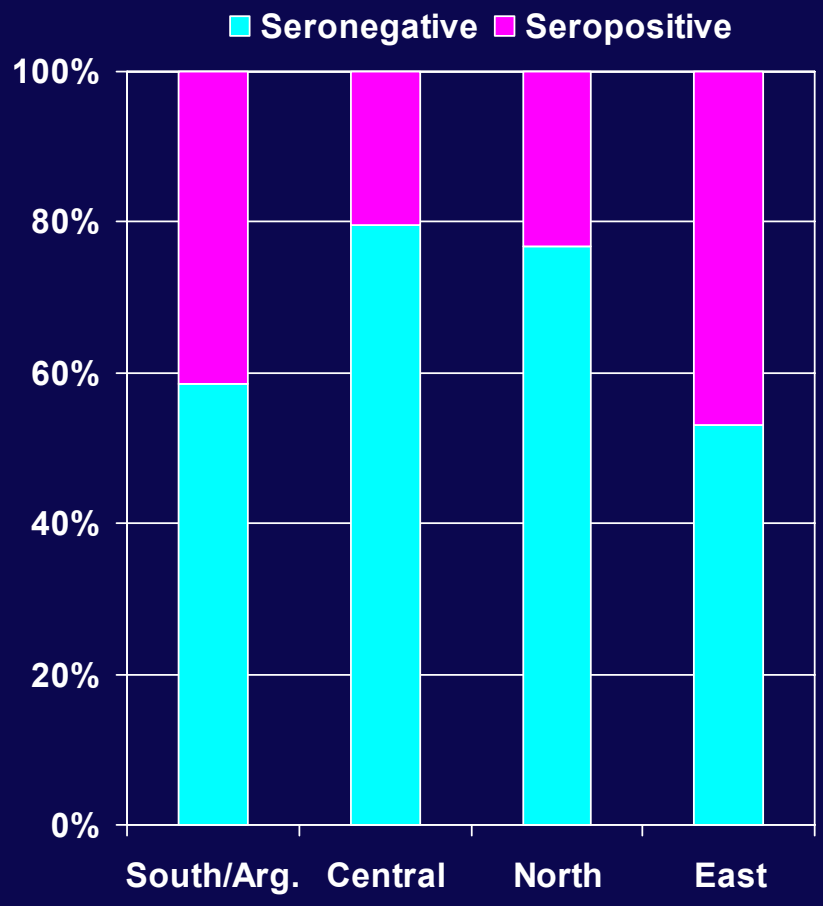
- Longitidunal cohort study initiated in 1994 of 16599 HIV-infected patients from 103 centres in 35 countries across Europe, Israel and Argentina
- Study collects wide range of clinical and demographic data (see www.cphiv.dk)
- Approximately 25% are coinfected with HCV, 75% of these are HCV-RNA positive[1]



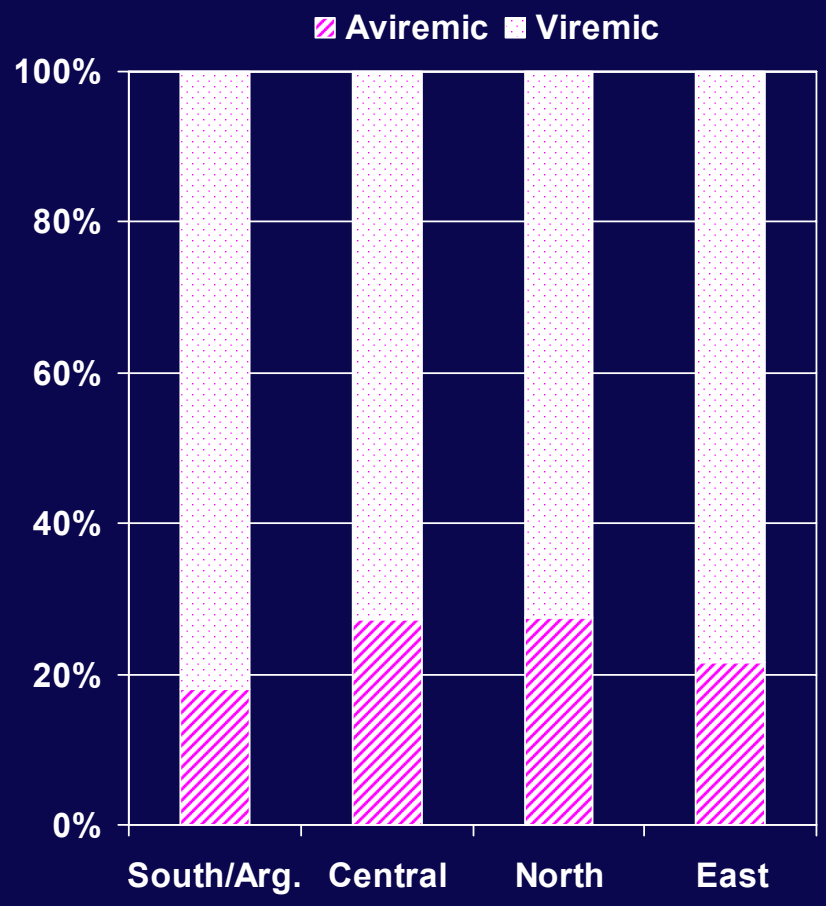
[1]Soriano et al, J Inf Dis 2008; 198:1337

Epidemiology of HCV coinfection across Europe

HCV serostatus[1]



HCV-RNA viremia[2]



	South/Arg.	Central	North	East
N	1677	1430	1545	1305
	654	466	376	442

EuroSIDA

[1]Rockstroh et al, J Inf Dis 2005;192:992. [2]Soriano et al, J Inf Dis 2008; 198:1337

Methods

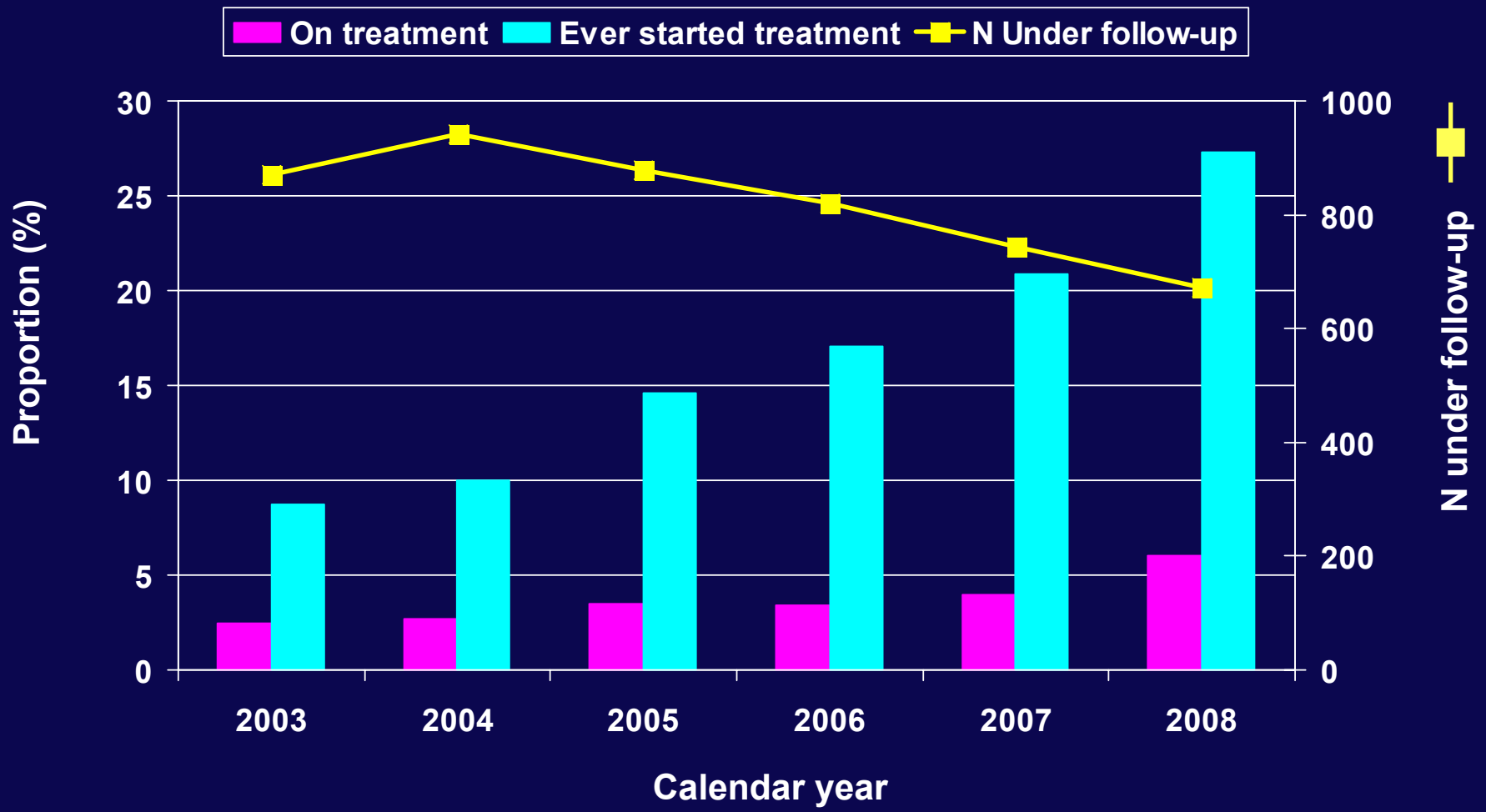
- Chronic HCV defined by positive HCV ab and detectable HCVRNA through central repository
- Baseline - date of first detectable HCV RNA test with genotype 1 - 4
- Anti-HCV treatment; starting one of the following
  - Interferon
  - peg-interferon
  - ribavarin
- LRE; liver related events
  - Death from liver related disease
  - Grade III/IV hepatic encephalopathy
- DEATH; death from any cause or LRE
- Incidence rates and Poisson regression

Results (N=1263*)

		N (%)
Gender	Male	879 (70)
HIV Exposure	IDU	944 (75)
Region	South / Argentina	362 (29)
	Central	319 (25)
	North	230 (18)
	East	352 (28)
Prior AIDS	Yes	333 (26)
On cART	Yes	783 (62)
		Median (IQR)
Age	Years	36 (31 – 41)
HCV RNA	Log_{10}IU/ml	5.8 (5.3 – 6.2)
CD4	/mm^3	301 (161 – 457)
HIV Viral load	Log_{10}copies/ml	2.8 (2.0 – 4.2)

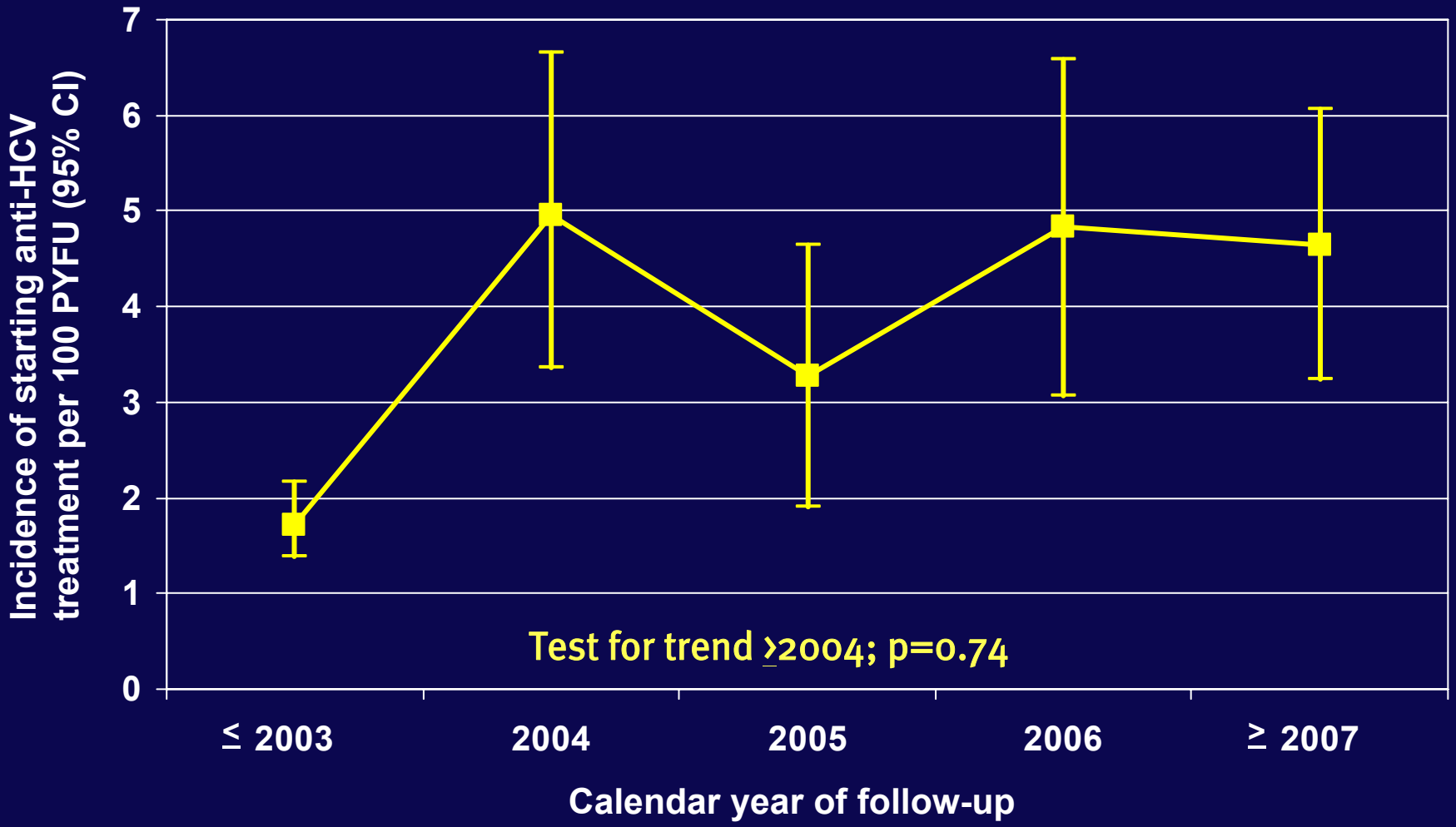
*Chronic hepatitis C defined by positive HCV ab and detectable HCV-RNA

Current and cumulative exposure to anti-HCV treatment



EuroSIDA

Incidence of starting anti-HCV treatment



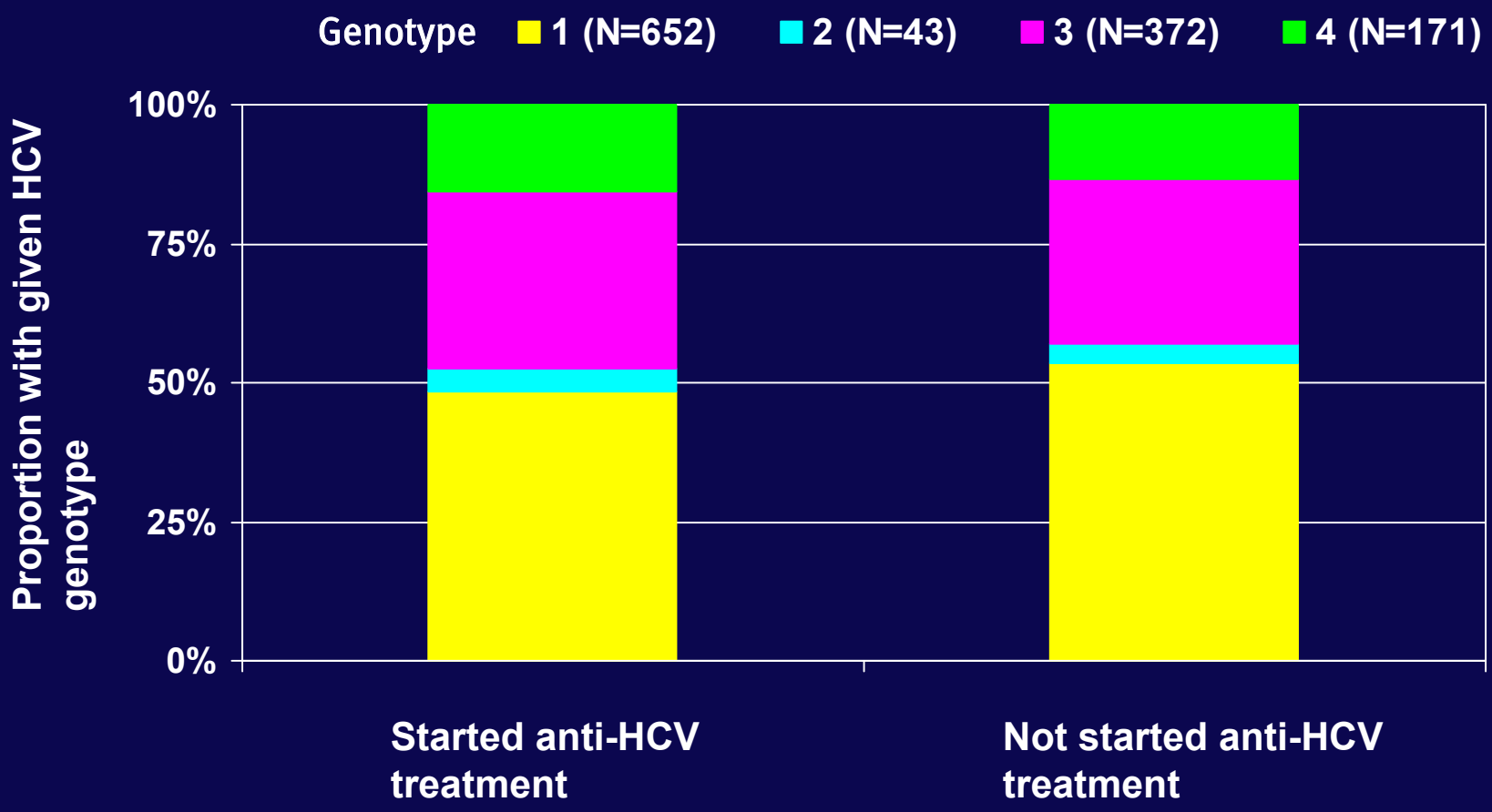
N starting	81	37	22	29	42

EuroSIDA

Characteristics of patients

All N (%)		Treated	Untreated	p
		211 (17)	1027 (83)	
Region	South / Argentina	68 (32)	282 (28)	0.021
	Central	65 (31)	246 (24)	
	North	31 (45)	199 (19)	
	East	47 (22)	300 (29)	
Prior AIDS	Yes	50 (24)	365 (35)	0.0010
CD4	‹200	11 (5)	260 (25)	‹0.0001
	201-350	52 (25)	253 (25)	
	›350	148 (70)	514 (50)	
HIV-RNA	‹500	172 (83)	638 (65)	‹0.0001
	500-10000	20 (10)	132 (14)	
	›10000	15 (7)	210 (21)	
HCV-RNA	›10^6	76 (36)	379 (37)	0.81
HCV Treatment	INF / peg-INF	31 (15)		
	INF / peg INF + RBV	180 (85)		

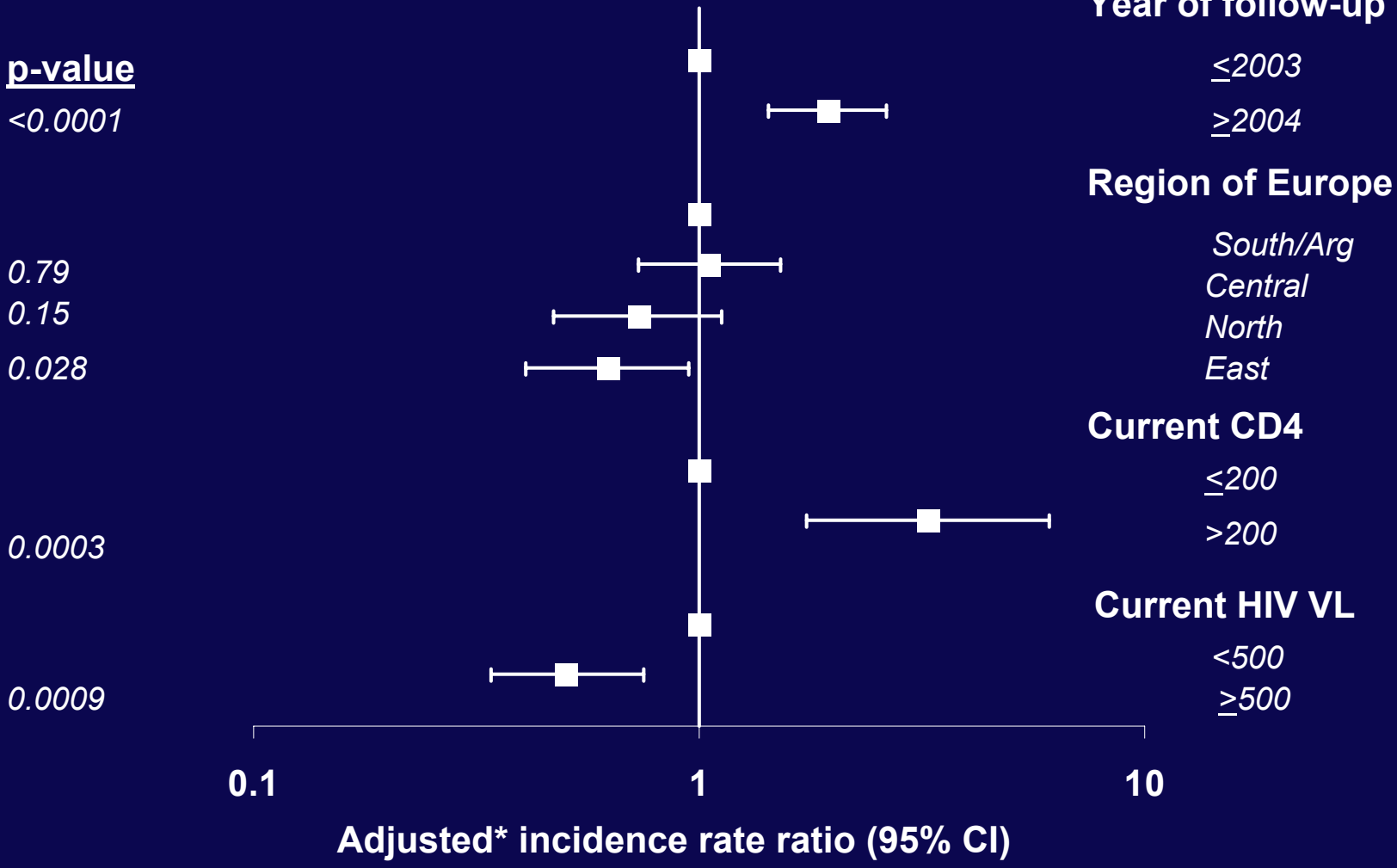
Distribution of HCV genotypes



	Started anti-HCV treatment	Not started anti-HCV treatment	
N	211	1027	p=0.53
Median HCV-RNA	5.78	5.77	p=0.71

EuroSIDA

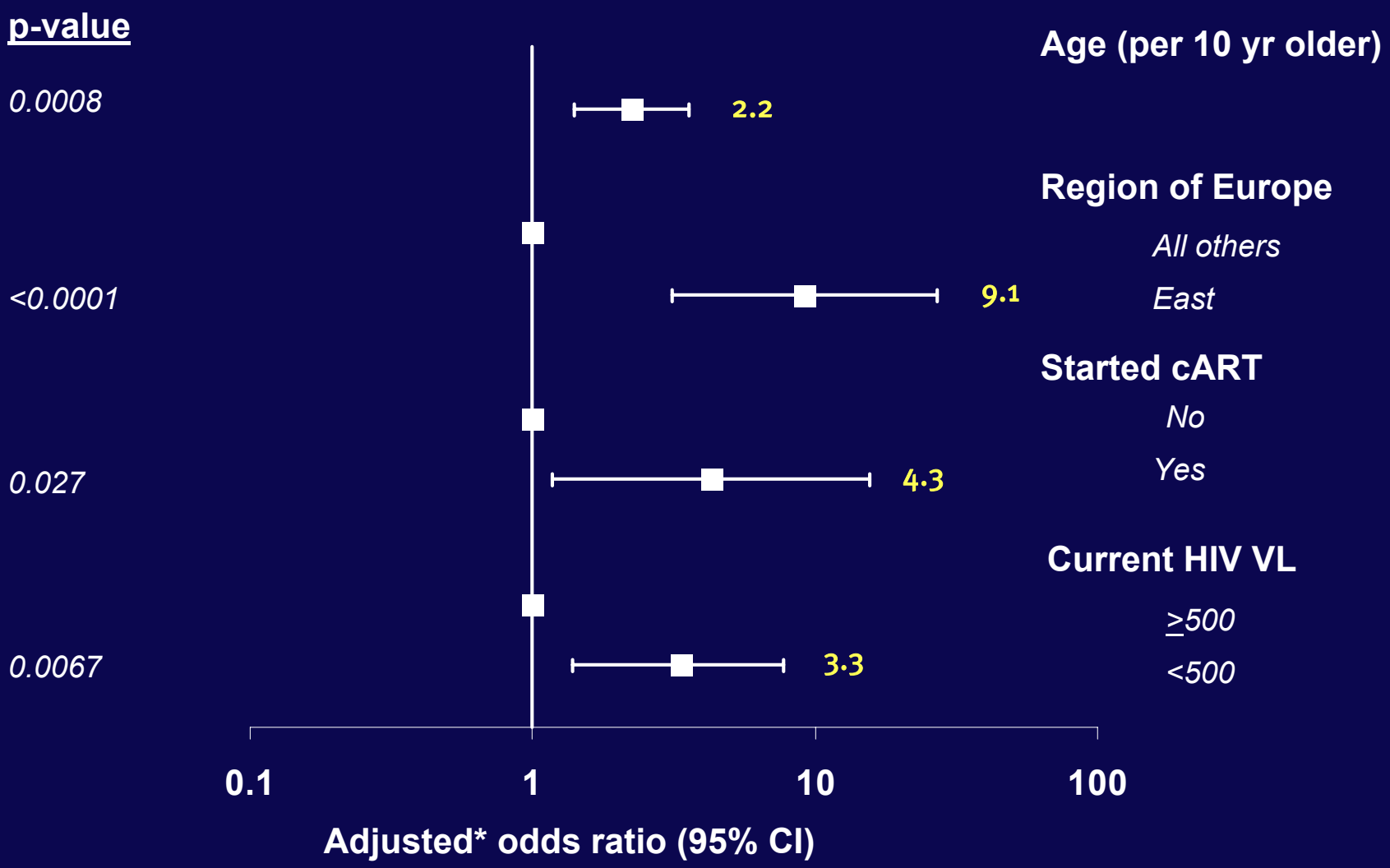
Factors associated with starting anti-HCV treatment



*Model additionally adjusted for gender, HIV exposure group, ethnic origin, ARV naïve status, use of cART, HBsAg status, age, CD4 nadir and HCV genotype

EuroSIDA

Starting anti-HCV treatment ≥2004 or <2003



EuroSIDA

Comparison of events in anti-HCV treated patients compared to untreated patients

	LRE[1]		DEATH[2]
Untreated	80	Events	262
	8192	PYFU	7242
	1.1 (0.8 – 1.3)	Rate (95% CI)	3.5 (3.1 – 4.0)
Treated	6	Events	12
	759	PYFU	768
	0.8 (0.3 – 1.7)	Rate (95% CI)	1.6 (0.8 – 2.7)
	0.73 (0.32 – 1.66)	Unadjusted IRR	0.44 (0.25 – 0.49)
	0.91 (0.37 – 2.18)	Adjusted* IRR	0.52 (0.28 – 0.95)

[1]Grade III/IV hepatic encephalopathy or death from liver related disease. [2]Death from any cause or LRE. *Adjusted for gender, HIV exposure group, ethnic origin, ARV naïve status, use of cART*, HBsAg status*, age, region, CD_4 nadir, CD_4*, viral load* and HCV genotype; *time-updated values

Summary

- Uptake of HCV treatment has increased across Europe after 2003
- Overall treatment remains low, particularly in Eastern Europe
- Majority of patients were infected with HIV through IDU
- Treatment more common in patients with higher CD4 counts and lower viral load; no difference according to HCV genotypes
- Anti-HCV treatment was associated with lower rate of DEATH* although confounding by indication cannot be ruled out

*Death from any cause or grade III / IV hepatic encephalopathy

The EuroSIDA Study Group

The multi-centre study group of EuroSIDA (national coordinators in parenthesis).
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, M Delforge, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent. **Bosnia-Herzegovina:** (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), I Zeltina, 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; A Grzeszczuk, R Flisiak, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, M Parczewski, 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, P Labarga, J Medrano, 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), Venhaelsan-Sodersjukhuset, Stockholm; 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 State Medical University; 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