



Factors associated with poor clinical outcome among HIV-infected patients with tuberculosis (TB) in Eastern Europe. The HIV/TB collaborative study

DN Podlekareva¹, A Mocroft², FA Post³, V Riekstina⁴, JM Miro⁵, H Furrer⁶, M Bruyand⁷, AM Panteleev⁸, E Girardi⁹, JJ Toibaro¹⁰, J Caylá¹¹, R Miller¹², N Obel¹³, AE Skrabin¹⁴, E Malashenkov¹⁵, JD Lundgren^{1,13}, O Kirk¹ and the HIV/TB study group

¹Copenhagen HIV Programme, University of Copenhagen, Faculty of Health Science, Denmark; ²Royal Free and University College Medical School, London, UK; ³King's College London School of Medicine, UK; ⁴State Agency of TB and Lung Diseases, Riga, Latvia; ⁵Hospital Clinic - IDIBAPS, University of Barcelona, Spain; ⁶University Hospital of Bern, Switzerland; ⁷INSERM, U 897, "epidemiology and biostatistics", Bordeaux, France; ⁸TB Hospital #2, St. Petersburg, Russia; ⁹Istituto Nazionale Malattie Infettive L Spallanzani, Rome, Italy; ¹⁰Hospital JM Ramos Mejia, Buenos Aires, Argentina; ¹¹Servicio de Epidemiología, Agencia de Salud Pública de Barcelona. CIBER Epidemiología y Salud Pública (CIBERESP), Spain; ¹²Mortimer Market Centre, London, UK; ¹³Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark; ¹⁴Research Institute of Pulmonology and Pulmonary Tuberculosis, Minsk, Belarus; ¹⁵Botkin Hospital of Infectious Diseases, St. Petersburg, Russia

OBJECTIVES

- To assess possible regional diversity in the clinical characteristics, management and outcome of HIV/TB patients in Europe and Argentina
 - Analyse risk factors associated with a fatal outcome after TB diagnosis in the cART era with special attention on Eastern Europe

METHODS

1075 consecutive HIV-patients starting TB treatment between 1/2004 and 12/2006 in 47 clinics across Europe and Argentina were included. Patients were stratified according to region of residence:

- Argentina (AR), N=115
 - Southern Europe (SE), N=210
 - Central/Northern Europe (CNE), N=168
 - Eastern Europe (EE), N=582

Kaplan-Meier estimation and Cox proportional hazards regression models were used to estimate the probability of death

RESULTS

Pronounced regional differences were observed in patients characteristics

- Patients from EE:
 - younger, white, and from the same country as where treated for TB (95%). Up to 80% had a history of injection drug use (IDU) and 46% coinfected with HCV (vs. 9-25% in other regions, $p<0.0001$)
 - Patients from CNE:
 - migrants from non-European countries (60%), female (53%) and with heterosexual HIV acquisition (65%)
 - Patients from SE:
 - more often had TB diagnosis in the past: 18% vs. 7%, 9% and 6% in AR, CNE and EE resp., $p<0.0001$
 - Patients from AR:
 - more pronounced immunodeficiency: median (IQR) CD4 cell count at Baseline: 92 (41-228), compared to 146 (55-291), 145 (54-284), 212 (89-463), in SE, CNE and EE resp., $p<0.0001$

Figure 1

Initial TB treatment regimens

Country	N	Initiated RHZE, %
AR	115	85
SE	210	63
CNE	168	77
EE	582	25

R – Rifampin, H – Isoniazid, Z – Pyrazinamide, E - Ethambutol

Figure 3

Kaplan- Meier progression to death within 1 year of TB diagnosis

P<0.0001

Proportion died

Months after TB diagnosis

N under FU:

	0	3	6	9	12
AR	115	104	96	83	69
SE	210	193	183	171	162
CNE	168	163	161	157	151
EE	582	485	395	339	281

Differences in diagnostic procedures, resistance patterns, TB treatment and cART Patients in EE:

- 69% had microbiologically or pathologically confirmed TB, vs. 72%, 79% and 86% in AR, SE and CNE respectively
 - 50% with performed resistance test were infected with *M. tuberculosis* resistant to at least one TB drug, vs. 7%, 13% and 7% respectively ($p<0.0001$)
 - 28% with resistance to at least Rifamycin, vs. 3%, 2% and 3% respectively ($p<0.0001$)
 - Were less likely to:
 - initiate TB treatment with four standard first line TB drugs (Figure 1)
 - receive cART during first year after TB diagnosis (Figure 2)

Outcome of TB disease and factors associated with death:

- Outcome according to WHO classification reported for 965 patients
 - Less patients from EE experienced Treatment success (cure/treatment completed): 48% vs. 64%, 66%, and 85% respectively
 - Death rates and factors associated with higher mortality rates are presented on Figures 3 and 4

CONCLUSIONS

- Pronounced differences observed clinical characteristics, management and survival prognosis after TB diagnosis in HIV/TB patients across Europe and Argentina
 - Higher mortality rate in EE compared with other regions can partially be explained by differences in:
 - patterns of anti-TB treatment
 - presence of TB drug-resistance
 - access to cART and baseline CD4 cell count
 - There is an urgent need to further understand why these differences exist and how outcome of HIV/TB in Eastern Europe can be improved

Figure 2

Use of cART during the 1st year after TB diagnosis

Timepoint (months)	AR	SE	CNE	EE
0	27	25	35	9
3	53	57	53	22
6	67	68	68	26
9	68	71	74	29
12	77	72	75	32

N under FU of known HIV+ at each timepoint:

Timepoint (months)	AR	SE	CNE	EE
0	106	202	158	515
3	103	191	162	481
6	96	183	161	395
9	83	171	157	339
12	69	162	151	281

Figure 4

Relative Hazards of death

Region: EE
AR
SE
CNE

CD4 at TB >200
≤ 200

Prior AIDS yes vs not

RHZ - based regimen
HZ - based regimen
Other regimens

Started cART vs not

MDR-TB* vs not

TB location: Pulmonary
Extra-Pulmonary
Disseminated

Univariate
Multivariate

* including resistance to at least Rifampin

The model was also adjusted for: age, gender, HIV and TB risk factors, date of HIV diagnosis in relation to TB diagnosis, calendar date of TB diagnosis, previous TB

Download poster at: www.cphiy.dk

Study group: Argentina, Buenos Aires: M. H. Losco (PI); Project Manager: J. I. Toibaro; Hospital Interzonal General de Agudos DR. D.PROISSEN: E. Warley, N. Tamayo, M. Cristina Ortiz; Hospital General: Agudos Donación F. Santonanni; P. Scapellato, E. Boltaro; Hospital Provincial Petrona V. de Cordero. San Fernando: F. Murano; Hospital San Juan de Dios (La Plata): M. Michans, J. Contarelli, L. Masseras; Hospital Interzonal HIGA Oscar Alende (Mar del Plata): J. Corral, M. Huilde.

C. Miglioranza: Hospital de Infectiosas Francisco Muñiz: M. Corti, H. Metta; Hospital General de Agudos Dr. T. Álvarez: A. Casiró, R. Cuini; Hospital Posadas: H. Laplume; Hospital Rawson (Cordoba): D. David, C. Marsons; C.A.I.C.M.: L. Supo, L. Trapé; Hospital Piñero: O. García Messina, O. Gear; Hospital General de Agudos J.M.Ramos Mejia: J. I. Toibaro, J. M. Brugera Belans, Minsk; University Hospital of Infectious Diseases: I. Karopov (PI), A. Vasilenko; Research Institute of Pulmonology and Thoracic Tuberculosis: E. Skrahina, A. Skrahina; Gomez University Hospital of Infectious Diseases: S. Zavhorjan, V. Mitsura, D. Ruzanov; University Hospital of Tuberculosis: V. Bondarenko; Svetoletsch: Mogen Region AIDS Centre: O. Druzenko, S. Padaduo. **Danmark:** Danish HIV Cohort: N. Obel (PI); Rigshospitalet; J. Gerstoft; Hvidovre University Hospital; G. Kromberg; Odense University Hospital; C. Pedersen; Aarhus University Hospitals; Skejby: C.S.Larsen; Herning Hospital; L. Nielsen; Helsingør Hospital; J. Jensen; **France:** Aquitaine Cohort: F. Dabis (PI); Epidemiology: G. Chêne, F. Dabis, S. Lawson-Ayayi, M. Bryand, R. Thibaut, M. Winnock; Infectious diseases-Internal Medicine: N. Bernard, M. Dupon, D. Lacoste, M. Dalvy, P. Merclé, P. Morlat, D. Neau, J. Pellegrin, J.M. Ragnaud; Immunology: J.F. Moreau, P. Blanco Viralology: H. Fleury, M. Lafon, B. Masquelier, I. Pellegrin Pharmacovigilance: Ghada Miremont Clinical Pharmacology; Dominique Breillith Statistical Analysis: M.J. Blaizeau, M. Decoin, S. Delveaux, P. Dubois, D. Dutoit, F. Dauchy, C. Hannapier, L. Houinou, S. Labarrère, G. Palmeret, D. Touchard, M. Longy-Boursier (P. Mercié, D. Malvy, T. Pistone, M. Receveur, P. Thibaut); M. Ragnaud (C. Cazorla, D. Chamberon, C. De La Taille, L. Haignaut, D. Neau, A. Ochoa), J.L. Pellegrin (J. Viillard, O. Caubert, C. Nouts), P. Couzigou (L. Castéra); Das Hospital; P. Loste (L. Caugnac) Bayonne Hospital; F. Bonnal (S. Farbes, M.C. Gernain), Libourne Hospital; J. Cecedalo (S. Tchangou); Mont de Marsan Hospital: S. De Witte; **Italy:** Clinica di Malattie Infettive, Modena: C. Mussini (PI), F. Prati, S. Castelletti; ICONA cohort: E. Girardi (PI) **Latvia:** Riga: State Agency of Tuberculosis and Lung Diseases; **Russia:** Riksteinska Institute of Latvia; P. Aldins **Romania:** Bucharest: Spitalul de Boli Infecțioase și Toxicoparitare; Dilescu (PI) **Russia:** St. Petersburg City TB Hospital; **Spain:** Barcelona: Institut d'IDIBAPS; University of Barcelona; J. M. Miro (PI), J. F. García-Gómez, A. Moreno-Martínez, J. González, F. García-Alcàide, E. Lázaro, J. M. Gatell; Hospital del Mar; P. Sanchez; J.L. Lopez-Colomes. Mutua de Terrassa; X. Martínez-Lacasa; Hospital Universitari Vall d'Hebron; V. Falgueras, J. M. Pujol; **Switzerland:** Swiss HIV Cohort: Zurich: R. Weber (PI); Basel: M. Battegay; Geneva: B. Hirschl; Lausanne: M. Cavassini; Lugano: E. Bernasconi; St. Gall: P. Schmid; Bern: H. Furrer; Data Center Lausanne: M. Rickenbach **United Kingdom:** London: King's Hospital; F. Post, L. Campbell; Mortimer Market Centre; R. Mallal; **Ukraine:** Kiev City AIDS Centre; N. Chernova; **USA:** New York: J. Traub, M. Filiberto