Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina

The HIV/TB Study Writing Group*

Background and objectives: Tuberculosis (TB) is a leading cause of death in HIV-infected patients worldwide. We aimed to study clinical characteristics and outcome of 1075 consecutive patients diagnosed with HIV/TB from 2004 to 2006 in Europe and Argentina.

Methods: One-year mortality was assessed in patients stratified according to region of residence, and factors associated with death were evaluated in multivariable Cox models.

Results: At TB diagnosis, patients in Eastern Europe had less advanced immunodeficiency, whereas a greater proportion had a history of intravenous drug use, coinfection with hepatitis C, disseminated TB, and infection with drug-resistant TB ($P < 0.0001$). In Eastern Europe, fewer patients initiated TB treatment containing at least rifamycin, isoniazid, and pyrazinamide or combination antiretroviral therapy ($P < 0.0001$). Mortality at 1 year was 27% in Eastern Europe, compared with 7, 9 and 11% in Central/Northern Europe, Southern Europe, and Argentina, respectively ($P < 0.0001$). In a multivariable model, the adjusted relative hazard of death was significantly lower in each of the other regions compared with Eastern Europe: 0.34 (95% confidence interval 0.17–0.65), 0.28 (0.14–0.57), 0.34 (0.15–0.77) in Argentina, Southern Europe and Central/Northern Europe, respectively. Factors significantly associated with increased mortality were CD4 cell count less than 200 cells/μl [2.31 (1.56–3.45)], prior AIDS [1.74 (1.22–2.47)], disseminated TB [2.00 (1.38–2.85)], initiation of TB treatment not including rifamycin, isoniazid and pyrazinamide [1.68 (1.20–2.36)], and rifamycin resistance [2.10 (1.29–3.41)]. Adjusting for these known confounders did not explain the increased mortality seen in Eastern Europe.

Conclusion: The poor outcome of patients with HIV/TB in Eastern Europe deserves further study and urgent public health attention.

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Keywords: combination antiretroviral therapy, eastern Europe, HIV/TB coinfection, mortality, multidrug-resistant tuberculosis, outcome, TB treatment

Introduction

Tuberculosis (TB) is a leading cause of morbidity and mortality in HIV-infected patients and may result from reactivation of latent *Mycobacterium tuberculosis* (MTB) infection as well as recent MTB transmission. In the absence of combination antiretroviral therapy (cART), high mortality rates have been reported among patients with HIV/TB, whereas the use of cART has been associated with improved survival, accelerated MTB clearance, and reduced recurrence rates [1–3]. In addition, cART has been shown to reduce the incidence of TB in HIV-infected patients [4].

Whereas several studies have reported on HIV/TB coinfection in Western Europe [1,3], the clinical epidemiology of HIV/TB in Eastern Europe remains poorly defined. The situation in this region is of particular concern, as it has one of the fastest growing HIV epidemics, with an overall prevalence of up to 2% in the

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worst affected countries and transmission fuelled by intravenous drug use (IDU) [5]. Coverage of cART for adults and children with advanced HIV disease in this region is under 25% [5]. In addition, the incidence of TB exceeds 0.1% in many countries, and transmission of drug-resistant MTB is a major problem [6,7]. Although the numbers of HIV/TB-coinfected patients are rapidly increasing in Eastern Europe, the prevalence of HIV in TB patients in Eastern Europe is likely to be severely underestimated [8]. Limited data suggest a 14-fold rise in HIV seroprevalence among TB cases in Latvia between 1998 and 2001 [9]. In addition, the prevalence of multidrug-resistant (MDR) TB is particularly high in this region. In the Baltic States, and parts of Russia and Ukraine, more than 10% of MTB isolates from new TB cases, and up to 64% of isolates from retreatment cases, are resistant to rifamycin and isoniazid (MDR) [7,9,10].

The combination of rising HIV prevalence, shared risk factors for HIV and MTB acquisition, low rates of cART use, and high rates of drug-resistant TB provides the ingredients for a potentially devastating HIV/TB epidemic. Moreover, in Eastern Europe, HIV and TB services are not well integrated, and several countries lack surveillance systems for these epidemics, whereas, in Western Europe, many HIV/TB-coinfected patients receive care for both diseases at the same medical institution from the same clinical team, and there is a well established surveillance infrastructure.

In 2006, we established the HIV/TB collaboration, based on the existing EuroSIDA infrastructure, a pan-European multicenter HIV cohort (www.eurosida.org). The purpose of this collaboration is to study patients with HIV/TB in Europe and Argentina with a special focus on Eastern Europe. Argentina has historically been part of the collaboration due to the similarities of HIV epidemiology with that of Southern Europe. However, we hypothesized that there might be significant differences in epidemiological and clinical characteristics of HIV/TB-coinfected patients, in particular, between Argentina and Southern Europe. In addition, there is little previous information about the HIV/TB epidemic in this region.

The aims of this study were to compare the clinical characteristics of HIV patients diagnosed with active TB and to analyze regional differences in patient management and outcomes and factors associated with death.

Methods

Cohort description

The HIV/TB study is a collaboration between 54 HIV and TB clinics from 11 European countries and Argentina (see Acknowledgement). Consecutive patients aged 16 years or older who initiated TB therapy between January 2004 and December 2006 and who were known to be HIV infected at TB diagnosis or diagnosed with HIV infection within 6 months of TB diagnosis were included.

The TB diagnosis was considered confirmed if MTB was cultured or MTB-DNA was demonstrated by PCR, probable if it was based on the presence of acid-fast bacilli or granulomatous inflammation, or presumptive TB if, in the absence of supportive microbiological or histological evidence, TB therapy had been initiated and the diagnosis of TB had not been subsequently ruled out.

Information was collected on standardized case report forms (CRFs, see www.cphiv.dk) and included demographic details, information on previous episodes of TB, clinical and radiographic features, results of microbiological, pathological, and biochemical investigations, details of treatment, and outcome of current TB episode. Outcomes were assessed at 1 year after TB diagnosis and according to the World Health Organization (WHO) standards: cure, treatment completed, treatment failure, death, defaulted/interrupted treatment, or transferred out/lost to follow-up (LTFU) [11]. HIV parameters, including demography data, CD4 cell counts, plasma HIV-RNA levels, details of antiretroviral therapy, chemoprophylaxis, viral hepatitis coinfection, and all AIDS-defining illnesses (other than TB, using the 1993 Centers for Disease Control and Prevention clinical case definitions) [12], were also collected. An extensive quality assurance program, which included site-monitoring visits in Eastern Europe and data quality control at the coordinating center, was maintained throughout the study. The study was approved by the Ethics Committees of participating clinics, as per local regulations, and the Danish Data Protection Agency (Datatilsynet).

Statistical methods

The sample size of 500 HIV/TB patients from Eastern Europe and 200 HIV/TB patients from Western Europe was calculated to ensure at least 100 fatal outcomes. The calculation was based on a 1-year mortality rate for HIV/TB-coinfected patients of 10% for patients receiving cART and 20% for treatment naive patients [2].

For comparative analysis, four regions were established according to patients' country of residence: Argentina ($N=115$, 11 clinics); Southern Europe ($N=210$, 10 clinics in Italy and Spain); Central/Northern Europe ($N=168$, 21 clinics in Denmark, France, Switzerland, and United Kingdom), and Eastern Europe ($N=582$, 12 clinics in Belarus, Latvia, Romania, Russia, and Ukraine).

The date of TB diagnosis (baseline) was defined as the date at which TB treatment was initiated, or the first smear or culture positive sample was obtained, whichever occurred earlier.

On the basis of clinical, radiological, microbiological, and pathological assessment, three mutually exclusive categories of extent of TB disease were defined. Patients were considered to have pulmonary TB if disease was limited to lungs or pleura or both, extrapulmonary TB if disease was in a single-organ system (excluding lungs and pleura), or disseminated TB if they had miliary TB, TB in at least two organ systems (one of which could be lungs or pleura), or if MTB had been isolated from blood or bone marrow.

Initial TB treatment was divided into three groups: regimens containing at least isoniazid (H), rifampicin (or, any other rifamycin) (R), and pyrazinamide (Z); regimens containing at least HZ (but not R); and any other drug combinations. All available CD4 cell counts were used to estimate values at 0, 3, 6, 9, and 12 months from the date of TB diagnosis, using measurements closest to, and obtained within 6 months of each time point.

Kaplan–Meier estimation and Cox proportional hazards regression models were used to estimate the probability of death. All variables were modeled as fixed variables in the univariable and multivariable models. The model was adjusted for the following a priori chosen variables: region of residence, age, sex, country of birth, risk factors for HIV and TB acquisition, HIV diagnosis preceding the date of TB diagnosis, CD4 cell count, prior AIDS, initiation of cART, date of TB diagnosis, previous TB, symptoms duration, type of anti-TB treatment, resistance to anti-TB drugs, and TB location. In supplementary analyses, we repeated the same model including CD4 cell count and cART as time-updated variables.

All analyses were performed using SAS (Statistical analysis software, Cary, North Carolina, USA) version 9.1.

Results

Patient characteristics

A total of 1075 patients were included in the present study. The diagnosis was confirmed in 646 (60%), probable in 152 (14%), and presumptive in 277 (26%) patients, and 9% had had a prior episode of TB. Although 91% of patients were known to be HIV infected at the time of TB diagnosis, only 175 (18%) of these were on cART. The median CD4 cell count at TB diagnosis was 174 cells/μl [interquartile range (IQR) 34–355], and 16% of patients with HIV-RNA measurement available had suppressed HIV-RNA levels less than 400 copies/ml. Median body weight at baseline was 60 kg (IQR 52–68 kg).

There were considerable differences in patient characteristics from different geographical regions (Table 1). Patients from Eastern Europe were younger, mostly white, and originated from the same country as where they were treated for TB. Patients from Eastern Europe more often had a history of IDU and were more often coinfected with hepatitis C. By contrast, the majority of patients from Central/Northern Europe were migrants from non-European countries, were of female sex, and had acquired HIV heterosexually. Patients from Argentina had more advanced disease, as illustrated by a lower median CD4 cell count and a higher proportion of patients with AIDS, whereas those in Eastern Europe had less advanced HIV disease. A high proportion of patients in all regions (49–60%) had the disseminated form of TB (Table 1).

TB diagnosis, drug resistance and therapy

The proportion of patients with confirmed TB was highest in Central/Northern Europe, whereas TB diagnosis relied more heavily on smear microscopy, histology or clinical features in Eastern Europe and Argentina (Table 2). Results of TB drug susceptibility testing were available for 513 (81.6%) of 629 patients in whom MTB was isolated. Pan-susceptible isolates were obtained from 93% of patients in Central/Northern Europe and Argentina, 87% in Southern Europe, and in only 50% of patients in Eastern Europe ($P < 0.0001$). Isoniazid, rifamycin, and multidrug resistance were all more common among isolates obtained from patients from Eastern Europe at any time during TB treatment (Table 2). Similar results were obtained when this analysis was confined to resistance tests performed on MTB isolates obtained within 3 months of TB diagnosis (data not shown).

Patients in Eastern Europe were less likely to initiate treatment, containing three main anti-TB drugs (i.e. RHZ-based regimens): 45 vs. 87%, 78%, and 86% of patients in Central/Northern Europe, Southern Europe, and Argentina, respectively (Table 2). Of those, the standard recommended first-line therapy for previously untreated cases (RHZE) was initiated by 57, 89, 82, and 99% of patients in Eastern Europe, Central/Northern Europe, Southern Europe and Argentina, respectively. Streptomycin and second-line agents were largely used in Eastern Europe as a part of the initial regimen (35 and 29%, respectively).

Antiretroviral therapy

Of the 981 patients known to be HIV infected at TB diagnosis, 281 (28.6%) had a history of cART, and 175 (18%) were taking cART at TB diagnosis. Use of cART increased over time from TB diagnosis in all four regions, and by 12 months, 71–77% of patients in Central/Northern Europe, Southern Europe, and Argentina, compared with 31% of patients in Eastern Europe, were receiving cART ($P < 0.0001$) (Fig. 1). For those who (re)initiated cART after TB diagnosis, the median interval between TB diagnosis and cART initiation was 2.3 (IQR 1.1–4.3) months with no regional differences. Nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens were more commonly used in Eastern Europe

Table 1. Baseline characteristics of HIV/TB-coinfected patients in Europe and Argentina.

N, % of total		EE 582 (54.1)	CNE 168 (15.6)	SE 210 (19.5)	AR 115 (10.7)	*P*
Demographics						
Age	Years, median (IQR)	30.3 (26.2–35.0)	37.5 (31.7–44.5)	37.7 (31.7–43.5)	35.8 (30.2–42.6)	<0.0001
Sex	M (%)	416 (71.5)	79 (47.0)	162 (77.1)	73 (63.5)	<0.0001
Origin[a]	Same as centre (%)	555 (95.4)	52 (31.0)	101 (48.1)	98 (85.2)	<0.0001
	Other non-European country (%)	3 (0.5)	101 (60.1)	90 (42.9)	11 (9.6)	
Hepatitis B status[b]	HBV surface-Ag positive (%)	62 (10.6)	11 (6.6)	14 (6.7)	2 (1.7)	0.012
Hepatitis C status[c]	HCV positive (%)	267 (45.9)	15 (8.9)	53 (25.2)	15 (13.0)	<0.0001
TB parameters						
TB risk factor[d]	IDU (%)	412 (80.3)	19 (14.3)	64 (35.2)	28 (36.8)	<0.0001
(>1 allowed)	Prison (%)	126 (24.6)	2 (1.5)	12 (6.6)	7 (9.2)	<0.0001
	Alcohol (%)	176 (34.3)	6 (4.5)	30 (16.5)	23 (30.3)	<0.0001
	Family (%)	72 (14.0)	14 (10.5)	8 (4.4)	39 (51.3)	<0.0001
Previous TB[e]	Yes (%)	34 (6.1)	15 (9.4)	32 (18.1)	8 (7.3)	<0.0001
TB location	Pulm (%)	211 (36.3)	44 (26.2)	80 (38.1)	46 (40.0)	<0.0001
	Expulm (%)	23 (4.0)	38 (22.6)	25 (11.9)	13 (11.3)	<0.0001
	Diss (%)	348 (59.7)	86 (51.2)	105 (50.0)	56 (48.7)	0.0003
HIV parameters						
HIV risk factor[f]	IDU (%)	414 (71.1)	16 (9.5)	51 (24.3)	19 (16.5)	<0.0001
	Hetero (%)	90 (15.5)	109 (64.9)	57 (27.1)	65 (56.5)	
HIV +ve	≥3 months before TB diagnosis (%)	414 (71.1)	107 (63.7)	130 (61.9)	79 (68.7)	<0.0001
CD4 cell count[g]	Cells/μl, median (IQR)	212 (89–463)	145 (54–284)	146 (55–291)	92 (41–228)	<0.0001
CD4 cell count ≤ 200[h]	Yes (%)	197 (47.1)	96 (60.8)	119 (62.3)	62 (69.7)	<0.0001
HIV-RNA[i]	Log_{10} copies/ml, median (IQR)	5.1 (4.3–5.7)	4.8 (3.0–5.4)	5.0 (3.6–5.6)	4.9 (3.8–5.4)	0.0090
Prior AIDS	Yes (%)	100 (19.4)	29 (18.4)	64 (31.7)	67 (63.2)	<0.0001

Eastern Europe (EE): Belarus, Latvia, Romania, Russia, Ukraine; Central/Northern Europe (CNE): France, Denmark, Switzerland, United Kingdom; Southern Europe (SE): Italy, Spain; Argentina (AR). Baseline defined as the date of TB diagnosis. Diss, disseminated; expulm, extrapulmonary; IDU, intravenous drug use; IQR, interquartile range; HCV, hepatitis C virus; M, male; pulm, pulmonary.
[a]Origin was unknown for 37 patients: EE 14 (2.4%), CNE 10 (5.9%), SE: 7 (3.3%), AR 6 (5.2%), $P = 0.10$.
[b]No significant differences comparing the proportions with unknown HBV status, $P = 0.29$.
[c]No significant differences comparing the proportions with unknown HCV status, $P = 0.17$.
[d]TB risk factor was unknown for 171 patients: EE 69 (11.9%), CNE 35 (20.8%), SE 28 (13.3%), AR 39 (33.9%), $P < 0.0001$.
[e]Data on previous TB were unknown for 71 patients: EE 25 (4.3%), CNE 8 (4.8%), SE 33 (15.7%), AR 5 (4.4%), $P < 0.0001$.
[f]HIV risk group was unknown for 70 patients: EE 34 (5.8%), CNE 5 (3.0%), SE 30 (14.3%), AR 1 (0.9%), $P < 0.0001$.
[g]CD4 cell count was unknown for 219 patients: EE 164 (28.2%), CNE 10 (6.0%), SE 19 (9.1%), AR 26 (22.6%), $P < 0.0001$.
[h]Of those with known CD4 cell count.
[i]HIV-RNA was unknown for 573 patients: EE 478 (82.1%), CNE 15 (8.9%), SE 31 (14.8%), AR 49 (42.6%), $P < 0.0001$.

and Argentina (82 and 86%, compared with 74 and 71% in Central/Northern Europe and Southern Europe, $P = 0.0029$), whereas protease inhibitor (PI)-based regimens were used by 8% in Argentina, 11% in Eastern Europe, and 26% in both Southern Europe and Central Northern Europe ($P = 0.0029$).

CD4 cell counts increased steadily following TB diagnosis in all four regions. At 12 months, median (IQR) CD4 cell counts were 258 (121–497), 221 (50–390), 224 (102–422), and 147 (49–225) cells/μl in Eastern Europe ($n = 213$), Central/Northern Europe ($n = 149$), Southern Europe ($n = 155$), and Argentina ($n = 57$), respectively ($P = <0.0001$).

TB outcome

Treatment outcome was available for 965 patients (90%). Overall, 570 patients (59%) were classified as treatment success (cure or treatment completed or both), and this proportion was highest in Cenral/Northern Europe (85%), followed by 66, 64, and 48% in Southern Europe, Argentina, and Eastern Europe, respectively ($P < 0.0001$). Treatment failure or defaulted/interrupted treatment was reported for 13, 4, 6, and 12% of patients in Eastern Europe, Central/Northern Europe, Southern Europe, and Argentina, respectively ($P < 0.0001$).

At 12 months from TB diagnosis, 201 patients (19%) were known to have died, and 141 patients (13%) had developed an additional AIDS-defining disease other than TB (14, 5, 21, and 24% of patients in Eastern Europe, Central/Northern Europe, Southern Europe, and Argentina, respectively, $P < 0.0001$). The cumulative probability of death at 12 months was 33% [95% confidence interval (CI) 29–37] in Eastern Europe, 14% (7–21) in Argentina, 10% (5–14) in Southern Europe, and 8% (4–12) in Central/Northern Europe, $P < 0.0001$ (Fig. 2), and death was considered to be TB-related in 144 patients (72%).

Before adjustment, patients from Argentina, Southern Europe, and Central/Northern Europe were at 64–81%

Table 2. Diagnosis, drug susceptibility tests, and initial treatment of TB in HIV-infected patients in Europe and Argentina.

N	EE 582	CNE 168	SE 210	AR 115	*P*
TB diagnosis, *N* (% of total)					
Confirmed TB[a,b]	302 (51.9)	134 (79.8)	158 (75.2)	52 (45.2)	<0.0001
Probable TB[c]	102 (17.5)	11 (6.6)	8 (3.8)	31 (27.0)	<0.0001
Presumptive TB[d]	178 (30.6)	23 (13.7)	44 (21.0)	32 (27.8)	<0.0001
TB culture and drug susceptibility[e], *N* (%)					
Culture +ve (% of total)	302 (51.9)	129 (76.8)	146 (69.5)	52 (45.2)	<0.0001
Resistance tests					
Ever performed (% of culture+)	252 (83.4)	102 (79.1)	129 (88.4)	30 (57.7)	<0.0001
Pan-susceptible (% of ever performed)	125 (49.6)	95 (93.1)	112 (86.8)	28 (93.3)	<0.0001
H-resistant[f]	58 (23.0)	7 (6.9)	10 (7.8)	2 (6.7)	<0.0001
R-resistant[g]	70 (27.8)	3 (2.9)	3 (2.3)	1 (3.3)	<0.0001
MDR[h]	31 (12.3)	3 (2.9)	2 (1.6)	1 (3.3)	0.0002
Initial TB treatment, *N* (% of total)					
Type of treatment					
RHZ-based	259 (44.5)	146 (86.9)	163 (77.6)	99 (86.1)	<0.0001
HZ-based	101 (17.3)	5 (3.0)	4 (1.9)	7 (6.1)	<0.0001
Other	222 (38.1)	17 (10.1)	43 (20.5)	9 (7.8)	<0.0001

Eastern Europe (EE): Belarus, Latvia, Romania, Russia, Ukraine; Central/Northern Europe (CNE): France, Denmark, Switzerland, United Kingdom; Southern Europe (SE): Italy, Spain; Argentina (AR). Patients with no data reported on diagnostic procedures, but having resistance test done are assumed to be culture positive. H, isoniazid; MDR, multidrug resistant; R, rifamycin; Z, pyrazinamide.
[a]Confirmed TB is TB documented by either culture or PCR.
[b]PCR data not available for AR and EE.
[c]Probable TB is TB documented by either microscopy or histology.
[d]Presumptive diagnosis based on clinical findings, initiation of TB treatment, which was not stopped because TB diagnosis was subsequently ruled out.
[e]Detected at any time during TB treatment.
[f]Resistance to at least H.
[g]Resistance to at least R.
[h]Resistance to at least R and H.

lower risk of death than those from Eastern Europe [RH 0.36 (95% CI 0.21–0.64), 0.25 (0.15–0.40), and 0.19 (0.11–0.34) for Argentina, Southern Europe, and Central/Northern Europe, respectively]. These regional differences did not change substantially after adjusting for factors that could potentially affect prognosis in multivariable Cox proportional hazard models (Fig. 3). IDU as a risk factor for TB acquisition was strongly associated with increased risk of death in the univariable model (RH 2.58, 95% CI 1.92–3.47), but not in multivariable analysis (RH 1.74, 0.93–3.23, $P = 0.081$), perhaps due to the close association between region and TB risk groups.

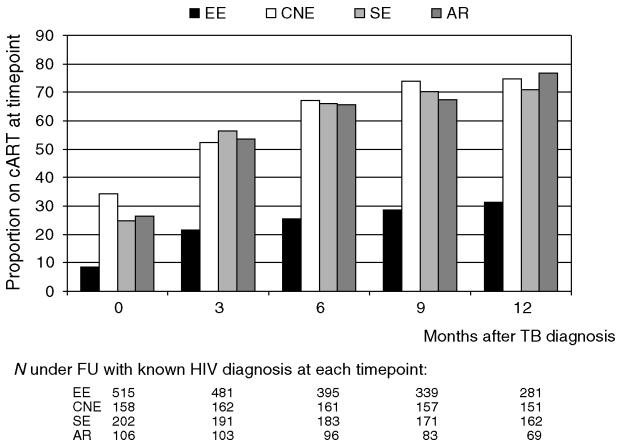

Fig. 1. Use of combination antiretroviral therapy in HIV/TB-coinfected patients according to the region of residence. Eastern Europe (EE): Belarus, Latvia, Romania, Russia, Ukraine; Central/Northern Europe (CNE): France, Denmark, Switzerland, United Kingdom; Southern Europe (SE): Italy, Spain; Argentina (AR). FU, follow-up.

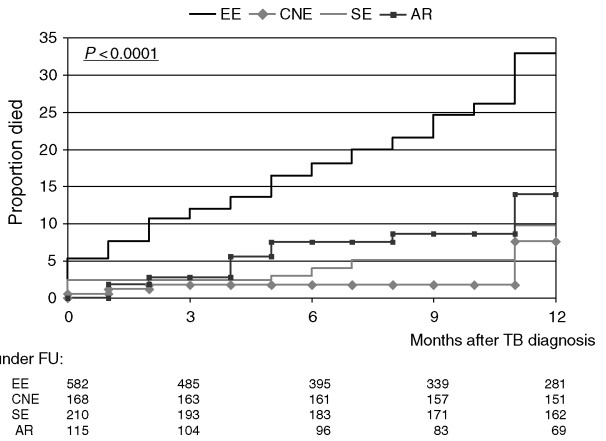

Fig. 2. Kaplan–Meier analysis of cumulative probability of death within 1 year of TB diagnosis in HIV-infected patients according to the region of residence. Eastern Europe (EE): Belarus, Latvia, Romania, Russia, Ukraine; Central/Northern Europe (CNE): France, Denmark, Switzerland, United Kingdom; Southern Europe (SE): Italy, Spain; Argentina (AR). The median (IQR) follow-up was 11 (5–12), 12 (12–12), 12 (12–12), and 12 (8–12), months in EE, CNE, SE, and AR, respectively, $P < 0.0001$. FU, follow-up; IQR, interquartile range.

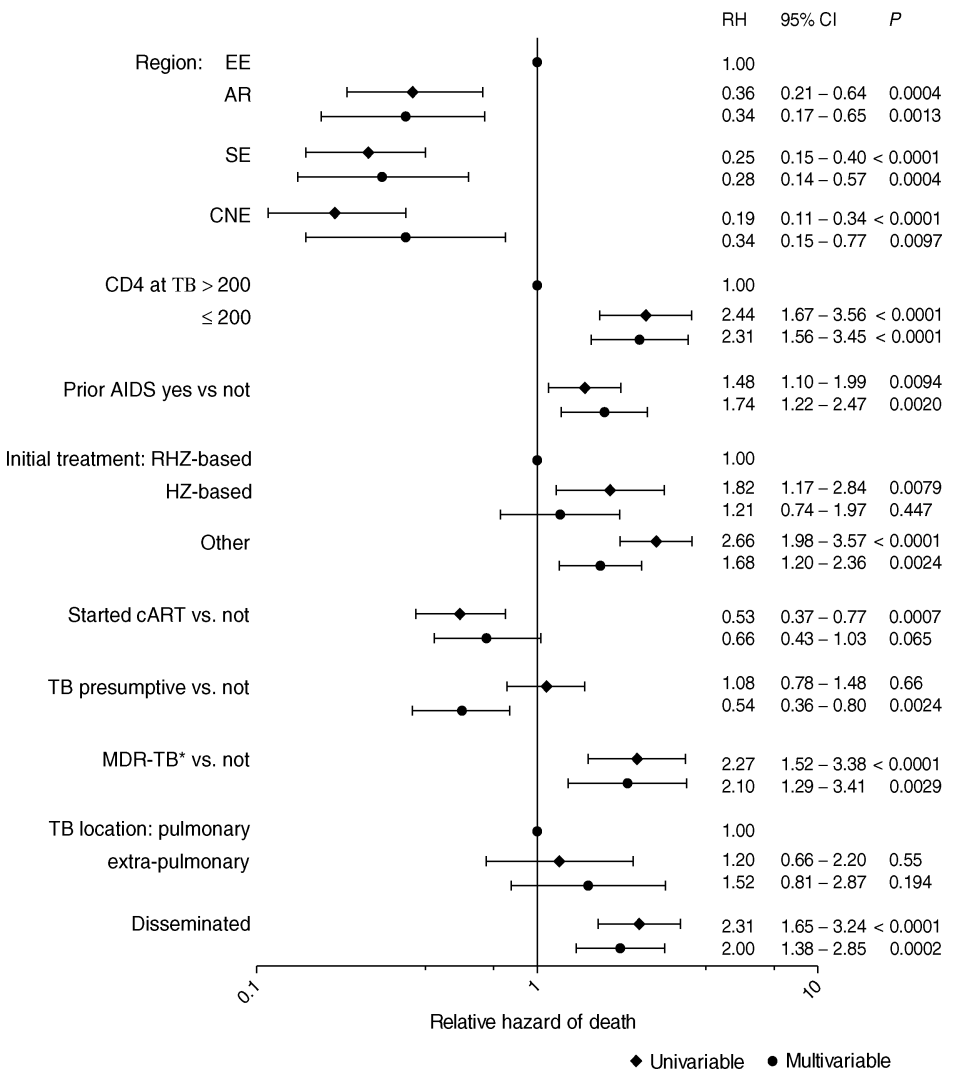

Fig. 3. Relative hazards of death among HIV/TB-coinfected patients. Eastern Europe (EE): Belarus, Latvia, Romania, Russia, Ukraine; Central/Northern Europe (CNE): France, Denmark, Switzerland, United Kingdom; Southern Europe (SE): Italy, Spain; Argentina (AR). Symbol asterisk indicates MDR-TB cases including cases with resistance to at least rifamycin. The model was also adjusted for age, sex, origin, TB and HIV risk factors, date of HIV diagnosis in relation to TB diagnosis, calendar date of TB diagnosis, previous TB diagnosis, and symptom duration prior to TB diagnosis.

Patients with CD4 cell counts of 200 cells/μl or less were at more than two-fold higher risk of death compared with those with CD4 cell counts more than 200 cells/μl, as were patients with prior non-TB AIDS diagnoses. In the univariable analysis, patients who had started cART at or before the date of TB diagnosis were at lower risk of death compared with those who did not start cART, though this was no longer significant after adjustment for other factors including CD4 cell count. Initiation of TB treatment regimens not containing RHZ, the presence of rifamycin resistance, and disseminated TB were associated with increased risk of death in the adjusted analyses (Fig. 3).

Several supplementary analyses were performed. In a model incorporating time-updated CD4 cell count and cART use, the regional differences remained essentially unchanged. Further, the associations between the prognostic factors listed above and outcome of TB remained similar when restricting the analysis to clinics in Eastern Europe or to patients with confirmed (and probable TB) (data not shown).

Discussion

The present study is the first multinational study of HIV/TB and reveals pronounced regional differences in clinical characteristics, management, and outcome of patients across Europe and Argentina. HIV/TB patients in Eastern

Europe, compared with those in other regions, were at three-fold to five-fold increased risk of death. Several factors, including low CD4 cell count, prior AIDS, disseminated TB, MTB drug resistance, use of non-RHZ-containing initial TB treatment regimens and nonuse of cART, were associated with increased hazard of death. However, these factors only partially explained the observed regional differences. Our results emphasize that TB remains a serious comorbidity among HIV-infected patients, especially when cART is not readily available.

In immunocompromised patients, early TB diagnosis and prompt institution of appropriate chemotherapy are likely to be the most important conditions for achieving optimal clinical outcomes. In Southern Europe and Central/Northern Europe, the TB diagnosis was confirmed and RHZ-based TB therapy used in a high proportion of patients (78–87%). In Argentina, low rates of MTB drug resistance allowed successful management of patients with RHZ-based TB therapy in the absence of TB culture results. By contrast, the high rate of MTB drug resistance in Eastern Europe necessitates routine use of mycobacterial culture and TB drug susceptibility testing to confirm the diagnosis and guide appropriate TB treatment. The low proportion of confirmed TB and consequent limited data on drug susceptibility at baseline are likely to have resulted in suboptimal TB therapy in many patients in Eastern Europe. Infection with rifamycin-resistant MTB isolates was associated with increased mortality in our study, a finding that is consistent with a recent meta-analysis, which reported a similar association, particularly in patients in whom TB treatment regimens were not guided by the results of susceptibility tests [13].

Empirical TB treatment in areas with high MDR-TB prevalence should, in accordance with international guidelines, include RHZ along with one or more second-line drugs [14,15]. We noted that streptomycin and second-line drugs were commonly used in Eastern Europe, often as part of regimens not containing RHZ. This practice may have arisen from an anticipated high rate of MDR-TB as well as other factors such as differences in drug accessibility and local patterns of delivery of care. The exclusion of RHZ from initial TB regimens is likely to have resulted in suboptimal TB treatment regimens in several patients with pan-susceptible TB, and it may have promoted selection of (additional) TB drug resistance. Initiation of TB treatment, which did not contain RHZ, was associated with increased mortality in our study and contributed to poor outcome in Eastern Europe.

The majority of patients included in this study had CD4 cell counts less than 200/μl and established HIV diagnoses, yet many were not receiving cART when they developed TB. A substantial proportion of these TB episodes might have been prevented by earlier cART initiation and thus avoidance of severe immunodeficiency. Although the optimal timing of cART in HIV/TB remains to be established, most experts would recommend initiation of cART within 8 weeks of starting TB treatment in patients with CD4 cell counts less than 200/μl as cART-induced increases in CD4 cell count are associated with improved outcome of HIV/TB patients [1,16,17]. It is interesting to note that clinical practice in Argentina, Southern Europe, and Central/Northern Europe resulted in similar timing of cART, whereas low cART use in Eastern Europe may be partially explained by higher median CD4 cell counts in this region. Deferred cART initiation in HIV/TB patients has been associated with increased mortality, including patients with CD4 cell counts more than 200/μl [18]. Underexposure to cART in Eastern Europe may have been the result of clinical challenges such as IDU, in addition to political and socio-economical challenges in this region [5,19].

The present study has several limitations. First, this is a retrospective study, and a possible lack of routine HIV testing of all TB patients in some countries may have given rise to an incomplete patient sample. Although LTFU levels in our study are not higher than in other cohort studies [20,21], it might reflect some regional differences in the capability to provide clinical information for 12 months after the TB diagnosis. However, we have performed an extensive data quality assurance program, including monitoring visits to Eastern Europe, where participating clinics had little experience with observational studies and data collection. Although Eastern Europe was considered a single region, it should be emphasized that, in fact, Eastern Europe is a heterogeneous region and that the healthcare infrastructure differs considerably across countries. Some countries are represented by a single city, which is unlikely to truly reflect the situation in the whole country. Availability of anti-TB drugs is likely to have differed between regions and within regions, particularly in Eastern Europe. Moreover, the participating clinics were generally major HIV and TB centers of excellence, and thus the cohort might not necessarily be representative for all HIV/TB populations in Eastern Europe. Our results may thus reflect a 'best-case' scenario, with the real life situation in many parts of Eastern Europe, which may be considerably worse.

The results of this study emphasize that the healthcare needs of HIV/TB patients in Eastern Europe are poorly met. Improvements in outcome are likely to require actions at community, hospital, and government levels. Several recommendations can be made based on the study findings. Integration of HIV and TB care is important, as it will allow earlier access to cART and assist the management of overlapping drug toxicities, complex drug–drug interactions, and difficult adherence issues [19,22,23]. Widespread use of mycobacterial culture and

universal TB drug susceptibility testing at baseline are essential for optimal management of TB. RHZ should be a part of all initial TB regimens, with the possible inclusion of a fluoroquinolone and second-line aminoglycoside in Eastern Europe, until the results of drug susceptibility testing have become available. Furthermore, all patients should be offered cART within 2 months of TB diagnosis (if not yet on cART). As marginalized groups (i.e. IDU, prisoners, alcohol addicts, homeless people) are overrepresented among HIV/TB patients in Eastern Europe, access and adherence to TB and HIV treatment should receive particular attention [19], and initial hospitalization for directly observed TB and HIV therapy may be essential in this region [24]. Treatment adherence and methadone support programs will be instrumental, and the development of HIV drug resistance will need to be closely monitored. Strict measures to prevent transmission of MDR-TB should be coupled with access to new anti-TB drugs for the treatment of MDR-TB when these become available. Until then, epidemiological surveillance for emergent extensively drug-resistant (XDR)-TB [25] should be carried out.

Conclusion

The poor outcome of patients with HIV/TB in Eastern Europe deserves further study and urgent public health attention. Universal use of TB culture and drug susceptibility testing, coupled with implementation of WHO-recommended TB treatment regimens to which effective second-line agents may be added, is a clear priority. Access to cART should be improved through programs able to reach out and support marginalized groups. Finally, efforts to reduce TB transmission and improved surveillance of the HIV and TB epidemics in Eastern Europe are required, and prospective studies with longer follow-up will allow evaluation of whether the proposed measures will be able to improve the poor outcomes of patients with HIV/TB in this region. For now, HIV/TB coinfection remains a formidable challenge for clinicians in Eastern Europe.

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