

# Tuberculosis-related mortality in people living with HIV in Europe and Latin America: an international cohort study



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## Summary

**Background** Management of tuberculosis in patients with HIV in eastern Europe is complicated by the high prevalence of multidrug-resistant tuberculosis, low rates of drug susceptibility testing, and poor access to antiretroviral therapy (ART). We report 1 year mortality estimates from a multiregional (eastern Europe, western Europe, and Latin America) prospective cohort study: the TB:HIV study.

**Methods** Consecutive HIV-positive patients aged 16 years or older with a diagnosis of tuberculosis between Jan 1, 2011, and Dec 31, 2013, were enrolled from 62 HIV and tuberculosis clinics in 19 countries in eastern Europe, western Europe, and Latin America. The primary endpoint was death within 12 months after starting tuberculosis treatment; all deaths were classified according to whether or not they were tuberculosis related. Follow-up was either until death, the final visit, or 12 months after baseline, whichever occurred first. Risk factors for all-cause and tuberculosis-related deaths were assessed using Kaplan-Meier estimates and Cox models.

**Findings** Of 1406 patients (834 in eastern Europe, 317 in western Europe, and 255 in Latin America), 264 (19%) died within 12 months. 188 (71%) of these deaths were tuberculosis related. The probability of all-cause death was 29% (95% CI 26–32) in eastern Europe, 4% (3–7) in western Europe, and 11% (8–16) in Latin America ( $p < 0.0001$ ) and the corresponding probabilities of tuberculosis-related death were 23% (20–26), 1% (0–3), and 4% (2–8), respectively ( $p < 0.0001$ ). Patients receiving care outside eastern Europe had a 77% decreased risk of death: adjusted hazard ratio (aHR) 0.23 (95% CI 0.16–0.31). In eastern Europe, compared with patients who started a regimen with at least three active antituberculosis drugs, those who started fewer than three active antituberculosis drugs were at a higher risk of tuberculosis-related death (aHR 3.17; 95% CI 1.83–5.49) as were those who did not have baseline drug-susceptibility tests (2.24; 1.31–3.83). Other prognostic factors for increased tuberculosis-related mortality were disseminated tuberculosis and a low CD4 cell count. 18% of patients were receiving ART at tuberculosis diagnosis in eastern Europe compared with 44% in western Europe and 39% in Latin America ( $p < 0.0001$ ); 12 months later the proportions were 67% in eastern Europe, 92% in western Europe, and 85% in Latin America ( $p < 0.0001$ ).

**Interpretation** Patients with HIV and tuberculosis in eastern Europe have a risk of death nearly four-times higher than that in patients from western Europe and Latin America. This increased mortality rate is associated with modifiable risk factors such as lack of drug susceptibility testing and suboptimal initial antituberculosis treatment in settings with a high prevalence of drug resistance. Urgent action is needed to improve tuberculosis care for patients living with HIV in eastern Europe.

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## Introduction

The high prevalence of multidrug-resistant tuberculosis in eastern Europe presents a substantial challenge to the management of the combined epidemic of tuberculosis and HIV.<sup>1–3</sup> The number of people with both tuberculosis and HIV is increasing rapidly and the mortality rate of these patients in this region is among the highest in the world,<sup>2,4–7</sup> but little published evidence from eastern Europe exists on the management of co-infected patients and risk factors for excess mortality. We have previously described the clinical aspects of the tuberculosis–HIV epidemic in eastern Europe, when the retrospective TB:HIV study was done.<sup>4</sup> The reasons for the high mortality rate in eastern Europe are complex and multifactorial.

The TB–HIV epidemic in this region is mainly driven by injecting drug users, a population group that needs a special multidisciplinary health-care approach to maintain retention in care and good treatment adherence.<sup>2,5–8</sup> Many of these patients are not engaged with health-care services despite awareness of their HIV diagnosis and are therefore not receiving antiretroviral therapy (ART), which allows immunodeficiency to progress and severe tuberculosis disease to develop.<sup>4</sup> Meanwhile, management of those patients with HIV and tuberculosis who are engaged in health care seems to be suboptimal.<sup>4,8</sup> Initiation of ART in this region is often delayed, even after TB is diagnosed.<sup>4</sup> Medical treatment of tuberculosis is inadequate, as shown by a high prevalence of drug-resistant mycobacteria and by diverse use of only partly effective tuberculosis drug

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See Online for appendix

## Research in context

### Evidence before this study

Evidence about the co-epidemic of tuberculosis and HIV in eastern Europe is generally scarce with poor surveillance systems and few clinical studies. Few studies have provided data for patients co-infected with tuberculosis and HIV in this region. We searched PubMed for articles published before Dec 11, 2015, with the terms "HIV", "tuberculosis", "Eastern Europe", "Europe", "Latin America", "drug-resistance", "MDR-TB", "XDR-TB", and "injecting drug abuse", and "outcome" in different combinations. We included only studies published in English or Russian. Several cohort studies and surveillance databases had previously reported a significantly reduced incidence of tuberculosis and improved mortality after implementation of antiretroviral therapy in high-income countries. The protective effect of antiretroviral therapy, especially in patients with severe immune suppression, has also been shown. A few studies have reported about antituberculosis drug resistance in different countries in eastern Europe. Our group has previously published results from a retrospective cohort of patients co-infected with HIV and tuberculosis, in which we documented 1-year mortality of around 30% in patients with HIV and tuberculosis in eastern Europe, which was at least three times higher than in patients from western Europe and Argentina. Otherwise, we did not identify any prospective data about the management and outcomes of patients with tuberculosis and HIV co-infection in eastern Europe.

### Added value of this study

To the best of our knowledge, this is the first prospective international cohort study on the epidemiology and clinical aspects of patients co-infected with tuberculosis and HIV across Europe and Latin America. We provide detailed clinical data about tuberculosis drug resistance and the clinical management of patients co-infected with tuberculosis and HIV in Europe and Latin America. We have specifically focused on countries from

eastern Europe where the tuberculosis and HIV epidemic is of particular concern because of rapidly increasing rates of co-infected patients, and where the prevalence of multidrug-resistant tuberculosis is among highest in the world. The study is the first to show the suboptimum management of patients with both tuberculosis and HIV originating from eastern Europe along with very high rates of multidrug-resistant tuberculosis, resulting in alarmingly high mortality rates in the region, with the main cause of death being tuberculosis related. Mortality was especially high in patients who started antituberculosis treatment with an inadequate number of active drugs according to the drug susceptibility test result or who did not have a drug susceptibility test done. Furthermore, the study highlights concerns of low use of antiretroviral therapy in eastern Europe. Finally, the study addresses not only clinical but also public health issues related to tuberculosis-HIV co-infection, especially in eastern Europe.

### Implications of all the available evidence

The findings from our study draw attention to the increasing problem of the tuberculosis-HIV epidemic in eastern Europe and emphasise the urgent need for restructuring the health-care approach to patients with co-infection in this region. The results of this study emphasise the importance of integrating tuberculosis and HIV services, and of the provision of other health-care and social services to these vulnerable patients. Improvement and implementation of more accurate and rapidly available tuberculosis diagnostics and drug susceptibility tests are needed in eastern Europe to ensure timely and adequate antituberculosis treatment. Such an approach is essential to assure patients' retention in care and initiation of antiretroviral therapy when indicated. More studies are needed to address these issues further to improve the outcomes for co-infection with HIV and tuberculosis in the eastern European region.

regimens.<sup>8,9</sup> Opioid substitution therapy is rarely prescribed in the region, either because it is not available or is prohibited.<sup>8,10</sup> Finally, social support for injecting drug user populations in eastern Europe is very scarce (Rakhmanova AG, St Petersburg AIDS Centre, Russia, personal communication).

Supporting the theory that management of tuberculosis in patients with HIV in eastern Europe is inadequate, we previously found that most deaths were linked to untreated tuberculosis disease, and rarely to other opportunistic infections.<sup>11</sup> The coepidemic in eastern Europe is a public health emergency that continues to grow.<sup>12</sup> Despite this fact, little direct documentation of its detrimental effects exists. We designed a prospective study of a large cohort of HIV-positive patients diagnosed with tuberculosis in countries of eastern Europe, western Europe, and Latin America.<sup>8</sup> The latter two regions were chosen to provide a comparison with eastern Europe and to establish a

benchmark for management of tuberculosis in people living with HIV. The aim of the present report is to assess and compare 1-year mortality after tuberculosis diagnosis across regions. Additionally, we aimed to assess whether or not prognostic markers identified at diagnosis of tuberculosis translated into excessive death rates.

## Methods

### Study design and participants

The TB:HIV prospective study was initiated in 2011 within the EuroCoord collaboration. The study is a collaboration of clinicians from 62 HIV and tuberculosis clinics in 19 countries in eastern Europe, western Europe, and Latin America. Details of the study infrastructure have been published previously.<sup>8</sup> Briefly, patients were eligible for enrolment if they were HIV positive (before, or up to 3 months after a diagnosis of tuberculosis), 16 years of age or older, and diagnosed with active

For the EuroCoord collaboration see <http://www.chip.dk>

tuberculosis disease between Jan 1, 2011, and Dec 31, 2013. Participating clinics had to enrol all consecutive patients with HIV and tuberculosis diagnosis within the aforementioned timeframe; each patient was then followed up for 2 years.

The study was approved by the ethics committees of participating countries or clinics and written informed consent was obtained if required by local and national regulations. All patients' data were obtained from patients' medical records or via database exchange with HICDEP format.

### Procedures and definitions

Demographic, clinical, and laboratory data, and data about patients' outcomes were collected on case report forms for both tuberculosis disease and HIV infection at the time of tuberculosis diagnosis and at 6 months, 12 months, and 24 months of follow-up (study protocol and case report forms are available online).<sup>8</sup> Clinical information at the time of death was collected on specific coding causes of death case report forms.<sup>11,12</sup> These forms were assessed by two clinicians at the coordinating centre and the underlying causes of death were categorised as tuberculosis-related, or not. Data were extensively quality assured both at the coordinating centre, and through site visits with data monitoring of all deaths, multidrug-resistance cases, and a random sample of 10% of the remaining participants.

Antituberculosis drugs initiated within 10 days of when the first antituberculosis drug was started were considered to comprise an initial regimen, and tuberculosis treatment was categorised as RHZ-based (containing at least a rifamycin, isoniazid, and pyrazinamide), or other (panel). Initial antituberculosis treatment was further assessed according to the number of active drugs in the regimen based on results of locally performed drug susceptibility tests on a *Mycobacterium tuberculosis* sample taken up to 1 month before or after initiation of antituberculosis treatment (baseline drug susceptibility test). For the primary analysis, we judged all *M tuberculosis* isolates with some drug susceptibility test results available to be susceptible to drugs for which there was no indication of resistance (ie, if no data were available for a specific drug, the isolate was considered susceptible to that drug). All patients with available results for both rifamycin and isoniazid at baseline were classified into three groups (panel): multidrug-resistant tuberculosis (resistance to both rifamycin and isoniazid); mono-resistance (resistance to either rifamycin or isoniazid but not multidrug resistant); and drug-susceptible tuberculosis (susceptible to rifamycin and isoniazid). A fourth category of patients comprised those with no available baseline drug susceptibility test data for rifamycin and isoniazid. Patients with mono-resistance to either isoniazid (n=34) or rifamycin (n=6) were grouped together because of the small numbers of patients.

### Statistical analysis

All patients enrolled into the TB:HIV study who met inclusion criteria and who started antituberculosis treatment were included in the present analyses. All patients were stratified into three geographical regions according to their country of residence: eastern Europe, western Europe, or Latin America (panel). Comparative analyses were done across regions. Baseline characteristics were compared with  $\chi^2$  or Kruskal-Wallis tests as appropriate.

The endpoint was defined as overall and tuberculosis-related death within the first 12 months after treatment initiation. Follow-up was either until death, the final visit, or 12 months after baseline, whichever occurred first. In the analysis of tuberculosis-related mortality, patients who died of any other causes were censored at the date of death. Unknown causes of death were judged not related to tuberculosis.

All-cause and tuberculosis-related mortality rates were analysed with Kaplan-Meier estimates for patients stratified by geographical region, drug susceptibility, and the number of active drugs in the initial regimen (three or more, fewer than three, or unknown). For this analysis, western Europe and Latin America were combined because of the low number of deaths. The number of active drugs in the initial regimen was calculated retrospectively based on the results of the baseline drug susceptibility test.

For more on HICDEP format see <http://www.hicdep.org>

For the study protocol see <http://www.chip.dk>

### Panel: Study definitions

#### Regions

- Eastern Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, and Russia
- Western Europe: Belgium, Denmark, France, Italy, Spain, Switzerland, and the UK
- Latin America: Argentina, Chile, and Mexico

#### Tuberculosis diagnosis

- Definite: positive culture or PCR for *Mycobacterium tuberculosis*
- Probable: acid-fast bacilli or granulomatous inflammation on smear or tissue biopsy specimens
- Presumptive: tuberculosis treatment initiated and not subsequently stopped because the tuberculosis diagnosis was ruled out

#### Tuberculosis location

- Pulmonary: tuberculosis localised to the lungs, larynx, or tracheobronchial tree
- Disseminated: any of the following:
  - Tuberculosis documented in at least two organ systems (one of which could be lungs)
  - Miliary tuberculosis, or
  - Isolation of *M tuberculosis* from blood or bone marrow

#### Tuberculosis drug resistance

- Multidrug resistance: *M tuberculosis* resistant to both rifamycin and isoniazid
- Mono-resistance: resistance to either rifamycin or isoniazid

#### Tuberculosis treatment

- RHZ-based: treatment regimen containing at least a rifamycin (R), isoniazid (H), and pyrazinamide (Z)
- Other: any other antituberculosis drug combinations

Risk factors for death were analysed with Cox regression analysis. Because of co-linearity, two multivariate models were tested: one adjusted for multidrug-resistant tuberculosis and the other adjusted for number of active drugs in the initial regimen. Other variables defined a priori were age, sex, region of residence, history of injecting drug use, type of tuberculosis diagnosis (definite vs not), clinical presentation of tuberculosis (disseminated vs not), presence of multidrug-resistant tuberculosis, drugs used for initial tuberculosis treatment (RHZ-based vs other), number of active antituberculosis drugs in the initial regimen, hepatitis C status, CD4 cell count, and use of ART (defined as a combination of at least three antiretroviral drugs from any class as a time-updated variable).

**Role of the funding source**

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

A total of 1406 patients were eligible for the current analyses (table 1). In all three regions, patients who died were more likely to have lower CD4 cell counts, and in eastern and western Europe patients who died also had a lower bodyweight compared with those alive. Disseminated tuberculosis and initial antituberculosis treatment regimen with fewer than three drugs were much more common in patients who died than in those alive in eastern Europe.

*M tuberculosis* was cultured from 360 (43%) of the total population of 834 people in eastern Europe, 205 (65%) of 317 in western Europe, and 79 (31%) of 255 in Latin America (p<0.0001). Baseline drug susceptibility test data were available for 291 (35%) people in eastern Europe, 202 (64%) in western Europe, and 83 (33%) in Latin America (p<0.0001). Furthermore, of these patients, 254 (87%) of 291, 176 (87%) of 202, and 65 (78%) of 83, respectively, had resistance data for both rifampicin and isoniazid. Multidrug-resistant tuberculosis was diagnosed in 99 (39%) of 254 people in eastern Europe, six (3%) of 176 in western Europe, and 11 (17%) of 65 in

	Eastern Europe (n=834)			Western Europe (n=317)			Latin America (n=255)		
	Dead	Alive	p value	Dead	Alive	p value	Dead	Alive	p value
Overall	223 (27%)	611 (73%)	..	13 (4%)	304 (96%)	..	28 (11%)	227 (89%)	..
Male patients	160 (72%)	466 (76%)	0.18	10 (77%)	194 (64%)	0.39	18 (64%)	168 (74%)	0.27
Age (years)	35 (31–40)	35 (31–41)	0.69	45 (37–52)	40 (33–47)	0.07	37 (33–48)	39 (30–45)	0.58
Same country of origin* as centre	216 (99%)	602 (99%)	0.99	9 (69%)	90 (30%)	0.04	23 (89%)	206 (93%)	0.21
Bodyweight (kg)†	57 (49–65)	62 (56–69)	<0.0001	51 (50–54)	62 (54–71)	0.03	55 (49–60)	60 (51–73)	0.16
HBsAg positive‡	15 (7%)	35 (6%)	0.86	1 (8%)	18 (6%)	0.47	3 (11%)	8 (4%)	0.08
HCV antibody positive§	120 (54%)	313 (51%)	0.21	5 (39%)	56 (18%)	0.25	5 (18%)	22 (10%)	0.05
Ever injecting drug use¶	151 (68%)	414 (69%)	0.80	5 (39%)	60 (20%)	0.15	4 (15%)	42 (19%)	0.79
<b>HIV disease</b>									
CD4 count (cells per µL)	43 (17–108)	140 (50–290)	<0.0001	34 (16–77)	149 (45–342)	0.008	61 (18–125)	109 (41–294)	0.02
RNA (log copies per mL)**	5.5 (4.9–5.9)	5.1 (4.2–5.7)	0.0009	5.0 (2.4–5.5)	4.8 (2.3–5.6)	0.95	4.5 (2.3–6.3)	4.7 (1.9–5.5)	0.44
Receiving ART	36 (16%)	116 (19%)	0.35	8 (62%)	130 (43%)	0.18	11 (39%)	88 (39%)	0.96
Disseminated tuberculosis††	171 (77%)	314 (52%)	<0.0001	4 (31%)	157 (52%)	0.14	11 (39%)	107 (47%)	0.43
<b>Diagnosis</b>									
Definite	102 (46%)	270 (44%)	0.11	10 (77%)	210 (69%)	0.61	11 (39%)	83 (37%)	0.52
Probable	36 (16%)	70 (12%)		1 (8%)	18 (6%)		10 (36%)	64 (28%)	
Presumptive	85 (38%)	271 (44%)		2 (15%)	76 (25%)		7 (25%)	80 (35%)	
RHZ-based treatment	166 (74%)	470 (77%)	0.46	12 (92%)	274 (90%)	0.99	22 (79%)	208 (92%)	0.04
Multidrug-resistant tuberculosis‡‡	39 (58%)	60 (32%)	0.00002	0	6 (4%)	0.99	4 (50%)	7 (12%)	0.02
<b>Active drugs in the initial regimen§§</b>									
≥3	39 (18%)	162 (27%)	<0.0005	7 (54%)	190 (63%)	0.64	6 (21%)	69 (30%)	0.04
<3	37 (17%)	53 (9%)		0	5 (2%)		3 (11%)	5 (2%)	
Unknown	147 (66%)	396 (65%)		6 (46%)	109 (36%)		19 (68%)	153 (67%)	

Data are n (%) or median (IQR). Western Europe=Belgium, Denmark, France, Italy, Spain, Switzerland, and the UK. Eastern Europe=Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, and Russia. Latin America=Argentina, Chile, and Mexico. HBsAg=hepatitis B surface antigen. HCV=hepatitis C virus. ART=antiretroviral therapy. RHZ=rifampicin, isoniazid, and pyrazinamide. \*21 patients had missing data for country of origin. †744 patients had missing data for weight at baseline. ‡446 patients had missing data for hepatitis B status. §430 patients had missing data for hepatitis C status. ¶60 patients had missing data for this HIV risk factor. ||178 patients had missing baseline CD4 cell counts. \*\*458 patients had missing baseline HIV RNA values. ††One patient had a tuberculosis type that could not be ascertained. ‡‡The denominator was those who were tested for multidrug resistance: eastern Europe 254 (67 dead and 187 alive); western Europe 176 (7 dead and 169 alive); and Latin America 65 (8 dead and 57 alive). §§The denominator was the total number of those dead or alive in each region.

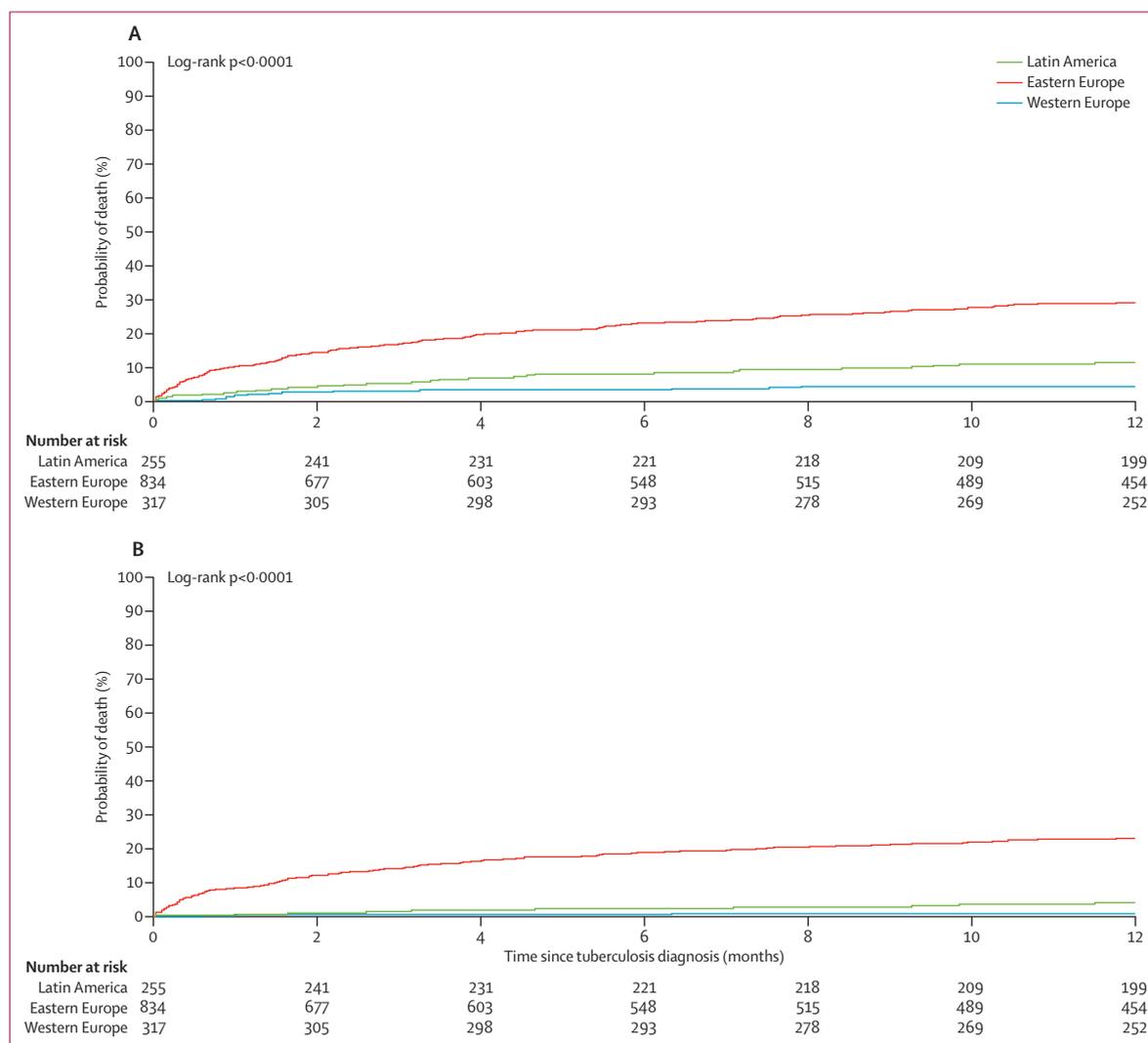
**Table 1: Demographic and clinical characteristics of the 1406 study participants according to their mortality status at 12 months**

Latin America. The proportion of multidrug-resistant tuberculosis cases was higher in patients who died than in those alive in eastern Europe and Latin America, but not in western Europe (table 1). Of those with a baseline drug susceptibility test, initial antituberculosis therapy included at least three active drugs in 473 (82%) of 576 cases: 201 (69%) of 291 in eastern Europe, 197 (98%) of 202 in western Europe, and 75 (90%) of 83 in Latin America ( $p<0.0001$ ).

At baseline, 736 (88%) of 834 patients in eastern Europe, 304 (96%) of 317 in western Europe, and 244 (96%) of 255 in Latin America were known to be HIV positive, of whom 152 (21%), 136 (45%), and 99 (41%), respectively, were receiving ART ( $p<0.0001$ ). Furthermore, of those with an HIV RNA measurement before or at baseline, 20 (4%) of 453 in eastern Europe, 57 (20%) of 291 in western Europe, and 18 (10%) of 172 in

Latin America had undetectable HIV RNA at the time of the tuberculosis diagnosis. The proportion of patients who started ART before their tuberculosis diagnosis was similar in those who died and stayed alive in all three regions (table 1). By 12 months, 320 (67%) of 477 patients who remained under follow-up in eastern Europe had initiated ART, compared with 231 (92%) of 252 in western Europe, and 170 (85%) of 200 in Latin America ( $p<0.0001$ ).

At 1 year, 264 (19%) of 1406 patients had died: 223 (27%) of 834 in eastern Europe, 13 (4%) of 317 in western Europe, and 28 (11%) of 255 in Latin America. The cumulative probability of death from any cause at 12 months was 29% (95% CI 26–32) in eastern Europe, compared with 4% (3–7) in western Europe and 11% (8–16) in Latin America ( $p<0.0001$ ; figure 1A). Within eastern Europe, mortality ranged from 3% to 40% across



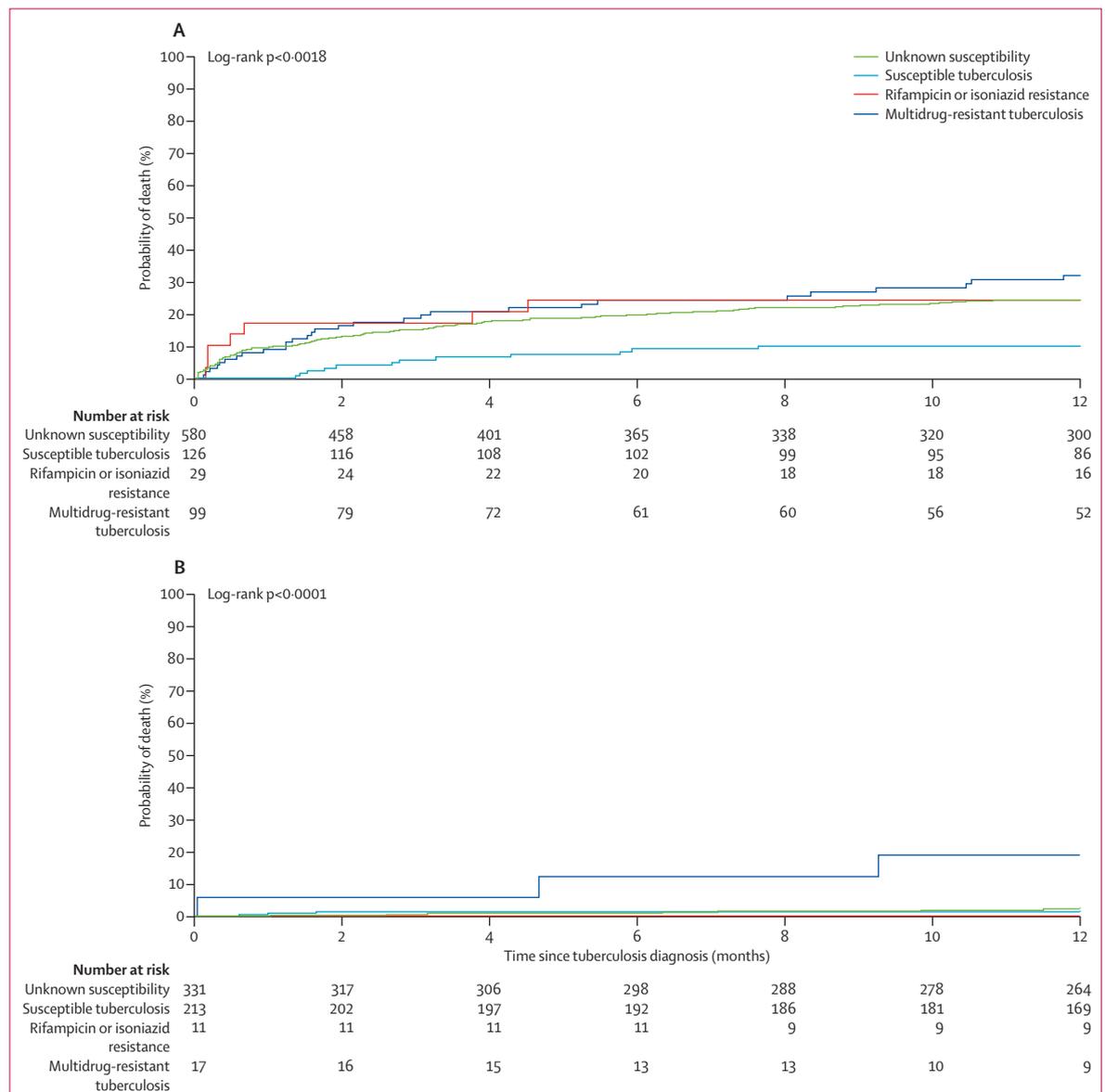
**Figure 1: Probability of death in patients with tuberculosis and HIV**

(A) All-cause mortality. (B) Tuberculosis-related mortality. Western Europe countries: Belgium, Denmark, France, Italy, Spain, Switzerland, and the UK. Eastern Europe countries: Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, and Russia. Latin America countries: Argentina, Chile, and Mexico.

the nine different countries. Completed Coding Causes of Death case report forms were available for 254 (95%) of the 264 patients who died: 216 (97%) of 223 in eastern Europe, all 13 (100%) in western Europe, and 25 (89%) of 28 in Latin America. Of these 254 patients, 130 (51%) had an autopsy done (129 in eastern Europe, one in western Europe, and none in Latin America). Tuberculosis was judged to be the underlying cause of death in 175 (79%) of 223 cases in eastern Europe, three (23%) of 13 in western Europe, and ten (36%) of 28 in Latin America ( $p < 0.0001$ ); the cumulative probability of tuberculosis-related death at 12 months in eastern Europe was 23% (95% CI 20–26), whereas it was 1%

(0–3) in western Europe and 4% (2–8) in Latin America ( $p < 0.0001$ ; figure 1B).

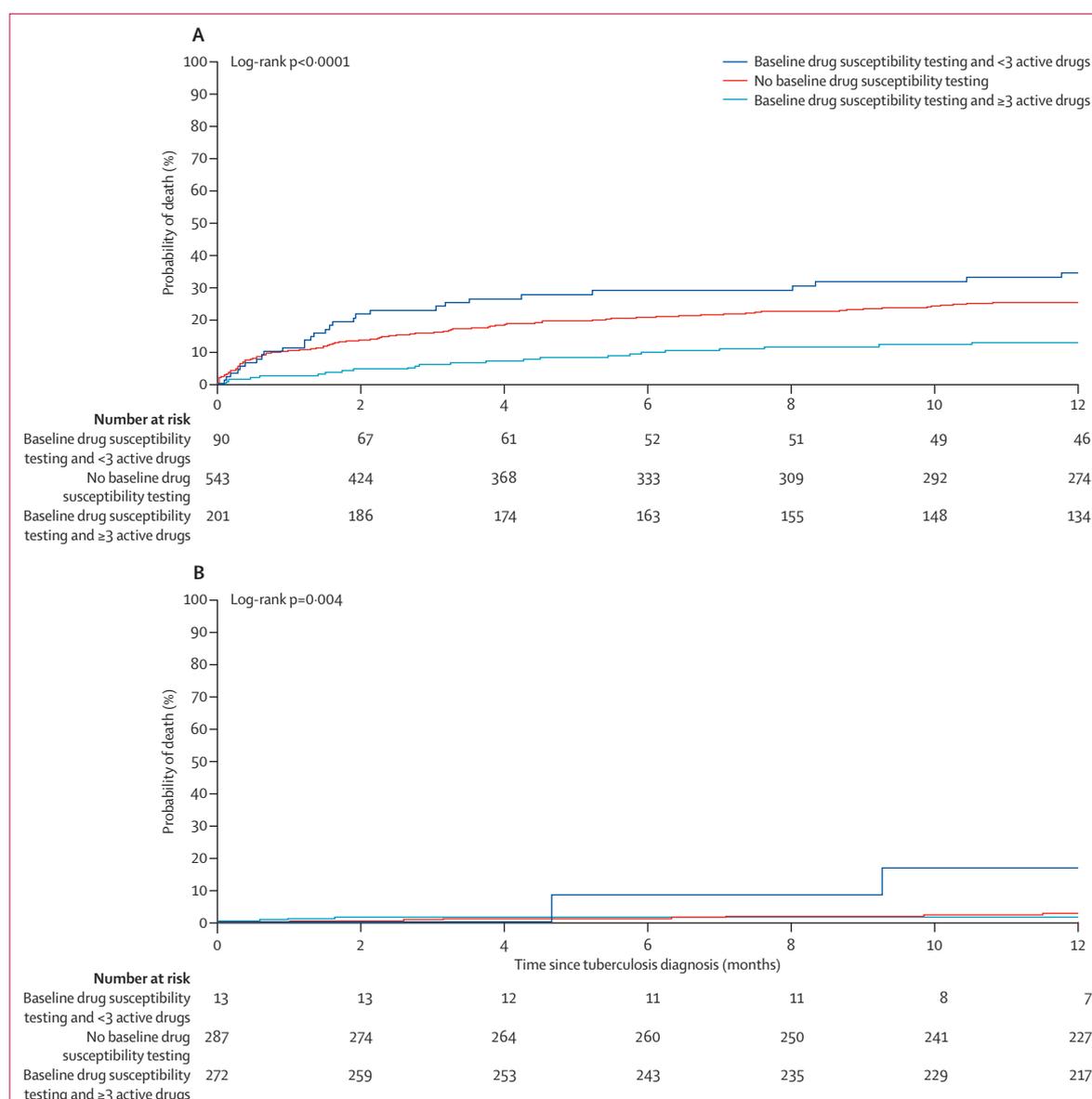
The 1 year probability of tuberculosis-related death was strongly affected by multidrug-resistant tuberculosis status and the number of active drugs in the initial treatment regimen. Tuberculosis-related mortality ranged from 10% (95% CI 6–17) in patients without multidrug-resistant tuberculosis to 32% (23–43) in those with multidrug-resistant tuberculosis in eastern Europe, and from 1% (0–4) to 19% (7–49) in western Europe and Latin America combined (figure 2). Patients in eastern Europe who started antituberculosis treatment with three or more active drugs had a substantially lower risk of death from



**Figure 2:** Probability of tuberculosis-related death, according to multidrug-resistant tuberculosis status (A) Patients with tuberculosis and HIV in eastern Europe. (B) Patients with tuberculosis and HIV in western Europe and Latin America.

the disease at 12 months (13%, 95% CI 9–18) than patients who started treatment with fewer than three active drugs (34%, 25–46) or those with no baseline drug susceptibility test results (25%, 21–29;  $p < 0.0001$ ; figure 3). In western Europe and Latin America combined, differences according to the activity of the initial regimen were less pronounced, but still notable: 1% (0–39) of those taking three or more active drugs died compared with 17% (4–52) of those taking less than three active drugs and 3% (1–6) for no baseline drug susceptibility test results ( $p = 0.004$ ; figure 3B). In multivariable Cox proportional hazard models for all-cause mortality, patients from western Europe and Latin America had a 68% reduced risk of

death compared with those from eastern Europe (adjusted hazard ratio 0.33 [95% CI 0.23–0.48],  $p < 0.0001$ ; table 2). Two multivariate models were considered (table 2); one model included antituberculosis drug susceptibility, and the other the number of active drugs in the initial antituberculosis regimen. The probability of death was roughly three-times higher in patients with multidrug-resistant tuberculosis (first model) and in those whose initial antituberculosis regimen contained fewer than three active drugs (second model). Other significant risk factors for death in both models were female sex, the presence of disseminated tuberculosis, lower CD4 cell count, and non-use of ART. Initiation of an RHZ-based



**Figure 3: Probability of tuberculosis-related death, according to drug susceptibility test status**

(A) Patients with tuberculosis and HIV in eastern Europe. (B) Patients with tuberculosis and HIV in western Europe and Latin America.

	Overall deaths (1406 patients; 264 deaths)						Tuberculosis-related death in eastern Europe (834 patients; 175 tuberculosis-related deaths)			
	Univariate analysis		Multivariate analysis 1		Multivariate analysis 2		Multivariate analysis 1		Multivariate analysis 2	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Sex										
Female	1	..	1	..	1	..	1	..	1	..
Male	0.94 (0.72-1.22)	0.625	0.71 (0.54-0.95)	0.019	0.70 (0.53-0.93)	0.015	0.62 (0.44-0.87)	0.006	0.60 (0.43-0.85)	0.004
Age (per 10 years)	0.90 (0.78-1.03)	0.124	1.11 (0.95-1.29)	0.188	1.13 (0.97-1.32)	0.104	0.99 (0.81-1.22)	0.932	1.02 (0.83-1.25)	0.853
Region										
Eastern Europe	1	..	1	..	1	..	NA	..	NA	..
Western Europe and Latin America	0.23 (0.16-0.31)	<0.0001	0.33 (0.23-0.48)	<0.0001	0.33 (0.23-0.48)	<0.0001	NA	..	NA	..
Definite tuberculosis diagnosis										
Yes	1	..	1	..	1	..	1	..	1	..
No	1.17 (0.92-1.49)	0.194	1.00 (0.73-1.36)	0.988	0.87 (0.61-1.23)	0.430	0.97 (0.66-1.42)	0.877	0.84 (0.56-1.27)	0.418
Disseminated tuberculosis disease										
No	1	..	1	..	1	..	1	..	1	..
Yes	2.21 (1.69-2.87)	<0.0001	1.82 (1.39-2.39)	<0.0001	1.78 (1.36-2.34)	<0.0001	3.28 (2.21-4.87)	<0.0001	3.21 (2.16-4.76)	<0.0001
Drug resistance										
No	1	..	1	..	..	..	1	..	..	..
Multidrug resistance	4.89 (3.07-7.80)	<0.0001	3.32 (2.05-5.37)	<0.0001	..	..	3.81 (1.93-7.51)	<0.0001	..	..
Single-drug resistance*	2.81 (1.33-5.92)	0.007	1.68 (0.79-3.55)	0.178	..	..	2.27 (0.89-5.77)	0.086	..	..
Unknown	2.52 (1.71-3.71)	<0.0001	1.93 (1.23-3.03)	0.004	..	..	2.45 (1.27-4.72)	0.007	..	..
Drug susceptibility test status										
Baseline drug susceptibility test and ≥3 active drugs†	1	..	1	..	1	..	1	..	1	..
Baseline drug susceptibility test and <3 active drugs†	4.21 (2.78-6.35)	<0.0001	..	..	2.90 (1.90-4.44)	<0.0001	..	..	3.17 (1.83-5.49)	<0.0001
No baseline drug susceptibility test	2.11 (1.55-2.88)	<0.0001	..	..	1.89 (1.26-2.86)	0.002	..	..	2.24 (1.31-3.83)	0.003
RHZ-based treatment										
Yes	1	..	1	..	1	..	1	..	1	..
No	1.65 (1.24-2.18)	<0.0005	1.24 (0.93-1.66)	0.147	1.30 (0.97-1.75)	0.075	1.15 (0.81-1.62)	0.435	1.19 (0.84-1.69)	0.322
Injecting drug use										
No	1	..	1	..	1	..	1	..	1	..
Yes	1.81 (1.41-2.32)	<0.0001	1.17 (0.89-1.55)	0.266	1.18 (0.89-1.56)	0.258	1.10 (0.79-1.54)	0.573	1.10 (0.79-1.55)	0.567

(Table 2 continues on next page)

treatment was significantly associated with improved survival in the univariate model only (table 2). We obtained similar results when we analysed risk factors for tuberculosis-related death in eastern Europe (table 2).

### Discussion

The 1-year cumulative probability of death in patients with HIV and tuberculosis disease in eastern Europe

continues to be very high (29%) and substantially higher than in another middle-income region (Latin America, 11%) and a high-income region (western Europe, 5%). In more than two-thirds of those who died in eastern Europe, the cause of death was considered to be tuberculosis, and the excess mortality in this region could not be explained by regional differences in other clinical and demographic prognostic factors such as sex,

	Overall deaths (1406 patients; 264 deaths)						Tuberculosis-related death in eastern Europe (834 patients; 175 tuberculosis-related deaths)			
	Univariate analysis		Multivariate analysis 1		Multivariate analysis 2		Multivariate analysis 1		Multivariate analysis 2	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
(Continued from previous page)										
CD4 count (cells per $\mu$ L)										
Missing	2.18 (1.41–3.36)	<0.0005	1.75 (1.12–2.74)	0.02	1.74 (1.11–2.73)	0.015	2.63 (1.45–4.77)	0.002	2.64 (1.45–4.79)	0.001
≤50	2.29 (1.56–3.38)	<0.0001	2.45 (1.66–3.62)	<0.0001	2.40 (1.63–3.55)	<0.0001	3.46 (2.02–5.95)	<0.0001	3.36 (1.96–5.78)	<0.0001
51–100	1.27 (0.80–2.02)	0.318	1.33 (0.83–2.13)	0.236	1.35 (0.84–2.16)	0.216	1.94 (1.04–3.63)	0.038	1.95 (1.04–3.65)	0.038
101–200	1	..	1	..	1	..	1	..	1	..
201–350	0.60 (0.34–1.06)	0.080	0.62 (0.35–1.10)	0.103	0.63 (0.35–1.12)	0.116	0.81 (0.38–1.76)	0.602	0.82 (0.38–1.78)	0.616
>350	0.23 (0.11–0.51)	<0.0002	0.28 (0.13–0.60)	0.001	0.28 (0.13–0.60)	0.001	0.26 (0.08–0.90)	0.033	0.26 (0.08–0.89)	0.032
Antiretroviral therapy‡										
Yes	1	..	1	..	1	..	1	..	1	..
No	1.77 (1.35–2.31)	<0.0001	1.36 (1.02–1.81)	0.034	1.40 (1.05–1.86)	0.021	1.41 (0.99–2.01)	0.057	1.39 (0.98–1.97)	0.068

Eastern Europe=Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, and Russia. Western Europe=Belgium, Denmark, France, Italy, Spain, Switzerland, and the UK. Latin America=Argentina, Chile, and Mexico. HR=hazard ratio. NA=not applicable. RHZ=rifampicin, isoniazid, and pyrazinamide. \*Resistance to either rifampicin or isoniazid. †Number of active tuberculosis drugs was calculated only for patients with available drug susceptibility test results. ‡Time-updated variable. Multivariate 1 model is adjusted for multidrug-resistant tuberculosis status (multidrug-resistant tuberculosis/non-multidrug-resistant tuberculosis/unknown), but not for number of active antituberculosis drugs in the initial treatment, according to the drug susceptibility test results. Multivariate 2 model is adjusted for the number of active antituberculosis drugs in the initial treatment, according to the drug susceptibility test results, but not for multidrug-resistant tuberculosis status.

**Table 2: Hazard ratios of all-cause mortality in all 1406 patients in the TB:HIV study and tuberculosis-related deaths in 834 patients from eastern Europe**

CD4 cell count at time of tuberculosis diagnosis, receipt of ART, disseminated tuberculosis disease, documented multidrug-resistant tuberculosis, or choice of initial antituberculosis regimen.

These results should be interpreted in the context of the documented high prevalence of multidrug-resistant tuberculosis in eastern Europe, which is among the highest in the world.<sup>2,13</sup> In our study, 39% of patients had multidrug-resistant tuberculosis at the time of starting antituberculosis therapy (ie, primary multidrug-resistant tuberculosis). Worldwide, only 20% of patients with multidrug-resistant tuberculosis are receiving adequate antituberculosis treatment,<sup>2</sup> and treatment success rates are about 50% in Russia, and vary between 36% and 80% in the rest of the world.<sup>2,14–16</sup> Treatment of multidrug-resistant tuberculosis needs a sophisticated multidisciplinary approach, drawing on expertise from many specialties. Favourable outcomes depend on many factors, in particular the activity of the antituberculosis treatment regimen provided, the duration of treatment, and the patients' adherence.<sup>17</sup> To design an adequate empirical antituberculosis regimen (ie, before the availability of drug susceptibility test results) is a difficult task and naturally relies on knowledge of the prevailing antituberculosis drug resistance pattern in a particular location.<sup>18</sup> In our study, in settings with a low prevalence of multidrug-resistant tuberculosis such as western Europe and Latin America, the initial treatment regimen

included at least three active drugs in most patients, and mortality rates for patients without drug susceptibility tests (accordingly without the possibility of targeting the subsequent treatment) were similar to those in patients starting at least three active drugs (according to the subsequent drug susceptibility test results). Although the results should be interpreted cautiously, this finding suggests that many patients who did not have drug susceptibility tests were infected with susceptible *M tuberculosis* strains and standard RHZ-based treatment was efficient. The situation is different in eastern Europe where there is a high prevalence of multidrug-resistant tuberculosis. Here, the mortality in patients without drug susceptibility tests and in patients who started fewer than three active antituberculosis drugs was much higher than in those who started treatment with at least three active drugs. These data underscore the importance of constructing an initial empirical regimen of sufficiently high activity, and of obtaining an initial drug susceptibility test in high multidrug-resistant tuberculosis settings; the latter allows subsequent individualised antituberculosis treatment guided by the drug susceptibility test results.

Although phenotypic drug susceptibility testing remains the gold standard for the detection of *M tuberculosis* resistance, genotypic tests significantly reduce the time needed for determination of resistance, especially rifampicin resistance, and rapid genotypic tests have recently become more available and are of

high value for potentially quicker adjustment of an initial antituberculosis treatment.<sup>10,17–19</sup> However, the number of drugs assessed within these tests is currently low, which is a disadvantage in the context of high multidrug-resistant tuberculosis prevalence. In the provision of a tuberculosis service, ensuring availability of diagnostics and drug susceptibility testing (especially rapid testing) and access to antituberculosis drugs for treatment of multidrug-resistant tuberculosis to improve the outcome from the disease is of paramount importance, but is still not the case in many countries of eastern Europe.<sup>10</sup> Therefore, these key steps in the successful management of tuberculosis should be in every way promoted and actively encouraged by health-care policy makers.

We have previously documented high mortality rates in eastern Europe (nearly 30%) in a previous retrospective precursor of the TB:HIV study (done during 2004–06), which largely included the same clinics as the present study.<sup>4</sup> Although direct comparisons should be made with caution because of the small differences in participating clinics or countries, mortality rates do not seem to have improved since the retrospective study, and the prevalence of multidrug-resistant tuberculosis is higher in the present study.<sup>4,8</sup> By contrast, uptake of ART in patients with HIV and tuberculosis has improved in all study regions, probably because of the accumulating evidence for the clinical benefit of starting ART after tuberculosis diagnosis, especially in patients with pronounced immunodeficiency.<sup>20–22</sup> However, patients continue to present with tuberculosis at low CD4 cell counts, and in the present study only two-thirds of the patients in eastern Europe who remained under follow-up at 12 months after tuberculosis diagnosis had started ART.

Tuberculosis and HIV inpatient and outpatient services in many eastern European countries are disintegrated, and a patient with tuberculosis and HIV often has to visit several health-care institutions to obtain treatment for both diseases (Skrahina AM [Republican Research and Practical Centre for Pulmonology and TB, Minsk, Belarus], Rakhmanova AG [St Petersburg AIDS Centre, Russia], personal communication).<sup>10</sup> The inferior tuberculosis-related results in eastern Europe described in this report call for an improvement of tuberculosis management, including integration of HIV and tuberculosis services and involvement of other services addressing other social and health issues that these patients might face.<sup>23,24</sup> Although the benefits of opioid substitution therapy for people who inject drugs have been documented, this service is still illegal, or is only scarcely available, in many countries in eastern Europe.<sup>10,25</sup> Because of its infrequent use in the present study, the role of opioid substitution therapy could not be analysed in detail.

Importantly, eastern Europe is a very heterogeneous region and, in agreement with our previous report of pronounced variability within the region in the prevalence

of multidrug-resistant tuberculosis and in the management of patients with HIV and tuberculosis co-infection, we recorded large variation in 1-year mortality across the area. However, the number of patients enrolled in the various clinics in eastern Europe did not allow for more detailed analyses of differences within the region.<sup>8,10</sup>

The main strengths of the TB:HIV study are the prospective design with inclusion of consecutive patients, the standardised data collection, and an extensive quality assurance programme. The limitations include that some patients with HIV and tuberculosis might have been missed, especially those who were severely ill with a poor prognosis because they were not able to reach health care, and that loss to follow-up in this population of patients is generally high and might also have affected our results, although efforts have been invested in the study to reduce this problem as much as possible.<sup>26</sup> Furthermore, the HIV and tuberculosis clinics participating in the study are major university-affiliated clinics with well established infrastructure and scientific experience. Therefore, the situation is unlikely to completely represent the situation in the entire eastern European region, and our findings might well underestimate the problems for HIV-positive patients with tuberculosis in eastern Europe. The analysis of resistance to antituberculosis drugs and the number of active drugs is based on the reported data of resistance tests being done locally. If some drug susceptibility test results were present for a given patient but missing for a drug in the patient's initial regimen, this drug was considered to be active. Therefore, the number of active drugs might be overestimated as discussed elsewhere.<sup>8</sup> Sensitivity analyses with more conservative assumptions, including an analysis in which we only calculated the number of active drugs for individuals with complete drug susceptibility testing data for all the drugs they received at baseline, led to consistent results (data not shown). The few patients with resistance only to either isoniazid or rifamycin were grouped together, despite an awareness of different clinical consequences for these two groups of patients.

Finally, the present study was not designed to directly assess factors such as the patients' adherence to treatment and socioeconomic factors (eg, family structure, unemployment, and poverty) that might affect outcomes for patients and provide further explanation for the recorded regional differences. Data about these factors from this region are scarce and further research and epidemic surveillance are warranted.

Within the TB:HIV study, detailed analyses are in progress addressing management following the tuberculosis diagnosis and include detailed analyses of antituberculosis treatment patterns for patients with fully susceptible tuberculosis and those with multidrug-resistant disease in relation to drug susceptibility test results obtained during the course of antituberculosis treatment. Additionally, the role of the prevailing resistance patterns in relation to the choice of proper

empirical antituberculosis treatment will be analysed further. This work will be based on resistance data from the participating clinics and also from centralised analyses of *M tuberculosis* strains.

In conclusion, we have documented an alarmingly high mortality rate in patients with HIV and tuberculosis in eastern Europe. The poorer outcome in this region compared with western Europe and Latin America was associated with a lower availability of tuberculosis culture tests and drug susceptibility tests, suboptimum initial antituberculosis treatment regimens, and patients' late presentation with severe immune suppression and disseminated tuberculosis disease. An urgent need therefore exists to improve and restructure the health-care approach for patients with HIV and tuberculosis in this region. Widespread availability of drug susceptibility testing, highly active antituberculosis regimens, and timely initiation of ART are needed to improve survival. Last, but not least, integration of HIV and tuberculosis services and support from other health and social services will improve retention in care and thus help to provide an improved outcome for this vulnerable patient population. WHO and the European Respiratory Society have recently launched plans for tuberculosis elimination in 33 low-incidence countries by 2035, which implies strategies outlined previously, and a new focus on latent tuberculosis.<sup>27</sup> Although these countries should be encouraged to implement the outlined interventions, similar tuberculosis elimination plans urgently need to be developed and promoted for countries with a high incidence of tuberculosis.

#### Contributors

DNP, AMWE, AS, AM, JDL, and OK designed the study and analysis plan and wrote the first draft of the report. AS did the statistical analyses under supervision of AM and with support for data interpretation by DNP, OK, and JDL. AMWE and DNP coordinated the study. FAP, AMS, AP, HF, RFM, MHL, JT, JMM, AV, EG, MB, and NO collected data. All authors interpreted data and critically reviewed and commented on the draft report. All authors have approved the final version of the report.

#### Declaration of interests

AM has received personal fees from honoraria, consultancy fees, speaker fees, and travel support from Bristol-Myers Squibb (BMS), Merck, BI, Pfizer, Gilead, and Wragge LLC, outside the submitted work. HF has received grants from Swiss National Science Foundation during the conduct of the study; and grants from ViiV, Gilead, MSD, Janssen, AbbVie, Roche, BMS, all paid to his institution, outside the submitted work. JMM has received academic and research grants, personal fees for lectures and consultancy from AbbVie, BMS, Gilead Sciences, Merck, Novartis, and ViiV Healthcare outside the submitted work. RFM has received personal fees from ViiV, Janssen, Merck, and Gilead, outside the submitted work. EG has received grants from Gilead Sciences, and personal fees from Abbot Diagnostics, Janssen, Gilead Sciences, and ViiV Healthcare, outside the submitted work. DNP, AMWE, AS, FAP, AMS, AP, MHL, JT, AV, MB, NO, JDL, and OK declare no competing interests.

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For the EuroCoord network see <http://www.EuroCoord.net>

For the IAS conference see <http://www.ias2015.org/>

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