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

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MOAB0203 - Excess TB mortality in HIV patients in Eastern Europe: restructured approach to care needed.

Abstract

Background: Management of tuberculosis (TB) in HIV-patients in Eastern Europe (EE) is challenged by high multi-drug resistant (MDR)-TB prevalence, low rates of drug susceptibility testing (DST) and poor access to antiretroviral therapy (ART). We report one-year mortality estimates from a multi-regional (EE, Western Europe (WE) and Latin America (LA)) prospective cohort study: The TB:HIV Study.

Methods: Consecutive HIV+ patients with TB diagnosis between 1/1/2011 and 31/12/2013 were enrolled from 62 HIV and TB clinics in 19 countries. Deaths within 12 months after starting TB therapy were classified according to whether they were TB-related or not. Risk factors for all-cause and TB-related deaths were assessed using Kaplan-Meier (K-M) estimates and Cox models.

Findings: Among 1406 patients (EE=834, WE=317, LA=255), 264 (19%) died within 12 months; 188 (71%) of deaths were TB-related. The K-M probability of all-cause and TB-related death was 29% (95% CI 26-32%), 4% (3-7%) and 11% (8-16%) (p<0.0001) and 23% (20-26%), 1% (0-3%) and 4% (2-8%) (p<0.0001) in EE, WE, and LA, respectively. Patients receiving care outside EE had a 77% decreased risk of death (adjusted Hazard Ratio; aHR=0.23, 95%CI=0.16-0.31). In EE, patients who started less than three active anti-TB drugs were at increased risk of TB-death compared to patients who started at least three active drugs (aHR=3.17, 95%CI=1.83-5.49), as did patients without baseline DST (aHR=2.24, 95%CI=1.31-3.83). Other prognostic factors for increased TB-mortality were disseminated TB and a low CD4-cell count. In EE, fewer patients were receiving ART at TB diagnosis and 12 months later (18%, 44%, 39% and 67%, 92%, 85% in EE, WE, and LA, respectively; p<0.0001).

Interpretation: TB/HIV-patients in EE remain at nearly four-fold increased risk of death compared to patients from WE and LA, even after adjustment for other potential risk factors. This greater mortality rate is associated with modifiable risk factors such as lack of DST and initial anti-TB treatment with less than three active drugs in a setting of high MDR-TB prevalence. These data call for urgent action to improve TB care for HIV-patients in EE.

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Introduction

Eastern Europe (EE) presents major challenges in terms of management of the Tuberculosis (TB)/HIV epidemic, mainly due to the high rates of multi-drug resistant (MDR) TB.[1-3] The numbers of TB/HIV coinfected people are rapidly increasing, and mortality of TB/HIV patients in this region remains among the highest in the world[2, 4-7], there is very little published evidence from EE on management of coinfected patients and risk factors for excess mortality. We have previously described the clinical aspects of TB/HIV epidemic in EE, when the retrospective TB:HIV study was conducted. (ref AIDS article) The reasons for high mortality in EE are complex and multifactorial. The TB/HIV epidemic in EE is mainly driven by injecting drug users (IDU), a population group that requires a special multidisciplinary health care approach in order to maintain retention in care and good treatment adherence.[2,5-8] Many of these patients are not engaged with healthcare despite of awareness of their HIV diagnosis, thus are not receiving antiretroviral therapy (ART), allowing immunodeficiency to progress and severe TB disease to develop.[4] On the other hand, management of TB/HIV patients who are engaged in healthcare seems to be suboptimal.[4,8] Initiation of ART is frequently delayed, also after TB is diagnosed.[4] Medical treatment of TB is inadequate, reflected by a high prevalence of resistant *Mycobacteria* and by diverse use of only partly effective TB drug regimens.[8,9] Opioid substitution therapy (OST) is seldom prescribed in the region, either because it is not available or is prohibited.[8,10] Finally, social support for IDU populations in EE is very limited (A. Rakhmanova, personal communication). As proof of suboptimal management of TB in TB/HIV patients in EE, we had previously found that most deaths in this region were linked to untreated TB disease; rarely to other opportunistic infections.[11] The TB/HIV epidemic in EE is a public health emergency that continues to expand.[1-2] Despite this fact, there is little direct documentation of its detrimental impact. We therefore designed a prospective study

of a large cohort of HIV-positive patients diagnosed with TB in countries of EE, Western Europe (WE) and Latin America (LA) .[8] The latter two regions were chosen to provide a comparison with EE and to establish a benchmark for TB/HIV management. The aim of the current report is to assess and compare one-year mortality after TB diagnosis across regions. Further, we aimed to assess whether prognostic markers identified at diagnosis of TB translated into excessive death rates.

Methods

Study design and definitions

The TB:HIV prospective study was initiated in 2011 within the EuroCoord collaboration (www.chip.dk). The study is a collaboration of clinicians from 62 HIV and TB clinics in 19 countries in EE, WE, and LA. Details of the study infrastructure have previously been published.[8] Briefly, patients were eligible for enrolment if they were HIV-positive (prior to, or up to three months after TB diagnosis), 16 years of age or older, and diagnosed with active TB disease between Jan 1, 2011 and Dec 31, 2013. Participating clinics had to enrol all consecutive HIV-patients with TB diagnosis within the above timeframe; each patient was then followed-up for two years.

The study was approved by the Ethics Committees of participating countries/clinics and informed consent obtained if required by local and national regulations. All patients' data were obtained from patients' medical records or via database exchange using HICDEP format (www.hicdep.org).

Demographic, clinical and laboratory data, and data on patients' outcomes were collected on case report forms (CRF) for both TB disease and HIV-infection at the time of TB diagnosis and at 6, 12 and 24 months of follow-up (FU) (Study protocol and CRFs are available at www.chip.dk).[8] Clinical information at the time of death was collected on specific Coding Causes of Death (CoDe) CRFs.[11, 12] The CoDe forms were assessed by two clinicians at the coordinating centre and the underlying causes of death were categorised as TB-related, or not. Data were extensively quality assured both at the coordinating centre, and through site visits with data monitoring of all deaths, multi-drug resistance (MDR)-TB cases, and a random sample of 10% of the remaining participants.

Anti-TB drugs initiated within ten days after the first anti-TB drug was started were considered to comprise an initial regimen, and TB treatment was categorised as RHZ-based (containing at least a

rifamycin (R), isoniazid (H), and pyrazinamide (Z)), or "other" (Box). Initial anti-TB treatment was further assessed according to the number of active drugs in the regimen based on results of locally performed drug susceptibility tests (DST) on a *Mycobacterium tuberculosis (Mtb*) sample taken up to one month before or after initiation of anti-TB treatment (baseline DST). For the primary analysis, we considered all *Mtb* isolates with some DST results available to be susceptible to drugs for which there was no indication of resistance (i.e. if no were data available for a specific drug, the isolate was considered to be susceptible to that drug). All patients with available results for both R and H at baseline were classified into three groups (Box): 1) MDR-TB (resistance to both R and H); 2) mono-resistance (resistance to either R or H but not MDR); 3) drug-susceptible TB (susceptible to R and H). A fourth category of patients comprised those with no available baseline DST data for R and H. Of note, patients with mono-resistance to either isoniazid (N=34) or rifamycin (N=6) were grouped together due to the small numbers.

Statistical analysis

All patients enrolled into the TB:HIV study who met inclusion criteria and who started anti-TB treatment were included in the current analyses. All patients were stratified into three geographical regions according to their country of residence: EE, WE, or LA (Box). Comparative analyses were performed across regions. Baseline characteristics were compared using Chi-squared or Kruskal-Wallis tests as appropriate.

The end-point was defined as overall and TB-related death within the first 12 months after treatment initiation. Follow-up was either until death, the last visit or 12 months after baseline, whichever occurred first. In the analysis of TB-related mortality, patients who died of any other

causes were censored at the date of death. Unknown causes of death were considered not TB-related.

All-cause and TB-related mortality rates were analysed using Kaplan-Meier estimates for patients stratified by 1) geographical region; 2) drug susceptibility; 3) number of active drugs in the initial regimen (three or more, less than three, or unknown). For this analysis, WE and LA were combined due to the small number of deaths. The number of active drugs in the initial regimen was calculated retrospectively based on the results of the baseline DST.

Risk factors for death were analysed using Cox regression analysis. Due to co-linearity, two multivariate models were tested, one adjusted for MDR-TB, another adjusted for number of active drugs in the initial regimen. Other *à priori* defined variables were: age, gender, region of residence, history of IDU, type of TB diagnosis (definite vs. not), clinical presentation of TB (disseminated vs. not), presence of MDR-TB, drugs used for initial TB treatment (RHZ-based vs. other), number of active anti-TB drugs in the initial regimen, hepatitis C (HCV) 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 sponsor 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. Baseline characteristics, stratified by region of residence and vital status at 12 months are shown in table 1. In all three regions, patients who died were more likely to be HCV-positive and to have lower CD4- cell counts and lower body weight and disseminated TB disease compared to those alive.

MTB was cultured from 360 (43%), 205 (65%) and 79 (31%) of the total population in EE, WE and LA respectively, p<0·0001, and baseline DST data were available for 291 (35%), 202 (64%), and 83 (33%), in EE, WE, and LA respectively; p<0·0001. Of those with baseline DST, 254 (87%, EE), 176 (87%, WE), and 65 (78%, LA) had resistance data for both R and H. MDR-TB was diagnosed in 99 (39%), 6 (3%), and 11 (17%) of those tested for both R and H in EE, WE and LA, respectively. The proportion of MDR-TB cases was higher among patients who died vs. those alive in EE and LA (table 1). Among those with a baseline DST, initial anti-TB therapy included at least three active drugs in 473 (82%) of cases (201 [69%] in EE, 197 [98%] in WE, and 75 [90%] in LA; p<0·0001).

At baseline, 736 (88%), 304 (96%) and 244 (96%) of patients in EE, WE, and LA were known to be HIV-positive, of those 152 (21%), 136 (45%), and 99 (41%) (p<0·001) were receiving ART. Further, of those with an HIV-RNA measurement before/at baseline, 20 (4%), 57 (20%), and 18 (10%) had an undetectable HIV-RNA at time of the TB diagnosis. The proportion of patients who started ART prior to their TB diagnosis was similar among those who died and stayed alive in all three regions (table 1). By 12 months, 320 (67%) of patients who remained under follow-up in EE had initiated ART vs. 231 (92)% in WE, and 170 (85%) in LA; p<0·0001.

At one year, 264 (19%) patients had died: 223 (27%) in EE; 13 (4%) in WE, and 28 (11%) in LA. The cumulative probability of death from any cause at 12 months was 29% (95% CI 26-32) in EE compared to 4% (3-7%) in WE, and 11% (8-16%) in LA (p<0·0001) (figure 1a). Within EE, mortality ranged from 3% to 40% in nine different countries. Completed CoDe forms were available for 254 (95%) patients (216/97%, 13/100%, and 25/89% of deaths in EE, WE, and LA, respectively), of those 130 (51%) had an autopsy performed (129, 1, and 0 in EE, WE, and LA, respectively). TB was considered the underlying cause of death in 175 (79%), 3 (23%), and 10 (35%) cases in EE, WE, and LA, respectively (p<0·0001); the cumulative probability of TB-related death at 12 months in EE was 23% (95% CI 20-26%) and significantly lower in WE and LA, 1% (0-3%) and 4% (2-8%), respectively; p<0·0001 (figure 1b).

The one-year probability of TB-related death was strongly affected by MDR-TB status and the number of active drugs in the initial regimen. TB-related mortality ranged from 10% (95% CI 6-17%) in patients without MDR-TB to 32% (23-43%) in patients with MDR-TB in EE and from 1% (0-4%) to 19% (7-49%) in WE and LA combined (figures 2a and 2b). Patients in EE who started anti-TB treatment with three or more active drugs had a substantially lower probability of death from TB (13%, 95% CI 9-18%) compared with patients starting less than three active drugs (34%, 25-46%) or patients with no baseline DST results (25%, 21-29%), (p<0·0001) (figure 3a). In WE and LA, differences according to the activity of the initial regimen were less pronounced, but still notable, (1% (0-39%), 17% (4-52%) and 3 (1-6%) respectively; p=0·004 (figure 3b). In multivariable Cox proportional hazard models for all-cause mortality, patients from WE and LA were at 68% reduced risk of death compared to patients from EE (adjusted Hazard Ratio 0·33 (95% CI 0·23-0·48%); p<0·0001) (table 2). Two multivariable models were considered (table 2), one model included anti-TB drug-susceptibility, and the other the number of active drugs in the initial anti-TB regimen. The

probability of death was approximately three-fold higher in patients with MDR-TB (first model) and in those whose initial anti-TB regimen contained fewer than three active drugs (second model). Other significant risk factors for death in both models were female gender, presence of disseminated TB, lower CD4-cell count, and non-use of ART. Initiation of an RHZ-based treatment was significantly associated with improved survival in the univariate model only (table 2). Similar results were obtained when analyzing risk factors for TB-related death in EE (table 2).

Discussion

This study demonstrates that the one-year cumulative probability of death among HIV-positive patients with TB disease in EE continues to be very high, namely 29%, and substantially higher than in LA, another middle-income region, and in WE, a high-income region, 11% and 5%, respectively. In over two-thirds of those who died in EE, the cause of death was considered to be TB, and the excess mortality in this region could not be explained by regional differences in other clinical and demographic prognostic factors such as gender, CD4-cell count at time of TB diagnosis, receipt of ART, disseminated TB disease, documented MDR-TB, or choice of initial empiric anti-TB regimen.

These results should be interpreted in the context of the documented high prevalence of MDR-TB in EE, which is among the highest in the world.[2,13] In our study, 39% patients had MDR-TB at the time of starting anti-TB therapy (i.e. primary MDR-TB). Globally, only 20% of patients with MDR-TB are currently receiving adequate anti-TB treatment,[2] and treatment success rates for MDR-TB are about 50% in Russia, and vary between 36% and 80% in the rest of the world.[2,14-16] Treatment of MDR-TB requires a sophisticated multidisciplinary approach, drawing on expertise from many specialties, and favorable outcomes depend on numerous factors, in particular the activity of the anti-TB treatment regimen provided, the duration of treatment and the patients' adherence.[17] Designing an adequate empiric anti-TB regimen (i.e. prior to availability of DST results) is a difficult task and naturally relies on knowledge of the prevailing anti-TB drug resistance pattern in a given location.[18] In our study, in settings with low MDR-TB prevalence such as WE and LA, the initial treatment regimen included at least three active drugs in the majority of patients, and mortality rates for patients without DST (accordingly without the possibility of targeting the subsequent

treatment) were similar to mortality rates among those starting at least three active drugs (according to the subsequent DST results) (figure 3b). Although the results should be cautiously interpreted, this suggests that many patients, for whom DST was not performed, were infected with susceptible *Mtb* strains and standard RHZ-based treatment was efficient. The situation is different in the MDR-TB high-prevalent EE, where the mortality among patients without DST as well as among patients who started less than three active anti-TB drugs was much higher, than among those who started treatment with at least three active drugs (figure 3a). These data underscore the importance of constructing an initial empiric regimen of sufficient high activity, as well as obtaining an initial DST in high MDR-TB settings; the latter allowing for subsequent individualized anti-TB treatment guided by the DST results.

While phenotypic DST remains the gold standard for the detection of *Mtb* resistance, genotypic tests significantly decrease the time required for determination of resistance, in particular rifampicin resistance, and rapid genotypic tests have recently become more available and are of high value for potentially quicker adjustment of an initial anti-TB treatment. [10,17-19] The number of tested drugs within these tests, however, is currently limited, which is a disadvantage in the context of high MDR-TB prevalence. In providing a TB service, it is of paramount importance to ensure availability of diagnostics and DST (in particular, rapid DST), as well as access to anti-TB drugs for treatment of MDR-TB in order to improve the outcome from TB, which is still not the case in many countries of EE.[10] Therefore these main steps in the successful management of TB should be in every way promoted and actively encouraged by healthcare policymakers.

We have previously documented high mortality rates in EE (nearly 30%) in a previous retrospective precursor of the TB:HIV study (done during 2004-2006), which largely included the same clinics as in the present study.[4] Although direct comparisons should be done with cation due to certain

differences in participating clinics/countries, mortality rates do not appear to have improved since the retrospective study, and the prevalence of MDR-TB is higher in the present study.[4,8] In contrast, uptake of ART among HIV-patients with TB have improved in all regions, probably due to the accumulating evidence for the clinical benefit of starting ART following TB diagnosis, especially among patients with pronounced immunodeficiency.[20,21,22] However, patients continue to present with TB at low CD4-cell counts and in the present study only two-thirds of the patients in EE who remained under follow-up at 12 months after TB diagnosis had started ART.

TB and HIV in- and out-patient services in many EE countries are currently disintegrated, and an TB/HIV patient often has to visit several healthcare institutions to get treatment for both diseases. [10, A. Skrahina and A. Rakhmanova, personal communication] The inferior TB-related results in EE described above call for an improvement of TB management including integration of HIV and TB services as well as involvement of other services addressing other social and health issues these patients may face. [23,24] Although the benefits of OST for persons who inject drugs have been documented, this service is still illegal, or is only limited, in many countries in EE. [10,25] Due to the infrequent use in the present study, the role of OST could not be analysed in detail.

It should be stressed that EE is a very heterogeneous region and in agreement with our previous report of pronounced variability within EE in the prevalence of MDR-TB and in the management of TB/HIV patients, we found large variation in one-year mortality across the region, but the number of patients enrolled in the various clinics in EE did not allow for more detailed analyses of differences within EE. [8,10]

Among the strengths of the TB:HIV study are the prospective design with inclusion of consecutively enrolled patients, the standardized data collection, and an extensive quality assurance programme. The limitations include that some HIV-patients with TB might have been missed, especially those who were severely sick with a poor prognosis and that loss to follow-up (LTFU) in this patient population is general high and may also affect our results, although efforts have been invested in the study to reduce this issue as much as possible.[26] Further, the HIV and TB clinics participating in the study are major university affiliated clinics with well-established infrastructure and scientific experience. Thus the situation is not likely to completely reflect the situation in the entire EE region and our findings may well underestimate the problems for HIV-patients with TB in EE. The analysis of resistance to anti-TB drugs and the number of active drugs is based on the reported data of resistance tests being performed locally. If some DST 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. Thus, the number of active drugs may be overestimated as discussed elsewhere.[8] Sensitivity analyses with more conservative assumptions, including an analysis where we only calculated the number of active drugs for individuals with complete DST data for all the drugs they received at baseline, led to consistent results (data not shown). The small number of patients with mono-resistance 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 evaluate factors such as the patients' adherence with treatment and socio-economic factors (e.g. family structure, unemployment, poverty), that might affect patients' outcome and provide further explanation for the observed regional differences. Data on 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 TB diagnosis and including detailed analyses of anti-TB treatment patterns for patients with fully susceptible TB and patients with MDR-TB in relation to DST results obtaining during the course of anti-TB treatment. Also, the role of the prevailing resistance patterns in relation to the choice of proper empiric anti-TB treatment will be further analysed. This work will be based on resistance data from the participating clinics as well as from centralized analyses of *Mtb* strains.

In conclusion, we have documented an alarmingly high mortality rate in HIV-patients with TB in EE. The poorer outcome in EE was associated with a lower availability of TB culture tests and DST, suboptimal initial anti-TB treatment regimens, as well as patients' late presentation with severe immune suppression and disseminated TB disease. There is therefore an urgent need to improve and restructure the healthcare approach for TB/HIV patients in this region. Promoting and encouraging widespread availability of DST, making available highly active regimens of anti-TB treatment, and timely initiation of ART are needed in order to improve survival. Last, but not least, integrating HIV and TB services as well as ensuring support from other health and social services will improve retention in care and thus ensure an improved outcome for this vulnerable patient population. WHO and European respiratory Society had recently launched plans for TB Elimination in 33 low-incidence countries by 2035, which implies strategies outlined above, as well as new focus on latent TB.[27] While these countries should be encouraged to implement outlined interventions, similar TB Elimination plans need to be urgently developed and promoted for the TB high-incidence countries.

Research in context

Evidence before this study

Evidence on the TB/HIV epidemic in Eastern Europe is generally scarce with poor surveillance systems and few clinical studies. Only few studies have provided data on patients coinfected with TB and HIV in this region. We searched PubMed for articles published before Dec 11, 2015, using the terms “HIV”, “tuberculosis”, “Eastern Europe”, “Europe”, “Latin America”, “drug-resistance”, “MDR-TB”, “XDR-TB”, and “injecting drug abuse”, and “outcome” in different combinations. Several cohort studies and surveillance databases had previously reported on significantly reduced incidence of TB and improved mortality after implementation of antiretroviral therapy (ART) in Western countries. Protective effect of ART, particularly in patients with severely immune suppression has also been demonstrated. A limited number of studies have reported on anti-TB drug resistance in different countries in Eastern Europe. Our group has previously published results from a retrospective cohort of TB/HIV coinfected patients, where we documented a one year mortality rate of 30% among HIV-patients with TB in Eastern Europe, which was at least three fold higher than among patients from Western Europe and Argentina. Otherwise, prospective data on management and outcomes of TB/HIV coinfected patients in Eastern Europe were not identified.

Added value of this study

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

where the TB/HIV epidemic is of special concern due to rapidly increasing rates of coinfected patients, and where the prevalence of MDR-TB is among highest in the world. The study is the first to demonstrate the suboptimal management of TB/HIV patients originating from Eastern Europe along with very high rates of MDR-TB, resulting in alarmingly high mortality rates in the region, with the main cause of death being TB-related. Mortality was particularly high in patients who started anti-TB treatment with suboptimal number of active drugs according to the drug susceptibility test (DST) result or without DST performed. Further, the study highlights concerns of low use of antiretroviral therapy (ART) in Eastern Europe. Finally, the study addresses not only clinical but also public health issues related to the HIV/TB coinfection, particularly in Eastern Europe.

Implications of all the available evidence

The findings from our study highlight the increasing problem of TB/HIV epidemic in Eastern Europe and emphasize the urgent need for restructuring the healthcare approach to TB/HIV coinfected patients in this region. The study underscores the importance of integrating TB and HIV services, as well as offering other healthcare and social services to these vulnerable patients. Improvement and implementation of more accurate and rapidly available TB diagnostics and DST are needed in Eastern Europe in order to ensure timely and adequate anti-TB treatment. It is essential to assure patients' retention in care and initiation of ART when indicated. More studies are needed to further address these issues in order to improve the devastating situation for TB/HIV coinfection in the East European region. As long as published data from the region remain limited, the current study can be considered as the first clinical database on TB/HIV patients from Eastern Europe.

Declaration of interests

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

		Eastern Europe			Western Europe			Latin America		
		Dead	**Alive**	**P**	**Dead**	**Alive**	**P**	**Dead**	**Alive**	**P**
Total, N (%)		**223 (26.7)**	**611 (73.3)**		**13 (4.1)**	**304 (95.9)**		**28 (11.0)**	**227 (89.0)**	
Gender	Male, N (%)	160 (71.7)	466 (76.3)	0.18	10 (76.9)	194 (63.8)	0.39	18 (64.3)	168 (74.0)	0.27
Age	Years, median [IQR]	35 (31 - 40)	35 (31 - 41)	0.69	45 (37 - 52)	40 (33 - 47)	0.07	37 (33 - 48)	39 (30 - 45)	0.58
Origin[1]	Same country as centre, N (%)	216 (99.5)	602 (99.3)	0.99	9 (69.2)	90 (29.9)	0.04	23 (88.5)	206 (92.8)	0.21
Weight[2]	Kg, median [IQR]	57 (49 - 65)	62 (56 - 69)	<0.0001	51 (50 - 54)	62 (54 - 71)	0.03	55 (49 - 60)	60 (51 - 73)	0.16
Hepatitis B[3]	HBsAg positive, N (%)	15 (6.7)	35 (5.7)	0.86	1 (7.7)	18 (5.9)	0.47	3 (10.7)	8 (3.5)	0.08
Hepatitis C[4]	HCV Ab positive, N (%)	120 (53.8)	313 (51.2)	0.21	5 (38.5)	56 (18.4)	0.25	5 (17.9)	22 (9.7)	0.05
IDU[5]	Ever IDU	151 (68.3)	414 (69.2)	0.80	5 (38.5)	60 (20.0)	0.15	4 (14.8)	42 (18.8)	0.79
HIV disease	CD4 count median [IQR][6]	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 median [IQR][7]	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, N (%)	36 (16.1)	116 (19.0)	0.35	8 (61.5)	130 (42.8)	0.18	11 (39.3)	88 (38.8)	0.96
TB Type	Disseminated, N (%)[8]	171 (76.7)	314 (51.4)	<0.0001	4 (30.8)	157 (51.6)	0.14	11 (39.3)	107 (47.1)	0.43
Diagnosis	Definite, N (%)	102 (45.7)	270 (44.2)	0.11	10 (76.9)	210 (69.1)	0.61	11 (39.3)	83 (36.6)	0.52
	Probable, N (%)	36 (16.1)	70 (11.5)		1 (7.7)	18 (5.9)		10 (35.7)	64 (28.2)	
	Presumptive, N (%)	85 (38.1)	271 (44.4)		2 (15.4)	76 (25.0)		7 (25.0)	80 (35.2)	
Treatment	RHZ based, N (%)	166 (74.4)	470 (76.9)	0.46	12 (92.3)	274 (90.1)	0.99	22 (78.6)	208 (91.6)	0.04
Resistance	MDR-TB, N (%)[9]	39 (58.2)	60 (32.1)	0.0002	0 (0)	6 (3.6)	0.99	4 (50.0)	7 (12.3)	0.02
Active Drugs in the initial regimen[10]	≥3, N (%)	39 (17.5)	162 (26.5)	0.0005	7 (53.9)	190 (62.5)	0.64	6 (21.4)	69 (30.4)	0.04
	<3, N (%)	37 (16.6)	53 (8.7)		0 (0)	5 (1.6)		3 (10.7)	5 (2.20)	
	Unknown, N (%)	147 (65.9)	396 (64.8)		6 (46.2)	109 (35.9)		19 (67.9)	153 (67.4)	

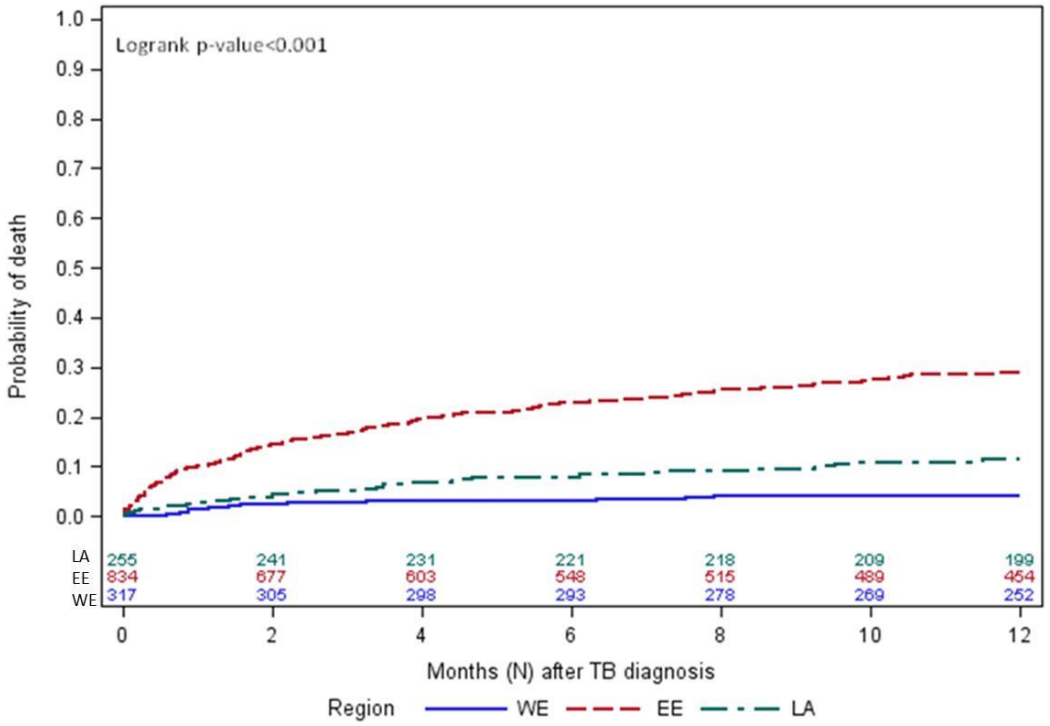
1. 21 individuals had missing data on origin
2. 744 individuals had missing data on weight at baseline
3. 446 individuals had missing data on hepatitis B status
4. 430 individuals had missing data on hepatitis C status
5. 60 individuals had missing data on HIV risk factor.
6. 178 individuals had missing baseline CD4-cell counts
7. 458 individuals had missing baseline HIV-RNA values
8. 1 individual had a TB type that could not be determined
9. The denominator was those, who were tested for MDR: EE 254 (67 dead and 187 alive); WE 176 (7 dead and 169 alive); and LA 65 (8 dead and 57 alive)
10. The denominator was a total N of those dead/alive in each region

Western Europe (Belgium, Denmark, France, Italy, Spain, Switzerland, United Kingdom); Eastern Europe (Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, Russia); Latin America (Argentina, Chile, and Mexico);

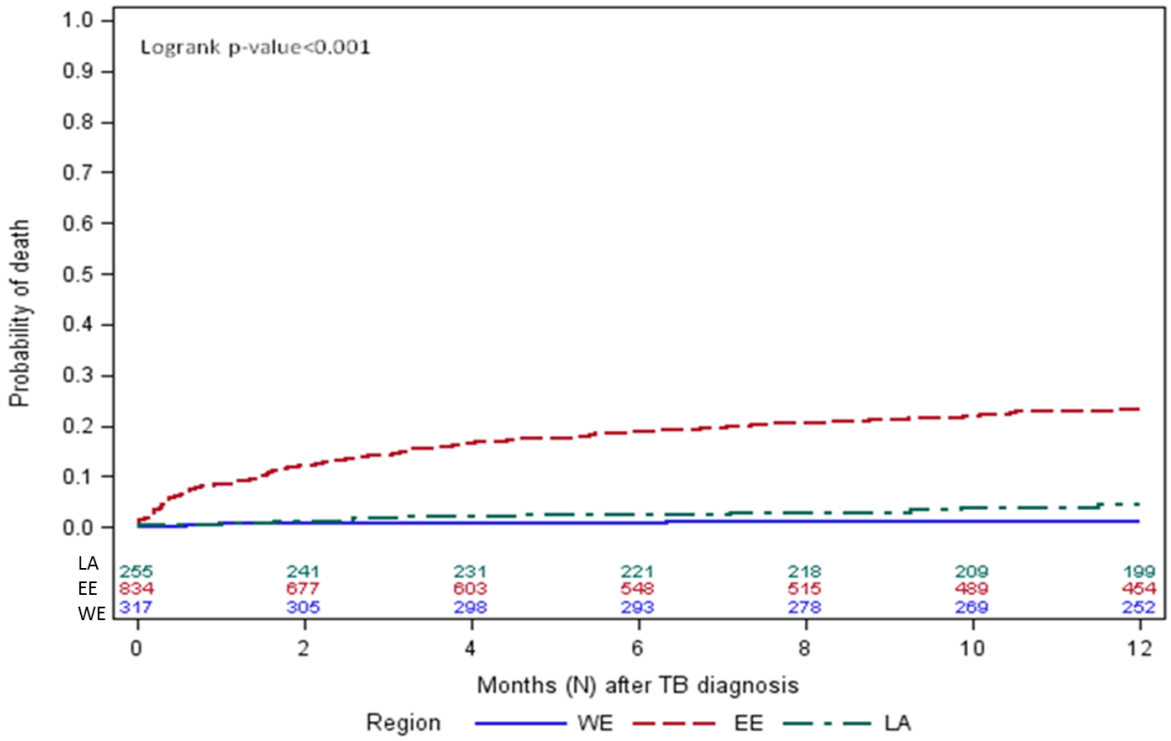
IDU: injecting drug use; TB: tuberculosis; RHZ: rifampicin, isoniazid, pyrazinamide; MDR-TB: multi-drug resistant tuberculosis; ART: antiretroviral therapy

Figure 1. Probability of death from all causes (a) and TB-related death (b) among 1406 TB/HIV patients according to their region of residence

a)



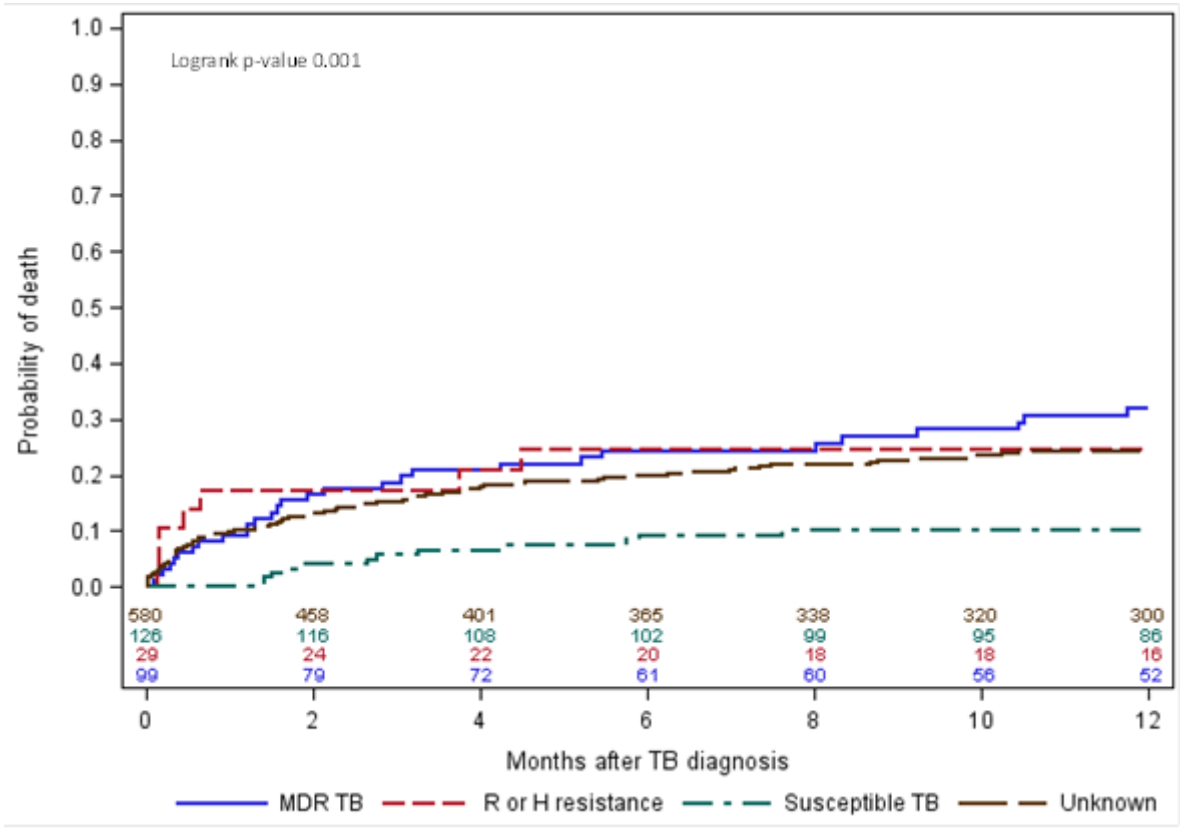
b)



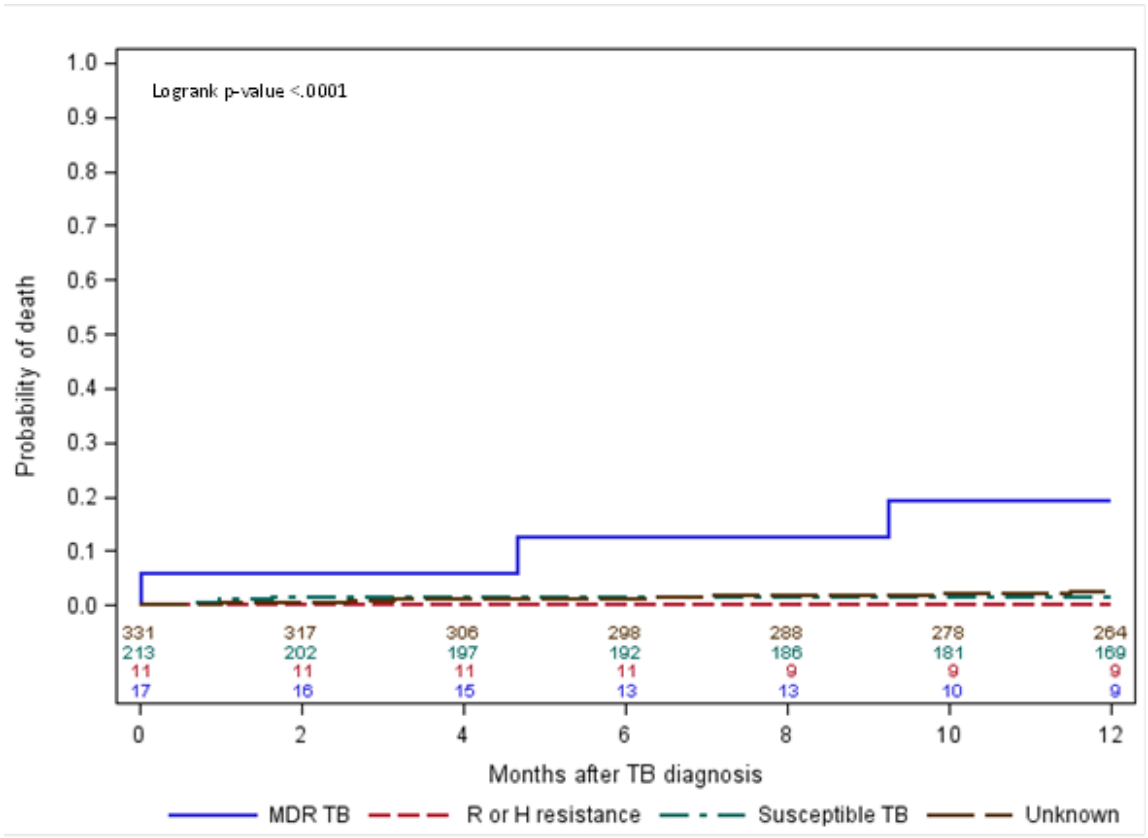
WE: Western Europe (Belgium, Denmark, France, Italy, Spain, Switzerland, United Kingdom); EE: Eastern Europe (Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, Russia); LA: Latin America (Argentina, Chile, and Mexico)

Figure 2. Probability of TB-related death among 834 TB/HIV patients in (a) Eastern Europe and among 572 TB/HIV patients in (b) Western Europe and Latin America according to their MDR-TB status

a)



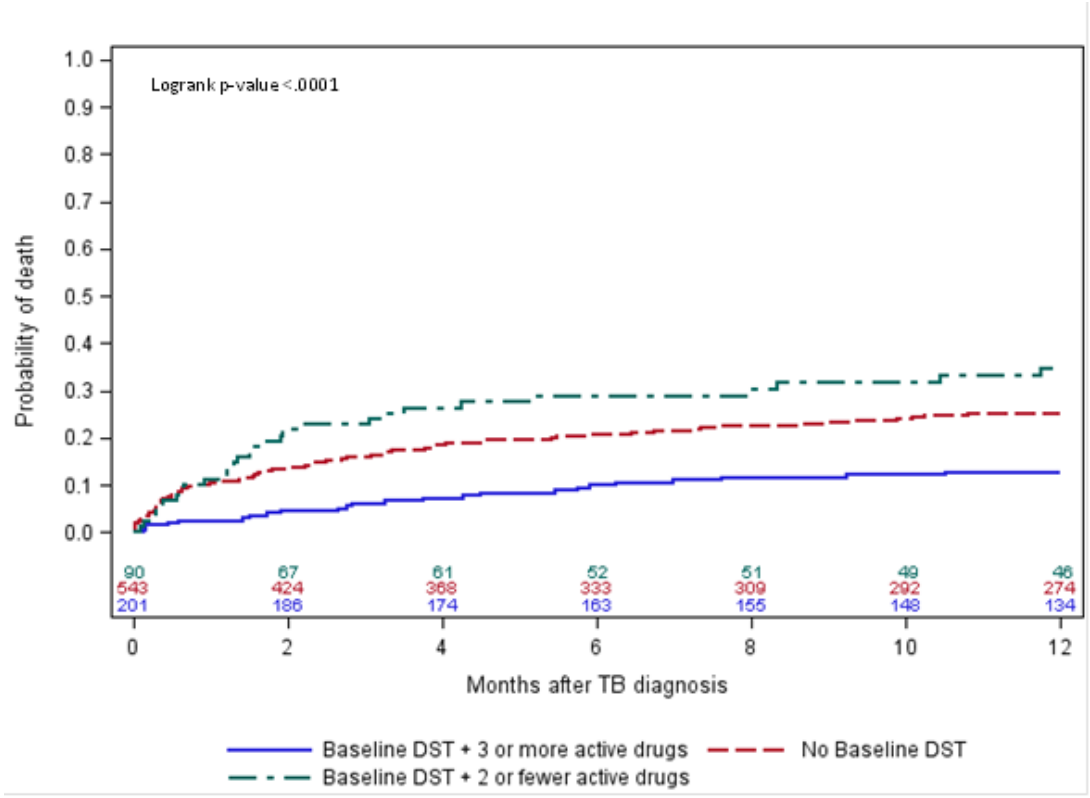
b)



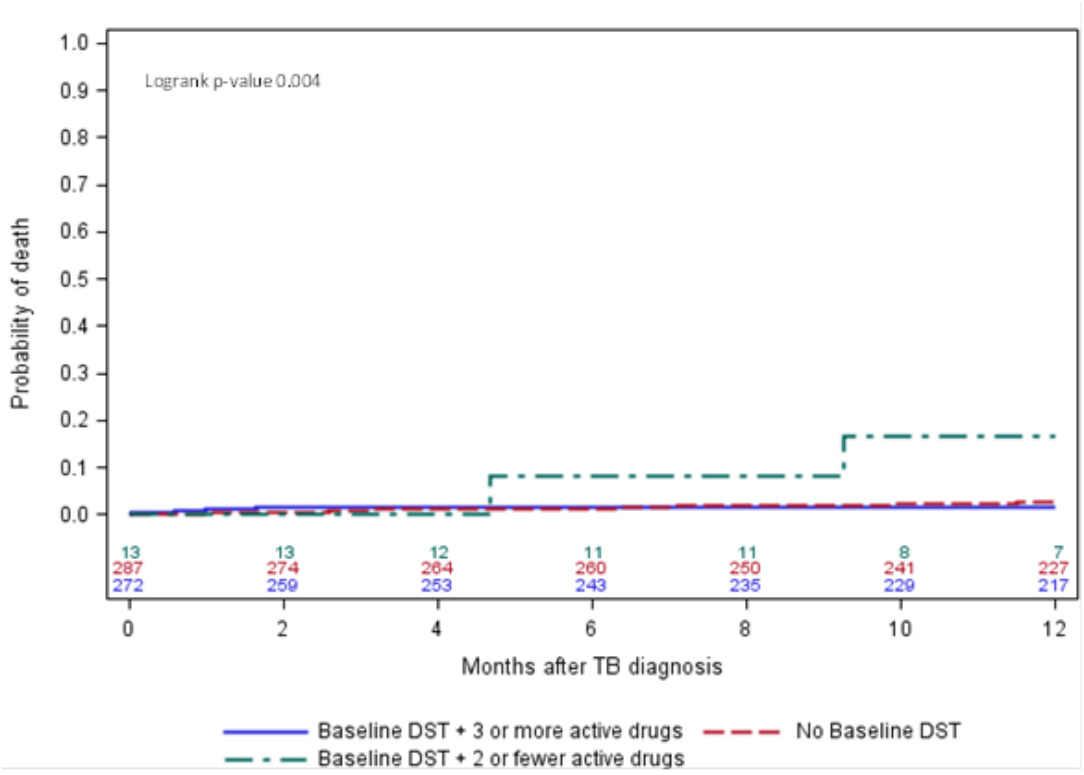
MDR-TB: multi-drug resistant tuberculosis; R: rifampicin; H: isoniazid

Figure 3. Probability of TB-related death among 834 TB/HIV patients in (a) Eastern Europe and 572 TB/HIV patients in (b) Western Europe and Latin America according to their drug susceptibility status

a)



b)



DST: drug susceptibility test

Table 2. Hazard ratios of all-cause mortality among all 1406 TB:HIV study patients and TB-deaths among 834 patients from Eastern Europe

		Overall death (N patients =1407; N death =265						TB-death in Eastern Europe (N patients =835; N death =223)			
		Univariate		Multivariate 1		Multivariate 2		Multivariate 1		Multivariate 2	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Gender	**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		N/A		N/A	
	WE and LA	0.23 (0.16 - 0.31)	<0.0001	0.33 (0.23 - 0.48)	<0.0001	0.33 (0.23 - 0.48)	<0.0001				
Definite TB 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	**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
MDR-TB	**No**	1		1		1		1			
	Yes	4.90 (3.07 - 7.80)	<0.0001	3.32 (2.05 - 5.37)	<0.0001			3.81 (1.93 - 7.51)	0.0001		
	Mono-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		
DST status	**Baseline DST + ≥3 active drugs**	1				1				1	
	Baseline DST + ≤2 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 DST	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
IDU	**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
CD4 count	**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)	<.0001	2.40 (1.63 - 3.55)	<.0001	3.46 (2.02 - 5.95)	<.0001	3.36 (1.96 - 5.78)	<.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	0.82 (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
ART**	**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

[#] mono-resistance: resistance to either Rifampicin or Isoniazid

*Number of active TB drugs was calculated only for patients with available DST results

**time updated variable;

Multivariate 1 model is adjusted for MDR-TB status (MDR-TB/Non-MDR-TB/unknown), but not for number of active anti-TB drugs in the empiric treatment, according to the DST results

Multivariate 2 model is adjusted for number of active anti-TB drugs in the empiric treatment, according to the DST results, but not for MDR-TB status

N/A = not applicable

Eastern Europe (Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, Russia); WE: Western Europe (Belgium, Denmark, France, Italy, Spain, Switzerland, United Kingdom); LA: Latin America (Argentina, Chile, and Mexico)

MDR-TB: multi-drug resistant tuberculosis

DST: drug susceptibility test

RHZ: rifampicin, isoniazid, pyrazinamide;

IDU: injecting drug use

ART =antiretroviral therapy

Box. Study definitions

Region	Eastern Europe	Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, Russia
	Western Europe	Belgium, Denmark, France, Italy, Spain, Switzerland, United Kingdom
	Latin America	Argentina, Chile, and Mexico
TB diagnosis	Definite	Positive culture or PCR for *Mycobacterium tuberculosis*
	Probable	Acid fast bacilli or granulomatous inflammation on smear or tissue biopsy specimens
	Presumptive	TB treatment initiated and not subsequently stopped because the TB diagnosis was ruled out
TB location	Pulmonary	TB localised to the lungs, larynx, or tracheobronchial tree
	Disseminated	Either of the following: i) TB documented in at least two organ systems (one of which could be lungs) ii) miliary TB, or iii) isolation of *Mtb* from blood or bone marrow
TB drug resistance	MDR	*Mycobacteria tuberculosis* resistant to both rifamycin and isoniazid
	Mono resistance	Resistance to either rifamycin or isoniazid
TB treatment	RHZ-based	Treatment regimen containing at least a rifamycin (R), isoniazid (H), and pyrazinamide (Z)
	Other	Any other anti-TB drug combinations

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Role of each of the contributing authors

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

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