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Title: One-year mortality of HIV-positive patients treated for rifampicin- and isoniazid-susceptible tuberculosis in Eastern Europe, Western Europe and Latin America.

The TB:HIV Study writing Group*¶

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Short title: Mortality in HIV patients with susceptible tuberculosis

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Abstract (word count 247)

Objectives: The high mortality among HIV/tuberculosis (TB) co-infected patients in Eastern Europe (EE) is partly explained by the high prevalence of drug-resistant TB. It remains unclear whether outcomes of HIV/TB patients with rifampicin/isoniazid-susceptible TB in EE differ from those in Western Europe (WE) or Latin America (LA).

Methods: One-year mortality of HIV-positive patients with rifampicin/isoniazid-susceptible TB in EE, WE and LA was analysed and compared in a prospective observational cohort study. Factors associated with death were analysed using Cox regression models

Results: 341 patients were included (EE 127, WE 165, LA 49). Proportions of patients with disseminated TB (50%, 58%, 59%) and initiating rifampicin+isoniazid+pyrazinamide-based treatment (93%, 94%, 94%) were similar in EE, WE and LA respectively, while receipt of antiretroviral therapy (ART) at baseline and after 12 months was lower in EE (17%, 39%, 39%, and 69%, 94%, 89%). The one-year probability of death was 16% (95%CI 11%-24%) in EE, vs. 4% (2%-9%) in WE and 9% (3%-21%) in LA; $p<0.0001$. After adjustment for injecting drug use (IDU), CD4-cell count and receipt of ART, those residing in EE were at nearly 3-fold increased risk of death compared to those in WE/LA (aHR 2.79 (1.15-6.76); p=0.023).

Conclusions: Despite comparable use of recommended anti-TB treatment, mortality of patients with rifampicin/isoniazid-susceptible tuberculosis remained higher in EE when compared with WE/LA. The high mortality in EE was only partially explained by IDU, use of ART and CD4 cell count. These results call for improvement of care for TB/HIV patients in EE.

Key words: tuberculosis, HIV, treatment, drug -susceptibility testing, death, Eastern Europe, Western Europe, Latin America, TB:HIV study

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Introduction

Currently, tuberculosis (TB) is a public health emergency in Eastern Europe (EE). [1] The incidence of TB among HIV-infected populations is rapidly increasing in this region, and the situation is complicated by an increase in the prevalence of multi-drug resistant (MDR) TB. [2-4] We have previously documented an excess mortality rate among TB/HIV patients in EE, which can only partially be explained by the high prevalence of MDR-TB, suboptimal access to drug susceptibility testing (DST), and as a consequence, use of inadequate anti-TB treatment regimens. [5]

One of the risk factors for development of MDR-TB is previous (inadequate) TB treatment which permitted drug resistance to be selected or amplified. [6, 7] By contrast, high rates of MDR-TB among new TB cases without a history of prior TB, as well data from modelling studies, suggest that transmission of drug resistant TB plays an important role in the ongoing epidemic of MDR-TB in EE. [8, 9] From a patient as well as from a public health perspective it is therefore important to appropriately treat drug sensitive (DS) TB, ensuring that patients are cured and their infection is eliminated. This strategy would help prevent the development and potential further spread of MDR-TB. Treatment of MDR-TB is complex due to the drug burden, prolonged treatment duration, adverse effects, high cost, and the limited availability of many drugs in low- and middle-income regions. [10-12] Besides, the overall success rate of treating MDR-TB is only around 50%. [13] By contrast, treatment of drug susceptible (DS)-TB is inexpensive, requires fewer clinical (nurse- and doctor-led) resources, and first-line drugs are widely available in resource-limited settings. [14, 15] Provided that recommendations for treatment of DS-TB are used and adhered to both by clinicians and patients, successful TB outcome can be achieved in a majority of patients, which is according to World Health Organisation (WHO) 2015 standards. [16]

In the presence of HIV coinfection, it is also of paramount importance to adequately treat the underlying HIV infection. [17] Timely initiation of antiretroviral therapy (ART) improves immune

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function and hence prevents of active TB disease, or in the settings of already developed TB, significantly improves outcome. [18, 19]

We hypothesised that mortality rates among TB/HIV patients with DS-TB in EE would be comparable to those in Western Europe (WE) and Latin America (LA). The present analysis aimed to assess and compare mortality rates of HIV patients with drug susceptible TB across regions and identify risk factors associated with mortality. Further, we aimed to describe management of HIV co-infection in patients with DS-TB.

Methods

The current analyses were conducted within the prospective TB:HIV cohort study. Details of the study design and methodology have been published elsewhere. [20] Briefly, HIV-positive persons aged 16 years or older who were diagnosed with TB between January 2011 and December 2013 in 62 participating HIV and TB clinics in 19 countries from EE, WE or LA [1] were enrolled and followed-up for 24 months. Demographic, clinical and laboratory information was prospectively collected on case report forms at TB diagnosis, 6, 12 and 24 months thereafter. The study received approval from Ethics Committees in all countries as per local regulations.

The current analysis is limited to 12 months of follow-up and the database was closed for analysis in May 2015, when all 12 months follow-up data were collected. Baseline was defined as the date when anti/TB treatment was initiated. Drug susceptibility tests (DST), obtained within 4 weeks of baseline were used to confirm mycobacterial susceptibility to rifampicin and isoniazid. Patients without a DST and those with rifampicin- and/or isoniazid-resistant TB were excluded from the current analyses. Patients were stratified by their region of residence. Descriptive statistics were

[1] Eastern Europe (EE) (21 clinics in Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, Russia), Western Europe (WE) (28 clinics in Belgium, Denmark, France, Italy, Spain, Switzerland, United Kingdom), and Latin America (LA) (13 clinics in Argentina, Chile, and Mexico).

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used for baseline characteristics. Study definitions in terms of certainty of TB diagnosis, clinical presentation of TB disease, TB treatment regimens, ART regimens and region of residence have previously been published and re-used in the current analysis for consistency. [5]

Treatment of underlying HIV-infection was analysed by calculating proportion of patients receiving antiretroviral therapy (ART) at baseline, 3, 6, 9 and 12 months, and by assessing immuno-virological status of the cohort at the same time-points. Response to ART was assessed among those who started ART at or within 6 months after their TB diagnosis. It was done by calculating proportion of patients with HIV-RNA <500 copies/ml in the time period 2-7 months after starting ART out of those alive and still under follow-up. ART was defined as a combination of at least three antiretroviral drugs of any class.

Mortality was compared using Kaplan-Meier survival analysis in which patients were censored at their last clinic visit, date of death, or after 12 months of follow-up, whichever occurred first. Risk factors for death were identified by Cox proportional hazard models that included region of residence, where WE and LA were combined due to the small numbers of deaths in these regions. Following "*a priori*" defined variables were tested in the uni- and multivariate models: gender, age (per 10 years increase), history of injection drug use (IDU: yes or no), extent of TB disease (pulmonary or disseminated), use of rifampicin, isoniazid and pyrazinamide in the initial anti-TB treatment regimen, baseline CD4 cell count (as a categorical variable), and use of ART (yes/no) as a time-updated variable.

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Results

Of the 1406 TB/HIV patients in the TB:HIV study, 644 (46%) had culture confirmed TB (360 of 834 enrolled participants in EE, 205 of 317 in WE, and 79 of 255 in LA, respectively). Of the 644 patients, 495(77%) had baseline DST results for both rifampicin and isoniazid available, and finally 341/495 (69%) were infected with *Mycobacterium tuberculosis* susceptible to both rifampicin and isoniazid. The regional distribution was EE 127, WE 165, and LA 49. These 341 patients were included in the present analyses (figure 1).

The baseline clinical and demographic characteristics of these patients are described in table 1. Compared with WE and LA, patients in EE were slightly younger and a greater proportion in this region was co-infected with hepatitis C. The most common risk factors for TB/HIV acquisition in EE were: history of IDU, excess alcohol consumption, and/or imprisonment. The proportion of patients with excess alcohol consumption was comparably high in LA, but not in WE. More than 90% of patients in all three regions commenced anti-TB treatment that included rifampicin, isoniazid, and pyrazinamide. At the time of TB diagnosis, patients from all regions had advanced immunodeficiency and over half presented with disseminated TB. Despite similar degrees of immunodeficiency and HIV RNA levels, a smaller proportion of those in EE were receiving ART at baseline.

In Kaplan-Meier analyses of the duration of TB therapy, the time by which 50% of patients had stopped therapy was longer than the guideline-recommended six months in all 3 regions: 8.7 months (IQR 7.1-9.7) in EE, 9.0 (8.3-9.1) in WE and 9.8 (9.0-11.5) in LA. There was no evidence that the time to stopping TB treatment differed between regions (p=0.28).

Management of HIV infection after initiation of anti-TB treatment is presented in figure 2. The use of ART increased over time in all three regions, but remained significantly lower in EE. The

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proportion of patients receiving ART in Eastern Europe increased from 17% to 54% during the first three months after start of anti-TB treatment. Proportion of patients on ART in the two other regions was significantly higher at any time point and at 12 months 94% and 89% of patients in WE and LA respectively, were on ART compared with 69% in EE, p<0.001(figure 2). Despite the increase in ART uptake, the proportion of patients with suppressed HIV-RNA (<500 copies/ml), among those who were on ART, was lower in EE compared with WE and LA. At 12 months after TB diagnosis, 48% of patients on ART in EE had HIV RNA<500 compared with 86% and 71% in WE and LA, respectively, p<0.001(figure 2).

In addition to describing ART use, HIV RNA and CD4-cell status cross-sectionally at time-points after TB diagnosis (Figure 2), we also looked at the response to ART following the date of ART initiation among those who started ART at or after TB diagnosis. This analysis showed that in the time period 3-6 months after starting ART, 36% of individuals still alive and under follow-up in EE compared to 85% in WE and 80% in LA had HIV RNA<500 copies/ml (p<0.001).

At one year from baseline, 68 patients (54%) in EE, 117 (71%) in WE and 30 (61%) in LA had completed at least 6 consecutive months of anti-TB treatment, p=0.009. Seventeen patients (13%) in EE, 17 (10%) in WE, and 7 (14%) in LA were lost to follow up, p=0.63. Twenty (16%) deaths had occurred in EE, 7 (4%) in WE and 4 (8%) in LA, p=0.0031. In EE TB was indicated as the underlying cause of death in 13 (70%) cases, compared with 2 (29%) and 1 (25%) in WE and LA, respectively. A majority (9 out of 13) of TB-related death in EE occurred within the first 4 months after baseline. The cumulative probability of all cause death after one year was 16% (95% CI 11%-24%) in EE, 4% (2%-9%) in WE and 9% (3%-21%) in LA (figure 3), and numbers did not allow for more detailed analysis on intra-regional variability. In the adjusted model the only significant risk factor for death was region of residence. Thus, treatment of rifampicin and isoniazid susceptible TB in EE was associated with an almost 3-fold increased risk of death compared to WE and LA

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combined (adjusted Hazard Ratio 2.79; 95% CI 1.15-6.76) (figure 4). Association of ART initiation with patients' prognosis was marginally significant in the unadjusted model only. This association disappeared after adjustment likely due to the small numbers and limited statistical power. IDU was also a significant predictor of death before adjustment, however this also became non-significant after adjustment due to the high correlation with the region of residence (figure 4).

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Discussion

This study demonstrates greater mortality rate among HIV patients infected with rifampicin-and isoniazid-susceptible TB in EE compared with WE and LA. This difference persisted after adjustment for clinical characteristics such as IDU, low immune status at the time of TB diagnosis, and receipt of ART during follow up. While mortality was similar across the regions within the first 1-2 months, patients in EE continued to experience high death rates throughout the first year post-TB diagnosis. By contrast with EE, TB/HIV coinfected patients in LA, another middle-income region, and in WE, a high income region, experienced low mortality rates, reflecting high standards of TB and HIV care in the latter mentioned regions. [17, 21, 22] The differences in TB outcome were only partially explained by factors, related to HIV management, in particular use of ART and CD4 cell levels, or by other factors included in the model. This underscores the fact that some other factors, probably on a higher level than individual clinics and that we were not able to test, play an important role in patients' survival, as for example: national and regional healthcare and social infrastructure.

A vast majority of patients from all regions initiated their anti-TB treatment with the standard recommended regimen, i.e. rifampicin, isoniazid, and pyrazinamide-based, indicating that these drugs are widely available and clinicians follow standard recommendations for TB treatment. [14] This is however not enough to ensure a good outcome, particularly in the settings of HIV coinfection. ART should be initiated as soon as possible after TB diagnosis, if a patient was not already receiving it. [23-25] In our study, management of HIV infection in EE was suboptimal. Even though ART coverage had increased with time, both usage of ART and response to ART was still much lower than in the other regions, inferring that ART was not properly prescribed and/or taken. By contrast, HIV management in WE was according to the standards; ART coverage was over 90% and nearly 90% of patients on ART achieved viral suppression. [26] LA showed results

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very close to those in WE, demonstrating that appropriate HIV care is also possible in resource-constrained settings. In our study, initiation of ART did not play a significant role in patients' survival after adjustment for other risk factors for death. However, binary adjustment for ART initiation (yes vs. no) may not fully reflect the impact of ART on mortality, and there are other aspects of HIV treatment that we could not adjust for due to the lack of data, and therefore not fully capture all aspects of HIV care. Scale up of ART still remains paramount in the management of HIV infection, although it is also important to ensure that effective drugs are used and that adherence is maximised. In the present study the most common reason for not starting ART by two months after start of anti-TB treatment was patients' refusal (data not shown), suggesting perhaps that patients may not fully appreciate or are not aware of the life-saving effects of ART. Other factors, as for example, concerns of toxicity, lack of food and/or accommodation might also play a role and need to be overcome. It is therefore a major task not only for clinicians, but also for community and social services to educate, engage and retain patients in care.

One of the drivers of the TB/HIV epidemic in EE is IDU, a marginalised population with poor access to and uptake of health services, resulting in late presentation of both HIV and TB, poor rates of TB treatment completion, and frequent ART interruptions. [27] Healthcare systems in EE need to better account the special needs of this large patient population, considering its lifestyle and ability to accept continuous treatment. [27] Measures should be taken to help IDU patients to remain in care and overcome structural barriers, improve health literacy and minimise stigma. There is a need for a patient-centred integrated multidisciplinary approach, involving both HIV and TB clinicians, as well as social support and provision of opiate substitution therapy, which is currently poorly available. [28-31] Integration of HIV and TB services, although improving, is still suboptimal in EE and close collaboration of physicians from both specialities is limited. Healthcare infrastructure continues to be driven by a strong vertical system, not allowing for interdisciplinary

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collaboration. [12] Community involvement and patients' education and support services need to be improved as well.

Of note, we were not able to document any significant differences in mortality within EE in explorative analyses stratified by IDU status (yes vs. no), perhaps due to limited numbers, but it may also be due to high prevalence of risk factors such as alcohol abuse and imprisonment among non-IDU individuals. This highlights the need for an approach that supports vulnerable patient groups in addition to individuals who are IDU. Prevalence of HCV coinfection is rather high among HIV/TB patients in EE (app. 50% in our study), thus management of this disease should also be integrated.

The study has several strengths and limitations. As a prospective cohort study, our data reflect the "real life" situation in the participating clinics/countries in terms of data availability, such as DST, HIV-RNA, CD4 cell count, at the same time limiting interventions and more careful study of the risk factors, associated with death. Many clinics in EE do not have the infrastructure to support patients' retention in care. Moreover, patients may have to attend different facilities for inpatient and outpatient treatment. Thus the loss to follow-up rate might be high, although major attempts have been taken to minimise it. All missing data were queried, all death, MDR-TB cases and at least 10% of random patients were monitored and guidelines on how to minimise LTFU was developed (www.cphiv.dk). The study did not collect detailed data on issues of special relevance for IDU individuals, such as adherence and whether there is an ongoing IDU and how that influences the patients' life. Due to the limited statistical power, risk factors of death could not be studied in more detail. The fact that the multivariate model did not remove the difference between regions does not exclude the possibility that the variables adjusted for in this model were on the causal pathway. There might be an issue of residual confounding, where the quality and availability of the variables (e.g. HIV-related) is insufficient to capture the biological changes that truly occurred. End-stage

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liver disease due to HCV coinfection might have contributed to the excess mortality in EE. However, we were not able to explore this further due to the statistical power limitations. Detailed analysis of causes of death and contributing factors is currently under development. Finally, there may be a general lower life expectancy in EE due to differences in socio-economic status, lifestyle, diets etc. This is, however, difficult to address in a clinical study and further research is needed.

Conclusion

In conclusion, this study documents an unacceptable high mortality among HIV-positive patients with drug-susceptible TB in EE despite widespread use of World Health Organization recommended anti-TB treatment regimens as initial therapy. Management of HIV infection was suboptimal in this region, but did not fully explain the high mortality. Healthcare provision for the TB/HIV population in EE needs to be urgently reviewed and improved. This requires a high level of political commitment both locally and globally, and may be achieved by improving collaboration between TB and HIV clinicians, as well as strengthening the existing healthcare infrastructure.

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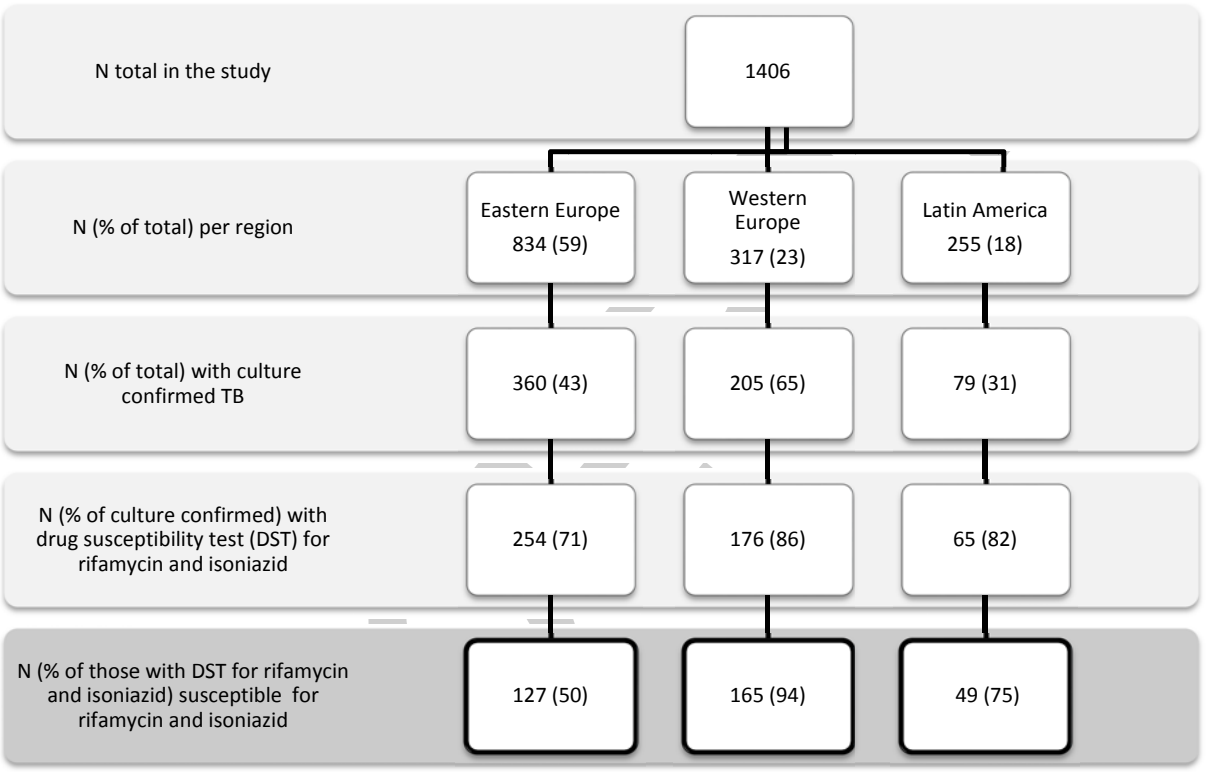
Figure 1. Flow chart of TB:HIV Study patients with rifampicin- and isoniazid- susceptible tuberculosis included in the analyses



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

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Table 1. Baseline demographic and clinical characteristics of 341 HIV patients with rifampicin- and isoniazid-susceptible tuberculosis

		Eastern Europe N(%)	Western Europe N(%)	Latin America N(%)	P
Total		***127***	***165***	***49***	
Gender	Male	98 (77.2)	109 (66.1)	36 (73.5)	0.108
Age	Years, Median (IQR)	36.5 (30.9 - 42.6)	38.8 (33.0 - 46.2)	38.2 (29.2 - 44.8)	0.037
Weight	Kg, Median (IQR)	58.0 (50.0 - 66.0)	60.0 (54.0 - 68.0)	55.0 (45.5 - 65.5)	0.225
TB/HIV Risk Factors	Ever Injecting drug use, N (%)	76 (60.3)	31 (18.8)	8 (16.3)	<.001
	History of imprisonment, N (%)	16 (12.6)	5 (3.0)	4 (8.2)	0.008
	History of excess alcohol consumption, N (%)	27 (21.3)	20 (12.1)	13 (26.5)	0.026
Laboratory Markers	Haemoglobin (g/dl), median (IQR)*	11 (9 - 13)	11 (9 - 12)	11 (10 - 13)	0.158

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	Albumin (g/dl), median (IQR)[#]	29 (24 - 33)	30 (25 - 34)	26 (22 - 33)	0.484
TB Disease	Disseminated, N (%)	64 (50.4)	95 (57.6)	29 (59.2)	0.39
TB Treatment	RHZ-based, N (%)	118 (92.9)	155 (93.9)	46 (93.9)	0.935
	RHZ+E, N (%)	98 (83.1)	128 (82.6)	43 (93.5)	0.181
	RHZ+S, N (%)	1 (0.8)			0.426
	RHZ+ES, N (%)	10 (8.5)	3 (1.9)	1 (2.2)	0.024
Hepatitis C[@]	Ever, N (%)	61 (48.0)	27 (16.4)	6 (12.2)	<0.001
HIV Status					
Antiretroviral therapy	Yes. N (%)	21 (16.5)	64 (38.8)	19 (38.8)	<0.001
CD4 cell count, mm^3/ml^1	Median (IQR)	103.5 (35.0 - 258.0)	123.0 (35.0 - 280.0)	78.0 (28.0 - 218.0)	0.31
HIV RNA, log_{10} copies/ml[2]	Median (IQR)	5.2 (4.3 - 5.7)	5.0 (2.9 - 5.7)	4.7 (2.5 - 5.6)	0.289

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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)

*Data for haemoglobin available for 98 (77) patients in EE, 146 (88) in WE, and 41 (84) in LA

[#]Data for albumin available for 38 (30) patients in EE, 113 (68) in WE, and 26 (53) in LA

[@]Ever tested positive for hepatitis C antibodies or hepatitis C RNA. Data for hepatitis C available for 91 (72) patients in EE, 121 (73) in WE, and 36 (73) in LA. Missing data are included in the denominator.

[1]Baseline CD4 cell count was available for 102 (80), 162 (98) and 43 (88) patients in EE, WE, and LA

[2]Baseline HIV RNA data were available for 68 (54), 157 (95) and 40 (82) patients in EE, WE, and LA

R = Rifampicin; H = Isoniazid; Z = Pyrazinamide; E = Ethambutol; S = Streptomycin

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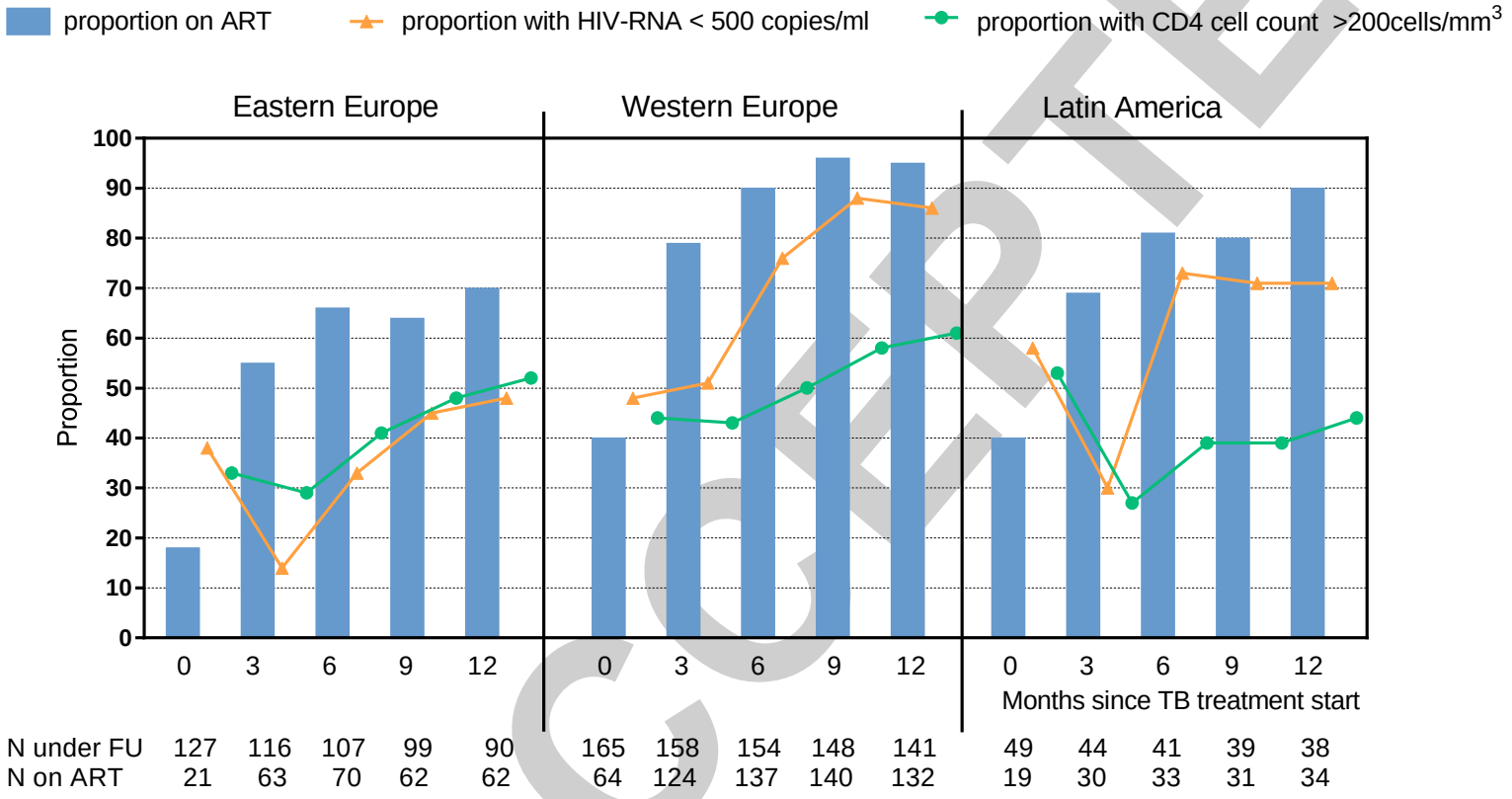
Figure 2: Use of antiretroviral therapy (ART), HIV-RNA and CD4-cell count status in 341 HIV-patients with drug-susceptible tuberculosis during 12 months after initiation of anti-TB therapy



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Proportion on ART calculated as proportion of TB/HIV patients being on ART at a given time point among those alive and not lost to follow-up

Proportion with HIV-RNA <500 copies/ml and proportion with CD4 cell count >200 cells/mm^3 calculated as proportion of those alive, not lost to follow-up and being on ART at a given time point

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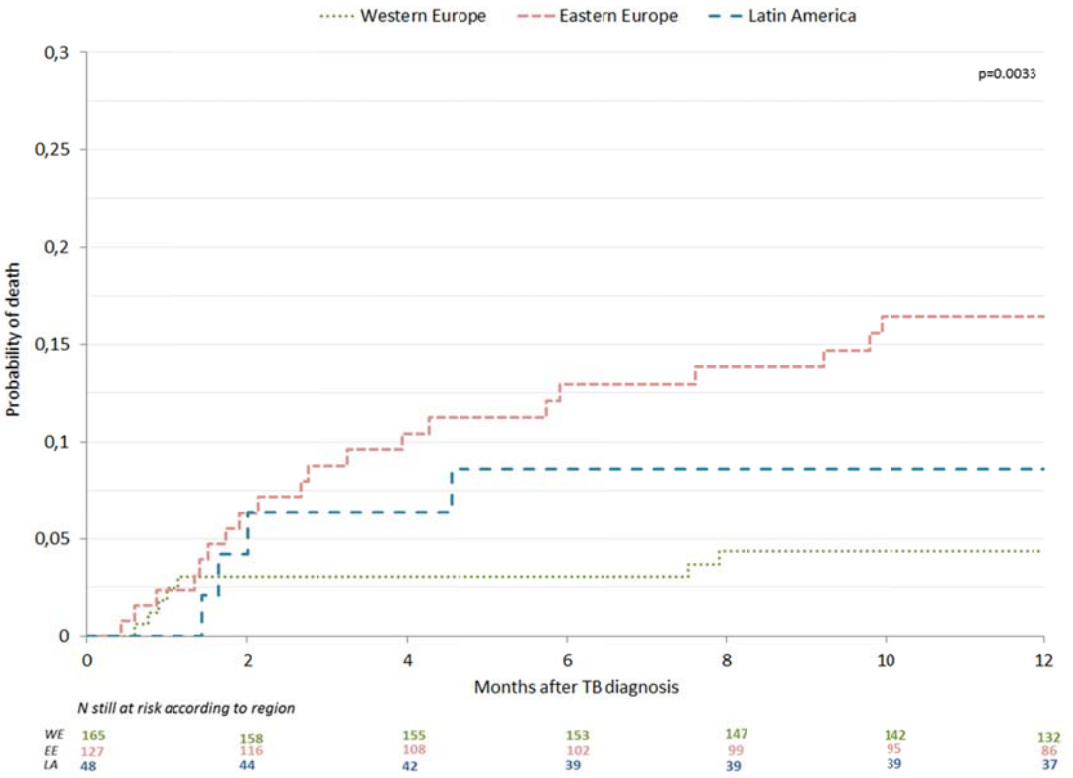
Figure 3. Probability of death among 341 HIV patients with rifampicin- and isoniazid-susceptible tuberculosis according to their region of residence



Number of deaths: 20 in EE, 7 in WE and 4 in LA.

EE: 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)

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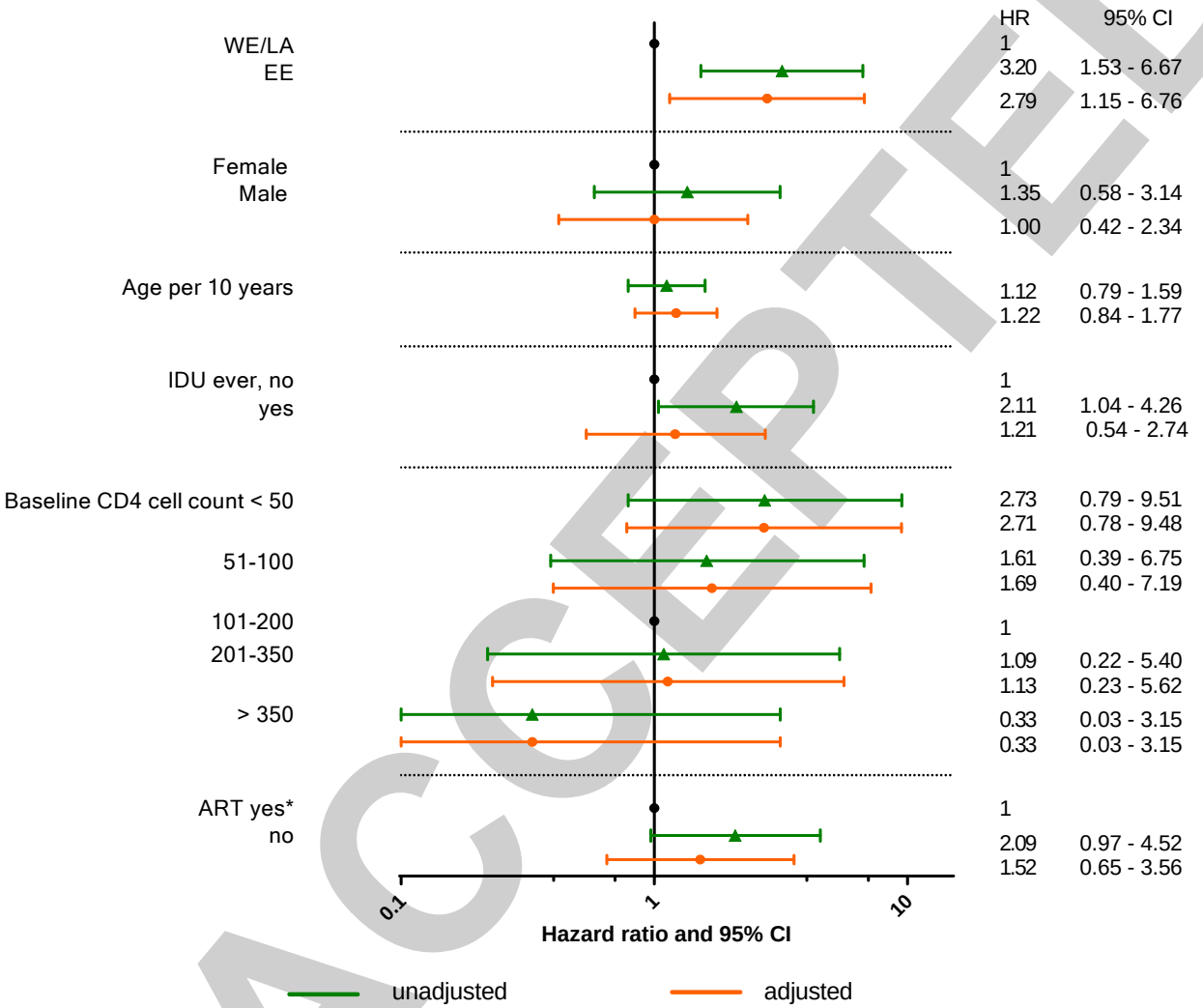
Figure 4. Cox proportional hazard model of factors associated with death in 341 HIV patients with rifampicin- and isoniazid-susceptible tuberculosis



***ART was included as a time updated variable**

Number of deaths = 31: 20 in Eastern Europe, 7 in Western Europe and 4 in Latin America.

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EE: 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)

IDU, injecting drug use; ART, antiretroviral therapy; CD4 cell count measurement (cells/mm^3)

HR, hazard ratio; CI, confidence interval;

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DNP, 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. AMWE, OK and DNP coordinated the study. AP, AMS, JMM, AR, HF, RFM, MHL, JT, AV, and EG 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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