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Multi-drug-resistant tuberculosis in HIV positive patients in Eastern Europe

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Summary Observational data from Eastern Europe on the management and outcome of multi-drug-resistant tuberculosis (MDR TB) in HIV positive populations remain sparse in the English-language literature.

We compared clinical characteristics and outcomes of 55 patients who were diagnosed with HIV and MDR TB in Eastern Europe between 2004 and 2006 to 89 patients whose *Mycobacterium tuberculosis* isolates were susceptible to isoniazid and rifampicin.

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Patients with HIV and MDR TB were young and predominantly male with high rates of intravenous drug use, imprisonment and hepatitis C co-infection. Eighty-four per cent of patients with MDR TB had no history of previous TB drug exposure suggesting that the majority of MDR TB resulted from transmission of drug-resistant *M. tuberculosis*. The use of non-standardized tuberculosis treatment was common, and the use of antiretroviral therapy infrequent. Compared to those with susceptible tuberculosis, patients with MDR TB were less likely to achieve cure or complete tuberculosis treatment (21.8% vs. 62.9%, $p < 0.0001$), and they were more likely to die (65.5% vs. 27.0%, $p < 0.0001$).

Our study documents suboptimal management and poor outcomes in HIV positive patients with MDR TB. Implementation of WHO guidelines, rapid TB diagnostics and TB drug susceptibility testing for all patients remain a priority in this region.

Introduction

Multi-drug-resistant tuberculosis (MDR TB) is a major public health problem in parts of Eastern Europe (EE). In Russia, Latvia and Belarus, the reported prevalence of MDR TB ranges 18—35% in new TB cases and 46—77% in retreatment cases.[1,2] TB drug resistance may arise through the selection of mutations in patients whose TB treatment regimens are poorly active or intermittently adhered to or through inter-person transmission of drug-resistant *Mycobacterium tuberculosis* (MTB), and is associated with an increased risk of death and treatment failure.[3]

Despite a low population prevalence of HIV infection (<1%), some 1.3 million people are living with HIV in EE, with limited (~25%) antiretroviral therapy (ART) coverage among those meeting the WHO 2010 criteria in several countries.[4] Observational data from EE on the management and outcome of MDR TB in HIV positive populations remain sparse in the English-language literature; the aim of this study was to describe and compare the clinical characteristics, management and outcomes of patients with MDR TB and drug-susceptible TB from EE (Belarus, Latvia, Romania, Russia, Ukraine) that were included in the TB/HIV study.[5]

Patients and methods

The TB/HIV study is an observational study of patients diagnosed in 2004—2006 in Europe and Argentina.[5] Patients were included in the current analyses if they had received their TB treatment in EE and the results of TB drug susceptibility testing (DST; conducted in local laboratories using Lowenstein-Jensen slopes and proportional methods) were available for rifamycins (R) and isoniazid (H) from specimens obtained up to 1 month after starting TB therapy (baseline). Follow up included visits and events up to April 2010. We used logistic and Cox regression, respectively, to identify factors associated with MDR TB and death.

Results

Of the 587 HIV/TB patients from EE, 175 (29.8%) had baseline DST results available, with 89 MTB isolates (51% [95% CI 43%—58%]) susceptible to RH, 58 (33% [26%—40%]) resistant to R (of which 55 resistant to RH), and 28 (16% [11%—21%]) susceptible to R with resistance to H. The prevalence of MDR TB ranged from 24% to 66% in the individual clinics/countries. Where evaluated, the prevalence of resistance to other TB drugs among RH-susceptible and MDR isolates was 0% (0/11) and 62.5% (10/16) to pyrazinamide (Z), 1.2% (1/86) and 53.7% (29/54) to ethambutol (E), and 3.8% (3/79) and 98.0% (49/50) to streptomycin (S), $p = 0.0010$, <0.0001 and <0.0001, respectively. Resistance to fluoroquinolones and second-line injectables was detected in 1/19 and 28/143 patients, respectively.

Baseline characteristics of the patients stratified by resistance profile are shown in the Table 1. Compared to patients with RH-susceptible TB, those with MDR TB were younger, more likely to have a history of IV drug use, prior TB drug exposure, known HIV infection prior to their TB diagnosis as well as HBV and HCV co-infection. Only 14% of patients with known HIV infection received ART when they developed TB. Although prior TB drug exposure was more common among patients infected with MDR TB, the majority of MDR TB (83.6%) arose in patients with no history of TB treatment or TB prophylaxis. Logistic regression analysis of all parameters listed in the Table 1 identified 3 factors to be associated with MDR TB: prior TB drug exposure (aOR 7.9 [95% CI 2.4, 6.5]), pulmonary TB (vs. disseminated TB, aOR 2.5 [1.2, 5.0]) and a history of incarceration (aOR 2.1 [1.0, 4.4]).

Patients started a median of 4 (inter-quartile range [IQR] 4-4) TB drugs. Initial regimens contained R, H, Z, E and S in 88.8%, 96.6%, 80.9%, 78.7% and 20.2% of patients with RH-susceptible TB and in 74.6%, 96.4%, 63.6%, 63.6% and 27.3% of those with MDR TB ($p = 0.026$, 0.93, 0.021, 0.049 and 0.33, respectively), and at least 1 additional anti-TB drug in 20.2% and 52.7% of patients respectively. Only 69.7% of patients with RH-susceptible TB and 45.5% of patients with MDR TB commenced therapies containing at least RHZ ($p = 0.0039$). The Kaplan—Meier estimated median (IQR) time that patients with MDR TB were maintained on their initial regimen was 39 (20—62) days compared with 61 (21—97) days for patients without DST results ($p = 0.005$). A median of 1 (IQR 1-1) new TB drug was incorporated in the subsequent regimen of patients with MDR TB.

By April 2010, a smaller proportion of patients with MDR TB had attained cure (rendered MTB culture negative) or completed treatment (no symptoms or signs of active disease after a complete course of TB therapy) (21.8% vs. 62.9% for those with RH-susceptible TB, $p < 0.0001$), while a greater proportion had died (65.5% vs. 27.0%, $p < 0.0001$). Patients with MDR TB were at particularly high risk of death during the first year following TB diagnosis (Fig. 1A), and

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patients with disseminated TB experienced higher mortality than those with localised pulmonary/extra-pulmonary TB only, irrespective of MDR status (Fig. 1B). In Cox regression models, MDR TB (vs. RH-susceptible TB, aHR 2.28 [95% CI 1.00, 5.20], $p = 0.050$) and disseminated TB (vs. localised pulmonary/extra-pulmonary TB, aHR 1.99 [1.10, 3.59], $p = 0.022$) were the only factors found to be associated with an increased risk of death.

Discussion

TB/HIV patients in EE constitute an extremely challenging population, with high rates of socioeconomic deprivation, IV drug use, hepatitis co-infection and poor access to ART. MDR TB was present in one third of HIV positive patients who had baseline DST results. Unlike reports from the general MDR TB population in EE,[6] the majority of cases was among patients without a history of TB treatment, i.e. MDR TB was acquired through transmission of drug-resistant *M. tuberculosis* strains. R and H resistance was frequently accompanied by resistance to Z, E and/or S, resulting in inadequate first line regimens that created an opportunity for the selection of additional drug resistance mutations, especially when these treatments were administered for prolonged periods. The addition of a single drug to failing initial regimens, which in part reflects limited access to drugs and past management strategies, provided further opportunities for the selection of second-line drug resistance mutations, thus setting the scene for the generation of XDR TB that could potentially become resistant to all locally available drugs.

A sub-optimal proportion of patients with RH-susceptible TB (70%) received RHZ-containing first line TB treatment. We have recently shown that use of RHZ-containing regimens was associated with reduced risk of death.[7] Whereas initial regimens of patients with RH-susceptible TB contained on average 4 drugs, frequent use of regimens not containing RHZ may have provided less effective TB therapy and thereby contributed to the high death rate in this population. In addition, the infrequent use of cART and high rates of social deprivation, IV drug use, homelessness and alcohol consumption were likely contributors to the poor outcome. Unfortunately, our study had insufficient power to examine the relative importance of these factors.

Despite the known high rates of MDR TB in EE, less than one third of patients had TB DST performed at baseline. Many of the patients without DST were likely to have been infected with R, H or RH resistant isolates and thus to have been treated with inadequate TB therapy. An overestimation of the number of active drugs in subsequent regimens of patients without DST increased the potential for loss of drugs that could have been used to construct fully active or at least partially active regimens. In regions such as EE, all TB diagnoses should be confirmed by culture to allow DST to be performed and optimal treatment regimens to be constructed. In many centres, this may require closer collaboration between HIV physicians and phtysiologists. The introduction of rapid diagnostics to detect rifamycin-

Table 1 Baseline characteristics by resistance profile in Eastern Europe.

	MDR TB ($n = 55$)	RH-susceptible TB ($n = 89$)	*P*-value
Age (median (IQR))	30.2 (25.2–36.0)	31.9 (27.5–39.2)	0.042
Male	41 (74.6)	63 (70.8)	0.62
IDU TB risk factor	47 (85.5)	57 (64.0)	0.0053
Prison TB risk factor	18 (32.7)	21 (23.6)	0.23
Alcohol TB risk factor	14 (25.5)	35 (39.3)	0.088
Family TB, TB risk factor	8 (14.6)	13 (14.6)	0.99
Homeless TB risk factor	0	4 (4.5)	0.11[a]
Other TB risk factor	2 (3.6)	1 (1.1)	0.31[a]
Previous TB drug exposure	9 (16.4)	3 (3.4)	0.0061
Pulmonary TB	29 (52.7)	36 (40.5)	0.15
Extrapulmonary TB	2 (3.6)	1 (1.1)	0.31[a]
Disseminated TB	24 (43.6)	52 (58.4)	0.084
HCV +	34 (61.8)	36 (40.5)	0.013
HCV −	1 (1.8)	11 (12.4)	
HCV unknown	20 (36.4)	42 (47.2)	
HBV +	11 (20.0)	5 (5.6)	0.028
HBV −	22 (40.0)	43 (48.3)	
HBV unknown	22 (40.0)	41 (46.1)	
HIV 3 months prior to TB treatment	47 (85.5)	51 (57.3)	0.0004
On ART at TB diagnosis	3 (6.4) ($n = 47$)	11 (21.6) ($n = 51$)	0.032
AIDS	17 (31.0)	29 (32.6)	0.83
CD4 count/mm^3 (Median (IQR))	164 (36–356)	203.5 (63–440)	0.51
HIV-RNA log10 (Median (IQR))	4.89 (3.46–5.83)	5.16 (4.55–5.67)	0.86

Abbreviations: MDR, multi-drug resistant ; RH, rifampicin and isoniazid; IDU, intravenous drug use; HCV, hepatitis C; HBV, hepatitis B; ART, antiretroviral therapy; AIDS, acquired immunodeficiency syndrome.
[a] Unstable *p*-value estimate due to small numbers.

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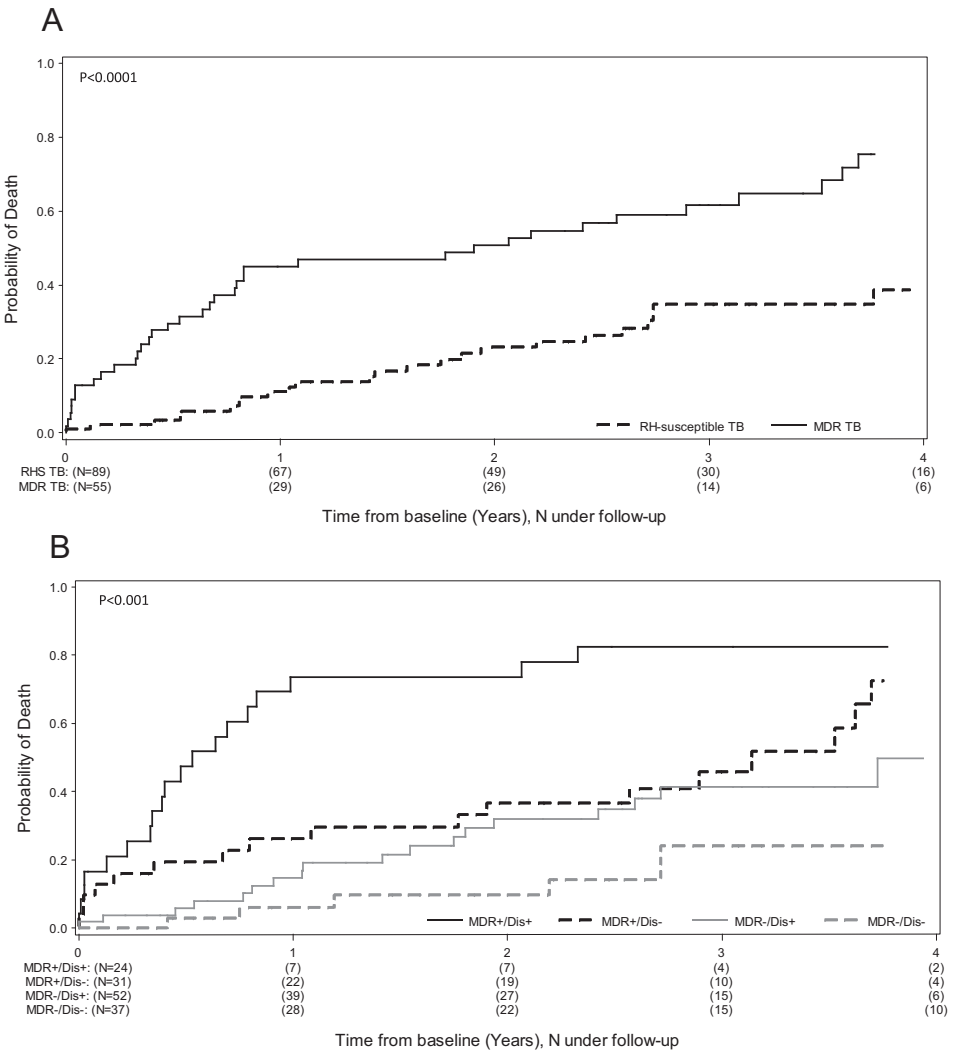

Figure 1 Cumulative incidence of death among patients with TB in Eastern Europe. A Patients stratified by the presence of multi-drug-resistant (MDR) vs. rifamycin and isoniazid (RH) susceptible tuberculosis (TB). B Patients stratified by the presence of MDR vs. RH-susceptible TB, and by disseminated vs. localised (extra-)pulmonary TB.

resistant TB[8] is a priority in this region and will allow for improved and timely allocation of available TB drugs.

Our data are observational, limited by the relatively small numbers of patients with baseline DST results, and reflective of clinical practice in 2004—2006. In addition, patients with a history of TB were overrepresented, which could lead to an overestimation of the prevalence of drug-resistant TB. Nevertheless information about TB treatment and outcomes from observational studies in EE is comparatively rare. The high rates of transmitted drug resistance emphasise the importance of interventions to reduce person-to-person spread of MTB. The high prevalence of R- and RH resistant TB requires urgent widespread implementation of the recent advances in TB diagnostics to detect R-resistant TB at first presentation[8] and improved access to DST for and use of second-line agents. In centres, regions or countries where this is not yet standard of care, WHO recommended RHZ-based regimens should be initiated in those found to have R/RH-susceptible TB.[9] Although the majority of patients were known to be HIV positive at the time of TB diagnosis, very few patients received ART. Combination ART should be used more widely to reduce the risk of TB in general[10] and to improve outcomes of drug-susceptible and drug-resistant TB in HIV co-infected patients. A prospective study is currently underway to provide insight into whether the management of TB/HIV has improved since the time of the present analyses.[11]

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Conflict of interest

None of the authors have a financial conflict of interest to declare in relation to this work.

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