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

Frank A. Post \textsuperscript{a,*,} Daniel Grint \textsuperscript{b}, Anne Marie Werlinrud \textsuperscript{c}, Alexander Panteleev \textsuperscript{d}, Vieja Riekstina \textsuperscript{e}, Evgeniy A. Malashenkov \textsuperscript{f}, Alena Skrahina \textsuperscript{g}, Dan Duiculescu \textsuperscript{h}, Daria Podlekareva \textsuperscript{c}, Igor Karpov \textsuperscript{i}, Vasily Bondarenko \textsuperscript{j}, Nelly Chentsova \textsuperscript{k}, Jens Lundgren \textsuperscript{c,l}, Amanda Mocroft \textsuperscript{b}, Ole Kirk \textsuperscript{c,l}, Jose M. Miro \textsuperscript{m}, for the HIV-TB Study Group \textsuperscript{n}

\textsuperscript{a} King’s College London School of Medicine, London SE5 9RJ, UK
\textsuperscript{b} University College London, London, London NW3 2PF, UK
\textsuperscript{c} Copenhagen HIV Programme, University of Copenhagen, Copenhagen, Denmark
\textsuperscript{d} TB Hospital #2, St. Petersburg, Russia
\textsuperscript{e} State Agency of TB and Lung Diseases, Riga, Latvia
\textsuperscript{f} Botkin Hospital of Infectious Diseases, St. Petersburg, Russia
\textsuperscript{g} Research Institute of Pulmonology and Pulmonary Tuberculosis, Minsk, Belarus
\textsuperscript{h} Spitalul de Boli Infectioase si Tropicale, Bucharest, Romania
\textsuperscript{i} Minsk State Medical University, Department of Infectious Diseases, Minsk, Belarus
\textsuperscript{j} Gomel Regional TB Hospital, Gomel, Belarus
\textsuperscript{k} Kiev City AIDS Centre, Kiev, Ukraine
\textsuperscript{l} Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark
\textsuperscript{m} Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain

Accepted 19 September 2013
Available online

Keywords
Tuberculosis; HIV; MDR; Resistant; Eastern Europe

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.
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 15–35% 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.6 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 93.7% (29/31) 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 8, 9, 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

Please cite this article in press as: Post FA, et al., Multi-drug-resistant tuberculosis in HIV positive patients in Eastern Europe, J Infect (2013), http://dx.doi.org/10.1016/j.jinf.2013.09.034
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 phthisiologists.

The introduction of rapid diagnostics to detect rifamycin-

---

**Table 1** Baseline characteristics by resistance profile in Eastern Europe.

<table>
<thead>
<tr>
<th></th>
<th>MDR TB (n = 55)</th>
<th>RH-susceptible TB (n = 89)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median (IQR))</strong></td>
<td>30.2 (25.2–36.0)</td>
<td>31.9 (27.5–39.2)</td>
<td>0.042</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>41 (74.6)</td>
<td>63 (70.8)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>IDU TB risk factor</strong></td>
<td>47 (85.5)</td>
<td>57 (64.0)</td>
<td>0.0053</td>
</tr>
<tr>
<td><strong>Prison TB risk factor</strong></td>
<td>18 (32.7)</td>
<td>21 (23.6)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Alcohol TB risk factor</strong></td>
<td>14 (25.5)</td>
<td>35 (39.3)</td>
<td>0.088</td>
</tr>
<tr>
<td><strong>Family TB, TB risk factor</strong></td>
<td>8 (14.6)</td>
<td>13 (14.6)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Homeless TB risk factor</strong></td>
<td>0</td>
<td>4 (4.5)</td>
<td>0.11*</td>
</tr>
<tr>
<td><strong>Other TB risk factor</strong></td>
<td>2 (3.6)</td>
<td>1 (1.1)</td>
<td>0.31*</td>
</tr>
<tr>
<td><strong>Previous TB drug exposure</strong></td>
<td>9 (16.4)</td>
<td>3 (3.4)</td>
<td>0.0061</td>
</tr>
<tr>
<td><strong>Pulmonary TB</strong></td>
<td>29 (52.7)</td>
<td>36 (40.5)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Extrapulmonary TB</strong></td>
<td>2 (3.6)</td>
<td>1 (1.1)</td>
<td>0.31*</td>
</tr>
<tr>
<td><strong>Disseminated TB</strong></td>
<td>24 (43.6)</td>
<td>52 (58.4)</td>
<td>0.084</td>
</tr>
<tr>
<td><strong>HCV +</strong></td>
<td>34 (61.8)</td>
<td>36 (40.5)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>HCV –</strong></td>
<td>1 (1.8)</td>
<td>11 (12.4)</td>
<td>0.31*</td>
</tr>
<tr>
<td><strong>HCV unknown</strong></td>
<td>20 (36.4)</td>
<td>42 (47.2)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>HBV +</strong></td>
<td>11 (20.0)</td>
<td>5 (5.6)</td>
<td>0.0028</td>
</tr>
<tr>
<td><strong>HBV –</strong></td>
<td>22 (40.0)</td>
<td>43 (48.3)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>HBV unknown</strong></td>
<td>22 (40.0)</td>
<td>41 (46.1)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>HIV 3 months prior to TB treatment</strong></td>
<td>47 (85.5)</td>
<td>51 (57.3)</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>On ART at TB diagnosis</strong></td>
<td>3 (6.4) (n = 47)</td>
<td>11 (21.6) (n = 51)</td>
<td>0.032</td>
</tr>
<tr>
<td><strong>AIDS</strong></td>
<td>17 (31.0)</td>
<td>29 (32.6)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>CD4 count/mm(^3) (Median (IQR))</strong></td>
<td>164 (36–356)</td>
<td>203.5 (63–440)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>HIV-RNA log10 (Median (IQR))</strong></td>
<td>4.89 (3.46–5.83)</td>
<td>5.16 (4.55–5.67)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

**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.

* Unstable \( p \)-value estimate due to small numbers.

---

Please cite this article in press as: Post FA, et al., Multi-drug-resistant tuberculosis in HIV positive patients in Eastern Europe, J Infect (2013), http://dx.doi.org/10.1016/j.jinf.2013.09.034
resistant TB 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 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 RH-based regimens should be initiated in those found to have R/RH-susceptible TB. 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 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.

Acknowledgements

Study funding

Data collection in Eastern Europe (Belarus, Latvia, Russia, Ukraine) was funded by the Copenhagen HIV Programme and the EuroSIDA study. Primary support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773) and the 6th Framework (LSHP-CT-2006-018632) programmes. Current support also includes unrestricted grants from Bristol-Myers Squibb, GlaxoSmithKline, Roche, Gilead, Pfizer, Probability of Death

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.

Please cite this article in press as: Post FA, et al., Multi-drug-resistant tuberculosis in HIV positive patients in Eastern Europe, J Infect (2013), http://dx.doi.org/10.1016/j.jinf.2013.09.034
Drug-resistant TB in Eastern Europe

Merck and Co., Tibotec and Boehringer-Ingelheim. DP was funded through a post-doctoral scholarship from the Danish Council for Independent Research, Denmark.

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

TB/HIV study team

Study sites in Eastern Europe

References