Major challenges in clinical management of TB/HIV coinfected patients in Eastern Europe compared with Western Europe and Latin America

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for the TB:HIV study group in EuroCoord

The HIV Drug Therapy Conference 2014
Background

- Tuberculosis (TB) is the most common co-infection among HIV-positive patients and the most common cause of death.

- Eastern Europe:
  - Rapidly increasing incidence of HIV\(^1\)
  - Overlapping risk groups for HIV and TB (IDUs)\(^1,4\)
  - The world’s highest proportions of multi-drug resistant TB (MDR-TB\(^*\))\(^2\)
  - Inadequate surveillance systems, data on TB/HIV patients remain scarce\(^3\)

\(^1\)UNAIDS Report, 2013
\(^2\)WHO Global Tuberculosis Report, 2013
\(^3\)Abubakar et al., Lancet, 2013
\(^4\)Podlekareva et al., AIDS, 2009

\(^*\)MDR-TB = Resistance against Rifampicin and Isoniazid
Aims

• Compare clinical characteristics of TB/HIV coinfected patients in three European regions and Latin America at time of TB diagnosis

• Identify factors associated with having MDR-TB

• Assess the activity of empiric anti-TB therapy in relation to subsequent drug-susceptibility test (DST) results
TB:HIV Study

- TB:HIV Study: Prospective, observational cohort study of TB/HIV coinfectcd patients

- Inclusion criteria: Consecutively enrolled HIV-positive patients >16 years, diagnosed with TB between 2011 – 2013

- Collaboration of 62 TB and HIV clinics:
  - **Eastern Europe**, (21 clinics in Belarus, Estonia, Georgia, Latvia, Lithuania, Poland, Romania, Ukraine, Russia),
  - **Western Europe** (19 clinics in Belgium, Denmark, France, Switzerland, United Kingdom)
  - **Southern Europe** (9 clinics in Italy and Spain)
  - **Latin America** (13 clinics in Argentina, Chile, and Mexico)
Clinical characteristics of 1413 TB/HIV patients at time of TB diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Eastern Europe N = 844</th>
<th>Western Europe N = 152</th>
<th>Southern Europe N = 164</th>
<th>Latin America N = 253</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, IQR)</td>
<td>35 (31 - 40)</td>
<td>37 (32 - 48)</td>
<td>42 (33 - 48)</td>
<td>38 (30 - 45)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gender (female, %)</td>
<td>24.9</td>
<td>44.1</td>
<td>27.4</td>
<td>26.5</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (white, %)</td>
<td>95.2</td>
<td>26.2</td>
<td>72.3</td>
<td>19.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CD4 count (median, (IQR))</td>
<td>107 (35 - 254)</td>
<td>149 (35 - 360)</td>
<td>129 (38 - 315)</td>
<td>96 (35 - 289)</td>
<td>0.12</td>
</tr>
<tr>
<td>HIV+ more than 3 months before TB diagnosis</td>
<td>75.2</td>
<td>54.0</td>
<td>60.4</td>
<td>62.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HIV treatment, cART (%)</td>
<td>16.6</td>
<td>39.5</td>
<td>43.9</td>
<td>35.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TB Risk Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- IDU (%)</td>
<td>61.1</td>
<td>9.2</td>
<td>29.3</td>
<td>15.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>- In prison in last 2 years (%)</td>
<td>18.6</td>
<td>2.6</td>
<td>4.9</td>
<td>6.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TB in the past, yes (%)</td>
<td>13.4</td>
<td>10.1</td>
<td>14.5</td>
<td>16.5</td>
<td>0.36</td>
</tr>
<tr>
<td>Current OST, yes¹ (%)</td>
<td>3.7</td>
<td>66.7</td>
<td>48.8</td>
<td>0</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

¹OST = Opioid Substitution Therapy. The denominator is IDU (HIV) risk group.
TB localisation

- Disseminated: 100%
- Extrapulmonary: 79%
- Pulmonary: 21%

Eastern Europe: 719 cases, 844 people
Western Europe: 160 cases, 152 people
Southern Europe: 206 cases, 164 people
Latin America: 242 cases, 253 people

Statistical significance: p < 0.0001
Diagnosis of TB and availability of DST results

Region

- Eastern Europe N=844
- Western Europe N=152
- Southern Europe N=164
- Latin America N=253

- Presumptive TB
- Probable TB
- Definite TB without DST
- Definite TB with DST

p < 0.0001
Anti-TB drug-resistance among patients with DST results within one month of TB diagnosis

459/569 DSTs were tested for both Rifampicin and Isoniazid
Factors associated with MDR-TB in multivariable logistic regression analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Gender: Female (vs male)</th>
<th>Ethnicity: Non-white (vs white)</th>
<th>Age: Per 10 year increase</th>
<th>Region: Eastern Europe (vs other)</th>
<th>Previous TB: Treatment (vs no treatment)</th>
<th>TB risk factor: IDU</th>
<th>Other: Other</th>
<th>Adjusted odds ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR 0.90 95% CI 0.49 - 1.67 p 0.74</td>
<td>aOR 1.01 95% CI 0.43 - 2.36 p 0.99</td>
<td>aOR 0.91 95% CI 0.67 - 1.23 p 0.53</td>
<td>aOR 7.19 95% CI 3.28-15.78 p &lt;0.01</td>
<td>aOR 3.42 95% CI 1.88 - 6.22 p &lt;0.01</td>
<td>aOR 2.03 95% CI 1.00 - 4.09 p 0.05</td>
<td>aOR 5.23 95% CI 0.91-30.12 p 0.06</td>
<td>aOR 1.33 95% CI 0.49 - 3.59 p 0.57</td>
</tr>
</tbody>
</table>

The model was also adjusted for:
- Hepatitis B
- TB localisation
- HIV+ more than three months prior to TB
Proportion with MDR-TB and RHZ-based empiric therapy in countries in Eastern Europe

1R=Rifampicin, H=Isoniazid, Z=Pyrazinamide
Susceptibility of empiric anti-TB treatment in relation to subsequent DST results

Active drugs calculated from comparing empiric anti-TB therapy and subsequently known DST results within the first month of TB therapy. MTB isolates were assumed to be susceptible to all drugs for which no DST results were available.
Would empiric anti-TB treatment with rifampicin, isoniazid, pyrazinamide and ethambutol have been better?

Proportions, %

Eastern Europe: N=298/830
- 0 active TB drugs: 20%
- 1 active TB drugs: 40%
- 2 active TB drugs: 40%
- >=4 active TB drugs: 10%

Western Europe: N=94/151
- 0 active TB drugs: 60%
- 1 active TB drugs: 20%
- 2 active TB drugs: 20%
- >=4 active TB drugs: 0%

Southern Europe: N=104/162
- 0 active TB drugs: 50%
- 1 active TB drugs: 30%
- 2 active TB drugs: 10%
- >=4 active TB drugs: 10%

Latin America: N=89/253
- 0 active TB drugs: 65%
- 1 active TB drugs: 30%
- 2 active TB drugs: 5%
- >=4 active TB drugs: 0%

Hypothetically assuming empiric anti-TB treatment had been initiated with rifampicin, isoniazid, pyrazinamide and ethambutol

p < 0.0001
Limitations

• Observational study; selection bias

• Hospitals/clinics were not necessarily representative of their country/region

• Full anti-TB DST results were not available for all patients
Summary

• Large differences in clinical characteristics of TB/HIV coinfected patients across Europe and Latin America

• The situation in Eastern Europe was characterised by:
  ▪ Lower proportion of definite TB diagnosis and DST results
  ▪ High levels of MDR-TB and no correlation between proportion of MDR-TB and RHZ-based empiric therapy
  ▪ Fewer active drugs in empiric therapy

• Pronounced variation between countries within Eastern Europe in levels of MDR-TB and in the empiric anti-TB regimens prescribed
Perspectives

• Given the very low CD4 cell counts observed, important to maintain patients under follow-up and initiate cART when appropriate

• Clear need for improving and implementing more accurate and rapidly available diagnostics

• Improve empiric anti-TB therapy, particularly in high resistance settings such as Eastern Europe

• The long-term clinical consequences will be further analysed as FU data accumulates (www.chip.dk under TB:HIV study)
Acknowledgements

The TB:HIV Study Group

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Statistical centre: L. Shepherd, A. Schultz, A. Mocroft.


Sources of funding: This study was funded by the European Union 7th Framework (FP7/2007-2013, EuroCoord n° 260694) programme and The Danish Council for Independent Research (DFF); Research Council, Copenhagen University Hospital, Rigshospitalet.

We thank the patients who participated in the study and the staff involved at the participating hospitals.