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

Anne Marie W. Efsen, Anna Schultze, Frank A. Post, Alexander Panteleev, Hansjakob Furrer, Robert Miller, Marcelo H. Losso, Javier Toibaro, Aliaksandr Skrahin, Jose M. Miro, Joan A. Caylà, Enrico Girardi, Mathias Bruyand, Niels Obel, Daria N. Podleakareva, Jens D. Lundgren, Amanda Mocroft, Ole Kirk

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 coinfected 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>&lt;.0001</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, yes (%)</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

Proportion, %

Disseminated
Extrapulmonary
Pulmonary

Eastern Europe
N=844

Western Europe
N=152

Southern Europe
N=164

Latin America
N=253

Region

p < 0.0001
Diagnosis of TB and availability of DST results

- **Proportion, %**
- **Presumptive TB**
- **Probable TB**
- **Definite TB without DST**
- **Definite TB with DST**

Region

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

DST results: 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

Eastern Europe N=243
Western Europe N=66
Southern Europe N=89
Latin America N=61

0% 20% 40% 60% 80% 100%
Proportion, %

- Rifampicin resistant/Isoniazid resistant (MDR-TB)
- Rifampicin susceptible/Isoniazid resistant
- Rifampicin resistant/Isoniazid susceptible
- Rifampicin susceptible/Isoniazid susceptible

Map indicating regions:
- Eastern Europe
- Western Europe
- Southern Europe
- Latin America
Factors associated with MDR-TB in multivariable logistic regression analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Lower Odds</th>
<th>Higher Odds</th>
<th>aOR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (vs male)</td>
<td></td>
<td></td>
<td>0.90</td>
<td>0.49 - 1.67</td>
<td>0.74</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>1.01</td>
<td>0.43 - 2.36</td>
<td>0.99</td>
</tr>
<tr>
<td>Non-white (vs white)</td>
<td></td>
<td></td>
<td>0.91</td>
<td>0.67 - 1.23</td>
<td>0.53</td>
</tr>
<tr>
<td>Age Per 10 year increase</td>
<td></td>
<td></td>
<td>0.91</td>
<td>0.67 - 1.23</td>
<td>0.53</td>
</tr>
<tr>
<td>Region Eastern Europe</td>
<td></td>
<td></td>
<td>7.19</td>
<td>3.28 - 15.78</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous TB Treatment</td>
<td></td>
<td></td>
<td>3.42</td>
<td>1.88 - 6.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IDU</td>
<td></td>
<td></td>
<td>2.03</td>
<td>1.00 - 4.09</td>
<td>0.05</td>
</tr>
<tr>
<td>Prison</td>
<td></td>
<td></td>
<td>5.23</td>
<td>0.91 - 30.12</td>
<td>0.06</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td>1.33</td>
<td>0.49 - 3.59</td>
<td>0.57</td>
</tr>
<tr>
<td>Family</td>
<td></td>
<td></td>
<td>2.06</td>
<td>0.45 - 9.35</td>
<td>0.35</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td>0.88</td>
<td>0.24 - 3.21</td>
<td>0.84</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

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?

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

Eastern Europe
N=298/830

Western Europe
N=94/151

Southern Europe
N=104/162

Latin America
N=89/253

Proportions, %

0 active TB drugs
1 active TB drugs
2 active TB drugs
3 active TB drugs
>=4 active TB drugs

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

Eastern Europe: Belarus: Belarusian State Medical University, Department of Infectious Disease: I. Karpov (PI), A. Vassilenko; Republican Research and Practical Centre for Pulmonology and TB (Minsk): A. Skrahina (PI), D. Klimuk, A. Skrahin, O. Kondratenok and A. Zalutskaya; Gomel State Medical University (Gomel): V. Bondarenko (PI), V. Mitsura, E. Kozorez, O. Tumash; Gomel Region Centre for Hygiene: O. Suetov (PI) and D. Paduto. Estonia: East Viru Central Hospital (Kohtla-Jarve): V. Iljina (PI) and T. Kummik. Georgia: Infectious Diseases, AIDS and Clinical Immunology Research Center (Tbilisi): N. Bolokadze (PI), K. Mshvidobadze and N. Lanchava; National Center for Tuberculosis and Lung Diseases of Georgia (Tbilisi): L. Goginashvili, L. Mikhalishvili and N. Babilshvili. Latvia: Infectology Centre of Latvia (Riga): B. Rozental (PI), I. Zeltina and I. Janushkevich. Lithuania: Centre for Communicable Diseases and AIDS (Vilnius): I. Caplinskienė (PI), S. Caplinskas, Z. Kancauskiene. Poland: Wojewodzki Szpital Zakaźny/Medical University of Warsaw (Warszawa): R. Podlasiński (PI), A. Wiercinska-Drapalo (PI), M. Thompson and J. Kozłowska; Wojewódzki Szpital Specjalistyczny/Infectious Diseases Hospital (Bialystok): A. Grezszczuk (PI); Jozef Strus Multidisciplinary City Hospital (Poznan): M. Bura (PI); Warsaw University School of Medicine (Warszawa): B. Knyz (PI) and M. Inglot; Jagiellonian University Medical College (Krakow): A. Garlicki (PI) and J. Loster. Romania: Dr. Victor Babes Hospital (Bucharest): D. Duiculescu (1 PI) and S. Tetroadov. Russia: Botkin Hospital of Infectious Diseases (St. Petersburg): A. Rakhmanova (PI), O. Panteleeva, A. Yakovlev, A. Kozlov, A. Tyukalova and Y. Vlasova; City TB Hospital No. 2 (St. Petersburg): A. Panteleev (PI); Center for Prevention and Control of AIDS (Veliky, Novgorod): T. Trofimov (PI); Medical University Povoljski Federal Region. Ukraine: Crimean Republican AIDS Centre (Simferopol): G. Kyselyova (PI).

Western Europe: Belgium: CHU Saint-Pierre (Brussels): MC Payen (PI), K. Kabeya and C. Necco. Denmark: Rigshospitalet (Cph): N. Obel (PI); Hvidovre University Hospital: K. Thorsteinsson. France: Aquitaine Cohort. Cohort administration: F. Dabis (PI) and M. Bruyand. Participating Centers and Physicians: Bordeaux University Hospital: P. Morlat; Arcachon Hospital: A. Dupont; Dax Hospital: Y. Gerard; Bayonne Hospital: F. Bonnal; University Hospital: J. Ceccaldi; Mont-de-Marsan Hospital: S. De Witte; Pau Hospital: E. Moulin; Périgueux Hospital: P. Lataste; Villeuneuve-sur-Lot Hospital: I. Chossat. Switzerland: Swiss HIV Cohort Study (SHCS, www.shcs.ch): Cohorte administration: M. Saget and M. Rickenbach. Participating Centers and Physicians: University Hospital Basel: L. Elzi and M. Battegay; University Hospital Bern: H. Furrer (PI); Hospital Cantonal Universitaire, Geneve: D. Scuiler and A. Calmy; Centre Hospitalière Universitaire Vaudois, Lausanne: M. Cavassini; Hospital of Lugano: A. Brown and E. Bernason; Cantonal Hospital St. Gallen: M. Hoffmann and P. Vernazza; University Hospital Zurich: J. Fehr and Prof. R. Weber. This study has been co-financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant # 348522) and by SHCS project 666. The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians. Some members of the Swiss HIV Cohort Study are: Aubert V, Battegay M, Bernasconi E, Bön J, Buchar HC, Burton-Jeangros C, Calmy A, Cavassini M, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerynck D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösl I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kvarai H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schönli-Affolter F, Schmid P, Schübchapp J, Speck R, Tarr P, Tenenti A, Trkola A, Vernazza F, Weber R, Yerly S. United Kingdom: Mortimer Market Centre (London): R. Miller (PI) and N. Vera; St. Mary’s Hospital: G. Cooke (PI) and S. Mullaney; North Manchester General Hospital: E. Wilkins (PI) and V. George; Sheffield Teaching Hospitals: P. Collini (PI) and D. Dockrell; King’s College Hospital (London): F. Post (PI), L. Campbell, R. Brum, E. Mabonga and P. Saigal. Queen Elizabeth Hospital: S. Kegg (PI); North Middlesex University Hospital: J. Ascough and A. Waters. Leicester Royal Infirmary: J. Dhar (PI) and M. Lashmanganya.


Statistical centre: L. Shepherd, A. Schultz, P. 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 participating at the participating hospitals.