TB in HIV-positive patients in Europe

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Rigshospitalet & University of Copenhagen, Denmark
Epidemiology
Estimated numbers of TB cases and deaths globally 1990-2011

- TB incidence
- All TB cases
- HIV-associated TB cases
- TB deaths
- TB deaths among HIV-negative people
- HIV-associated TB deaths

HIV-associated TB deaths are classified as HIV deaths according to ICD-10.
Figure B: Estimated TB incidence per 100 000 population, European Region, 2011
### Risk factors of TB among European HIV-positive patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>aIRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count (per doubling)</td>
<td>0.64 (0.58-0.70)</td>
</tr>
<tr>
<td>HIV-RNA (&gt;10,000 v. &lt;500 cp/ml)</td>
<td>3.24 (2.07-5.09)</td>
</tr>
<tr>
<td>Intravenous drug use (v. MSM)</td>
<td>1.85 (1.04-3.28)</td>
</tr>
<tr>
<td>Geographic origin (Africa v. Europe)</td>
<td>2.79 (1.30-5.99)</td>
</tr>
<tr>
<td>Region of follow-up (Eastern v. Western Europe)</td>
<td>4.25 (2.79-6.49)</td>
</tr>
</tbody>
</table>

Kruk, *AIDS* 2011
Marked CD4 gradient in TB incidences in untreated HIV-positive patients – results from the pre-cART era

Current CD4:
- <200 cells/mm³: 21.9 (17.9-26.6)
- 200-349: 6.4 (4.5-8.9)
- 350-500: 3.2 (1.9-5.0)
- >500: 3.3 (2.3-4.8)

Lodi, Thorax 2013
Increasing TB incidence due to HIV in the early 1990’s in Spain

TB of all AIDS cases: Spain (all) 1996: 39%
Catalonia 1994: 37%

Vall Mayans, AIDS 1997
Castilla, AIDS 1997
Patients with undiagnosed HIV infection – late presenters

HIV testing of patients diagnosed with tuberculosis increased in Denmark during the period from 2007 to 2009

M Perch,¹ PH Andersen² and A Kok-Jensen²

¹Section of Lung Transplantation, Department of Cardiology, Copenhagen University Hospital, Rigshospitalet and
²Department of Infectious Disease Epidemiology, Statens Serum Institut, Copenhagen, Denmark

We examined the trends of HIV testing among patients notified with TB in Denmark during a 3-year period from 2007 to 2009. We were able to obtain HIV testing status for 96%. There

- HIV testing increased from 43% of TB-patients in Denmark in 2007 to 63% in 2009
MDR-TB
Percentage of new tuberculosis cases with MDR-TB*

* MDR-TB: multidrug-resistant tuberculosis (resistance to, at least, isoniazid and rifampicin)

Note: Figures are based on the most recent year for which data have been reported, which varies among countries.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
Percentage of previously treated tuberculosis cases with MDR-TB*

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* MDR-TB: multidrug-resistant tuberculosis (resistance to, at least, isoniazid and rifampicin)

Note: Figures are based on the most recent year for which data have been reported, which varies among countries.
Role of combination antiretroviral therapy (cART)
Decline in TB incidences when cART was introduced

Kirk, AJRCCM 2000; modified
Effect of cART duration on TB incidence

Incidence (event/1000 PYFU)

Months since cART initiation

Girardi, CID 2005
TB incidences following cART initiation - influence of CD4 level

- CD4 <50/mm³
- CD4 50-199/mm³
- CD4 200-349/mm³
- CD4 >350/mm³
TB incidences following cART initiation
- pronounced effect at low CD4

CD4 <50/mm$^3$

TB incidences following cART initiation - pronounced effect at low CD4

CD4 <50/mm$^3$
TB: HIV studies –
Western Europe, Argentina, Eastern Europe including ex-Soviet countries
Retrospective TB:HIV study

- 1075 consecutive HIV-patients with TB 2004-2006

Diagnosis of TB was:
- **Confirmed**: culture, PCR
- **Probable**: smear microscopy, histology
- **Presumptive**: TB therapy initiated – and not subsequently stopped because TB diagnosis was ruled out

AR N=115  EE N=582  SE N=210  CNE N=168
### Characteristics of HIV-patients with TB (2004-2006)

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<tr>
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<th>CNE n=168</th>
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<th>AR n=115</th>
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<tr>
<td><strong>Age</strong></td>
<td>30 (26-35)</td>
<td>38 (32-45)</td>
<td>38 (32-44)</td>
<td>36 (30-43)</td>
</tr>
<tr>
<td><strong>Transmission - IDU</strong></td>
<td>80.3</td>
<td>14.3</td>
<td>35.2</td>
<td>36.8</td>
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<tr>
<td><strong>HCVAb+</strong></td>
<td>45.9</td>
<td>8.9</td>
<td>25.2</td>
<td>13.0</td>
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<tr>
<td><strong>Origin (‘non-European’)</strong></td>
<td>0.5</td>
<td>60.1</td>
<td>42.9</td>
<td>9.6</td>
</tr>
<tr>
<td><strong>History of being in prison</strong></td>
<td>24.6</td>
<td>1.5</td>
<td>6.6</td>
<td>9.2</td>
</tr>
<tr>
<td><strong>Confirmed TB</strong></td>
<td>51.9</td>
<td>79.8</td>
<td>75.2</td>
<td>45.2</td>
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<td><strong>Disseminated TB</strong></td>
<td>59.7</td>
<td>51.2</td>
<td>50.0</td>
<td>48.7</td>
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<tr>
<td><strong>Rifamycin resistance</strong></td>
<td>27.8</td>
<td>2.9</td>
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<td><strong>Rifamycin, isoniazid and pyrazinamide as part of initial therapy</strong></td>
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Use of cART in HIV-patients during the 1st year after TB diagnosis

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<th>Months after TB diagnosis</th>
<th>AR</th>
<th>SE</th>
<th>CNE</th>
<th>EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>106</td>
<td>202</td>
<td>158</td>
<td>515</td>
</tr>
<tr>
<td>3</td>
<td>103</td>
<td>191</td>
<td>162</td>
<td>481</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>183</td>
<td>161</td>
<td>395</td>
</tr>
<tr>
<td>9</td>
<td>83</td>
<td>171</td>
<td>157</td>
<td>339</td>
</tr>
<tr>
<td>12</td>
<td>69</td>
<td>162</td>
<td>151</td>
<td>281</td>
</tr>
</tbody>
</table>

N under FU:
- AR: 106 103 96 83 69
- SE: 202 191 183 171 162
- CNE: 158 162 161 157 151
- EE: 515 481 395 339 281

Podlekareva, AIDS 2009
Mortality within the 1\textsuperscript{st} year after a TB diagnosis

\begin{itemize}
\item \textbf{EE:} 582, 485, 395, 339, 281
\item \textbf{CNE:} 168, 163, 161, 157, 151
\item \textbf{SE:} 210, 193, 183, 171, 162
\item \textbf{AR:} 115, 104, 96, 83, 69
\end{itemize}

Podlekareva, \textit{AIDS} 2009
Mortality rates in HIV/TB patients in Eastern Europe remain high long time after TB diagnosis

![Graph showing mortality rates over time after TB diagnosis.]

Podlekareva ERJ 2013
Causes of death in HIV-positive people with TB

<table>
<thead>
<tr>
<th>Time from TB diagnosis to death</th>
<th>EE 3-12 months</th>
<th>WEA 12 months</th>
<th>EE 12 months</th>
<th>WEA 12 months</th>
</tr>
</thead>
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<tr>
<td>TB progression</td>
<td>65</td>
<td>13</td>
<td>77</td>
<td>13</td>
</tr>
<tr>
<td>Non-TB AIDS</td>
<td>77</td>
<td>13</td>
<td>77</td>
<td>13</td>
</tr>
<tr>
<td>Non-AIDS infections</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Toxicity to anti-TB drugs</td>
<td>77</td>
<td>13</td>
<td>77</td>
<td>13</td>
</tr>
<tr>
<td>Other diseases</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>77</td>
<td>13</td>
<td>77</td>
<td>13</td>
</tr>
</tbody>
</table>

N 142 25 77 13 65 12

Podlekkareva, ERJ 2013
Prognostic factors (TB-associated death)

- Time after TB diagnosis, months:
  - < 3
  - 3 - 12
  - > 12

- CD4 cell count, cells/mm³ *:
  - > 351
  - 201 - 350
  - 101 - 200
  - 51 - 100
  - <= 50

- HIV-RNA per log10 increase*:
  - <= 50
  - 51 - 100
  - 101 - 200
  - 201 - 350
  - > 351

- IRR (95% CI):
  - 1.55 (1.13-2.14)
  - 1.89 (0.60-5.95)
  - 0.58 (0.44-0.78)
  - 2.00 (0.71-5.62)
  - 0.04 (0.02-0.08)
  - 0.12 (0.04-0.35)
  - 3.48 (2.54-4.76)
  - 0.71 (0.23-2.23)
  - 0.51 (0.34-0.77)
  - 0.14 (0.02-1.32)
  - 0.16 (0.10-0.26)
  - 0.29 (0.08-1.10)
  - 0.34 (0.26-0.45)
  - 0.45 (0.20-0.99)
  - 2.83 (1.93-4.15)
  - 1.89 (0.73-4.89)
  - 0.29 (0.22-0.40)
  - 0.32 (0.14-0.77)
  - 0.53 (0.33-0.86)
  - 1.01 (0.25-4.03)
  - 1
  - 1.03 (0.69-1.53)
  - 1.67 (0.49-5.64)
  - 1.44 (0.92-2.25)
  - 2.94 (0.86-10.06)
  - 2.86 (1.98-4.12)
  - 3.80 (1.18-12.17)
  - 1.70 (1.37-2.12)
  - 1.10 (0.81-1.49)

Podlekareva, ERJ 2013
Prognostic factors (TB-associated death)

Time after TB diagnosis, months
- < 3
- 3 - 12
- > 12

IRR (95% CI)
- 1
- 1.55 (1.13-2.14)
- 1.89 (0.60-5.95)
- 0.58 (0.44-0.78)
- 2.00 (0.71-5.62)

WEA v. EE
- IDU vs. not
  - 3.48 (2.54-4.76)
  - 0.71 (0.23-2.23)

Initial RHZ-regimen
- Rifamycin-resistance vs. not
  - 2.83 (1.93-4.15)
  - 1.89 (0.73-4.89)

Started cART or not
- CD4 cell count, cells/mm³
  - > 351
    - 0.53 (0.33-0.86)
    - 1.01 (0.25-4.03)
  - 201 - 350
    - 1.03 (0.69-1.53)
    - 1.67 (0.49-5.64)
  - 101 - 200
    - 1.44 (0.92-2.25)
    - 2.94 (0.86-10.06)
  - 51 - 100
    - 2.86 (1.98-4.12)
    - 3.80 (1.18-12.17)

CD4 count <50 cells/mm³
- HIV-RNA per log10 increase*
  - 1.70 (1.37-2.12)
  - 1.10 (0.81-1.49)

Podlekareva, ERJ 2013
Mortality according to presence of resistance in 144 patients from Eastern Europe

Post and Miro, under review

<table>
<thead>
<tr>
<th>Time from baseline (Years)</th>
<th>RH-susceptible TB</th>
<th>MDR TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(67)</td>
<td>(29)</td>
</tr>
<tr>
<td>1</td>
<td>(49)</td>
<td>(26)</td>
</tr>
<tr>
<td>2</td>
<td>(30)</td>
<td>(14)</td>
</tr>
<tr>
<td>3</td>
<td>(16)</td>
<td>(6)</td>
</tr>
</tbody>
</table>

P<0.01
Reported health system organisation and integration of care aspects – a survey

- HIV and TB services at the same hospital: 100% in Eastern Europe, 90% in Western Europe (p<0.001)
- HIV and TB treated by the same doctor: 55% in Eastern Europe, 55% in Western Europe (p<0.001)
- TB treatment follow-up at the same clinic: 37% in Eastern Europe, 100% in Western Europe (p<0.001)
- All TB pts offered an HIV test: 90% in Eastern Europe, 90% in Western Europe (p=1.000)
- HIV pts regularly screened for TB: 82% in Eastern Europe, 40% in Western Europe (p=0.018)
- HIV/TB pts OST available: 100% in Eastern Europe, 55% in Western Europe (p<0.001)

M Mansfeld, 14th European AIDS Conference 2013
Summary

• Despite marked overall improvements over the last decade, TB- and HIV coinfection remain a substantial problem in Europe
• TB patients need to be tested for HIV!
• The situation in Eastern Europe is of special concern:
  - HIV and TB care need to be better integrated
  - OST programmes often not available
  - High level of MDR-TB
  - Poor outcome in HIV-positive patients with a TB diagnosis
  - Concern of increasing TB rates in Eastern Europe, if severe immune deficiency develops (i.e. HIV-infections should be diagnosed and cART initiated timely)
  - PLEASE NOTE: heterogeneous region
Future

• Continued need for research to gain a better understanding of the disease and improve treatment efficacy (regimen, duration etc)

• Ongoing prospective TB:HIV study within EuroCoord
  • The aim is to explore the regional differences across Europe and the factors associated with these differences
  • Currently approximately 1300 coinfected patients enrolled
Acknowledgements

TB:HIV study group:

Steering Committee: M. Bruyand, J. Caylá, D. Duiculesku, H. Furrer, E. Girardi, M. H. Losso, J.D. Lundgren, R. Miller, J.M. Miro, N. Obel, A. Panteleev (Co-Chair), F. Post (Co-Chair), A. Skrahin, J. J. Toibaro

Statistical centre: L Shepherd, A Mocroft

Coordinating centre: D Podlekareva, AM Werlinrud Efsen, M Mansfeld, B Aagaard, BR Nielsen, AH Fisher, D Raben, RS Brandt, O Kirk

Funding: EuroCOORD, EU 7th framework programme,
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Thank you!