Causes of death in HIV-infected patients with active TB disease


EACS 2011, Belgrade Serbia
14th October 2011
HIV/TB collaborative project

• Consecutive HIV-patients with tuberculosis (TB) between 1/2004 and 12/2006 (N=1078)
• Laboratory confirmed and presumptive TB diagnosis
• Recurrence of TB - either relapse of the same TB case or re-infection with *mycobacterium tuberculosis* after treatment for original TB case has been completed

• Collaboration of HIV and TB clinicians from:
  – Western Europe and Argentina (WEA) Denmark, France, Italy, Spain, Switzerland and the United Kingdom
  – Eastern Europe (EE): Belarus, Latvia, Romania, Russia and Ukraine
A 3-fold higher one-year mortality risk in patients from Eastern Europe (EE) compared with patients from Western Europe and Argentina (WEA)\textsuperscript{1}

\textsuperscript{1}AIDS 2009, 23:2485–2495
Background

In 2009 - 2010: additional data collection and extended follow-up

A 3-fold higher one-year mortality risk in patients from Eastern Europe (EE) compared with patients from Western Europe and Argentina (WEA)\(^1\)

\(^1\)AIDS 2009, 23:2485–2495
Objectives

• To assess and compare:
  – Mortality rates and causes of death
  – Risk factors for TB-related death
in HIV/TB patients across EE and WEA in order to identify targets for improved patient management
Methods

- Crude mortality rates stratified by time after TB diagnosis: <3 months, 3-12 months, >12 months (per 100 person years of follow-up (PYFU))
- Deaths were categorised as being directly related or unrelated to TB
- Poisson regression was used to identify factors associated with TB related death
- The Coding of Death in HIV (CoDe) procedure used to ascertain immediate and underlying COD\(^1\)
  - Information on COD collected on CoDe Case Report Forms
- Immediate COD - endpoint for the present analysis (disease/condition directly leading to death)

\(^1\)Kowalska et al Epidemiology 2011
## HIV/TB study cohort

<table>
<thead>
<tr>
<th></th>
<th>EE</th>
<th>WEA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>585</td>
<td>493</td>
<td></td>
</tr>
<tr>
<td>TB culture confirmed, %</td>
<td>55</td>
<td>67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TB recurrence, %</td>
<td>14</td>
<td>4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death %</td>
<td>49</td>
<td>13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- TB-related death %</td>
<td>76</td>
<td>37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% of deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to death (IQR) [Months]</td>
<td>8.7 (2.5 - 19.5)</td>
<td>5.1 (1.6 - 13.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>No data beyond 1 year</td>
<td>222 (38.0%)</td>
<td>81 (16.4%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Baseline characteristics of HIV/TB patients

<table>
<thead>
<tr>
<th></th>
<th>EE Dead N=284</th>
<th>EE Alive N=301</th>
<th>WEA Dead N=63</th>
<th>WEA Alive N=430</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: male, %</td>
<td>77</td>
<td>66</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>Origin: same as centre, %</td>
<td>94</td>
<td>97</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>HCV positive, %</td>
<td>49</td>
<td>43</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>TB risk factor: IDU, %</td>
<td>79</td>
<td>65</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>R-resistance, %</td>
<td>52</td>
<td>18</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>RHZ-based therapy, %</td>
<td>37</td>
<td>53</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>Expulm/diss TB, %</td>
<td>72</td>
<td>56</td>
<td>68</td>
<td>66</td>
</tr>
<tr>
<td>On cART at TB, % of HIV+</td>
<td>11</td>
<td>23</td>
<td>63</td>
<td>52</td>
</tr>
<tr>
<td>CD4 count, median (IQR)</td>
<td>148</td>
<td>311</td>
<td>86</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>(59-322)</td>
<td>(143-514)</td>
<td>(28-200)</td>
<td>(55-289)</td>
</tr>
</tbody>
</table>

R-rifamycin, H – isoniazid, Z – pyrazinamide
The crude mortality rate in HIV/TB patients stratified by time from TB diagnosis

<table>
<thead>
<tr>
<th>Time from TB Diagnosis</th>
<th>Crude Incidence Rate per 100 PYFU (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3 months</td>
<td>61.4 (95% CI)</td>
</tr>
<tr>
<td>3-12 months</td>
<td>18.6 (95% CI)</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>17.4 (95% CI)</td>
</tr>
</tbody>
</table>

N under FU
- EE: 585
- WEA: 493

N deaths
- EE: 81
- WEA: 22

p < 0.0001
Causes of death among HIV/TB patients according to the time of death

**TB-related death**
- Initial TB case
- Non-TB AIDS
- TB recurrence
- Non-AIDS infections
- Hepatitis B and C
- Toxicity to anti-TB drugs
- Other diseases
- Unknown

**Time from TB diagnosis to death**
- < 3 months
- 3-12 months
- > 12 months

**N with CoDe form**
- 80
- 18
- 79
- 16
- 114
- 13

*Copenhagen HIV Programme*
Causes of death among HIV/TB patients according to the time of death

- Initial TB case
- Hepatitis B and C
- Non-TB AIDS
- Non-TB infections
- Other diseases
- Unknown
- Toxicity to anti-TB drugs

Time from TB diagnosis to death:
- < 3 months
- 3-12 months
- > 12 months

N with CoDe form:
- EE: 80, 18
- WEA: 79, 16
- Total: 114, 13

COPENHAGEN HIV PROGRAMME
Causes of death among HIV/TB patients according to the time of death

Time from TB diagnosis to death

- Initial TB case
- Hepatitis B and C
- Non-TB AIDS
- Non-AIDS infections
- Toxicity to anti-TB drugs
- TB recurrence
- TB-related death
- Other diseases

<table>
<thead>
<tr>
<th>Time from TB diagnosis to death</th>
<th>EE</th>
<th>WEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td>80</td>
<td>18</td>
</tr>
<tr>
<td>3-12 months</td>
<td>79</td>
<td>16</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>114</td>
<td>13</td>
</tr>
</tbody>
</table>

COPENHAGEN HIV PROGRAMME
Incidence rate ratios (IRR) for TB related death

- WEA vs EE
- IDU vs. not
- HCVpos vs. neg
- Started cART vs. not*
- Initial RHZ-treatment
- Rifamycin-resistance vs. not
- CD4 cell count per 100 cells* increase
- HIV-RNA per log10 increase*

* Time updated

Univariable Multivariable
Incidence rate ratios (IRR) for TB related death

### Variables
- IDU vs. not
- WEA vs EE
- HCVpos vs. neg
- Started cART vs. not*
- Initial RHZ-treatment
- Rifamycin-resistance vs. not
- CD4 cell count per 100 cells* increase
- HIV-RNA per log10 increase*

### Results

#### Univariable

<table>
<thead>
<tr>
<th>Variable</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDU vs. not</td>
<td>0.15 (0.06-0.39)</td>
</tr>
<tr>
<td>WEA vs EE</td>
<td>0.05 (0.03-0.09)</td>
</tr>
<tr>
<td>HCVpos vs. neg</td>
<td>0.30 (0.22-0.42)</td>
</tr>
<tr>
<td>Started cART vs. not*</td>
<td>0.42 (0.19-0.93)</td>
</tr>
<tr>
<td>Initial RHZ-treatment</td>
<td>0.34 (0.25-0.45)</td>
</tr>
<tr>
<td>Rifamycin-resistance vs. not</td>
<td>3.69 (2.66-5.12)</td>
</tr>
<tr>
<td>CD4 cell count per 100 cells*</td>
<td>1.97 (0.82-4.71)</td>
</tr>
<tr>
<td>HIV-RNA per log10 increase*</td>
<td></td>
</tr>
</tbody>
</table>

#### Multivariable

<table>
<thead>
<tr>
<th>Variable</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDU vs. not</td>
<td></td>
</tr>
<tr>
<td>WEA vs EE</td>
<td></td>
</tr>
<tr>
<td>HCVpos vs. neg</td>
<td></td>
</tr>
<tr>
<td>Started cART vs. not*</td>
<td></td>
</tr>
<tr>
<td>Initial RHZ-treatment</td>
<td></td>
</tr>
<tr>
<td>Rifamycin-resistance vs. not</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count per 100 cells*</td>
<td></td>
</tr>
<tr>
<td>HIV-RNA per log10 increase*</td>
<td></td>
</tr>
</tbody>
</table>

* Time updated
Strengths and limitations

• Large cohort of HIV/TB patients from across Europe and Argentina
• Follow-up at least 2 years after TB diagnosis
• Detailed information on causes of death (including autopsy reports)
• CoDe procedure applied

• Higher rate of LTFU in Eastern Europe compared to Western Europe and Argentina
• Retrospective data collection
Summary

- Persistently higher mortality rates observed in HIV/TB patients in Eastern Europe
  - Low proportion with culture confirmed TB
- TB remained the dominant cause of death in Eastern Europe - even after 12 months of TB diagnosis
  - Low usage of RHZ-based anti-TB treatment and cART
- Initiation of a standard anti-TB treatment and cART were significantly associated with reduced incidence of TB-related death
Implications

- Target interventions to optimise management of HIV/TB patients and limit TB-mortality in Eastern Europe should include:
  - Improved diagnostic procedures for TB and resistance testing
  - Adequate treatment regimens
    - RHZ-based initial treatment subsequently adjusted according to the resistance patterns
  - Widespread use of cART
- Prospective TB:HIV study is currently recruiting patients and aims to address issues outlined above
The HIV/TB Collaboration Study Group

(principal investigator/ representing person):

Argentina (MH Losso) Buenos Aires; Belarus Minsk (I Karpov), Gomel (V Mitsura), Svetlogorsk (O Suetnov); Denmark (N Obel) Danish HIV Cohort; France (M Bruyand) Aquitaine Cohort; Italy Brescia (A Matteeli); Bergamo (F Maggiolo); Modena (C Mussini); Rome (E Girardi); ICONA cohort (E Girardi); Latvia (V Riekstina) Riga; Romania (D Duiculescu) Bucharest; Russia St Petersburg (A Panteleev & A Rakhmanova); Novgorod the Great (S Buzunova); Spain (JM Miro) Barcelona; Switzerland (H Furrer) Swiss HIV Cohort; United Kingdom London (F Post & R Miller); Ukraine (N Chentsova) Kiev; EuroSIDA cohort (JD Lundgren)

Coordinating centre (CHIP) D Podlekareva, AM Werlinrud, D Grint, A Mocroft, J Kjær, M Ellefson, O Kirk