INTEGRATED DOTS/ DOTS PLUS IN LATVIA

Associated professor, Vaira Leimane
WHO International Training Centre on Treatment and Management of MDR-TB
First DOTS Plus Consultants course 9-15 May, Riga, Latvia
BACKGROUND: TB IN LATVIA

- Independent Baltic state since 1991
- DOTS implemented countywide in 1996
- MDR-TB management started in 1997
- Latvia consistently ranked among countries with highest rates of MDR TB worldwide
PRESENTATION OUTLINE

- EPIDEMIOLOGICAL SITUATION
- IMPLEMENTATION TB/MDR TB CONTROL PROGRAMS
- PROGRESS AND RESULTS IN TB CONTROL
Primary and Acquired MDR TB Incidence Rates, 1994-2005

Since 1998 the total number of annually registered MDR TB cases decreased 2.2 times, for previously treated cases 4.4 times.
Proportion of Extensively Resistant Patients According to Patterns of Resistance

![Graph showing the proportion of extensively resistant patients over time, with MDR-TB+3 SLD and MDR-TB+INJ+FQ compared. The chi-square test for trend is 12.4, P < 0.001.](image-url)
XDR-TB (MDR-TB+INJ+FQ) Among 3 Patient Categories
Number of TB/HIV Patients (Including Prisoners), 1994-2004

- Total
- MDR-TB/HIV
National TB Program (Financed by Government) within the Health Care reform

- Well functioning DOTS program with additional treatment of MDR TB (within resources available)
- Collaboration and coordination between community, local governments, social services and international agencies
- Established centralized procurement and distribution of all anti-tuberculosis drugs
TB and MDR-TB Control in Latvia

Includes

Civil sector

Prison sector
NATIONAL TB CONTROL PROGRAM

Accepted first NTP, based on WHO-recommended DOTS strategy ALL FIVE ELEMENTS in 1995

Treatment of MDR TB patients in 1997

Established drug resistance surveillance 1997
DOTS PLUS IMPLEMENTATION

- DOTS-plus project accepted by WHO Green Light Committee in January **2001**
  - Approval for 350 patients for drugs
  - Full coverage with treatment

- Center of Excellence founded in **2000**
  - International training centre for treatment and management for MDR TB
  - First training course in **January 2001**

- Established MDR-TB database, data management, and information system **2002 -2003**
STRUCTURE OF DOTS-PLUS PROGRAM

EXPERT CONSILIUM

- TREATING PHYSICIANS
- PHARMACY
- LABORATORY
- TB/MDR TB REGISTRY
- AMBULATORY TREATMENT
- SUPERVISION BOARD OF EXPERTS

- NURSES
- HOSPITALS
- SOCIAL WORKERS

SPECIALIZED DIVISIONS

- PHARMACY
- LABORATORY
- TB/MDR TB REGISTRY

- AMBULATORY TREATMENT
- SUPERVISION BOARD OF EXPERTS

EXPERT CONSILIUM
Proficiency testing were provided once for OF and other second line drugs
USE OF LABORATORY DIAGNOSTIC METHODS FOR DST

- **DST** provide for all cc+ patients on L/J – absolute concentration method

- **BACTEC/MIGIT**
  - Priority I - for high MDR-TB risk patient SS (+)
  - Priority II – all SS+ cases for better infection control purposes

- **INNO Lipa test** – from direct specimen for SS+ high risk for MDR-TB patients
DST for MDR-TB treatment management

- DST to second line drugs perform when DST to I line drugs shows MDR-TB

- Repeat DST to I line drugs from specimen obtained before start of MDR-TB Tx to detect resistance amplification during Tx with I line drugs

- During MDR-TB treatment DST repeat if conversion not achieved after 4-6 months of treatment
MDR TB REPORTING AND RECORDING

CENTRAL LAB.  
All DST RESULTS

TB REGISTRY

MDR TB REGISTRY

Consilium
Enrollment in MDR TB cohort

District TB doctor
Enrollment form
Follow-up form
### SECOND LINE DRUGS USED AND DST

<table>
<thead>
<tr>
<th>DST available</th>
<th>DST available</th>
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<tbody>
<tr>
<td>• Aminoglycoside</td>
<td>• Prothionamide</td>
</tr>
<tr>
<td>• Streptomycine</td>
<td>• Cycloserine, Terzindon</td>
</tr>
<tr>
<td>• Kanamycine</td>
<td>• Para-aminosalicylic Acid</td>
</tr>
<tr>
<td>• Capreomycine</td>
<td>• Thiacethasone</td>
</tr>
<tr>
<td>• Ofloxacin, Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>DST not available:</td>
<td></td>
</tr>
<tr>
<td>Clarithromycine; Amoxicillin/Clavulanate;</td>
<td></td>
</tr>
</tbody>
</table>
RESISTANCE TO INDIVIDUAL DRUGS (%) 2003-2005
MDR-TB Treatment Strategy - I

✓ ETR based on DST to I line drugs until DST to 2nd line drugs becomes available

✓ Use 5-7 most powerful drugs available

✓ ITR based on DST to II and II line drugs

✓ Injectables drug use

✓ Daily until culture conversion confirmed

✓ Continue at least 6 months after culture conversion

✓ Use 12 month if TX regimen contains only 4 drugs

✓ Use entire course of TX if extensive lung damage and/or week TX regimen
MDR-TB Treatment Strategy II

- Four oral drugs with preliminary susceptibility if possible, continue until completion of treatment
- Treatment duration after culture conversion
  - 12 – 18 months
- Treatment in hospital until culture conversion
- Ambulatory treatment DOT 5-6 times per week
TREATMENT CHARACTERISTICS

- 107 distinct regimens
- Median treatment duration: 18 months (1 – 38 mos)
- Median of 6 drugs used (range 3 - 8) for 3 months or more
  - Most common were ofloxacin, prothionamide, thiacetazone, pyrazinamide, ethambutol
- Use of injectable drugs
  - kanamycin, capreomycin, streptomycin
  - Median duration of use 12 months
  - Range of use 1-36 months
  - After culture conversion, median 9 months of use
- Defaulting patients with median treatment time of 7 months (range 2 – 16)
Initial sputum culture conversion in 129 patients of 167 culture positive patients who had culture conversion

15% (37) patients had negative culture at Tx start

2 May 2006, Annals of Internal Medicine, Vol 144 N6; 650-670;
Duration of Treatment for Good Outcomes - 135

- Median 20 months
- Range 12-36 months

Treatment duration

- After culture conversion - Median 18 months, range 12-28
- No adherent defaulted after median 7, ranged 2-16 m.
TREATMENT OUTCOMES STRATIFIED BY RESISTANCE PATTERNS 2000-2003, 820 PATIENTS

Cure  Complheation  Death  Default  Failed  Continue Tx  HIV+

HREZ MDR-TB All

HR+3SLD

HR+INJ+FQ

# RISK FACTORS FOR POOR OUTCOME AMONG 172 ADHERENT PATIENTS

Cox Proportional-Hazards Multivariate Regression Model*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.9 (0.4-2.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Female</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Age over 40</td>
<td>1.4 (0.7-2.6)</td>
<td>0.31</td>
</tr>
<tr>
<td>Less than 40</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Low body-mass index &lt;18.5</td>
<td>2.3 (1.1-4.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;18.5</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Resistance to ofloxacin No</td>
<td>2.6 (1.2-5.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Resistance to ofloxacin Yes</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Category of MDR TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 previously treated for MDR-TB</td>
<td>5.7 (1.9-16.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>2 previously treated for TB</td>
<td>1.9 (0.7-5.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>1 never treated for TB</td>
<td>Ref.</td>
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</tbody>
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### RISK FACTORS FOR FASTER TIME TO CULTURE CONVERSION

**Weibull Proportional-Hazards Multivariate Regression Model***

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity to ofloxacin</td>
<td>6.1</td>
<td>3.2 - 11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sensitivity to PZA</td>
<td>1.9</td>
<td>1.3 – 2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>No history of heavy alcohol use</td>
<td>1.5</td>
<td>1.1 – 2.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Use of streptomycin in final regimen</td>
<td>2.1</td>
<td>1.1 – 4.4</td>
<td>0.048</td>
</tr>
</tbody>
</table>

*n=168. Those starting culture-negative were excluded.*

In addition severity of disease – X-ray cavities, bacillary load, with low BMI – converts more slowly

*Lancet January 2005, Vol 365, 318-26*
THE IMPACT OF MDR-TB MANAGEMENT ON CASE DETECTION RATE 1991-2005

Source: Latvian National TB Control Program, published Eurosurveillance, March 2006
### Yearly Cumulative Data on MDR-TB (01.01.2004)

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<tbody>
<tr>
<td>2002</td>
<td>181 (23%)</td>
<td>348 (44%)</td>
<td>101 (13%)</td>
<td>64 (8%)</td>
<td>101 (13%)</td>
</tr>
<tr>
<td>2004</td>
<td>156 (24%)</td>
<td>303 (46%)</td>
<td>85 (13%)</td>
<td>51 (8%)</td>
<td>67 (10%)</td>
</tr>
</tbody>
</table>

(59 of TB)
Conclusions

- Acquired MDR-TB is decreasing in Latvia
- 2/3 of patients who started treatment in DOTS plus was cured
- Addressing treatment default could improve DOTS Plus program effectiveness
- XDR-TB is increasing, particularly for patients who has been treated with II line drugs before
- Cure rate of XDR –TB decrease to 28% for patients with XDR =INJ+ FQ comparatively 58% XDR = MDR + 3SLD and 66% for All MDR-TB
CHALLENGES TO PREVENT AND CONTROL DR-TB IN LATVIA

- Strengthening DOTS, improving Tx outcomes for drug sensitive cases
- Rapid diagnosis of MDR-TB and isolation
- MDR-TB in children
  - Contact investigation
- Treatment defaults and interruptions
  - Improving compliance
  - Compulsory treatment
- Infection control
  - In health care settings
  - Isolation of patients on palliative care
- Genotyping to detect chain of transmission is the next steps to improve MDR TB control in Latvia
- New drugs and treatment regimens
- HIV/AIDS and MDR-TB