[Are we ready to try the] Short(er) Course Regimen for MDR TB?

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(Many slides courtesy Charles Daley)
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Curry CTCA Course

Short(er) Course Regimen for MDR-TB

Outline
- Current treatment approach
- Short course regimen
- Implications for high-resource, low incidence areas like California
- Barriers to implementation

New Grouping of MDR-TB Drugs

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone</td>
<td>Second-line</td>
<td>Other Core</td>
<td>Add-on agents</td>
</tr>
<tr>
<td></td>
<td>injectable</td>
<td>Core</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Amikacin</td>
<td>Ethionamide/Prothionamide</td>
<td>D1: Pyrazinamide Ethambutol</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Capreomycin</td>
<td>Cycloserine/Thioacetazone</td>
<td>High-dose INH</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>Kanamycin</td>
<td>Ethambutol</td>
<td>D2: Bedaquiline</td>
</tr>
<tr>
<td></td>
<td>(Streptomycin)</td>
<td></td>
<td>Delamanid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D3: P-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Imipenem/meropenem</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amoxicillin/Clavulanate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Thiaacetazone)</td>
</tr>
</tbody>
</table>
Building a Treatment Regimen with 2016 Update

Step 1 Group A (one)
- Levofloxacin
- Moxifloxacin
- Gatifloxacin

Step 2 Group B (one)
- Kanamycin
- Amikacin
- Capreomycin

Step 3 Group C (two)
- Ethionamide/Prothionamide
- Clofazimine
- Cycloserine/Terizidone
- Linezolid

Step 4 Group D1
- Pyrazinamide (include)
- Ethambutol*
- High-dose INH*

Group D2
- Bedaquiline
- Delamanid

Group D3
- Imipenem/Meropenem
- Amoxicillin/Clavulanate
- P-aminosalicylic acid

≥5 likely effective including 4 core drugs, PZA and consider*

Treatment of MDR-TB

Duration of Therapy

- An intensive phase of at least 8 months’ duration is recommended
  (conditional recommendation, very low quality of evidence)

- A total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment
  (conditional recommendation, very low quality of evidence)

WHO 2011 Update

Treatment Outcomes in Patients with MDR-TB, 2007-2012 Cohorts

WHO, Global Tuberculosis Report 2015
Short Course Standardized Regimen for MDR-TB

4(+KCGEHZP/5 GEZC

Completion – 5.3%  Death – 5.3%
Cure – 82.5%  Default – 5.8%
Success – 87.8%  Failure – 0.5%
Relapse – 0.5%


Countries Using Short(er) Course MDR-TB Regimen

Countries using the shorter MDR-TB regimen
(in addition, Ethiopia, South Africa, Viet Nam and Mongolia are participating in the clinical trial)
# Short Course Standardized Regimen for MDR-TB

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intensive</th>
<th>Continuation</th>
<th>Number</th>
<th>Cum. %</th>
<th>Treatment Success %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3EOHZP</td>
<td>12 OEHZP</td>
<td>59</td>
<td>13.8</td>
<td>68.9</td>
</tr>
<tr>
<td>2</td>
<td>3(+)KCOEHZP</td>
<td>12 OEHZP</td>
<td>44</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3(4)KCOE2P</td>
<td>12 O2E2P</td>
<td>35</td>
<td>8.2</td>
<td>57.1</td>
</tr>
<tr>
<td>4</td>
<td>3(+)KCOEHZP</td>
<td>12 OHEZ</td>
<td>45</td>
<td>10.5</td>
<td>66.7</td>
</tr>
<tr>
<td>5</td>
<td>3(+)KCOEHZP</td>
<td>12 OHEZC</td>
<td>38</td>
<td>8.9</td>
<td>84.2</td>
</tr>
<tr>
<td>6</td>
<td>4(+)KCGEHZP</td>
<td>5 GEZC</td>
<td>206</td>
<td>48.2</td>
<td>87.8</td>
</tr>
</tbody>
</table>

C = clofazimine, E = ethambutol, G = gatifloxacin, H = isoniazid, K = kanamycin, O = ofloxacin, P = prothionamide, Z = pyrazinamide

3(4) = minimum of 3 mos, prolonged to 4 months if no conversion by end of 3 mos
3(+) = minimum of 3 mos, prolonged until conversion achieved
4(+) = minimum of 4 mos, prolonged until conversion achieved


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# Short Course Standardized Regimen for MDR-TB

![Chart](Larger image on previous page)

Completion – 5.3%
Cure – 82.5%
Success – 87.8%
Death – 5.3%
Default – 5.8%
Failure – 0.5%
Relapse – 0.5%


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# Countries Using Short(er) Course MDR-TB Regimen

![Map](Larger image on previous page)

Countries using the shorter MDR-TB regimens are participating in the clinical trial.
WHO Policy Recommendation
Shorter Course MDR-TB Regimen

Recommendation:
In patients with RR or MDR-TB
• who have not been treated with second-line drugs and
• in whom resistance to FQNs and SLI agents has been excluded or is considered to be highly unlikely
a shorter MDR-TB regimen of 9-12 mos may be used instead of a conventional regimen (conditional recommendation, very low certainty in the evidence)

WHO 2016 Update

Short(er) Course Regimen for MDR-TB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Phase (7 drugs)</th>
<th>Continuation Phase (4 drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin*</td>
<td>0 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>600 mg</td>
<td>1200 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>100 mg</td>
<td>2000 mg</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>100 mg</td>
<td>2000 mg</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>100 mg</td>
<td>2000 mg</td>
</tr>
<tr>
<td>Isoniazid*</td>
<td>100 mg</td>
<td>2000 mg</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>10 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

*High dose

WHO Guideline Drug Doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than 30 kg</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>800 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Isoniazid*</td>
<td>300 mg</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>250 mg</td>
</tr>
<tr>
<td>Kanamycin†</td>
<td>15 mg per kilogram body weight (maximum 1 g)</td>
</tr>
</tbody>
</table>

†For adults over 59 years of age, the dose will be reduced to 10 mg/kg (max dose 750 mg).


Short-Course Therapy for MDR-TB
Choosing the MDR-TB Regimen

CRITERIA: Do any of the following apply?

- Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- Pregnancy
- Extrapulmonary disease
- At least one medicine in the shorter MDR-TB regimen not available in the programme

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**NO**

- Shorter MDR-TB regimen
  - Intensive phase
    - Duration: 4-6 months
    - Composition: 4 second-line drugs
  - Continuation phase
    - Duration: 5 months
    - Composition: 2 second-line drugs

*Supported by selected first-line TB drugs*

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**YES**

- Individualised ("conventional") MDR/RR-TB regimens
  - Intensive phase
    - Duration: Up to 8 months
    - Composition: 4 or more second-line drugs
  - Continuation phase
    - Duration: 12 months or more
    - Composition: 3 or more second-line drugs

*Supported by selected first-line TB drugs*
Choosing the MDR-TB Regimen

CRITERIA: Do any of the following apply?
- Confirmed resistance or suspected indifference to a medicine in the shorter MDR-TB regimen (except second line agents)
- Exposure to ≥ 3 second-line medicines to the shorter MDR-TB regimen for ≥ 3 months
- Maintenance of ≥ 3 medicines in the shorter MDR-TB regimen or risk factors (e.g., drug-drug interactions, pregnancy, extrapulmonary disease, All-tright use of medicine in the shorter MDR-TB regimen not available in the program)

Shorter MDR-TB regimen

Indolent ("conventional") MDR-TB regimen

Treatment Success*

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>Shorter MDR-TB Regimen (N=1116)</th>
<th>Conventional MDR-TB Regimen (N=5850)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>90.3%</td>
<td>78.3%</td>
</tr>
<tr>
<td>PZA susceptible; FQN susceptible</td>
<td>98.8%</td>
<td>88.8%</td>
</tr>
<tr>
<td>PZA resistant; FQN susceptible</td>
<td>88.8%</td>
<td>88.8%</td>
</tr>
<tr>
<td>PZA susceptible; FQN resistant</td>
<td>80.0%</td>
<td>80.0%</td>
</tr>
<tr>
<td>PZA resistant; FQN resistant</td>
<td>67.9%</td>
<td>67.9%</td>
</tr>
</tbody>
</table>

*Treatment success – cure or completed

WHO 2016 Update

Studies Analyzed for WHO Guideline

http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-webannexes-eng.pdf?ua=1

<table>
<thead>
<tr>
<th>Status</th>
<th>Published</th>
<th>Published</th>
<th>Published</th>
<th>Ongoing</th>
<th>Ongoing</th>
<th>Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data on Relapse 2 yrs p Rx?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Eligible</td>
<td>640</td>
<td>124</td>
<td>323</td>
<td>NR</td>
<td>1169</td>
<td>114</td>
</tr>
<tr>
<td>MDR or Rif-confirmed</td>
<td>527*</td>
<td>97*</td>
<td>237*</td>
<td>117*</td>
<td>1169**</td>
<td>76*</td>
</tr>
<tr>
<td>Excluded</td>
<td>34 (6.4%)</td>
<td>32 (33.0%)</td>
<td>87 (36.7%)</td>
<td>52 (44.4%)D</td>
<td>761 (65.1%)D</td>
<td>52 (68.4%)O</td>
</tr>
<tr>
<td>Included</td>
<td>493 (93.5%)</td>
<td>65 (67.0%)</td>
<td>150 (63.3%)</td>
<td>65 (55.6%)</td>
<td>408 (34.9%)</td>
<td>24 (31.5%)</td>
</tr>
</tbody>
</table>

*** 409/761 never initiated short regimen; 65 with prior exposure to second-line drugs; 1 with XDR-TB; 112 lost prior to initiation; 34 died prior to initiation; 197 other.
D Majority of exclusions were accounted for by participants in whom short MDR-TB treatment was ongoing, or had ended recently: Uzbekistan, 39/32, Swaziland, 47/32.
### Extent of Disease

![Extent of Disease Diagram](http://apps.who.int/iris/bitstream/10665/250125/5/9789241549639-webannexes-eng.pdf?ua=1)

### PZA and EMB Resistance

![PZA and EMB Resistance Diagram](http://apps.who.int/iris/bitstream/10665/250125/5/9789241549639-webannexes-eng.pdf?ua=1)

### Eligibility For Short-course Regimen for MDR-TB in Europe

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Drug Resistance in MDR-TB (%)</th>
<th>Eligible for Short-Course Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>SLID</td>
</tr>
<tr>
<td>Austria</td>
<td>80</td>
<td>41</td>
</tr>
<tr>
<td>France</td>
<td>114</td>
<td>30</td>
</tr>
<tr>
<td>Germany</td>
<td>70</td>
<td>23</td>
</tr>
<tr>
<td>Portugal</td>
<td>200</td>
<td>51</td>
</tr>
<tr>
<td>TBoNet</td>
<td>148</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>612</td>
<td>37</td>
</tr>
</tbody>
</table>

*16 countries in Europe

Lange C, et al. AJRCCM 2016;194:1029
Projected Incidence of MDR-TB with Different Regimens

Assumptions: Short-course regimen would double treatment access and achieve long-term efficacy seen in cohort studies

Projected Incidence of MDR-TB with Different Regimens

Assumptions: 30% of MDR-TB case ineligible

Projected Incidence of MDR-TB with Different Regimens

Assumptions: Short-course regimen would double treatment access and achieve long-term efficacy seen in cohort studies

![Graph showing projected incidence of MDR-TB with different regimens.]


Projected Incidence of MDR-TB with Different Regimens

Assumptions: 30% of MDR-TB case ineligible

![Graph showing projected incidence of MDR-TB with different regimens.]


Barriers to Implementing

- Clofazimine availability
- Full DST info → few qualify by strict criteria
- How to substitute for adverse events or resistance
- Disbelief in regimen – “Why does it work?”
Global Barriers to Implementation of Shorter Course MDR-TB Regimen

• Laboratory
  – Availability of SL-LPA
  – Availability of phenotypic DST

• Drugs
  – Availability of clofazimine
  – Lack of pediatric formulations of clofazimine
  – Avoiding stock-outs of drugs

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