Patient-centered approach in MDR-TB care

Tauhid Islam, MD, MPH
WHO/WPRO/STB
Outline

• Drug resistant TB: Current status
• Model of care
• New drugs and regimen
• Our role
March 24, 1882, Berlin Physiological Society

“In the future the fight against this terrible plague of mankind will deal no longer with an undetermined something, but with a tangible parasite, whose living conditions are for the most part known and can be investigated further.”

[Image: Photograph of an elderly man with a white beard and mustache, wearing a suit and bow tie. Image of microscopic bacteria.]
• 1943 — **Streptomycin** isolated in laboratory of Selman Waxman
• 1944 — Shown to be active against *Mycobacterium tuberculosis*
• 1944 — Given to the first human TB patient in November 1944
Other TB drugs:

1948 — para-aminosalicylic acid (PAS)
1948 — thioacetazone
1951 — isonicotinic hydrazide (INH)
1952 — pyrazinamide
1952 — cycloserine
1957 — rifampin
1962 — ethambutol

2012 --- Bedaquiline
2013 ---- Delaminid
Drug resistance: a surprise?

1942 — Rene Dubos — hypothesized that “selection” would occur with the use of antibiotics

1943 — Salvador Luria and Max Delbruck — demonstrated that random genetic mutations occur even in the absence of selection
• Resistant to individual drugs arise by spontaneous point mutation (@one in $10^6$ to $10^8$)
• Drug resistance emerged with each new drug used
• Less drug resistance was observed when drugs were used in combination
• Inadequate or poorly administered treatment allows for selection of a drug resistant strain to become dominant
• Resistant strains from patients retained their ability to be transmitted to others
History

• Basic principles of TB treatment:
  – Safest, most effective therapy in the shortest time
  – Multiple drugs
  – Direct observation

• DOTS and WHO
  – 1993- declaration as global emergency (127 countries adopted DOTS within 3 years)

• DOTS Plus
  – 1999

• PMDT

• 62nd WHA in 2009
  – Resolution on MDR-TB
  – Urged all Member States to achieve universal access for Dx and Tx of MDR-TB
DRUG RESISTANT TB: CURRENT STATUS
MDR-TB a public health crisis
An ancient and evergreen disease

Approximately 2 billions are infected

12 million prevalent TB cases

680,000 prevalent MDR-TB cases
Why major challenge?

- Even if most TB patients in the world are not drug-resistant (5% of total TB burden), the burden of MDR-TB in the world poses a formidable challenge to the prospect of controlling TB.

- Drug susceptible strain may be replaced by drug resistant strain.
- Highly lethal in HIV populations (80-98% case fatality reported), overall treatment success rate less than 50%.
- Complicated long treatment.
- Catastrophic expenditure (200-400 times costly than drug susceptible TB).
- Huge burden on existing human resource and technical capacity.

ACT NOW!
The epidemic: MDR-TB, 2012

~ 300,000 MDR-TB cases among notified pulmonary TB patients

~ 450,000 incident cases
~ 680,000 prevalent cases

80% in 12 countries
2/3 in top 5
56% in top 3
## Estimated % of TB cases that have MDR-TB

<table>
<thead>
<tr>
<th></th>
<th>Est % of new TB cases with MDR-TB</th>
<th>Confidence interval</th>
<th>Est % of retx TB cases with MDR-TB</th>
<th>Confidence interval</th>
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</thead>
<tbody>
<tr>
<td>AFR</td>
<td>2.3</td>
<td>0.2–4.4</td>
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<td>4.4–17</td>
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<tr>
<td>AMR</td>
<td>2.2</td>
<td>1.4–3.0</td>
<td>14</td>
<td>4.7–22</td>
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<tr>
<td>EMR</td>
<td>3.5</td>
<td>0.1–11</td>
<td>33</td>
<td>12–54</td>
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<tr>
<td>EUR</td>
<td>16</td>
<td>10–22</td>
<td>45</td>
<td>39–52</td>
</tr>
<tr>
<td>SEAR</td>
<td>2.2</td>
<td>1.6–2.8</td>
<td>16</td>
<td>11–21</td>
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<tr>
<td>WPR</td>
<td>4.7</td>
<td>3.3–6.1</td>
<td>22</td>
<td>18–27</td>
</tr>
<tr>
<td>Global</td>
<td>3.6</td>
<td>2.1–5.1</td>
<td>20</td>
<td>13–27</td>
</tr>
</tbody>
</table>
Proportion of MDR among new TB cases
Latest available data, 1994-2012

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 lines on maps represent approximate border lines for which there may not yet be full agreement.

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Proportion of MDR among previously treated TB cases
Latest available data, 1994-2012

Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire – Saint Eustatius and Saba, Cook Islands, Iceland, Sao Tome and Principe, and Lebanon refer to only a small number of notified cases (<10).

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 lines on maps represent approximate border lines for which there may not yet be full agreement.

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To date, 92 countries have reported at least one XDR-TB case.
Region wise:
Estimated MDR-TB burden

China: 59,000
Philippines: 13,000
Vietnam: 3800

WPR: 25%
SEAR: 30%
AFR: 13%
AMR: 2%
EMR: 6%
EUR: 24%
Category wise:
Estimated burden of MDR-TB

- 28% MDR-TB from retx
- 72% MDR-TB from new
## MDR-TB notification and enrolment

MDR cases reported vs estimated among notified TB, 2012

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>2012</th>
<th></th>
<th></th>
<th>Ratio</th>
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<tr>
<td></td>
<td>Estimated</td>
<td>Reported</td>
<td></td>
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</tr>
<tr>
<td>African</td>
<td>38,000</td>
<td>18,129</td>
<td>48%</td>
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<tr>
<td>American</td>
<td>7,100</td>
<td>2,967</td>
<td>42%</td>
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<tr>
<td>East Med.</td>
<td>18,000</td>
<td>2,236</td>
<td>12%</td>
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<tr>
<td>European</td>
<td>74,000</td>
<td>36,708</td>
<td>50%</td>
<td></td>
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<tr>
<td>S-E Asian</td>
<td>90,000</td>
<td>19,202</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>West Pacific</td>
<td>74,000</td>
<td>4,473</td>
<td>6%</td>
<td></td>
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<tr>
<td>Global</td>
<td>300,000</td>
<td>83,715</td>
<td>28%</td>
<td></td>
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</tbody>
</table>
Increasing trend

China

Vietnam

Cambodia

Philippines

Mongolia
MDR-TB cases detected and started on treatment

- Detected among notified: 77,000 in 2009, 94,000 in 2012
- Enrolled on treatment: 94,000

Doubling in detection and treatment, 2009–2012

Increasing gap between detection and treatment

Still large detection gap:
- About 1 in 3 TB patients with MDR-TB detected
- About 1 in 4 on treatment
Outcomes of MDR-TB treatment

MDR-TB cohorts 2007-2010, global*

- Cured
- Completed
- Died
- Treatment failed
- Lost to follow-up
- Not evaluated

<table>
<thead>
<tr>
<th>Year</th>
<th>Cured</th>
<th>Completed</th>
<th>Died</th>
<th>Treatment failed</th>
<th>Lost to follow-up</th>
<th>Not evaluated</th>
<th>Total</th>
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<td>2007</td>
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<td>2009</td>
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<td>23250</td>
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<tr>
<td>2010</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>34281</td>
</tr>
</tbody>
</table>

*number of cases observed shown on the right
A poor drug-resistant tuberculosis programme is worse than no programme: time for a change

C-Y. Chiang,*# A. Van Deun,*# D. A. Enarson*

*International Union Against Tuberculosis and Lung Disease, Paris, France; #Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; †Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium

TUBERCULOSIS (TB) services aim to prevent the transmission of TB through early diagnosis of infectious TB patients and rendering them non-infectious by effective treatment. Keeping TB patients alive by treatment but failing to cure them would promote the spread of TB in the community. Achieving a high proportion of treatment success is a fundamental principle in the development of the internationally recom-
Outcomes of MDR-TB treatment

MDR-TB cohorts 2007-2010, global*

- Cured
- Completed
- Died
- Treatment failed
- Lost to follow-up
- Not evaluated

2007: 10,959 cases
2008: 15,565 cases
2009: 23,250 cases
2010: 34,281 cases

*number of cases observed shown on the right
MODEL OF CARE
What means patient-centred care for a person with MDR-TB?
What means patient-centred care for a health care worker?
What means patient-centred care for a donor?

<table>
<thead>
<tr>
<th>Cost</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>![Neutral] / ![Sad/Frowning]</td>
</tr>
<tr>
<td>-</td>
<td>![Happy/Frowning] / ![Sad/Frowning]</td>
</tr>
</tbody>
</table>
Patient-centred care

means that the health system and interventions are designed (and delivered) with respect for the patient’s rights, preferences, values and needs [...] the patient is treated as a partner rather than just as a recipient

Massaut S (Patient centered approach strategy. TBCTA)
The World Health Report 2008

Primary Health Care

Now More Than Ever

World Health Organization
### Table 3.1 Aspects of care that distinguish conventional health care from people-centred primary care

<table>
<thead>
<tr>
<th>Conventional ambulatory medical care in clinics or outpatient departments</th>
<th>Disease control programmes</th>
<th>People-centred primary care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus on illness and cure</td>
<td>Focus on priority diseases</td>
<td>Focus on health needs</td>
</tr>
<tr>
<td>Relationship limited to the moment of consultation</td>
<td>Relationship limited to programme implementation</td>
<td>Enduring personal relationship</td>
</tr>
<tr>
<td>Episodic curative care</td>
<td>Programme-defined disease control interventions</td>
<td>Comprehensive, continuous and person-centred care</td>
</tr>
<tr>
<td>Responsibility limited to effective and safe advice to the patient at the moment of consultation</td>
<td>Responsibility for disease-control targets among the target population</td>
<td>Responsibility for the health of all in the community along the life cycle; responsibility for tackling determinants of ill-health</td>
</tr>
<tr>
<td>Users are consumers of the care they purchase</td>
<td>Population groups are targets of disease-control interventions</td>
<td>People are partners in managing their own health and that of their community</td>
</tr>
<tr>
<td><strong>Table 3.2</strong> Person-centredness: evidence of its contribution to quality of care and better outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved treatment intensity and quality of life – Ferrer (2005)&lt;sup&gt;54&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better understanding of the psychological aspects of a patient's problems – Gulbrandsen (1997)&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved satisfaction with communication – Jaturapatporn (2007)&lt;sup&gt;56&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved patient confidence regarding sensitive problems – Kovess-Masféty (2007)&lt;sup&gt;57&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased trust and treatment compliance – Fiscella (2004)&lt;sup&gt;52&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better integration of preventive and promotive care – Mead (1982)&lt;sup&gt;50&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What else apart from anti-TB drugs are these patients in need of?

- **Psychological support** (depression, affirming life in face of death, voice fears)
- **Social support** (involve family and community)
- **Involving patient** in treatment decision (willing to stop TB treatment?)
- **Management of symptoms** (breathlessness, pain, etc)
- **Nutritional support**
- **Spiritual counselling whenever is requested/demanded**
Implications of these lessons for designing a model of care

- Ethics of TB care matter
- Effectiveness (treatment outcomes)
- Cost-effectiveness (price to pay for the outcome achieved)
- Sustainability
  - Which model can handle the estimated country MDR-TB burden until the epidemic subsides?
"I want to give back what was given to me. I want to be a nurse and help others who are sick"

Charlene

Any model that produces this result is, probably, the best model of care
6. Models of care for managing MDR-TB

Recommendation

Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (conditional recommendation, ++/very low quality evidence).
NEW DRUGS AND REGIMEN
Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

1 Ongoing projects without a lead compound series can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

2 Combination regimens: first clinical trial (NC001) of a novel TB drug regimen testing the three drug combination of PA-824, moxifloxacin, and pyrazinamide was initiated November 2010 and completed in 2011 with promising results. The second clinical trial (NC002) of this regimen was launched in March 2012 and will test the efficacy of the regimen in drug-sensitive and multidrug-resistant patients. The third clinical trial (NC003) will evaluate PA-824, TMC-207, pyrazinamide and clofazimine in combinations and is scheduled to begin September 2012.
Mechanisms of action of new compounds in clinical development for tuberculosis

Study C208 (Stage 2) secondary endpoint: sputum culture conversion rates at weeks 24 and 72, modified intention-to-treat population

<table>
<thead>
<tr>
<th>Week</th>
<th>Bedaquiline (n = 67)</th>
<th>Placebo (n = 66)</th>
<th>Absolute difference (percentage points)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>52 (77.6)</td>
<td>38 (57.6)</td>
<td>0.014</td>
<td>20.0</td>
</tr>
<tr>
<td>72</td>
<td>47 (70.1)</td>
<td>37 (56.1)</td>
<td>0.092</td>
<td>14.0</td>
</tr>
</tbody>
</table>

Source: Adapted from Food and Drug Administration clinical pharmacology review (9).

Abbreviation: 95% CI = 95% confidence interval.
WHO recommends that bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation, very low confidence in estimates of effects).
Five conditions for the inclusion of bedaquiline in the adult treatment regimen of MDR-TB

- Treatment is administered under closely monitored conditions
- Proper patient inclusion
- Patient informed consent obtained
- Adherence to principles of designing a WHO-recommended MDR-TB regimen
- Pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions.

WHO Interim policy guidance 2013
Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Survival Analysis of Days to Sputum-Culture Conversion, According to Culture Medium Type

A Mycobacterial Growth Indicator Tube System

B Solid Medium

Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis

- Favourable outcomes were observed in 143 (74.5%) out of 192 patients who received delamanid for 6 or more months, compared to 126 (55%) out of 229 patients who received delamanid for 2 or less months.

Eur Respir J 2013; 41: 1393–1400
**Table 3. Active Tuberculosis Disease Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Includes new drug(s)</th>
<th>May shorten DS-TB treatment</th>
<th>May shorten DR-TB treatment</th>
<th>May make DR-TB treatment more effective</th>
<th>For DR-TB, may reduce pill burden or improve tolerability</th>
<th>May have price, registration, or other access barriers</th>
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<tr>
<td>C215</td>
<td>III</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>STREAM</td>
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<td>bedaquiline</td>
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<td>X</td>
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<tr>
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<td>MARVEL A5319</td>
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<td>X</td>
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<td></td>
<td>PA-824</td>
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<td></td>
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</tbody>
</table>

*Clinicaltrials.gov identifier; for more details, see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

DR-TB: drug-resistant tuberculosis
DS-TB: drug-sensitive tuberculosis
Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun1,2, Aung Kya Jai Maug3, Md Abdul Hamid Salim3, Pankaj Kumar Das3, Mihir Ranjan Sarker3, Paul Daru3, and Hans L. Rieder1,4

1International Union Against Tuberculosis and Lung Disease, Paris, France; 2Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; 3Damien Foundation Bangladesh, Dhaka, Bangladesh; and 4Institute of Social and Preventive Medicine, University of Zurich, Switzerland

Rationale: Based on expert opinion, the global guidelines for management of multidrug-resistant tuberculosis impose lengthy and often poorly tolerated treatments.

Objectives: This observational study evaluated the effectiveness of standardized regimens for patients with proven multidrug-resistant tuberculosis previously untreated with second-line drugs in low-income countries.

Methods: Consenting patients were sequentially assigned to one of six standardized treatment regimens. Subsequent cohorts were treated with regimens adapted according to results in prior cohorts. The study was designed to minimize failure and default while reducing total treatment duration without increasing relapse frequency.

Measurements and Main Results: We report the treatment outcome of all patients with laboratory-confirmed, multidrug-resistant tuberculosis enrolled from May 1997 to December 2007. The most effective treatment regimen required a minimum of 9 months of treatment with gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout the treatment period supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of a minimum of 4 months, giving a relapse-free cure of 87.9% (95% confidence interval, 82.7–91.6) among 206 patients. Major adverse drug reactions were infrequent and manageable. Compared with the 221 patients treated with regimens based on ofloxacin and commonly prothionamide throughout, the hazard ratio of any adverse outcome was 0.39 (95% confidence interval, 0.26–0.59).

Conclusions: Serial regimen formulation guided by overall treatment effectiveness resulted in treatment outcomes comparable to those obtained with first-line treatment. Confirmatory formal trials in populations with high levels of human immunodeficiency virus coinfection and in populations with higher initial prevalence of resistance to second-line drugs are required.

Keywords: chemotherapy; fluoroquinolones; cohort studies; drug resistance; costs

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

In the absence of evidence from controlled clinical trials for multidrug-resistant tuberculosis (resistant to isoniazid and rifampin), the current global guidelines for its management are based on expert opinion, recommending lengthy, poorly tolerated, and expensive treatment options. As a result, implementation has been difficult, and results have remained modest.

What This Study Adds to the Field

This observational study shows that a short, standardized treatment regimen based on a fourth-generation fluoroquinolone combined with other second-line drugs and supplemented by potentially still active first-line drugs was highly effective in a setting among largely HIV-negative patients without a history of prior treatment with second-line drugs.

cases (4–7). This paradox may be due to the practical challenges in implementing the current guidelines and the less than optimal use of existing drugs. Recommended treatment regimens are very long, often poorly tolerated, and difficult to monitor (3, 8).

Standardized treatment regimens with first-line drugs are highly successful in drug-susceptible tuberculosis and fairly efficacious in isoniazid-only-resistant tuberculosis (9). Treatment standardization has also been advocated as a feasible and effectively cost-effective approach for multidrug-resistant tuberculosis.
Treatment outcomes observed in Bangladesh for MDR-TB cases treated with a 9-month regimen

A regimen consisting of a minimum of 4 months of KmCfzGfxEHZPto, prolonged if necessary until conversion was achieved, followed by 5 months of GfxEZCfz, was reported to give high, relapse-free cure rate in MDR-TB patients [van Deun et al, 2010].

Completion 5.3%
Cure 82.5%
Death 5.35
Default 5.8%
Failure 0.5%
Relapse 0.5%

Km=kanamycin; Cfz=clofazimine; Gfx=gatifloxacin; E=ethambutol; H=high-dose isoniazid; Z=pyrazinamide; Pto=prothionamide

4. Duration of second-line anti-tuberculosis regimens

Recommendations

4.1 In the treatment of patients with MDR-TB, an intensive phase of at least 8 months’ duration is recommended (conditional recommendation, ⊗⊗⊗⊗/very low quality evidence).

4.2 In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, ⊗⊗⊗⊗/very low quality evidence).

Benefits

When selecting the duration of treatment, the analysis allowed a choice to be made within a narrow margin of a few consecutive months, thus reducing the likelihood of prolonging treatment unnecessarily. While shorter regimens would confer clear benefits and be preferred, evidence for the effectiveness of a 9-month regimen for MDR-TB patients has up to now been limited to data from one setting (included in this review) (16). The Guideline Development Group supports further investigation of the safety and effectiveness of shorter regimens using the randomized controlled trial design in order to strengthen evidence for their potential use for the treatment of drug-resistant TB.
The use of short regimens for treatment of multidrug-resistant tuberculosis

10 August 2012 | The current WHO guidelines on treatment regimens for MDR-TB recommend an intensive phase of treatment of 8 months and a total duration of treatment of 20 months for most patients (1). The guidelines were developed following the GRADE process for guideline development that has been adopted by WHO, and recommendations were based on an analysis of more than 9,000 cases treated in observational studies. The results from an observational study in Bangladesh showed much better rates of treatment success using regimens having a duration of 12 months or less compared with those usually achieved when the longer regimens are used (2). However, there is much less evidence on the effectiveness and safety of these so-called “short-regimens” compared with regimens lasting 20 months.

WHO’s position is that regimens which are markedly different from the ones which represent the current norm and have undergone GRADE review should only be used within the context of research and under close monitoring for a period of at least 12 months beyond the end of treatment. This follow-up after treatment completion is aimed at early identification of those patients who may have a high risk of relapse and acquired resistance. Proper attention to drug regulatory and ethical issues will be needed to facilitate the gathering of additional evidence that can be used for future updates of current WHO guidelines on the treatment of MDR-TB. Until sufficient evidence is available to inform a policy update, WHO is advising countries to introduce short MDR-TB treatment regimens only in projects that adhere to the following criteria:

CURRENT GUIDELINES
Composition of second-line anti-tuberculosis regimens

Recommendations

3.1 In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation,  قادرية/very low quality evidence).

3.2 In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, قادرية/very low quality evidence).

3.3 In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, قادرية/very low quality evidence).

3.4 In the treatment of patients with MDR-TB, four second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase (conditional recommendation, قادرية/very low quality evidence).

3.5 In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, قادرية/very low quality evidence).
## Odds ratios of treatment success by duration of intensive phase and total treatment

<table>
<thead>
<tr>
<th>Duration of intensive phase of treatment</th>
<th>Total duration of treatment&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration (months)</strong></td>
<td><strong>Observations</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>1–2.5</td>
<td>308</td>
</tr>
<tr>
<td>2.6–4.0</td>
<td>1406</td>
</tr>
<tr>
<td>4.1–5.5</td>
<td>481</td>
</tr>
<tr>
<td>5.6–7.0</td>
<td>377</td>
</tr>
<tr>
<td><strong>7.1–8.5</strong></td>
<td>172</td>
</tr>
<tr>
<td>8.6–20</td>
<td>792</td>
</tr>
<tr>
<td>27.6–30.5</td>
<td>106</td>
</tr>
</tbody>
</table>
**STEP 1**  Choose an injectable (Group 2)

<table>
<thead>
<tr>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin</td>
</tr>
<tr>
<td>Amikacin</td>
</tr>
<tr>
<td>Capreomycin</td>
</tr>
</tbody>
</table>

**STEP 2**  Choose a higher generation fluoroquinolone (Group 3)

<table>
<thead>
<tr>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Moxifloxacin</td>
</tr>
</tbody>
</table>

Levoﬂoxacin and moxifloxacin can overcome ofloxacin resistance in some circumstances; for most patients the fluoroquinolone is tolerated well and worth using if there is a chance of efficacy. However moxifloxacin is known to have additive QT prolonging effects and should be avoided when possible.

**STEP 3**  Add (three) Group 4 drugs

<table>
<thead>
<tr>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethionamide/prothionamide</td>
</tr>
<tr>
<td>Cycloserine/terizidone</td>
</tr>
<tr>
<td>Para-aminosalicylic acid (PAS)</td>
</tr>
</tbody>
</table>

**STEP 4**  Add Group 1 drugs

<table>
<thead>
<tr>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>Ethambutol</td>
</tr>
</tbody>
</table>

Pyrazinamide is routinely added in most regimens; ethambutol can be added if the criteria for an effective drug are met.

**STEP 5**  Add bedaquiline and other Group 5 drugs as necessary

<table>
<thead>
<tr>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
<tr>
<td>Clofazimine</td>
</tr>
<tr>
<td>Amoxicillin/ clavulanate</td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
</tr>
<tr>
<td>Meropenem</td>
</tr>
<tr>
<td>High-dose isoniazid</td>
</tr>
<tr>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Thioacetazone</td>
</tr>
</tbody>
</table>

Group 5 drugs other than bedaquiline are added based on the number of Group 4 drugs for which there is a high degree of confidence in efficacy:

- Confidence in all three Group 4 drugs: adding other Group 5 drugs is not necessary
- Confidence in only two Group 4 drugs: add one other Group 5 drug
- Confidence in only one Group 4 drugs: add two other Group 5 drugs
- Confidence in no Group 4 drugs: add three other Group 5 drugs
OUR ROLE
Standard for diagnosis (6)

Standard for treatment (7)

Standard for addressing HIV and comorbid situation (4)

Standard for public health and prevention (4)
“We have to make this people’s fight. Each one has a name and a family. They are not just numbers.”