Monitoring of MDR-TB treatment and Outcome Assessment

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By the end of this presentation, participants would be able to describe...

• Steps in the treatment of MDR-TB
• Patient-centred care and treatment support
• Monitoring of treatment
• Outcome analysis
• Management of failure and XDR-TB
• Palliative care
Steps in the treatment of MDR-TB

• Review treatment history and DST results to design a MDR-TB regimen
  – Standardized regimen for MDR-TB patients never previously treated with second line drugs
  – Individualized regimen for those previously treated with second line drugs
    – GenoType MTBDRsl to detect resistance to second line injectables and quinolone
• Initiation of MDR-TB treatment: add drugs step-by-step, watch adverse reactions
• Providing treatment support and supportive directly observed therapy
• Monitor sputum conversion
• Manage patients with persistent positive sputum
Adverse drug effects and adherence

Treatment support is essential

- Frequent contacts between health care workers and patients are essential, especially during the intensive phase of MDR-TB treatment
  - Admission for a period of time is helpful in ensuring that patients can tolerate drugs
  - Supportive directly observed therapy should be arranged after discharge

- Principle in the management of adverse drug effects
  - Minor: re-assurance, be supportive, and ensure adherence
  - Major: withdraw the drug
Patient-centred care

• The patient-centred approach of the WHO TB strategy consists of enabling patients to exercise their rights and fulfill their responsibilities with transparency, respect and dignity, by giving due consideration to their values and needs.

• A patient-centred approach to programmatic management of drug-resistant TB may increase the chances of successful treatment outcomes, and improve wellbeing and financial risk protection by improving adherence to treatment, benefiting patients and society as a whole.
Strategies for reducing treatment default in drug-resistant TB

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
<th>Studies n</th>
<th>Patients</th>
<th>Defaulting (95%CI)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>Standardised</td>
<td>17</td>
<td>4289</td>
<td>9.30 (5.60–13.00)</td>
<td>*</td>
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<tr>
<td></td>
<td>Individualised</td>
<td>58</td>
<td>13826</td>
<td>16.60 (13.30–19.90)</td>
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<td></td>
<td>Mixed</td>
<td>2</td>
<td>139</td>
<td>14.10 (8.50–19.90)</td>
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<tr>
<td>DOT</td>
<td>None</td>
<td>10</td>
<td>3352</td>
<td>26.20 (15.50–37.00)</td>
<td>*</td>
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<tr>
<td></td>
<td>Partial</td>
<td>24</td>
<td>6635</td>
<td>16.90 (12.00–21.90)</td>
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<tr>
<td></td>
<td>Always</td>
<td>36</td>
<td>7635</td>
<td>12.10 (9.40–14.80)</td>
<td>0.01</td>
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<tr>
<td>DOT provider</td>
<td>HCW</td>
<td>22</td>
<td>6069</td>
<td>18.10 (13.50–22.70)</td>
<td>*</td>
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<tr>
<td></td>
<td>Family/HCW</td>
<td>9</td>
<td>954</td>
<td>6.10 (2.10–10.00)</td>
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<td></td>
<td>Mix</td>
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<td>2345</td>
<td>9.60 (6.70–12.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DOT location</td>
<td>Facility</td>
<td>36</td>
<td>9845</td>
<td>17.30 (13.40–21.30)</td>
<td>*</td>
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<tr>
<td></td>
<td>Home/mixed</td>
<td>23</td>
<td>4010</td>
<td>8.90 (6.40–11.40)</td>
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<td>Education</td>
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<td>68</td>
<td>16799</td>
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<tr>
<td></td>
<td>Yes</td>
<td>10</td>
<td>1495</td>
<td>9.30 (5.20–13.30)</td>
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<tr>
<td>Cohort size</td>
<td>&lt;100</td>
<td>40</td>
<td>1582</td>
<td>11.30 (8.70–13.90)</td>
<td>*</td>
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<tr>
<td></td>
<td>100–499</td>
<td>25</td>
<td>6055</td>
<td>15.30 (11.80–18.80)</td>
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<td></td>
<td>500–999</td>
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<td>4857</td>
<td>18.70 (9.50–27.90)</td>
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<tr>
<td></td>
<td>&gt;1000</td>
<td>5</td>
<td>5800</td>
<td>24.50 (14.80–34.20)</td>
<td>0.005</td>
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<tr>
<td>Counselling</td>
<td>No</td>
<td>62</td>
<td>15492</td>
<td>15.10 (12.10–18.10)</td>
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<tr>
<td></td>
<td>Yes</td>
<td>16</td>
<td>2802</td>
<td>14.00 (9.10–18.90)</td>
<td>0.7</td>
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<tr>
<td>Legal action</td>
<td>Yes</td>
<td>5</td>
<td>2421</td>
<td>12.30 (1.50–23.10)</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>73</td>
<td>15873</td>
<td>15.10 (12.40–17.80)</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Patient Adherence to Tuberculosis Treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organisation of treatment and care for TB patients</td>
<td>Access to services (urban ambulatory, distance, transport); health centre problems (long waiting hours, queues, physical condition of clinic); treatment requirements (continuity; charging for drug, number of tablets, DOT, flexibility, and choice); relationship between treatment provider and patient (poor follow up, increased contact, maltreatment of patients)</td>
</tr>
<tr>
<td>Interpretation of illness and wellness</td>
<td>Individual interpretations of recovery; perceptions of TB recognition of TB as a disease</td>
</tr>
<tr>
<td>Financial burden</td>
<td>Conflict between work and treatment; costs of treatment; expenses exceeding available resources; more pressing issues to attend to; increased expenditure on food</td>
</tr>
<tr>
<td>Knowledge, attitudes, and beliefs about treatment</td>
<td>Limited understanding of treatment, duration, and consequences of default; beliefs about treatment efficacy; denial and difficulty accepting diagnosis; use of other medication; treatment requirements</td>
</tr>
<tr>
<td>Law and immigration</td>
<td>Completion cards; impact on immigration status; fear of detention</td>
</tr>
<tr>
<td>Personal characteristics and adherence behaviour</td>
<td>Substance abuse; mental illness; ethnic characteristics; residential mobility; religion; personal motivation; gender; difficult cases; structured environment; personal agency</td>
</tr>
<tr>
<td>Side effects</td>
<td>Real, anticipated, or culturally interpreted; insufficient information; insufficient communication; insufficient attention.</td>
</tr>
<tr>
<td>Family, community, and household influence</td>
<td>Peer influence; stigma; providing for family; family support; marriage</td>
</tr>
</tbody>
</table>

Social support in MDR-TB management

- Informational support: training and education
- Emotional support: strengthen self-esteem through empathy, trust, encouragement and care
- Companionship support: makes a person feel that he or she belongs to the social network
- Material support: all commodities, including financial products
Financial burden for tuberculosis patients in low- and middle-income countries

FIGURE 2 Breakdown of direct and indirect costs before and during treatment (eight studies). Percentages are proportion of respective sub-component cost out of the total cost.
Financial burden for tuberculosis patients in low- and middle-income countries

• The total cost was equivalent to 58% (range 5–306%) of reported annual individual and 39% (4–148%) of reported household income.
• Cost as percentage of income was particularly high among poor people and those with multidrug-resistant TB.
• Commonly reported coping mechanisms included taking a loan and selling household items.
• there is a need to ensure that TB patients and affected families receive appropriate income replacement and other social protection interventions

Conclusions: MDR-TB patients are extremely vulnerable to stigma and extreme financial hardship. Provision of counselling and financial support may not only reduce their vulnerability, but also increase cure rates.
Effects of Ecuador’s national monetary incentive program on adherence to treatment for drug-resistant tuberculosis

Figure  Time to default from MDR-TB treatment, 2010–2012, Ecuador. 1-year default rates: pre-program = 26.7%; program = 9.5%. MDR-TB = multidrug-resistant tuberculosis.
Essential Support for MDR-TB treatment

• Partnership with patients to obtain the highest possibility of cure
• Health education on MDR-TB
• Ensuring tolerability of an effective MDR-TB regimen
• Hospitalization if necessary, taking time and financial cost of patients into consideration
• Supervised treatment and follow-up visits in a supportive manner that is convenient to patients
• Address adverse effects in an timely manner
• Enables and incentive, including financial support
Monitoring response of treatment

• Monthly sputum examination in intensive phase (and/or until sputum conversion)
  – Sputum smear
  – Sputum culture

• Regular sputum examinations after sputum conversion

• Chest X-ray: play a limited role in quantifying treatment response as compared with sputum examination
Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh

- Status at end of intensive phase (3 months), $n=58$
  - Smear negative 81%
  - Culture negative 88%
  - Smear positive 14%
  - Culture positive 5%

Regimen: 3KCOPHZE/12OPHZE/6EP
kanamycin (K), clofazimine (C), ofloxacin (O), prothionamide (P)

Culture conversion in smear-positive MDRTB cases

Smear Positive (n=405)

Months after the start of 2nd line anti-TB medications
Outcome of new MDR-TB never previously treated with second line drugs, Taipei

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Success</th>
<th>Failed (Percent)</th>
<th>Died</th>
<th>Defaulted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>299</td>
<td>52.1</td>
<td>10.4</td>
<td>9.4</td>
<td>29.1</td>
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<tr>
<td>First line</td>
<td>61</td>
<td>57.4</td>
<td>*</td>
<td>11.5</td>
<td>31.2</td>
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<tr>
<td>Second ine without Fluoroquinolone</td>
<td>113</td>
<td>38.9</td>
<td>16.8</td>
<td>14.2</td>
<td>30.1</td>
</tr>
<tr>
<td>Second ine with Fluoroquinolone</td>
<td>125</td>
<td>59.2</td>
<td>9.6</td>
<td>4.0</td>
<td>27.2</td>
</tr>
</tbody>
</table>

Each dose is given by DOT.

A treatment card is marked for each observed dose.

Courtesy: Lee JJ
# Outcome of multidrug-resistant tuberculosis patients

<table>
<thead>
<tr>
<th></th>
<th>Taipei 1992-1996</th>
<th>Eastern Taiwan 2011*</th>
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<tbody>
<tr>
<td>Success</td>
<td>52%</td>
<td>78%</td>
</tr>
<tr>
<td>Died</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Failed</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Loss-to-follow-up</td>
<td>29%</td>
<td>0%</td>
</tr>
</tbody>
</table>


* Lee JJ (unpublished data)
Outcome of MDR-TB: cured

• A patient who has completed treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment.

• If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

Guidelines for the programmatic management of drug-resistant tuberculosis, WHO, 2008
Outcome of MDR-TB: Failed

- if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive.

- if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events.


Guidelines for the programmatic management of drug-resistant tuberculosis, WHO, 2008
Outcome of MDR-TB: failed

- Not defined as sputum positive at n months.
- cannot be used prospectively to guide clinical management of MDR-TB

- A failing regimen should be changed to prevent amplification of drug resistance

  - If modifications are made to the MDR-TB treatment regimen due to failure of sputum conversion, patients should be classified as failed

‘Failed’ defined as sputum-positive after n months of treatment

The value of $n$

– depends on the regimens used, the DST patterns and previous use of second-line drugs,
– need to be defined using information from the field.
– likely to be 8–12 months in settings without fluoroquinolones or if the bacilli are fully resistant to fluoroquinolones
– could be 6–10 months if fluoroquinolones such as levofloxacin or moxifloxacin are indicated and used

Outcome of MDR-TB treatment: definition of failure

1. lack of bacteriological response accompanied by lack of clinical improvement
   - at 6 months of treatment for patients not previously treated with second-line drugs – and
   at 12 months for patients previously treated with second-line drugs or patients with
   extensively drug-resistant tuberculosis (XDR-TB).

Outcome of MDR-TB treatment: definition of failure

2. bacteriological reversion with concomitant clinical deterioration after initial response,

3. adverse drug events.
   - defined as two or more drugs have to be replaced

Definitions and reporting framework for tuberculosis – 2013 revision
Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Cured

- Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Treatment failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:

1. lack of conversion by the end of the intensive phase, or
2. bacteriological reversion in the continuation phase after conversion to negative, or
3. evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or
4. adverse drug reactions (ADRs).
Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

• For Treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase applied by the programme.

• If no maximum duration is defined, an 8-month cut-off is proposed.

• For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply.
Revised Definitions of Multidrug-Resistant Tuberculosis Treatment Outcomes: Closer to the Reality?

Table 1. Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis, Using the 2008 and 2013 World Health Organization Definitions (N = 1,455)

<table>
<thead>
<tr>
<th></th>
<th>2008 Definitions</th>
<th>2013 Definitions</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Cure</td>
<td>505</td>
<td>34.7</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>303</td>
<td>20.8</td>
</tr>
<tr>
<td>Success</td>
<td>808</td>
<td>55.5</td>
</tr>
<tr>
<td>Death</td>
<td>127</td>
<td>8.7</td>
</tr>
<tr>
<td>Failure</td>
<td>165</td>
<td>11.3</td>
</tr>
<tr>
<td>Lost to follow-up*</td>
<td>333</td>
<td>22.9</td>
</tr>
<tr>
<td>Not evaluated†</td>
<td>22</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Defaulter in the 2008 definitions.
†Transferred out or still receiving treatment in the 2008 definitions.
Revised Definitions of Multidrug-Resistant Tuberculosis Treatment Outcomes: Closer to the Reality?

• After applying the revised 2013 definitions, 112/505 (22.2%), 79/303 (26.1%), 67/127 (52.8%), 122/333 (36.6%), and 6/22 (27.3%) of the patients with MDR-TB classified as cured, treatment completed, death, defaulter, and still receiving treatment or transfer out with the 2008 definitions were reclassified as treatment failure, respectively.

• The 2013 definition of a failing treatment better corresponds to an ineffective treatment and better reflects the reality faced by patients and clinicians. It should act as a red flag for the clinician, indicating that the treatment must be changed.
We also think that a 6-month cutoff for culture conversion is more appropriate programmatically to have time to receive culture results to be able to make the decision on a potential treatment change at 8 months,

Treatment Outcomes of MDR-TB: A Systematic Review and Meta-Analysis

• Factors associated with worse outcome (odds ratio)
  – male gender 0.61 [0.46–0.82],
  – alcohol abuse 0.49 [0.39–0.63],
  – low BMI 0.41 [0.23–0.72],
  – smear positivity at diagnosis 0.53 [0.31–0.91],
  – fluoroquinolone resistance 0.45 [0.22–0.91]
  – XDR resistance pattern 0.57 [0.41–0.80].

• Factors associated with successful outcome (odds ratio)
  – surgical intervention 1.91 [1.44–2.53],
  – no previous treatment 1.42 [1.05–1.94],
  – fluoroquinolone use 2.20 [1.19–4.09]

Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia

• Of 608 MDR-TB patients, 29 (4.8%) had baseline XDR-TB.

• Treatment failure ($p=0.0008$)
  – XDR tuberculosis 31%
  – non-XDR tuberculosis 8.5%

• Treatment cure or completion ($p=0.04$)
  – XDR tuberculosis 48.3%
  – non-XDR tuberculosis 66.7%

Resistance to anti-tuberculosis drugs by multidrug-resistant tuberculosis (MDR-TB) patient group

<table>
<thead>
<tr>
<th>Pooled treatment outcomes#</th>
<th>MDR-TB only</th>
<th>MDR-TB +INJr</th>
<th>MDR-TB +FQr</th>
<th>XDR-TB</th>
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</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>4763</td>
<td>1130</td>
<td>426</td>
<td>405</td>
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<tr>
<td>Treatment success</td>
<td>64 (57-72)</td>
<td>56 (45-66)</td>
<td>48 (36-60)</td>
<td>40 (27-53)</td>
</tr>
<tr>
<td>Treatment failure or relapse</td>
<td>4 (2-6)</td>
<td>12 (9-15)</td>
<td>18 (14-21)</td>
<td>22 (15-28)</td>
</tr>
<tr>
<td>Died</td>
<td>8 (5-11)</td>
<td>8 (3-14)</td>
<td>11 (3-19)</td>
<td>15 (8-23)</td>
</tr>
<tr>
<td>Defaulted</td>
<td>18 (12-24)</td>
<td>16 (7-24)</td>
<td>12 (1-23)</td>
<td>16 (8-24)</td>
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Cascade of regimens

<table>
<thead>
<tr>
<th>Rifampicin</th>
<th>Quinolone</th>
<th>Treatment approach</th>
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<tbody>
<tr>
<td>Susceptible</td>
<td></td>
<td>First line anti-TB treatment</td>
</tr>
<tr>
<td>Resistant</td>
<td>Susceptible</td>
<td>Second line anti-TB treatment (9 month regimen)</td>
</tr>
<tr>
<td>Resistant</td>
<td>Resistant</td>
<td>New drugs and potential group 5 drugs</td>
</tr>
</tbody>
</table>
Palliative care for MDR-TB patients

CHIANG Chen-Yuan MD, MPH, DrPhilos
Director, Department of Lung Health and NCDs
WHO Definition of Palliative care
http://www.who.int/cancer/palliative/definition/en/

- Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.
WHO Definition of Palliative care
http://www.who.int/cancer/palliative/definition/en/

Palliative care
• provides relief from pain and other distressing symptoms;
• affirms life and regards dying as a normal process;
• intends neither to hasten or postpone death;
• integrates the psychological and spiritual aspects of patient care;
• offers a support system to help patients live as actively as possible until death;
• offers a support system to help the family cope during the patients illness and in their own bereavement;
• uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
• will enhance quality of life, and may also positively influence the course of illness;
• is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.
Palliative and end-of-life care for MDR-TB patients

- Multidrug-resistant tuberculosis is costly, difficult to treat, and poses a global threat to tuberculosis control.
- The high burden of disease and treatment for patients, poor cure rates, and high mortality bring distress to patients, families, and caregivers.
- Relief of the patient’s suffering associated with disease and its management has been restricted mostly, and not adequately, to physical aspects.
- Little attention has been paid to palliative care of patients and families, such as for physical, psychosocial, social, and spiritual difficulties.

Palliative and end-of-life care for MDR-TB patients

• Early delivery of palliative care recognises that life-threatening illness carries with it a substantial burden of suffering for patients, families, and care givers, whether or not the disease can be cured.

• Embracing palliative care will contribute to ensuring that patients are “permitted to live out their life with minimal suffering and loss of dignity”

Management of patients after MDR-TB treatment failure

- suspending therapy or changing it to a supportive care regimen

- WHY?
Patient’s quality of life

• The drugs used in MDR-TB treatment have significant adverse effects, and continuing them while the treatment is failing may cause additional suffering.
Public health concern

• continuing a treatment that is failing can amplify resistance in the patient’s strain, and will result in a waste of resources.
Approach to suspending therapy

- discussions among the clinical team
- approaching the patient and the family
- patient understands, accepts and agrees with the supportive care offered
  - especially difficult for the patient as treatment is often viewed as his or her only hope
  - Strong support, care and sympathy must be given to the patient and family
End-of-life supportive measures

- Pain control and symptom relief
- Relief of respiratory insufficiency: oxygen
- Nutritional support
- Regular medical visits
- Continuation of ancillary medicines
- Hospitalization, hospice care or nursing home care
- Preventive measures: oral care, prevention of bedsores and muscle contractures
- Infection control measures
Palliative and end-of-life care for MDR-TB patients

• All attending workers need to be trained in essential skills to assess and control patients’ difficulties, and local palliative care services must be able to provide consultancy for and manage complex cases. These skills should be part of human resource development curricula.

• Research is needed to inform clinical guidance and policy on how to deliver better care for individuals throughout the disease course.