Drug-resistant tuberculosis (DR-TB) is more difficult to treat than forms of disease that are still responsive to the antimicrobials used to treat TB. DR-TB threatens global progress towards the targets set by the End TB Strategy of the World Health Organization (WHO). There is thus a critical need for evidence-based policy recommendations on the treatment and care of patients with DR-TB, based on the most recent and comprehensive evidence available. The WHO consolidated guidelines on drug-resistant tuberculosis treatment fulfill the mandate of WHO to inform health professionals in Member States on how to improve treatment and care for patients with DR-TB.

Between 2011 and 2018, WHO developed several evidence-based policy recommendations on the treatment and care of patients with DR-TB. These policy recommendations were released as part of eight WHO guidelines with their associated annexes (see Box 1), the latest being the updated WHO guidelines for the treatment of multidrug- and rifampicin-resistant TB (MDR/RR-TB) issued in December 2018. These guidelines have been developed by WHO-convened Guideline Development Groups (GDGs), using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to summarize the evidence, and formulate policy recommendations and accompanying remarks. GDGs are composed of multidisciplinary groups of external experts with experience in different aspects of the programmatic and clinical management of DR-TB, as well as affected individuals. The methods used to develop the recommendations complied with the requirements of WHO’s Guideline Review Committee (GRC), and the GRC has overseen the development of each of these guidelines.

Box 1
WHO treatment guidelines that have been incorporated in the WHO consolidated guidelines on drug-resistant tuberculosis treatment


The present Consolidated guidelines include a comprehensive set of WHO recommendations for the treatment and care of DR-TB, derived from these WHO guidelines documents. The consolidated guidelines include policy recommendations on treatment regimens for isoniazid-resistant TB (Hi-TB) and MDR/RR-TB, including longer and shorter regimens, culture monitoring of patients on treatment, the timing of antiretroviral therapy [ART] in MDR/RR-TB patients infected with the human immunodeficiency virus (HIV), use of surgery for patients receiving MDR-TB treatment, and optimal models of patient support and care.

The full list of policy recommendations that are currently valid for the programmatic management of DR-TB, grouped into eight sections, is provided below. For full details of the guidelines and associated evidence base please see [www.who.int/tb/areas-of-work/drug-resistant-tb/](http://www.who.int/tb/areas-of-work/drug-resistant-tb/). The new guidance will be complemented with further advice on their implementation in a revised edition of WHO’s “how-to” handbook for TB programmes.
**RESEARCH AND DEVELOPMENT**

1. **REGIMENS FOR ISONIAZID-RESISTANT TUBERCULOSIS (HR-TB)**
   - In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.
   - In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.

2. **THE COMPOSITION OF LONGER MDR-TB REGIMENS**
   - In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment after bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.
   - Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.
   - Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.
   - Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.
   - Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.
   - Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.
   - Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.
   - Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens.
   - Pyrazinamide should be included in the treatment of MDR/RR-TB patients on longer regimens.
   - Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.
   - Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.
   - Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.
   - p-Aminosalicylic acid may be included in the treatment of MDR/RR-TB patients only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.
   - Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens.

3. **THE DURATION OF LONGER MDR-TB REGIMENS**
   - In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient’s response to therapy.
   - In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient’s response to therapy.
   - In MDR/RR-TB patients on longer regimens that contain amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient’s response to therapy.

4. **USE OF THE STANDARDIZED, SHORTER MDR-TB REGIMEN**
   - In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens.

5. **MONITORING PATIENT RESPONSE TO MDR-TB TREATMENT USING CULTURE**
   - In MDR/RR-TB patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals.

---

1. Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid; Group B = clofazimine, cycloserine/terizidone; Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, p-aminosalicylic acid.

2. Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin (amoxicillin–clavulanic acid). When included, clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.
START OF ANTIRETROVIRALS IN PATIENTS ON SECOND-LINE ANTITUBERCULOSIS REGIMENS

Antiretroviral therapy is recommended for all patients with HIV and DR-TB requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment.

SURGERY FOR PATIENTS ON MDR-TB TREATMENT

In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen.

CARE AND SUPPORT FOR PATIENTS WITH MDR/RR-TB

Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment.

A package of treatment adherence interventions3 may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option.4

One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers:

a) tracers5 and/or digital medication monitor;6
b) material support7 to the patient;
c) psychological support8 to the patient;
d) staff education.9

The following treatment administration options may be offered to patients on TB treatment:

a) Community- or home-based directly-observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment.

b) DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment.

c) Video-observed treatment (VOT) may replace DOT when video communication technology is available, and it can be appropriately organized and operated by health-care providers and patients.

Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.

A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment.

ABOUT DRUG-RESISTANT TB

Most anti-TB medicines have been used for decades, and resistance to them is widespread. TB strains that are resistant to at least one anti-TB medicine have been documented in every country surveyed.

Isoniazid-resistant TB (Hr-TB), is caused by bacteria that do not respond to isoniazid but in which rifampicin remains effective. Isoniazid and rifampicin are some of the most important anti-TB medicine and patients with Hr-TB need different regimens from those with drug-susceptible disease.

Rifampicin-resistant tuberculosis (RR-TB) is caused by bacteria that do not respond to rifampicin, one of the most powerful anti-TB medicines. These patients require MDR-TB treatment.

Multidrug-resistant tuberculosis (MDR-TB) is caused by bacteria that do not respond to, at least, isoniazid and rifampicin, the two most powerful anti-TB medicines.

Patients with multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) require treatment with second-line treatment regimens, which are more complex than those used to treat patients without drug-resistant TB.

Extensively drug-resistant TB (XDR-TB) is a form of MDR-TB which is also resistant to two groups of second-line anti-TB medicines, making it more difficult to treat.

3 Treatment adherence interventions include social support such as material support (e.g. food, financial incentives, transport fees), psychological support, tracers such as home visits or digital health communications (e.g. SMS, telephone calls), medication monitor and staff education. The interventions should be selected based on an assessment of the individual patient’s needs, provider’s resources and conditions for implementation.

4 Treatment administration options include directly observed treatment (DOT), non-daily DOT, video-observed treatment (VOT), or unsupervised treatment.

5 Tracers refer to communication with the patient, including home visits or via short message service (SMS), telephone (voice) call.

6 A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor can have audio reminders or send an SMS to remind the patient to take medications, along with recording when the pill box is opened.

7 Material support can be food or financial support: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives or financial bonus. This support addresses the indirect costs incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate the consequences of income loss related to the disease.

8 Psychological support can be counselling sessions or peer-group support.

9 Staff education can be adherence education, chart or visual reminders, educational tools and desktop aids for decision-making and reminders.

More information: http://www.who.int/tb/areas-of-work/drug-resistant-tb/