WHO operational handbook on tuberculosis

Module 4: Treatment

Drug-resistant tuberculosis treatment

World Health Organization

WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment

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Abbreviations

aDSM	active tuberculosis drug safety monitoring and management
AE	adverse event
AIDS	acquired immunodeficiency syndrome
aOR	adjusted odds ratio
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BPaL	a regimen of bedaquiline, pretomanid and linezolid for 6–9 months
CNS	central nervous system
CSF	cerebrospinal fluid
DOT	directly observed treatment
DRS	drug-resistance surveillance
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
ECG	electrocardiography
FDC	fixed-dose combination (of medicines)
GDF	Global Drug Facility
GDG	guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
Hr-TB	confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis
IPD	individual patient data
LPA	line probe assay
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug- or rifampicin-resistant tuberculosis
MGIT	mycobacteria growth indicator tube
MIC	minimum inhibitory concentration
NTP	national tuberculosis programme
PAS	*p*-aminosalicylic acid
PI	protease inhibitor
PK/PD	pharmacokinetics/pharmacodynamics
PLHIV	people living with HIV
RCT	randomized controlled trial

RR-TB	rifampicin-resistant tuberculosis
SAE	serious adverse event
TB	tuberculosis
VOT	video observed treatment
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

1. Introduction

The World Health Organization (WHO) has produced this *WHO operational handbook on tuberculosis* to provide practical advice to complement the latest *WHO consolidated guidelines on tuberculosis, drug-resistant tuberculosis treatment* (hereafter referred to as the "WHO consolidated guidelines"). This document provides information on the choice and design of regimens for the treatment of drug-resistant tuberculosis (DR-TB), including multidrug- or rifampicin-resistant TB (MDR/RR-TB), and confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis TB (Hr-TB) *(1)*.

The strategies described in this module are mainly based on the latest WHO recommendations *(1-3)*, which were formulated by guideline development groups (GDGs) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach *(4)*. However, in many cases, the recommendations lacked the level of clinical and programmatic detail needed for implementation. This module complements the guidelines with practical advice based on best practices and knowledge from fields such as pharmacokinetics, pharmacodynamics, microbiology, pharmacovigilance, and clinical and programmatic management.

2. Commonly used terms and key definitions in drug-resistant TB treatment

This section briefly describes some of the main terms that are used in this module and elsewhere.

Drug susceptibility testing (DST) refers to in vitro testing using either molecular, genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine *(5, 6)*.

Isoniazid-resistant TB (Hr-TB) is caused by *Mycobacterium tuberculosis* strains resistant to isoniazid and susceptible to rifampicin.

Rifampicin-resistant TB (RR-TB) is caused by *M. tuberculosis* strains that are resistant to rifampicin. RR-TB strains may be susceptible to isoniazid or resistant to it (i.e. MDR-TB), or resistant to other first-line or second-line TB medicines.

Multidrug-resistant TB (MDR-TB) is caused by *M. tuberculosis* strains that are resistant to at least both isoniazid and rifampicin.

Multidrug- or rifampicin-resistant TB (MDR/RR-TB) is the term used in this handbook and elsewhere to group MDR-TB and RR-TB cases together as MDR/RR-TB; both MDR-TB and RR-TB cases are eligible for treatment with MDR-TB regimens. MDR/RR-TB usually refers to all patients affected by either MDR-TB or RR-TB.

MDR-TB treatment refers to treatment options for patients with MDR/RR-TB.

Extensively drug-resistant TB (XDR-TB) is TB that is resistant to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.[1]

Extensive (or advanced) TB disease refers to the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

Severe extrapulmonary TB refers to the presence of miliary TB or TB meningitis. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe (adapted from Wiseman et al., 2012 *(7)*).

[1] The current definition of XDR-TB is likely to change, given the phasing out of injectables, the likelihood of patterns of resistance that are more relevant to current and future regimens, and advances in diagnostic methods and DST. Changes to the definition of XDR-TB will be the subject of future expert consultation, and will be included in revised WHO surveillance and reporting guides. Choosing appropriate regimens for patients with strains showing MDR-TB plus additional resistance to fluoroquinolones (so called "pre-XDR") is becoming more important and feasible thanks to rapid advances in molecular DST.

A ***second-line TB medicine (or drug)*** is an agent used for the treatment of drug-resistant TB. Some first-line TB medicines that are used to treat drug-susceptible TB (e.g. ethambutol, isoniazid and pyrazinamide) may also be used in MDR-TB regimens. Streptomycin is now considered a second-line TB medicine and is used only as a substitute for amikacin when amikacin is not available, or when there is confirmed resistance to amikacin but confirmed susceptibility to streptomycin, and when an all-oral regimen cannot be constituted.

A ***shorter MDR-TB regimen*** refers to a course of treatment for MDR/RR-TB lasting less than 12 months, which is largely standardized.

Longer MDR-TB regimens are used for treatment of MDR/RR-TB, last at least 18 months and are designed using a hierarchy of recommended medicines, to include a minimum number of TB medicines considered to be effective based on drug-resistance patterns or patient history.

Empiric treatment refers to the initiation of treatment before laboratory confirmation of the drug-resistance pattern. Empiric regimens can be either *standardized* (in which the composition and duration are to a large extent fixed) or *individualized* (i.e. adapted to the local epidemiological situation or specific needs of a particular patient or patient group).[2] In general, the more information available on the drug-resistance pattern, the less a regimen is considered an empiric treatment and the more likely it is that the treatment will be effective without exposing patients to unnecessary medicines that are unlikely to be effective. Hence, having the full range of rapid molecular testing helps in getting patients on a definitive regimen with a high probability of cure.

The ***likelihood of effectiveness*** of a medicine is judged on the basis of one or more of the following: confirmed susceptibility in the individual patient; confirmed susceptibility in the presumed source case; no known resistance to another drug that has cross-resistance to the medicine; rare use of the drug in a geographical area or setting (possibly supported by low drug-resistance levels from surveillance activities); and no previous use of the medicine in a regimen that failed to cure the individual patient.[3]

Off-label use refers to the use of a pharmaceutical agent for an indication, age group, dosage, duration or route of administration that differs from what was approved by a national drug regulatory authority *(8)*. Several agents (e.g. fluoroquinolones, clofazimine and linezolid) have been used off-label for the treatment of MDR-TB. However, because sufficient evidence has been collected on efficacy and safety of their use in TB treatment so far, the current use of these drugs is no longer considered as off-label. The decision to use drugs off-label is usually based on clinical judgement, when clinicians expect better treatment for patients by using the drugs beyond what is prescribed by the national drug regulatory authorities. This has been seen with the use of bedaquiline or delamanid beyond 6 months (see Section 6 of this module).

An ***adverse event*** is any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but that does not necessarily have a causal relationship with the treatment.

A ***serious adverse event*** is an adverse event that leads to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly. Serious adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included. Serious

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[2] For example, an empiric MDR-TB regimen may be used in diagnosed TB patients who are close contacts of an MDR/RR-TB patient and whose diagnosis of MDR/RR-TB is not yet confirmed by a diagnostic test, or in confirmed MDR/RR-TB patients who are still waiting for second-line DST (e.g. line probe assay results for identification of fluoroquinolone resistance). In certain patients (e.g. children or those who are exposed to a confirmed MDR/RR-TB case), a definitive diagnosis is not always possible, and initiation of empiric treatment would be the best option for their prognosis.

[3] Where there is uncertainty about the effectiveness of a certain agent, it can still be included in the regimen, but it should be considered supernumerary to the target number of medicines needed (usually a minimum of at least four effective agents at the start of treatment). In the case of uncertainty about effectiveness, clinical judgment is often necessary to decide whether an agent is "likely to be effective" and whether the benefit from its inclusion outweighs any added toxicity, pill burden, or other downsides.

adverse events may require a drastic intervention, such as termination of the drug suspected of having caused the event.

Operational research or ***implementation research*** has been defined as "the use of systematic research techniques for programme decision-making to achieve a specific outcome" *(9)*. In the context of this document, such research can also be described as applied research that aims to develop the critical evidence base that informs the effective, sustained and embedded adoption of interventions within a health system, to improve health or patient outcomes. It deals with the knowledge gap between efficacy, effectiveness and current practice to produce the greatest gains in disease control *(10)*. Operational research also provides decision-makers with information to enable them to improve the performance of their health programmes *(11)*.

3. Key considerations in drug-resistant TB treatment

3.1 Access to DST

The current guidelines for drug-resistant TB treatment stress the need for access to reliable, quality-assured DST, to be provided by national TB programmes (NTPs) and associated laboratories, to inform the use of the WHO-recommended regimens. Rapid molecular testing is making it increasingly feasible for NTPs to detect MDR/RR-TB and other types of resistance, and to use the results to guide treatment decisions *(12, 13)* (see also Sections 4–7). Hence, rapid molecular testing should be available and accessible, to ensure DST for at least rifampicin and fluoroquinolones, given that DST for both of these agents is essential for selecting the most appropriate initial regimen. While NTPs build capacity to ensure access to DST, they should also build capacity of a surveillance system to determine the local prevalence of drug-resistant TB strains and to guide programmatic management. Such information can only be accurately determined by appropriate surveillance, whether it be based on data from routine diagnostic DST in TB patients (i.e. continuous surveillance) or from special surveys representative of the entire TB patient population (i.e. drug-resistance surveys) *(14)*. Local TB drug-resistance surveillance (DRS) data should provide accurate estimates of the frequency of resistance to at least rifampicin and isoniazid in new patients, and to fluoroquinolones among MDR/RR-TB cases, as well as some information about the frequency of resistance in relevant subgroups of re-treatment cases (e.g. recurrence or failure after a first-line anti-TB regimen and return after loss to follow-up). Some drug-resistance surveys are now using rifampicin resistance as the main target indicator, given that all RR-TB cases are eligible for an MDR-TB treatment regimen *(1, 15)*.

WHO recommends the use of the approved rapid molecular DST as the initial test to detect drug resistance before the initiation of appropriate therapy for all TB patients, including new patients and patients with a previous history of TB treatment. The increased recognition of drug resistance and improved access to rapid molecular testing have led more programmes to test for at least rifampicin resistance at the start of TB treatment. In addition to Xpert MTB/RIF® for rifampicin, a line probe assay (LPA) can detect mutations commonly associated with resistance to rifampicin, isoniazid, fluoroquinolones and second-line injectable agents. No rapid molecular testing is currently available for ethambutol or pyrazinamide. Results from LPA typically become available within a few days of testing and can thus be used to decide upon the initial regimen for treatment of Hr-TB, or some other forms of mono-resistant or poly-resistant TB. Apart from its rapidity, LPA can also provide information on the mutation patterns, which can influence the choice of treatment (e.g. if only the *inh*A mutation is present, it is likely that isoniazid can still be effective at high dose, whereas if the *kat*G mutation alone or both *inh*A and *kat*G are present, isoniazid is no longer effective, even at high dose). If rifampicin resistance is detected, rapid molecular tests for resistance to isoniazid and fluoroquinolones should be performed promptly, to inform the decision on which regimen to use for the treatment *(16)*. Rapid molecular testing for both rifampicin and fluoroquinolones is widely available; countries have accumulated experience in using these rapid tests, and access is also supported by the main donors where necessary. Commercially available rapid molecular methods (e.g. the second-line LPAs) detect about 85% of fluoroquinolone-resistant isolates *(13)*. Culture-based DST for fluoroquinolones

should be considered when the prevalence of resistance to these drugs is high, or when resistance is suspected despite the molecular tests being negative.

Country programmes need to work towards the establishment of DST for all TB medicines for which there are now agreed reliable and reproducible methods (e.g. bedaquiline, linezolid, clofazimine, delamanid and pyrazinamide). The critical concentrations for various drugs were either established for the first time (bedaquiline, delamanid, clofazimine and linezolid) or revised (fluoroquinolones) in a WHO technical consultation in 2017 *(17)*. If available, targeted or whole genome sequencing (or sequencing of the *pncA* gene) will be used as a reference method to detect pyrazinamide resistance. Susceptibility to ethionamide/prothionamide may in part be inferred from the results of molecular testing for isoniazid resistance (i.e. presence of mutations in the *inhA* promotor region) using LPA. Phenotypic DST for cycloserine/terizidone, ethambutol, ethionamide/prothionamide, imipenem/meropenem or *p*-aminosalicylic acid is not routinely recommended because results may be unreliable *(16)*.

The inability to undertake DST routinely in all patients despite all possible efforts should not be a barrier to starting patients on a potentially life-saving MDR-TB regimen, but should always be considered in a context of the potential risk of prescribing ineffective treatment and amplifying drug resistance, with a subsequent decrease in the likelihood of a successful treatment outcome. If DST for second-line TB medicines is not yet available, the clinician or the TB programme manager needs to estimate the likelihood of effectiveness of the medicines used, informed by the patient's history of use of second-line TB medicines, the drug-resistance pattern of the contact or index case, and recent representative drug-resistance surveillance data. Therefore, a reliable clinical history of exposure to second-line TB medicines should be considered when designing a treatment regimen, but this should not be the primary source of evidence to guide clinical judgement. For paediatric patients, it is not always possible to obtain a DST result, owing to the difficulty of obtaining an adequate specimen or the lack of bacteriological confirmation; hence, the treatment design is usually based on the drug-resistance pattern of the index case. In the absence of individual DST, relevant population surveillance data are essential to inform the choice and design of MDR-TB treatment regimens. In addition to TB DRS findings, it is important for practitioners to know which medicines have been in frequent use in a given geographical setting or patient groups. If DST is not routinely available for individual patients, storage of *M. tuberculosis* isolates collected at baseline or during treatment monitoring can be considered for performing whole genome sequencing in case of treatment failure.

The DST results are generally used to guide the choice of chemotherapy in TB and MDR-TB regimens. When based on externally quality-assured laboratory work, DST to isoniazid, rifampicin and fluoroquinolones is most useful for clinical purposes. Methods for phenotypic DST – on mycobacteria growth indicator tube (MGIT) – for bedaquiline, linezolid, clofazimine, pyrazinamide and delamanid have now also been validated *(16, 17)*. Mutations in the promotor region of the *inh*A gene are detected by the first-line LPA; these mutations confer resistance to thioamides. Rapid implementation and use of these methods are needed to ensure antimicrobial stewardship, to accompany transition to new regimens. A standardized DST method for pretomanid is being developed and will be made available in the near future. Capacity to test for at least bedaquiline and linezolid should be established as a priority; however, regimen adoption and implementation (in line with recent WHO recommendations) can and should proceed while this DST capacity is being established.

Phenotypic DST for ethambutol, ethionamide and prothionamide may be inaccurate and not reproducible, especially in settings that lack proper external quality assurance. Moreover, no agreed DST methods have been established for some other second-line drugs (e.g. cycloserine/terizidone, imipenem-cilastatin/meropenem and PAS) *(16)*.

Despite some of the uncertainties about DST, NTPs should strive to test for drug resistance and limit empiric treatment to a minimum. The patient's clinical response to treatment should always be carefully monitored. If there is poor treatment response, undiagnosed resistance should be considered, as should alternative explanations for failure to respond to treatment (e.g. poor or erratic adherence to treatment, immune reconstitution inflammatory syndrome [IRIS] or the presence of comorbidities) *(18)*.

3.2 Safety monitoring and management, provision of patient support and management of comorbidities

All treatment delivered should align with WHO-recommended standards, including patient-centred care and support, informed consent where necessary, principles of good clinical practice, active TB drug safety monitoring and management (aDSM), and regular patient monitoring to assess regimen effectiveness. Health care providers must offer careful clinical and bacteriological follow-up to assess TB treatment response, with general laboratory support to monitor and manage adverse events and comorbidities. The provision of social support is essential to enable adherence to treatment *(5)*. Certain programmatic components (e.g. aDSM) *(5, 19)* are recommended for all patients on any MDR-TB regimen. An appropriate schedule of laboratory tests and clinical examinations should be included in the patient's treatment chart to identify adverse events *(5)*. In some settings where aDSM may not have been fully rolled out and national guidelines may not yet be fully updated, patients should not be made to wait until programme components are fully in place before they can receive potentially life-saving interventions. The WHO consolidated guidelines also reinforce the message that patient support is critical for good adherence and improved outcomes *(1)*.

3.3 Options in drug-resistant TB treatment regimens

The regimen notations used in the tables and throughout this document highlight the number of months for which a relevant combination of medicines is used and if certain drugs are used for a different duration this is also noted using subscript in brackets. The following are examples of regimen notations:

- Regimen for isoniazid-resistant TB: **6 (H)REZ-Lfx** (6-month treatment regimen composed of rifampicin, ethambutol, pyrazinamide, levofloxacin. Isoniazid can be added if 4-drug FDC (HREZ) will be used).
- Shorter regimen for MDR/RR-TB: **4–6 Bdq$_{(6\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E** (shorter all-oral bedaquiline-containing regimen).
- Shorter regimen for MDR/RR-TB with quinolone resistance: **6–9 Bdq-Pa-Lzd** (6–9 month treatment regimen composed of bedaquiline, pretomanid and linezolid – BPaL regimen).
- Longer regimen for MDR/RR-TB: **18 Bdq$_{(6\ m)}$-Lfx/Mfx-Lzd-Cfz** (18-month treatment regimen composed of bedaquiline for the first 6 months and levofloxacin or moxifloxacin, linezolid, clofazimine for 18 months).

Isoniazid is one of the most important components of first-line TB treatment regimens. Patients with Hr-TB who are treated with 2HREZ/4HR[4] stand a much higher risk of treatment failure, relapse or acquisition of additional resistance than those who have drug-susceptible TB. The acquisition of MDR-TB is a serious consequence of inadequate treatment of Hr-TB, given that it would necessitate a much longer treatment with more second-line agents. **A 6-month regimen using rifampicin, ethambutol, pyrazinamide and levofloxacin 6(H)REZ-Lfx is the recommended treatment option for patients with confirmed Hr-TB and rifampicin-susceptible TB**. The 6(H)REZ regimen is prescribed for Hr-TB patients in whom rifampicin susceptibility is unknown and levofloxacin cannot be used, or for Hr-TB patients with fluoroquinolone resistance, levofloxacin intolerance, or other contraindications.

For MDR/RR-TB patients without previous exposure to second-line medicines for more than 1 month, where there is no fluoroquinolone resistance and the patients do not have extensive TB disease or severe extrapulmonary TB, the preferred treatment option is a **shorter all-oral bedaquiline-containing**

[4] 2HREZ/4HR is isoniazid, rifampicin, ethambutol and pyrazinamide daily for 2 months, followed by four months of isoniazid and rifampicin.

regimen (**4–6 Bdq$_{(6\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E**[5]). In settings with a high probability of resistance to other medicines in the regimen (or in patients with confirmed resistance to other medicines), further modifications of the shorter all-oral bedaquiline-containing regimen using priority grouping of second-line TB medicines may be implemented under operational research. The efficacy, safety and tolerability of such modifications to regimens shorter than 12 months are unknown and should therefore be evaluated under operational research conditions *(1)*.There are situations in which a longer regimen may be preferred for these patients.

MDR/RR-TB patients with extensive TB disease, severe forms of extrapulmonary TB, additional resistance to fluoroquinolones or exposure to treatment with second-line medicines for more than 1 month will benefit from **an individualized longer regimen** designed using the WHO priority grouping of medicines recommended in the WHO consolidated guidelines (Table 6.1).

The **6–9 month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL)** may be used under operational research conditions in patients with MDR/RR-TB and additional fluoroquinolone resistance who have not had previous exposure to bedaquiline or linezolid (defined as <2 weeks). This regimen may not be considered for programmatic use worldwide until additional evidence on efficacy and safety has been generated. However, in individual patients for whom the design of an effective regimen based on existing recommendations is not possible, the BPaL regimen may be considered as a last resort under programmatic conditions (outside operational research). This implementation requires high prevailing standards of monitoring treatment response and adverse events, and provision of effective patient support.

Decisions on appropriate regimens should be made based on likely efficacy, safety, patient preference and clinical judgement, also taking into account the results of susceptibility testing, patient treatment history, severity and site of the disease.

[5] Bedaquiline is used for 6 months. Levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine are used for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide.

4. Regimen for rifampicin-susceptible and isoniazid-resistant TB

WHO released its first evidence-based guidance for the treatment of Hr-TB using the GRADE approach in 2018 *(1)*. The guidance is based on these two recommendations:

> **Recommendation 1.1 In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.**
> *(Conditional recommendation, very low certainty in the estimates of effect)*
>
> **Recommendation 1.2 In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.**
> *(Conditional recommendation, very low certainty in the estimates of effect)*

The recommendations made were conditional *(4)* and had very low certainty of evidence.

The basic regimen can be summarized as:

Hr-TB regimen: 6(H)REZ-Lfx

All medicines in this regimen are to be used daily for 6 months. When fixed-dose combination formulations are used, isoniazid is included but is not obligatory for the regimen. If levofloxacin cannot be used because there is fluoroquinolone resistance or intolerance or other contraindications to the use of fluoroquinolone, then 6(H)REZ may be prescribed daily for 6 months.

4.1 Eligibility

The Hr-TB regimen is recommended once isoniazid resistance has been confirmed and rifampicin resistance excluded. Rifampicin resistance needs to be excluded using rapid molecular tests (e.g. Xpert MTB/RIF) before levofloxacin is used; this is to avoid the inadvertent treatment of MDR/RR-TB with an inadequate regimen. Ideally, DST for fluoroquinolones and pyrazinamide is also performed.

It is not advisable to give a regimen for Hr-TB unless isoniazid resistance is confirmed or highly suspected (e.g. confirmed TB patient who is the close contact of a documented Hr-TB case). This will avert the unnecessary use of levofloxacin and prolonged pyrazinamide exposure in TB patients who may be cured with 2HREZ/4HR. Once the Hr-TB regimen has been started, if the results of initial DST reveal isoniazid susceptibility, the regimen may be modified so that the patient effectively completes a course of first-line TB treatment.

The recommendations apply to both adults and children, including people living with HIV (PLHIV). Thus, HIV testing and treatment of PLHIV with antiretroviral therapy (ART) is important, and the aim

is to start ART within 8 weeks of TB treatment initiation (regardless of CD4 count), or within the first 2 weeks in patients with profound immunosuppression (e.g. CD4 counts <50 cells/mm^3) *(20)*. The regimen is also likely to be effective in patients with extrapulmonary Hr-TB; however, consultation with appropriate specialists is advised.

Hr-TB treatment is expected to be started if either of the following circumstances apply:

- Hr-TB is confirmed and rifampicin resistance ruled out before TB treatment is started – in such cases, the 6(H)REZ-Lfx regimen is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be introduced. Should DST results taken at the start eventually show susceptibility to isoniazid, then levofloxacin is stopped and the patient continues treatment in order to complete a 2HREZ/4HR regimen; or
- Hr-TB is discovered after the start of treatment with the 2HREZ/4HR regimen (this includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance while on first-line treatment) – in such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance has been excluded, a full 6-month course of (H)REZ-Lfx is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this. A report of resistance during treatment presents the clinician with a challenge, because the results may no longer reflect the drug susceptibility of the current bacterial population, given that an inadequate regimen – at times a functional monotherapy – may have favoured the acquisition of additional resistance in the interval. The unexpected discovery of resistance to one agent should prompt the clinician to repeat DST for other agents in the regimen. The example in Box 4.1 illustrates a typical situation that could arise.

4.2 Composition and duration of the regimen

The duration of Hr-TB treatment is driven by the need to complete 6 months of a fluoroquinolone-containing regimen. This implies that, when Hr-TB is diagnosed *after* the start of a first-line regimen, the companion medicines (HREZ) would end up being given for more than 6 months.

In patients with cavitary disease and with persistent positivity on sputum smear and culture, prolongation of (H)REZ-Lfx beyond 6 months could be considered on a case-by-case basis. Prolongation of treatment increases the risk of toxicity, particularly from pyrazinamide and ethambutol, which are usually only given for 2 months in the first-line TB regimen. The evidence reviewed for the WHO guidance on Hr-TB precluded a recommendation to limit the pyrazinamide duration to less than 4 months when a fluoroquinolone is given.

Levofloxacin is the preferred fluoroquinolone for Hr-TB regimens, for two reasons. First, exposure to moxifloxacin decreases markedly when it is combined with rifampicin *(21)*. This effect has not been reported in the case of levofloxacin, possibly because this interaction has attracted less study. Second, levofloxacin appears to cause less QT interval prolongation than moxifloxacin.

Levofloxacin is included in Hr-TB regimens except in the following instances: when rifampicin resistance cannot be tested for, when there is documented resistance or known intolerance to fluoroquinolones, and when there is pre-existing prolongation of the QT interval and pregnancy. If a fluoroquinolone cannot be used, a patient with Hr-TB can still be treated with 6(H)REZ; streptomycin is not required in such cases.

For patient convenience and ease of administration, the HREZ fixed-dose combination (FDC) may be used to treat Hr-TB (since no REZ FDC is currently available). The dosage of other first-line agents in the Hr-TB regimen is the same as in the standardized first-line 2HREZ/4HR regimen. The inclusion of isoniazid in the regimen has not been shown to lead to substantial benefit or harm to patients; however, isoniazid may attenuate the hepatotoxicity of pyrazinamide *(22, 23)*. High-dose

isoniazid (10–15 mg/kg per day) may still be effective when used in combination regimens in the presence of isolated *inh*A mutations linked to low minimum inhibitory concentration (MIC), even in "fast acetylators" (i.e. those who metabolize isoniazid rapidly) *(24)*. In the presence of both *inh*A and *kat*G mutations, addition of isoniazid (even at a high dose) is unlikely to add value to the regimen.

Box 4.1. Evaluation of a typical scenario – a delayed DST result in a patient on a first-line regimen

Before starting the 2HREZ/4HR regimen, a patient with rifampicin-susceptible TB confirmed by Xpert MTB/RIF has a sputum sample sent to a regional laboratory for phenotypic DST. Three months later, the results are returned to the treating physician; they show susceptibility to ethambutol and pyrazinamide but resistance to isoniazid. The patient has meanwhile adhered to his treatment regimen, gained weight and been symptom free for 2 months.

What does the clinician need to think about and do?

- ➔ Given that the DST results are 3 months old, the initial resistance pattern may no longer be indicative of the current situation, because the bacteria may have acquired additional resistance.
- ➔ Since the beginning of the third month, the patient should have been in the continuation phase with isoniazid and rifampicin (which are usually in FDC); however, in reality, the patient is on rifampicin monotherapy. Resistance to rifampicin may have developed and needs to be checked even if the clinical progress suggests that the regimen is working. Xpert MTB/RIF needs to be repeated.
  - If rifampicin resistance is detected, the patient should be started on MDR-TB treatment (as detailed in Sections 5–7).
  - If rifampicin resistance is not detected, the patient should be switched to the (H) REZ-Lfx regimen for 6 months. Ideally, DST to quinolones should be performed.

Patients with Hr-TB may have a higher risk of acquiring additional resistance and MDR-TB, which may manifest in the course of the same treatment episode or in a subsequent relapse. The effect of additional resistance to ethambutol and pyrazinamide on the treatment of Hr-TB is unclear.

4.3 Considerations for implementation

The regimens recommended for treatment of Hr-TB do not have an intensive and a continuation phase – this simplifies the delivery and monitoring of treatment. Treatment is given daily, and intermittent treatment should be avoided. Relevant measures to support adherence, such as directly observed treatment (DOT), social support and the use of digital technologies should be considered to ensure favourable treatment outcomes *(2)*.

The cost of medicines to compose a full 6(H)REZ regimen with levofloxacin is higher than the cost of a 2HREZ/4HR regimen used for drug-susceptible TB *(25)*. Nonetheless, the 6(H)REZ regimen is an affordable and feasible intervention, even in low-income settings. Use of FDCs simplifies treatment and lowers costs, and the use of dispersible formulations of HRZ, ethambutol and levofloxacin is preferred in children. As with the treatment of other forms of TB, the expenses associated with the proper delivery of care (e.g. DST, adherence support and clinical monitoring) far exceed the cost of medicines.

There is currently no diagnostic platform approved for the detection of Hr-TB that matches the rapidity and convenience of Xpert MTB/RIF for rifampicin resistance, although a new Xpert cartridge that can detect isoniazid resistance is in the pipeline. First-line LPA can detect isoniazid resistance; it requires infrastructure that is typically available in a provincial or central level facility. Typical processing time for an LPA specimen is about 2–3 days, owing to batching. DST based on liquid culture (or MGIT) could also detect Hr-TB at the level of a reference laboratory, but this means an obligatory processing delay of at least 10 days. Testing on solid media is also an option, but it takes several months to obtain results; hence, this approach is of limited use for baseline testing and monitoring of treatment response.

Current epidemiological data indicate that more than three quarters of the global burden of Hr-TB occurs among previously untreated ("new") TB cases. Previous TB treatment is thus not a strong indicator of risk of Hr-TB – the correlation with previous TB treatment is weaker than it is with MDR-TB. Reserving isoniazid DST to such patients is therefore unlikely to yield many Hr-TB cases. There are various concerns about empirical Hr-TB treatment of previously treated TB cases, without prior drug susceptibility testing. First, such treatment will lead to unnecessary overtreatment with fluoroquinolones and prolongation of pyrazinamide use in many patients. Most re-treatment cases will not have Hr-TB and can be cured with a 2HRZE/4HR regimen. Second, unless rifampicin resistance is excluded at the baseline, patients with MDR/RR-TB would be exposed to an inadequate regimen, with the risk of acquiring additional resistance, including fluoroquinolones. Third, this policy would deflect the focus of the programme from testing new (previously untreated) TB patients, who usually harbour the main burden of Hr-TB. Finally, this approach would risk creating once again a "re-treatment regimen", similar to the situation that prevailed in many settings until recently with the indiscriminate use of the streptomycin-containing 8-month "Category 2" regimen in all previously treated TB patients.

In a situation where access to DST is good, a logical diagnostic algorithm would start with Xpert MTB/RIF as the initial test for all patients evaluated for TB. Cases in whom TB is confirmed and rifampicin resistance is not detected would be further tested with LPA. Liquid culture may replace LPA, but the additional delay in getting results is a disadvantage.

4.4 Treatment monitoring

The clinical monitoring of patients on Hr-TB treatment follows similar principles to those that apply to other first-line TB regimens (Sections 5.4 and 6.8). Bacteriological monitoring of sputum generally follows the same schedule as drug-susceptible TB, with direct microscopy at months 2, 5 and 6. It is desirable, however, to perform a culture together with smear microscopy (or at least in the last month of treatment) to check for any emergent resistance, especially to rifampicin. Non-response to treatment should be investigated with DST.

Liver and kidney function and other blood tests may be necessary, based on clinical manifestations and medications in use. Electrocardiography (ECG) for patients on 6(H)REZ-Lfx is not usually required unless there are other risks for QT interval prolongation. The first-line TB agents may cause adverse drug reactions, which are mostly mild, not serious and self-limiting, or manageable with basic measures. TB practitioners are likely to be more familiar with the use of these medicines than with levofloxacin, which has a fairly good safety profile in both adults and children when used at the dose recommended in Annex I, even when taken for longer than 6 months (as in MDR-TB regimens – see Section 6.2 and Table 6.4). Dosage adjustment is recommended if creatinine clearance is below 50 mL/min, in consultation with a specialist *(5)*. Adverse drug reactions should be reported to the spontaneous pharmacovigilance systems required by national regulations, as for other drug-related harms. In patients on regimens for Hr-TB, aDSM is not mandatory.

As with all other notifiable TB cases, patients with Hr-TB should be registered in the TB register, regardless of whether treatment has started, or whether a regimen containing second-line TB medicines is being given *(26)*. The case may be retained in the TB register for the purposes of monitoring treatment response and interim or final outcomes. Cases without Hr-TB may be enumerated with

Box 6.1. Summary notation to describe second-line regimens for MDR/RR-TB

A longer regimen is usually denoted using abbreviations for the individual agents and the duration of use in months; for example:

18 Bdq(6 m or longer)-(Lfx or Mfx)-Lzd-(Cfz or Cs)

In this example, the first 6 months of treatment comprises four second-line agents. The remaining 12 months includes the same agents except for bedaquiline, bringing the total duration to 18 months. All medicines apart from bedaquiline are given 7 days a week. Bedaquiline, when prescribed on-label, is given daily for the first 2 weeks and three times weekly thereafter (see Annex I for more details on dosing). Regimens without an injectable agent (i.e. all-oral regimens) are considered not to have an initial phase.

6.1 Eligibility

Any patient – child or adult – with MDR/RR-TB is eligible for treatment with either a shorter all-oral bedaquiline-containing MDR-TB regimen or, if this cannot be used, a longer MDR-TB regimen *(1)*.

Given the conditionality of the recommendation for the use of the shorter all-oral bedaquiline-containing MDR-TB regimen, the health care provider and patient may agree to use a longer treatment regimen if the patient is eligible for the shorter all-oral bedaquiline-containing MDR-TB regimen based on that person's individual circumstances. If the shorter all-oral bedaquiline-containing MDR-TB regimen cannot be used, the patient needs to be reassessed, with a view to starting a longer MDR-TB regimen. A patient started on the shorter all-oral bedaquiline-containing MDR-TB regimen can later be transferred to a longer MDR-TB regimen, should the need arise. However, once a patient is placed on a longer MDR-TB regimen for at least 4 weeks, normally that patient can no longer be switched to the shorter all-oral bedaquiline-containing MDR-TB regimen because this 4-weeks treatment would represent an exposure to second-line medicines.

MDR/RR-TB alone or with additional resistance: Both shorter and longer regimens are more likely to be effective if the composition is guided by reliable DST. If rifampicin resistance is detected, rapid molecular tests for resistance to isoniazid and fluoroquinolones should be performed promptly, to inform the decision about which medicines to use for the treatment of MDR/RR-TB. Ideally, all MDR/RR-TB patients are tested for resistance to fluoroquinolones as a minimum before starting MDR-TB treatment. DST can be performed for anti-TB medicines for which there are now agreed reliable and reproducible methods (e.g. bedaquiline, linezolid, clofazimine, delamanid and pyrazinamide). Phenotypic DST for ethambutol, cycloserine/terizidone, imipenem/meropenem, ethionamid/prothionamid and *p*-aminosalicylic acid is not reliable and is not routinely recommended. Hence, other approaches may be needed, to determine the likelihood of effectiveness of selected medicines. If one or more agents are unlikely to be effective, then they need to be replaced (or, if they are included in the regimen, not counted as effective) in order to have at least four effective agents to start with. The design of longer regimens for MDR-TB with additional resistance to fluoroquinolones or other second-line drugs follows a similar logic to that used for other MDR-TB patients. The capacity for DST for new and repurposed second-line drugs may not be available in all national reference laboratories, but it is imperative that this capacity is established as soon as possible *(16, 17)*.

Rifampicin-resistant TB: Any patient with rifampicin-resistant TB – whether a child or an adult – in whom isoniazid resistance is absent or unknown, needs to be treated with a recommended MDR-TB regimen. The regimen could be a shorter all-oral bedaquiline-containing regimen or a longer MDR-TB

regimen if the former cannot be used. High-dose isoniazid has also been shown to be an important component in paediatric regimens *(15)*. Although high-dose isoniazid is not included in Groups A–C, it may still be used in patients with confirmed susceptibility, or in the presence of mutations that do not usually confer complete resistance to isoniazid.

6.2 Medicines used in longer MDR-TB treatment regimens

The classification of medicines used in MDR-TB treatment regimens was revised following the evidence-informed update of the WHO guidelines on drug-resistant TB treatment in 2018. TB medicines to be used for treatment of MDR/RR-TB are categorized into Groups A, B and C (Table 6.1) *(1)*. This new classification is based on drug class, and level of certainty in the evidence on effectiveness and safety (i.e. balance between benefit and risk of harm). The data analysed relate mainly to adult patients who received regimens in recent years. Groups A–C feature the medicines to be used to compose longer MDR-TB regimens (Section 6.3). **WHO considers that, under programmatic conditions, only these medicines (Groups A–C) have a role in MDR-TB longer treatment regimens**. In addition to agents from Groups A–C, the potential role for clavulanic acid, high-dose isoniazid and gatifloxacin is also discussed (see footnotes of Table 6.1 and "Other medicines" in this section).

Table 6.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine and abbreviation	
Group A: **Include all three medicines**	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: **Add one or both medicines**	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: **Add to complete the regimen, and when medicines from Groups A and B cannot be used**	Ethambutol	E
	Delamanid[c,e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem-cilastatin *or* meropenem[g]	Ipm-Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

DST: drug susceptibility testing; ECG: electrocardiography; GDG: guideline development group; IPD-MA: individual patient data meta-analysis; MDR-TB: multidrug-resistant TB.

[a] This table is intended to guide the design of longer MDR-TB regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized, as detailed in Section 5). Medicines in Group C are ranked by decreasing order of usual preference for use

subject to other considerations. The 2018 IPD-MA for longer regimens included no patients on thioacetazone (T) and too few patients on gatifloxacin (Gfx) and high-dose isoniazid (Hh) for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies (see online Annex 8 of the WHO consolidated guidelines) *(1)*.

[b] Bedaquiline is usually administered 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally three times per week for 22 weeks (total duration of 24 weeks). Evidence on the safety and effectiveness of bedaquiline use beyond 6 months and in patients below the age of 6 years was insufficient for review in 2018. Therefore, the use of bedaquiline beyond 6 months was then implemented following best practices in "off-label" use *(37)*. New evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG in 2019. The GDG could not assess the impact of prolonged bedaquiline use on efficacy, owing to the limited evidence and potential residual confounding in the data. However, the evidence supports the safe use of bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. The use of bedaquline beyond 6 months still remains as off-label use, and in this regard best practices in off-label use still apply.

[c] Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review in 2018. In 2019, new evidence on both the safety and effectiveness of concurrent use of bedaquiline and delamanid was made available to the GDG. With regard to safety, the GDG concluded that the data suggested no additional safety concerns regarding concurrent use of bedaquiline and delamanid. Both medicines may be used concurrently among patients who have limited other treatment options available to them, and if sufficient monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place. The data on the effectiveness of concurrent use of bedaquiline and delamanid were reviewed by the GDG, but due to the limited evidence and potential residual confounding in the data, the GDG could not proceed with a recommendation on effectiveness *(1)*.

[d] Use of Lzd for at least 6 months was shown to increase effectiveness, although toxicity may limit its use. The analysis suggested that using Lzd for the whole duration of treatment would optimize its effect (about 70% of patients on Lzd with data received it for more than 6 months, and 30% for 18 months or the whole duration). No patient predictors for early cessation of Lzd could be inferred from the IPD subanalysis.

[e] Evidence on the safety and effectiveness of Dlm beyond 6 months and in patients below the age of 3 years was insufficient for review. Use of Dlm beyond these limits should follow best practices in "off-label" use *(8)*.

[f] Z is only counted as an effective agent when DST results confirm susceptibility.

[g] Every dose of Imp-Clv and Mpm is administered with oral clavulanic acid, which is only available in formulations combined with amoxicillin (Amx-Clv). Amx-Clv is not counted as an additional effective TB agent and should not be used without Imp-Cln or Mpm.

[h] Am and S are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. S is to be considered only if Am cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (S resistance is not detectable with second-line molecular line probe assays and phenotypic DST is required). Kanamycin (Km) and capreomycin (Cm) are no longer recommended for use in MDR-TB regimens.

[i] These agents only showed effectiveness in regimens without Bdq, Lzd, Cfz or Dlm, and are thus only proposed when other options to compose a regimen are not possible.

The most notable differences between the current and previous classification of longer regimen components are an upgrade in the priority of bedaquiline, linezolid, clofazimine and cycloserine/terizidone; placement of delamanid in group C; and lowering of priority for pyrazinamide, amikacin, streptomycin, ethionamide/prothionamide and PAS, relative to other treatment options. A number of agents that were featured previously in these groups are not included any more because they are:

- no longer recommended (e.g. ofloxacin, capreomycin and kanamycin);
- rarely used in longer regimens or unavailable on the market (e.g. high-dose isoniazid and gatifloxacin); or
- an adjunct agent and are not intended to be used alone (e.g. clavulanic acid is used only in combination with the carbapenems).

The new classification facilitates design of the treatment regimen for patients with drug-resistant TB who are eligible for a fully oral longer regimen. Table 6.1 summarizes the general steps to include agents for the longer MDR-TB regimen according to the latest WHO guidance, with more details provided in Table 6.5 for some of the most common situations and patient subgroups that clinicians and NTPs may encounter. The section below provides some background information on the individual agents; the available technical medicine information sheets provide the prescriber with further details on each medicine *(5)*. The updated weight-based dosages for adults and children are provided in Annex I.

Group A

This group includes the fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid. These medicines were found to be highly effective in improving treatment outcomes and reducing deaths in the evidence reviewed in 2018 for WHO guidelines *(1)*, and it is strongly recommended that they are included in all longer MDR-TB regimens and used for all MDR/RR-TB patients eligible for longer regimens unless there is a toxicity issue or drug resistance.

Levofloxacin and ***moxifloxacin*** are later-generation fluoroquinolones, and their use in the meta-analysis that informed the WHO guidelines (2018 update) resulted in a significantly lower risk of treatment failure or relapse and death *(1, 15, 38, 39)*. Levofloxacin and moxifloxacin are equally effective in fluoroquinolone-sensitive patients, and either of them can be considered for MDR-TB treatment. Ciprofloxacin and ofloxacin are less effective in MDR-TB treatment and are no longer recommended. No quality-assured preparations of gatifloxacin have been commercially available since the drug was removed from the market when an observational study identified dysglycaemia-related safety concerns in patients aged more than 65 years *(40)*.

Fluoroquinolones are known to prolong the QT interval; this may predispose some patients to *torsades de pointes*, which may result in sudden death. There is variability between the fluoroquinolones in this effect; however, overall, the prolongation is considered minimal or moderate (for moxifloxacin). Cardiac monitoring is required when using drugs that prolong the QT interval *(5)*. Moxifloxacin has a more pronounced effect on QT prolongation than levofloxacin. Levofloxacin and moxifloxacin have also been associated with dysglycaemia metabolic disorders *(41, 42)*. However, most of these reports have been from patients treated for conditions other than MDR/RR-TB, and the benefit-to-harm ratio is expected to be higher when fluoroquinolones are used in MDR/RR-TB (which is outside their usual indication), given the limited alternatives for treating this serious condition.

Rapid molecular DST is available and reliable for levofloxacin and moxifloxacin. If DST to moxifloxacin confirms resistance, or if history suggests that it has not been effective (e.g. if used in a failing regimen for an extended time), it should not be used. Under such circumstances, levofloxacin is also unlikely to be effective and the fluoroquinolones would need to be replaced in the regimen. High-dose moxifloxacin can be used in case of resistance to levofloxacin and low-level resistance to moxifloxacin.

Bedaquiline. In the individual patient data meta-analysis used as evidence for the WHO guidelines, bedaquiline use resulted in significantly fewer episodes of treatment failure, relapse and death *(3)*. There is limited experience with the use of bedaquiline in children aged under 6 years but growing experience of its use in adolescents and the elderly, patients with extrapulmonary TB disease and HIV-infected patients in particular. In an early trial, an increased risk of death was observed in patients on bedaquiline-containing regimens (9/79; 11.4%) when compared with the placebo group (2/81; 2.5%), although not all the deaths were directly related to bedaquiline *(43, 44)*. This risk has not been definitively attributed to bedaquiline or any known toxicities (e.g. QT interval prolongation). Additional analyses of observational study data did not reproduce this finding; rather, they highlighted the improved survival of patients treated with regimens containing bedaquiline *(45)* and the favourable safety profile of bedaquiline when the drug is used alongside other TB medicines, including medicines with the similar QT prolongation (e.g. moxifloxacin, clofazimine and delamanid) *(46–51)*. The recent data review for the WHO consolidated guidelines *(1)* suggested no additional safety concerns for the use of bedaquiline beyond 6 months, concurrently with delamanid or in pregnancy *(1, 48, 93)* (see Sections 6.1 and 6.2). The available data suggested that the concurrent use of bedaquiline and delamanid does not increase the risk of clinically meaningful QT prolongation. The emergence of bedaquiline resistance should be monitored in settings where it is used.

Bedaquiline is metabolized by the cytochrome P450 system enzymes in the liver. Drugs that induce or inhibit this system of enzymes will result in drug–drug interactions that can affect the blood levels of bedaquiline. Cytochrome P450 inducers decrease blood levels of bedaquiline, resulting in the possibility of inadequate levels of bedaquiline in the body for elimination of TB infection. Conversely,

cytochrome P450 inhibitors increase blood levels of bedaquiline, resulting in the possibility of an increased risk of toxicity. Table 6.2 provides examples of drugs that should be avoided if bedaquiline is used.

Table 6.2. Possible drug–drug interactions of bedaquiline with other medicines *(52–54)*

Drug–drug interactions	Medicines	Notes and instructions
Strong/moderate inducers of cytochrome P450[2] may decrease blood levels of bedaquiline	Efavirenz[a] Rifamycins: Rifampicin Rifapentine Rifabutin Phenytoin Carbamazepine Phenobarbital St. John's Wort	[a] Efavirenz (EFV) will result in low levels of bedaquiline in the blood. Therefore, it is advised to substitute nevirapine (NVP) or an integrase inhibitor for EFV when used with bedaquiline. [b] For a more comprehensive list of drugs that affect and are affected by the cytochrome P450 system, see the *Drug interactions* webpages of the Department of Medicine of Indiana University *(52)*.
Strong/moderate inhibitors of cytochrome P450 may increase blood levels of bedaquiline	Ritonavir-boosted protease inhibitors[c] Oral azole antifungals (can be used up to 2 weeks): Itraconazole Fluconazole[d] Macrolide antibiotics other than azithromycin[e]: Clarithromycin Erythromycin	[c] Ritonavir-boosted protease inhibitors (PIs) will result in high levels of bedaquiline in the blood. It is suggested to substitute the PI with an integrase inhibitor (INSTI), such as dolutegravir (DTG) or raltegravir (RAL). If a ritonavir-boosted PI must be used, an ECG should be performed every 2 weeks for the first 8 weeks. [d] All four oral azoles inhibit CYP3A4; itraconazole and posaconazole are more potent inhibitors than fluconazole or voriconazole *(55)*. [e] Azithromycin does not inhibit CYP isoenzymes but does prolong the QT interval so this drug may be avoided for this reason.
Possible interactions: medicines metabolized by CYP3A4 may increase bedaquiline exposure	Elvitegravir[f] Cobicistat[f] Emtricitabine[f] Tenofovir alafenamide[f]	[f] Concomitant use of bedaquiline with these drugs has not been well studied; however, their concomitant use for more than 14 consecutive days should be avoided. Because bedaquiline is also metabolized by CYP3A4, these drugs may increase bedaquiline exposure, which could potentially increase the risk of adverse reactions.

Linezolid has shown anti-TB activity in vitro and in animal studies, and its effectiveness in humans was demonstrated in the meta-analysis conducted for the WHO guidelines, as well as in recent trials involving XDR-TB patients *(1, 56–60)*. Lowering the dose from 600 mg daily to 300 mg daily may reduce toxicity but its impact on treatment effectiveness is not well known (although early bactericidal activity [EBA] studies suggest that the higher dose is more effective) *(61)*. When serious adverse effects arise, linezolid may need to be stopped. The IPD meta-analysis informing the WHO guidelines (performed in 2018) included information from more than 300 patients who were treated with linezolid for at least 1 month, mostly on 600 mg daily. About 30% of patients received linezolid for 1–6 months, but over 30% received it for more than 18 months, and these patients had the lowest frequency of

treatment failure, loss to follow-up and death. This analysis also suggests that the optimal duration of use would be about 20 months, corresponding to the usual total duration of a longer MDR-TB regimen; however, such an analysis does not account for survivorship bias (meaning that those who complete the full length of treatment are more likely to have a successful outcome, given that deaths and losses to follow-up occur earlier) *(1)*.

The evidence from the WHO consolidated guidelines *(1)* suggests that linezolid be used as long as it is tolerated. If toxicity develops, the drug dosing should be either reduced or stopped *(5)*. There may be improved outcomes if linezolid is used for the full duration of treatment. However, it likely has its greatest added effect (including protection of other second-line drugs against acquired drug resistance) during the first months of treatment when the bacillary load is highest *(61)*.

Major adverse events related to linezolid include anaemia, peripheral neuropathy, gastrointestinal disorders, optic neuritis and thrombocytopenia. These adverse events are well documented to be dose related. The adverse events are significantly more frequent when the linezolid daily dosage exceeds 600 mg *(62)*. The longer a patient uses linezolid, the higher the risk of experiencing a serious adverse effect.

Linezolid can have drug–drug interactions with drugs that affect the body's serotonin levels. Serotonergic syndrome, which can be serious and life threatening, can result when linezolid is given concomitantly with certain drug classes.

Table 6.3. Possible drug–drug interactions of linezolid with other medicines *(53)*

Drug–drug interactions	Medicines	Notes and instructions
Increasing serotonin levels that may result in serotonergic syndrome	• Serotonin re-uptake inhibitors (SSRIs): fluoxetine and paroxetine • Tricyclic antidepressants: amitriptyline and nortriptyline • Serotonin 5-HT1 receptor agonists • Monoamine oxidase inhibitors (MAO): phenelzine and isocarboxazid • Other serotoninergic agents: meperidine and bupropion or buspirone and quetiapine	Every effort should be made to avoid the use of drugs that have drug–drug interactions or overlapping toxicity with linezolid. However, there may be circumstances in which no other option is available, and the potential benefits outweigh the risks of using linezolid. For example, a patient with fragile mental health with a high risk of suicide who must have linezolid in the regimen (i.e. there are no other anti-TB drug options) could also require a serotoninergic medication.

Group B

This group of medicines includes clofazimine and cycloserine or terizidone, which were found to be effective in improving treatment outcomes but limited in reducing deaths in the evidence reviewed in 2018 for WHO guidelines *(1)*. One or both drugs can be added to ensure that a longer regimen starts with at least four effective medicines.

Clofazimine. Clofazimine is an anti-leprosy medicine that has shown in vitro activity against *M. tuberculosis*, and has been used as a second-line TB medicine for several years. The meta-analysis conducted for the WHO guidelines reinforced the evidence for the effectiveness and safety profile of clofazimine *(1)*. When used with drugs that prolong the QT interval (e.g. bedaquiline, fluoroquinolones and delamanid), clofazimine may cause additive QT prolongation. ECG monitoring

should be implemented when used with bedaquiline or if several QT prolonging drugs are also part of the regimen. Non-TB drugs that cause QT prolongation should be avoided if possible. Common adverse events are orange or red discolouration of skin, conjunctiva, cornea and body fluids; dry skin, pruritus, rash, ichthyosis and xerosis; gastrointestinal intolerance; and photosensitivity. Patients should be well informed from the outset of the reversible skin colour changes that occur in most patients. The orange-brown skin changes are reversible a few months after the drug is stopped and are not considered dangerous. Dry skin changes can also be common but are not considered dangerous. These skin changes can be quite concerning to patients and reassurance is required. Clofazimine is not recommended for use in pregnancy or breastfeeding owing to limited data (some reports of normal outcomes, some reports of neonatal deaths) and to pigmentation of the infant if the drug is used during breastfeeding. Clofazimine is partially metabolized by the liver; hence, caution or adjustment of the dose is required for patients with severe hepatic insufficiency.

Cycloserine is a bacteriostatic drug that inhibits cell wall synthesis, and it has no known cross-resistance to other TB medicines. ***Terizidone*** (composed of two molecules of cycloserine) may be used instead of cycloserine. Cycloserine and terizidone are considered interchangeable. Because of difficulties in interpreting DST (there is no reliable genotypic or phenotypic DST for cycloserine or terizidone), cycloserine or terizidone should only be considered when other criteria of likelihood of effectiveness are met; for example, any reliable evidence on population levels of drug resistance, and prior use of cycloserine or terizidone based on a reliable clinical history (see Section 3). Patients should be well informed of the potential adverse events of cycloserine. A major drug adverse event is central nervous system (CNS) toxicity, including inability to concentrate and lethargy. More serious CNS side-effects include seizure, depression, psychosis and suicidal ideation, which usually occur at peak concentrations of more than 35 mcg/mL but may also be seen in the normal therapeutic range. Other side-effects include peripheral neuropathy and skin changes. Skin problems include lichenoid eruptions and Stevens-Johnson syndrome. The use of these drugs in pregnancy has not been well studied, but no teratogenicity has been documented. Cycloserine can be used in pregnant women if there are no other better choices. It can be used while breastfeeding, and the infant should be given vitamin B6 if breastfed *(5)*.

Group C

Group C comprises both TB and repurposed medicines that are positioned at a lower priority than the Group A and B agents, either because they are less effective (ethambutol, delamanid, pyrazinamide, ethionamide/prothionamide and *p*-aminosalicylic acid) or because they are more toxic and cumbersome to administer parenterally (imipenem-cilastatin, meropenem, amikacin and streptomycin). These drugs are usually included in a longer regimen if it cannot be composed with Group A and B agents alone.

Ethambutol is a TB medicine that is used in first-line regimens and may be added to longer MDR-TB regimens. At recommended dosages, the safety profile of ethambutol is good. Due to difficulties in interpreting its DST, ethambutol should only be considered when other criteria of likelihood of effectiveness are met (e.g. evidence on population levels of drug resistance and prior use of ethambutol based on a reliable clinical history) (see Section 3.1).

Delamanid Based on current knowledge on the effectiveness and safety of delamanid from the assessment for the WHO guidelines, delamanid is recommended for use as a Group C agent in adults and children aged 3 years or more *(1)*. The available evidence of delamanid use is currently limited to the on-label 6 months duration alongside other medicines in a longer regimen; prolongation beyond 6 months can be considered on a case-by-case basis *(1, 8)*. More evidence on the efficacy of delamanid in different age groups and durations of use would be helpful to better guide its use. Achieving an appropriate dose in children aged 3–5 years will be easier when the special formulation used in trials in these age groups becomes available. The recent data review for the WHO guidelines *(1)* suggested that there are no additional safety concerns for concurrent use of delamanid with bedaquiline (see

Section 6.4). The combined QT effects of bedaquiline and delamanid, compared with bedaquiline or delamanid alone (added to multidrug background therapy), were evaluated in a randomized controlled trial (RCT) of 75 patients (>3000 ECGs). The average QTcF prolongation attributable to bedaquiline was 12.3 ms, and to the combination of bedaquiline and delamanid was 20.7 ms. No participants had grade 3 or 4 of QT prolongation *(49)*.

Pyrazinamide has been routinely added to MDR-TB regimens except where there is a reasonable clinical contraindication for its use (e.g. hepatotoxicity), or other serious adverse effect or drug resistance. However, reliable DST for pyrazinamide is not widely accessible; hence, this drug has often been used without DST or regardless of documented resistance. In the longer regimens, pyrazinamide is recommended for inclusion only when DST results confirm susceptibility, and it is then counted as one of the effective agents; in any other cases, if it is included in the regimen, it is not counted as an effective drug *(41, 44)*.

Imipenem-cilastatin and ***meropenem*** are the only carbapenems that have an established role in MDR-TB regimens, although there is limited experience in the use of ertapenem *(63)*. Both drugs are administered intravenously – a major drawback that limits their more widespread use outside hospitals, especially in resource-constrained settings *(64–68)*. Daily intravenous injections are not usually feasible unless there is a surgically fitted port, with a catheter connection to a major vein. Meropenem with clavulanate as part of regimens (usually also containing linezolid) for patients with MDR-TB and XDR-TB has shown improved culture conversion and survival *(69–71)*. Clavulanic acid (as co-amoxyclav) is not a TB medicine but is an adjunct agent given orally each time a carbapenem dose is administered, about 30 minutes before the intravenous infusion. When included in a regimen, clavulanic acid is not counted as one of the TB agents, and it should not be used without the carbapenem.

Amikacin and ***streptomycin*** are the only two aminoglycoside antibiotics that are still recommended for use in MDR-TB regimens when options for composition of the treatment regimen are limited. When the evidence of their use in longer MDR-TB regimens was reviewed in 2018, amikacin and streptomycin were associated with lower rates of treatment failure or relapse and death when used in people with *M. tuberculosis* strains susceptible to amykacin or streptomycin, although they share the disadvantages and serious toxicities (i.e. ototoxicity and nephrotoxicity) of other injectable agents that are no longer recommended (i.e. kanamycin and capreomycin). Amikacin and streptomycin may be used in adults aged 18 years or more, in situations where an effective regimen cannot otherwise be designed using oral agents, when susceptibility is demonstrated, and when adequate measures are in place to monitor for adverse events. Given the profound impact that hearing loss can have on the acquisition of language and the ability to learn at school, the use of injectable agents in children should be exceptional and limited to salvage therapy, and the treatment needs to be provided under strict monitoring to ensure early detection of ototoxicity. Amikacin is preferred over streptomycin, which is used only as a substitute when amikacin is not available or there is confirmed resistance to it. The latest analysis from patients on longer regimens has shown a higher risk of serious adverse events in patients on amikacin than on streptomycin *(1)*. The use of these medicines requires the availability of DST for confirming drug susceptibility, and hearing monitoring for detecting drug toxicity. The patient should be informed about drug toxicity, and consent should be obtained before treatment. Given the high frequency of streptomycin resistance in patients with MDR/RR-TB in many settings, and its extensive historical use as part of older first-line TB regimens in many countries, streptomycin is unlikely to have much use in MDR-TB regimens.

Ethionamide and ***prothionamide.*** In WHO guidance, ethionamide and protionamide are considered interchangeable. The WHO consolidated guidelines make a conditional recommendation *against* their use in longer MDR-TB regimens, reserving them for situations where multiple, more effective agents (e.g. bedaquiline, linezolid and clofazimine) cannot be used.

***P*-aminosalicylic acid (*PAS*)** can be considered as the last resource for treatment of MDR/RR-TB. The drug is recommended in the WHO consolidated guidelines only for use in the treatment of MDR/RR-TB patients on longer regimens if bedaquiline, linezolid, clofazimine or delamanid are not used,

or if better options to compose a regimen are not possible. There is no indication of cross-resistance of PAS to other anti-TB drugs *(1)*.

Other medicines

A number of medicines previously recommended as potential components of MDR-TB longer treatment regimens do not feature in Groups A–C. This section outlines the reasons for this, and provides some background information about these medicines (dosing details are also included in the revised schedules in Annex I).

Gatifloxacin use in MDR-TB was largely limited to the earlier studies of the standardized shorter MDR-TB regimen in Bangladesh and Cameroon *(33, 72)*. Dysglycaemia in elderly patients receiving gatifloxacin as a broad-spectrum antibiotic led to its withdrawal from the market *(40, 73)*. Although it is possible to use gatifloxacin in a programme with well-organized aDSM, the lack of quality-assured formulations on the market precludes its use.

High-dose isoniazid (10–15 mg/kg) is not included in Groups A–C given the rarity of its use in contemporary longer regimens for adults. It is also a relatively safe medicine, as shown recently in experience with its use at the 10 mg/kg dose, where only 0.5% of 1006 patients in a multicentric observational study of the shorter MDR-TB regimen reported grade 3 or 4 neurotoxicity *(74)*. Other evidence suggests that it may also be useful in the longer MDR-TB regimens. First, in the systematic review and IPD meta-analysis commissioned by WHO in 2015 to describe treatment outcomes in children with MDR-TB (which included 975 children in 18 countries), the use of high-dose isoniazid was associated with treatment success among children with confirmed MDR-TB (adjusted odds ratio [aOR] 5.9, 95% confidence interval [CI]: 1.7–20.5, P=0.007) *(75)*. Second, in a randomized, double-blinded, placebo-controlled clinical trial among adults with MDR-TB, participants who received high-dose isoniazid (16–18 mg/kg) (added to kanamycin, levofloxacin, prothionamide, cycloserine and PAS) were significantly more likely to experience culture conversion at 6 months of treatment than those receiving placebo or standard-dose isoniazid (5 mg/kg) (73.8% versus 48.8% or 45.0%, respectively), with median time to culture conversion significantly reduced in the high-dose isoniazid arm (3.4 versus 6.6 or 6.4 months, respectively). Genotypic DST was not performed, but about 60% of participants had *M. tuberculosis* isolates for which isoniazid MICs were between 0.2 and 5 mcg/mL. Peripheral neuropathy was more common with high-dose isoniazid, but pyridoxine was not given in the trial *(76)*. Third, a more recent EBA study among patients with MDR-TB – wherein the isoniazid resistance was mediated by isolated *inh*A mutations – who were randomized to receive isoniazid at 5, 10 or 15 mg/kg, demonstrated that doses of 10–15 mg/kg of isoniazid daily exhibited bactericidal activity similar to standard-dose isoniazid (5 mg/kg) given to patients with drug-susceptible TB *(77)*. Strains with isolated *kat*G or both *kat*G and *inh*A mutations are unlikely to respond even to high-dose isoniazid, given the typically high isoniazid MICs in those strains. The WHO consolidated guidelines recommend that high-dose isoniazid can also be used in the regimens of adults and children with confirmed susceptibility to isoniazid, or in the presence of mutations that do not confer high-level resistance to isoniazid (i.e. isolated *inh*A mutations) *(1, 15)*.

Kanamycin and capreomycin are injectable agents that are no longer recommended components for any MDR-TB regimen, following the data analysis for the update of WHO guidelines in 2018, which showed an increased risk of treatment failure, relapse or death when their use was compared with regimens without them *(1)*. In addition, these agents present a considerable inconvenience to the patient, and are associated with serious toxicities that may result in permanent damage to hearing and kidney function unless the outcomes are closely monitored.

The risk of serious adverse events from second-line TB medicines was reported in the results of a meta-analysis of the individual IPD for the WHO guidelines update, presented in Table 6.4 *(1)*. The level of serious adverse event provides important information on the likelihood that a certain medicine may need to be stopped at some point during treatment because of its intolerability (particularly linezolid, which has the highest risk of serious adverse events).

Table 6.4. Serious adverse events in patients on longer MDR-TB regimens[a] *(1)*

Medicine	Absolute risk of SAE	
	Median (%)	95% credible interval
Bedaquiline	2.4	[0.7, 7.6]
Moxifloxacin	2.9	[1.4, 5.6]
Amoxicillin–clavulanic acid	3.0	[1.5, 5.8]
Clofazimine	3.6	[1.3, 8.6]
Ethambutol	4.0	[2.4, 6.8]
Levofloxacin	4.1	[1.9, 8.8]
Streptomycin	4.5	[2.3, 8.8]
Cycloserine/terizidone	7.8	[5.8, 10.9]
Capreomycin	8.4	[5.7, 12.2]
Pyrazinamide	8.8	[5.6, 13.2]
Ethionamide/prothionamide	9.5	[6.5, 14.5]
Amikacin	10.3	[6.6, 17.0]
Kanamycin	10.8	[7.2, 16.1]
P-aminosalicylic acid	14.3	[10.1, 20.7]
Thioacetazone	14.6	[4.9, 37.6]
Linezolid	17.2	[10.1, 27.0]

GDG: guideline development group; IPD: individual patient data.

[a] From an "arm-based network" meta-analysis of a patient subset from the 2016 IPD for which adverse events resulting in permanent discontinuation of a TB medicine (27 studies) or classified as grade 3–5 (3 studies) were reported. Slight differences between the final estimates cited in the resultant publication *(78)* and the values derived at the time of the GDG as shown in this table are due to the fact that an expanded dataset was used in the publication – these differences bear no consequence on the conclusions drawn on the use of these medicines. There were insufficient records on delamanid, imipenem–cilastatin and meropenem to estimate risks. Agents that are not in Groups A–C are italicized.

6.3 Composition of the longer MDR-TB regimens

When designing these regimens, a number of basic principles need to be respected, in line with the best available evidence on composition of the regimens, as per the latest WHO guidelines *(1)*.

6.3.1 Choice of components for the longer MDR-TB regimens

A stepwise approach guides the design of longer MDR-TB regimens (Table 6.1 and Table 6.5). The treatment of patients with rifampicin mono-resistant TB, as well as those who have resistance to second-line agents in addition to MDR-TB (including XDR-TB), follows the same principles. The selection of agents follows a priority order based on the revised classification of regimen components, and a fully oral regimen is preferred.

The analyses conducted for the WHO consolidated guidelines support the current recommendation that most patients can be successfully treated with a regimen starting with four agents that are likely or confirmed to be effective. If bedaquiline is stopped at month 6, the regimen will still have three effective agents for the rest of the treatment duration. However, if another agent needs to be stopped because of toxicity, then that medicine would need to be replaced by another one, or bedaquiline could be continued throughout the treatment under "off-label" use. If the choice is to replace a medicine, instead of prolonging the use of bedaquiline, the replacement medicine would be chosen either from Group B (unless both clofazimine and cycloserine/terizidone are already included) or from Group C. The choice from Group C is usually determined by the order in which the medicines are ranked, and by the individual circumstances of the patient and setting. Recent review of the observational data has shown no additional safety concerns when bedaquiline was used for longer than 6 months; however, no solid evidence was available to indicate whether longer use added efficacy. The clinicians may therefore consider continuing bedaquiline for longer than 6 months, and adding some flexibility for regimen design and the number of effective drugs *(1)*.

To minimize the need to replace agents in the regimen, in addition to the option of prolonging the use of bedaquiline beyond 6 months, it is possible to start the regimen with five agents instead of four. This increases the pill burden and chances of adverse reactions, but may be justified, particularly when:

- two of the four agents are likely to be stopped before the end of treatment (e.g. if bedaquiline is stopped at month 6 and linezolid is stopped early because of toxicity);
- reliable DST is not available for one or more of the agents in the regimen but background resistance to the agent is known to be high; and
- the regimen cannot be constructed from at least four effective agents from Groups A and B.

Regimen composition may often need to be adjusted after the start of treatment once additional information from the clinical history or DST results emerges. However, if signs of non-response or impending treatment failure emerge, then the regimen should be reviewed completely rather than adjusted. A medicine may be avoided if there is high likelihood that the patient has developed, or will develop, a contraindication to it. Contraindications may depend on a history of severe reactions to the medicine or an allied substance, pregnancy or breastfeeding, co-administration of medicines that may cause interactions or have overlapping toxicities (e.g. QT interval prolongation) and problems with end-organ function (e.g. kidney or liver dysfunction). Box 6.2 outlines some of the key considerations when choosing individual medicines for a longer MDR-TB regimen.

Other tests for resistance to agents such as pyrazinamide, and for mutation patterns commonly associated with resistance to isoniazid and the thioamides, may help to inform the composition of the regimen. Currently, there is no validated rapid test for pyrazinamide susceptibility, and phenotypic testing may require several weeks to produce a reliable result; a decision to include or replace pyrazinamide should not delay the start of treatment.

Resistance beyond MDR-TB, including MDR-TB with fluoroquinolone resistance, reduces the likelihood of treatment success *(79, 80)*. The risk of MDR-TB with fluoroquinolone resistance is much higher in some settings (e.g. in Eastern European countries). Untreated, MDR-TB with fluoroquinolone resistance has a high mortality, particularly in PLHIV, and strains that have acquired resistance have shown little if any attenuation in transmissibility; such strains have been implicated in extensive outbreaks, with much of the global burden attributed to primary transmission *(81–83)*.

With the lowered importance of aminoglycosides in MDR-TB treatment regimens, the utility of diagnosis of an MDR-TB with injectable resistance, as currently defined, has lost its value. However, resistance to fluoroquinolones remains an important finding for all regimens. The steps in Table 6.1 apply also to the design of a fluoroquinolone resistance regimen for MDR-TB; in addition, they cover MDR-TB with fluoroquinolone resistance among other resistance patterns.

no experience of the use of this medicine in other combinations, pretomanid is not recommended for use outside the context of the BPaL regimen. Safety signals related to pretomanid include hepatologic, gastrointestinal, dermatologic and reproductive adverse effects.

WHO recommendation on the use of BPaL regimen (1)

Recommendation 4.1 A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks.
(Conditional recommendation, very low certainty in the estimates of effect)

7.1 Eligibility

A patient is eligible for treatment with the BPaL regimen if he or she:

- is diagnosed with bacteriologically confirmed pulmonary TB and has laboratory-confirmed resistance to rifampicin and fluoroquinolones with or without resistance to injectable agents; and
- is aged at least 14 years at the time of enrolment; and
- weighs 35 kg or more; and
- is willing and able to provide informed consent to be enrolled in the operational research project and to adhere to the follow-up schedule (signed or witnessed consent if the patient is illiterate, signed or witnessed consent from a child's parent or legal guardian); and
- if the patient is a premenopausal woman, is not pregnant or breastfeeding and is willing to use effective contraception; and
- has no known allergy to any of the BPaL component drugs; and
- has no evidence in DST results of resistance to any of the component drugs, or has not been previously exposed to any of the component drugs for 2 weeks or longer; and
- has no extrapulmonary TB (including meningitis, other CNS TB, or TB osteomyelitis).

Patients who are not eligible for the BPaL regimen can benefit from the individualized longer treatment regimen that is composed of medicines using the priority grouping of medicines shown in Table 6.1.

Contraindications: There are no absolute contraindications for the use of any drug in the treatment of MDR-TB and MDR-TB with fluoroquinolone resistance (a disease that poses serious risk of death or debilitation to the patient if treated inadequately). However, there are relative contraindications for the BPaL regimen, and some of the most relevant of these are listed in Table 7.1. If the clinician judges that the potential benefits outweigh the potential risk (also taking into account alternative treatment options), then treatment may proceed with caution. In these situations, advice should be sought from the assigned TB expert committee.

Table 7.1. Relative contraindications to the use of the BPaL regimen for treatment of patients with MDR/RR-TB with additional fluoroquinolone resistance

Relative contraindication	Notes
Concurrent use of medications that have known interactions or overlapping toxicities with BPaL component drugs	Inducers of CYP450 enzymes: • Efavirenz • Rifamycins • Antiepileptics Inhibitors of CYP450 enzymes: • Ritonavir-boosted PIs • Fluconazole or itraconazole • Clarithromycin or erythromycin Drugs that prolong the QT interval Drugs that increase serotonin level
High risk of cardiac arrhythmia	Baseline QTcF >500 ms History of syncopal episodes, ventricular arrhythmias, heart failure or severe coronary artery disease Family history of long-QT syndrome
Severe anaemia, thrombocytopenia or leukopenia	Haemoglobin level < 8.0 g/dL Platelet count < 75 000/mm^3 Absolute neutrophil count < 1000/mm^3
Severe hepatic failure	AST/ALT > 3.0 × ULN Total bilirubin > 2.0 × ULN Albumin < 32 g/L
Severe renal failure	Serum creatinine > 3.0 × ULN Owing to limited experience with the use of this regimen, caution should be exercised in patients with severe renal failure
Severe neuropathy	Peripheral neuropathy of grade 3 or grade 4

ALT: alanine transaminase; AST: aspartate transaminase; BPaL: bedaquiline, pretomanid and linezolid for 6–9 months; CYP: cytochrome; MDR/RR-TB: multidrug- or rifampicin-resistant TB; PI: protease inhibitor; ULN: upper limits of normal.

7.2 Composition and duration of the regimen

The BPaL regimen comprises three components – bedaquiline, pretomanid and linezolid – that are used as a package. Bedaquiline and linezolid are used in longer regimens (see Section 6.2) and bedaquiline is also used in the shorter all-oral regimen (see Section 5).

Pretomanid is a new medicine, and its safety and effectiveness have not been established for its use in combination with medicines other than bedaquiline and linezolid as part of the BPaL regimen *(96, 97)*. Pretomanid is a nitroimidazole (i.e. in the same chemical class as delamanid) and is a prodrug that is metabolically activated by a nitroreductase, producing various metabolites that are responsible for its therapeutic action. Pretomanid inhibits cell wall biosynthesis and, under anaerobic conditions,

it causes respiratory poisoning of the bacterial cell through the release of reactive nitrogen species. Pretomanid possesses activity in both replicating and non-replicating *M. tuberculosis* bacilli (Abdel-Rahman SM. unpublished data, Children's Mercy Hospital, Kansas City, United States of America, November 2019). In vitro, preclinical and clinical data support a role for pretomanid as part of the BPaL regimen. Because there is no experience of the use of this medicine in other combinations, pretomanid is not currently recommended for use outside the context of the BPaL regimen. Pretomanid is currently being further tested as part of combination regimens for the treatment of both drug-susceptible and drug-resistant TB.[16] The most common adverse reactions observed in patients treated with pretomanid in combination with bedaquiline and linezolid included damage to the nerves (peripheral neuropathy), acneiform dermatitis, anaemia, nausea, vomiting, headache, increased liver enzymes (transaminases and gamma-glutamyltransferase), indigestion (dyspepsia), rash, pruritus, increased pancreatic enzymes (hyperamylasemia), decreased appetite, increased transaminases and gamma glutamyl transpeptidase, visual impairment, low blood sugar (hypoglycemia), abdominal pain, musculoskeletal pain and diarrhoea *(96, 97)*. Data from the animal model study also suggested the side-effect of infertility related to pretomanid (Abdel-Rahman SM. unpublished data, Children's Mercy Hospital, Kansas City, United States of America, November 2019) *(96)*. The WHO GDG (November 2019) highlighted the potential difficulties in monitoring of infertility in a programmatic setting. Additional human sperm studies recommended by the United States Food and Drug Administration (US FDA) are being carried out by TB Alliance; however, the findings were not available at the time of the GDG meeting *(1)*. Infertility is a serious issue because it affects both patients and their families; given this potential side-effect, the balance of the desirable and undesirable effects of the treatment needs to be carefully discussed with the patient, who should be involved in the treatment decision.

The BPaL regimen comprised pretomanid administered at 200 mg once daily, bedaquiline administered at 400 mg once daily for the first 2 weeks of treatment (days 1–14) and then 200 mg three times a week thereafter, and linezolid at 1200 mg per day.

Table 7.2. Dosing of component drugs for adults and adolescents (aged 14 and over)

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	1200 mg once daily (adjustable)

Dose modifications for bedaquiline and pretomanid are not allowed. Linezolid high dose (1200 mg once daily) in the BPaL regimen can be reduced after the first month of treatment in patients with linezolid-induced peripheral neuropathy or myelosuppression.

Following the regimen used in the Nix-TB study, the linezolid dosage is 1200 mg per day. At the time the study commenced, all study participants first received 600 mg of linezolid twice a day because that was the approved dose used to treat bacterial infections for up to 28 days at the time. However, in May 2018, the protocol was changed to dosing of 1200 mg of linezolid once a day. Dose reduction to 600 mg daily and further to 300 mg daily or temporary cessation of linezolid was permitted for up to 35 consecutive days for any known linezolid adverse reactions of myelosuppression, peripheral neuropathy and optic neuropathy. If toxicity prohibited further treatment with linezolid, then patients

[16] A Phase III trial (called SimpliciTB) of BPaMZ, targeting patients with drug-susceptible TB or MDR-TB, is being implemented. The primary end-point is culture conversion at 2 months, with a secondary end-point of cure 6 months after completion of therapy. A previous Phase IIb study of this BPaMZ regimen showed almost 100% culture conversion at 2 months in patients with MDR-TB. ZeNix, a follow-on trial of Nix-TB, is exploring lower doses and shorter durations of linezolid within Nix-TB to minimize toxicity.

could remain on bedaquiline and pretomanid provided that they had received the 1200 mg per day dose for at least the first 4 consecutive weeks, were sputum smear negative or had only trace or scanty results, and were responding to treatment based on clinical monitoring and follow-up.[17] Missed doses of linezolid were not made up during the Nix-TB study, and dose modifications for bedaquiline and pretomanid were not allowed *(1, 95)*.

With the experience of linezolid use in the Nix-TB study, the following modifications of linezolid dosing in the management of adverse events may be considered for the BPaL regimen:

- Linezolid can be temporarily interrupted, or the dosage can be reduced after the first month.
- The dose of linezolid can be reduced from 1200 mg once daily to 600 mg or 300 mg once daily.

The BPaL regimen is given for a duration of 6–9 months. The standard treatment duration is 6 months. If the sputum culture taken after 4 months of treatment is positive, patients can receive an additional 3 months of treatment (total 9 months). The full BPaL regimen can be temporarily interrupted for a maximum of 35 consecutive days. Any missed days will be made up by extending the duration of the regimen by the number of days missed, but this must not be more than 35 days.

7.3 Key subgroups

Children. Children (0–13 years) were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could have been performed. It is recommended that children with pulmonary MDR/RR-TB with additional resistance to fluoroquinolones be given the same consideration for longer treatment regimens as adults, to include components with a safety profile that is better established. Bedaquiline is currently only recommended for children aged 6 years and above.[18] Additional data on the use of BPaL in children, when eligible, would be useful, and this may be a feature of carefully planned and monitored operational research studies or clinical trials.

PLHIV. PLHIV represented half of those enrolled in the Nix-TB study. However, it was impossible to perform any adjusted stratified analyses for PLHIV, due to the sample size. PLHIV were eligible to enrol in the Nix-TB study if they had a CD4 count of more than 50 cells/uL and if they were using permitted antiretroviral medications.[19] In the operational research context, clinicians or investigators may consider and decide on the eligibility criteria for enrolment, which may be different from the Nix-TB study regarding CD4 count. It is important to note drug–drug interactions when administering TB and HIV medications in combination, including the documented interactions between bedaquiline and efavirenz. There are two important drug–drug interactions between antiretroviral drugs and bedaquiline, also mentioned above: efavirenz induces metabolism of bedaquiline – its co-administration with bedaquiline may result in reduced bedaquiline exposure and loss of activity, and it is therefore not recommended; and ritonavir may increase bedaquiline exposure, which could potentially increase the risk of bedaquiline-related adverse reactions, so the combination of bedaquiline with ritonavir should be avoided or be administered with caution (see Table 6.2) *(52–54)*. ART regimens should be modified to avoid these drugs for an HIV-positive patient treated with a BPaL regimen. Efavirenz also reduces pretomanid exposures significantly; therefore, an alternative antiretroviral agent should be considered if pretomanid or the BPaL regimen is to be used *(96)*. Regimens including zidovudine should be used with special caution because both zidovudine and linezolid may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.

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[17] Overall, 18 (17.3%) patients in the Nix-TB study (*n*=109) completed a full course of linezolid at the 1200 mg dose, 38 (36.5%) completed with a 600 mg dose, 16 (15.4%) completed with a 300 mg dose and 32 (30.7%) stopped linezolid early due to an adverse event. Additional studies are underway to assess the optimal dosing and duration of linezolid for the treatment of drug-resistant TB.

[18] Based on the results of an RCT conducted by the manufacturer, the US FDA has extended approval for the use of bedaquiline for children aged 5 years and above *(32)*. However, these data have not yet been assessed by WHO.

[19] These permitted antiretroviral treatments were: nevirapine in combination with any nucleoside reverse transcriptase inhibitors (NRTIs), lopinavir/ritonavir in combination with any NRTIs; tenofovir/lamivudine/abacavir (if normal renal function); triple NRTI therapy comprising zidovudine, lamivudine and abacavir (noting the increased risk of peripheral nerve toxicity with zidovudine and linezolid), and raltegravir in combination with NRTIs.

Pregnant and lactating women were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could be performed, and safety of the BPaL regimen in pregnant and lactating women has not been established. In such cases, it is recommended that a longer regimen be individualized to include components with a safety profile that is better established. The safety of pretomanid in pregnant and lactating women has not been established. The use of bedaquiline in pregnancy has been shown to be associated with infants born with a lower mean birth weight than infants whose mothers did not take bedaquiline; however, this did not appear to be a clinically significant finding when infants were followed over time. Breastfeeding is not recommended for women taking BPaL.

Extrapulmonary TB. Patients with extrapulmonary TB were excluded from the Nix-TB study. Therefore, the WHO recommendations for longer MDR-TB regimens apply to patients with extrapulmonary disease, including for those with TB meningitis. There are few data on the CNS penetration of bedaquiline or pretomanid.

Patients with very limited treatment options. In some instances, patients will have extensive drug-resistance profiles that may make it difficult (or impossible) to construct a regimen based on existing recommendations. In such situations, the patient's life may be endangered. Therefore, for individual patients for whom it is not possible to design an effective regimen based on existing recommendations, the BPaL regimen may be considered as a last resort under prevailing ethical standards.

7.4 Considerations for implementation

Given the limited evidence on the use of BPaL, and the concerns mentioned above, the implementation of the BPaL regimen should be in the context of operational research only. Despite the promising treatment success rates observed in the Nix-TB study, the regimen may not currently be considered for programmatic use worldwide until additional evidence on efficacy and safety has been generated. Operational research is intended to generate this evidence. The implementation of the BPaL regimen in the context of operational research implies that:

- a study protocol needs to be developed and submitted to a national ethics board or any other ethics approval committees;
- pre-specified inclusion and exclusion criteria are in place;
- an appropriate schedule of safety monitoring and reporting is in place (including aDSM):
- a pre-defined schedule of clinical and microbiologic monitoring is in place, preferably including post-treatment completion follow-up;
- individual patient informed consent is obtained;
- patient support is provided; and
- a standardized reporting and recording system is used, including for adverse events.

Details on a generic operational research protocol, data collection and other aspects that can be adapted for the BPaL operational research can be found in the ShORRT research package developed by WHO and TDR *(36)*.

Patients should be fully informed about the regimen, and especially that it includes a new compound, pretomanid. Individual patient informed consent is necessary but should not be overly burdensome for patients – consent forms should be adapted, contextualized and streamlined so that they are easy for patients to understand. As part of the informed consent process, patients should be advised of the reproductive toxicities seen in animal studies and advised that the potential effects on human male fertility have not been adequately evaluated. A medication guide is available as part of the pretomanid product label, and it may be used when informing patients. In any operational research study involving the BPaL regimen, the principles of good clinical practice should apply. All efforts need to be made to carefully select eligible patients and then, once patients are enrolled, to provide effective patient support to enable adherence to treatment and close monitoring for adverse events and response to treatment.

DST is an important implementation consideration, which will need further enhancement in many countries given the increasing potential use of bedaquiline and linezolid (even for longer regimens for MDR/RR-TB) and the inclusion of new medicines – such as pretomanid – in MDR-TB treatment regimens. Baseline DST will confirm eligibility for the BPaL regimen; therefore, the establishment and strengthening of DST services will be a vital implementation consideration. For patients with confirmed MDR/RR-TB, the MTBDRsl assay is considered as the initial test, in preference to culture and phenotypic DST, to detect resistance to fluoroquinolones and, if necessary, to the second-line injectable drugs *(94)*. If DST is available for bedaquiline or linezolid, it is highly desirable that this is also carried out at baseline. DST for pretomanid is being developed. In settings in which laboratory capacity for DST to fluoroquinolones is not yet available, it will be difficult to carry out operational research on BPaL. Patients with strains resistant to any of the medicines used in the BPaL regimen should commence treatment with a longer MDR-TB regimen. In addition, because access to DST should be improved for all component medicines of the BPaL regimen, there will be a need to have the medicine powders available and to have data on the MIC distribution of all *M. tuberculosis* lineages that are circulating globally.

In the Nix-TB study, all medications were administered with food throughout and study medications were supervised according to local site practices, as a form of patient support. It was necessary for patients to complete 6 months (i.e. 26 weeks of prescribed doses) within 8 months; for those who had treatment extended, it was necessary for patients to complete 9 months of treatment (i.e. 39 weeks of prescribed doses) within 12 months *(1)*.

Preventing treatment interruption is important to increase the likelihood of treatment success. Measures to support patient adherence tailored to patient needs are important to retain patients on treatment and to ensure good treatment outcomes, such as a relevant model of care, DOT provided in the community or at home and by a trained treatment supporter, social support and digital health interventions for communication with the patient (see Section 9) *(1, 2)*.

7.5 Treatment monitoring

7.5.1 Monitoring treatment response and outcome assignment

Response to treatment is monitored on the basis of monthly sputum smear microscopy and culture (ideally at the same frequency). This is similar to the schedule used in patients on longer MDR-TB regimens. While awaiting updated definitions, the treatment outcome definitions and reporting framework for patients on the shorter MDR-TB regimen are the same as those for patients on longer MDR-TB regimens *(26)*.

Treatment must be administered under closely monitored conditions to enable optimal drug effectiveness and safety, and to monitor for the acquisition of emerging drug resistance, should it arise. Given that the BPaL regimen is a new and shorter regimen that includes a novel medicine and is being implemented under operational research conditions, it is also important to follow up patients after the completion of treatment, to ensure that there is no relapse. In the Nix-TB study, monitoring after completion of treatment was carried out monthly for months 1–3, then at 3-monthly intervals thereafter. Follow-up after treatment completion was for a total of 24 months; however, at the time of data analysis, about half of the patients had been followed up for this period. The analysis of the Nix-TB study data indicated that treatment failure or recurrence occurred in three patients (2.8% of patients overall), taking into account the period of post-treatment completion follow-up.

7.5.2 Monitoring safety

Due to the rather high level of adverse events experienced by patients in the Nix-TB study (as described previously in this section), safety for patients who receive BPaL needs to be actively

monitored, following the aDSM framework. Patients need to be tested at baseline and then monitored during treatment using schedules of relevant clinical and laboratory testing. According to the product label of pretomanid, baseline assessments before initiation of the BPaL regimen include assessments for symptoms and signs of liver disease (e.g. fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly) and the conduct of laboratory tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase and bilirubin, complete blood count and serum potassium, calcium and magnesium – which should be corrected if abnormal). Treating clinicians should also obtain an ECG before starting a patient on treatment. The baseline monitoring schedule of the Nix-TB study was much more comprehensive than this, and included a thorough baseline clinical assessment, then weekly patient monitoring until week 20, followed by 4–6 weekly monitoring thereafter, partly dependent on whether the patient had treatment for 6 months in total or whether treatment was extended by another 3 months (to 9 months in total).

Detailed schedules of baseline and follow-up monitoring, including after the completion of treatment, should be developed for any BPaL operational research protocol, with standardized measures for recording adverse events. The WHO framework for aDSM needs to be applied to patients on any type of MDR-TB regimen, to ensure appropriate action and an acceptable level of monitoring for and prompt response to adverse events – alongside monitoring for treatment outcomes, including early monitoring for treatment failure. Additional evidence generated on adverse events will be important to build the evidence base on the safety of the BPaL regimen in varied settings.

The monitoring of changes in dosing and duration of linezolid in particular (when needed) will also be important to inform the future evidence base on the wider use of the BPaL regimen and the tolerability of linezolid in this regimen. Based on a pharmacokinetic toxicodynamic model that was developed based on the Nix-TB study data (Savic R., University of California, San Francisco, unpublished data, November 2019), it was concluded that the pharmacokinetics related to linezolid are nonlinear in patients with MDR-TB with fluoroquinolone resistance, and individual linezolid concentration times are the best predictor of toxicity in this model. Higher toxicity rates were observed at higher total daily doses, with comparable toxicity rates for BID and QD[20] dosing schedules. Data modelling indicated that anaemia can be managed by closely monitoring changes in haemoglobin over the first 4 weeks of treatment. In particular, decreases in haemoglobin of more than 10% from baseline should trigger a reduction in the dose of linezolid; haemoglobin levels recover well after dose reductions. Peripheral neuropathy and optic neuritis should be closely monitored. Thrombocytopenia was potentially not a major concern at high dose linezolid for MDR-TB in patients with fluoroquinolone resistance *(1)*.

Adverse events related to pretomanid, particularly potential safety signals related to male infertility, were observed in animal (murine and simian) models. The panel highlighted the potential difficulties in monitoring of infertility in a programmatic setting *(1)*. Additional human sperm studies recommended by the United States (US) Food and Drug Administration (FDA) will be carried out by the TB Alliance; however, these data were not available for the GDG to consider at the time of the meeting. The GDG determined that infertility is a serious issue because it affects not only patients but also their families. Judgement about the balance of the desirable and undesirable effects needs additional research evidence to be generated before a decision can be taken on whether to implement the BPaL regimen worldwide under programmatic conditions.

A schedule for monitoring examinations should be established and applied to all patients receiving treatment with the BPaL regimen. Patients should undergo appropriate evaluation at baseline, and during and after treatment *(5)*. This should include necessary clinical evaluations, bacteriological and laboratory tests, radiology and ECG examinations (see the sample schedule in Table 7.3). The baseline visit refers to the beginning of the treatment with the BPaL treatment regimen. The monitoring schedule should take into account the following considerations:

[20] Where BID is twice daily and QD once daily.

- laboratory and ECG monitoring should be continued at monthly intervals (where indicated) for the duration of treatment (i.e. 9 months in the case of treatment prolongation);
- more frequent monitoring may be advisable in specific situations, including elderly people, patients infected with HIV, those affected by hepatitis (caused by hepatitis B virus [HBV] or hepatitis C virus [HCV]) or diabetes mellitus, or with moderate to severe hepatic or renal impairment; and
- in the case of electrolyte disturbances or ECG abnormalities, more frequent monitoring should be performed.

Active pharmacovigilance should be performed, as well as proper management of adverse events and prevention of complications from drug–drug interactions. The NTP should thus actively monitor drug safety to ensure proper patient care, to report any adverse events to the responsible drug safety authority in the country, and to inform national and global policy.

7.5.3 Modification or discontinuation of treatment

Safe management of adverse events may warrant dose reduction or discontinuation of the component drugs. However, the BPaL regimen has been studied as a standardized course of treatment. Modification of the regimen through early discontinuation or replacement of any of the component drugs may result in poor treatment outcomes. Although dose modification of bedaquiline and pretomanid is not allowed, dose modification of linezolid is acceptable after the first month of treatment in cases of adverse events (see Section 6.5, which describes some acceptable modifications of duration in relation to missed doses).

The BPaL regimen may need to be discontinued in some patients. In such cases, patients need to be evaluated and treatment switched to an individualized longer regimen, based on the WHO guidelines for regimen design using priority grouping of medicines.

The most common situations in which the regimen may be discontinued are the following:

- *Intolerable toxicity* – One or more drugs may need to be suspended permanently owing to severe toxicity. In such cases, the clinician (or, preferably, clinical committee or consilium) should review the medical history and assess the patient carefully to determine what regimen should be prescribed.
- *Treatment failure* – If clinical and bacteriological responses to treatment are poor, a change in the treatment regimen should be considered. DST should be repeated, whether or not the regimen is changed, to inform future management decisions.
- *Resistance to drugs in the BPaL regimen* – For patients who submit a sputum sample for culture-based second-line DST at the beginning of treatment, results may not be available until after treatment has started. If resistance to BPaL component drugs is discovered after treatment is initiated, it will be necessary to discontinue the regimen.
- *Pregnancy during treatment* – For patients who become pregnant during treatment, it will be necessary to discontinue the BPaL regimen.

Regarding the discontinuation of any component of the BPaL regimen due to severe toxicity, the following factors should be taken into account:

- If either bedaquiline or pretomanid needs to be discontinued, the entire BPaL regimen should also be discontinued.
- If linezolid is permanently discontinued during the initial 4 consecutive weeks of treatment, the entire regimen should be discontinued.
- Temporary cessation of linezolid (due to a linezolid-specific toxicity) or of the full regimen is allowed for suspected drug-related toxicity. Re-introduction of the regimen could be considered after a cessation of no more than 35 consecutive days.
- If linezolid needs to be permanently discontinued at a later stage of the regimen, when the patient has already completed the initial 4 consecutive weeks of treatment with the linezolid 1200 mg daily dose, clinicians should assess patient status and consider discontinuing the regimen or continuing administration of bedaquiline and pretomanid for the rest of the regimen.

Table 7.3. An example of the schedule of baseline, routine and post-treatment monitoring examinations for the BPaL regimen

Examination	Baseline	2 weeks	Monthly	End of treatment	6- and 12-months post-treatment
Clinical evaluation					
Clinical assessment[a]	X	X	X	X	X
Psychosocial assessment[b]	X	X	X	X	X
Weight/BMI	X	X	X	X	X
Performance status	X				
Peripheral neuropathy screen	X	X	X	X	
Visual acuity and colour discrimination screen	X	X	X	X	
Assessment and follow-up of adverse events	X	X	X	X	X
Outcome consultation				X	X
Bacteriological evaluations					
Sputum smear	X		X	X	X
Sputum culture	X		X	X	X
Sputum drug susceptibility testing[c]	X		If smear or culture positive		
Other samples (smear/culture/DST)	X		If no documented response to treatment		
Radiology, ECG & laboratory evaluations					
Chest X-ray	X			X	X
ECG	X	X	X	X	
Full blood count	X	X	X	X	
Liver function tests (AST, ALT, bilirubin)	X	X	X	X	
Serum electrolytes	X				
Urea, creatinine	X				
Pregnancy test	X				
HIV/HBV/HCV tests	X				
BSL/HbA1c	X				

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BSL: blood sugar level; DST: drug susceptibility testing; ECG: ECG: electrocardiography; Hb: haemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; TB: tuberculosis.

[a] Vital signs, TB symptom screen, pain, nausea, appetite and nutrition, diarrhoea, candidiasis. Clinical assessment should focus on a) monitoring response to treatment and b) addressing common symptoms associated with TB treatment and long-term antibiotic use, with the goal of supporting adherence.

[b] Food security, housing, mental state, substance use. Psychosocial assessment should offer an opportunity to assess supportive factors for treatment adherence and should be directly linked to relevant interventions wherever possible per country specific questionnaires.

[c] Xpert MTB/RIF, Hain GenoType MTBDRsl, culture-based second-line DST, next generation sequencing. If available, this should include Xpert/XDR and DST for the BPaL component drugs.

8. Adjuncts to MDR-TB treatment

8.1 Surgery in treatment of M/XDR-TB

Surgery has been employed in the treatment of TB since before the advent of chemotherapy. With the challenging prospect that more cases of M/XDR-TB are virtually untreatable with all available drugs or risk having serious sequelae, there has been re-evaluation of the role of pulmonary surgery as a means to reduce the amount of lung tissue with intractable pathology and to reduce the bacterial load. Large case series have reported that resection surgery may be safe and an effective adjunct when skilled thoracic surgeons and excellent postoperative care are available *(98, 99)*.

The updated WHO consolidated guidelines include a conditional recommendation for elective partial lung resection (lobectomy or wedge resection) as an adjunct to the chemotherapy of MDR/RR-TB and XDR/TB patients. The recommendation does not apply to radical pneumonectomy, which had no statistically significant effect *(98)*. This policy was based on evidence from an IPD meta-analysis to evaluate the effectiveness of different forms of elective surgery as an adjunct to combination medical therapy for MDR-TB *(98)*, and a systematic review and study-level meta-analysis *(100)*.

The relative benefits of surgery are expected to depend substantially on the population subgroups that are targeted. The reviews for the guideline update in 2016 *(15)* could not provide a refined differentiation of the type of patient who would be best suited to an intervention, or the type of intervention that would carry the most benefit. The effect is expected to be moderate in the average patient considered appropriate for surgery. The odds of success for patients with XDR-TB were statistically significantly lower when they underwent surgery compared with other patients (adjusted OR: 0.4, 95% CI: 0.2–0.9) *(98)*. This finding is likely to be biased, given that patients who underwent surgery would have had other factors predisposing then to poor outcomes – factors that could not be adjusted for. Programmes with limited access to surgery may target patients who remain sputum smear positive, who have resistance to many drugs and who have localized pulmonary disease. Computerized tomography, pulmonary function testing and quantitative lung perfusion or ventilation may have a role in the preoperative work-up.

Resection surgery should be timed to give the patient the best possible chance of cure with the least risk of harm. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality are lower (e.g. when the disease is still localized to one lung or one lung lobe). Generally, at least 2 months of therapy should be given before resection surgery, to decrease the bacterial infection in the surrounding lung tissue. Prognosis appears to be better when partial lung resection is performed after culture conversion. Even with successful resection, the total duration of treatment and the duration of treatment after culture conversion should be guided by the recommendations in Sections 5–7.

Partial lung resection for patients with MDR/RR-TB is only to be considered when good surgical facilities, staffed by trained and experienced surgeons, are available. Many programmes will have limited access to surgical interventions. In programmes with suboptimal surgical facilities and with no trained thoracic surgeons, resection surgery may increase morbidity or mortality. Specialized

surgical facilities should include stringent infection control measures (given that infectious material and aerosols are generated in large quantities during surgery), mechanical ventilation and postoperative pulmonary hygiene manoeuvres. After resection, direct laboratory testing of the resection material (lung lesion) will be useful. If the results of laboratory testing differ between the resected material and other clinical specimens, the treating clinician may need to adjust treatment based on the results obtained from the resected material or other clinical specimens.

There are still many uncertainties about the role of surgery in MDR-TB treatment. All data available for the 2016 recommendations were from observational data from case series, which may be biased. For instance, it is likely that in choosing patients to be operated on there would have been systematic exclusion of patients deemed unfit for surgery and anaesthesia, such as older patients and those who were very sick with comorbidities (e.g. no patient with HIV in the dataset had undergone surgery) or extensive disease. There were not enough data on adverse events, surgical complications or long-term sequelae – some of which may be fatal – to allow a meaningful analysis. Conversely, the effectiveness of surgery may have been underplayed in the analysis because of the lack of a suitable control group.

8.2 Use of corticosteroids

Corticosteroids have been used to support the treatment of serious and severe consequences of TB, such as miliary TB, respiratory insufficiency, CNS involvement and pericarditis.

The WHO *Guidelines for treatment of drug-susceptible TB and patient care 2017 update* made the following recommendations *(2)*:

> **In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used.**
> *(Strong recommendation, moderate certainty in the evidence)*
>
> **In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.**
> *(Conditional recommendation, very low certainty in the evidence)*

The recommendations are limited to these two forms of extrapulmonary TB. In patients with TB meningitis, evidence from RCTs *(101–105)* showed lower rates of death, severe disability and relapse when patients received steroids with TB treatment. The mortality benefit increased with increasing severity of TB meningitis. Adverse events and severe adverse events, including severe hepatitis, were lower in the patients receiving steroids. In patients with TB pericarditis, studies showed a benefit to steroid treatment with regard to death, constrictive pericarditis and treatment adherence *(106–113)*.

Although the evidence and the recommendations primarily relate to non-MDR-TB, there is no reason why these recommendations should not apply also to patients with MDR/RR-TB, on the condition that the patient is still receiving the TB treatment regimen. Corticosteroids are immunosuppressive and therefore can weaken the body's response to fight TB; hence, they should only be used if clearly indicated and if the patient is on an adequate effective regimen. If corticosteroids are used in an inadequate regimen, this could accelerate the patient's deterioration. Oral treatment can be given, but when a more immediate response is needed injectable corticosteroids are often used initially.

8.3 Use of immunomodulators

An expert group studying the potential of immunomodulators in 2007 remarked upon their potential to improve M/XDR-TB care, in particular by shortening treatment and boosting the immunity of cured patients to avert recurrence *(114)*. The group concluded, however, that none of the candidate agents that were reviewed showed proof of efficacy, and they recommended further development and evaluation of existing immunotherapy agents to find an effective adjunct to chemotherapy. More

recently, a Phase I non-randomized trial of M/XDR-TB patients in Belarus (Republic of) reported much higher treatment success in patients given infusions of autologous bone marrow-derived mesenchymal stromal cells with their drug-resistant chemotherapy than controls who were not infused *(115)*. No serious adverse events were observed in a pilot study preceding this trial *(116)*. The findings support further trials to assess more fully the potential of this therapeutic approach.

The possible contribution of agents that have been proposed to improve cure or reduce treatment duration when used in conjunction with recommended TB chemotherapy (e.g. interferon gamma – a soluble cytokine, essential for antimycobacterial host defences) has yet to be fully elucidated. However, as part of a review of the evidence of the effectiveness of individual medicines for the WHO consolidated guidelines *(1)*, the evidence on the use of interferon gamma as an adjunctive treatment was reviewed.

The literature review yielded a number of studies on interferon gamma as an adjunct treatment for TB; however, most of the studies either did not include a comparison group (and therefore we were not able to generate estimates of effect) or had other methodological flaws (e.g. small sample sizes, incomplete reporting on blinding, randomization or adjustment for potential confounders), and one included patients who received a 12-month MDR-TB regimen *(117–120)*. No RCTs were found, and it appears that the only randomized, placebo-controlled, multicentre trial of adjunctive interferon gamma for patients with MDR-TB was the InterMune study, which was halted prematurely due to deaths in the experimental arm *(121)*. The lack of high-quality evidence that demonstrates efficacy means that adjunctive treatment with interferon gamma cannot be proposed as part of M/XDR-TB regimens under programmatic conditions.

8.4 Treatment of HIV coinfected MDR/RR-TB patients

With regard to ***HIV infection***, a specific recommendation was made in 2011 on the use of ART in all patients with HIV and drug-resistant TB *(20, 38)*:

> **Recommendation 6.1 ART is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment.** *(Strong recommendation, very low quality evidence)*

Delaying ART increases the risk of dying among HIV-infected TB patients. ART should be started in all TB patients living with HIV, regardless of their CD4 cell count. The therapy should be initiated as soon as possible within the first 8 weeks of TB treatment, or within the first 2 weeks in patients with profound immunosuppression (e.g. CD4 counts <50 cells/mm^3). In children with HIV and active TB, ART should be initiated as soon as possible and within 8 weeks following the initiation of anti-TB treatment, regardless of the CD4 cell count and clinical stage *(20)*.

There may be a potential for overlapping, additive toxicities or for drug–drug interactions between some antiretroviral medicines and the injectable agents, moxifloxacin and clofazimine; however, there are usually no grounds to warrant modifications of the MDR-TB or the ART regimens. It is not recommended to use bedaquiline and efavirenz in combination (see Section 6.2). The medicine information sheets in Part 3 of the companion handbook *(5)* provide information on individual medicines used to treat MDR/RR-TB and their drug interactions. In addition, information on HIV drug interactions is available on the HIV Drug Interactions webpage *(54)*. Antiretroviral treatment regimens need to be optimized, and should be initiated early, in accordance with WHO recommendations *(5, 38)*. Close monitoring for response and toxicity is advised for patients on both TB and HIV treatment. Other comorbidities (e.g. diabetes and mental health disorders) should be managed accordingly *(5)*.

9. Patient support to enable adherence to treatment

Treatment support of patients using a patient-centred approach is needed to maximize treatment adherence and enable early detection of patients who are not responding to treatment. Community-based or home-based DOT is conditionally recommended over health facility-based DOT or unsupervised treatment. DOT administered by trained lay providers or health care workers is conditionally recommended over DOT administered by family members or unsupervised treatment. Video (virtual) observed treatment (VOT) can replace DOT when the technology is available, and can be appropriately organized and operated by health care providers and patients *(1, 2, 122)*.

Apart from DOT, several other interventions are considered important to promote treatment adherence and a patient-centred approach. NTPs need to improve patient access to a package of treatment adherence interventions, in conjunction with the selection of a suitable treatment administration option, which is defined as material support (e.g. food, financial incentives and reimbursement of transport fees), psychological support, home visits, use of information technology, medication monitors and staff education. Moreover, counselling and patient education on the disease and on treatment adherence are strongly recommended *(1, 2, 122)*. The following recommendations from the WHO *Guidelines for treatment of drug-susceptible tuberculosis and patient care 2017 update (2)* continue to apply to patients with drug-susceptible and drug-resistant TB:

Recommendation 8.1 Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment
(Strong recommendation, moderate certainty in the evidence)

Recommendation 8.2 A package of treatment adherence intervention[21] may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option[22]
(Conditional recommendation, low certainty in the evidence)

Recommendation 8.3 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) **tracers[23] or digital medication monitor[24]** *(conditional recommendation, very low certainty in the evidence);*

[21] Treatment adherence interventions include social support such as material support (e.g. food, financial incentives, and transport fees); psychological support; tracers such as home visits or digital health communication (e.g. SMS, telephone call); medication monitoring; and staff education. The interventions should be selected on the basis of the assessment of individual patient's needs, provider's resources and conditions for implementation.

[22] Treatment administration options include DOT, VOT, non-daily DOT (e.g. not every dose supervised treatment, weekly or a few times per week supervision), or unsupervised treatment.

[23] Tracers refer to communication with the patient, including via SMS, telephone (voice) calls, or home visit.

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

b) **material support to patient**[25] *(conditional recommendation, moderate certainty in the evidence);*

c) **psychological support**[26] **to patient** *(conditional recommendation, low certainty in the evidence)*

d) **staff education**[27] *(conditional recommendation, low certainty in the evidence).*

Recommendation 8.4 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** *(conditional recommendation, moderate certainty in the evidence)*

b) **DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members or unsupervised treatment** *(conditional recommendation, very low certainty in the evidence)*

c) **Video observed treatment (VOT) can replace DOT when the video communication technology is available and can be appropriately organized and operated by health care providers and patients** *(conditional recommendation, very low certainty in the evidence)*

Recommendation 8.5 Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization *(1)*
(Conditional recommendation, very low certainty in the estimates of effect)

Recommendation 8.6 A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment *(1, 2, 123)*
(Conditional recommendation, very low certainty in the estimates of effect)

The implementation of the recommended patient-centred care interventions is particularly important in improving treatment outcomes of patients on MDR-TB treatment *(124)*. Various models and toolkits for patient-centred supportive care have been developed and piloted for implementation in different settings *(125)*.

[25] Material support can be food or financial support such as: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives, or financial bonus. This support addresses 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.

[26] Psychological support can be counselling sessions or peer-group support.

[27] Staff education can be adherence education, charts or visual reminders, educational tools and desktop aids for decision-making and reminders.

10. Programmatic implementation of MDR-TB regimens

Introducing the longer and shorter MDR-TB regimens entails a series of steps that are the same as those necessary when an NTP introduces a new MDR-TB treatment component. Some key points are summarized below.

Policy and operational documents

Policy and operational documents that govern the main components of the programme would need to be revised. Such documents include the national strategic plan for TB, treatment guidelines and algorithms, diagnostic algorithms, the essential medicines list, regulations (e.g. importation of clofazimine and pretomanid), drug orders and training material. No immediate changes are usually needed to the second-line TB treatment register (although WHO is revising the definitions and reporting framework for TB in 2020) *(26)*. The TB treatment card may be changed to allow the tabulation of results of periodic testing for treatment response and adverse reactions (this may have already been done for the purposes of aDSM) *(19)*. Any changes should also cover for use of the regimen in private practice.

National MDR-TB expert committee and/or technical working group

A national MDR-TB expert committee or technical working group (the consilium or its equivalent structure within the NTP) will assist health care providers as early as possible to:

- coordinate policy changes and activities related to the introduction of the revised MDR-TB regimens in both the public and private sectors (e.g. training, communication, establishing patient eligibility for the different MDR-TB regimens);
- train staff in the clinical aspects of aDSM;
- provide patient support; and
- provide technical and clinical advice.

Additional support may be provided by other experts at national and international (e.g. regional Green Light Committee (rGLC)) level. This needs to consider any phased implementation process, such as the initial introduction in one or a few centres before full scale-up, or whether implementation is also occurring in the private sector.

Electronic recording and reporting

There is a need to improve the quality of patient data using standardized variables, such as data on DST pattern, prescribed treatment, treatment outcomes and adverse drug reactions. Collection and

utility of these data are important for future evidence-based recommendations, especially given the lack of RCTs on the management of drug-resistant TB *(126)*. If digital patient records do not already exist, it is important that the programme management considers their introduction, at least for surveillance, if not for case management as well *(127)*. If patient records are already digital, changes may be needed in the electronic recording and reporting system to allow individuals belonging to MDR-TB regimen cohorts of interest (e.g. shorter regimen, bedaquiline-containing regimens and operational research subgroups) to be identifiable, and for certain options to be included in the monitoring framework (e.g. addition of clofazimine and registration of ECG findings). It is crucial for programmes to maintain such data diligently and prospectively, so that they can contribute to programme evaluation and to global policy-making (the development of the WHO consolidated guidelines benefited hugely from experience of patient treatment within programmes) *(29, 30)*. The treatment outcome cohort reports for MDR/RR-TB need not change (for the digital and paper version). Moreover, electronic tools can enhance the quantification of consumables; for example, volumes of medicine can be calculated automatically using QuanTB, an application that is available for download free of charge.[28]

Estimates (epidemiological and logistics)

Estimates are needed by the NTP and other health care providers, to determine the number of MDR/RR-TB patients eligible for the longer and shorter MDR-TB regimens, to revise the budget accordingly, and to submit the corresponding requests for drug orders taking into account the existing stock of medicines. These estimates of MDR/RR-TB patients likely to be enrolled are based on current notification trends and an expected increase as per national and subnational plans. The programme first establishes the number of MDR-TB enrolments expected in the coming years, depending on the future increase in programme capacity (e.g. as part of a project supported by a grant from the Global Fund to Fight AIDS, TB and Malaria). Then, based on knowledge from surveillance, eligibility and estimated rate of scale-up, different patient groups are defined; for example, those expected to receive different variants of the longer MDR-TB regimens and those likely to receive a shorter MDR-TB regimen. When estimating the caseload to put on treatment, it is necessary to factor in not just eligibility, but also what would be feasible to achieve within a given time, to ensure that all elements are in place for starting and maintaining patients on treatment (e.g. training and provision of an adequate framework for patient monitoring and support). Associated programme and patient costs other than the medicines themselves usually dominate the total cost for both longer and shorter MDR-TB regimens (e.g. treatment of adverse events, hospitalization, diagnostic consumables, other clinical care and social support); however, total costs are expected to be lower for shorter regimens, given the shorter duration of treatment.

Management of the supply chain and storage conditions for pharmaceuticals

Management of the supply chain and storage conditions for pharmaceuticals have to be reviewed to ensure that TB drug orders are made in good time and are correctly quantified to avert overstocking or shortages. The NTP must ensure an uninterrupted supply of TB medicines through proper quantification, supply planning and rigorous quarterly monitoring, with a functional early warning system to avoid stock-outs and subsequent treatment interruptions. Likewise, other consumables (e.g. medicines for symptomatic relief and adverse reactions, syringes, diagnostic kits, medication for management of adverse effects, masks and N95 respirators) will be needed to ensure that the intervention is delivered as per internationally recommended standards *(128)*. The principles for the quantification of medicines needed for the longer and shorter MDR-TB regimens are similar. The health care provider needs to have some basic details about how many patients will be treated and when they will start; the expected increment in caseload over successive years; the average body weight of

[28] Available at http://siapsprogram.org/tools-and-guidance/quantb/.

the patients; whether children will also be enrolled; the expected losses (from interruptions, deaths and transfers to another regimen); current stock on hand, including expiry dates and orders of medicines already in the pipeline and not yet delivered; and whether some medicines will be exchanged during the period (e.g. amikacin has been replaced by bedaquiline following the 2019 revision). It is best to split an order of medicines, the first part for the patients expected to be started within 6 months, and then to adjust the second part of the order based on the actual enrolments. Technical assistance to strengthen the procurement and supply and to establish an early warning system for stock-outs can be accessed via the Global Drug Facility (GDF; email gdf@stoptb.org), regional Green Light Committee (GLC) secretariats housed in WHO regional offices, or WHO country offices. GDF provides support to many national TB programmes on the procurement and supply chain aspects of phase-in and phase-out plans of products or regimens and can procure child-friendly formulations.

Active TB drug safety and monitoring (aDSM) is particularly important given the increased use of newer and repurposed medicines in combination MDR-TB regimens. aDSM defines the active and systematic clinical and laboratory assessment of patients on MDR-TB treatment to detect, manage and report suspected or confirmed drug toxicities *(19)*. aDSM applies the principles of active pharmacovigilance to the specific needs and context of national TB programmes and is embedded within the routine patient monitoring function (e.g. treatment outcome cohort monitoring) of NTPs. The management of patient safety is an inherent part of aDSM, inseparable from its monitoring component. The recording and reporting activities of aDSM primarily target serious adverse events as a priority requirement, but any adverse event during treatment administration that may or may not be related to drug toxicity needs to be managed to limit harms to patients. MDR-TB treatment sites may also monitor non-serious adverse events which are of clinical significance or of special interest to the programme, as part of more comprehensive aDSM. In aDSM, besides the spontaneously reported reactions, adverse events are also elicited as part of a patient monitoring plan comprising a set of questions and oftentimes an array of laboratory or clinical tests at defined periods of time, before, during and after treatment.

When planning important changes for the national TB treatment policy to align to the latest WHO recommendations, the programme needs to balance the will to provide the best possible options for patients according to the latest evidence with the programmatic circumstances and the implications of such changes (e.g. need to re-train staff, reprogramming funds). Table 10.1 presents another checklist for chief considerations for the programme manager when implementing the MDR-TB regimens that are currently recommended. The programme needs to balance the need to provide access to new medicines for which the evidence is still incomplete with the need to protect patients from avoidable toxicity, the emergence of resistance to the new agents and observance of proper ethical conduct and respect for patient rights.

Table 10.1. Checklist to assess programme readiness for introduction of novel regimens

Parameter		
Access to new medicines is a priority as per national TB programme guidelines?	Yes	No
Well-functioning MDR-TB programme component in place?	Yes	No
MDR-TB expert committee(s) available to oversee use and support policy development and/or clinical decision-making?	Yes	No
Staff training is up to date with the latest developments?	Yes	No
Diagnostic capacity for WHO-recommended second-line DST available?	Yes	No
Clinical monitoring capacity, especially ECG, liver function, audiometry and electrolytes available?	Yes	No
Key components of aDSM in place?	Yes	No
Drug registration or other provision to allow importation of the new and repurposed medicines in place?	Yes	No
Quantification and drug procurement procedures in place?	Yes	No
Mechanism for patient informed consent in place?	Yes	No
Electronic recording and reporting system in place or needs updating?	Yes	No

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Annex I: Dosage by weight band for medicines used in multidrug-resistant TB regimens, adults and children

A. Dosing of medicines used in second-line multidrug-resistant-TB regimens by weight band (patients 15 years or older)

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients 15 years or older[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
A	Levofloxacin	–[c]	250 mg tab	3	3	4	4	4	1.5 g	
			500 mg tab	1.5	1.5	2	2	2		
			750 mg tab	1	1	1.5	1.5	1.5		
	Moxifloxacin	Standard dose[c,d]	400 mg tab	1	1	1	1	1	400 mg	
		High dose[c,d]	400 mg tab	1 or 1.5	1.5	1.5 or 2	2	2	800 mg	
	Bedaquiline	–[c]	100 mg tab	4 tabs od for first 2 weeks; then 2 tabs od M/W/F for 22 weeks					400 mg	
	Linezolid	–[c]	600 mg tab	(<15 y)	(<15 y)	1	1	1	1.2 g	For dosing of linezolid for the BPaL regimen, refer to Section 7, Table 7.2.
B	Clofazimine	–[c]	50 mg cap or tab[e]	2	2	2	2	2	100 mg	
			100 mg cap or tab[e]	1	1	1	1	1	100 mg	
	Cycloserine or terizidone	10–15 mg/kg	250 mg cap	2	2	3	3	3	1 g	

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients 15 years or older[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
C	Ethambutol	15–25 mg/kg	400 mg tab	2	2	3	3	3	–	
	Delamanid	–[c]	50 mg tab	2 bd	2 bd	2 bd	2 bd	2 bd	200 mg	
	Pyrazinamide	20–30 mg/kg	400 mg tab	3	4	4	4	5	–	
			500 mg tab	2	3	3	3	4		
	Imipenem-cilastatin	–[c]	500 mg + 500 mg powder for injection, vial (10 mL)	2 vials (1 g + 1 g) bd					–	To be used with clavulanic acid.
	Meropenem	–[c]	1 g powder for injection, vial (20 mL)	1 vial 3 times per day or 2 vials bd					–	To be used with clavulanic acid.
	Amikacin	15–20 mg/kg	500 mg/2 mL solution for injection, ampoule[f]	2.5 mL	3 mL	3–4 mL	4 mL	4 mL	1 g	
	Streptomycin	12–18 mg/kg	1 g powder for injection, vial[f]	Calculate according to the dilution used					1 g	
	Ethionamide or prothionamide	15–20 mg/kg	250 mg tab	2	2	3	3	4	1 g	Once daily dose advised but can start with 2 divided doses until tolerance improves.
	P-aminosalicylic acid	8–12 g/day in 2–3 divided doses	PAS sodium salt (equivalent to 4 g PAS acid) sachet	1 bd	1 bd	1 bd	1 bd	1 to 1.5 bd	12 g	
			PAS acid (4 g) sachet	1 bd	1 bd	1 bd	1 bd	1 to 1.5 bd		

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients 15 years or older[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
	Isoniazid	4–6 mg/kg (standard dose)[d]	300 mg tab	2/3	1	1	1	1	–	100 mg isoniazid tablet can facilitate the administration of certain dosages. Pyridoxine is given with isoniazid in patients at risk (e.g. those with HIV or malnutrition).
		10–15 mg/kg (high dose)[d]	300 mg tab	1.5	1.5	2	2	2		
Other medicines[g]	Clavulanic acid[h]	–[c]	125 mg clavulanic acid as amoxicillin/ clavulanate, 500 mg/ 125 mg tab[h]	1 bd	1 bd	1 bd	1 bd	1 bd	–	Only to be used with carbapenems.
	Gatifloxacin	–[c]	400 mg tab	2	2	2	2	2	800 mg	Currently, there is no availability of gatifloxacin on the market. Gatifloxacin is not used in persons <18 years.
	Pretomanid[i]	–[c]	200 mg tab	1	1	1	1	1	200 mg	Only to be used as part of the BPaL regimen, together with bedaquiline and linezolid.

(<15 y): follow the separate dose schedule for patients younger than 15 years of age; bd: two times a day; BPaL: regimen of bedaquiline, pretomanid and linezolid for 6–9 months; cap: capsule; HIV: human immunodeficiency virus; im: intramuscular; iv: intravenous; g: gram; kg: kilogram; mL: millilitre; mg: milligram; M/W/F: Monday, Wednesday, Friday; soln: solution; susp: suspension; MDR-TB: multidrug-resistant TB: MDR/RR-TB: multidrug- and rifampicin resistant tuberculosis; tab: tablet; WHO: World Health Organization.

a Dosages were established by the guideline development groups for the WHO guidelines on drug-resistant tuberculosis treatment (2018 and 2020 updates) and the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). Owing to the pharmacokinetic properties of certain medicines, the doses proposed may exceed the mg/kg per day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients <30 kg, the schedule for those aged <15 years should be followed, unless otherwise indicated. If multiple dose options are given for one weight band, the lower or

higher option should be selected, depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg per day should be aimed for, and is more feasible with oral or parenteral fluids, and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range, to minimize the adverse therapeutic consequences of over- and under-exposure, respectively (especially for injectable agents, linezolid and fluoroquinolones).

b Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

c No weight-based dosing is proposed.

d The higher dose may be used except when: there is risk of toxicity; levels are expected to be lowered because of pharmacokinetic interactions, malabsorption or other reasons; or the strain has low-level drug resistance.

e Tablets are expected to become available in the near future.

f The weight-based daily dose is for 6 or 7 days per week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. For iv use, the volume may be increased.

g Amoxicillin/clavulanic acid is only recommended as a companion agent. Because of a lack of data from the latest analysis on longer MDR-TB regimens in adults, gatifloxacin, isoniazid and thioacetazone are not included in the grouping table of medicines used for longer regimens. Pretomanid is recommended to be used only as part of the package of the BPaL regimen.

h Only available in combination with amoxicillin as co-amoxyclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed-dose combination). It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.

i Use for age 14 years or older.

See the text of the handbook for more details on the use of medicines.

B. Dosing of medicines used in second-line multidrug-resistant TB regimens by weight band (patients under 15 years)[a]

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients under 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
A	Levofloxacin	15–20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	(>14 y)	1.5 g	
			250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14 y)	1.5 g	
	Moxifloxacin	10–15 mg/kg	100 mg dt	0.8	1.5	2	3	4	(>14 y)	(>14 y)	400 mg	Use 10 mg/kg in <6 months.
			400 mg tab[c]	2 mL[c]	3 mL[c]	5 mL[c]	0.5 or 0.75	1	(>14 y)	(>14 y)	400 mg	
	Bedaquiline	–	100 mg tab	–	–	–	2 tabs od for 2 weeks; then 1 tab od M/W/F for 22 weeks		4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks		–	Only in patients aged >5 years (lower dose from 15–29 kg; higher dose from >29 kg).
			20 mg dt	–	–	–	10 dts od for 2 weeks; then 5 dts od M/W/F for 22 weeks		20 dts od for 2 weeks; then 10 dts od M/W/F for 22 weeks			
	Linezolid	15 mg/kg od in 1–15 kg 10–12 mg/kg od in >15 kg	20 mg /mL susp	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL[d]	600 mg	
			600 mg tab[c]	0.25	0.25	0.25	0.5	0.5	0.5	0.75[d]		
B	Clofazimine	2–5 mg/kg	50 mg cap or tab[e]	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)	100 mg	Give on alternate days if dose in mg/kg/day is too high.
			100 mg cap or tab[e]	M/W/F	M/W/F	1 alt days	1 alt days	1	(>14 y)	(>14 y)	100 mg	
	Cycloserine or terizidone	15–20 mg/kg	125 mg mini capsule (cycloserine)[c]	1	1	2	3	4	(>14 y)	(>14 y)	1 g	
			250 mg cap[c]	4–5 mL[c]	5–6 mL[c]	7–10 mL[c]	2	2	2	(>14 y)	1 g	

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients under 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
C	Ethambutol	15–25 mg/kg	100 mg dt	1	2	3	4	–	–	(>14 y)	–	
			400 mg tab[c]	3 mL[c]	4 mL[c]	6 mL[c]	1	1 or 1.5	2	(>14 y)		
	Delamanid	–	50 mg tab	–	–[f]	–[f]	–[f]	1 bd	1 bd	2 bd	200 mg	Only in patients aged >2 years (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years).
	Pyrazinamide	30–40 mg/kg	150 mg dt	1	2	3	4 or 5	–	–	(>14 y)	–	
			400 mg tab	0.5	0.75	1	1.5 or 2	2.5	3	(>14 y)		
			500 mg tab	0.5	0.5	0.75 or 1	1.5	2	2.5	(>14 y)		
	Imipenem-cilastatin	–	500 mg + 500 mg powder for injection, vial (10 mL)	–	–	–	–	–	–	–	–	Not used in patients aged <15 years (use meropenem).
	Meropenem	20–40 mg/kg iv every 8 hours	1 g powder for injection, vial (20 mL)	2 mL	4 mL	6 mL	8–9 mL	11 mL	(>14 y)	(>14 y)	–	To be used with clavulanic acid.
	Amikacin	15–20 mg/kg	500 mg/2 mL solution for injection, ampoule[g]	0.4 mL	0.6 mL	0.8–1.0 mL	1.2–1.5 mL	2.0 mL	(>14 y)	(>14 y)	1 g	
	Streptomycin	20–40 mg/kg	1 g powder for injection, vial[g]	Calculate according to the dilution used					(>14 y)	(>14 y)	1 g	
	Ethionamide or prothionamide	15–20 mg/kg	125 mg dt (ethionamide)	1	1	2	3	4	4	(>14 y)	1 g	
			250 mg tab	0.5	0.5	1	2	2	2	(>14 y)	1 g	

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients under 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
C	*P*-aminosalicylic acid	200–300 mg/kg in 2 divided doses	PAS acid (4 g) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)	–	Full dose can be given once daily if tolerated.
			PAS sodium salt (equivalent to 4 g PAS acid) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)		
			PAS sodium salt 60% w/w (9.2 g; equivalent to 4 g PAS acid) sachet	1.5 g bd	2–3 g bd	3–4 g bd	4 or 6 g bd	6 or 8 g bd	8–12 g bd	8–12 g bd	–	
Other medicines[h]	Isoniazid	15–20 mg/kg (high dose)	50 mg/5 mL soln	8–10 mL	15 mL	20 mL	–	–	–	–	–	300 mg isoniazid tablet can be used in patients >20 kg. Pyridoxine is always given with high-dose isoniazid in children (12.5 mg od in those aged <5 years and 25 mg od in those aged >4 years).
			100 mg tab	1	1.5	2	3	4	4	(>14 y)		
	Clavulanic acid[i]	–	62.5 mg clavulanic acid as amoxicillin/clavulanate, 250 mg/62.5 mg, powder for oral solution, 5 mL	2 mL bd[i]	3 mL bd[i]	5 mL bd[i]	8 mL bd[i]	10 mL bd[i]	(>14 y)	(>14 y)	–	Only to be used with carbapenems.

(>14 y): follow the separate dose schedule for patients older than 14 years of age; alt: alternate; bd: two times a day; cap: capsule; dt: dispersible tablet; g: gram; im: intramuscular; iv: intravenous; kg: kilogram; mL: millilitre; mg: milligram; M/W/F: Monday, Wednesday, Friday; soln: solution; susp: suspension; tab: tablet.

a Dosages were established by the guideline development groups for the WHO guidelines on drug-resistant tuberculosis treatment (2018 and 2020 updates) and the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients >30 kg, follow the schedule for >14 years old unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/d+B48ay should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosage are available. Fractioning of tablets into halves or less should be avoided if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure respectively (especially for injectable agents, linezolid and fluoroquinolones).

b Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

c Dissolving in 10 mL of water may facilitate administration in patients in lower weight bands and avoids fractioning solid formulations, although bioavailability is uncertain (use of dispersible tablets is preferred if available).

d In individuals >44 kg a dose of 600 mg od is proposed.

e Tablets are expected to become available in the near future.

f May be used in children 3–5 years of age. Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg paediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved.

g Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. Dosing closer to the upper limit of the mg/kg/day is more desirable. For iv use, the volume may be increased.

h These agents are only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of a lack of data from the latest analysis on longer MDR-TB regimens in adults (isoniazid).

i Only available in combination with amoxicillin as co-amoxyclav. Only to be used with carbapenems, in which case they are given together, e.g. 125 mg bd or 125 mg 3 times daily in the 24–30 kg weight band.

See the text of the handbook for more details on the use of medicines.