WHO operational handbook on tuberculosis

Module 4: treatment and care

World Health Organization

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- Asma Humayun drafted Section 2 on people-centred care, Section 3.1 on social support, including introduction, information and educational support, psychological and emotional support (sections 3.1.1 and 3.1.2), and Section 4 on health education and counselling,
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Abbreviations and acronyms

aDSM	active tuberculosis drug-safety monitoring and management
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
aOR	adjusted odds ratio
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
BDLC	a regimen of bedaquiline, delamanid, linezolid and clofazimine
BDLLfxC	a regimen of bedaquiline, delamanid, linezolid, levofloxacin and clofazimine
BLLfxCZ	a regimen of bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide
BLMZ	a regimen of bedaquiline, linezolid, moxifloxacin and pyrazinamide
BMI	body mass index
BPaL	a regimen of bedaquiline, pretomanid and linezolid
BPaLC	a regimen of bedaquiline, pretomanid, linezolid and clofazimine
BPaLM	a regimen of bedaquiline, pretomanid, linezolid and moxifloxacin
CB	clinical breakpoint
CC	critical concentration
CI	confidence interval
CLD	chronic liver disease
CNS	central nervous system
CSF	cerebrospinal fluid
CRF	chronic renal failure
CTP	Child–Turcotte–Pugh
CXR	chest radiography
DAA	direct-acting antiviral
DDI	drug–drug interaction
DRS	drug-resistance surveillance
DR-TB	drug-resistant tuberculosis
DS-TB	drug-susceptible tuberculosis
DST	drug susceptibility testing
ECG	electrocardiography
EMM	event monitoring device for medication support
FDC	fixed-dose combination (of medicines)

GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBV	hepatitis B virus
HCV	hepatitis C virus
HCW	health care worker
HIV	human immunodeficiency virus
HR	isoniazid–rifampicin
HRZE	isoniazid–rifampicin–ethambutol–pyrazinamide
(H)RZE	(isoniazid optional)–rifampicin–ethambutol–pyrazinamide
Hr-TB	rifampicin-susceptible, isoniazid-resistant tuberculosis
IMCI	integrated management of childhood illness
IPD	individual patient data (or dataset)
IRIS	immune reconstitution inflammatory syndrome
IV	intravenous
LC-aNAAT	low-complexity automated NAAT
LC-mNAAT	low-complexity manual NAAT
LFT	liver function test
LPA	line probe assay
LTFU	loss to follow-up
MC-aNAAT	moderate-complexity automated NAAT
MC-mNAAT	moderate-complexity manual NAAT
MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug- or rifampicin-resistant tuberculosis
MGIT	mycobacterial growth indicator tube
MIC	minimum inhibitory concentration
mWRD	molecular WHO-recommended rapid diagnostic
NAAT	nucleic acid amplification test
NGS	next-generation sequencing
NTM	non-tuberculosis mycobacteria
NTP	national tuberculosis programme
PHC	primary health care
PLHIV	people living with HIV
pre-XDR-TB	pre-extensively drug-resistant tuberculosis
PTB	pulmonary tuberculosis
RCT	randomized controlled trial
rGLC	regional Green Light Committee
RR-TB	rifampicin-resistant tuberculosis
SAM	severe acute malnutrition
SDG	Sustainable Development Goal
SMS	short message service or text message
SoC	standard of care

TB	tuberculosis
TDM	therapeutic drug monitoring
TPT	tuberculosis preventive treatment
VST	video-supported treatment
WHO	World Health Organization
WHO/GTB	Global Programme on Tuberculosis & Lung Health of the World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

TB medicines

Am	amikacin
B or Bdq	bedaquiline
C or Cfz	clofazimine
Cs	cycloserine
D or Dlm	delamanid
E	ethambutol
Eto	ethionamide
FQ	fluoroquinolone
H	isoniazid
Hh	isoniazid high dose
Ipm–Cln	imipenem–cilastatin
L or Lzd	linezolid
Lfx	levofloxacin
M or Mfx	moxifloxacin
Mpm	meropenem
P or Rpt	rifapentine
Pa	pretomanid
PAS	*p*-aminosalicylic acid
Pto	prothionamide
R	rifampicin
S	streptomycin
Trd	terizidone
Z or PZA	pyrazinamide

Definitions

Adverse event: Any untoward medical occurrence that may present in a person with tuberculosis (TB) during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with the treatment.

Bacteriologically confirmed TB case: A case from whom a biological specimen is positive by smear microscopy, culture or a World Health Organization (WHO) recommended rapid diagnostic (e.g. Xpert® MTB/RIF).

Bacteriologically confirmed: when a biological specimen is positive by smear microscopy, culture or a rapid diagnostic test for TB recommended by WHO.

Clinically diagnosed: when a person who does not fulfil the criteria for bacteriological confirmation has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment.

Drug-resistant TB (DR-TB): TB disease caused by a strain of *Mycobacterium tuberculosis* complex that is resistant to any TB medicines.

Drug susceptibility testing (DST): In vitro testing using either molecular, genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.[1]

Drug-susceptible TB (DS-TB): A bacteriologically confirmed or clinically diagnosed case of TB, without evidence of infection with strains resistant to isoniazid and rifampicin.

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

Extensively drug-resistant TB (XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid).

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

Multidrug- or rifampicin-resistant TB (MDR/RR-TB): The term used in this handbook and elsewhere to group MDR-TB and RR-TB cases; 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.

New case: a person with TB disease who has never been treated for TB or has only previously ever taken TB drugs for less than 1 month.

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[1] Implementing tuberculosis diagnostics: a policy framework. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/bitstream/10665/162712/1/9789241508612_eng.pdf)

Non-severe pulmonary TB: A form of TB defined as intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion; or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern.

Operational research or **implementation research**: "the use of systematic research techniques for programme decision-making to achieve a specific outcome".[2] In the context of this document, these terms are also applied to 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. Such research deals with the knowledge gap between efficacy, effectiveness and current practice to produce the greatest gains in disease control.[3] Operational research also provides decision-makers with information to enable them to improve the performance of their health programmes.[4]

People-centred (or person-centred) care is defined as "providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions".

Pre-extensively drug-resistant TB (pre-XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).

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

Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to rifampicin.

Serious adverse event: 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. Includes adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening.

Severe extrapulmonary TB: presence of miliary TB, TB meningitis, osteoarticular or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe.

Social support in this document is defined as support to TB patients that includes informational and educational support (health education and counselling), psychological or emotional support, material support and companion support.

TB case: the occurrence of TB disease in a person.

TB disease: a disease in humans caused by the *M. tuberculosis* complex, which comprises eight distinct but closely related organisms – *M. bovis*, *M. caprae*, *M. africanum*, *M. microti*, *M. pinnipedii*, *M. mungi*, *M. orygis* and *M. canetti*. The most common and important agent of human disease is *M. tuberculosis*.

TB patient: a person who is in care for TB disease.

Treatment adherence interventions include social support such as: patient education or information support and counselling; material support (e.g. food, financial enablers, transport fees); psychological support; tracers such as home visits or digital health communications (e.g. short message service

[2] Allotey P, Reidpath DD, Ghalib H, Pagnoni F, Skelly WC. Efficacious, effective, and embedded interventions: implementation research in infectious disease control. BMC Public Health. 2008;8:1–6. doi: https://doi.org/10.1186/1471-2458-8-343.

[3] Guide to operational research in programmes supported by the Global Fund. Geneva: The Global Fund & World Health Organization; 2007 (https://medbox.org/document/guide-to-operational-research-in-programs-supported-by-the-global-fund#GO).

[4] Expanding capacity for operations research in reproductive health: summary report of a consultative meeting, World Health Organization, Geneva, Switzerland, December 10–12. Geneva: World Health Organization; 2003 (https://apps.who.int/iris/handle/10665/67936).

[SMS], telephone calls); medication monitors; and staff education. The interventions should be selected on the basis of the assessment of the individual patient's needs, values and beliefs, and the provider's resources and conditions for implementation.

Treatment administration options include: various suitable forms of treatment support, such as regular community- or home-based treatment support and video-supported treatment; and less preferable forms of treatment administration such as health facility-based treatment support and self-administered or unsupervised treatment.

Treatment support: Used here to describe an approach to supporting patients who are taking prescribed doses of TB medicines, to help ensure adherence to treatment and maximize its efficacy. Treatment support needs to be provided in the context of people-centred care and should be based on the individual patient's needs, acceptance and preferences. It includes aspects of support, motivation and understanding of patients without coercion. Historically, this group of interventions were labelled as "directly observed treatment".

Executive summary

The WHO operational handbook on tuberculosis, Module 4: treatment and care provides practical guidance on implementing recommendations to achieve national and global impact in tuberculosis (TB) management. It consolidates three key components of the WHO consolidated guidelines on tuberculosis treatment: drug-susceptible TB (DS-TB) treatment, drug-resistant TB (DR-TB) treatment, and tuberculosis care and support. This consolidated operational handbook complements the WHO consolidated guidelines on TB treatment, assisting Member States, technical partners and other stakeholders who are involved in the programmatic management, adoption and uptake of WHO policies.

Chapter 1. Drug-susceptible TB treatment

This chapter outlines standardized approaches to managing DS-TB, including the widely used 6-month regimen and the recently introduced 4-month regimens.

Evidence-based regimens and approaches are presented to facilitate the implementation of current and new policies across various populations aiming to achieve high cure rates, preventing treatment failure, and reduce the risk of drug resistance. Additionally, it offers normative guidance on monitoring treatment response and defining outcomes.

Chapter 2. Drug-resistant TB treatment

The chapter unpacks the complexities around the treatment of DR-TB and provides comprehensive guidance to facilitate the management of all forms of drug-resistant TB, from rifampicin-resistant (RR-TB) and rifampicin-susceptible but isoniazid-resistant TB to multidrug-resistant (MDR-TB) and more advanced drug resistance. The chapter also offers guidance on adjuncts to TB treatment and some unique aspects of programmatic management.

Chapter 3. Tuberculosis care and support

A holistic, patient-centred approach is central to this guidance, with a focus on addressing the psychosocial and nutritional needs of individuals undergoing treatment. Recommendations include managing adverse events to enhance adherence and outcomes, while promoting equitable access to care through community-based and integrated health systems.

Annexes

Annexes provide practical resources and technical details, such as information sheets for TB medicines, protocols for managing adverse events, and weight-based dosing guidelines for all age groups.

Overall, this consolidated handbook underscores a multidisciplinary approach to combating TB, balancing robust clinical strategies with patient-centred care to improve treatment outcomes and thus reduce the global TB burden.

Chapter 1
Drug-susceptible TB treatment

1. Introduction

This chapter on the treatment of drug-susceptible tuberculosis (DS-TB) complements the chapter on drug-susceptible tuberculosis treatment of the *WHO consolidated guidelines on tuberculosis Module 4: Treatment and care (1)*. It provides practical advice based on best practices and knowledge from fields such as pharmacokinetics, pharmacodynamics, microbiology, pharmacovigilance, and clinical and programmatic management.

The focus of this chapter is on tuberculosis (TB) treatment because all implementation considerations on patient care and support during treatment, for both DS-TB and drug-resistant TB (DR-TB), have been merged in Chapter 3 on tuberculosis care and support.

The update of the guidelines and implementation handbook for treatment of DS-TB is important in the context of the End TB Strategy, which recommends treatment and patient support for all people with TB *(2)*. This update by WHO is based on the best available evidence on the treatment of DS-TB and is intended to assist national TB programme (NTP) managers, national policy-makers and medical practitioners in a variety of geographical, economic and social settings.

WHO recommendations on DS-TB treatment

Treatment of DS-TB using the 6-month regimen	
1.1	New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR. *(Strong recommendation, high certainty of evidence)*
1.2	Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy. *(Strong recommendation, high certainty of evidence)*
1.3	In all patients with pulmonary DS-TB, the use of thrice-weekly dosing is not recommended in either the intensive or the continuation phases of therapy, and daily dosing remains the recommended dosing frequency. *(Conditional recommendation, very low certainty of evidence)*
1.4	The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in the treatment of patients with DS-TB. *(Conditional recommendation, low certainty of evidence)*
1.5	In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended. *(Strong recommendation, high certainty of evidence)*

Treatment of DS-TB using 4-month regimens	
2.1	Patients aged 12 years or older with pulmonary DS-TB may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM). *(Conditional recommendation, moderate certainty of evidence)*
2.2	In children and adolescents aged between 3 months and 16 years with non-severe TB (without suspicion or evidence of multidrug- or rifampicin-resistant TB [MDR/RR-TB]), a 4-month treatment regimen (2HRZ(E)/2HR) should be used. *(Strong recommendation, moderate certainty of evidence)*
DS-TB treatment and antiretroviral therapy in people living with HIV	
3.1	It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients. *(Strong recommendation, high certainty of evidence)*
3.2	Antiretroviral therapy (ART) should be started as soon as possible within 2 weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV. Adults and adolescents *(Strong recommendation, low to moderate certainty evidence)* Children and infants *(Strong recommendation, very low certainty of evidence)*
The use of adjuvant steroids in the treatment of tuberculous meningitis and pericarditis	
4.1	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 of evidence)*
4.2	In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used. *(Conditional recommendation, very low certainty of evidence)*

2. Key considerations in DS-TB treatment

2.1 TB diagnostics and DST

Innovative rapid molecular tests to diagnose both pulmonary and extrapulmonary TB in all populations are strongly recommended over sputum smear microscopy and culture methods, because rapid tests can provide same day results *(3)*. Some of the innovative tests also provide drug susceptibility results for rifampicin (R), isoniazid (H) and fluoroquinolones (FQ), allowing rapid confirmation of diagnosis, and timely and effective treatment allocation. Based on the data from global TB drug-resistance surveillance, rifampicin-resistant TB (RR-TB) is rare when people are first diagnosed with TB, but it is reaching alarming proportions in some countries. Globally, the burden of multidrug-resistant TB (MDR-TB) or RR-TB (MDR/RR-TB) is stable *(4)*. For more than 10 years, the best estimate of the proportion of people diagnosed with TB for the first time who had MDR/RR-TB has remained at about 3–4%, and the best estimate among those previously treated for TB has remained at about 18–21% *(3)*. The highest proportions (>50% in previously treated cases) are found in countries in eastern Europe and Central Asia *(4)*.

Resistance to FQ in new TB patients without resistance to rifampicin is rare in most of the countries with available data (1.0–1.2%), although some countries show higher proportions (3.4–11.2%) *(5–9)*. Isoniazid-resistant and rifampicin-susceptible TB is the most prevalent form of drug resistance worldwide (besides streptomycin resistance), with estimates rising to 7% among those newly diagnosed and 8–11% among those previously treated *(4, 10)*. Isoniazid-resistant TB is associated with a higher risk of acquiring further drug resistance and evolving towards MDR-TB, which is defined by resistance to both isoniazid and rifampicin *(11–13)*.

These data reiterate the importance of full transition from sputum smear microscopy to the widespread use of rapid diagnostic tests, especially in those with recurrent TB. Regular country reports to WHO and several surveys clearly demonstrate that the policy of using rapid molecular TB diagnostic tests has been widely adopted in countries with a significant burden of TB. However, the use of rapid TB testing has yet to surpass the use of smear microscopy *(14–16)*.

With the range of available anti-TB medicines and treatment regimens, drug susceptibility testing (DST) for key drugs is crucial for the choice of an appropriate treatment strategy. For medicines with high potency against *Mycobacterium tuberculosis* – rifampicin, moxifloxacin (M) and isoniazid – rapid tests for drug susceptibility are now available and evidence-based recommendations for their use are given in relevant WHO documents *(3, 17)*.

Resistance to rifampicin renders all of the available regimens for DS-TB ineffective; if rifampicin is used, it may cause both treatment failure and development of additional resistance to other drugs in the regimen. This finding means that the treatment strategy for DR-TB needs to be changed. Among new TB patients without resistance to rifampicin, resistance to FQ is very low; this allows a general strategy of starting these patients on DS-TB regimens (including the 4-month regimen with moxifloxacin described in Section 4), without obligatory DST for FQ. This general strategy should be regularly revisited and updated in response to the drug-surveillance data of the country or specific

setting, to prevent potential misuse of moxifloxacin (an important medicine for treatment of DR-TB) and increased antimicrobial resistance. Resistance to isoniazid leads to decreased efficacy of the 6-month regimen (described in Section 3) and requires use of the specific regimens that include FQ. The effect of isoniazid monoresistance on the efficacy of the 4-month regimen with rifapentine (P) and moxifloxacin has not been studied; however, the efficacy of the 4-month regimen for children (2HRZ(E)/2HR, described in Section 5) is expected to be affected.

In summary, in settings where rapid, molecular-based DST is available, the results should guide the choice of regimen. Although universal DST is the goal, priority should be given to testing patients undergoing retreatment at, or before, the start of that retreatment – at least for isoniazid and rifampicin resistance. Whenever rifampicin resistance is confirmed, testing for resistance to FQ will be important in the design of an effective treatment regimen.

In settings where rapid DST results are not routinely available to guide the management of individual patients, the approach to treatment selection can be guided by clinical judgement and consideration of the epidemiology of TB and its drug-resistant forms in the specific setting. In TB patients whose treatment has failed or in other patient groups with a high likelihood of MDR/RR-TB, the clinician's decision may lean towards an empirical MDR-TB regimen *(17)*.

2.2 Care and support during TB treatment

All treatment delivered should align with WHO-recommended standards, including patient-centred care and support, informed consent where necessary, principles of good clinical practice, and regular patient monitoring to assess regimen effectiveness and patient safety (**Chapter 3**). Clinical monitoring of people on treatment is important, and this handbook includes information on both treatment monitoring and the usefulness of post-treatment follow-up for special cases (e.g. long-term complications of TB or TB sequelae).

2.3 Options in treatment of DS-TB

In patients with presumptive or confirmed DS-TB, there are several regimens that can be used based on current WHO policy. The 6-month regimen has become the standard of care all over the world but efforts have been made to develop effective shorter regimens to treat DS-TB. Several trials were designed to assess whether a shorter treatment regimen can remain highly effective and raise no additional safety concerns. Based on the results of recent randomized controlled trials (RCTs), WHO has recommended two different 4-month regimens: one based on the Study 31 trial[5] and one based on the SHINE trial[6] *(1)*.

Current recommendations cover regimens that differ in duration, composition and dosing of drug components. In addition, the eligible populations (depending on the available evidence) differ in terms of age and TB disease severity. The three recommended regimens are as follows:

- The 6-month regimen (2HRZ(E)4HR, described in **Section 3**) comprises 2 months of isoniazid, rifampicin, pyrazinamide (Z) and ethambutol (E), followed by 4 months of isoniazid and rifampicin. This regimen is recommended in all patient populations. In children (usually defined as being aged <10 years), the inclusion of ethambutol in the first 2 months of treatment is recommended in settings with a high prevalence of HIV,[7] in settings with isoniazid resistance or in children living with HIV (CLHIV), but can otherwise be omitted, resulting in the 2HRZ/4HR regimen *(19)*.

[5] Study 31 is a Phase III trial: TBTC Study 31/ACTG A5349 *(1)*, also referred to as S31/A5349.

[6] SHINE is the Shorter Treatment for Minimal Tuberculosis in Children trial, a large Phase III trial to evaluate duration of TB treatment in children with non-severe DS-TB.

[7] Defined as countries, subnational administrative units or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5% *(18)*.

- The 4-month regimen HPMZ (described in **Section 4**) comprises 2 months of isoniazid, rifapentine, moxifloxacin and pyrazinamide, followed by 2 months of rifapentine, isoniazid and moxifloxacin. This regimen is recommended for all those aged above 12 years, whatever the severity of TB disease.
- The 4-month regimen HRZ(E) (described in **Section 5**) comprises 2 months of isoniazid, rifampicin and pyrazinamide, with or without ethambutol, followed by isoniazid and rifampicin for 2 months for those aged between 3 months and 16 years, with non-severe pulmonary or peripheral lymph node TB. The use of ethambutol in the first 2 months of treatment is recommended in settings with a high prevalence of HIV, in settings with isoniazid resistance[8] or in children and adolescents living with HIV.

Choice criteria for regimens in different age groups are summarized in **Table 1.2.1**.

Table 1.2.1. Guide for regimen selection for DS-TB

<table>
<tr><th rowspan="2">Regimen</th><th colspan="5">Age</th></tr>
<tr><th>0-3 months</th><th>3 months-10 years</th><th>10-12 years</th><th>12-16 years</th><th>>16 years</th></tr>
<tr><td>2HRZ(E)/4HR</td><td colspan="2">Ethambutol should be added in settings with a high background prevalence of isoniazid resistance or HIV infection or in CLHIV</td><td colspan="3">Independent of disease severity or HIV status</td></tr>
<tr><td>2HRZ(E)/2HR</td><td colspan="4">Non-severe TB, > 3 kg, add ethambutol in settings with a high background prevalence of isoniazid resistance or HIV infection or in CALHIV</td><td></td></tr>
<tr><td>2HPMZ/2HPM</td><td colspan="3"></td><td colspan="2">Independent of disease severity or HIV status</td></tr>
<tr><td rowspan="3">Additional factors to be considered if several regimens are possible</td><td colspan="4">Disease severity</td><td></td></tr>
<tr><td colspan="5">Patient or family preference</td></tr>
<tr><td colspan="5">Access and cost of regimen component drugs</td></tr>
</table>

CALHIV: children and adolescents living with HIV; CLHIV: children living with HIV; DS-TB: drug-susceptible TB; HIV: human immunodeficiency virus; TB: tuberculosis.

Note: all the regimens envisage daily dosing of all medicines.

As shown in **Table 1.2.1**, the age ranges presented in the current recommendations are as follows: from 3 months to 16 years for one 4-month regimen (for 2HRZ(E)/2HR regimen), 12 years and above for the other 4-month regimen (for 2HPMZ/2HPM regimen) and any age for the 6-month regimen (2HRZ(E)/4HR). There is some overlap between age groups; for example, several regimen options are available for the age range 3 months to 12 years (i.e. 2HRZ(E)/2HR and 2HRZ(E)/4HR) and for the age range 12–16 years (i.e. 2HRZ(E)/4HR, 2HPMZ/2HPM and 2HRZ(E)/2HR). The choice of regimen may also be influenced by clinical factors (e.g. severity of the disease, hepatic or renal failure, uncontrolled diabetes and HIV status), contextual factors (e.g. HIV or prevalence of isoniazid resistance) and access factors (e.g. availability of rifapentine and moxifloxacin, and cost of the regimen). For example, severity of TB disease (based on the definition of non-severe TB presented in **Box 2.1**) will determine the choice of the regimen for those aged between 3 months and 16 years.

[8] WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance; NTPs should establish definitions for their own countries.

Box 2.1. Definition of non-severe pulmonary TB

For the purpose of determining treatment duration for DS-TB, non-severe pulmonary TB is defined as any of the following:

- intrathoracic lymph node TB without airway obstruction;
- pulmonary TB confined to one lobe with no cavities and no miliary pattern; or
- uncomplicated pleural effusion (without pneumothorax or empyema).

All patients weighing more than 3 kg and aged between 3 months and 16 years, with non-severe TB based on the definition presented in Box 2.1, should be treated with the 4-month regimen 2HRZ(E)/2HR, with or without ethambutol. It is preferred that CLHIV who receive the 4-month regimen receive that regimen *with* ethambutol for the first 2 months of treatment, irrespective of the background prevalence of HIV. In addition, it is strongly recommended that ethambutol be added to the 4-month regimen for the first 2 months in settings with a high background prevalence of isoniazid resistance or HIV infection.

The 6-month regimen comprising 2HRZ(E)/4HR can be used in all patients in all age groups, independent of the disease severity and HIV status. However, in patients aged under 10 years, ethambutol can also be omitted in patients who are HIV-negative or in settings with a low prevalence of HIV and isoniazid resistance.

In patients with DS-TB aged 12 years or more, another possible treatment option is the regimen comprising 2HPMZ/2HPM. This regimen can be used in patients with both severe and non-severe forms of the disease, and in people living with HIV (PLHIV). Access, the pill burden and the cost of the HPMZ regimen may present barriers for implementation until rifapentine becomes more widely and readily available at costs comparable with rifampicin, and the fixed-dose combination (FDC) tablet is developed and becomes available. In some cases, patient and family preference may also guide the choice of the regimen if several regimen options apply to the patient once all other factors have been considered.

In summary, for treatment of DS-TB, WHO recommends either a 6-month regimen or, in specific subgroups of patients, either of two new 4-month regimens (as presented in **Table 1.2.1**).

In patients who require TB retreatment, rapid DST should be performed to guide the regimen approach; that is, to determine whether the treatment should be for DS-TB or DR-TB. In 2017, the WHO Guideline Development Group (GDG) agreed to abolish the former Category II standard 8-month regimen (2HRZES/1HRZE/5HRE), which comprised an intensive phase of 3 months (2 months of isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin followed by 1 month without streptomycin), followed by a continuation phase of 5 months with isoniazid, rifampicin and ethambutol. The GDG put forward a good practice statement that this 8-month regimen should no longer be prescribed, and that DST should be conducted to inform the choice of the treatment regimen.

The three current regimen formulations and their durations are summarized below.

6-month regimen

New patients with pulmonary TB should receive a regimen containing rifampicin for 6 months. This 6-month treatment regimen, 2HRZ(E)/4HR, comprises isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months followed by isoniazid and rifampicin for 4 months.

4-month regimens

Patients aged 12 years or more with pulmonary DS-TB may receive the 4-month regimen 2HPMZ/2HPM, which comprises rifapentine, isoniazid, pyrazinamide and moxifloxacin (2 months of isoniazid, rifapentine, moxifloxacin and pyrazinamide, followed by 2 months of isoniazid, rifapentine and moxifloxacin).

Children and adolescents aged between 3 months and 16 years with non-severe DS-TB should receive the 4-month regimen 2HRZ(E)/2HR, which comprises isoniazid, rifampicin and pyrazinamide, with or without ethambutol, for 2 months followed by isoniazid and rifampicin for 2 months.

Severe forms of TB such as tuberculous meningitis and osteoarticular TB may require additional clinical evaluation and judgement, and longer treatment regimens. Daily or weekly pyridoxine supplementation is suggested when giving isoniazid to patients with such forms of TB.

3. Treatment of DS-TB using the 6-month regimen

All patients with DS-TB without documented resistance to isoniazid and rifampicin may be treated using the 6-month rifampicin-containing regimen 2HRZ(E)/4HR, which comprises isoniazid, rifampicin, pyrazinamide and ethambutol, for 2 months followed by isoniazid and rifampicin for 4 months *(1)*.

This regimen is based on the historical TB treatment studies conducted by the Medical Research Council of the United Kingdom of Great Britain and Northern Ireland (United Kingdom) in the 1980s *(20)*, and it has been widely adopted worldwide. The regimen ensures a successful outcome in about 85% of patients globally, and has a low proportion of unfavourable outcomes and adverse events (AEs), although the success rate varies among WHO regions and is lower in PLHIV *(1, 4)*. This regimen is estimated to have averted 66 million deaths during the 20 years from 2000 to 2020.

The core WHO recommendations for the treatment of DS-TB using 6-month regimen are summarized below, with remarks.

No.	Recommendation
1.1	**New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR** ***(Strong recommendation, high certainty of evidence)***

Remarks:

A: This recommendation also applies to extrapulmonary TB except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy.

B: WHO recommends that national TB control programmes provide supervision and support for all TB patients to ensure completion of the full course of therapy.

C: WHO recommends drug-resistance surveys (or surveillance) for monitoring the effectiveness of the treatment programme, and for designing standard regimens.

WHO recommends daily dosing as the best frequency throughout the entire course of treatment, as included in the recommendation below:

No.	Recommendation
1.2	**Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy** **(Strong recommendation, high certainty of evidence)**

Daily administration reduces the rate of acquired drug resistance by up to 3.3 times when comparing patients who received a daily regimen for the entire duration with those who received intermittent dosage (1). The effect of a patient missing one or more doses (either accidentally or due to stock-outs) is much more significant if the regimen is intermittent. The term "daily" indicates an intake of anti-TB

drugs for 7 days per week. In patients with DS-TB, WHO does not recommend thrice-weekly dosing for either the intensive or the continuation phase of treatment as described in this recommendation:

No.	Recommendation
1.3	**In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy and daily dosing remains the recommended dosing frequency** **(Conditional recommendation, very low certainty of evidence)**

WHO recommends the use of FDC tablets, as included in the recommendation below:

No.	Recommendation
1.4	**The use of fixed-dose combination tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB** **(Conditional recommendation, low certainty of evidence)**

WHO recommends not prolonging the continuation phase of treatment of the 6-month regimen in new pulmonary TB patients if a sputum smear is found to be positive at the end of the intensive phase of treatment, as included in the recommendation below:

No.	Recommendation
1.5	**In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended** **(Strong recommendation, high certainty of evidence)**

3.1 Eligibility

Any patient – whether a child or an adult – with DS-TB is eligible for this regimen. The regimen is considered safe for pregnant women; it can also be used in children of all ages, although ethambutol can be omitted for patients who are HIV-negative or in settings with a low prevalence of HIV or isoniazid resistance. Patients without a history of TB disease and treatment are less likely to have strains resistant to first-line medicines, although infection by the resistant strains often cannot be ruled out, especially in resource-limited settings. Where possible, it is best to ascertain susceptibility to the medicines used; susceptibility to isoniazid and rifampicin (the most potent drugs in the regimen) is particularly important.

In patients with evidence of resistance to isoniazid or rifampicin, this regimen cannot be used; instead, a specific regimen needs to be designed, as described elsewhere *(17)*.

3.2 Composition and duration of the regimen 2HRZE/4HR

The WHO guidelines recommend treating people with DS-TB with a 6-month regimen composed of four first-line TB medicines: isoniazid, rifampicin, pyrazinamide and ethambutol *(1)*. The regimen is a combination of those four drugs (i.e. HRZE) for 2 months followed by isoniazid and rifampicin (i.e. HR) for 4 months, administered daily. In children (usually defined as being aged <10 years) in settings with a high background prevalence of isoniazid resistance or HIV infection, or in CLHIV, ethambutol should be used in the first 2 months of treatment; in all other situations ethambutol can be omitted, resulting in a 2HRZ/4HR regimen *(19)*.

As a general rule, WHO does not recommend prolonging the regimen beyond 6 months *(1)*, because there is evidence that prolongation does not significantly increase efficacy. The first 2 months of treatment, which includes four drugs, is usually enough for the strong bactericidal activity of this regimen to be effective. Thus, the presence of one or more sputum smear results that are still positive after 2 months usually indicates the presence of dead bacilli; however, in some cases, it might be due to undetected resistance to one or more drugs. If the patient is not improving clinically and radiologically, and drug resistance or potential failure is suspected, rapid diagnostic testing to exclude these scenarios should be undertaken promptly, together with culture and DST, to provide a basis for any adjustment of the treatment strategy *(21)*.

The systematic reviews on the dosages of the first-line medicines (rifampicin, isoniazid, ethambutol, and pyrazinamide) used in the treatment of drug-susceptible tuberculosis in adults and children were conducted. The reviews concluded that the WHO-recommended doses for rifampicin, isoniazid, ethambutol and pyrazinamide remain valid in adults and children. (**Annexes 1 and 2**)

3.3 Considerations for implementation

The 6-month rifampicin-based regimen is the standard regimen for the treatment of DS-TB in many countries and has been for many years; thus, there is a great deal of experience in using this regimen.

Rapid diagnostic testing and universal DST is a recommended target for all NTPs *(3)*. In settings where DST results are not yet routinely available to guide the management of individual patients, patient history and clinical judgement are used to make decisions on the empirical use of this regimen.

Diagnostic challenges include being a long distance from the facilities where quality TB diagnostics are available, technical difficulties in implementing these tests and difficultly in accessing health services. The coronavirus disease (COVID-19) pandemic has further complicated rapid and universal access to quality TB diagnosis. Also, diagnosis of TB in children is particularly challenging.

NTPs should obtain and use their country-specific drug-resistance surveillance (DRS) to estimate the level of MDR/RR-TB. Periodic drug-resistance surveys or ongoing surveillance in each country are essential for monitoring the impact of the regimen and the overall treatment programme *(1)*.

To improve treatment adherence and minimize the acquisition of MDR/RR-TB, it is critical for NTPs to ensure adequate treatment support in the context of patient-centred care. Implementing treatment support and care requires resources to ensure optimal adherence and provide patient education and counselling *(1)*. It is important to educate and support patients, to ensure that they complete treatment with all the prescribed doses within the planned period of time *(1)*.

Daily dosing is considered optimal because it reduces the probability of selecting resistant mutants. However, such dosing may be challenging for NTPs in terms of providing daily treatment support.

The use of FDCs may provide programmatic benefits by making it easier to order medicines, simplifying supply chain management, reducing the occurrence of stock-outs, and facilitating drug delivery and prescription. FDCs with proven bioavailability may also provide additional benefits, especially in settings with many TB patients and a limited number of health care workers, because FDCs reduce the need for additional health care staff and for training in dosing and dispensing of medications, while contributing to a lower pill burden for patients. However, because use of FDCs lacks the flexibility that is available when using loose tablet formulations, FDCs do not always provide optimal dosing in all individuals *(1)*.

NTPs need to procure a quantity of loose or single drug formulations for certain treatment conditions. Having single drug formulations available would also be beneficial to programmes in cases of adverse reactions to TB medications, when drugs must be reintroduced one at a time (see Section 8 for details) *(1)*.

3.4 Subgroups

This 6-month regimen can be used in all subgroups, including PLHIV and children. This regimen can also be used in patients with extrapulmonary TB, except those with TB affecting the central nervous system or with osteoarticular forms of TB.

3.4.1 People living with HIV

The interactions of rifampicin (the mainstay of TB treatment) with antiretroviral therapy (ART) are of concern in HIV-associated TB. When the 6-month rifampicin-containing regimen is used, these drug interactions may result in decreased concentrations of antiretroviral drugs. In 2016, WHO published key considerations for managing concomitant TB and HIV therapy *(22)*. Standard, rifampicin-containing anti-TB treatment was recommended in combination with efavirenz-based ART. Conversely, key contraindicated drug combinations were rifampicin with nevirapine and protease inhibitors. In people with HIV-associated TB receiving these drugs, rifabutin (where available) was suggested as a suitable substitute for rifampicin.

Rifampicin is known to lower plasma concentrations of the HIV medication dolutegravir. This has led to concerns about efficacy and the development of HIV resistance due to lower levels of dolutegravir. In such cases, WHO guidelines recommend adjusting the dose by offering 50 mg of dolutegravir twice per day (instead of a single daily dose of 50 mg) *(22)*. These recommendations are still in place, although evidence that doubling the dose of dolutegravir might not be necessary is emerging. A study from Botswana demonstrated the efficacy and safety of a standard-dose dolutegravir-based regimen compatible with an efavirenz-based regimen for HIV-positive TB patients who received rifampicin *(23)*.

3.4.2 Children

Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with a low prevalence of HIV or of isoniazid resistance, or children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug regimen (HR) for 4 months at the dosages specified in **Annex 4**. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in infants *(19)*.

The reduced pill burden afforded by using the recommended FDCs may be especially valuable in patients with comorbidities (notably HIV infection) and in paediatric patients (who may have some difficulty in swallowing a large quantity of medications). Therefore, the availability of palatable dispersible formulations specifically tailored to children is of paramount importance.

Patients with some specific medical conditions (e.g. intolerance to certain TB drugs, or impairment of liver or renal function) are likely to require individualized adjustment of medication dose; however, this can only be done with single drug formulations.

3.5 Treatment monitoring

Standard treatment monitoring should be ensured to assess the treatment response and any AEs.

The available tools for treatment monitoring are bacteriological examinations (sputum smear, culture and DST), chest radiography (CXR) and clinical examination by the treating physician.

The important timepoints of the necessary TB monitoring examinations are after 2 months of treatment (especially if the patient does not improve, and underlying drug resistance and possible failure are suspected) and at the end of treatment.

If the sputum specimen obtained at the end of the intensive phase of treatment (i.e. end of month 2) is positive on smear microscopy, and the patient does not show clinical and radiological improvement, sputum culture and DST should be performed. Based on these results, the patient should be reassessed to identify possible risk factors for failure and the treatment strategy should be changed if necessary.

Culture and DST are important for determining whether the bacilli are alive and whether any previously undetected resistance is present.

Malabsorption of drugs and drug–drug interactions (DDIs) can occur, especially in PLHIV or those with diabetes, in critical care or receiving concomitant medications. Where the clinician suspects malabsorption, it is useful to undertake evaluation and monitoring of the blood levels of the drugs composing the regimen; this can be done using therapeutic drug monitoring *(24)*. Section 9 provides additional details on clinical monitoring in cases of AEs due to anti-TB drugs, and on treatment monitoring with sputum smear, culture and radiology.

4. Treatment of DS-TB using the 4-month 2HPMZ/2HPM regimen

Three Phase III trials (i.e. REMoxTB, OFLOTUB and RIFAQUIN) failed to demonstrate non-inferiority of shorter regimens used to treat DS-TB *(25–27)*. The recent Phase III trial Study 31 *(1)* assessed the safety and efficacy of two 4-month regimens for the treatment of DS-TB *(28)*. Patients from 13 countries were recruited for this multicentre, open-label, three-arm non-inferiority RCT, which was carried out in adolescents and adults (aged ≥12 years) with smear and culture positive pulmonary DS-TB *(28)*.

The 4-month rifapentine-moxifloxacin arm demonstrated non-inferiority when compared with the standard of care (the WHO-recommended 2HRZE/4HR regimen). The primary *efficacy* end-point of Study 31 was TB disease-free survival at 12 months after randomization, whereas the primary *safety* end-point was the proportion of participants with Grade 3 or higher AEs during the study's drug treatment.

The proportion of patients who were cured was 84.5%, with 99.7% retention on treatment and 0.4% all-cause mortality recorded within 14 days of the end of treatment. Grade 3 or higher AEs were noted in 18.8% of participants in the rifapentine-moxifloxacin arm compared with 19.3% in the standard 2HRZE/4HR regimen *(28)*.

The slight difference in all-cause mortality and AEs during treatment, and the slight increase in retention on treatment compared with the 6-month 2HRZE/4HR regimen allowed WHO to recommend this shorter regimen, as follows:

No.	Recommendation
2.1	**People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide[9]** **(Conditional recommendation, moderate certainty of evidence)**

4.1 Eligibility

Adults and children aged 12 years or older with a body weight of more than 40 kg and affected by pulmonary DS-TB are eligible for this regimen, including those who are also HIV-positive with a CD4 count of more than 100 cells/mm^3 and patients with diabetes. The following exceptions, detailed in Section 4.4.2, should be highlighted:

- patients weighing less than 40 kg;
- patients with severe extrapulmonary TB (e.g. tuberculous meningitis, disseminated TB, osteoarticular TB or abdominal TB);
- PLHIV with a CD4 count of less than 100 cells/mm^3;
- children and adolescents aged under 12 years; and
- pregnant, breastfeeding and postpartum women.

[9] Two months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide, followed by two months of isoniazid, rifapentine, and moxifloxacin

4.2 Composition and duration of the regimen

The regimen evaluated by Study 31 comprised 8 weeks of daily isoniazid, rifapentine, moxifloxacin and pyrazinamide, followed by 9 weeks of daily isoniazid, rifapentine and moxifloxacin (2HPMZ/2HPM).

For this regimen, daily dosing (i.e. 7 days per week, as used in Study 31) is suggested, taking advantage of a treatment supporter or video-supported treatment (VST).

The dose of rifapentine used was fixed at 1200 mg and moxifloxacin at 400 mg. Other medicines were provided at standard recommended doses (**Annex 4**). The study was based on the regimen with moxifloxacin; therefore, replacement of moxifloxacin by another FQ cannot be recommended.

As is the case for other regimens, WHO does not recommend prolonging the regimen beyond the planned duration of 4 months.

The first 2 months of treatment, which includes four drugs, is usually enough for the strong bactericidal activity of this regimen to be effective. Thus, the presence of one or more sputum smear results that are still positive after 2 months usually indicates the presence of dead bacilli; however, in some cases, it might be due to undetected resistance to one or more drugs. If the patient is not improving clinically and radiologically, and drug resistance or potential failure is suspected, rapid diagnostic testing to exclude this possibility should be undertaken promptly, together with culture and DST, to provide a basis for any adjustment of the treatment strategy.

4.3 Considerations for implementation

Several factors need to be considered when deciding on the implementation of this regimen: DST, treatment support, pill burden, cost of medicines, administration of the shorter regimen with food, training of health care workers and criteria guiding the choice of regimen. These factors are discussed below.

DST

Although DST use must, in principle, be universal, it is not yet available in all settings. However, rapid DST for key medicines, including isoniazid, rifampicin and the FQ, is rapidly expanding. WHO recommends rapid genotypic testing for TB and RR-TB as an initial test at diagnosis; if DST for the FQ and isoniazid can be performed at the same time, this can make it easier to allocate the most appropriate regimen, although the testing has implications for costs, logistics and laboratory workload.

In practical terms, although highly desirable, baseline DST for FQ would not be necessary for patients with confirmed rifampicin-susceptible TB by a reliable, WHO-recommended rapid molecular diagnostic test. The prevalence of FQ resistance in patients without confirmed rifampicin resistance is usually low *(5–9)* but can reach 15% in patients with documented DR-TB *(4)*. In settings where the prevalence of resistance to FQ in patients with DS-TB is higher because of their widespread use for other conditions, DST for the FQ would be highly recommended at baseline to exclude FQ resistance.

Treatment support

In Study 31, patients received treatment 7 days per week. At the early stages of the introduction of this regimen, treatment support with observation may be important given the current pill burden and the lack of an FDC formulation. Current WHO recommendations support the use of observation but also other forms of patient support; overall, even though this regimen is shorter, patient support remains a key element of TB programming.

Pill burden

Currently, the overall pill burden will be high for patients who receive this 4-month regimen, because there is no FDC tablet for this regimen. This may affect acceptability by patients; however, this situation may change as uptake of this regimen improves, creating a demand for the regimen and its component medicines.

Cost of medicines

Currently, the cost of the shorter regimen is substantially higher than that of the 6-month 2HRZE/4HR regimen, mainly due to the inclusion of rifapentine. Again, this situation may change as uptake of this regimen improves, creating a demand for the regimen and its component medicines. Several pharmaceutical companies are ready to bring quality-assured rifapentine to the market, including generic forms. The availability of rifapentine for this regimen may also depend on the uptake of rifapentine-containing regimens for TB prevention.

Administration of the shorter regimen with food

In some settings, administration of the shorter regimen with food may present a challenge. In Study 31, a flat dose of 1200 mg of rifapentine was given daily, with food. Pharmacokinetic and pharmacodynamic modelling predicted that a rifapentine dose of 1200 mg without food would yield an area under the curve (AUC) similar to that of a rifapentine dose of 900 mg with a high fat meal. Given that the target rifapentine AUC lies somewhere between that achieved with a very high fat meal and a rifapentine dose of 900–1200 mg, the strategy proposed was a rifapentine dose of 1200 mg with a modest food requirement, the rationale that a very high fat meal may not be feasible under routine TB care conditions, whereas dosing with food may be feasible. For some medicines (e.g. moxifloxacin), food may delay absorption.

Training of health care workers

Training will be necessary when introducing the 4-month regimen into a programmatic setting. However, this is a requirement for any new programmatic intervention, and the ability to shorten treatment and potentially treat more patients may offset the initial investments in training.

Criteria guiding the choice of regimen

Eligibility criteria for the regimen, age and patient preference should guide the choice between the 6-month and 4-month regimens. Other local factors can be important, such as the availability and cost of rifapentine.

4.4 Subgroups

Data from Study 31 allowed subgroup analyses for four patient groups: PLHIV, people with diabetes, people with a low body weight (i.e. a body mass index [BMI] <17.9 kg/m^2) and patients with extensive pulmonary TB disease (using a cut off of >50% lung parenchyma affected) on CXR. Although no statistically significant differences appeared when comparing the 4-month regimen to the current standard 2HRZE/4HR regimen, the number of patients in some of these subgroups was small *(1)*.

Additional pharmacokinetic analyses being undertaken by the trial investigators will be available in the future and may provide additional information on drug exposures in these groups. Other subgroup analyses conducted as part of the trial included analyses by age group, sex, presence of cavities, cavity size, sputum smear grade, smoking history, Xpert® cycle threshold values and time to positivity (days) with the mycobacterial growth indicator tube (MGIT) liquid culture automated system.

4.4.1 Subgroups in which the shorter regimen can be used

The shorter regimen can be used in PLHIV, people with diabetes (although the evidence is modest), people with extensive pulmonary TB disease, and children and adolescents *(1)*.

People living with HIV

Study 31 included a sufficient proportion of PLHIV (about 8%), most of whom were on ART. Thus, sufficient evidence is available to support the use of the regimen when the CD4 count is *not* below 100 cells/mm^3.

People with diabetes

There are scant data on the use of this regimen among people with diabetes, but additional information from pharmacokinetic analysis will become available in the future. Thus, although the shorter regimen may be considered as an option, it may be prudent to monitor this patient group closely for hepatotoxicity, and eventually consider therapeutic drug monitoring whenever feasible, if malabsorption is suspected (because of diabetes or interactions with hypoglycaemic drugs). More information on the regimen's effectiveness in this group will also be important because diabetes is common in some countries. Additional information on the management of patients with liver problems is given in Section 8.

People with extensive pulmonary TB disease

The trial reported on the presence of cavitation and the extent of disease on CXR, as a percentage and cavity size (absent, <4 cm or ≥4 cm). For some subgroups, there was limited or no evidence on the use of the shorter regimen, but the use of this shorter regimen could be considered because favourable outcomes were reported using it in patients with extensive pulmonary disease.

Children and adolescents

The 4-month regimen including rifapentine and moxifloxacin (2HPMZ/2HPM) may be selected for adolescents aged 12 years and over and weighing at least 40 kg with pulmonary TB, regardless of disease severity *(29)*. Factors to consider before selecting this regimen are that:

- the regimen should not be used in children and adolescents aged under 12 years; and
- the regimen should not be used in adolescents with forms of extrapulmonary TB such as tuberculous meningitis, disseminated (miliary) TB, osteoarticular TB or abdominal TB.

4.4.2 Subgroups in which the regimen is not recommended

For some subgroups, there was no evidence (because they were ineligible for inclusion in the trial). The use of the shorter regimen outside of the research environment is not indicated in the subgroups giving below.

Patients weighing less than 40 kg

Low body weight can indicate severe forms of TB disease; therefore, close follow-up and use of the 6-month regimen may be preferable in this subgroup, as there is more experience with this regimen.

Patients with extrapulmonary TB

In patients with extrapulmonary TB – such as tuberculous meningitis, disseminated (miliary) TB, osteoarticular TB and abdominal TB – the regimen is not recommended.

PLHIV with a CD4 count of less than 100 cells/mm³

A low CD4 count is indicative of severe immunosuppression, leading to concerns about an increased risk of relapse in this group.

Children and adolescents aged under 12 years

There is presently no evidence on the use of this regimen in children and adolescents aged under 12 years.

Pregnant, breastfeeding and postpartum women

There is currently no evidence available on the use of this regimen in women who are pregnant, breastfeeding or postpartum.

4.5 Treatment monitoring

The current guidance on monitoring the response to treatment of DS-TB is unchanged. WHO does not recommend baseline electrocardiogram (ECG) monitoring for those receiving the shorter regimen (unless clinically indicated), and laboratory monitoring such as liver function tests (LFT) is the same for both regimens *(1)*. Some countries may have different requirements for LFT and ECG monitoring because of the "black box" warnings for moxifloxacin (related to QTc prolongation). Clinical monitoring is recommended in some countries for rare but possible AEs related to moxifloxacin that are common to other FQ (e.g. tendonitis, *Clostridium difficile* diarrhoea and peripheral neuropathy) and such monitoring should be carried out according to the country's policies.

NTPs need to monitor patients' condition with regular clinical follow-ups and may perform at least smear microscopy after 2 months of treatment to monitor treatment response bacteriologically. Lack of clinical or bacteriological response to treatment may need to trigger further clinical and radiological assessment, complemented by sputum smear culture and DST. Although the regimen can be continued while awaiting results of these assessments, once the results are available they will provide the clinician with the evidence to change the regimen or treatment strategy. Additional information on treatment monitoring is given in **Section 9**.

5. Treatment of DS-TB using the 4-month 2HRZ(E)/2HR regimen

As in adults, TB treatment in children and adolescents includes an intensive phase of 2 months followed by a continuation phase of 2–4 months. In the intensive phase, tubercle bacilli are rapidly killed to prevent disease progression and transmission, and the development of drug resistance. In the continuation phase, dormant bacilli are eliminated to effect cure and prevent relapse. The choice of TB treatment regimen depends on the severity of disease and age. The decision on whether to include a fourth medicine – ethambutol – in the intensive phase depends on the patient's HIV status, or on the prevalence of HIV or isoniazid resistance in the setting. In children and adolescents aged between 3 months and 16 years with non-severe TB, a 4-month treatment course is recommended. This recommendation is based on the evidence from the SHINE trial, a large phase III trial to evaluate duration of TB treatment in children with non-severe drug-susceptible TB. The trial showed that a 4-month treatment regimen (2 months of isoniazid, rifampicin and pyrazinamide, with or without ethambutol, followed by 2 months of isoniazid and rifampicin, 2HRZ(E)/2HR) was non-inferior to the standard 6-month regimen (2 months of isoniazid, rifampicin and pyrazinamide, with or without ethambutol, followed by 4 months of isoniazid and rifampicin, 2HRZ(E)/4HR) *(1, 30)*.

No.	Recommendation
2.2	**In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used** **(Strong recommendation, moderate certainty of evidence)**

5.1 Eligibility

The eligibility criteria in children and adolescents are summarized in **Box 5.1** *(31)*.

Box 5.1. Eligibility criteria for the 4-month regimen (2HRZ(E)/2HR) in children and adolescents aged between 3 months and 16 years, in various settings

A. In children and adolescents who have undergone bacteriological testing and CXR, a 4-month treatment regimen should be started in children and adolescents meeting all of the following three criteria:

➔ CXR findings consistent with non-severe TB (CXR should ideally be done at baseline):

- intrathoracic lymph node TB without significant airway obstruction; or
- PTB confined to one lobe with no cavities and no miliary pattern; or
- uncomplicated pleural effusion (without pneumothorax or empyema);

- TB that is negative, trace, very low or low using Xpert MTB/RIF or Ultra, or smear negative (if Xpert MTB/RIF or Ultra not available);
- the child or adolescent has mild symptoms that do not require hospitalizationa .

B. In settings without access to CXR, a 4-month treatment regimen may be implemented in children and adolescents meeting the following criteria:

- TB that is negative, trace, very low or low using Xpert MTB/RIF or Ultra, or smear-negative (if Xpert MTB/RIF or Ultra not available); AND the child or adolescent has mild symptoms that do not require hospitalization[a].

OR

- isolated extrathoracic (peripheral) lymph node TB, without confirmed or suspected involvement of other extrapulmonary sites of disease; AND the child or adolescent has mild symptoms that do not require hospitalizationa.

C. In the absence of bacteriological testing and CXR, a 4-month treatment regimen may also be started in children meeting either of the following criteria:

- isolated extrathoracic (peripheral) lymph node TB, without confirmed or suspected involvement of other extrapulmonary sites of disease; AND the child has mild symptoms that do not require hospitalization;

OR

- the child has a clinical diagnosis of pulmonary TB AND the child has mild symptoms that do not require hospitalization[a].

Children and adolescents who are started on the 4-month regimen without chest radiography need to be followed up monthly:

- TB symptoms are expected to have resolved within one month of treatment initiation;
- The child or adolescent is expected to be completely well, including a normal nutritional status (similar to before they developed symptoms of TB) after 4 months of treatment.

Treatment should be continued for a total of 6 months in children and adolescents who have not responded clinically (demonstrating weight gain and/or resolution of TB symptoms) after 4 months of treatment. They should be evaluated for DR-TB and non-TB-related disease (e.g. malignancy or HIV-related lung disease) as well as poor treatment adherence.

a Mild symptoms that do not require hospitalization means:
  - none of the danger or high-priority signs;[b]
  - no asymmetrical and persistent wheezing;
  - no signs of extrapulmonary TB other than peripheral lymph node TB; and
  - none of the following: severe acute malnutrition, respiratory distress, high fever (over 30 °C), severe pallor, restlessness, irritability or lethargy.

b Danger or high-priority signs and symptoms are cough longer than 2 weeks, fever longer than 2 weeks, lethargy, weight loss, haemoptysis, night sweats, swollen lymph nodes, tachycardia and tachypnoea.

5.2 Composition and duration of the regimen

The regimen evaluated by the SHINE trial comprised 2 months of daily isoniazid, rifampicin and pyrazinamide, with or without ethambutol (2HRZ(E)), followed by daily isoniazid and rifampicin (2HR).

In the SHINE trial, ethambutol was included in the first 2 months of treatment, depending on the local policy in place at the recruitment site, for both the 4-month regimen and the comparator 6-month regimen. All CHILDREN AND ADOLESCENTS LIVING WITH HIV in the SHINE trial received ethambutol in the first 2 months of treatment (regardless of which regimen they received). It is therefore preferred that children and adolescents living with HIV who receive the 4-month regimen receive ethambutol for the first 2 months of treatment, irrespective of the background prevalence of HIV. In addition, it is recommended that ethambutol be added to the 4-month regimen for the first 2 months in settings with a high background prevalence of isoniazid resistance or HIV infection. Also, for this regimen, daily dosing (i.e. 7 days per week), ideally under direct observation, is suggested, taking advantage of a treatment supporter or VST.

The doses are the same as those recommended for the 6-month regimen 2HRZE/4HR (**Annex 4**).

Treatment should be continued for 6 months or should be modified in children and adolescents who have not responded clinically (i.e. have not demonstrated weight gain or resolution of TB symptoms) after 4 months of treatment. These people should be evaluated carefully for DR-TB, non-TB-related disease (e.g. malignancy or HIV-related lung disease) and poor treatment adherence. The first 2 months of treatment, which includes three or four drugs, is usually enough for the strong bactericidal activity of this regimen to be effective. If the patients are sputum smear negative (or paucibacillary) and no cavities are present in CXR, then the presence of one or more sputum smear results that are positive after 2 months may indicate undetected resistance to one or more drugs. If the patient is not improving clinically and radiologically (e.g. cavities appear), and drug resistance or potential failure are suspected, rapid diagnostics to exclude this should be done promptly together with culture and DST, to provide a basis for any adjustment of the treatment strategy.

5.3 Considerations for implementation

Assessing severity of disease

Access to CXR is an important implementation consideration for assessing the severity of TB disease in children and young adolescents, and is useful in making a decision about the duration of treatment *(1)*. At lower levels of the health care system, access to CXR is often limited or the quality of CXR and the capacity for interpretation may be suboptimal; this can have equity implications, because of the out-of-pocket expenses it might cause. Therefore, the feasibility of CXR varies by setting. It is important to clearly define "non-severe" disease, and NTPs are encouraged to scale up access to quality CXR and train health care providers in its interpretation. If the severity of TB disease in children can be adequately determined under programmatic conditions, then implementation of a 4-month regimen is highly feasible.

The feasibility of assessing the severity of TB disease is a major consideration for implementation, particularly in settings without access to CXR or the capacity for CXR interpretation, and in settings without access to WHO-recommended diagnostic tests. CXR is a critical tool for evaluation of the severity of intrathoracic disease. Extensive or advanced pulmonary TB disease in children aged under 15 years is usually defined by the presence of cavities or bilateral disease on CXR *(17)*. As indicated above, non-severe TB disease refers to peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion; or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern.

Detailed implementation guidance is provided in the operational handbook on the management of TB in children and adolescents *(31)*. The guidance takes into consideration differences in the health care system and country context, including the availability of diagnostic tools for making a diagnosis and assessing disease severity. This guidance includes criteria for assessing disease severity (including clinical criteria in the absence of CXR or rapid diagnostics or other bacteriological tests) to determine eligibility for the shorter regimen.

Continuum between TB infection and disease

The continuum between TB infection and TB disease is an important consideration for implementation. Implementation of the 4-month regimen for the treatment of non-severe TB narrows the differences between recently recommended regimens for TB preventive treatment (TPT) *(32)* and treatment of non-severe forms of TB disease in children. This is particularly relevant to the TPT regimen that uses 3 months of daily isoniazid and rifampicin (3HR).

Contact investigation

The scale-up of contact investigation approaches is another implementation consideration. The scale-up can improve early case detection of children with non-severe disease who may benefit from the 4-month regimen.

Child-friendly formulations

NTPs are encouraged to prioritize the use of child-friendly FDC formulations for TB treatment in children up to 25 kg body weight; for example, the 3-FDC HRZ 50/75/150 mg (with or without the addition of dispersible ethambutol) and the 2-FDC HR 50/75 mg *(19)*.

Training of health care workers

Another critical factor in successful implementation of the shorter regimen is capacity-building of health care workers at all levels of the health system on diagnostic approaches (including treatment decision algorithms), eligibility for the 4-month regimen and monitoring of children on first-line TB treatment. Training will be necessary when introducing this shorter regimen into a programmatic setting. However, this is a requirement for any new programmatic intervention and the ability to shorten treatment and potentially treat more patients may offset the initial investment in training.

5.4 Subgroups

5.4.1 Subgroups in which the regimen is recommended

Children with peripheral lymph node TB

Although the numbers of children with peripheral lymph node TB in the SHINE trial were small (N=19 in the 16-week arm and N=21 in the 24-week arm), there was no difference in the proportion of unfavourable outcomes between the two arms. The SHINE trial also found that 16 weeks of treatment was not inferior to 24 weeks of treatment in children with both peripheral lymph node disease and pulmonary disease (N=182 in the 16-week arm and N=171 in the 24-week arm). These results may provide reassurance for clinicians regarding a seemingly delayed clinical response to TB treatment, which is frequently seen in children with peripheral lymph node TB (where lymph nodes remain enlarged even after treatment).

Children and adolescents living with HIV

Children and adolescents living with HIV were eligible for enrolment in the SHINE trial; 65 (11%) children and adolescents living with HIV were enrolled in the 16-week arm and 62 (10%) in the 24-week arm, with 49% of children and adolescents living with HIV in the 16-week arm and 43% in the 24-week arm being on ART at the time of enrolment. Among children and adolescents living with HIV, 20% in both arms had a CD4 count of less than 200 cells/mm^3, and 51% of children and adolescents living with HIV in the 16-week arm and 63% in the 24-week arm were classified as "severe" according to the WHO immunological classification for established HIV infection *(33)*. In this subgroup, the 16-week regimen was again not inferior to the 24-week regimen, although the 95% confidence interval (CI) for the difference from the control arm in the unfavourable rate was wide (risk difference –4.3, 95% CI: –14.9 to 6.2).

Clinicians may consider treating children and adolescents living with HIV with non-severe TB for 4 months, depending on the degree of immunosuppression, ART status and presence of other opportunistic infections *(34)*. These children and adolescents will need to be monitored closely, especially at 4 months of treatment, and treatment will need to be extended to 6 months if there is insufficient progress.

5.4.2 Subgroups in which the regimen is not recommended

Children with severe acute malnutrition

No separate subgroup analysis could be conducted for children with severe acute malnutrition (SAM)[10] in the SHINE trial owing to the low numbers (30 children with SAM in the 16-week arm and 33 in the 24-week arm). Because SAM is defined as a danger sign, even if children with SAM have a non-severe form of TB, they should preferably receive 6 months of TB treatment.

5.5 Treatment monitoring

All children and adolescents initiated on TB treatment should undergo a monitoring assessment at the following intervals as a minimum:

- *HIV-negative children and adolescents* – 2 weeks and 4 weeks after the start of treatment, at the end of the intensive phase (after 2 months) and at completion of treatment at 4 months; and
- *Children and adolescents living with HIV* – 2 weeks and 4 weeks after the start of treatment, then every month until completion of treatment at 4 months or 6 months (depending on the regimen used).

Clinical monitoring requirements for the shorter regimen are the same as for the 6-month regimen. Treatment outcomes are determined at the end of treatment; that is, at 4 months for the shorter regimen.

Monitoring should include the following as a minimum:

- assess for resolution or persistence of TB-related symptoms, symptoms of side-effects of medicines and other symptoms;
- measure weight and adjust dosages as necessary, depending on weight gain;
- assess adherence; that is, review the treatment card and discuss with the patient, carers and other treatment supporters; and
- collect follow-up sputum samples for smear microscopy 2 months after the start of treatment and at treatment completion from any child who was Xpert MTB/RIF positive, Xpert Ultra positive, smear positive or culture positive at diagnosis, if the treatment site has the capacity to perform the test.

[10] Defined as weight-for-height Z-score below −3 or mid-upper-arm circumference below 115 mm *(33)*.

Symptomatic improvement and weight gain are the most valuable markers of treatment success or failure *(29)*. If a follow-up smear is positive, the patient should complete additional investigations to assess for drug resistance (Xpert MTB/RIF or Ultra, TB culture and DST or molecular tests for drug resistance) and other causes of poor treatment response. Possible causes of a poor response include *(29)*:

- incorrect dosage;
- adherence being compromised by AEs; or
- the child or adolescent:
  - not taking the drugs as prescribed or having poor gastrointestinal absorption of one or more of the drugs;
  - living with HIV and having developed immune reconstitution inflammatory syndrome (IRIS) or having an opportunistic infection;
  - being (severely) malnourished, and SAM not being managed appropriately; or
  - having another comorbidity or illness.

In children who cannot expectorate, a repeat specimen at the end of treatment is not necessary if the specimen collected at 2 months is negative. Repeat sample collection at 2 months in children with unconfirmed TB is not indicated unless there is an inadequate clinical response without symptomatic and nutritional improvement. Follow-up CXR is not needed if the child is responding well to TB treatment. Children commonly have a slow radiographic response to treatment and may have persistent radiographic abnormalities at treatment completion *(29)*, but this does not mean they are not responding to treatment.

6. Treatment of DS-TB in people living with HIV

Recommendations on DS-TB treatment and ART in PLHIV:

No.	Recommendation
3.1	**It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients** **(Strong recommendation, high certainty of evidence)**

No.	Recommendation
3.2	**ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.**[a] **Adults and adolescents** **(Strong recommendation, low to moderate certainty of evidence);** **Children and infants** **(Strong recommendation, very low certainty of evidence)**

[a] Except when signs and symptoms of meningitis are present.

Patients with HIV infection and TB have an increased risk of death, treatment failure and relapse *(4)*. There is evidence that PLHIV with TB coinfection who are treated with ART respond much better to anti-TB treatment and have improved outcomes; therefore, ART is of paramount importance *(22, 35)*.

6.1 Eligibility

The recommendation on starting ART in TB patients has recently been expanded to include all patients, regardless of CD4 count. Although all three regimens (**Table 1.2.1**) can be initiated in PLHIV, the 6-month regimen is a preferred option in those with a CD4 count of less than 100 cells/mm^3.

6.2 Composition and duration of the regimen

All people living with HIV with DS-TB may be treated using the same duration of TB treatment as HIV-negative TB patients. There is much experience of treating these patients with the 6-month rifampicin-containing regimen 2HRZE/4HR *(1, 36)*. The 4-month regimen with rifapentine and moxifloxacin has also been shown to perform well in patients who are also HIV-positive *(1)*. The evidence on the use of this 4-month regimen in people living with HIV was limited to those with a CD4 count of above 100 cells/mm^3; hence, the CD4 count value below 100 cells/mm^3 is currently used in excluding people living with HIV from the shorter regimen. For people living with HIV with a CD4 count above that threshold, both regimens can be used.

Children living with HIV were eligible for enrolment in the SHINE trial. In view of the limited evidence available from the trial, clinicians may consider treating children living with HIV with non-severe TB for 4 months with 2HRZE/2HR, depending on the degree of immunosuppression and ART status, as well as the presence of other opportunistic infections. These children and adolescents will need to be monitored closely, especially at 4 months of treatment.

As discussed above, all people living with HIV (especially those with TB) should receive ART. People with HIV-associated TB who are responding to ART should not expect a less favourable outcome to a treatment episode than those who are HIV-negative. Therefore, people living with HIV with DS-TB can benefit from currently recommended treatment regimens. For further information, see WHO's *The use of antiretroviral drugs for treating and preventing HIV infection (22)*, *WHO consolidated guidelines on tuberculosis: Module 6: tuberculosis and comorbidities, second edition (37)* and *WHO operational handbook on tuberculosis: module 6: tuberculosis and comorbidities (38)*.

6.3 Considerations for implementation

There are no new implementation considerations beyond the current standards of care for people living with HIV. NTPs need to work closely with HIV programmes to further expand HIV testing and ART coverage among TB patients. A particular exception highlighted in the recommendation on timing of the ART relates to situations when signs and symptoms of meningitis are present. In general, it is recommended to start ART within 2 weeks of initiating TB treatment; however, caution is needed in people living with HIV with tuberculous meningitis, because immediate ART is significantly associated with more serious AEs. Thus, delaying ART for 4–8 weeks after initiation of TB treatment might be considered in these situations *(39)*. In patients commencing ART with a CD4 count of less than 100 cells/mm^3, while steroids may reduce TB-related IRIS, more data are needed on their use in preventing IRIS in patients with low CD4 counts.

6.4 Treatment monitoring

There are no new monitoring and evaluation considerations beyond the current standard of care for people living with HIV. In view of the subgroup considerations, NTPs may consider monitoring specifically for relapse in this group of TB patients. More details on treatment monitoring are given in Section 9.

7. Treatment of extrapulmonary TB

Extrapulmonary TB is active TB in organs other than the lungs. About 15% of the 7 million incident TB cases globally notified in 2018 were extrapulmonary TB; among WHO regions, prevalence ranged from 8% in the Western Pacific; to 15–17% in Africa, the Americas, Europe and South-East Asia; and to 24% in the Eastern Mediterranean *(4)*. The WHO European Region is facing an increasing notification rate of extrapulmonary TB: in this region seven countries (Finland, the Netherlands, Norway, Sweden, Türkiye, the United Kingdom and Uzbekistan) reported more than 30% of cases *(40)*.

Overall, among both adults and children, about two of every three extrapulmonary TB cases are represented by pleural and lymph node TB *(41)*. In settings with a high prevalence of HIV infection, lymph node TB represents about 10% of all TB cases *(42)*. Osteoarticular, urogenital, intra-abdominal, pericardial and meningeal TB are less frequent *(41)*. Tuberculous meningitis is important both for being clinically severe and for being largely preventable in children by vaccinating with bacille Calmette–Guérin (BCG), ideally at birth *(43)*.

Compared with pulmonary TB, extrapulmonary TB is more difficult to diagnose because it can mimic other organ-specific diseases, clinical samples for bacteriological situations are difficult to obtain for culture, and digital imaging is not always available. In addition, extrapulmonary TB is often paucibacillary *(41)*. Pericardial, meningeal and disseminated (miliary) TB forms are more likely to result in a fatal outcome.

7.1 Eligibility

Adults with extrapulmonary TB are eligible for the 6-month 2HRZE/4HR regimen, except for those with TB of the central nervous system, bone or joint, for which some expert groups suggest longer therapy (i.e. 9–12 months).

Children aged between 3 months and 16 years with extrapulmonary TB limited to peripheral lymph nodes (i.e. without involvement of other sites of disease) should be treated with the 4-month regimen (2HRZ(E)/2HR).

In children and adolescents with tuberculous meningitis, two alternative regimens can be used: a 12-month regimen (strong recommendation) and a 6-month regimen described below (conditionally recommended). The 6-month tuberculous meningitis regimen is not currently recommended for use in children and adolescents living with HIV.

7.2 Composition and duration of the regimen

Pulmonary and extrapulmonary TB disease in adults can be treated with the same regimens, the 6-month 2HRZE/4HR being the core regimen. Outside WHO recommendations, some experts suggest 9–12 months of treatment for tuberculous meningitis (given the serious risk of disability and mortality) *(41)*, and 9 months of treatment for osteoarticular TB (given the difficulties in assessing treatment response) *(41, 44–46)*.

Treatment of extrapulmonary TB is similar to that of pulmonary TB, being centred around the 6-month 2HRZE/4HR regimen; however, the regimen can be prolonged up to 12 months for tuberculous

meningitis, osteoarticular TB or other types of extrapulmonary TB, as decided by clinicians. The 4-month 2HPMZ/2HPM regimen was not studied in extrapulmonary TB and thus cannot be recommended at this time. Furthermore, extrapulmonary TB is usually more difficult to diagnose, and evaluation of its outcomes can be more challenging because of the absence of bacteriological evidence in most patients and the need for cross-sectional imaging; hence, there is little quality evidence on this type of TB.

Following infection with *M. tuberculosis*, young children are at high risk of developing the most severe forms of disease, the most devastating being tuberculous meningitis, which predominantly affects young children (peak age of onset, 2–4 years). WHO currently recommends a 12-month regimen to treat tuberculous meningitis in children, comprising isoniazid, rifampicin, pyrazinamide and ethambutol given daily for the first 2 months, followed by isoniazid and rifampicin given daily for an additional 10 months (2HRZE/10HR) *(19)*. Recommended doses to be used in this regimen are the same as those for the treatment of pulmonary TB. This regimen can be used in all children and adolescents, including those who are HIV-positive.

An alternative option of a shorter regimen is also conditionally recommended. This shorter regimen is recommended for children and adolescents with bacteriologically confirmed or clinically diagnosed tuberculous meningitis (without suspicion or evidence of MDR/RR-TB); it is a 6-month intensive regimen that comprises isoniazid, rifampicin, pyrazinamide and ethionamide (6HRZEto) *(19)*. It is preferable to use child-friendly, dispersible and FDC medicines in children when possible.

In cases of non-severe TB, the 4-month 2HRZ(E)/2HR regimen (see Section 5 for details) can be used for children and adolescents with peripheral lymph node TB, intrathoracic lymph node TB without airway obstruction and uncomplicated TB pleural effusion *(1)*.

Children with peripheral lymph node TB were included in the SHINE trial, and the results showed that the 4-month regimen (2HRZ(E)/2HR) can be used in children and adolescents aged between 3 months and 16 years with extrathoracic lymph node TB, which falls under the definition of non-severe TB *(1)*. These results should provide reassurance for clinicians regarding a seemingly delayed clinical response to TB treatment, which is often seen in children with peripheral lymph node TB (where lymph nodes remain enlarged even after treatment).

7.3 Use of adjuvant steroids in the treatment of tuberculous meningitis and pericarditis

Treatment with corticosteroids is recommended for tuberculous meningitis and pericarditis because the benefits outweigh the potential harms of corticosteroid therapy *(1, 22, 38, 44, 47)*.

In patients with tuberculous meningitis, evidence from RCTs *(48–52)* showed lower rates of mortality, death or severe disability, and disease relapse when patients were treated with steroids in addition to anti-TB treatment. The mortality benefit increased with the increasing severity of disease. Additionally, rates of AEs and severe AEs, including severe hepatitis, were lower in patients receiving steroids; hence, steroids should be given regardless of the severity of meningitis.

In patients with tuberculous pericarditis, a systematic review *(53–60)* found a benefit to steroid treatment in relation to death, constrictive pericarditis and treatment adherence. When the studies were considered individually, the largest (1400 patients) and most recent study – the Investigation of the Management of Pericarditis (IMPI) study – showed no benefit of steroids *(55)*. However, a factor complicating these findings is HIV infection. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. This raises the question as to whether immunosuppressed patients may have had a different benefit from steroids when compared with HIV-negative people or people living with HIV who are on ART. In the IMPI study, a supplemental analysis of only HIV-negative patients showed a small mortality benefit with steroid treatment. However, another smaller study of 58 subjects, all of

whom were HIV-positive, found that steroids reduced mortality *(56)*. Other studies in the review did not address HIV and mortality.

With regard to the use of steroids in tuberculous pericarditis, in one study, an increase in HIV-related cancers (non-Hodgkin's lymphoma and Kaposi sarcoma) was observed *(55)*. However, this increase appeared to be caused by co-administration of immunotherapy (*M. indicus pranii*). The increase in cancers was not confirmed in another study *(39)*. Practitioners should evaluate when intravenous steroids are necessary, and when oral formulations may be equally effective.

7.4 Considerations for implementation

Provider-initiated HIV testing is recommended as part of the evaluation of all TB patients and patients in whom the TB disease is suspected. HIV testing is especially important in people with or suspected of having extrapulmonary TB, because of the increased frequency of extrapulmonary involvement in those with immunosuppression. Extrapulmonary TB is considered to be WHO clinical stage 4 HIV disease.

Based on the severity of signs and symptoms, and the likelihood of potential sequelae, the patient may need frequent treatment monitoring or post-treatment follow-up (or both).

Although surgery is sometimes required for diagnosis, it plays little role in the treatment of extrapulmonary TB, being reserved for management of late complications of disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis and neurological involvement from Pott's disease (spinal TB). For large, fluctuant lymph nodes that appear to be about to drain spontaneously, aspiration or incision and drainage may be beneficial. To prevent further complications and to manage similar situations in a timely manner, clinical monitoring may be needed in selected patients.

Apart from these specific situations, there are no additional recommendations beyond the standard of care. Additional details on treatment monitoring are given in Section 9 of this document.

8. Treatment of DS-TB in special situations

Treatment of DS-TB poses special issues in some subgroups of patients; in particular, those with diabetes, pregnant women, people aged over 65 years, and those with chronic kidney or liver disease.

8.1 Diabetes

Diabetes is a common condition, particularly in some countries, where up to 30–40% of TB patients are affected. The population attributable fraction of diabetes as a risk factor for TB is more than 10% in all WHO regions, except for Africa and the Western Pacific *(4)*. Diabetes was estimated to account for more than 10% of global TB deaths among HIV-negative individuals *(61)*.

Hyperglycaemia induces abnormalities in both the innate and adaptive immune response to *M. tuberculosis*, and diabetes increases the risk (twofold to fourfold) that TB infection will progress to disease; also, the response to treatment is often worse in those with diabetes. Among the mechanisms involved, bacterial recognition and phagocytosis are less effective in diabetes, with impairment of antigen-presenting cell recruitment and delay in activating the cellular immune response *(62)*. Clinically, this translates into an increased proportion of sputum smear positive patients, with more extensive pulmonary disease bilaterally, larger number of cavities and lymph node enlargement, and "atypical" findings of lower lobe lesions (especially in patients with poor glycaemic control). People with diabetes also suffer an increased rate of failure and death, and a higher risk of relapse *(62)*.

Diabetes has a negative effect on the pharmacology of some anti-TB drugs (e.g. rifampicin), with higher risk of development of drug resistance *(62)*. Rifampicin is a potent hepatic enzyme inducer, increasing the hepatic metabolism of sulphonyl urea derivatives and therefore lowering their plasma levels. No effect of rifampicin is known on the exposure of glucagon-like peptide-1 receptor agonists and only a slight effect on dipeptidyl peptidase-4 inhibitors. Although metformin is not metabolized by the P450 enzymes system, its hypoglycaemic effect may be increased by rifampicin, enhancing the expression of organic cation transporter and the hepatic uptake of metformin. Because insulin is not metabolized, no pharmacokinetic interactions with anti-TB drugs occur; therefore, some authors have recommended that it be used at the beginning of TB treatment, to achieve faster bacteriological sputum conversion and prevent DDIs *(62)*.

A higher proportion and sometimes a greater severity of AEs has been described in TB patients with diabetes (e.g. peripheral neuropathy due to isoniazid and ocular neuropathy due to ethambutol) *(62)*.

There is evidence that the problems described above reduce when diabetes is well controlled. Therefore, adequate control of diabetes, and collaboration between TB and diabetes services, are important, particularly in countries with a high prevalence of diabetes.

Implementation considerations

- Although the drugs used to treat DS-TB are generally well tolerated and are unlikely to cause serious AEs among people with diabetes, treatment monitoring is important to ensure rapid notification and prompt management of any side-effects that eventually appear.
- Management of these patients involves a multidisciplinary approach, in view of the additional need to control diabetes and the potential need to adjust drug dosing. A national or subnational body supporting the management of people with difficult-to-treat TB (i.e. a consilium) may be of help in specific cases *(63)*.
- Supporting adherence is an important management component when treating people with DS-TB and diabetes. Therefore, collaboration with partners in the community, including family members, carers, health care workers and welfare workers, is essential.
- Coordination of NTPs with diabetes services may be relevant in countries where TB is highly prevalent.

8.2 Pregnancy

Epidemiological information on TB in pregnancy is scarce. In the United Kingdom, women in early postpartum were twice as likely to develop TB as non-pregnant women *(64)*.

A recent population study in Mozambique evaluated the prevalence of TB in pregnancy and found that it was similar to that of the general population, although it was higher in women living with HIV *(65)*. The TB prevalence was 505 (95% CI: 242–926) per 100 000 pregnant women and 297 (95% CI: 61–865) per 100 000 postpartum women. Among pregnant women who were HIV-positive, TB prevalence was 1626 per 100 000 (95% CI: 782–2970) and among postpartum women who were HIV-positive, TB prevalence was 984 per 100 000 (95% CI: 203–2848).

In addition to the TB-related risks to the mother, TB during pregnancy has been associated with high perinatal mortality, small size for gestational age, preterm and low birth weight neonates *(66)*. Maternal TB disease is associated with poorer neonatal outcomes, in part because of social deprivation and other factors that are associated with a higher risk of TB during pregnancy *(67)*. Disseminated TB in the mother can cause congenital TB in the infant, but this is a rare condition *(68)*. Diagnosis of TB is often delayed during pregnancy, because of its nonspecific symptoms and overlapping presentation with other infectious diseases. Adverse perinatal outcomes are even more pronounced in women with advanced disease, late diagnosis, and incomplete or irregular drug treatment. Many antenatal clinics are unprepared to diagnose TB *(69)*. Because pregnancy is usually considered an exclusion criterion, there is a lack of data from clinical trials including this important category of patients. Standard treatment for DS-TB is considered safe in pregnancy and outweighs the grave risks posed by untreated TB. Measurement of liver function before the start of treatment is useful and, if the function is found to be abnormal, appropriate management is undertaken *(70, 71)*. Core issues related to the management of treatment during pregnancy relate to the safety of the child before and after birth, considering both the risk of transmission (i.e. mother-to-child) and the potential teratogenic effect of anti-TB drugs.

Neonatal TB is most commonly due to inhalation of tubercle bacilli. As long as the mother has received at least 2 weeks of treatment for DS-TB, isolation of the infant is not required *(72)*. This is particularly relevant because of the importance of breastfeeding for child health. Early diagnosis and treatment help to ensure the best possible outcome of TB in pregnancy for both mother and infant.

Pregnant women are usually treated with the standard 6-month 2HRZE/4HR regimen. Evidence on the use of the 4-month 2HPMZ/2HPM regimen during pregnancy is lacking *(1)*. Experts have suggested using pyridoxine to complement the anti-TB regimen in pregnancy, because deficiency is more likely to occur than in the general population *(73)*.

Implementation considerations

- The isolation needs of the mother should be reduced to the minimum necessary to prevent transmission to the child, to ensure that breastfeeding is not interrupted.
- Health education on the basics of infection control, with a special focus on personal protection and ventilation, is an important component of the management of treatment of DS-TB during pregnancy.
- Although the drugs used to treat DS-TB are generally well tolerated and are unlikely to cause AEs to the mother and the child, monitoring of AEs is important to ensure rapid notification and prompt management.
- Management of patients listed in this section (i.e. pregnant women and others) involves a multidisciplinary approach; a TB consilium to support the management of people with TB that is difficult to treat may be of help *(63, 74)*.
- Coordination of the NTP with antenatal clinics and HIV services is important, to ensure rapid diagnosis and effective treatment of TB in pregnancy.

8.3 Older people

TB in older people is particularly relevant in countries with low incidence of TB in the WHO regions of the Americas and Europe, and is a growing problem in Asia because of the increasingly ageing population *(4, 75)*. Outbreaks in nursing homes are frequently described, particularly in countries with a low incidence of TB *(76, 77)*. The occurrence of TB among older people is also related to the higher prevalence of comorbidities (e.g. diabetes, chronic renal impairment and smoking) in this age group. The disability-adjusted life-years lost due to TB in patients aged over 65 years range from 8.2% in Europe to 18.7% in East and Central Asia *(78)*.

The main challenges to successful treatment among older patients include poor drug tolerance, AEs and poor treatment adherence, all of which could potentially lead to unfavourable treatment outcomes.

Recent data from Japan on TB patients notified in 2017 indicate that the case-fatality rate increased with age, being 3.1% for those aged 0–64 years, 15.3% for those aged 65–74 years, 27.0% for those aged 75–84 years and finally 47.4% for those aged 85 years and over *(44, 75)*. A study in Nigeria described lower sputum smear conversion after the intensive phase of treatment in patients aged over 60 years, although only extrapulmonary TB and HIV coinfection were significant predictors of a poorer outcomes *(73)*.

Gastrointestinal upset and hepatitis are reported as the most frequent AEs in older people *(79, 80)*. In Japan, in patients aged 80 years or more treated for DS-TB with the 6-month regimen, the prevalence of hepatitis was higher among those receiving treatment with isoniazid, rifampicin, pyrazinamide and ethambutol than among those receiving isoniazid, rifampicin and ethambutol, although treatment outcomes were similar in the two groups *(81)*.

Clinical attention should be paid to older patients undergoing pyrazinamide treatment, to rapidly identify and manage any AEs that eventually appear. Guidelines from the American Thoracic Society consider the option of excluding pyrazinamide in patients aged over 80 years *(44)*.

Ethambutol is excreted by the kidney. A low glomerular filtration rate (GFR) (i.e. <30 mL/minute^{-1}) has a poor prognosis in the treatment of TB *(82)*. In older people, the dose should be reduced according to the estimated GFR, but the time between doses should also be increased, to ensure that high blood levels of the drug do not persist *(83)*.

Older individuals are likely to have several comorbidities and are therefore likely to be taking other medicines; hence, there is potential for DDIs *(84)*. The interaction between the anticoagulant warfarin and rifampicin is especially problematic, and either heparin or a non-vitamin K oral anticoagulant are considerably safer. Other important interactions include those with statins, analgesics (e.g. celecoxib

and losartan), oral antidiabetic medications, steroids, calcium channel blockers and theophyllines. When prescribing TB treatment in older people, it is always important to evaluate potential interactions among the different drugs prescribed to manage comorbidities *(73)*.

Among older people, particular care is also necessary to ensure correct adherence to the prescribed treatment within a multidisciplinary and patient-centred approach *(44, 85)*.

Implementation considerations

- Although the drugs used to treat DS-TB are generally well tolerated and are unlikely to cause AEs among older people, monitoring of AEs is important to ensure rapid notification and prompt management.
- Management of older people with TB involves a multidisciplinary approach, in view of the additional treatments that are often required to manage comorbidities and the potential need to adjust drug dosing. A TB consilium to support the management of people with TB that is difficult to treat may be of help *(63)*.
- Supporting adherence, taking into account age-related physical and psychological disabilities, is an important management component when treating DS-TB in older people. Thus, collaboration with partners in the community, including family members, carers, health care workers and welfare workers, is essential.
- Coordination of NTPs with geriatric services may be relevant in countries where TB in older people is increasingly notified.

8.4 Chronic renal failure

Patients with chronic renal failure (CRF) have more frequent AEs and higher mortality rates than patients without CRF. This has been attributed to increased host susceptibility from the cellular immunosuppressive effects of CRF and to social determinants of health among those with CRF *(86)*.

The severity of renal insufficiency is classified using creatinine clearance: it is *mild* when the rate of clearance is 60–120 mL/minute, *moderate* at 30–59 mL/minute, *severe* at 10–29 mL/minute and *very severe* at below 10 mL/minute. According to some experts, for patients with DS-TB on dialysis, a thrice-weekly dosing of pyrazinamide and ethambutol should be administered after the dialysis cycle *(62, 86)*. Creatinine clearance is calculated using the following formula:

body weight (kg) × (140 minus age in years) × 0.85 (in women) / 72 × creatinine value

Dose adjustments in adults with creatinine clearance below 30 mL/minute are as follows (unless otherwise indicated):

- *Pyrazinamide*: 25–35 mg/kg per dose, three times per week after dialysis.
- *Ethambutol*: 15–25 mg/kg per dose, three times per week after dialysis.
- *Rifapentine and moxifloxacin*, which are both used in regimens for DS-TB, do not require renal dose adjustment *(17, 87)*.

Experts recommend close monitoring of creatinine every week or every 2 weeks, and adequate hydration *(71)*. Given the frequent occurrence of electrolyte disturbances in CRF, weekly monitoring of electrolytes is also recommended.

In the case of severe hypokalaemia, treatment is with intravenous potassium chloride (KCl) at 10 mEq/hour^{-1} (10 mEq of KCl will raise the serum potassium by 0.1 mEq/L^{-1}). If the potassium level is low, checking the magnesium is recommended by experts; if this is not possible, empirical treatment

with magnesium (i.e. magnesium gluconate at 1000 mg twice daily) should be considered in all cases of hypokalaemia. The use of spironolactone, 25 mg daily, is suggested in refractory cases *(71)*.

Given the risk of QT prolongation (particularly due to moxifloxacin) and electrolyte imbalance, an ECG should be performed, taking into account that hypokalaemia may be refractory if the concurrent hypomagnesaemia is not corrected; the risk is higher if the intensive phase of treatment is prolonged for any reason; and electrolyte disturbances are reversible, although the disturbance might last weeks or months.

Implementation considerations

- Both the diagnosis of CRF and the treatment of TB in patients with CRF are challenging. There is little evidence to support evidence-based guidance for these patients.
- Given the complexities of the management of TB disease in patients with CRF, a close collaboration between infectious disease specialists, pulmonologists and nephrologists in this patient population is necessary. A TB consilium to support the management of people with TB that is difficult to treat may be of help *(63, 74)*.

8.5 Chronic liver disease

Isoniazid, rifampicin or pyrazinamide may cause hepatotoxicity. In the management of TB in patients with chronic liver disease (CLD), experts recommend monitoring aminotransferases (i.e. alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) on a weekly basis initially, and fortnightly after the second month of treatment. In cases where aminotransferase are five or more times higher than the upper limit of normal (with or without symptoms), or three or more times higher in the presence of symptoms or jaundice (i.e. bilirubin >3 mg/dL^{-1}), the treatment should immediately be withdrawn. The responsible drugs should be identified, and a sequential reintroduction implemented once enzyme levels have returned to normal. The drug reintroduction should be performed one drug at a time, starting with the drug considered to be the least hepatotoxic, as follows:

- when aminotransferases return to less than two times the upper limit of normal, rifampicin may be restarted with ethambutol;
- after 3–7 days, after checking aminotransferases, isoniazid may be reintroduced, with subsequent rechecking of liver enzymes; and
- if symptoms recur or aminotransferases increase again, the last drug added should be stopped and replaced with another from the list of the recommended drugs *(71)*.

If the clinical pattern indicates cholestasis, rifampicin may be the responsible drug. If the patient has prolonged or severe hepatotoxicity but tolerates isoniazid and rifampicin, a rechallenge with pyrazinamide may be hazardous. In this situation, pyrazinamide may be permanently discontinued, with treatment eventually extended to 9 months *(71)*. In patients with advanced CLD, coagulation factors should be carefully monitored *(44, 88–90)*.

NTPs should consider stocking an extra supply of drugs to modify the HRZE regimen in the treatment of special situations such as CLD. Among the drugs that can be considered safe to use in patients with CLD are ethambutol and FQ *(71)*. Given their important bactericidal and sterilizing action, where possible, isoniazid or rifampicin (or both) should be included *(71)*.

A patient's N-acetyltransferase (NAT) status affects their risk profile. Slow acetylators have a higher possibility of liver injury, so an isoniazid dose of 2.5–5 mg/kg/day may be adequate in such patients; in rapid acetylators, in contrast, the isoniazid dose may be increased to 7.5 mg/kg/day.

The Child–Turcotte–Pugh (CTP) score is based on albumin, bilirubin, prothrombin time/international normalized ratio (PT/INR), ascites and encephalopathy. The CTP score can be used as a predictor of tolerance to anti-TB drugs and the treatment outcome, as shown in Table 8.1 *(91)*.

Table 1.8.1. CTP score parameters

Parameter	1 point	2 points	3 points
Ascitis	None	Mild	Moderate to severe
Serum albumin (g/dl)	>3.5	2.8–3.5	<2.8
Bilirubin, total (mg/dl)	<2	2–3	>3
Hepatic encephalopathy	No	Grade I–II	Grade III–IV
Prothrombin time (INR)	<1.7	1.7–2.3	>2.3

CTP: Child–Turcotte–Pugh; INR: international normalized ratio.

Table 1.8.2. Estimated survival at 1 and 2 years based on CTP

Class	Score points	Survival after 1 year (%)	Survival after 2 years (%)
A	5–6	100	85
B	7–9	80	60
C	10–15	45	35

CTP: Child–Turcotte–Pugh.

In people with DS-TB with stable CLD (CTP ≤7), a treatment regimen that includes isoniazid, rifampicin and ethambutol is likely to be tolerated, with the exclusion of pyrazinamide (which is the most hepatotoxic drug in the 6-month regimen). Some experts suggest that, in this situation, the isoniazid and rifampicin continuation phase be prolonged to 7 months, after a 2-month intensive phase with the three drugs *(91)*.

In patients with more severe CLD (CTP 8–10), it is advisable to use only one potentially hepatotoxic drug, preferably rifampicin; however, if CLD is very advanced (CTP ≥11), it is advisable to not use any hepatotoxic drug *(71, 86)*. Some authors advise using a temporary liver-sparing regimen early in treatment to reduce bacillary load and transmission risks while waiting for transaminase levels to decrease.

When there is a need to design regimens for special situations, collaboration with clinicians who have specific experience in CLD and the support of an expert committee (e.g. TB consilium) are recommended *(44, 63)*.

Implementation considerations

- In people with DS-TB and CLD, evaluation of the degree of impairment of the liver function is necessary, to design the best possible regimen that is sufficiently effective while not being aggressive for the liver. Given the clinical severity of these patients, collaboration with clinicians who have specific experience in CLD and the support of an expert committee (e.g. TB consilium) is recommended.
- The NTP should ensure a stock of individual formulations to manage patients with CLD who are unable to tolerate the standard recommended regimens.
- Treatment outcomes are often less favourable in patients with CLD than in patients without CLD.

9. Monitoring treatment response

This section focuses on monitoring the progress of treatment and identifying any problems that may arise during treatment of DS-TB. Examples of such problems are adverse drug reactions or delayed response to treatment, which might require additional investigations to decide whether to continue the therapy or change the treatment strategy.

All patients should be monitored to assess their response to therapy. Regular monitoring of patients also facilitates adherence to treatment and completion of treatment.

Although people with DS-TB are much less likely than those with MDR-TB to fail treatment, it is important to outline the principles of effective monitoring where drug resistance and possible failure are suspected. Regular clinical examination (with monitoring of body weight), CXR and laboratory monitoring make it easier to determine whether something is wrong and thus take rapid action.

All patients, their treatment supporters and health workers should ideally be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), slow clinical improvement, symptoms of adverse drug reactions or treatment interruptions. Patient weight should be monitored each month, and dosages should be adjusted if weight changes. When possible, radiological monitoring may also be useful. Regular clinical examinations should be performed by the treating physician.

A written record of all medications given, bacteriological response and AEs should be maintained for every TB patient on the TB treatment card.

9.1 Clinical examination

The classic symptoms of TB – cough, sputum production, fever and weight loss – generally improve within the first few weeks of treatment. Cough and sputum production can persist after sputum conversion in patients with extensive lung damage (often due to late diagnosis), but even in those with extensive lung damage, improvement is usually seen within 1–2 months of effective treatment. Persistent fever, weight loss or recurrence of any of the classic symptoms of TB should prompt investigation for possible treatment failure, undetected resistance to one or more drugs in the current treatment regimen or untreated comorbidities. The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure. For children, height and weight should be measured monthly to ensure that they are growing normally. Normal growth rate usually resumes after a few months of successful treatment. For adults, weight should also be recorded monthly (height is only recorded at the start of treatment, to calculate BMI).

The frequency of clinical visits depends on the patient's clinical condition and evolution. On average, for an outpatient with no specific problems, clinical examination is usually done every week during the first month and once per month thereafter if the patient is stable. More frequent clinical examinations may be necessary, depending on the clinical condition of the patient.

At every visit, the patient should be asked about the occurrence of AEs; also, any potential difficulties in treatment adherence should be discussed with the patient and their treatment supporter.

Clinical visits should coincide with bacteriological and clinical laboratory examination schedules, to limit time and transportation constraints for the patient.

In extrapulmonary DS-TB, it is essential to monitor the clinical evolution to assess the treatment response because, in general, bacteriological monitoring is difficult.

9.2 Chest radiography

In the first few months of treatment, the patient's chest radiograph may appear unchanged or show only slight improvement. Although there are no formal recommendations on this, it is prudent to undertake CXR at baseline, at the end of the second month of treatment and at the end of treatment, to document progress and to use for comparison if the patient's clinical condition changes at any time after the achievement of treatment success *(92)*. A chest radiograph at the end of treatment is also useful to optimally manage TB pulmonary sequelae after treatment *(92)*.

For extrapulmonary TB (in particular TB of the bone or joint), both radiographic examination and computed tomography (CT) can provide information on the evolution of the disease. However, some changes detected by CXR may never return to baseline; hence, the response often needs to be evaluated based on both clinical and radiographic findings. In contrast with pulmonary TB treatment, it is difficult to define what constitutes a cure in extrapulmonary TB.

9.3 Sputum smear and culture

Response to treatment in pulmonary TB patients is also monitored by bacteriological sputum smear examination and culture. For pulmonary DS-TB, the most important evidence of improvement is conversion of the sputum culture to negative. For extrapulmonary TB, sputum smears and cultures are only performed during the monitoring period if the patient develops pulmonary signs, or in the rare situation when materials valid for microbiological examinations are collected from the extrapulmonary site.

For people with DS-TB, sputum smear microscopy may be performed at the end of the second month of treatment. Sputum specimens should also be collected for smear examination at each follow-up sputum check. Specimen collection should not interrupt treatment, and specimens should be transported to the laboratory promptly; if a delay in transport is unavoidable, specimens should be refrigerated or kept as cool as possible.

A positive sputum smear at the end of the second month may indicate any of the following:

- even though the treatment response was good, non-viable bacteria remain present and are visible by microscopy;
- resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load (this often occurs in cases of late diagnosis);
- a poor treatment response occurred for one of the following reasons:
- the initial phase of therapy was poorly supervised and patient adherence was poor;
- anti-TB drugs were of suboptimal quality;
- doses of anti-TB drugs are below the recommended range;
- the patient has comorbid conditions that interfere with either adherence or treatment response (e.g. diabetes or cancer);
- the patient may have undetected DR-TB that is not responding to first-line treatment; or
- although this is rare, the patient either does not absorb, or has suboptimal absorption of, one or more anti-TB drugs *(74)*.

Sputum culture can be used for treatment monitoring. Although monthly culture is recommended for MDR/RR-TB cases *(17, 74, 93, 94)*, this can also be useful for DS-TB, particularly at the end of the second month of treatment and at the end of treatment if the patient does not improve clinically, or at any other time if failure is suspected because of possible drug resistance. Where drug resistance is suspected, DST needs to be performed – the core of which is to test for resistance to isoniazid, rifampicin and moxifloxacin (if used) – and, if possible, to undertake DST using rapid tests for second-line drugs *(92)*.

The reasons behind a positive culture during treatment monitoring are the same as those mentioned above for sputum smear; however, a difference is that a positive culture indicates that viable bacilli are present.

Molecular tests such as Xpert MTB/RIF are not used to monitor response to treatment.

Although sputum smear is useful because of its much shorter turnaround time, sputum culture is much more sensitive for detection of ongoing active disease or treatment failure. Therefore, culture is useful to monitor the progress of treatment. Sputum smear and culture examinations depend on the quality of the sputum produced, so care should be taken to obtain adequate specimens and transport them to the laboratory according to standard procedures, to maintain the viability of the bacilli and thus obtain a valid culture result. A tracking system should be in place for all specimens sent for culture until results are obtained by the referring facility or clinician.

Where sputum smears and cultures are persistently positive for acid-fast bacilli, it is necessary to undertake assessment for non-TB mycobacteria (NTM), because colonization or infection with NTM secondary to TB in a damaged lung is not uncommon. In such cases, even where TB is adequately treated, treatment may need to be directed towards the NTM as well. Additional imaging and possibly bronchoscopy should be considered, to confirm the diagnosis of NTM infection leading to disease *(95)*.

Culture conversion is not equivalent to cure. Some patients may initially convert and later revert to positive sputum culture, usually when undetected drug resistance is present. In rare cases, malabsorption can be the cause.

DST should be repeated for patients who remain smear and culture positive, or for whom treatment failure is suspected. In such cases, it is usually not necessary to repeat DST within 2–3 months of the previous DST. **Table 1.9.1** summarizes the activities involved in and the frequency of monitoring.

Table 1.9.1. Summary of activities for monitoring treatment response

Monitoring evaluation	Suggested frequency
Evaluation by clinician and monitoring for AEs	*During the first 2 months of treatment*: Every day during the first weeks if the patient is hospitalized (e.g. for life-threatening conditions or severe comorbidities) and, where possible, at least on a weekly basis if the person is treated as an outpatient, until the treatment is well tolerated. Once the person is stable, a monthly visit is suggested. *After the second month of treatment*: Monthly assessments unless there is a medical necessity to see the patient more often. The treatment supporter sees the patient daily between consultations and signals any concerns to the clinician. VST will allow continuous monitoring. *For monitoring for AEs*: Daily at every encounter by the treatment supporter, or when possible when performing VST.

Monitoring evaluation	Suggested frequency
Sputum smears and culture	Monitoring smears and culture important after the second month of treatment (during hospitalization, can be done more often). Culture can be done monthly if feasible. It is important to perform culture at the end of treatment.
Chest radiograph	At baseline, after the second month of treatment and at the end of treatment, except where clinical needs suggest a higher frequency.
Body weight	At baseline, during clinical visits and based on clinical needs. The need for dosage adjustments should be evaluated if necessary.
Height	At the start of treatment for all (to be able to assess BMI throughout treatment) and monthly for children (to assess growth).
Rapid molecular testing	Xpert MTB/RIF or Xpert Ultra at baseline (recommended) to ensure rapid diagnosis and exclude DR-TB. These tests cannot be used for treatment monitoring.
DST	Undertaken where possible. It should be repeated for patients who do not improve clinically and radiologically, remain sputum smear and culture positive, or revert to positive after having converted.

AE: adverse event; BMI: body mass index; DR-TB: drug-resistant TB; DST: drug susceptibility testing; TB: tuberculosis; VST: video-supported treatment.

9.4 Assessment of patients when treatment failure is suspected

Any patient not clinically responding to therapy after several weeks should be considered as being at risk for failure. In particular, patients should be considered as being at high risk for treatment failure if they had at least 3 months of full adherence to what was deemed to be an effective treatment regimen with quality-assured drugs, but show evidence of active disease – either clinical, radiographic or bacteriological (DST or culture) – or reappearance of disease. The following steps are recommended in such a situation.

Confirm treatment

The treatment card should be reviewed to confirm that the patient has fully adhered to treatment.

Look for undetected comorbidities

Some undetected comorbidities mimic treatment failure through clinical and chest radiographic deterioration that occurs simultaneously with repeated culture-negative and smear-negative results. These comorbidities (e.g. NTMs, fungal infections, lung infections or a pulmonary malignancy) should be diagnosed and treated appropriately. Illnesses that may decrease absorption of medicines (e.g. chronic diarrhoea) or may result in immune suppression (e.g. HIV infection) should also be excluded.

Review the bacteriological data

A single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. In such cases, subsequent cultures that are negative help to prove that

the apparently positive result did not reflect treatment failure. Positive smears with negative cultures may be caused by the presence of dead bacilli and thus do not necessarily indicate treatment failure.

Review the DST

If there is evidence of acquired resistance to any drug, treatment failure is likely and a new regimen for DR-TB may need to be started promptly.

Review CXR

If comparison of CXR at baseline and at the current time shows no improvement or deterioration of the CXR image, this may indicate failure of TB treatment.

Review treatment regimen

The treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If any resistance appears that was not present or evident previously, the patients should be managed as DR-TB or MDR-TB with a new regimen, and rapid action should be taken to ensure that adequate infection control measures are implemented.

Consider malabsorption

In rare cases, genetic reasons mean that one or more drugs are not well absorbed, leading to suboptimal blood levels, suboptimal effect of the drug and potential development of drug resistance. Therapeutic drug monitoring, based on collection of a dried drop of blood (which can be easily sent by normal mail to one of the laboratories performing the test), makes it possible to evaluate the drug level in the blood and, eventually, to adjust the dose. Although not yet recommended by WHO, other clinical guidelines do recommend this test in specific cases (*44*).

Absorption of drugs is reduced in severely ill patients admitted to the critical care department with conditions such as central nervous system TB or acute respiratory distress syndrome. In such cases, intravenous anti-TB treatment should be considered until the situation improves and a nasogastric tube can be used.

10. Outcome definitions

DS-TB is largely curable with treatment that is affordable and widely accessible. If a TB treatment regimen is not administered correctly, it may fail to deliver a relapse-free cure, thus increasing transmission and accelerating the emergence of drug resistance. Monitoring the effectiveness of TB treatment is thus critically important in both clinical practice and surveillance, to maximize the quality of individual patient care and the effectiveness of public health action. Hence, standardized TB treatment outcome definitions have been a feature of WHO policies and national TB surveillance systems for many years as a cornerstone of effective TB strategies. This standardization has allowed the monitoring of TB treatment outcomes over time at national and global levels.

Standardized treatment outcome definitions for DS-TB have been in widespread use for more than 3 decades, and outcome definitions for DR-TB were first proposed in 2005 *(96)*. The development of DR-TB treatment outcome definitions was based on the outcome definitions for DS-TB in use at the time. The DR-TB treatment outcome definitions were adopted by WHO soon after and remained largely unchanged until 2013, when WHO updated its TB definitions and reporting framework *(97)*. As treatment regimens for DR-TB have significantly changed in composition and duration, an update of the treatment outcome definitions and monitoring parameters was necessary.

10.1 Treatment outcome definitions

In November 2020, the WHO Global TB Programme (WHO/GTB) convened an online consultation and released new definitions of TB treatment outcomes, which were the same for DS-TB and DR-TB *(98–100)*.

The principles guiding the update of the definitions were as follows:

- applicability to treatment regimens of different duration;
- a lessening of the traditional division between the intensive and continuation phases;
- identification of appropriate criteria for bacteriological conversion (or reversion) in relation to the definitions of "treatment failed", "cured" and "treatment completed" that are grounded in knowledge from microbiology;
- consideration of the use of appropriate diagnostics for treatment monitoring;
- setting of clear parameters for defining treatment failure, based on reliable evidence of non-response or other reasons that lead to a decision to change or stop treatment; and
- aiming for practical clinical and programmatic monitoring, and feasible implementation.

A new optional definition, "sustained treatment success", was also proposed for use in operational research only. Post-treatment follow-up may be useful, when or if it is feasible, for patients suffering from post-treatment sequelae, for example *(101)*.

The new treatment outcome definitions are summarized in **Table 1.10.1**.

The 2020 treatment outcome definitions allow all patients with either DS-TB or DR-TB to have a treatment outcome assigned when completing treatment (cure or treatment success) or when unfavourable events occur (e.g. loss to follow-up [LTFU], failure or death).

Although the definitions of treatment outcomes have been harmonized, minor differences remain between those for DS-TB and DR-TB (e.g. treatment monitoring by sputum culture for DR-TB and by sputum smear microscopy for DS-TB).

Despite some distinct treatment phases remaining in current regimens, the overall trend is towards monophasic regimens. Thus, it is best to avoid linking definitions to treatment phases; hence, the time thresholds for declaring cure or treatment failure have been revised.

Although the role of new bacteriological tests was considered, treatment monitoring will continue to rely on the available tools (i.e. sputum culture for DR-TB and sputum microscopy for DS-TB), despite their limitations.

10.2 Considerations for implementation

It is both important and feasible for NTPs to ascertain cure at the end of treatment. The notion of relapse-free cure or sustained treatment success after the end of treatment is critical; however, it is beyond the means of routine programmatic monitoring and is feasible only under operational research conditions (e.g. in special cohorts, in patients undergoing rehabilitation and during follow-up for post-TB lung disease). For this reason, the specific operational definition "sustained treatment success" was proposed (**Table 1.10.1**), with the possibility of assessing numbers of patients alive and free of TB at 6 months (for DS-TB and DR-TB) and at 12 months (for DR-TB only) after successful TB treatment.

Table 1.10.1. New definitions of TB treatment outcomes for both DS-TB and DR-TB

Outcome	Definition
Treatment failed	A patient whose treatment regimen needed to be terminated or permanently changed[a] to a new regimen or treatment strategy.
Cured	A patient with pulmonary TB with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response[b] and no evidence of failure.
Treatment completed	A patient who completed treatment as recommended by the national policy but whose outcome does not meet the definition for cure or treatment failure.
Died	A patient who died[c] before starting treatment or during the course of treatment.
Lost to follow-up	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome was assigned.[d]
Treatment success	The sum of all patients cured and treatment completed.
An optional definition was also proposed for use in operational research only	
Sustained treatment success	An individual assessed at 6 months (for DS-TB and DR-TB) and at 12 months (for DR-TB only) after successful TB treatment, who is alive and free of TB.

DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; TB: tuberculosis.

[a] Reasons for the change include:
- no clinical response or no bacteriological response, or both (see note 'b');
- adverse drug reactions; or
- evidence of additional drug-resistance to medicines in the regimen.

[b] "Bacteriological response" refers to bacteriological conversion with no reversion:
- "bacteriological conversion" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are negative; and
- "bacteriological reversion" describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

[c] Patient died for any reason.

[d] This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown; however, it excludes those lost to follow-up.

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Chapter 2
Drug-resistant TB treatment

1. Introduction

This chapter of the operational handbook provides practical advice to complement the latest guideline chapter on drug-resistant TB treatment as part of the *WHO consolidated guidelines on tuberculosis and care* (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 TB (DR-TB), including multidrug- or rifampicin-resistant TB (MDR/RR-TB), and confirmed rifampicin-susceptible, isoniazid-resistant TB (Hr-TB) *(1)*.

The strategies described in this chapter are 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)*. This chapter 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. The practical guidance aims to inform the development or revision of national policies and related implementation guidance (e.g. handbooks, standard operating procedures) on the management of DR-TB.

2. WHO recommendations on DR-TB treatment

Treatment of drug-resistant TB using 6-month regimens	
1.1	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*
1.2	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance. *(Conditional recommendation, very low certainty of evidence)*
Treatment of drug-resistant TB using 9-month regimens	
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*
2.2	WHO suggests using the 9-month all-oral regimens (**BLMZ, BLLfxCZ and BDLLfxZ**) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ. *(Conditional recommendation, very low certainty of evidence)*
2.3	WHO suggests against using 9-month DCLLfxZ or DCMZ regimens compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB. *(Conditional recommendation, very low certainty of evidence)*
Longer regimens for MDR/RR-TB	
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*

3.2	**Kanamycin and capreomycin** are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.4	**Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing **bedaquiline** may be used. *(Conditional recommendation, very low certainty of evidence)*
3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.6	**Clofazimine and cycloserine or terizidone** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.8	**Delamanid** may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* In children with MDR/RR-TB aged below 3 years **delamanid** may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.10	**Imipenem–cilastatin or meropenem** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[11]
3.11	**Amikacin** may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty in the estimates of effect)*

[11] Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent, and it should not be used without imipenem–cilastatin or meropenem.

3.12	**Ethionamide or prothionamide** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*
3.13	***P*-aminosalicylic acid** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*
3.14	**Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty of evidence)*[1]
3.15	In MDR/RR-TB patients on longer regimens, a **total treatment duration of 18–20 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.16	In MDR/RR-TB patients on longer regimens, a **treatment duration of 15–17 months after culture conversion** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.17	In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, **an intensive phase of 6–7 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
Regimen for rifampicin-susceptible and isoniazid-resistant TB	
4.1	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)*
4.2	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 of evidence)*
Monitoring patient response to MDR/RR-TB treatment using culture	
5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals. *(Strong recommendation, moderate certainty in the estimates of test accuracy)*
Start of antiretroviral therapy in patients on MDR/RR-TB regimens	
6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)*

Surgery for patients on MDR/RR-TB treatment	
7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*
Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration	
8.1	In patients with MDR/RR-TB and HCV co-infection, the WHO suggests the co-administration of HCV and TB treatment over delaying HCV treatment until after treatment of MDR/RR-TB is completed. *(Conditional recommendation, very low certainty of evidence)*

3. Key considerations in DR-TB treatment

3.1 Access to DST

The current guidelines for treatment of DR-TB stress the need for access to reliable, quality-assured DST, to be provided by NTPs and associated laboratories, to inform the use of the WHO-recommended regimens. Rapid molecular testing is making it increasingly feasible for NTPs to quickly detect MDR/RR-TB and other types of resistance, and to use the results to guide treatment decisions *(5, 6)*. Hence, rapid molecular testing should be made available and accessible to ensure DST for at least rifampicin, isoniazid and FQ, given that DST for these drugs is essential for selecting the most appropriate initial DR-TB regimen. If the capacity for rapid molecular testing is lacking, NTPs should promptly build such capacity, and should make efforts to ensure universal access to all patients initiating a regimen for any form of TB, including both drug-susceptible and drug-resistant forms. To meet the End TB Strategy targets, DST for rifampicin and isoniazid should be offered to all TB patients, and all RR-TB patients should be offered DST for FQ. In addition, DST for the drugs used in the newly recommended regimens is increasingly important.

In addition to building capacity to ensure the routine performance of DST for medicines used in the clinical management of all patients, NTPs need to build surveillance systems to determine the local prevalence of DR-TB strains to guide programmatic planning. This is especially important for drugs for which resistance testing is not routinely performed or where the resistance prevalence of the drug is expected to be low initially (e.g. pretomanid) and needs to be monitored over time. DRS can 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) *(7)*. Data from local TB DRS may provide baseline estimates of the prevalence of resistance, including among relevant subgroups of recurrent and re-registered individuals with TB disease (e.g. recurrence or new episode of TB or return after LTFU). It can also provide monitoring trends to inform DST algorithms and inform broader local policy decisions *(1, 8)*.

WHO recommends using WHO-recommended rapid diagnostics (WRD) as the initial tests to diagnose TB. The WRDs for the initial detection of TB (with or without drug resistance detection) include four classes of tests:

- low-complexity manual nucleic acid amplification tests (LC-mNAATs);
- urinary biomarker-based lateral flow LAM (LF-LAM) tests;
- low-complexity automated NAATs (LC-aNAATs) and
- moderate-complexity automated NAATs (MC-aNAATs).

Currently, only one test – loop-mediated isothermal amplification for detection of *Mtb* (TB LAMP) – is included in the class of LC-mNAATs, and the sole test – Determine TB LAM Ag – is included in the LF-LAM class, with neither test capable of detecting drug resistance. The class of LC-aNAATs for detection of TB and drug resistance includes the Xpert MTB/RIF Ultra, Truenat MTB Plus and MTB-RIF Dx tests. These tests detect the *Mtb* complex and resistance to rifampicin. The class of MC-aNAATs includes multiple tests produced by a range of manufacturers (Abbott, BD, Bruker/ Hain Lifesciences,

and Roche) that are used as initial tests to detect *Mtb* complex and resistance to rifampicin and isoniazid. This class of tests is suitable for intermediate to central laboratories due to their infrastructural requirements. However, the initiation of a pertinent TB treatment regimen should not be delayed while waiting for DST results; hence, it is critical to ensure access to WRDs for the initial detection of TB at all levels of the health care system, either through onsite testing or through a functional sample transportation system.

A person with confirmed rifampicin-susceptible or rifampicin-resistant TB should be tested for isoniazid resistance to ensure appropriate treatment. The MC-aNAATs provide this result upfront but follow-on molecular tests recommended by WHO (i.e. Xpert MTB/XDR, line probe assay [LPA] and targeted next-generation sequencing [NGS]) can detect resistance to isoniazid, FQ, pyrazinamide, ethionamide and injectable drugs. Except for the first-in-class of the follow-on LC-aNAATs – the Xpert MTB/XDR that detects resistance to isoniazid, FQ, ethionamide and injectable drugs – the follow-on tests are more complex and require specialized infrastructure, qualified staff, biosafety conditions and a well-functioning sample transportation system. The first-line LPA detects resistance to rifampicin and isoniazid, the second-line LPA detects resistance to FQ and injectable drugs, and the first-in-class test of high-complexity hybridization NAATs detects resistance to pyrazinamide. The limited availability of LC-aNAATs and MC-aNAATs makes routine isoniazid resistance testing challenging in many settings.

The follow-on class of targeted NGS can detect resistance to rifampicin, isoniazid, pyrazinamide, ethambutol, FQ, bedaquiline, linezolid, clofazimine, amikacin and streptomycin. Tese technologies are best suited for use at the reference laboratory level. Targeted NGS can provide DST results in a few days, excluding sample transportation and reporting *(9)*.

The interpretation of the results of molecular DST may be complex and it includes multiple steps. For resistance to isoniazid, mutations in two genes (*inh*A and *kat*G*)* are interrogated. If a mutation is present only in *inh*A, it is likely that isoniazid can still be effective at a high dose, whereas a mutation in *kat*G alone or mutations in both *inh*A and *kat*G render isoniazid no longer effective, even at a high dose *(10)*. For many anti-TB drugs, only selected mutations are known or can be detected by molecular tests; thus, depending on the type of the test, risk of resistance in a particular patient and result, the use of culture-based DST may still be needed. This would apply in the case of a negative LPA result for isoniazid, FQ or injectable drug resistance, especially if prevalence of resistance to these drugs is high or resistance is suspected in a particular patient. Similarly, in the case of negative result for resistance to bedaquiline, linezolid and clofazimine by targeted NGS and a high risk of resistance to these drugs in a particular setting or patient, the use of culture-based DST may still be needed. Further details on diagnostic tests recommended can be found in the relevant WHO consolidated guidelines *(9)* and operational handbook *(11)* in *Module 3: Diagnosis – rapid diagnostics for tuberculosis detection*.

Country programmes need to work towards the establishment of phenotypic DST for all TB medicines for which there are now agreed reliable and reproducible methods (e.g. bedaquiline, clofazimine, delamanid, FQ, isoniazid, linezolid and rifampicin). The critical concentrations for various drugs were either established for the first time (bedaquiline, clofazimine, delamanid, linezolid, pretomanid and cycloserine) *(12)* or revised (rifampicin and FQ) in WHO technical consultations *(13)*. Resistance to ethionamide/prothionamide may be inferred from the results of molecular testing for isoniazid resistance (i.e. presence of mutations in the *inh*A promotor region) using either automated or manual molecular tests. However, susceptibility to ethionamide/prothionamide cannot be inferred purely on the basis of the absence of a mutation in the *inh*A promotor gene using commercially available NAATs, because resistance can be conferred by other mutations in the *inh*A gene and its promotor and by mutations in the *eth*A gene that are not detected by these NAATs. A standardized phenotypic DST method using the mycobacterial growth indicator tube (MGIT) liquid culture automated system has been recently developed for pretomanid and cycloserine. Critical concentrations for pretomanid and cycloserine are included in the third edition of the operational handbook in *Module 3: Diagnosis – rapid diagnostics for tuberculosis detection*. Phenotypic DST for ethambutol, ethionamide/prothionamide,

imipenem/meropenem or *p*-aminosalicylic acid is not routinely recommended because results may be unreliable *(10)*.

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; however, treatment 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 treatment effectiveness. If DST for bedaquiline and linezolid 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 TB medicines, the drug-resistance pattern of the contact or source case, and recent representative DRS data. A reliable clinical history of exposure to bedaquiline and linezolid should thus be considered when designing a treatment regimen; however, this should be the main source of evidence to guide regimen design only in situations where phenotypic DST is not yet available. 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 regimen design should be 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 each geographical setting or patient groups. If DST is not routinely available for individual patients where there is treatment failure, storage of *Mtb* isolates collected at baseline or during treatment monitoring can be considered for performing phenotypic DST or whole genome sequencing at reference laboratories.

The adoption and implementation of a new regimen can and should proceed while the DST capacity is being established.

Despite some of the uncertainties about DST, NTPs should strive to test for resistance to a wide set of TB drugs and offer the most appropriate treatment regimen. The patient's clinical response to treatment should always be carefully monitored. If there is a poor treatment response, undiagnosed drug resistance or heteroresistance (i.e. the coexistence of susceptible and resistant organisms in the same patient) should be considered, as should alternative explanations for failure to respond to treatment, such as poor or erratic adherence to treatment, malabsorption, inadequate patient education or support, IRIS or the presence of comorbidities *(14)*.

3.2 Safety monitoring and management and provision of patient support

All treatment offered to people with MDR/RR-TB 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 the TB treatment response, with general laboratory support to monitor and manage AEs and comorbidities. The provision of social support is essential to enable adherence to treatment *(15)*. Certain programmatic components (e.g. aDSM) *(15, 16)* are recommended for all patients on any MDR/RR-TB regimen (**Annex 3**). An appropriate schedule of laboratory tests and clinical examinations should be included in the patient's treatment chart to identify AEs *(15)*. In settings where aDSM has not yet been fully rolled out and national guidelines have not been updated, patients should not be left to wait until all 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 treatment adherence and improved outcomes *(17)*.

3.3 Extensive pulmonary TB disease

For patients with extensive pulmonary disease, non-medical interventions (e.g., resection surgery) and respiratory support measures should be prioritized alongside medical treatment. Additionally, these patients should be thoroughly evaluated for post-tuberculosis lung disease (PTLD) following the completion of MDR/RR-TB treatment. PTLD is a globally under-recognized condition associated with reduced life expectancy and an increased risk of recurrent tuberculosis, underscoring the need for comprehensive post-treatment care and monitoring. *(18)*.

3.4 Regimen options in the treatment of DR-TB

In patients with MDR/RR-TB, several regimens are available based on current WHO guidelines. Key factors that influence the choice of treatment regimen include the drug-resistance profile, previous exposure to TB medicines, the patient's health history, the drug-resistance profile of close contacts, the patient's age and preferences, pregnancy status and the extent and localization of TB disease: pulmonary or extrapulmonary, with central nervous system (CNS) involvement or disseminated. The overall preference is for shorter, safer, better tolerable and more effective treatment regimens.

The evidence suggests that the balance of effects probably favours shorter and simpler regimens when compared with the standard of care (SoC); that is, 9-month or longer regimens. However, in cases of confirmed or presumed severe forms of extrapulmonary DR-TB (e.g. those with CNS involvement or dissemination to multiple organ systems) the treatment approach may require clinical judgement by an experienced specialist. These cases often necessitate longer regimens, inpatient care and, where there is CNS involvement, the inclusion of additional medicines with demonstrated efficacy in penetrating the blood–brain barrier. Among other considerations, the choice of regimen should be carefully tailored to the patient's clinical condition and the extent of disease dissemination, ensuring optimal treatment outcomes.

A shorter duration of treatment is preferred by patients and presents several advantages. For example, it decreases the risk of LTFU; is less of a burden on the patient, their household and the health system; and minimizes health care costs and unemployment stress.

Among available options, 6-month regimens are preferred over the 9-month or 18–20-month regimens, and 9-month regimens are preferred over the 18–20-month regimens.

- **The 6-month BPaLM regimen (6 Bdq-Pa-Lzd-Mfx**[12]) – comprising bedaquiline, pretomanid, linezolid and moxifloxacin – is a preferred regimen for adults and adolescents aged 14 years and older and is recommended for patients with MDR/RR-TB or pre-extensively drug-resistant TB (pre-XDR-TB). Patients with unknown FQ resistance can be initiated on the BPaLM regimen while waiting for DST results. In cases where resistance to FQ (pre-XDR-TB) is identified before or after initiation of treatment, moxifloxacin can be omitted and the BPaL regimen can be initiated or continued, because there is probably no added benefit of using a drug with demonstrated resistance that may have toxicities. The duration of the BPaLM regimen is largely standardized for 6 months (26 weeks), whereas BPaL can be extended to a total of 9 months (39 weeks). It is suitable for people with confirmed pulmonary TB and all forms of extrapulmonary TB, except for cases involving the CNS, osteoarticular TB and disseminated (miliary) TB. The regimen is applicable regardless of HIV status. It is not recommended during pregnancy.
- **The 6-month BDLLfxC regimen (6 Bdq-Dlm-Lzd-Lfx-Cfz)** – comprising bedaquiline, delamanid, linezolid, levofloxacin and clofazimine – is an alternative regimen for individuals with MDR/RR-TB or pre-XDR-TB and may be used for children, adolescents below 14 years of age and pregnant or breastfeeding women. Depending on the availability of FQ DST results, the regimen may be used with or without levofloxacin or clofazimine. In cases of unknown FQ resistance, BDLLfxC can be

[12] The regimen notations used throughout this document highlight the number of months for which a relevant combination of medicines is used; where certain drugs are used for a different duration, this is also noted, using subscript in brackets.

initiated without delay; BDLLfx is used for FQ-susceptible TB, and BDLC (bedaquiline, delamanid, linezolid and clofazimine) for FQ-resistant TB. Treatment is typically for 6 months (24 weeks) but may be extended by an additional 3 months, for a total duration of up to 9 months (36 weeks).[13] This regimen may be offered to individuals with any extent of pulmonary TB disease, as well as most forms of extrapulmonary TB, except for cases involving the CNS, osteoarticular TB or disseminated forms with multiorgan involvement.

[13] The duration of treatment (24 weeks or 36 weeks) is aligned with the evidence available from the clinical trial. However, if the national programmes find it challenging to implement, they may choose to standardize the duration across regimens, e.g., 26 weeks for 6 months and 39 weeks for 9 months.

Table 2.3.1. Regimen options and factors to be considered for selection of treatment regimens for patients with MDR/RR-TB

Regimen	MDR/RR-TB FQ-susceptible	MDR/RR-TB FQ susceptibility not known	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB disease	Extra-pulmonary TB	Age below 14	Pregnant & breastfeeding woman
6-month regimens								
BPaLM/BPaL	BPaLM	BPaLM	BPaL	No	Yes	Yes[1]	No	No
BDLLfxC/BDLLfx/BDLC	BDLLfx	BDLLfxC	BDLC				Yes	Yes
9-month regimens								
BLMZ	Yes	No	No	No	Yes	Yes[1]	Yes	Yes
BLLfxCZ								
BDLLfxZ								
4–6 $Bdq_{(6\,m)}$-Lfx/ Mfx-Cfz-Z-E-Hh-Eto or $Lzd_{(2\,m)}$ / 5 Lfx/ Mfx-Cfz-Z-E)	Yes	No	No	No	No	Yes[1]	Yes	Yes[3]
Longer regimens								
Individualized 18-month regimen	No[2]	No[2]	No[2]	Yes	No[2]	No[2]	No[2]	No[2]
Additional factors to be considered if several regimens are possible	• Patient's age and preferences • Disease extent and localization • Drug intolerance or adverse events • Treatment history, previous exposure to regimen component drugs, or likelihood of drug effectiveness • Access to and price of the regimen component drugs • Pill burden							

[1] except for CNS TB, osteoarticular TB & disseminated TB with multi-organ involvement.

[2] should not be used unless shorter regimen options are not available.

[3] Only Lzd variation: 4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh- Lzd(2 m) / 5 Lfx/Mfx-Cfz-Z-E).

In patients with MDR/RR-TB and in whom resistance to FQ has been excluded, **modified 9-month regimens (BLMZ, BLLfxCZ** and **BDLLfxZ)** are available and are generally preferred over longer (18-month) regimens. These regimens comprise bedaquiline in various combinations with levofloxacin/moxifloxacin, linezolid, clofazimine, delamanid and pyrazinamide. These regimens may be used for children, adolescents below 14 years of age and pregnant or breastfeeding women. Available options include the following:

- **BLMZ** is the first choice among the recommended modified 9-month regimens. In terms of the balance of health effects it is preferable to both BLLfxCZ and BDLLfxZ. Also, at the time of the review, it had a lower pill burden, fewer AEs, balanced efficacy and cost and appeared either preferable or equivalent for all other decision criteria. It comprises bedaquiline, linezolid, moxifloxacin and pyrazinamide.
- **BLLfxCZ** is the second option if BLMZ is unsuitable. BLLfxCZ, compared to BDLLfxZ has a similar but slightly preferable balance of health effects, significantly lower cost and a lower pill burden than BDLLfxZ. It comprises bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide. Although effective, it is considered second because of the inclusion of clofazimine, which affects the safety of this regimen.
- **BDLLfxZ** is the third option for patients who cannot use BLMZ or BLLfxCZ. It comprises bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide. Although delamanid has a favourable safety profile, its current high price and limited Phase 3 trial data make this regimen less favourable.

If none of the above regimens can be used, an alternative option is the previously recommended 9-month regimen, which offers variations incorporating ethionamide or linezolid.

- **9-month regimens** (**4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto or Lzd(2 m) / 5 Lfx/Mfx-Cfz-Z-E)**: These regimens can be used in patients with MDR/RR-TB and in whom resistance to FQ has been excluded. Therefore, access to rapid DST is required before starting a patient on one of these regimens. The 9-month regimens are not appropriate for patients with extensive TB disease, and only linezolid containing variation can be used for pregnant and breastfeeding women. The 9-month all-oral regimen comprises bedaquiline (used for 6 months) in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine (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 treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid.

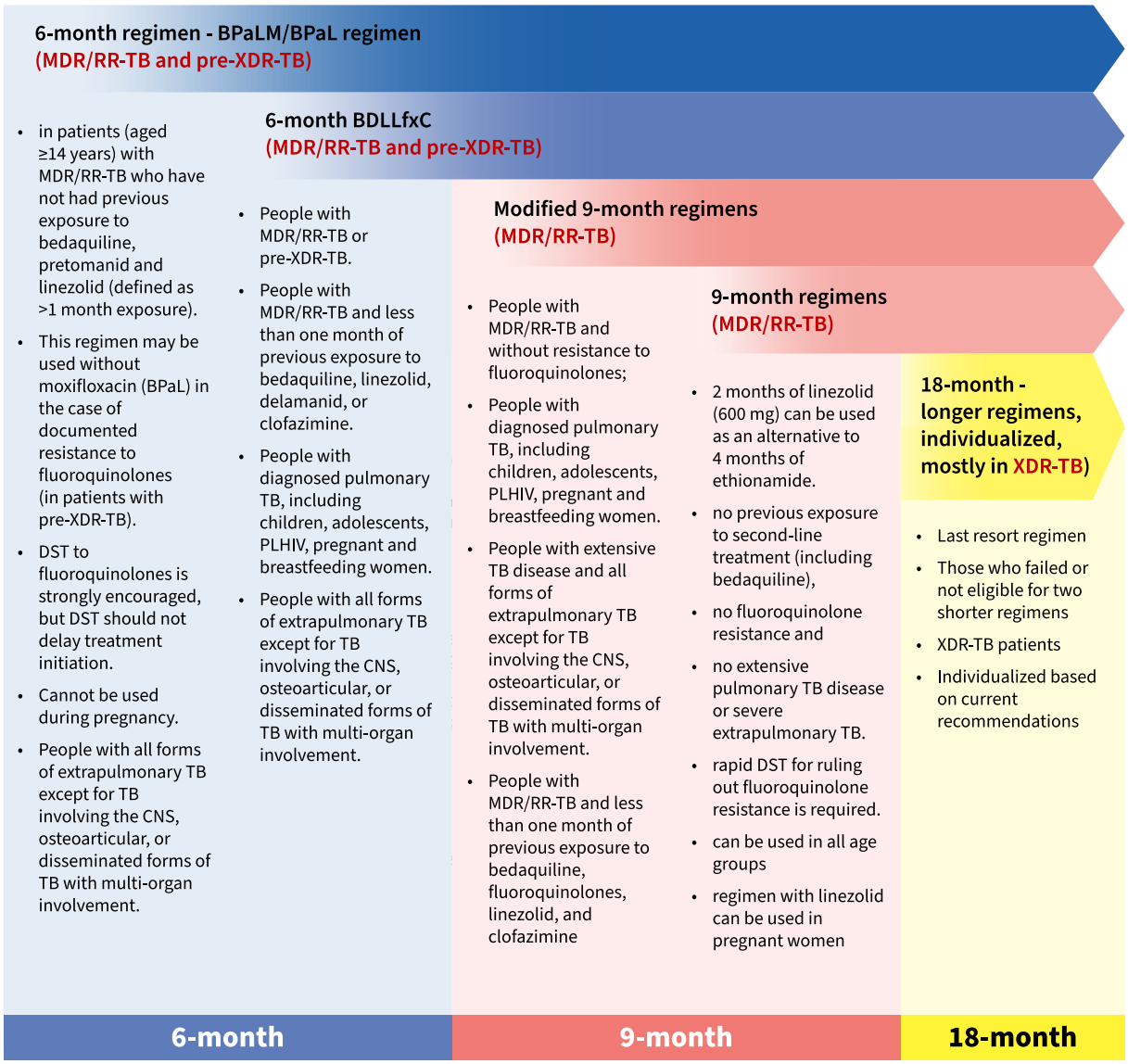
If none of the previously mentioned treatments are viable, the final, last resort option would be to use the individualised, longer regimens.

- **Longer, individualized regimens (≥18 months)**: These regimens are reserved for patients with MDR/RR-TB who do not eligible for, or have not responded well to, the 6- or 9-month regimens; they are also used for patients with XDR-TB or drug intolerance. These regimens are individualized based on drug-resistance profiles, hierarchical grouping of second-line TB medicines, treatment history and patient characteristics. The regimens typically last at least 18 months and are used as a last resort.

There is no evidence directly comparing the two 6-month regimens, so the choice cannot be guided by evidence alone. However, various eligibility factors and significant price differences between these regimens can help NTPs in making their decision on which regimen to adopt and include in their national guidelines. For children, adolescents under 14 years of age, and pregnant or breastfeeding women, the BDLLfxC is the only 6-month regimen option available. This regimen should be prioritized for these groups. In cases where MDR/RR-TB patients have FQ resistance excluded and are not eligible for 6-month regimens, 9-month regimens should be considered.

Decisions on an appropriate regimen should be made based on likely efficacy, safety, patient preference and clinical judgement, also taking into account the results of DST, patient treatment history, age, severity and site of the disease (**Table 2.3.1** and **Fig. 2.3.1**).

Fig. 2.3.1. Regimen options for MDR/RR-TB treatment



MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis.

4. Treatment of DR-TB using 6-month regimens

4.1 The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen

This section refers to the 6-month (or 26-week) treatment regimen for MDR/RR-TB; that is, the bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen. This regimen should be the initial choice for all eligible patients diagnosed with MDR/RR-TB. The recommendation in the updated WHO guidelines states:

No.	Recommendation
1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.
2. This recommendation applies to the following:
   - People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
   - People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular or disseminated forms of TB with multiorgan involvement.
   - Adults and adolescents aged 14 years and older.
   - All people regardless of HIV status.
   - Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
3. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.
4. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.[14]

The BPaL regimen (bedaquiline, pretomanid, and linezolid) was first evaluated in the Nix-TB study (2015–2017, South Africa), which assessed its safety, efficacy, and pharmacokinetics for treating

[14] Dosages of the other drugs are given in **Table 2.4.1**.

MDR/RR-TB, pre-XDR-TB, and patients who were intolerant or non-responsive to prior treatments. Based on promising results, the WHO recommended BPaL in 2019 under operational research conditions for MDR-TB patients with fluoroquinolone resistance and limited prior exposure to bedaquiline and linezolid.

Subsequent trials, including TB-PRACTECAL and ZeNix, further investigated BPaL-based regimens, leading to the WHO's 2022 treatment guideline update. The TB-PRACTECAL trial was a Phase 2–3, open-label randomized controlled trial involving 419 patients across Belarus, South Africa, and Uzbekistan. Conducted by Médecins Sans Frontières (MSF) and the London School of Hygiene & Tropical Medicine (LSHTM), the trial compared three BPaL-based regimens (including BPaLM and BPaLC) against the locally approved standard of care (SoC), which was based on WHO recommendations at the time. Meanwhile, the ZeNix trial focused on optimizing linezolid dosing to improve safety and efficacy.

The work leading to the WHO's 2022 guideline update analyzed data from these trials on several BPaL-based regimens and compared them to standard-of-care treatments and large MDR/RR-TB cohorts from South Africa and other countries. The BPaLM regimen demonstrated the highest treatment success rate (89%) in the TB-PRACTECAL trial, significantly outperforming standard regimens, which had success rates ranging from 52% to 75%. These findings solidified BPaL-based regimens as a transformative option for treating drug-resistant TB *(19)*.

4.1.1 Eligibility

The BPaLM/BPaL regimen may be offered to patients with MDR/RR-TB in the following situations:

- pulmonary TB or most forms of extrapulmonary TB, except TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement;
- age 14 years or older;
- no known allergy to any of the BPaLM component drugs;
- no evidence of resistance to bedaquiline, linezolid, delamanid or pretomanid, or patient has not been previously exposed to any of the component drugs for 4 weeks or longer; when exposure to the component drugs is greater than 4 weeks in duration, the patient may receive the BPaLM regimens if resistance to the specific medicines with such exposure has definitively been ruled out;
- all people regardless of HIV status;
- not XDR-TB according to the 2021 WHO definitions *(20)*;
- not pregnant or breastfeeding.

DST for FQ is strongly encouraged in people with MDR/RR-TB; also, although it should not delay initiation of the BPaLM regimen, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen (in cases of documented resistance to FQ, BPaL without moxifloxacin would be initiated or continued). In cases of possible FQ resistance (e.g. a history of >4 weeks of FQ use or close contact with a person infected with an FQ-resistant strain), it is best to initiate the BPaLM regimen until DST for FQ is available, to decide whether moxifloxacin should be continued, with moxifloxacin subsequently being dropped from the regimen if FQ resistance is confirmed. If the result of FQ DST is never determined or is not done, the BPaLM regimen should be used throughout. In cases of documented resistance to FQ, BPaL without moxifloxacin should be initiated or continued. If FQ resistance develops while an individual is receiving the BPaLM regimen but susceptibility to other drugs in this regimen is confirmed, moxifloxacin can be discontinued. In this scenario, BPaL can be continued because there is no benefit in retaining an ineffective drug that may cause toxicities.

Several groups of patients, as described below, were excluded from the ZeNix and TB-PRACTECAL trials. Because no data about the safety of BPaLM/BPaL in those groups are available, the inclusion of such patients should be considered with caution. The exclusions are relative, and interventions may be taken to address the underlying conditions. Once those conditions have improved or resolved, such patients can be started on BPaLM/BPaL. In some cases, the underlying condition can be managed

effectively. For instance, individuals with iron deficiency anaemia and haemoglobin (Hb) levels of less than 8 g/dL can receive iron supplementation. Once Hb rises above 8 g/dL, the BPaLM/BPaL can be initiated with close monitoring and weekly complete blood count. Similarly, QT prolongation of 500 ms due to hypokalaemia can be improved by correcting potassium levels, helping to normalize the QTcF.

The following conditions should be assessed, and appropriate precautions taken:

- Patients with a very low BMI (<17 kg/m^2) should be monitored closely. Although the ZeNix-TB trial excluded those with a BMI of less than 17 kg/m^2, TB-PRACTECAL had no such exclusion criterion and 167 (40%) of those in TB-PRACTECAL had a BMI of less than 17 kg/m^2. Low BMI should not be an absolute contraindication when commencing the BPaLM/BPaL regimen. In the multicountry operational research study, a cohort of 71 individuals with a BMI lower than 17 kg/m^2 enrolled in the BPaL regimen achieved a success rate of 94% *(21)*.
- Linezolid is associated with peripheral neuropathy; therefore, those with preexisting peripheral neuropathy of Grade 3–4 should be considered carefully before commencing the BPaLM/BPaL regimen. These advanced grades of neuropathy cause significant disability, which may be exacerbated by the use of linezolid. Alternatively, to decrease the risk of peripheral neuropathy exacerbation, a 9-month linezolid-sparing regimen could be used.
- Linezolid is also associated with anaemia, neutropenia and thrombocytopenia, and caution is advised in patients with these conditions, particularly in those with a Hb level of less than 8 g/dL, a neutrophil count of less than 750/mm^3 or a platelet count of less than 150 000/mm^3 (See **Annex 2**).
- Patients with liver enzymes at levels three times greater than the upper limit of normal were excluded from both the ZeNix and TB-PRACTECAL trials, because bedaquiline and pretomanid are both associated with increases in liver enzymes. Other causes of transaminase elevation should be ruled out (e.g. concomitant hepatotoxic medicines for other comorbidities or CLD). In such patients, BPaLM/BPaL may be started when the liver enzymes improve.
- Known history of cardiac disease – including baseline corrected QT interval by Fridericia (QTcF) of more than 500 ms – raises concern, particularly in individuals with syncopal episodes, significant arrythmias, personal or family history of congenital QTc prolongation, torsade de pointes (tdP), bradyarrhythmia or cardiomyopathy. Both bedaquiline and moxifloxacin can prolong QT interval. While reports of serious AEs and mortality associated with QTc prolongation are rare, caution is strongly advised.

Where patients are moribund or have advanced TB disease, symptom control and palliative care may be more appropriate than initiation of treatment. Decisions should be guided by clinical judgement and the patient's preferences.

4.1.2 Composition, dosing and duration of the regimen

Composition

The BPaLM regimen comprises four medications: bedaquiline, pretomanid, linezolid and moxifloxacin. In contrast, the BPaL regimen includes three of those medications but excludes moxifloxacin, making it suitable for patients with confirmed FQ resistance.

Pretomanid, the new drug in the regimen, is a nitroimidazole and a prodrug that is metabolically activated by a nitroreductase, producing various metabolites that are responsible for its therapeutic action. Pretomanid acts as a bactericidal agent by inhibiting cell wall biosynthesis; thus, it has an excellent sterilizing capacity. Further information about the mechanism of action and AEs of each drug can be found in **Annex 1**.

Dosing

The same doses for bedaquiline, pretomanid and linezolid are used in the BPaLM/BPaL regimen. Bedaquiline is dosed at 400 mg once daily for 2 weeks, then 200 mg three times per week afterwards,

according to the product label. However, in the ZeNix trial, bedaquiline was administered at 200 mg daily for 8 weeks followed by 100 mg daily. Pharmacokinetic simulations showed that administration of bedaquiline as daily dosages was comparable to the labelled regimen (400 mg daily for 14 days followed by 200 mg three times a week) *(22)*. Any difference was marginal and unlikely to be expressed as a meaningful difference in response. This daily bedaquiline dosing regimen was evaluated in the ZeNix trial *(23)* and is being further evaluated in the SimpliciTB trial *(24, 25)*. Such dosing may be more convenient for patients and health care providers because it allows for daily dosing of all drugs throughout the regimen and thus may improve adherence. Pretomanid is administered at 200 mg once daily (see **Table 2.4.1**). Linezolid dosing is administered at 600 mg once daily and moxifloxacin at 400 mg once daily (in the BPaLM regimen).

Table 2.4.1. Dosing of component drugs for adults and adolescents (aged ≥14 years) for BPaLM and BPaL

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg three times per week afterwards OR 200 mg daily for 8 weeks, then 100 mg daily afterwards
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin.

It is preferable to continue linezolid at the full dose for the entire duration of the regimen. However, the dose of linezolid can be reduced to 300 mg or the drug can be discontinued if there is significant toxicity (depending on the severity of specific AEs or serious AEs) associated with linezolid, including optic neuritis, peripheral neuropathy or myelosuppression; the drug can be restarted later where possible. Dose modification of linezolid should be avoided during the first 9 weeks of therapy if possible. Further considerations on linezolid dosing are discussed below in Section 4.2.4. Dose modifications for bedaquiline, moxifloxacin and pretomanid are not recommended. Given the lack of evidence for the use of other FQ, the GDG was unable to recommend the substitution of moxifloxacin with levofloxacin.

In the ZeNix trial, all medications were administered with food throughout, because the bioavailability of bedaquiline (and pretomanid) increases when taken with meals. Therefore, it is preferable that the BPaLM/BPaL regimen is administered with food.

Duration

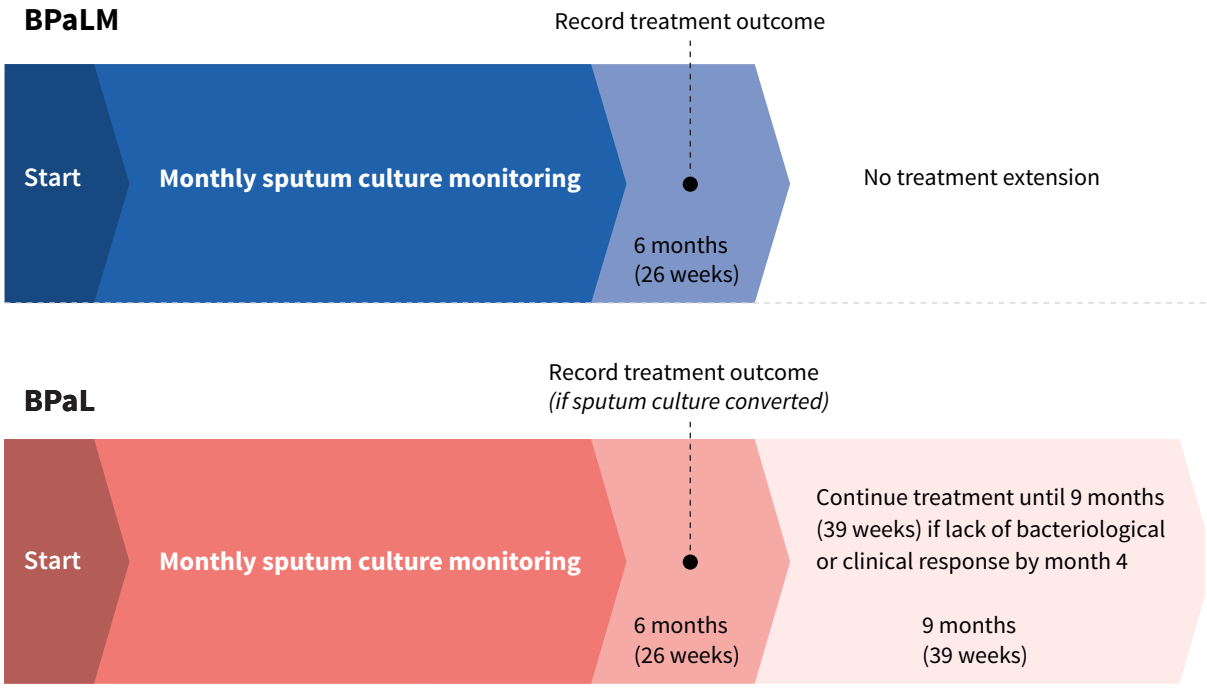
During the GDG meeting, the slight differences in the treatment duration of the BPaLM and BPaL regimens, as studied in the TB-PRACTECAL and ZeNix trials, were acknowledged and discussed, and the panel suggested standardizing treatment duration of BPaLM to 6 months (26 weeks) during programmatic implementation. For BPaL, the GDG suggested the possibility of an extension to a total of 9 months (39 weeks) if no culture conversion or clinical response by month 4 (**Fig. 2.4.1**). All medicines in the regimen would be used throughout the treatment, including the extension from 26 to 39 weeks (when BPaL is used). Ideally, missing doses of all three or four drugs in the regimen should be avoided; however, if doses are missed, any interruption of longer than 7 days should be made up

for by extending the treatment duration (for the number of missed doses); therefore, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively.

Patients with susceptibility to FQ can be started on the BPaLM regimen for 6 months (26 weeks). In the case of resistance to FQ at the baseline that is identified after treatment initiation, moxifloxacin may be discontinued and the regimen can be continued as BPaL. When the regimen is BPaL from the start or is changed to BPaL, it can also be extended to a total of 9 months (39 weeks), continuing from the start of the therapy with a BPaL-based regimen. This extension of the BPaL regimen would be needed only in cases where there is a lack of culture conversion or clinical response (based on the radiological response and clinical judgement of the treating physician) by month 4. Close monitoring of treatment response is necessary for patients needing treatment extension. Once a decision has been made to extend treatment beyond 6 months, further sputum culture results must be followed up, to ensure that culture conversion occurs soon after month 4 on treatment. If the month 5 and 6 culture results remain persistently positive, treatment failure should be suspected, particularly if the patient has had suboptimal adherence to treatment or shows other signs of poor clinical or radiological response to treatment. This includes conducting DST to detect any acquired drug resistance to the component medicines. Extension of BPaL to 9 months should be undertaken with caution in patients with a high number of missed linezolid dosages – switching to an individualized longer regimen may be considered instead of a BPaL extension.

For individuals who switch from BPaLM to BPaL, the treatment start date should be considered as the date BPaLM was initiated, because the patient remained on treatment with three effective drugs during the entire treatment period.

Fig. 2.4.1 Duration of treatment with BPaLM and BPaL regimen options



4.1.3 Modifications of treatment

Linezolid modification

Linezolid is by far the most toxic drug in the BPaL-based regimens and is among the TB medicines with the highest incidence of adverse events *(26)*. Although it is preferred to continue linezolid at the

full dose for the entire duration, the dose may need to be reduced to 300 mg or discontinued (and restarted when possible) if there is significant toxicity.

Linezolid is associated with myelosuppression (anaemia, neutropenia and thrombocytopenia), with peripheral neuropathy and optic neuropathy, and the AEs were noted more frequently in regimens using high-dose linezolid (1200 mg daily). In the ZeNix study, 31% (14/45) of participants in the study arm using linezolid 1200 mg daily for up to 26 weeks experienced an AE of Grade 3 or more compared with 20% (9/45) of participants in the intervention arm using 600 mg daily of linezolid for 26 weeks, and 19.6% (20/102) of participants in the BPaL arm using linezolid 600 mg or 300 mg daily in the TB-PRACTECAL trial. In the multicountry BPaL operational research study, AEs of Grade 3 or higher were noted in 25.3% (75/297) of participants among those started with linezolid 1200 mg per day and 9.4% (5/53) among those started with linezolid 600 mg per day *(21)*.

The most common AEs resulting in dose modifications or early interruption of linezolid in the Nix-TB study (1200 mg dose of linezolid used) were peripheral neuropathy (81%) and myelosuppression (48%), but these AEs were often not severe and they improved with dose reductions or cessation of the drug. A toxicodynamic modelling study using Nix-TB data showed lower percentages of patients with severe peripheral neuropathy (median 5% versus 19%) and severe anaemia (1% versus 15%) in patients using 600 mg daily compared with 1200 mg linezolid daily *(27)*. Hence, care should be taken for patients who have an Hb level of less than 8 g/dL or a platelet count of less than 150 000/mm^3.

Myelosuppression (even of Grade 3 or 4) is often reversible with a short (e.g. 1-to-2-week) break from linezolid followed by resumption of the drug at a reduced dose of 300 mg per day, if needed, or to 600 mg per day, as tolerated; severe anaemia may need to be treated with blood transfusion.

Although optic neuritis was infrequent, it is an important AE that can result in the permanent discontinuation of linezolid. In the Nix-TB study, two patients had optic neuritis during the fourth or fifth month of the BPaL regimen using 1200 mg per day, and symptoms resolved in both patients after permanent discontinuation of the regimen. In the LIFT-TB study, optic neuritis occurred in two patients given 600 mg of linezolid per day, and both improved and resolved after discontinuation.

In the ZeNix and TB-PRACTECAL trials, more than 90% of participants were able to complete more than 75% of the maximal intended dose and duration of linezolid. In the multicountry operational research study, in the 600 mg daily dose group (n=53), 25% had linezolid dose modification due to AE (6 patients with linezolid dose reduction, 2 with interruption and 5 with permanent discontinuation). Despite these modifications, treatment success was 84.6% (1 person died and 1 was not evaluated) *(21)*.

Actions should be taken either before starting treatment or during treatment with BPaL-based regimens to address the common toxicities associated with linezolid. Such actions include dose reduction to 300 mg per day, temporary interruption after 9 weeks of 600 mg per day or permanent discontinuation after 18 weeks of treatment.

Examples of changes in linezolid dosing are given in **Box 2.4.1**.

Box 2.4.1. Examples of changes in linezolid dosing within the BPaLM / BPaL regimen

- A patient diagnosed with MDR/RR-TB by GeneXpert completes 10 weeks of treatment with BPaLM, with 600 mg of linezolid. When on routine follow-up, the person is found to have Grade 2 or moderate anaemia with Hb 7.5 g/dL. This adverse event necessitates the temporary cessation of linezolid, with bedaquiline, pretomanid and moxifloxacin continued. After 2 weeks, the Hb has risen to 10.4 g/dL and linezolid is restarted at 600 mg daily. The patient is monitored by weekly Hb counts. After a month, the Hb is >10.5 g/dL. Hence, the patient is continued on treatment with linezolid, bedaquiline, moxifloxacin and pretomanid, with monthly follow-ups, until the end of treatment.
- A patient diagnosed with pre-XDR-TB completes 16 weeks of treatment with BPaL, with 600 mg of linezolid; they experience symptoms of Grade 2 or moderate paraesthesia in their feet, hampering completion of daily life activities. This AE necessitates a temporary cessation of linezolid, with bedaquiline and pretomanid continued. After 2 weeks of symptomatic care and linezolid-free treatment, the patient's symptoms improve and linezolid is restarted at 300 mg daily. However, within 4 weeks, the paraesthesia symptoms reappear at Grade 3. Linezolid must be ceased permanently. Given that there is less than 8 weeks of treatment remaining, the patient completes 6 more weeks of therapy with bedaquiline and pretomanid. The patient has negative sputum cultures in the remaining months until week 26, achieving a successful treatment outcome on the BPaL regimen.
- A patient diagnosed with MDR/RR-TB by GeneXpert completes 4 weeks of treatment with BPaLM, with 600 mg of linezolid; they experience symptoms of severe paraesthesia in the feet, preventing them from performing their daily life activities. This AE necessitates the cessation of linezolid. Because permanent discontinuation of linezolid was needed within the first 9 weeks of therapy, the entire regimen must be discontinued, and the patient moved to another regimen.

Modifications of linezolid dose were made in the Nix-TB, ZeNix and TB-PRACTECAL trials when toxicity associated with linezolid was suspected. Although no analysis was undertaken to determine whether individuals with dose reductions had poorer treatment outcomes than those who continued 600 mg daily for the complete duration, overall treatment success was high in all investigational arms.

Dose modification and temporary interruption of linezolid is acceptable after the first 9 weeks of treatment with 600 mg of linezolid per day in case of AEs. However, this principle should not override the need to avoid permanent disabilities. In some circumstances, linezolid may need to be permanently stopped and a decision made on whether to continue the other drugs to complete treatment or start a new treatment. After 9 weeks of consecutive administration of 600 mg of linezolid per day, the dose of linezolid can be reduced to 300 mg, if necessary (see examples in **Box 2.4.2**) or the drug may be ceased for 1–2 weeks.

Pharmacokinetic studies have suggested that dose optimization of linezolid may differ among patients *(28)*. Therapeutic drug monitoring (TDM) is a novel approach that can be used, where available, to optimize linezolid dose and minimize AEs, without compromising effectiveness *(29)*.

Further research is encouraged and is ongoing, to help ascertain how to optimize TDM in the treatment of individuals with MDR/RR-TB who are prescribed linezolid.

The findings from a dosing strategy study evaluating Nix-TB study data suggested that monitoring neuropathy symptoms and Hb levels may help to guide linezolid dosing to avoid toxicities. A decrease in Hb level of 10% or more after 4 weeks of treatment may help to identify those at high risk for severe anaemia *(27)*. However, further research on dosing strategies is needed to optimize when and how to reduce the dose of linezolid.

Modification or discontinuation of full BPaLM/BPaL regimen

The only experience using the full BPaLM/BPaL regimens stems from two clinical trials; hence, it is suggested that the programmatic implementation be aligned with this experience. Safe management of AEs may warrant dose reduction or discontinuation of the component drugs. However, the BPaLM/BPaL regimen has been studied as a standardized course of treatment with allowable modifications at certain points in the treatment course (**Table 2.4.2**). Modification of the regimen outside the recommended durations or replacement of any of the component drugs may result in poor treatment outcomes.

Temporary cessation of full BPaLM/BPaL regimen

Dose modification of bedaquiline and pretomanid is not recommended; rather, temporary cessation of the full regimen is allowed for suspected drug-related toxicity for the following durations:

- not more than 2 weeks of consecutive treatment interruption of all medicines in the regimen; or
- not more than 4 weeks cumulative of non-consecutive treatment interruption of all medicines in the regimen.

Reintroduction of the full regimen could be considered after the temporary cessation. Missed doses need to be made up and added to at the end of treatment.

The durations given above for temporary cessation of the full regimen provide general guidance for conducting a clinical review and possibly changing to an individualized longer regimen.

Permanent discontinuation of BPaLM/BPaL and change to another regimen

The BPaL-based regimen may need to be permanently discontinued in some patients for whom the interruption goes beyond the recommended duration. In such cases, patients need to be evaluated and their 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 and shifted to another regimen are treatment failure, inability to use linezolid for enough time owing to AEs (see **Table 2.4.2**), or pregnancy that occurs during treatment.

As an exception, patients who have started a different regimen (e.g. BPaL or BPaLM) may change to one of the BDLLfxC regimens if they can no longer use or access pretomanid (e.g. if a patient becomes pregnant after starting BPaL or BPaLM, or if pretomanid drug supply is interrupted). In such scenarios, the bedaquiline dosing schedule from the BPaLM regimen may be carried over into the BDLLfxC regimen to prevent excessively prolonged treatment durations that could arise from adding the full duration of the new regimen. While this approach may be logical and patient-centered, it is important to note that there is no available evidence to support it. Each case must be carefully reviewed, and clinical judgment should be applied on an individual basis.

Table 2.4.2. Modifications of treatment with the BPaLM/BPaL regimen

Full regimen modification				
BPaLM	If moxifloxacin alone is discontinued due to FQ resistance, the regimen can be continued as BPaL.			
BPaLM or BPaL	If either bedaquiline or pretomanid (or both) needs to be interrupted, the entire BPaLM/BPaL regimen should be temporarily interrupted for a maximum of: • 14 consecutive days; or • 4 weeks of non-consecutive cumulative days. Any interruption longer than 7 days should be made up for by extending the treatment duration.			
	If either bedaquiline or pretomanid needs to be permanently stopped, the entire regimen should be discontinued and the patient placed on an alternative regimen.			
BPaL	BPaL may be extended to a total of 9 months (39 weeks) if no culture conversion or clinical response by month 4. All medicines in the regimen are to be used during the extension from 26 to 39 weeks.			
Linezolid modification options in BPaLM or BPaL	**1–9 weeks of treatment**	**>9–18 weeks of treatment**	**>18–26 weeks of treatment**	**>26–39 weeks**
	600 mg daily, ideally continued throughout the regimen duration. If linezolid is permanently discontinued during the initial 9 weeks of treatment, the entire regimen should be discontinued.	If not tolerated, linezolid may be reduced to 300 mg daily until the end of the treatment, or resumed anytime to 600 mg daily, as tolerated, but ideally it should not be omitted.	If necessary, linezolid may be omitted until the end of treatment with bedaquiline, pretomanid and moxifloxacin remaining to complete the regimen; or linezolid may be restarted anytime at either 600 mg or 300 mg daily, as tolerated.	The BPaL regimen can be extended, if needed. The BPaLM regimen completes at 26 weeks.
			If linezolid is withheld in the later weeks of the regimen, with the total remaining duration of the regimen not exceeding 8 weeks, it is possible to consider completing the regimen with the remaining component drugs.	

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; FQ: fluoroquinolones.

Box 2.4.2. Examples of changes in the BPaLM or BPaL regimen

- A patient diagnosed with RR-TB by GeneXpert completes 10 weeks of treatment with BPaLM, when bedaquiline-associated hepatotoxicity necessitates the interruption of bedaquiline. However, bedaquiline or pretomanid (alone or combined) cannot be interrupted; rather, the entire BPaLM regimen needs to be stopped for not more than 14 consecutive days or not more than 4 weeks of non-consecutive cumulative doses. After 14 consecutive days of interrupting BPaLM, the ALT is still five times the upper limit of normal; therefore, the patient is moved to a longer regimen.
- A patient diagnosed with MDR-TB completes 6 weeks of treatment with BPaLM, but develops acute gastroenteritis with vomiting and diarrhoea. On follow-up, QTcF repeated 30 minutes apart is 506 and 509 ms with no symptoms. The BPaLM regimen is interrupted for 8 consecutive days because of QT prolongation due to hypokalaemia. Potassium supplementation is prescribed for 5 days, after which the ECG is repeated. Repeat ECG shows a QTcF of 390 ms. BPaLM is resumed until 26 weeks of treatment have been completed, with 8 days made up to complete the treatment.
- A patient diagnosed with RR-TB completes 26 weeks of treatment with BPaLM, but has frequent irregular interruptions of treatment. No single interruption lasts up to 14 consecutive days and the cumulative total is less than 28 non-consecutive days. Any missed doses of the full BPaLM regimen lasting more than 7 days should be made up at the end of the treatment, within an overall period of 7 months.
- A patient diagnosed with MDR-TB and who has no observed risk of additional FQ resistance is started on BPaLM treatment. However after 6 weeks, the patient's DST shows FQ resistance. Moxifloxacin should be stopped and the patient continued on BPaL.
- A patient diagnosed with MDR-TB and additional FQ resistance (i.e. pre-XDR-TB) is treated with BPaL. Bacteriological examination done in month 4 is found to be positive. Their BPaL treatment is to be extended to 39 weeks in total with close monitoring of treatment response, including DST for all component medicines for the last positive culture.

4.1.4 Key subgroups

The following subgroup analyses were available to the GDG in considering the eligibility criteria for the BPaLM/BPaL regimen: age, smear status, smoking status, pulmonary TB patients with radiological evidence of bilateral disease or radiological evidence of cavitation, PLHIV and previous TB. The GDG also considered the eligibility criteria as stipulated by each of the trials. Several groups of patients were excluded from the ZeNix and TB-PRACTECAL trials (e.g. extrapulmonary TB patients, pregnant or breastfeeding women, children and adolescents < 14 years). Inclusion of such patients should be considered with caution, because there are currently no available data regarding the safety of BPaLM/BPaL in such populations. This subsection summarizes the resulting considerations when prescribing the BPaLM/BPaL regimen.

Extensive pulmonary TB

The Nix-TB, ZeNix and TB-PRACTECAL studies included pulmonary TB patients with radiological evidence of bilateral disease or radiological evidence of cavitation. Hence, patients with extensive

pulmonary disease can be started on the BPaLM/BPaL regimen; however, close microbiological and clinical monitoring for culture conversion and clinical or radiological response should be maintained.

Extrapulmonary TB

WHO recommends the BPaLM/BPaL regimen for extrapulmonary TB, except for TB involving the CNS, osteoarticular TB and disseminated forms of TB with multiorgan involvement. The longer MDR-TB regimens apply to such patients. There is a single case study of a participant from the Nix-TB study that confirms the incidental use of BPaL in CNS TB with a favourable outcome *(30)*, but further studies are required to recommend the regimen for programmatic implementation in severe disseminated TB. Linezolid has excellent penetration of the cerebrospinal fluid (CSF) and brain, and studies involving a small number of participants indicated that bedaquiline penetrates well into the CSF, but there are no data on pretomanid on CSF or brain penetration (**Annex 1**).

People living with HIV

PLHIV represented 19.5% of those enrolled in the ZeNix trial, 51% of those enrolled in the Nix-TB study, and 26.7% of those enrolled in the TB-PRACTECAL trial. These patients were eligible to enrol in the ZeNix trial if they had a CD4 count of more than 100 cells/mm^3, and in TB-PRACTECAL regardless of CD4 count. Thus, patients can be enrolled in the BPaLM/BPaL regimen irrespective of the CD4 count; however, care should be taken when CD4 counts are below 100 cells/mm^3. In the LIFT-TB study, 14 patients had PLHIV, of whom 13 received linezolid 1200 mg daily. Treatment success was 92.9% (13/14); only one patient who was given 1200 mg per day failed treatment.

In the ZeNix trial, enrolled participants had to be taking permitted ARV medications.[15] Although there was no such criterion in TB-PRACTECAL, it is important to consider DDIs when administering TB and HIV medications in combination (see Section 4.1.1). The ARV drug efavirenz induces the metabolism of bedaquiline, so its co-administration with bedaquiline may result in reduced bedaquiline exposure and loss of activity; therefore, co-administration is to be avoided. Efavirenz also reduces pretomanid exposures significantly *(31)*; therefore, an alternative ARV agent (potentially dolutegravir, although there is currently insufficient evidence for this) should be used if the BPaLM/BPaL regimen is considered. Ritonavir increases bedaquiline exposure, which could potentially increase the risk of bedaquiline-related adverse reactions *(32)*; however, increased risk has not been noted in studies administering both drugs concurrently *(32–34)*, including in the ZeNix trial. Individuals who are prescribed both bedaquiline and ritonavir should be monitored closely for AEs, including QTc prolongation. Finally, ARV regimens including zidovudine should be avoided, if possible, because both zidovudine and linezolid may cause myelosuppression (more details in **Annex 2**).

Pregnant and breastfeeding women

Pregnant and breastfeeding women were excluded from both the ZeNix and TB-PRACTECAL trials; hence, no analysis specific to this subgroup of patients could be performed, and the safety of the BPaLM/ BPaL regimen (especially of pretomanid) in pregnant and breastfeeding women has not been established. For pregnant and breastfeeding women, the 6-month regimen BDLLfxC or 9-month regimens should be considered (**Sections 4.2 and 5**).

Children and adolescents

Children and young adolescents were excluded from the Nix-TB, ZeNix (0–13 years) and TB-PRACTECAL (0–14 years) studies; therefore, it was not possible to perform an analysis specific to this subgroup

[15] The permitted antiretroviral treatments were nevirapine in combination with tenofovir/abacavir or emtricitabine/lamivudine; lopinavir/ritonavir in combination with tenofovir/abacavir or emtricitabine/lamivudine; and integrase inhibitor in combination with tenofovir/abacavir or emtricitabine/lamivudine. For patients on efavirenz, therapy could be changed to rilpivirine with tenofovir/abacavir or emtricitabine/lamivudine.

of patients. Although bedaquiline, linezolid and FQ have been used to treat MDR/RR-TB in younger patients, there are no data about the use of pretomanid in this population, and further study is required to expand the use of BPaLM/BPaL to these patients.

Individuals aged 14 years and older were included in the Nix-TB and ZeNix trials, and individuals aged 15 years and older in TB-PRACTECAL; thus, such individuals can safely be started on the BPaLM/BPaL regimen under programme conditions. It is recommended that younger patients aged below 14 years with pulmonary MDR/RR-TB be given consideration for the newly recommended 6-month BDLLfxC regimen or 9-month regimens.

4.1.5 Implementation considerations

DST and resistance to the component medicines

DST for FQ is strongly encouraged in people with MDR/RR-TB. A WHO-recommended rapid molecular test should be used as an initial rapid test (in preference to culture and phenotypic DST) to detect resistance to FQ *(35)*. The results of the DST, when available, should guide the decision on the use or changes of this regimen; however, initiation of the BPaLM regimen should not be delayed by the wait for these results.

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 any of the regimen component drugs (except moxifloxacin) is discovered after treatment has been initiated, the regimen needs to be discontinued. Although DST for bedaquiline, pretomanid and linezolid is not easily accessible, in situations where it is available, it is highly desirable to carry this out at baseline. Patients with strains resistant to bedaquiline, pretomanid or linezolid should commence treatment with either a 9-month regimen or a longer, individualized MDR-TB regimen.

It is critical to know the resistance profile of the patient and thus exclude resistance to the anti-TB drugs composing the BPaLM/BPaL regimen. Molecular (genotypic) methods have considerable advantages, in particular with regard to their speed, the standardization of testing, their potentially high throughput and the reduced requirements for biosafety.

Many different rapid molecular DST methods are available for moxifloxacin (LPA, LC-aNAATs and targeted NGS). If resistance to moxifloxacin is detected, then moxifloxacin should be discontinued and the patient should be continued with the BPaL regimen.

Only one molecular method, targeted NGS, is available to detect resistance to bedaquiline and linezolid; where this method is available, it should be performed before the start of the BPaLM/BPaL regimen. The results of targeted NGS for bedaquiline and linezolid should be critically assessed, taking into account the prevalence of resistance to these drugs in tested populations and the risk of resistance in a particular patient.

Certain individuals are at high risk for resistance to bedaquiline and linezolid; for example, people with prior drug exposure, populations where the prevalence of resistance is above 5% and those with a history of contact with a person with TB with known drug resistance. For such individuals, a negative (sensitive) result of the targeted NGS phenotypic testing is advised. In addition, if resistance to bedaquiline is detected (in cases of low or high risk of this resistance in particular patients), the use of the phenotypic DST is still advised.

Finally, the critical concentrations for pretomanid phenotypic resistance detection have been established for the MGIT method, enabling NTPs to perform phenotypic DST.

If resistance to bedaquiline, pretomanid or linezolid is detected in patients with MDR/RR-TB, the BPaLM/BPaL regimen should not be offered, and the patient must switch to another appropriate treatment regimen.

If resistance to bedaquiline, linezolid or pretomanid develops while on the regimen, the treatment is considered to have failed, and individuals should be shifted to either a 9-month regimen or a longer individualized regimen (**Sections 5 and 6**).

In the absence of DST for bedaquiline, pretomanid and linezolid, treatment decisions will rely on the likelihood of effectiveness of these medicines, based on an individual patient's clinical history of exposure to the drugs and DRS data from the country or region. This should be considered an interim measure until the DST capacity for these drugs becomes available.

Further details on treatment modifications and follow-on DST for MDR/RR-TB patients based on results from targeted NGS can be found in the operational handbook *Module 3: Diagnosis – rapid diagnostics for tuberculosis detection (11)*.

History of exposure to component drugs

As detailed previously, DST for FQ is advisable before starting therapy. Where DST is unavailable, a careful history of previous exposure to TB therapy is critical. Where the treatment history suggests there may be resistance to one of the components of the regimen (i.e. exposure to bedaquiline, pretomanid or linezolid in an inadequate regimen for more than 1 month) and DST is unavailable, the BPaLM/BPaL therapy should not be commenced; instead, a longer individualized regimen should be considered. On the other hand, if there is greater than 1 month exposure to FQ that indicates probable resistance, the BPaLM regimen may be initiated and continued until resistance to FQ is confirmed.

Previous exposure to delamanid may suggest cross-resistance to pretomanid *(36)* and exposure to clofazimine may suggest cross-resistance to bedaquiline *(37)*. Caution should be exercised in such situations and, where possible, if DST for clofazimine, bedaquiline, pretomanid or delamanid is available, it should be used. However, the BPaLM regimen can be started in these situations and the treatment will be reviewed once the DST result to these drugs is available.

Drug–drug interactions

Vigilance or, preferably, drug substitution should be considered when certain medications are prescribed concurrently with the BPaLM/BPaL regimen. Common DDIs of the regimen components with other concomitant medicines are described in detail in **Annex 1** and **Annex 2**. In each of the above situations, if the clinician judges that the potential benefits outweigh the potential risk (also considering alternative treatment options), then treatment may proceed with caution.

Cost and cost–effectiveness analysis

A 6-month BPaLM treatment course for an MDR/RR-TB patient costs US$ 364 compared with US$ 926–998 for the 6-month BDLLfxC regimen, and US$ 209–1500 for the 9-month regimens. For a patient with pre-XDR-TB, a 6-month course of BPaL costs US$ 340 versus the cost of an 18-month treatment regimen (with no documented resistance to the Group A drugs, bedaquiline and linezolid) of US$ 453 *(38)*.[16]

Although there have been no cost–effectiveness studies looking at the BPaLM regimen, such studies for the BPaL regimen have demonstrated lower costs. Owing to the substantially shorter treatment duration and reduced need for hospitalization *(39, 40)*, it was estimated that the implementation of a national programme using BPaL for MDR/RR-TB would cost 57–78% less than conventional longer regimens, when including all costs (e.g. investigations, drugs and hospitalization) *(39)*. With

[16] Prices use the lowest price available from Global Drug Facility (GDF), effective from 1 January 2025, and are subject to change.

the decrease in the cost of bedaquiline and pretomanid in 2025, these analyses are becoming even more favourable for the implementation of the BPaLM/BPaL regimen.

Treatment support

Measures to support patient adherence tailored to patient needs are important to retain patients on treatment and ensure good treatment outcomes. Support should be provided through an effective model of care and measures should include support in the community or at home, social support and digital health interventions for communication with the patient *(41)* (see more details in **Chapter 3**). Early ambulatory care was employed by the ZeNix trial and is recommended for the programmatic implementation of the BPaLM/ BPaL regimen, because it complements the patient-centred approach to the management of TB. Patient support is particularly important for the BPaLM/BPaL regimen, to ensure adherence and avoid treatment interruption and LTFU. Interruption of all medicines is especially dangerous for the BPaLM/BPaL regimen and all other bedaquiline-based regimens because it effectively leaves patients on bedaquiline monotherapy owing to the long half-life of bedaquiline.

4.2 The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfxC) regimen

This section refers to the use of BDLLfxC – a new 6-month regimen containing bedaquiline, delamanid, linezolid, levofloxacin and clofazimine – for the treatment of MDR/RR-TB. This short regimen is particularly appropriate for people who are unable to benefit from the currently recommended 6-month BPaLM regimen owing, for example, to restricted access to pretomanid, being aged younger than 14 years, or being pregnant or breastfeeding. The recommendation in the updated 2025 guideline states:

No.	Recommendation (NEW)
1.2	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. Although it should not delay the initiation of the BDLLfxC, the test results should guide the decision on whether levofloxacin or clofazimine should be retained.
2. This recommendation applies to the following:
   a) People with MDR/RR-TB or pre-XDR-TB (i.e. MDR/RR-TB and resistance to fluoroquinolones).
   b) Patients with less than 1 month of previous exposure to bedaquiline, linezolid, delamanid or clofazimine. When exposure is greater than 1 month, these patients may still receive the regimen if resistance to the specific medicines involved in such exposure has been ruled out.
   c) People with diagnosed pulmonary TB of all ages, including children, adolescents, PLHIV, and pregnant and breastfeeding women.
   d) People with all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB, or disseminated forms of TB with multiorgan involvement.
   e) Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

3. When resistance to fluoroquinolones is unknown, the regimen should be started as BDLLfxC and then adjusted based on the DST results. In cases of quinolone susceptibility, clofazimine should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and levofloxacin (BDLLfx). In cases of resistance to fluoroquinolones, levofloxacin should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and clofazimine (BDLC).

Since the release of the previous WHO DR-TB guidelines in December 2022 *(42)*, data on a new 6-month oral regimen for MDR/RR-TB and pre-XDR-TB have become available from the BEAT Tuberculosis clinical trial in South Africa *(43)*. This was a pragmatic, open-label, RCT conducted at two government health facilities in different provinces between August 2019 and September 2022. The trial used a non-inferiority design to compare safety and efficacy of the study strategy with the SoC approach in South Africa *(44)*. People presenting to the hospital sites for diagnosis and treatment of MDR/RR-TB were asked to give written informed consent for trial participation and were then randomized to the study strategy (6 months of bedaquiline, delamanid, linezolid and either levofloxacin or clofazimine, or both) or the control strategy (WHO-recommended, mostly 9-month all-oral, bedaquiline-containing regimen for FQ-susceptible TB and longer regimen for FQ-resistant TB patients). The study strategy used a "tapering down" approach, whereby participants diagnosed with TB that was resistant to at least rifampicin would initiate a regimen composed of bedaquiline, delamanid, linezolid, levofloxacin and clofazimine. Once FQ DST results became available, either immediately or later, the regimen was altered as follows: clofazimine was withdrawn (and levofloxacin continued) when FQ susceptibility was confirmed, levofloxacin was withdrawn (and clofazimine continued) when FQ resistance was confirmed, and neither drug was withdrawn (both levofloxacin and clofazimine continued) in cases where FQ DST results were unavailable. This tapering down approach made provision for the potential delay in obtaining FQ DST results while still allowing rapid initiation of effective MDR/RR-TB treatment, which provided adequate cover for both FQ-susceptible and FQ-resistant strains from the outset.

The evidence for the novel 6-month BDLLfxC regimen that was used to inform PICO questions for the updated WHO guidelines was derived from BEAT Tuberculosis RCT. However, an unrelated study with a similar name – the BEAT-India (Building Evidence to Advance Treatment of TB) study – was a prospective open-label, single-group cohort study that was carried out at five sites in India between April 2019 and January 2021 *(45)*. The BEAT-India study only enrolled patients with pre-XDR-TB, but the 6-month study regimen (BDLC) was the same as that used for participants with pre-XDR-TB enrolled in the study strategy of the BEAT Tuberculosis trial. Although not considered in the PICO questions for these guidelines, the encouraging findings from the BEAT-India study also appear to support the recommendations for implementation of a 6-month regimen containing these medicines in settings outside of South Africa.

The BEAT Tuberculosis trial enrolled 402 participants: 202 to the study strategy and 200 to the control strategy. Most participants in the control strategy received the WHO-recommended 9-month regimen containing bedaquiline and linezolid. The study protocol allowed for enrolment of PLHIV, children aged over 6 years, adolescents, and pregnant and breastfeeding women. Patients with extensive or severe pulmonary TB were also included, as were people with non-severe extrapulmonary forms.

The results of this RCT support the programmatic use of a 6-month regimen containing bedaquiline, delamanid and linezolid, as well as levofloxacin or clofazimine (or both), in place of 9-month or longer regimens in patients with MDR/RR-TB or pre-XDR-TB who are unable to receive pretomanid within the BPaL or BPaLM regimens.

4.2.1 Eligibility

The 6-month BDLLfxC regimen may be offered in the following situations:

- people with MDR/RR-TB or pre-XDR-TB;

- people with MDR/RR-TB and less than 1 month of previous exposure to bedaquiline, linezolid, delamanid or clofazimine; when exposure is greater than 1 month, these patients may still receive the regimen if resistance to the specific medicines with such exposure has been ruled out;
- people with diagnosed pulmonary TB, including children, adolescents, PLHIV, pregnant and breastfeeding women;
- people with most forms of extrapulmonary disease except for TB involving the CNS, or osteoarticular or disseminated forms of TB with multiorgan involvement; and
- children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with MDR/RR-TB).

Note that children, adolescents and adults with any extent or severity of pulmonary TB disease[17] are eligible to receive this 6-month regimen. In addition, people with non-severe forms of extrapulmonary TB, such as uncomplicated pleural effusions or peripheral lymph node disease, are also eligible to receive this 6-month regimen.

The 6-month BDLLfxC regimen may also be offered to adults (who might otherwise have been eligible for BPaL or BPaLM) in settings where pretomanid is restricted, unavailable or contraindicated (e.g. in pregnancy or breastfeeding), or to patients who are unable to tolerate pretomanid.

The 6-month regimen is NOT appropriate for the following situations:

- patients with MDR/RR-TB with documented resistance to bedaquiline, delamanid, linezolid or clofazimine;
- people in whom the most recent episode of MDR/RR-TB treatment has failed; or
- people with severe extrapulmonary TB.[18]

4.2.2 Composition, dosing and duration of the regimen

The initial diagnosis of MDR/RR-TB is usually based on the results of mWRDs. DST for FQ is strongly encouraged in people with MDR/RR-TB, because the test results will guide the decision as to whether levofloxacin or clofazimine should be retained or dropped from the regimen. However, FQ DST results are not always immediately available at the time of diagnosis. For people who are eligible to receive this 6-month regimen, the absence of the FQ DST result should not delay initiation of treatment with a regimen containing all five drugs (i.e. bedaquiline, delamanid, linezolid, levofloxacin and clofazimine). The regimen may then be adjusted by withdrawal of either levofloxacin or clofazimine (or neither), depending on whether FQ DST was successful, and whether the result showed FQ resistance or susceptibility. Therefore, patients receiving this 6-month regimen are treated with either BDLLfxC, BDLLfx or BDLC.

These regimen variations should be given for a total of at least 24 weeks (i.e. 6 months). In some situations, e.g. lack of bacteriological or clinical response by month 4, treatment may be extended up to a total of 9 months (see **section 4.2.5**). If the month 5 and 6 culture results remain persistently positive, treatment failure should be suspected, particularly if the patient has had suboptimal adherence to treatment or shows other signs of poor clinical or radiological response to treatment.

Ideally, all component medicines of each regimen variation should be used for the full duration of treatment, but in some situations (described below), linezolid may have to be discontinued prematurely.

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[17] Extensive (advanced) pulmonary TB disease is the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children and young adolescents aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on CXR.

[18] Severe extrapulmonary TB is the presence of miliary TB and TB meningitis, osteoarticular and pericardial TB. In children and young adolescents aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without airway compression) are considered to be severe.

Composition

BDLLfxC regimen

People with MDR/RR-TB who meet the eligibility criteria may start treatment with the BDLLfxC regimen, then modify to either BDLLfx or BDLC once FQ DST results are available, as described below.

In cases where DST for FQ is unknown, or cannot be carried out at baseline, the regimen will include all five medicines – bedaquiline, delamanid, linezolid, levofloxacin and clofazimine – for the duration of treatment. If FQ DST can be repeated on a clinical sample taken at some point after starting treatment, the regimen may still be adjusted later according to the DST results, as described below.

BDLLfx regimen

In cases where the MDR/RR-TB strain is shown to be susceptible to FQ on DST, the regimen will include four medicines – bedaquiline, delamanid, linezolid and levofloxacin (i.e. BDLLfx).

If the DST result is available before the start of treatment and proves susceptibility to FQ, patients may commence the four-drug BDLLfx regimen immediately. If the DST result is delayed, the patient will initiate the BDLLfxC regimen and, once the DST result confirms FQ susceptibility, clofazimine can be ceased and BDLLfx continued for the remainder of treatment.

It is possible for a patient with confirmed FQ-susceptible MDR/RR-TB, who is receiving a BDLLfx regimen, to switch to BDLC if necessary; for example, intolerance to levofloxacin, limited availability of levofloxacin, or patient or provider preference.

BDLC regimen

In cases where the MDR/RR-TB strain is shown to be resistant to FQ on DST, the regimen will include four medicines – bedaquiline, delamanid, linezolid and clofazimine (i.e. BDLC).

If the DST result is available before the start of treatment and proves resistance to FQ, patients may start on the four-drug BDLC regimen immediately. If the DST result is delayed, the patient will initiate the BDLLfxC regimen; if the DST result then confirms FQ resistance, levofloxacin can be dropped and BDLC continued for the remainder of treatment.

There is a potentially higher concern for further drug resistance in strains of pre-XDR-TB; thus, every effort must be made in these cases to ensure that DST is undertaken as quickly as possible for other component drugs in the regimen. Detection of resistance to any of the drugs in this regimen will necessitate a rapid switch to another appropriate regimen.

Dosing

Dosing of medicines in the regimen for both adults and children should follow the latest WHO weight-based dosing tables (see **Annex 4**). All reasonable efforts should be made to ensure the availability of child-friendly formulations.

Bedaquiline

Bedaquiline may be dosed in one of two ways in this regimen. Historically, bedaquiline has been initiated with a relatively high loading dose (400 mg for adults), to be administered every day for the first 14 days, followed by a lower dose (200 mg for adults) to be administered three times a week for the remaining duration of treatment. Pragmatically, to allow at least 48 hours between doses, the thrice-weekly lower dose is usually administered on a Monday, Wednesday and Friday. This was the dosing schedule used in both strategies in the BEAT Tuberculosis trial in South Africa

and in the BEAT-India cohort study in India. However, with the introduction of the BPaLM regimen in 2022, an alternative bedaquiline dosing schedule was introduced. Bedaquiline may be initiated at a dose of 200 mg (for adults) to be administered daily for 8 weeks, followed by a lower dose of 100 mg (for adults), which is also administered daily. This alternative once-daily dosing schedule may be simpler and more practical for some patients to administer, and may be considered for adults using the BDLLfxC regimen. Children and adolescents require weight-based dosing of bedaquiline using dispersible formulations where appropriate and accessible. Bedaquiline dose adjustment is not required for patients with mild-to-moderate renal or hepatic impairment.

Delamanid

Delamanid is administered orally twice daily, at a dose of 100 mg for adults for the first 8 weeks, followed by 200 mg once daily for the rest of the treatment. This was the dosing schedule used in both strategies in the BEAT Tuberculosis trial and in the BEAT-India cohort study. Lower doses should be used for children and adolescents, and dispersible delamanid tablet formulations should be used where appropriate and accessible. The once-daily dosing of delamanid in children and younger adolescents has not yet been studied as of 2024. Delamanid dose adjustment is not required for patients with mild-to-moderate renal impairment or in those with mild hepatic impairment.

Linezolid

Linezolid is dosed orally at 600 mg once daily for adults. This was the dosing schedule used in both the BEAT Tuberculosis trial and the BEAT-India cohort study. For children and adolescents weighing less than 46 kg, weight-based dosing is required. Younger children should receive dispersible linezolid tablet formulations (or liquid suspensions) where appropriate and accessible. Linezolid dose adjustment is not required for patients with any renal or hepatic impairment.

Levofloxacin

Levofloxacin is dosed orally at 750–1000 mg once daily for adults, depending on weight. This was the dosing schedule used in both strategies in the BEAT Tuberculosis trial. Weight-based doses should be used for children and adolescents, and dispersible levofloxacin tablet formulations should be used where appropriate and accessible, as a priority for younger children. Levofloxacin dose adjustment is required for patients with renal impairment where creatinine clearance is less than 50 mL/min. No dose adjustment is required for patients with hepatic disease.

Clofazimine

Clofazimine is dosed orally at 100 mg once daily for adults. For children and adolescents, doses should follow the latest WHO weight-based dosing table (**Annex 4**), using clofazimine tablet formulations that can be dispersed or 50 mg gel capsules. Clofazimine dose adjustment is not required for patients with any renal impairment or for those with mild-to-moderate hepatic impairment.

Pregnancy and postpartum

In the absence of pharmacokinetic data and specific dosing recommendations for second-line TB medications during pregnancy and postpartum, pregnant or breastfeeding women included in either strategy of the BEAT Tuberculosis trial were dosed as described above for adults, based on their total body weight. Pharmacokinetic and safety data are severely lacking in this population, and the inclusion of pregnant and breastfeeding people in TB clinical research should be prioritized.

Duration

The expected duration of the BDLLfxC, BDLLfx and BDLC regimens is 6 months (24 weeks) but this may be extended to 9 months (36 weeks) if necessary.

Although most participants on the study strategy in the BEAT Tuberculosis trial had successful treatment outcomes following 24 weeks of BDLLfxC, BDLLfx or BDLC, some participants were required to extend treatment beyond 6 months. If patients had extensive pulmonary disease, had slow clinical response to treatment or sputum culture conversion had not occurred by the fourth month (week 16) on treatment with any of the BDLLfxC regimen variations, the study protocol allowed for the full duration of the regimen to be extended by another 3 months, up to a total of 9 months (36 weeks) of treatment. A similar approach was taken in the BEAT-India study, where the BDLC regimen was extended by 12 weeks for patients with pre-XDR-TB if the week 16 sputum sample was culture positive *(45)*. There are three main reasons for delayed culture conversion. The first is an extensive pulmonary TB disease as assessed on CXR. If possible, the CXR taken at the start of treatment should be reviewed and compared with the one taken at month 4 in this case. The second reason is non-adherence to treatment. It is necessary to check on-time pharmacy pickups and to confirm with the patient and any treatment supporter that all doses have been taken. The last reason is that there is undiagnosed resistance to one of the drug components of the regimen. This could have been present at the time of starting therapy or acquired during treatment. Where possible, a specimen should be sent for DST for bedaquiline, linezolid and delamanid.

In practice, sputum culture results usually take up to 6 weeks to be reported as negative. Therefore, bacteriological culture conversion (i.e. two consecutive cultures from samples taken on different occasions at least 7 days apart are negative) might only be confirmed after 5 or 6 months on treatment, which is when the results of samples taken at months 3 or 4 would become available. In some situations, e.g., where the full DST results are not available or where a person's symptoms are slow to improve, clinicians may use their discretion and choose to extend treatment to nine months for patients with extensive pulmonary disease. Once a decision has been made to extend treatment beyond 6 months, further sputum culture results must be followed up, to ensure that culture conversion occurs soon after month 4 on treatment. If the month 5 and 6 culture results remain persistently positive, treatment failure should be suspected, particularly if the patient has had suboptimal adherence to treatment or shows other signs of poor clinical or radiological response to treatment.

Extending treatment because of delayed culture conversion (by month 4) is applicable mostly to individuals with bacteriologically confirmed pulmonary MDR/RR-TB. For young children diagnosed with TB based on clinical criteria or for patients with extrapulmonary TB, this extension can be applied based on clinical assessment of the treatment response, while considering other potential causes for deterioration (e.g. undiagnosed resistance, poor adherence to therapy or other clinical factors). The absence of clinical improvement or culture conversion by month 6 should prompt a comprehensive evaluation of the treatment regimen to assess potential failure.

4.2.3 Modifications of treatment

Drug toxicity

Linezolid is the least well tolerated drug within the BDLLfxC regimens owing to its toxicity profile (well described in **Annexes 1 and 2**); hence, many patients may be unable to continue this drug for the full 6 months of treatment. Among the 402 participants in the BEAT Tuberculosis trial in South Africa, 10% experienced severe anaemia during their treatment course (see **Annex 2**). Of the 202 participants in the study strategy, 159 (79%) completed the entire 6-month course of treatment without interruptions. Eighteen participants (11%) had linezolid permanently discontinued during the 6-month treatment course owing to anaemia (n=3), optic neuritis (n=6) or peripheral neuropathy (n=9). Patients initiating

the BDLLfxC regimen should be supported to continue linezolid for at least the first 2 months (9 weeks) of treatment. Otherwise, an alternative regimen should be considered. Patients who experience severe AEs and have to stop linezolid beyond 2 months of treatment do not necessarily need to switch regimens, but this depends on the timing of drug withdrawal, the availability of other DST results and the patient's clinical response to treatment. For example, if a patient with FQ-susceptible MDR/RR-TB is responding well to treatment (bacteriologically and clinically) with BDLLfx but experiences a severe linezolid-related AE after 2 months of treatment, then linezolid could be withdrawn without having to switch regimens. See **Annex 2** for further details on the management of linezolid toxicity.

Severe AEs leading to withdrawal of other component drugs in the BDLLfxC regimen are rare, but permanent withdrawal of bedaquiline, delamanid or clofazimine would certainly necessitate changing to an alternative regimen. For example, if a patient's QT interval exceeds 500 ms at any point throughout treatment, then all drugs should be withheld, and other causes of QT prolongation (electrolyte disturbances, other non-essential drugs) excluded and appropriately managed, until the QT interval is back below 500 ms. If at least four effective component drugs cannot be reintroduced without persistent QT-interval prolongation above 500 ms, then an alternative regimen must be considered.

Drug substitution

Moxifloxacin has a much stronger effect on the QT interval than levofloxacin; therefore, moxifloxacin is not considered for substitution of levofloxacin within the BDLLfxC regimens. If levofloxacin is withdrawn from a BDLLfx regimen owing to levofloxacin-related toxicity before completion of treatment, clofazimine may be used to substitute levofloxacin; the patient can then be managed as if they had FQ-resistant MDR/RR-TB and can continue treatment with the BDLC regimen instead.

Missed doses

Ideally, missing doses of all four or five drugs in the BDLLfxC regimens should be avoided; however, many patients experience occasional treatment interruption. In general, if a patient misses less than 1 week's worth of doses over the course of their treatment, there is no need to extend treatment beyond the planned duration. However, any interruption longer than 7 consecutive or non-consecutive days (but <1 month) over the entire treatment course should be made up for by extending the treatment duration (to account for the number of missed doses). In total, 24 or 36 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively. This does not apply to specific medications that are interrupted owing to AEs.

Discontinuation and change to another treatment regimen

Occasionally, patients who have started the BDLLfxC regimens may have to discontinue the regimen and change to a different treatment regimen, or vice versa; for example, because of the risk of potential AEs of component drugs within the regimen (e.g. patients becoming pregnant while receiving pretomanid within BPaL or BPaLM); following receipt of DST results indicating resistance to component drugs within the regimen; or simply because clinicians and their patients may have reason to prefer a different regimen for which the participant is eligible. Examples of such situations are outlined below:

- Patients receiving treatment with BDLLfx, BDLC or BDLLfxC will have to change to a different regimen if bedaquiline or delamanid (or clofazimine in the case of FQ-resistant MDR/RR-TB) needs to be withdrawn at any point in treatment, or if linezolid use is limited by toxicity within the first 2 months of treatment. Drug withdrawal may be due to toxicity or intolerance, sustained interruption in drug supply or evidence of resistance to any of the drugs in the regimen (bedaquiline, delamanid, linezolid or clofazimine).

- Patients will have to change to a more appropriate regimen if the BDLLfxC regimens appear to be failing, as evidenced by poor clinical, bacteriological or radiological response (or further deterioration), or sustained reconversion of negative cultures to positive at any point in treatment.

4.2.4 Key subgroups

Extensive pulmonary TB and resistance to fluoroquinolones

Extensive pulmonary TB is defined as the presence of bilateral cavitary disease or extensive parenchymal damage on CXR. Patients with extensive pulmonary MDR/RR-TB disease were included in both the study strategy and the control strategy (but treated for 9 months) in the BEAT Tuberculosis trial in South Africa, and most of the participants in the BEAT-India study in India had extensive bilateral disease *(45)*; despite this, both studies reported high rates of treatment success with the 6-month study regimens. In some situations (e.g. where the full DST results are not available or where a person's symptoms are slow to improve), clinicians may use their discretion and choose to extend treatment to 9 months for patients with extensive pulmonary disease.

Patients with DR-TB who have extensive disease face greater challenges in treatment across all regimens and are at a higher risk of unfavourable outcomes and amplification of drug resistance. This risk is further elevated in those infected with pathogens that have advanced resistance profiles, particularly with additional resistance to fluoroquinolones. These patients may experience slightly worse outcomes compared to those without pre-XDR and develop resistance to regimen components. The evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. Nonetheless, clinicians should remain vigilant and closely monitor the treatment response in this group of patients and promptly take relevant actions (extending the duration of treatment or changing the regimen).

Extrapulmonary TB

The BEAT Tuberculosis trial in South Africa included patients with non-severe or uncomplicated extrapulmonary TB if they also had pulmonary disease; however, it excluded patients with tuberculous meningitis, miliary TB, and pericardial and osteoarticular disease. Therefore, the BDLLfxC regimens should not be offered to patients with severe or complicated extrapulmonary MDR/RR-TB disease involving the CNS, or osteoarticular and disseminated forms of TB because these patients require treatment with a regimen of longer duration.

People living with HIV

The 6-month BDLLfxC regimen was evaluated in a high HIV prevalence setting; 50% of participants enrolled on the BEAT Tuberculosis trial in South Africa were PLHIV. There is no reason to believe that this regimen would perform differently in people who initiate appropriate ART in a timely manner and are adequately supported to adhere to treatment for both diseases. In BEAT Tuberculosis 82.9% of PLHIV had a favorable treatment outcome with the six-month regimen compared with 89.7% of participants without HIV. As safer and more tolerable medications become more widely available, DDIs and overlapping toxicities are becoming less common. In settings where zidovudine is still used, co-administration of this drug with linezolid increases the risk of myelosuppression and thus should be avoided. Non-nucleoside reverse transcriptase inhibitors were prohibited in the BEAT Tuberculosis trial in South Africa because of DDIs with bedaquiline (efavirenz significantly reduces the concentration of bedaquiline, which may reduce efficacy of the drug). In addition, co-administration of efavirenz with delamanid increases the risk of neuropsychiatric adverse effects. Therefore, alternative ARVs should be used with the BDLLfxC regimens – in the BEAT Tuberculosis trial, ART for PLHIV included either dolutegravir or a protease inhibitor. There are no overlapping toxicities or DDIs between dolutegravir and any of the component drugs in the BDLLfxC regimens, but interactions with other integrase inhibitors and newer ARV drugs have not yet been studied.

Pregnant and breastfeeding women

Data on dosing and safety to support the optimal use of second-line anti-TB medicines during pregnancy remain sparse, highlighting the need for wider inclusion of pregnant and breastfeeding women in TB research. In general, the benefits (to both mother and fetus or infant) of providing effective MDR/RR-TB treatment to the mother far outweigh the potential risks posed by these medications to the fetus in-utero or to the breastfeeding infant.

The BEAT Tuberculosis trial allowed for the enrolment or retention of pregnant and breastfeeding women on both the study strategy and the control strategy. Among the 10 pregnant women enrolled in the BEAT Tuberculosis trial overall, four were randomized to the study strategy with the 6-month BDLLfxC regimens. All pregnancies in this trial resulted in singleton live births, with one preterm delivery. No drug-related and no severe AEs were reported among the women or their infants; however, one of the four women randomized to the study strategy experienced a relapse of TB following completion of treatment. Although numbers are too small to draw any definitive conclusions, these findings highlight the need to support and optimize adherence through treatment and provide post-treatment follow-up for at least 6 months beyond treatment completion, to rapidly identify cases of relapse in pregnant and postpartum women.

Care providers for pregnant women with MDR/RR-TB must also pay particular attention to the seamless continuity of care between antenatal and TB services, which are not integrated in most TB-endemic settings. Good communication with the patient and among various providers is essential to avoid unnecessary treatment modifications to the BDLLfxC regimens, and to reduce stigma and potential LTFU from treatment. Patients require considerable adherence support and monitoring of proper administration of MDR/RR-TB treatment and other medications in the early postpartum period, when chronic medication might not be prioritized, to ensure successful maternal treatment outcomes and minimal risk of TB transmission from mother to infant.

Children and adolescents

The BEAT Tuberculosis trial in South Africa allowed enrolment of children and adolescents aged above 6 years to either treatment strategy. In total, 30 younger patients aged 8–17 years were enrolled on the trial. Thirteen children were randomized to the study strategy group and all had bacteriologically confirmed MDR/RR-TB disease, of which 24% were FQ-resistant.

Most of the children and adolescents enrolled on the BEAT Tuberculosis trial were aged above 12 years. Bacteriological confirmation of MDR/RR-TB disease in children aged below 12 years often signifies severe disease. The high rate of treatment success among children and adolescents in this trial is encouraging; it supports the efficacy of this regimen for children of all ages with severe and non-severe pulmonary MDR/RR-TB disease. In the absence of bacteriological confirmation of disease in younger children, the decision to treat for MDR/RR-TB relies on clinical signs and symptoms of TB disease, radiological findings, and history of significant exposure to a person with microbiologically confirmed MDR/RR-TB. In these cases, treatment decisions and regimen choice should be based on the drug-resistance pattern of the isolate obtained from the index case.

Despite the small numbers of children included in the BEAT Tuberculosis trial, the evidence supporting the efficacy of this regimen in adults and adolescents may be extrapolated to children, provided the implementation considerations are followed. Therefore, children of all ages, with either severe or non-severe pulmonary disease, as well as those with uncomplicated extrapulmonary disease (peripheral lymph nodes or isolated mediastinal mass without airways compression) are likely to benefit from the 6-month BDLLfxC regimen.

All the component drugs in the BDLLfxC regimens have already been used in various combinations to treat MDR/RR-TB in children, and drug dosages have been established (and continue to be refined) for children of all ages. Child-friendly, dispersible formulations exist for all the component drugs in the

BDLLfxC regimens and are strongly preferred by children and their caregivers. TB programmes must prioritize procuring and providing these formulations for children with MDR/RR-TB. Although child-friendly formulations are the priority, the lack of these is not a barrier to providing children access to the BDLLfxC and other MDR/RR-TB regimens. Bedaquiline and delamanid tablets can be crushed and mixed in water for easier administration to young children without compromising the bioavailability of the drugs (in comparison to swallowing tablets whole), and linezolid is also available as a suspension for easier administration in children who are unable to swallow tablets.

Although children tend to tolerate treatment better than adults, the AEs associated with second-line anti-TB drugs remain significant for children, especially as they may be unable to adequately verbalize or describe the symptoms they experience. This underscores why shorter regimens and those involving fewer drugs, such as the BDLLfxC regimen, are particularly favored for children. However, it remains essential to stay vigilant about the potential adverse effects of these medications and to monitor children closely for any such reactions.

Peripheral neuropathy associated with linezolid is less commonly reported by children than adults, and severe myelosuppression may occur relatively quickly without any obvious symptoms, highlighting the importance of regular blood monitoring. Among all 30 child and adolescent participants enrolled on the BEAT Tuberculosis trial, there were three severe AEs related to linezolid (anaemia, peripheral neuropathy and optic neuritis). Compared with adults, children appear to experience more neuropsychiatric AEs related to delamanid; therefore, clinical monitoring should include regular assessment for persistent nightmares or night terrors with sleep disturbances *(46)*. In the BEAT Tuberculosis trial, none of the children enrolled in the study strategy discontinued delamanid due to neuropsychiatric AEs.

4.2.5 Implementation considerations

DST results

Although DST for FQ is strongly encouraged, initiation of MDR/RR-TB treatment is sometimes based on just a rifampicin-resistant DST result, and it may be the case that no further information on DST for other drugs is ever obtained. This may be due to limited diagnostics capacity, sample leakages, unsuccessful test results, or inability to perform DST on negative or contaminated TB cultures. In such cases, patients who fulfil other eligibility criteria for the 6-month regimens may initiate BDLLfxC and continue treatment with all five drugs. With increasing access to novel treatment regimens and the recent emergence of bedaquiline-resistant strains of MDR/RR-TB in some high TB burden settings *(47–49)*, wider access to more rapid diagnostics for timely detection of resistance to component drugs within the 6-month regimens is becoming more important. The 6-month BDLLfxC regimen is not considered effective and is not recommended for MDR/RR-TB with confirmed resistance to bedaquiline, linezolid, delamanid or clofazimine. Given the unavailability of DST in several settings or the considerable delay in obtaining DST results for these drugs, alongside the urgent need to initiate treatment early to reduce ongoing MDR/RR-TB transmission, NTPs are encouraged to use the results of surveillance testing to identify risk factors or groups of patients at increased risk of harbouring bedaquiline-resistant strains, and provide a framework for appropriate management of such patients.

History of exposure to component drugs

A thorough history of prior anti-TB treatment, as well as extent of exposure to people with confirmed MDR/RR-TB (and their full drug susceptibility profile), is necessary to assess an individual's risk of potential exposure to, or acquisition of, MDR/RR-TB with additional drug resistance. This is especially important in people initiating MDR/RR-TB treatment without confirmation of the full drug susceptibility profile of the infecting *Mtb* strain; for example, in people diagnosed with RR-TB and no further DST results, and in children with a clinical diagnosis of MDR/RR-TB disease. Prior exposure to bedaquiline, delamanid, linezolid or clofazimine for more than 1 month, particularly in a recent treatment episode

that was interrupted or failed, signifies a potentially increased risk of that person harbouring more extensively resistant MDR/RR-TB strains.

Management of anaemia and myelosuppression

The risk of myelosuppression associated with even relatively short exposures to linezolid is a significant concern in patients with anaemia at the time of MDR/RR-TB treatment initiation. Patients with TB often have anaemia of chronic disease, and iron deficiency is common in children with malnutrition. Pregnant women with TB are likely to be anaemic (for multiple reasons) before starting treatment. Therefore, pretreatment assessment of Hb, neutrophils and platelets is crucial in patients considering treatment with linezolid-based regimens. Children with a low baseline Hb are at risk of developing severe linezolid-induced haematological toxicity *(50)*. The 6-month BDLLfxC regimens may not be suitable for patients with a pretreatment serum Hb level below 8 g/dL. Blood transfusions can be beneficial in quickly correcting Hb levels before starting MDR/RR-TB treatment, enabling the initiation of linezolid. The acceptability and availability of blood transfusion in various settings must be taken into consideration and balanced alongside the risks and benefits of treating with shorter, linezolid-containing regimens. Treatment with an effective MDR/RR-TB regimen (even including linezolid) usually leads to improvement or resolution of anaemia once the disease is properly treated and the patient's appetite improves. Regular blood tests are necessary to monitor for linezolid-induced myelotoxicity; this may be challenging, especially in younger children, and health care providers could consider alternative feasible options for monitoring (e.g. rapid Hb tests on heelstick samples).

Blood transfusions during treatment may or may not be helpful in situations where Hb drops significantly owing to linezolid toxicity. The effects of a blood transfusion to correct linezolid-induced anaemia are often transient if exposure to linezolid is ongoing; however, a transfusion might assist a patient in completing at least the first 2 months of linezolid and may also help to avoid the person having to switch to a longer regimen. Aside from blood transfusions, it may be possible to manage linezolid-induced anaemia by pausing the drug for short periods (7–14 days) or reducing the dose of linezolid (although this is not recommended in patients weighing over 50 kg). In the BEAT-India study, where adults with pre-XDR-TB were treated with the 6-month BDLC regimen, patients were initiated on linezolid at a dose of 600 mg once daily; 100 (60%) of the 165 patients in this cohort had a BMI of less than 18.5 kg/m^2. The drug dose was reduced to 300 mg daily in 45 patients experiencing linezolid-induced severe AEs, following a temporary pause in linezolid dosing, and 40 of these 45 patients went on be cured of their disease. The approach to linezolid toxicity management in the BEAT Tuberculosis trial in South Africa, where 10% of participants receiving linezolid in the study strategy experienced severe anaemia (Hb <8 g/dL) *(51)*, was to withhold linezolid for a short period, rechallenge the drug at the same dose and transfuse the patient. Reduced doses of linezolid (<600 mg for adults) were not used in the BEAT Tuberculosis trial.

Owing to the morbidity associated with severe neutropenia and thrombocytopenia, the 6-month BDLLfxC regimen is also not suitable in patients with neutrophil levels of less than 750/mm3 or platelets below 150 000/mm3 before starting treatment. However, because these parameters may change quickly, it is advisable to repeat them before making a decision on withholding BDLLfxC.

QT-interval prolongation

The risk of QT-interval prolongation increases with exposure to an increasing number of QT-prolonging drugs in the regimen; hence, the risk is higher for patients receiving regimens containing bedaquiline and delamanid as well as clofazimine. Among these medicines, the effect of clofazimine appears to be the strongest, with a QT-interval change from baseline of almost 30 ms at currently recommended doses. The QT-prolonging effects of these drugs are likely to be additive in adults with normal baseline QT-interval values, and although the combination of these three drugs may not necessarily result in clinically significant QT-interval prolongation beyond 500 ms, patients receiving the BDLC or BDLLfxC regimens will have less leeway for further QT-interval variation. Therefore, patients with a QT

interval closer to 500 ms at baseline, or those with other risk factors for QT-interval prolongation (e.g. thyroid dysfunction, electrolyte disturbances, diabetes or concomitant use of other QT-prolonging medications) should be informed of their potentially higher risk of clinically significant QT-interval prolongation; such patients should receive closer ECG monitoring and have reversible causes of QT-interval prolongation corrected as soon as possible. Results from the BEAT-India study in India are encouraging; 165 adult participants received the 6-month BDLC regimen but none were reported to have QT-interval prolongation above 500 ms, despite some participants receiving higher (200 mg) daily doses of clofazimine *(45)*. The incidence of severe QT-interval prolongation also appears to be lower in children than in adults, possibly because of a combination of fewer cardiac comorbidities and exposure to relatively low anti-TB drug concentrations.

Treatment interruption

In the BEAT Tuberculosis trial in South Africa, patients on the study strategy whose treatment was interrupted for more than 4 consecutive weeks and who did not restart the 6-month BDLLfxC regimens were considered to be lost to follow-up. Treatment interruption over such a period increases the risk of selective drug pressure on MDR/RR-TB strains owing to the long half-life of bedaquiline (and, to some extent, clofazimine). Patients returning to care after 4 or more weeks of treatment interruption are likely to be at higher risk of harbouring further drug-resistant MDR/RR-TB strains, in which case the 6-month BDLLfxC regimen is inadequate. The risk of treatment failure is highest in patients without any evidence of sputum culture conversion before the period of interruption, and these patients require a different treatment regimen when they return to care.

Care and support

To ensure optimal efficacy of the BDLLfxC regimen, medications should preferably be administered with food, especially as this increases the bioavailability of some drugs (bedaquiline, delamanid, clofazimine). However, where possible, calcium-containing foods and supplements should be avoided for 2 hours before and after administration of levofloxacin because calcium binding renders the drug ineffective. People receiving the BDLLfxC regimen must be supported using a person-centred approach to ensure full adherence to treatment. The principles of person-centred care and support for people with TB are outlined in Chapter 3 of this handbook. Specific adherence challenges should be identified early in treatment, and locally feasible strategies employed to support patients at home and in their communities to complete the full duration of treatment; patients with such challenges should also be given information on appropriate treatment administration options. Child-friendly formulations of all drugs in the BDLLfxC regimen are available and should be procured and provided to all children with MDR/RR-TB.

Early counselling for patients and their treatment supporters should include information on potential side-effects that patients may experience with the BDLLfxC drugs, particularly the neuropsychiatric effects of delamanid in children (which may be alarming for parents) as well as the skin discolouration with clofazimine (which parents may not necessarily be expecting in infants exposed in-utero or while breastfeeding). In addition, patients (and their caregivers) initiating the 6-month regimens should be counselled before or early in treatment about the consequences of interrupting the 6-month BDLLfxC regimens, because subsequent treatment options when they return to care are likely to be more challenging in terms of toxicity and duration of treatment.

Cost–effectiveness analysis

Cost–effectiveness studies for the 6-month BPaL regimen and for the BDLC regimen in India (BEAT-India) demonstrated both regimens to be cost-saving compared with the longer MDR/RR-TB regimens, largely by virtue of the shorter duration of treatment with expensive medications. Although these findings may be roughly extrapolated to the 6-month BDLLfxC regimen, no cost–effectiveness analysis has been carried out specifically for the BDLLfxC regimens in South Africa.

5. Treatment of drug-resistant TB using 9-month regimens

This section refers to the treatment regimens for MDR/RR-TB that have standardized durations of 9 months with oral agents. Section 5.1 describes the seven-drug regimen, which utilizes linezolid or ethionamide, referred to as the "9-month regimen". Section 5.2 introduces a new set of three four- or five-drug regimens recently recommended by the WHO *(1)*, collectively referred to as the "modified 9-month regimens". All the 9-month regimens are administered orally.

Table 2.5.1. Overview of 9-month regimens

	Regimen	Duration	Core Drugs (months)	Variable/ Additional Drugs (months)	Key Features
Modified 9-month regimens (4–5 drugs)	9BLMZ	9 months	B, L, M, Z	-	All-oral regimen for fluoroquinolone-susceptible MDR/RR-TB.
	9BLLfxCZ		B, L, Lfx, Z	C	All-oral regimen for fluoroquinolone-susceptible MDR/RR-TB.
	9BLLfxDZ		B, L, Lfx, Z	D	All-oral regimen for fluoroquinolone-susceptible MDR/RR-TB.
9-month regimen (7 drugs)	**Ethionamide variation** 4–6 $B_{(6m)}$-Lfx/ M-C-Z-E-Hh-Eto / 5 Lfx/M-C-Z-E **Linezolid variation** 4–6 $B_{(6m)}$-Lfx/ M-C-Z-E-Hh-$L_{(2m)}$ / 5 Lfx/M-C-Z-E	9–11 months	B *(6)*, Lfx/M *(9–11)*, Z *(9–11)*, C *(9–11)*, E *(9–11)*, Hh *(4–6)*	Eto *(4–6)*, L *(2)*	All-oral regimen for fluoroquinolone-susceptible MDR/RR-TB. Ethionamide and linezolid are used for specific durations; duration depends on treatment response at month 4.

B: bedaquiline; C: clofazimine; D: delamanid; E: ethambutol; Eto: ethionamide; Hh: high-dose isoniazid; L: linezolid; Lfx: levofloxacin; M: moxifloxacin; Z: pyrazinamide.

5.1 The 9-month all-oral regimen for MDR/RR-TB

This section refers to a treatment regimen for MDR/RR-TB that has a duration of at least 9 months and uses a seven-drug, bedaquiline-containing combination that includes either linezolid or ethionamide. The GDG reviewed the evidence for this regimen during the 2019, 2020 and 2022 guideline updates. The recommendation in the consolidated 2025 guidelines *(1)* states:

No.	Recommendation
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. The 9-month all-oral regimen consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (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 treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).
2. A 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.
3. This recommendation applies to:
    a. people with MDR/RR-TB and without resistance to fluoroquinolones;
    b. patients without extensive TB disease and without severe extrapulmonary TB;
    c. patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;
    d. all people regardless of HIV status;
    e. children (and patients in other age groups) who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

In 2019, for the WHO guideline update, the South African Department of Health provided WHO with access to programmatic data on injectable-free regimens that had been used in South Africa since 2017, when most eligible patients were enrolled on a shorter regimen, with bedaquiline replacing the injectable. Since then, new data from patients receiving WHO-recommended shorter and longer MDR/RR-TB regimens have been incorporated into an individual patient dataset (IPD) in 2021; these data were presented to the GDG in 2022 to help inform the development of the updated WHO guidelines on DR-TB. In addition, routine data from the South African NTP were available to assess the 9-month all-oral regimen containing linezolid (600 mg daily) instead of ethionamide, for treatment of patients with FQ-susceptible MDR/RR-TB and without previous exposure to second-line TB drugs. The South African routine dataset of patients receiving the 9-month all-oral linezolid-containing regimen would also have excluded children aged below 6 years, as well as patients with extensive pulmonary TB disease and severe forms of extrapulmonary TB, because these patients were not considered eligible for this regimen under national DR-TB guidelines *(52)*. For the updated 2022 WHO guidelines, the 9-month linezolid-containing regimen used in South Africa was compared with the earlier dataset and the 2021 IPD from patients meeting the same eligibility criteria and who received

the WHO-recommended 9-month all-oral regimen containing ethionamide instead of linezolid, or the longer regimens designed based on the 2020 WHO recommendations.

Following review of the data presented, the GDG judged the benefits of the 9-month regimen with linezolid to be small and the undesirable effects to be moderate compared with the 9-month regimen with ethionamide. The certainty of evidence was judged to be very low. Based on this, the GDG judged that the balance of health effects does not favour either the 9-month regimen with linezolid or the 9-month regimen with ethionamide. Therefore, WHO has updated its conditional recommendation that, in eligible patients with MDR/RR-TB, the 9-month all-oral regimen may be used, and that 2 months of linezolid can be used as an alternative to 4 months of ethionamide within this shorter regimen *(1)*.

The implementation of these two variations of the 9-month all-oral regimen (i.e. including either linezolid for 2 months or ethionamide for 4 months) is to provide more flexible and effective treatment options for MDR/RR-TB. This regimen still requires combined use of seven agents (some with considerable toxicity), most of which will be continued for at least 9 months. Patients will need support to overcome the hardships associated with TB and its treatment, including daily adherence challenges, adverse drug reactions, indirect costs and stigma.

5.1.1 Eligibility

In settings where the 6-month MDR/RR-TB regimen is not yet available, or implementation of the regimen is not yet feasible, or for patients who are not eligible, selected patients with MDR/RR-TB may benefit from a 9-month all-oral regimen. Several eligibility criteria must be considered for this regimen, with additional considerations for the use of linezolid instead of ethionamide.

The 9-month all-oral regimen (with either ethionamide or linezolid) may be offered to the following patients with MDR/RR-TB (where resistance to at least rifampicin has been confirmed and resistance to FQ has been ruled out):

- those with no documented resistance or suspected ineffectiveness of bedaquiline, clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen);
- those with no exposure to previous treatment with bedaquiline, FQ,[19] clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen) for more than 1 month – when prior drug exposure is greater than 1 month, patients may still receive this regimen if resistance to the specific medicine with such exposure has been ruled out;
- those with no extensive or severe TB disease[20] and no severe extrapulmonary TB;[21]
- all people living with or without HIV;
- women who are pregnant or breastfeeding: and
- children and adults without bacteriological confirmation of TB or resistance patterns but who require MDR/RR-TB treatment based on clinical signs and symptoms of TB (including radiological findings) and history of contact with someone with confirmed MDR/RR-TB: these patients may be eligible for this regimen based on the drug resistance profile of the isolate obtained from the most likely index case.

Linezolid is associated with considerable toxicity, which necessitates close monitoring for signs of bone marrow suppression and neuropathies. Optic neuritis and peripheral neuropathies tend to be reported beyond 2 months of treatment with linezolid, whereas myelosuppression is significantly dose dependent and is more likely to occur during the first 2 months of exposure to the drug *(53, 54)*. Nevertheless, linezolid is far more effective than ethionamide and helps to maintain a relatively effective regimen, particularly in cases of MDR/RR-TB where phenotypic DST results are awaited to

[19] This includes exposure to FQs as either treatment or prevention of MDR/RR-TB.

[20] See Definitions section.

[21] See Definitions section.

confirm FQ susceptibility. Therefore, the 9-month all-oral regimen containing linezolid (instead of ethionamide) should be offered wherever possible to patients who fulfil the eligibility criteria above, as well as the following:

- serum Hb above 8 g/dL, neutrophils above 750 mm^3 and platelets above 150 000/mm^3 at the start of treatment; and
- no evidence of severe peripheral neuropathy, or any sign or suspicion of optic neuritis, at the start of treatment.

The 9-month all-oral regimen with ethionamide instead of linezolid, or a longer regimen without linezolid, may be more appropriate options for patients with very low Hb, neutrophils or platelets, severe peripheral neuropathy or concerns regarding vision. Mild or moderate peripheral neuropathy (Grade 1 or 2) may also be sufficient reason to offer a 9-month regimen that uses ethionamide, based on the patient's preference after discussing the risks and benefits of not including linezolid. However, the ethionamide-containing regimen must be avoided during pregnancy. The decision regarding which regimen offers the best option for cure in a patient may also depend on other considerations; for example, preferences of patients and clinicians, pill burden, drug formulations, regional DRS data, feasibility of monitoring for drug adverse effects, and availability of blood transfusion services or ophthalmology services, if required.

5.1.2 Composition, dosing and duration of the regimen

The two variations of the 9-month all-oral MDR/RR-TB regimen recommended by WHO *(1)* are described below.

Ethionamide variation

The ethionamide variation involves the initiation of bedaquiline, levofloxacin/moxifloxacin, clofazimine, ethionamide, ethambutol, isoniazid (high dose) and pyrazinamide. All seven drugs are given for 4 months, with the possibility of extending to 6 months if the patient's sputum remains bacteriologically positive at the end of the fourth month on treatment. Ethionamide and high-dose isoniazid are dropped after 4 or 6 months, depending on the decision to extend treatment based on smear status at month 4 of treatment. This is followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. Bedaquiline is usually given for 6 months but could be extended to 9 months, particularly if the initial phase is extended from 4 to 6 months due to a lack of sputum conversion at month 4.

The regimen is summarized as:

4–6 $B_{(6\ m)}$-Lfx/M-C-Z-E-Hh-Eto / 5 Lfx/M-C-Z-E

Initial phase: **4–6 $B_{(6\ m)}$-Lfx/M-C-Z-E-Hh-Eto**

Continuation phase: **5 Lfx/M-C-Z-E**

B: bedaquiline; C: clofazimine; D: delamanid; E: ethambutol; Eto: ethionamide; Hh: high-dose isoniazid; L: linezolid; Lfx: levofloxacin; M: moxifloxacin; Z: pyrazinamide.

Linezolid variation

The linezolid variation involves initiation of bedaquiline, linezolid, levofloxacin/moxifloxacin, clofazimine, ethambutol, isoniazid (high dose) and pyrazinamide. Linezolid is only given for the first 2 months of treatment. Clinical and haematological monitoring are crucial to detect early linezolid-associated AEs, particularly haematological events (sudden or significant drop in Hb, neutrophils or platelets). After

the initial 2 months, the remaining six drugs are given for another 2 months (with the possibility of extending by an additional 2 months if the patient's sputum remains bacteriologically positive at the end of the fourth month on treatment). High-dose isoniazid is dropped after 4 or 6 months, depending on the decision to extend treatment based on smear status at month 4 of treatment. This is followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. Bedaquiline is usually given for 6 months but could be extended to 9 months, particularly if the initial phase is extended from 4 to 6 months due to a positive sputum smear result at month 4.

The regimen is summarized as:

4–6 $B_{(6\ m)}$-$L_{(2\ m)}$-Lfx/M-C-Z-E-Hh / 5 Lfx/M-C-Z-E

Initial phase: **4–6 $B_{(6\ m)}$-$L_{(2\ m)}$-Lfx/M-C-Z-E-Hh**

Continuation phase: **5 Lfx/M-C-Z-E**

B: bedaquiline; C: clofazimine; D: delamanid; E: ethambutol; Eto: ethionamide; Hh: high-dose isoniazid; L: linezolid; Lfx: levofloxacin; M: moxifloxacin; Z: pyrazinamide.

Choice of fluoroquinolone

In terms of choice of FQ, either levofloxacin or moxifloxacin may be used in the 9-month all-oral regimen, because they have shown similar efficacy for treating MDR/RR-TB. Although levofloxacin results in a higher pill burden, it is often preferred because moxifloxacin is associated with a higher risk of QT interval prolongation *(55)*. Clinically significant, severe QT interval prolongation is relatively uncommon among patients treated with the 9-month all-oral regimens. However, the additive effect of co-administration of other QT-prolonging drugs (i.e. bedaquiline and clofazimine) within the shorter regimen should be considered when deciding on an appropriate regimen for individual patients with other risk factors for cardiotoxicity.

Dosing and frequency

The dosages of all drugs included in both variations of the 9-month all-oral regimen are outlined in the **Annex 4**. Most drugs, except for bedaquiline, are administered once a day, 7 days per week. In the 9-month regimen, bedaquiline is initially administered daily, with a higher loading dose for the first 2 weeks, followed by a lower maintenance dose on 3 days a week (with at least 48 hours between doses) thereafter. Alternatively, daily dosing of bedaquiline can also be considered. If one dose of bedaquiline is missed in the 2-week loading phase, the missed dose does not have to be made up and the patient can continue on the daily dosing schedule. If a dose of bedaquiline is missed in the maintenance phase but is remembered within that 48-hour dosing period, the dose should be administered as soon as possible, and the following dose adjusted to be taken 48 hours later, with resumption of the usual thrice-weekly dosing schedule thereafter. For example, if bedaquiline is dosed every Monday, Wednesday and Friday, then if the Wednesday dose is missed it can still be taken on Thursday, and then the following dose should be taken on Saturday, with a return to the usual dosing schedule on Monday. If bedaquiline is interrupted for more than 2 weeks (but <8 weeks) during the maintenance phase of dosing, the drug should be reloaded at the higher daily dose for 7 days before resuming the thrice-weekly dosing schedule. If bedaquiline is interrupted for less than 2 consecutive weeks during the maintenance phase, no reloading is required. If bedaquiline is interrupted for more than 8 consecutive weeks, then the patient and treatment plan should be reassessed because the patient will no longer be eligible to continue or restart the 9-month all-oral regimen.

5.1.3 Modifications of treatment

The 9-month all-oral MDR/RR-TB regimen should be implemented as a standardized package. It is not advisable to change the composition of the regimen or the duration of either the initial or continuation phase, with a few exceptions, as follows:

- Bedaquiline is usually given for 6 months but may be extended to 9 months if the initial phase of the regimen is extended from 4 to 6 months because of positive sputum smears at month 4 of treatment.
- Linezolid is only given for 2 months (instead of 4–6 months of ethionamide). If occasional doses of linezolid are missed during that time, the missed doses can be added on to the end of the 2-month period if the patient is tolerating the drug well; however, once FQ resistance has been definitively ruled out, it may not be strictly necessary to make up the missed doses. The linezolid dose should not be reduced to less than the recommended dose to reduce the severity of adverse effects. If the full dose of linezolid (600 mg in adults) is not tolerated for the first full 2 months of treatment (apart from occasionally missed doses, which can be added to the end of the 2-month period), then the patient must either switch to an ethionamide-containing 9-month regimen (provided FQ susceptibility is confirmed and the patient is not pregnant) or to an individualized longer regimen without linezolid. In selected cases where the risk of undetected resistance to FQ and other second-line TB drugs is very low and the patient is unable to tolerate linezolid but would greatly benefit from a shorter regimen (e.g. migrant populations and children), the treating clinician may, after weighing up the risks and benefits, choose to stop linezolid before 2 months and continue the 9-month all-oral regimen, with close monitoring for relapse or recurrence.
- Prothionamide may be used instead of ethionamide.
- Moxifloxacin may be used instead of levofloxacin, provided close ECG monitoring is feasible (should this be required).
- If, for any reason, a patient is unable to tolerate pyrazinamide or ethambutol within the 9-month regimen, then one (but only one) of these drugs may be dropped during the continuation phase without necessitating a switch to a longer regimen. If two or more of these drugs are not tolerated within the 9-month regimen, the treatment will have to switch to a longer regimen. If any of the other drugs within the 9-month regimen (bedaquiline, levofloxacin/moxifloxacin, linezolid/ethionamide or clofazimine) are stopped early because of toxicity or intolerance then the patient will also have to switch to a new regimen. Patients switching to a new regimen due to toxicity or intolerance need to be reported as "treatment failed" (**Section 10, Chapter 1**).
- At the fourth month of treatment on the 9-month regimen, the decision to extend the initial phase from 4 to 6 months is based on the bacteriological sputum smear status of the patient's sputum specimen. If the specimen is smear negative at month 4 (regardless of smear status at the start of treatment), the patient may move to the continuation phase of treatment. If the specimen is smear positive at month 4, the initial phase is prolonged to 6 months. The duration of the continuation phase remains fixed at 5 months.
- At the sixth month of treatment, the culture result from the specimen taken at month 4 and possibly month 5 should be available, as well as the smear results from the specimens taken at months 5 and 6. If the culture from the 4-month specimen is positive for *Mtb*, the clinician should undertake a full work-up to assess for the risk of treatment failure – this involves a comprehensive clinical assessment, review of treatment adherence to address specific challenges, radiological assessment and collection of another respiratory sample for bacteriological assessment, as well as repeat DST of the most recent positive culture to test for emerging resistance to second-line TB drugs. Similarly, if the month 5 and 6 culture results remain persistently positive, treatment failure should be suspected, particularly if the patient has had suboptimal adherence to treatment or shows other signs of poor clinical or radiological response to treatment.

Discontinuation and change to another treatment regimen

If a patient starts the 9-month all-oral MDR/RR-TB regimen but is later found to be ineligible following detection of *Mtb* resistance to FQ, the patient must change to a different regimen. Such patients might be eligible for a 6-month BPaL or BDLC regimen if their prior exposure to bedaquiline and linezolid was for less than 1 month and there is no demonstrated resistance to any components of the BPaL or BDLC regimen. The BPaL regimen may only be considered if the patient meets the eligibility criteria and the regimen is available and feasible in the setting. In cases where an eligible patient starts the 9-month all-oral MDR/RR-TB regimen but additional resistance is detected later in treatment (after initial DST indicated susceptibility to Group A and B drugs), it can be assumed that further acquisition of resistance may have emerged during that period of drug exposure; such patients should be considered for a treatment outcome of failure and should not continue with the 9-month regimen. The 6-month BPaL or BDLC regimen should not be offered to these patients because amplification may have occurred to linezolid and bedaquiline, key drugs in both the BPaL and BDLC regimens. The patient should switch to a longer individualized regimen, with repeated phenotypic DST to guide the composition of the longer regimen.

Patients who start a 6-month BPaLM or BDLLfxC regimen may change to the 9-month all-oral regimen, if required, provided they meet the necessary eligibility criteria for the 9-month regimen. This may be warranted when toxicity to linezolid develops early in the BPaLM or BDLLfx regimen and necessitates a linezolid-sparing regimen, such as the 9-month regimen with ethionamide.

Patients who start on a longer regimen but are subsequently found to be eligible for the 9-month all-oral regimen may change to the 9-month regimen if this is done within the first month of starting treatment. There is little experience in changing from longer to shorter regimens in this way; hence, clinical monitoring and adequate data collection are important to inform future treatment recommendations.

5.1.4 Key subgroups

People living with HIV

The 9-month all-oral MDR/RR-TB regimen was evaluated in a setting with a high HIV prevalence. In the dataset analysed for the 2022 WHO guidelines, over 70% of patients starting a shorter regimen were also living with HIV, and among those, more than 90% were receiving ART. A 9-month all-oral regimen is expected to perform similarly in PLHIV who initiate ART early, in accordance with WHO recommendations. However, clinicians should be mindful of the overlapping, additive toxicities and potential DDIs with ARV medicines and TB drugs. Co-administration of zidovudine and linezolid should be avoided because of the increased risk of myelosuppression. Boosted protease inhibitors can increase bedaquiline exposure, thereby increasing the risk of bedaquiline-related adverse drug reactions (e.g. QT interval prolongation), which may require closer monitoring. Efavirenz can reduce the concentration of bedaquiline; therefore, this antiretroviral drug should be avoided in patients receiving the 9-month all-oral regimen. There are no overlapping toxicities or DDIs with dolutegravir in patients receiving the shorter regimen with either linezolid or ethionamide. PLHIV receiving the 9-month all-oral regimen will need prophylactic medication for opportunistic infections, support for adherence to TB and antiretroviral medication, and close monitoring of the biomarkers of immune status.

Children

Although only six patients aged below 14 years were included in the analysis of the shorter regimen dataset from South Africa, the evidence supporting the use of this regimen in adults may be extrapolated to younger patients, provided the implementation considerations are followed. The benefits of a shorter regimen for a child with MDR/RR-TB should be weighed against the high pill

burden and the difficulties of administering each of the seven drugs in this regimen, particularly if child-friendly formulations of the drugs are not available. Bedaquiline is relatively well tolerated and easy to administer to children; adult-formulation bedaquiline tablets suspended in water have been shown to have the same bioavailability as tablets swallowed whole (**Annex 4**).

Aside from bedaquiline, the medicines that compose the 9-month all-oral regimen have been part of MDR/RR-TB regimens for many years, in similar combinations, for both adults and children. The associated adverse drug reactions have been widely described and the drug dosages established (**Annex 4**). Child-friendly formulations are now available for all second-line drugs and should be provided to children whenever possible. When these are not available, practical instructions for use of adult formulations for administration are available, so lack of formulation should not be a hindrance to treating children of all ages. This must be addressed as a priority by treatment programmes that include management of children with MDR/RR-TB.

With dosing and safety data available for use of bedaquiline in children aged below 6 years, the removal of the age restriction for the use of bedaquiline means that children of all ages with MDR/RR-TB may be offered the 9-month all-oral regimen if they meet the eligibility criteria *(56)*. Extent of disease is defined slightly differently for children than for adults, and most children with TB have less severe forms of the disease than adults.

Evidence from the SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children), which was the first and only large Phase 3 trial to evaluate the duration of TB treatment in children with non-severe drug-susceptible TB (DS-TB), suggests that pulmonary TB disease should be classified as severe (which may include extensive, advanced and complicated disease) or non-severe in children *(56)*. Despite the lack of comparable data among children with MDR/RR-TB disease specifically, the same definitions for severity of disease are likely to be appropriate when considering the use of a shorter regimen for children with MDR/RR-TB. Non-severe disease in children is defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion (without empyema or pneumothorax); or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern (evaluated on chest X-ray) *(56)*.

Bacteriological confirmation of MDR/RR-TB disease in younger children is relatively uncommon, and the decision to treat for MDR/RR-TB may rely on clinical signs and symptoms, radiological findings and significant exposure to someone with microbiologically confirmed MDR/RR-TB. In children without microbiological confirmation of TB disease or rifampicin resistance, the choice of regimen relies partly on the drug-resistance pattern of the isolate obtained from the most likely index case.

For most second-line TB drugs, adverse effects appear to be less frequent in children than in adults; however, close monitoring is still warranted in children, regardless of the regimen. Before a shorter regimen containing linezolid is offered to a child, the clinician must consider the feasibility of close monitoring, particularly for haematological side-effects, which requires repeated blood draws for at least the first 2 months of treatment. Visual acuity and colour vision are more difficult to monitor in younger children than in older children and adults. Ethionamide might be considered a safer alternative for children in some settings, but this should be balanced against the lower efficacy of the drug compared with linezolid, and the poor gastrointestinal tolerability and need to monitor for hypothyroidism.

Pregnant and breastfeeding women

Dosing and safety data to support the optimal use of second-line TB medicines during pregnancy are generally sparse. There have been case reports and observational data reporting successful treatment and pregnancy outcomes among women who received treatment (including bedaquiline-containing regimens) for MDR/RR-TB during pregnancy and postpartum, but pregnant and breastfeeding women are usually excluded from clinical drug trials and early access programmes. Even less is known about the effects of MDR/RR-TB treatment on the infant in-utero and after birth; however, in general, the

benefits (to both parent and child) of providing effective MDR/RR-TB treatment to the parent far outweigh the potential risks posed to the fetus in-utero or the breastfed infant.

Ethionamide is usually contraindicated in pregnancy because animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans. The physiologic effects of pregnancy, which lead to a relatively low Hb (due to the dilutional effect of increased blood volume) and a higher risk of peripheral neuropathies, may be exacerbated by the adverse effects of linezolid. Nevertheless, the 9-month all-oral regimen including linezolid instead of ethionamide may be considered for pregnant and breastfeeding patients who meet the eligibility criteria for the shorter regimen with linezolid, although closer monitoring is required.

More compelling evidence on the dosing and safety of specific anti-TB drugs among pregnant and breastfeeding women is needed to guide decision-making on the most appropriate regimen for treatment of MDR/RR-TB during pregnancy and postpartum. In addition, this population group requires considerable adherence support and monitoring of proper administration of MDR/RR-TB treatment, along with other chronic medications, to ensure successful treatment outcomes and minimal risk of TB transmission from mother to infant postpartum. Care providers must also pay particular attention to seamless continuity of care between antenatal and TB services, which are rarely integrated in most TB-endemic settings.

Extensive TB disease

Extensive (or advanced) TB disease in adults is defined as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In patients aged below 15 years, extensive (or advanced) disease is usually defined by the presence of cavities or bilateral disease on chest radiography. This highlights the importance of chest radiography as part of the diagnostic work-up for patients, along with the usual patient–clinician interaction. Patients with extensive MDR/RR-TB disease should not be treated with the 9-month all-oral regimen with either linezolid or ethionamide because of the lack of evidence on the impact of this regimen in this subgroup of patients.

Older patients

TB-related morbidity and mortality tends to be higher among older people than in the younger population. Patients aged 65 years and older with MDR/RR-TB are more vulnerable to the adverse effects of TB medications owing to physiological changes of ageing (e.g. increase in QT interval and decrease in estimated GFR [eGFR]), other comorbidities and overlapping, additive drug toxicities (owing to a higher likelihood of polypharmacy in older people). Advanced age has also been reported as a risk factor for linezolid-induced anaemia *(57)*. Whereas the 9-month all-oral regimen may be offered to eligible patients of any age, older people may require closer monitoring for drug-related AEs as well as closer adherence support and assistance to administer treatment daily or as prescribed.

Extrapulmonary TB

The dataset evaluated for the 2022 WHO guidelines included patients with uncomplicated extrapulmonary MDR/RR-TB disease. No evidence was available to discern the impact of the 9-month all-oral regimen with either linezolid or ethionamide in patients with severe extrapulmonary TB (defined in this document as the presence of miliary TB or TB meningitis). Although this definition does not specifically include osteoarticular or pericardial TB, a longer treatment regimen may be more suitable in these cases of extrapulmonary TB because of the relatively poor perfusion of TB drugs into the pericardial space and the lack of data on the efficacy of shorter MDR/RR-TB regimens in these cases. The 9-month all-oral regimen should not be offered to patients with severe or complicated extrapulmonary MDR/RR-TB disease. In children, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without airway compression) are considered severe *(56)* and may not be adequately treated with the 9-month all-oral regimen.

Patients with co-morbidities (other than HIV)

Patients with diabetes mellitus

The 9-month all-oral regimen may be used to treat MDR/RR-TB in patients with diabetes; however, there are currently no data on safety and outcomes of this regimen in this specific group. Type 2 diabetes is associated with several liver disorders; therefore, it is prudent to monitor closely for hepatotoxicity among these patients. Blood sugar levels may be difficult to control in patients with MDR/RR-TB and diabetes, and insulin may be required to gain adequate blood sugar control during treatment. Patients with diabetes are also at increased risk of peripheral neuropathies, which may be further exacerbated following exposure to linezolid and high doses of isoniazid. These patients must be counselled to report symptoms of peripheral neuropathies early because such symptoms may necessitate a change in regimen – either to the ethionamide-containing 9-month regimen (bearing in mind this will still include high doses of isoniazid in the initial phase), or a longer individualized regimen without linezolid.

Patients with hepatic dysfunction

The 9-month all-oral regimen may not be the most appropriate option for people with CLD because this regimen contains several potentially hepatotoxic drugs (e.g. pyrazinamide, isoniazid and ethionamide). Although this regimen may still be offered with close monitoring of liver enzymes in people with chronic stable liver dysfunction, a longer regimen with fewer hepatotoxic drugs may be preferable in some settings where closer monitoring is not feasible.

Patients with renal failure

The 9-month all-oral regimen may be used to treat MDR/RR-TB in patients with renal failure provided the dose or dosing interval of renally excreted drugs are adjusted for the patient's creatinine clearance. Levofloxacin (but not moxifloxacin), ethambutol and pyrazinamide require dose or frequency adjustment for adults with creatinine clearance of less than 30 mL/min. Treatment does not have to be extended unless indicated by lack of smear conversion at month 4 of treatment, as for patients with normal renal function.

Patients with anaemia

Patients with TB commonly have anaemia of chronic disease *(58)*, and treatment with an effective drug regimen (even one that includes linezolid) may lead to improvement or resolution of the anaemia once the disease is properly treated. Many patients with TB also suffer with nutritional deficiencies, and low Hb may also be a result of iron deficiency and low iron stores *(59)*. This deficiency may resolve naturally once effective TB treatment (even including linezolid) leads to resolution of TB symptoms and improvement in the patient's diet and appetite. Extended use (≥2 weeks) of linezolid has been associated with reversible myelosuppression *(60)*. Therefore, the linezolid-containing 9-month regimen must not be offered to patients with a pretreatment serum Hb below 8 g/dL that cannot be rapidly corrected (i.e. with blood transfusions) before starting MDR/RR-TB treatment. Similarly, owing to the morbidity associated with severe neutropenia and thrombocytopenia, the linezolid-containing 9-month regimen is not suitable in patients with neutrophils below 750/mm^3 or platelets below 150 000/mm^3 before starting treatment. Some patients respond well to an initial blood transfusion that raises their Hb above 8 g/dL and allows them to at least start a linezolid-containing regimen – linezolid will not necessarily cause myelosuppression in patients with baseline anaemia, although a baseline Hb below 10.5 g/dL has been reported as a risk factor for linezolid-induced anaemia *(57)*. It is not uncommon for Hb to drop again shortly after blood transfusion in a person with untreated chronic TB disease, but the temporary increase in Hb may allow enough time for a linezolid-containing

regimen to be effective in treating the TB disease, and the patient's Hb is likely to improve as the disease is brought under control.

Blood transfusions may not be a lasting solution in situations where Hb drops significantly from baseline because of linezolid toxicity when linezolid is continued. Although blood transfusions may help to reverse anaemia following withdrawal of linezolid, they may not resolve linezolid-induced myelosuppression with ongoing exposure to the drug. Therefore, if linezolid toxicity leads to a drop in Hb below 8 g/dL during the first 2 months of treatment, linezolid should be withdrawn and the regimen switched appropriately. More research is needed on the role of iron supplementation to treat anaemia during MDR/RR-TB treatment; however, oral supplementation of iron is often not well tolerated and is not immediately effective at the start of treatment, at a time when the pill burden can be overwhelming and the risk of multiple drug side-effects is high.

5.1.5 Implementation considerations

DST results

The 9-month all-oral regimen is not adequate for the treatment of patients with pre-XDR-TB or XDR-TB; it is also not adequate to treat MDR/RR-TB that has both *inh*A and *kat*G mutations. Therefore, DST is recommended at or before the start of this regimen to exclude resistance to at least FQ and to determine the mutations conferring resistance to isoniazid.

There are rapid DST methods available for pyrazinamide (LPA, targeted NGS), bedaquiline, clofazimine and linezolid (targeted NGS), which should be performed where available before start of the 9-month regimen. In addition, the critical concentrations for MGIT have been established, enabling NTPs to perform phenotypic DST. If resistance to these drugs is detected , the 9-month regimen should not be offered, or the patient must switch to a longer individualized treatment regimen. In the absence of DST for bedaquiline, linezolid and clofazimine, treatment decisions will rely on the likelihood of effectiveness of these medicines, based on an individual patient's clinical history and surveillance data from the country or region. This should be considered a last resort and an interim measure until the capacity for DST for these drugs becomes available.

Ideally, molecular (genotypic) DST (targeted NGS) for clofazimine, linezolid and bedaquiline should be performed at the time of treatment initiation. However sensitivity of this method for above-mentioned three drugs is suboptimal, that is why if negative results is obtained, but resistance in a particular patient is suspected, phenotypic, culture-based DST still should be performed. Further details on treatment modifications and follow-on DST for MDR/RR-TB patients based on results from targeted NGS can be found in operational handbook in *Module 3: Diagnosis – rapid diagnostics for tuberculosis detection (11)*.

The low-complexity automated nucleic acid amplification test (Xpert MTB/XDR) detects mutations associated with resistance to isoniazid, FQ, second-line injectable drugs and ethionamide in a single test and can be used in the decentralized settings. The targeted NGS solutions can detect resistance in rifampicin, isoniazid, pyrazinamide, ethambutol, FQ, bedaquiline, linezolid, clofazimine, amikacin and streptomycin, but only can be used in centralized, reference setting.

The first and second-line LPAs, are widely used to detect mutations conferring resistance to isoniazid, rifampicin, FQ, amikacin, as well as pyrazinamide; however, in future this test may be replaced by the Xpert MTB-XDR assay and/or targeted NGS in some settings.

In settings without access to the Xpert MTB-XDR cartridge, an LPA (MTBDR*plus*) can be used to detect the two most common mutations that confer resistance to isoniazid. These mutations are found in the *inh*A promoter and *kat*G regions, and they confer resistance to isoniazid at different levels. Low-level isoniazid resistance is conferred when only *inh*A mutations are present, and high-level resistance is conferred when mutations in the *kat*G gene are present. Mutations at the *inh*A

promoter region are also associated with resistance to ethionamide and prothionamide. High doses of isoniazid (15–20 mg/kg) are generally considered to be effective in the presence of low-level isoniazid resistance when used as part of combination therapy, but the efficacy of high doses of isoniazid in the presence of *kat*G mutations remains unclear. Nevertheless, high-dose isoniazid is always included in the 9-month all-oral regimen if either (but not both) of the mutations is present. The presence of mutations in both regions (i.e. *inh*A promoter and *kat*G genes) suggests that neither isoniazid at a high dose nor thioamides may be effective and therefore the 9-month all-oral regimen is not appropriate in these cases. In the South African setting, the detection of both mutations in MDR-TB strains was considered a surrogate marker for more extensive drug resistance at the time that the 9-month linezolid-containing regimen was introduced. Patients in South Africa who had MDR-TB with both mutations were not considered eligible for the 9-month regimen, and so were not included in the routine dataset presented to the GDG for review. Thus, the efficacy of the 9-month regimen in such cases is largely unknown. In the absence of information on isoniazid resistance or mutation patterns in the case of an individual patient, knowledge of the prevalence of both mutations among locally circulating RR-TB strains (e.g. from DRS in the relevant epidemiological setting) may also inform decisions as to which treatment regimen would be most appropriate. DST for ethambutol is not carried out routinely in most settings. Results of DST for ethambutol and pyrazinamide do not affect eligibility for the 9-month all-oral regimen.

The 9-month regimen is standardized and all seven drugs (including either ethionamide or linezolid) should be initiated from the outset. Pyrazinamide and ethambutol are inexpensive and generally well tolerated, and they may still be efficacious against MDR/RR-TB in people who are eligible for this regimen. However, some health care providers and patients, particularly children and their caregivers, might find the high pill burden posed by these medicines challenging despite the shorter duration of this treatment regimen.

Results of DST should not delay the start of an appropriate MDR/RR-TB treatment regimen, particularly if DST relies on phenotypic methods *(61, 62)*. **Box 2.5.1** and **Box 2.5.2** below provide examples of clinical scenarios and appropriate choices of regimens.

TB programmes must rapidly build the capacity to undertake DST, and all efforts must be made to ensure access to approved tests. If routine genotypic and phenotypic DST for clofazimine, linezolid and bedaquiline is not feasible for all patients diagnosed with MDR/RR-TB, then DST for these drugs must be prioritized for patients with positive TB sputum cultures at month 4 of treatment or beyond. Delayed conversion to negative cultures, or reversion to positive cultures, after 4 months of MDR/RR-TB treatment may be an early indication that treatment is failing, and clinicians must consider the possibility of acquired drug resistance *(63)*.

Box 2.5.1. Regimen selection at RR-TB diagnosis – no initial linezolid contraindications

Patient presents with signs and symptoms of TB disease and no previous treatment with second-line TB drugs, no extensive or severe pulmonary disease, no severe extrapulmonary TB, and no contact with pre-XDR-TB or XDR-TB; thus, there are **no contraindications to linezolid**.

➔ Diagnosis of RR-TB only or RR-TB with isoniazid susceptibility, pending results of FQ DST. This patient could start both versions of the 9-month regimen but the version with linezolid would be preferred if no inference can be made about resistance to ethionamide.

- This patient has the option to switch from the linezolid-containing regimen to the ethionamide-containing regimen if preferred (and if not pregnant) once FQ susceptibility is confirmed on DST and if no mutation was detected in the *inh*A promoter region.

➔ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *inh*A promoter region only, and pending results of FQ DST or susceptibility to FQs is confirmed. This patient could start the 9-month regimen with linezolid (but not with ethionamide owing to the *inh*A mutation).

➔ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *kat*G gene only, and pending results of FQ DST. This patient could start the 9-month regimen with linezolid (but preferably not with ethionamide) while DST results are awaited.

- This patient has the option to switch from the linezolid-containing regimen to the ethionamide-containing regimen if preferred (and if not pregnant) once FQ susceptibility is confirmed.

➔ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *kat*G gene only and confirmed susceptibility to FQs. This patient could start the 9-month regimen with either ethionamide (if not pregnant) or linezolid.

Box 2.5.2. Regimen selection at RR-TB diagnosis – linezolid contraindications

Patient presents with signs and symptoms of TB disease and no previous treatment with second-line TB drugs, no extensive or severe pulmonary disease, no severe extrapulmonary TB, and no contact with pre-XDR-TB or XDR-TB, but **with contraindications to linezolid**.

- ➔ Diagnosis of RR-TB only, or RR-TB with isoniazid susceptibility, pending results of FQ DST. This patient could start a longer regimen initially, but with the option to switch to a 9-month regimen with ethionamide (not linezolid because contraindicated) within the first month of treatment once FQ susceptibility is confirmed on DST, no mutation is detected in the *inh*A promoter region and the patient is not pregnant.
- ➔ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *inh*A promoter region only, and pending results of FQ DST or susceptibility to FQs is confirmed. This patient should preferably not receive the 9-month regimen with either ethionamide (owing to the *inh*A mutation) or linezolid (contraindicated) and should instead be considered for a longer regimen.
- ➔ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *kat*G gene only, and pending results of FQ DST. This patient could start a longer regimen initially while DST results are awaited, but with the option to switch to a 9-month regimen with ethionamide (not linezolid because contraindicated) if FQ susceptibility is confirmed and the patient is not pregnant.
- ➔ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *kat*G gene only and confirmed susceptibility to FQs. This patient is eligible to start the shorter regimen with ethionamide (not linezolid) if not pregnant.

Assessment of extent and severity of TB disease

The extent of a patient's TB disease is important in determining appropriate regimen options, in addition to the drug susceptibility of the *Mtb* and other considerations mentioned above. Patients with extensive disease are not eligible for the 9-month all-oral regimen with either linezolid or ethionamide.

Patients with severe extrapulmonary MDR/RR-TB are not eligible for a 9-month regimen with either linezolid or ethionamide. Poor penetration of first-line TB drugs through the pericardial tissues leads to low pericardial drug concentrations compared with plasma *(64)*, and although definitive data are lacking, drug penetration remains a concern for second-line TB drugs also. Treatment outcomes among patients treated with longer regimens for osteoarticular MDR/RR-TB are encouraging *(65)*, and there is evidence that linezolid penetrates bone tissue well *(66)*. However, due to the general lack of data on the efficacy of shorter regimens for treatment of these extrapulmonary manifestations of MDR/RR-TB, it remains prudent to treat such patients with longer regimens. In children and young adolescents aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without airway compression) are considered to be severe *(56)* and might not be adequately treated with the 9-month all-oral ethionamide- or linezolid-containing regimen.

Haematological assessment

Due to the risk of myelosuppression associated with even relatively short exposures to linezolid, pretreatment assessment of Hb, neutrophils and platelets is crucial in patients considering treatment

with a linezolid-containing regimen. Severe anaemia in patients with TB is a significant risk factor for poor treatment outcomes *(67)*, and patients with a low baseline Hb may be at risk of severe linezolid-induced haematological toxicity. The linezolid-containing 9-month regimen must not be offered to patients with a pretreatment serum Hb below 8 g/dL that cannot be rapidly corrected (i.e. with a blood transfusion) before starting MDR/RR-TB treatment. Similarly, due to the morbidity associated with severe neutropenia and thrombocytopenia, the linezolid-containing 9-month regimen is not suitable in patients with neutrophils below 0.75×10^9/L or platelets below 150×10^9/L before starting treatment.

5.2 The modified 9-month regimens for MDR/RR-TB

This section refers to the new modified 9-month treatment regimens for MDR/RR-TB developed in the endTB trial. The recommendations in the *WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care (1)* state:

No.	Recommendation (NEW)
2.2	WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Among these regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ. *(Conditional recommendation, very low certainty of evidence)*
2.3	WHO suggests against using 9-month DCLLfxZ or DCMZ regimens compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid.
2. This recommendation applies to the following:
    a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.
    b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women.
    c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement.
    d. People with MDR/RR-TB and less than 1 month of previous exposure to any of the component medicines of the regimen (apart from pyrazinamide and fluoroquinolones). When exposure is greater than 1 month, these patients may still receive one of the regimens if resistance to the specific medicines with such exposure has been ruled out.
    e. Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

The recommendations for the three new modified 9-month all-oral regimens for MDR/RR-TB are primarily based on findings from the endTB trial, a non-blinded, RCT with five experimental arms compared with a control group. The control arm of the endTB trial used the longer WHO-recommended regimen, because enrolment occurred before the 2022 WHO recommendation establishing BPaLM as the preferred regimen for MDR/RR-TB. After reviewing the trial data, the GDG has determined that the **BLMZ**, **BLLfxCZ** and **BDLLfxZ** regimens are preferred over the longer regimens currently in use.

The recommended four- and five-drug regimens include different combinations coming from a set of seven TB drugs commonly used in DR-TB treatment: bedaquiline (B), levofloxacin (Lfx), moxifloxacin (M), linezolid (L), clofazimine (C), delamanid (D) and pyrazinamide (Z). These regimens are specifically recommended for patients with MDR/RR-TB who do not have FQ resistance and they apply to diverse groups as outlined in the recommendation remarks (see **Section 5.2.1** below).

All three regimens demonstrated high efficacy, with week 104 treatment outcomes showing favourable results in 89% of patients on BLMZ (95% CI: 82–94%), 89% on BLLfxCZ (95% CI: 81–94%) and 85% on BDLLfxCZ (78–91%).

Among the modified 9-month regimens, BLMZ is preferred over BLLfxCZ, and BLLfxCZ is preferred over BDLLfxZ. The WHO GDG made this ranking based on an evaluation of all evidence and judgements made for individual regimens, together with multiple comparisons of three recommended regimens based on the following six decision criteria: balance of effects, resources required, cost–effectiveness, equity, acceptability and feasibility *(1)*. The rationale for the ranking can be summarized as follows:

- **BLMZ** was preferred over BLLfxCZ and BDLLfxZ:
  - BLMZ appeared preferable in terms of the balance of health effects compared with both BLLfxCZ and BDLLfxZ;
  - BLMZ has the lowest cost and pill burden, and appeared either preferable or equivalent for all other decision criteria; and
  - BLMZ was therefore deemed to be the preferred regimen among the three.
- **BLLfxCZ**, was preferred over **BDLLfxZ**:
  - BLLfxCZ, compared with BDLLfxZ, was deemed to have a similar but slightly preferable balance of health effects;
  - BLLfxCZ also has a significantly lower cost and a lower pill burden than BDLLfxZ;
  - the much greater cost of BDLLfxZ was judged as being likely to have negative effects on equity, acceptability and feasibility; and
  - BLLfxCZ was therefore deemed to be preferrable to BDLLfxZ.

Although all three regimens showed a similar proportion of participants experiencing Grade 3 or higher AEs, BLMZ consists of only four drugs, which may result in a lower pill burden and fewer side-effects. BLLfxCZ includes five drugs, with levofloxacin offering a better side-effect profile regarding QT prolongation than moxifloxacin; however, the inclusion of clofazimine, known for causing significant QT prolongation and other AEs, is a drawback. BDLLfxZ also contains five drugs, but while delamanid has a favourable side-effect profile, its high cost makes this regimen less favourable.

Two of the five regimens used in the endTB trial, DCLLfxZ and DCMZ, underperformed compared with the others, leading to a recommendation against their use. Specifically, the DCLLfxZ and DCMZ regimens exhibited much higher rates of failure and acquired drug resistance than the longer regimen and the three recommended modified 9-month regimens. The absence of bedaquiline, a potent bactericidal drug, may explain their reduced efficacy. Until further evidence clarifies their potential role, these regimens should not be used.

Additionally, the GDG had access to data from operational research cohorts that used various four- and five-drug 9-month regimens under programmatic conditions. However, these regimens often deviated from the three recommended regimens (BLMZ, BLLfxCZ and BDLLfxZ). Specifically, many operational research cohort regimens excluded pyrazinamide and frequently included cycloserine. Due to the limitations of evidence – primarily derived from observational studies that lack direct comparisons and are challenging to align with clinical trial data – the GDG was unable to directly compare these alternative 9-month regimens with the newly recommended modified 9-month regimens. Nevertheless, evidence from operational research studies, including one conducted across more than 13 eastern European countries using a regimen similar to BCLLfxZ (with cycloserine replacing pyrazinamide), provided valuable reassurance about the feasibility of implementing such regimens. It is expected

that this evidence will support and expedite the adoption of the recommended modified 9-month regimens, particularly in countries that participated in the operational research studies.

The role of the modified 9-month regimens within the broader range of WHO-approved treatments for MDR/RR-TB is discussed in detail in **Section 3.3**.

5.2.1 Eligibility

In settings where the 6-month MDR/RR-TB regimen is not yet available, or implementation of the regimen is not yet feasible, or for patients who are not eligible, selected patients with MDR/RR-TB may benefit from a 9-month all-oral regimen or modified 9-month regimens. The modified 9-month regimens may be offered to the following groups:

- People with MDR/RR-TB in whom resistance to FQ has been excluded.
- People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women.
- People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, or osteoarticular or disseminated forms of TB with multiorgan involvement.
- People with MDR/RR-TB and less than 1 month of previous exposure to any of the component medicines of the regimen (apart from pyrazinamide). When exposure is greater than 1 month, these patients may still receive one of the regimens if resistance to the specific medicines with such exposure has been ruled out.
- Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

The endTB trial specifically targeted patients with MDR/RR-TB who were FQ-susceptible. Before initiating any MDR/RR-TB regimen, it is essential to conduct a WHO-recommended rapid molecular diagnostic test to detect FQ resistance. In areas where testing is not feasible, it is advisable to opt for one of the 6-month regimens recommended for MDR/RR-TB regardless of FQ resistance.

Patients with extensive TB disease respond well to the three modified 9-month regimens. Other key subgroups of patients (e.g. children, pregnant women, PLHIV and people with other comorbidities such as diabetes and viral hepatitis) are discussed in **Section 5.2.3** below.

DDIs are common with many of the medications used in MDR-TB regimens, especially those involving bedaquiline. Details of interactions for drugs used in all WHO-recommended regimens is provided in **Annex 1** and **Annex 2**. In each of the above DDI situations, if the clinician determines that the potential benefits outweigh the risks (considering alternative treatment options), treatment may proceed with caution.

Patients who have resistance to bedaquiline or linezolid, regardless of FQ susceptibility, are not eligible for the 6-month regimens or any of the 9-month regimens. In these cases, an individualized longer treatment regimen (see **Section 6**) may be the only viable option.

5.2.2 Composition, dosing and duration of the regimen

The short names of the regimens with one-letter abbreviations for the drugs, the three-letter drug abbreviations, and the compositions of the modified 9-month regimens are given in **Table 2.5.2**. All the modified 9-month regimens have bedaquiline, linezolid and pyrazinamide as a core, with one or two additional drugs.

Table 2.5.2. The composition of the three modified 9-month regimens

Regimen name	Three-letter drug abbreviations	Composition with full drug names
BLMZ	9Bdq-Lzd-Mfx-PZA	**Bedaquiline-linezolid**-moxifloxacin-**pyrazinamide**
BLLfxCZ	9Bdq-Lzd-Lfx-Cfz-PZA	**Bedaquiline-linezolid**-levofloxacin-clofazimine-**pyrazinamide**
BDLLfxZ	9Bdq-Dlm-Lzd-Lfx-PZA	**Bedaquiline-**delamanid-**linezolid**-levofloxacin-**pyrazinamide**

Dosing and frequency of component medicines

The dosing for drugs in the modified 9-month regimens follows **Annex 4** for weight-based dosing of medicines used in MDR-TB regimens, for adults and children.[22] The dosing for linezolid and bedaquiline in these regimens:

- Bedaquiline is dosed at 400 mg (four 100 mg tablets) daily for the first 2 weeks, followed by 200 mg (two 100 mg tablets) three times a week (e.g. Monday, Wednesday and Friday) in adults for the full 9-month period. An alternative dosing regimen for bedaquiline involves taking 200 mg daily for the first 8 weeks, followed by 100 mg daily for the full 9-month period.
- Linezolid is given at 600 mg once daily for 16 weeks then reduced to 300 mg once daily or 600 mg three times a week until the end of treatment for an adult.

In the endTB trial, participants were randomized patients to one of these two reduced-dose strategies for linezolid. The was no significant difference in AEs or efficacy between the two dosing strategies, although the relatively small sample size limited the ability to draw definitive conclusions. Therefore, either linezolid dose reduction strategy is acceptable. Linezolid dosing may also be reduced or even permanently discontinued earlier if toxicity occurs before 16 weeks but ideally not earlier than 9 weeks, provided there is a good clinical response demonstrated by culture conversion, resolution of symptoms or no radiological worsening. In all three modified 9-month regimens dose reduction of linezolid was a standard practice, which differs slightly from linezolid dosing used in other treatment regimens.

Duration

In the modified 9-month regimens, all drugs are typically administered for the entire 9-month duration, and treatment extensions beyond this period for slow clinical responses are not routinely recommended.

If the regimen is suspended owing to clinical AEs or laboratory abnormalities, treatment should resume as soon as the patient's condition allows. Missed doses of more than 7 days and less than a month should be added up following standard case management.

For the modified 9-month regimens, a reasonable requirement is for patients to complete all doses within an 11-month timeframe, although this should be assessed on a case-by-case basis. Missing doses early in treatment is likely to have a greater negative impact on outcomes than those missed later in the regimen. For example, missing doses early in treatment, even if for less than 30 days, may require immediate repeat DST for all regimen drugs to assess potential resistance and determine whether a new treatment regimen is necessary.

[22] Slightly different dosing was used in the endTB trial for patients with lower body weight. Levofloxacin was dosed at 750 mg per day (versus 500 mg) for the >24–30 kg category, and pyrazinamide was dosed at 800 mg for >24–30 kg and >30–35 kg, and 1200 mg for >35–40 kg. These differences are minor, and programmes may adopt either the endTB trial dosing or the recommendations in **Annex 1** and **Annex 4**.

Treatment discontinuation

The clinical assessment and bacteriological response at month 4 are routinely used to evaluate whether the patient is responding to treatment. If there is no improvement by month 4 (either clinically or if the culture remains positive at month 4 and beyond), investigations for a possible treatment failure or acquired drug resistance should be carried out. If there is no improvement by month 6 and beyond, either clinically or if the culture remains positive, consideration should be given to stopping the regimen and transitioning to a new, typically longer (18-month) regimen. The new regimen composition should be based on DST results.

If FQ resistance develops during treatment with the modified 9-month regimen, or if resistance develops to any other drug in the regimen (except pyrazinamide) during treatment, treatment should be declared a failure. In such cases, a new, longer regimen tailored to the patient's DST profile should be initiated promptly.

Discontinuation of either pyrazinamide or linezolid owing to AEs may be considered and the regimen continued with the remaining drugs. However, if more than a single drug needs to be discontinued, the regimen should be stopped and an alternative treatment started.

5.2.3 Key subgroups

Various subgroup analyses were available to the GDG in considering the generalizability of the evidence on the modified 9-month regimens: age, PLHIV, previous TB treatments and viral hepatitis antibody status. The GDG also considered the eligibility criteria as stipulated by the endTB trial. The resulting considerations when prescribing the modified 9-month regimen are summarized below.

Children

Children were not included in the endTB trial. However, the medications that make up the modified 9-month all-oral regimens have been used for many years in MDR/RR-TB regimens for both adults and children, often in similar combinations. The associated adverse drug reactions are well documented (see **Annexes 1 and 2**), and weight-based dosing schedules for these drugs are provided in **Annex 4**. The **BLMZ** regimen is the preferred modified 9-month regimen because of the low pill burden and available child-friendly formulations. In situations where the child-friendly formulations are unavailable, practical guidance on adjusting adult formulations for children is provided *(68)*, ensuring that lack of paediatric-specific formulations does not hinder access to treatment.

AEs appear to be less frequent in children than in adults; however, close monitoring is still warranted in children, regardless of the regimen. In the modified 9-month regimens, linezolid is the most challenging drug to monitor for side-effects in children, particularly for haematological side-effects, which requires repeated testing during the treatment. Additionally, detecting signs of peripheral neuropathy, as well as changes in visual acuity and colour vision, can be more challenging in younger children than in older children and adults. Despite these challenges, it is crucial to rigorously monitor for these common AEs associated with linezolid. Further details are given in **Annex 2**.

Pregnancy

Data on the optimal management of MDR/RR-TB in pregnancy are limited. The endTB trial excluded pregnant patients before initiation of the regimen. Other studies provide evidence that MDR/RR-TB can be managed in pregnancy *(69)* but caution is warranted for many drugs and regimens. Given that the BLMZ modified 9-month regimen contains only four drugs and the individual drugs have been used in pregnancy, this regimen is the preferred option among the modified 9-month regimens.

Whenever a pregnant woman is placed on an MDR/RR-TB regimen, it is important to ensure close monitoring on safety and efficacy, which is crucial for improving care for pregnant women with MDR/RR-TB *(70)*.

Breastfeeding women

For reasons similar to those seen in pregnancy, BLMZ is a good regimen choice in breastfeeding women. This regimen offers four medicines that do have some history of being used in breastfeeding women, however, more evidence is needed.

For various reasons, breastfeeding is still the ideal strategy for women and their infants. This is true for women with MDR/RR-TB on treatment as well. Little is known about the safety of most second-line medications during breastfeeding, although the doses of medications that can be passed to the infant in breast milk are usually quite low. Appropriate infection control measures should be followed during breastfeeding. Mothers who have resources, or can be provided resources and training, for infant formula, clean water, fuel for boiling water and a heating device may choose to use infant formula.

People living with HIV

The three modified 9-month regimens evaluated in the endTB trial suggested good outcomes for PLHIV, and the subgroup analyses did not suggest any effect modification in this sub-population, compared to the overall trial population. However, the limited number of PLHIV across all treatment arms restricts the ability to make definitive comparisons or conclusions about outcomes in this population *(71)*.

The DDIs and overlapping toxicities with TB drugs and ART described in **Annex 1** and **Annex 2** apply to the modified 9-month regimens. More details on the management of MDR/RR-TB patients and HIV are described in **Section 8.3**.

Pulmonary TB

The endTB trial enrolled patients with all forms of pulmonary TB, ranging from mild disease to severe cases with extensive fibrosis and cavitation. This inclusive approach ensured a comprehensive evaluation of the regimens across a spectrum of disease severity. In the endTB trial, patients receiving the modified 9-month regimens had lower overall success rates if they had cavities or high-grade sputum smears; however, even in these subgroups, the success rates appeared better than in the control arm. These results underscore the importance of timely diagnosis and treatment initiation to minimize disease progression and improve patient prognosis. The modified 9-month regimens can be used in all forms of pulmonary TB.

Extrapulmonary TB

The endTB trial did not have exclusion criteria for extrapulmonary TB, but it enrolled few patients with extrapulmonary TB and no patients with severe forms of extrapulmonary TB. As a result, the efficacy of the modified 9-month regimens in treating severe forms of extrapulmonary TB (e.g. CNS TB, osteoarticular TB or disseminated TB) remains unproven.

Patients with comorbidities other than HIV

Patients with diabetes mellitus

The modified 9-month regimens can be used in people with diabetes; however, treatment of DR-TB is more complicated in this population:

- diabetes is a risk factor for renal disease and peripheral neuropathy;
- close monitoring for peripheral neuropathy is warranted in people with diabetes on linezolid, with a low threshold for lowering the dose or stopping the drug if peripheral neuropathy develops or exacerbates while on treatment; and
- treatment of diabetes with normalization of the HbA1C should occur concurrently with MDR-TB treatment.

Patients with hepatic dysfunction

Owing to the hepatotoxicity associated with pyrazinamide, alternative regimens may be more appropriate for patients with moderate to advanced liver disease. In the endTB trial, the modified 9-month regimens were not initiated in patients with ALT levels exceeding three times the upper limit of normal.

For hepatitis C infection, direct-acting antivirals (DAAs) are generally well tolerated when co-administered with MDR/RR-TB treatment *(72)*. Experience with DAAs alongside the modified 9-month regimens is limited; however, they can be safely used together in patients without advanced hepatic dysfunction or significant liver damage.

Patients with chronic renal insufficiency

Pyrazinamide is primarily excreted through the kidneys, and its metabolites can accumulate in patients with chronic renal insufficiency, increasing the risk of toxicity, including hyperuricemia and gout. In patients with impaired renal function, dose adjustment is essential to minimize these risks while maintaining therapeutic efficacy (**Annex 1**). All the other medications in the modified 9-month regimen are metabolized by the liver and do not need to be dose adjusted in chronic renal insufficiency.

Patients with anaemia

To manage anaemia in patients on the modified 9-month regimens (these regimens include linezolid, which causes myelosuppression), it is essential to assess and address both TB-related anaemia and potential linezolid-induced myelosuppression. In general, patients with a pretreatment Hb level below 8 g/dL should not start the regimen unless the anaemia can be rapidly corrected; for example, with blood transfusion, erythropoietin or a combination of both (**Annex 2** has additional details).

Nutritional deficiencies, such as iron deficiency, may improve as TB symptoms resolve with effective treatment, although oral iron supplementation is often poorly tolerated and not immediately effective. Myelosuppression can be life threatening; thus, careful monitoring of Hb, neutrophil and platelet levels is critical during treatment. In most cases, myelosuppression is reversible with temporary suspension of linezolid. If Hb levels fall to 8–10.5 g/dL, a reduced dose or temporary suspension should be considered. If Hb drops below 8 g/dL during the first 4 months of therapy because of linezolid toxicity, linezolid should be temporarily discontinued; if Hb does not recover, the linezolid may need to be permanently stopped. If the patient receives linezolid for less than 4 months, the regimen may need to be modified or a new regimen given. Temporary blood transfusions may allow the patient to initiate or continue treatment while the underlying TB is controlled, because anaemia often improves as the disease resolves. However, ongoing exposure to linezolid can exacerbate anaemia, and transfusions alone may not counteract its effects. Monitoring and timely management are key to balancing treatment efficacy with patient safety.

5.2.4 Implementation considerations

DST considerations

The endTB trial specifically targeted patients with MDR/RR-TB who were fluoroquinolone-susceptible. An mWRD for FQ resistance should be performed before initiating treatment. If testing is unavailable, one of the 6-month regimens outlined in **Section 4** should be considered, provided the patient meets eligibility criteria.

Patients who have resistance to bedaquiline or linezolid, regardless of fluoroquinolone susceptibility, are not eligible for the 6-month regimens or any of the 9-month regimens. In these cases, an individualized longer treatment regimen (see **Section 6**) may be the only viable option.

Extent of the disease

Patients with extensive TB disease responded well to the three modified 9-month regimens.

Drug-drug interactions (DDIs)

DDIs are common with many of the medications used in MDR-TB regimens, especially those involving bedaquiline. **Annex 1** and **Annex 2** provide details of drug interactions for all WHO-recommended regimens. In each of the above DDI situations, if the clinician determines that the potential benefits outweigh the risks (considering alternative treatment options), treatment may proceed with caution.

Role of pyrazinamide in the modified 9-month regimen

An unpublished analysis of the endTB trial is ongoing to evaluate further the role of pyrazinamide within the modified 9-month regimens. The highlights from this assessment are outlined below *(73)*.

Performance based on pyrazinamide sensitivity and resistance

In the endTB trial, patients receiving the modified 9-month regimens had lower overall success rates if they had baseline pyrazinamide resistance; however, even in this subgroup, the success rates appeared to be better than in the control arm, although the difference was not statistically significant. These data suggest that pyrazinamide sensitivity offers a marginal advantage but that pyrazinamide resistance does not severely impact the overall efficacy of the regimens – the modified 9-month regimens remain effective even in cases of pyrazinamide resistance.

Hepatotoxicity and discontinuation of pyrazinamide

Screening for elevation of liver enzymes was performed monthly throughout treatment, regardless of symptoms. In patients with risk factors for liver toxicity (e.g. alcohol abuse disorder or active viral hepatitis infection) liver enzyme testing should be conducted at least every 2 weeks during the first 2 months of treatment. If no signs or symptoms of hepatotoxicity develop, this should change to monthly liver enzyme testing for the remainder of the regimen. Elevation in liver enzymes, with or without accompanying symptoms, occurred frequently during treatment. Grade 3 hepatotoxicity was defined in the trial as ALT (SGOT) or AST (SGOP) levels greater than five times but less than or equal to 20 times the upper limit of normal. Transient Grade 3 or higher hepatotoxicity occurred in 18.3% of patients in BLMZ, 15.6% in BLLfxCZ, and 8.7% in BDLLfxZ in the safety population of the endTB trial; these differences were not statistically different across the regimens.

During the trial, suspension of pyrazinamide was recommended when liver enzyme levels exceeded five times the upper limit of normal. The drug was permanently discontinued in an average of 17% of patients, with no significant differences in the 73-week modified intention-to-treat treatment outcomes

among the three regimens. Most of the patients receiving the modified 9-month regimen received 39 weeks of pyrazinamide, and patients who permanently discontinued pyrazinamide received the drug for between 85 and 112 days, again with minimal variation between the regimens.

SoC for pyrazinamide management in the modified 9-month regimens

The following are suggested practices for managing pyrazinamide in the modified 9-month regimens:

- LFTs:
  - ALT and AST should be tested at baseline. More frequent testing should be considered in the presence of individual risk factors for liver toxicity.
- Pyrazinamide DST:
  - If DST is available, it should be used at baseline; however, regimens may still be used in the absence of pyrazinamide resistance testing or while waiting for results.
  - If the isolate is susceptible to pyrazinamide, the regimen should be continued, with pyrazinamide only discontinued if toxicity occurs.
  - If resistance to pyrazinamide is confirmed, the drug can be discontinued. This guidance, provided by the GDG, recognizes the potential for limited retained activity owing to possible synergy between bedaquiline and pyrazinamide *(74)*, even in the presence of pyrazinamide resistance. However, this synergy is likely to be modest and must be carefully weighed against pyrazinamide's toxicity profile.
  - In all cases, whether pyrazinamide-resistant or pyrazinamide-sensitive, standard practices on treatment outcome assessment should be followed regarding when to switch the regimen if the patient is not responding well to treatment (see **Section 9.7**).
- No pyrazinamide DST available:
  - In the absence of pyrazinamide DST, decisions regarding temporary suspension, permanent discontinuation or switching to regimens that do not employ pyrazinamide (6-month regimens or the longer regimen) should be based on the severity of pyrazinamide-induced hepatotoxicity. Principles for managing drug-induced hepatotoxicity are detailed in **Annex 2**.

In summary, the similarity in treatment outcomes between pyrazinamide-resistant and pyrazinamide-sensitive strains across all three modified regimens underscores the robustness of the modified 9-month regimens. Although pyrazinamide sensitivity appears to provide an advantage, the resistance does not significantly hinder treatment success. Thus, even though pyrazinamide contributes positively to treatment, it does not appear to be the critical driver of success in these regimens. Use of pyrazinamide requires careful monitoring. In patients with multiple risk factors for hepatotoxicity or advanced liver disease (with or without pyrazinamide resistance), more frequent liver enzyme monitoring or use of alternative regimens may be more appropriate. Regular LFTs and sound clinical judgement are critical to optimizing treatment outcomes while minimizing the risk of serious AEs.

Cost of the modified 9-month regimen

The price of medicines for the two modified 9-month regimens that do not include delamanid is relatively low (**Table 2.5.3**). However, the overall operational costs of implementing a 9-month treatment regimen may be higher than the 6-month regimens outlined in **Section 4**, primarily due to the longer duration of care. Additionally, the higher rates of hepatotoxicity associated with the 9-month regimens could result in increased costs for monitoring and managing liver-related complications. Apart from hepatotoxicity, the safety profile of the modified 9-month regimens is comparable to that of the 6-month regimens, with costs likely to be similar to those for managing other AEs.

Table 2.5.3. Prices and pill burden of the modified 9-month regimens

Modified 9-month regimen	Current regimen cost (US$)[a]	Pill burden (Daily)
BLMZ	209	7
BLLfxCZ	318	8
BDLLfxZ	1 500	11

[a] The lowest available prices from the Global Drug Facility, effective from 1 January 2025, which are subject to change *(38)*.

Care and support

To optimize treatment outcomes, all TB patients should receive a patient-centred approach combined with a comprehensive package of care and support. The excellent results of the modified 9-month regimens in the endTB trial may be attributed, in part, to the robust patient-centred approach that provided significant support throughout treatment and beyond. This support extended far beyond simply providing medication and addressed adherence, side-effect management and the overall well-being of patients. To replicate the same high rate of treatment success, similar support packages should be used for all DR-TB regimens.

The comprehensive, patient-centred care and support provided in the endTB trial was critical for achieving successful treatment outcomes. This approach should be considered essential for the implementation of all TB regimens. The recommended comprehensive support package to be used with modified 9-month regimens includes the following:

- **Patient education:** Patients should be educated through one-on-one counselling and printed materials to ensure that they understand their treatment, potential side-effects and the importance of adherence.
- **AE monitoring and management:** Regular monitoring for side-effects is a cornerstone of implementation of the modified 9-month regimens. Patients should be routinely screened for AEs, and medical staff trained to manage side-effects promptly and effectively.
- **Treatment support:** Patients should receive daily supervision of medication intake, either in-person or via digital tools where applicable, to maintain adherence and treatment fidelity. Treatment support is encouraged for the modified 9-month regimens.
- **Counselling and psychosocial support:** Patients should receive tailored counselling on treatment adherence, side-effect management and lifestyle adjustments. Psychosocial support can address emotional and social challenges associated with MDR-TB. Peer groups and community health workers can play a vital role in providing education, encouragement and adherence support.
- **Nutritional support:** Recognizing the impact of undernutrition on treatment outcomes, nutritional assessments and counselling, followed by nutritional interventions recommended by WHO are essential; this will ensure adequate nutrition during the treatment period, helping to improve recovery rates.
- **Financial assistance**: Providing some patients with financial support for transportation, food or other treatment-related expenses can reduce barriers to care. By alleviating financial burdens, patients can better focus on their recovery.

6. Treatment of drug-resistant TB using longer regimens

The design of longer regimens (18–20 months) is founded on grouping of medicines recommended for use in longer regimens based on the drug-resistance profile (**Table 2.6.1**).

In ideal conditions, only a small proportion of MDR/RR-TB patients should opt for longer regimens, because this indication is mainly for those who cannot benefit from either BPaLM/BPaL or the 9-month all-oral regimen. Reasons for not using the shorter regimens may be related to the age of the patients, additional resistance (including FQ resistance and other Group A medicines; i.e. XDR-TB), intolerance to key medicines used in shorter regimens, severity of disease, pregnancy, certain types of extrapulmonary TB or other complications needing an individualized approach.

Under many of these circumstances, only less potent and more toxic drugs are left to be used for treatment and lengthy regimens are therefore needed to cure without relapse. Longer regimens, especially if clinical conditions are complex (e.g. advanced disease with higher burden of bacilli and severe disease affecting critical organs) are usually associated with higher likelihood of toxicity, owing to factors such as longer drug exposure, higher intolerance, adverse effects and greater potential for DDIs in critically ill patients.

All these conditions that may lead to less patient-friendly regimens with higher pill burden and toxicity can increase the likelihood of unfavourable treatment outcomes such as treatment failure, LTFU and death. All DR-TB patients need a patient-centred approach with treatment adherence support and aDSM, but in longer regimens these activities become more crucial. Patients will need support to overcome the hardships associated with TB and its treatment, including daily adherence challenges, adverse drug reactions, indirect costs and stigma.

No.	Recommendation
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*

6.1 Eligibility

A longer treatment regimen should be proposed mainly when the BPaLM/BPaL or 9-month all-oral regimen cannot be used. **Section 4** and **Section 5** discuss the eligibility criteria for these shorter regimens.

A longer regimen is expected to be used in the following situations:

- severe extrapulmonary TB;
- additional resistance to key medicines of the BPaLM/BPaL regimen (except moxifloxacin) or the 9-month all-oral regimen;
- lack of response to shorter treatment regimens (e.g. treatment failure due to no bacteriological conversion, no clinical response, emerging resistance or LTFU);
- drug intolerance to the component medicines of the BPaLM/BPaL regimen (except moxifloxacin) or 9 months shorter all-oral treatment regimen; and
- pregnant and breastfeeding women who could not benefit from the 9-month shorter all-oral regimen owing to certain clinical conditions or children aged below 14 years who could not be treated with BPaLM/BPaL or who, for any reason, cannot opt for a 9-month regimen.

There is limited or no evidence of BPaLM/BPaL use in some patient groups; thus, a longer regimen could also be considered as an option for patients with low BMI (<17 kg/m^2), altered hepatic enzymes (3 times greater than the upper limit of normal), baseline anaemia (Hb <8 g/dL), thrombocytopenia (platelet count <150 000/mm^3) or preexisting peripheral neuropathy of Grade 3–4 *(23, 75, 76)*.

Any patient eligible for a longer regimen should undergo a pretreatment assessment to optimize the drug selection, reduce the chances of AEs and thus increase the probability of the favourable treatment outcomes. The pretreatment assessment includes:

- a detailed clinical history (including all comorbidities, medications and known intolerances), a physical examination, a blood test, chest X-ray or other imaging and bacteriological tests; and
- a list of current effective TB medicines available based on a clinical history of drugs taken before this treatment episode and guided by the DST results or sequencing of the most recent sample from the patient (or the index case).

In addition to the eligibility criteria and preclinical assessment, a clinician should also consider:

- development of a personalized treatment approach (patient-centred approach) and close follow-up, including food support if needed, to increase bioavailability of drugs, improve nutritional status and facilitate adherence;
- provision of advice on contraception for women of childbearing age;
- availability of ancillary medications (e.g. corticosteroids in the case of disseminated TB or TB meningitis or pericarditis, pretreatment blood transfusion in the case of severe anaemia and nutritional support) and other interventions (e.g. intravenous [IV] medication in the case of severe malnutrition and malabsorption, insertion of peripherally inserted central catheter, or surgery in the case of restricted options and meeting criteria for intervention); and
- provision of counselling, depending on the patient's comorbidities (e.g. HIV or diabetes) or preexisting conditions needing to be treated to optimize TB treatment outcomes.

6.2 Composition and duration of the regimens

When designing longer regimens, several basic principles need to be respected, in line with the best available evidence on composition of the regimens, as per the recommendations listed below.

No.	Recommendation
3.2	**Kanamycin and capreomycin** are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*

No.	Recommendation
3.4	**Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing **bedaquiline** may be used. *(Conditional recommendation, very low certainty of evidence)*
3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.6	**Clofazimine and cycloserine or terizidone** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.8	**Delamanid** may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* In children with MDR/RR-TB aged below 3 years **delamanid** may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.10	**Imipenem–cilastatin or meropenem** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[23]
3.11	**Amikacin** may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty of evidence)*
3.12	**Ethionamide or prothionamide** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*

[23] Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent, and should not be used without imipenem–cilastatin or meropenem.

No.	Recommendation
3.13	***P*-aminosalicylic acid** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*
3.14	**Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty of evidence)*[1]

6.2.1 Choice of components for the longer MDR-TB regimens

A stepwise approach guides the design of longer MDR-TB regimens (**Table 2.6.1**).

The selection of medicines follows a priority order based on the revised classification of regimen components, and a fully oral regimen is preferred. At least four drugs must be selected, starting from Group A and then from Group B. Group C drugs are usually included in a longer regimen if it cannot be composed with Group A and B agents alone. The choice of drugs from Group C is usually determined by the order in which the medicines are ranked, and by the individual circumstances of the patient and the setting. A recent review of the observational data found no additional safety concerns when bedaquiline was used for longer than 6 months; however, no clear evidence was available to indicate whether longer use added efficacy *(1)*. 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.

In the case of longer treatment regimens, an individual approach is needed. Therefore, apart from the drug classification, it is crucial to optimize drug selection according to the patient's clinical condition and the drug-resistance pattern. Considerations include:

- the clinical history of drugs taken in the past by the patient or the index case, or according to local resistance epidemiology in the country or region;
- the DST results – where available, is it of utmost importance to guide the drug selection using phenotypic or genotypic DST; in patients with extensive patterns of resistance, whenever possible, it is advised to perform whole genome sequencing; and
- selecting drugs according to their special features – in addition to susceptibility, key drug features and clinical particularities of the patient that may boost survival must be considered (e.g. likelihood of effectiveness, CNS penetration, drug–drug interaction profile, tolerance and patient preference, oral absorption and bioavailability).

Most anti-TB drugs are used once daily to achieve a high peak serum concentration that increases the bactericidal and sterilizing effect and to support adherence (to avoid missed or partial doses). The doses of anti-TB drugs by weight bands are outlined in the **Annex 4**. The essential information about TB medicines used in MDR/RR-TB treatment is described in detail in **Annex 1**.

Many patients may have comorbidities and AEs that need to be addressed separately. Hospitalization, surgery and other adjuvant treatment may be needed at certain stages of treatment. Comprehensive monitoring and treatment adherence support are important to ensure a favourable treatment experience. Access to palliative and end-of-life care services may be needed, with a patient-centred approach to relieve the suffering from the disease and its treatment *(77)*. Respiratory infection control measures at the sites where the patient is being treated, contact tracing and counselling are important accompanying measures for clinical care and public health.

Table 2.6.2 summarizes some common situations that a clinician may face, and the decisions that could be taken to adjust the treatment regimen accordingly. The suggested regimens may vary based on the individual clinical circumstances and the availability of medicines. **Table 2.6.2** is not exhaustive. Although it is recommended to use at least four effective agents initially, not all the regimens composed using this algorithm have been tested directly in either research or field conditions. Moreover, when Group C agents are included, the number of medicines in the regimen may exceed four, to reflect the uncertainty about the efficacy of some of these medicines. In such situations, the advice of a specialist is important to ensure the safest and most effective possible regimen.

6.2.2 Medicines used in longer MDR-TB treatment regimens

The classification of medicines used in MDR/RR-TB treatment regimens was revised following the evidence-informed update of the WHO guidelines on DR-TB treatment in 2018. TB medicines to be used for treatment of MDR/RR-TB are categorized into Groups A, B and C (**Table 2.6.1**) *(1)*. This classification is based on drug class and level of certainty in the evidence on effectiveness and safety (i.e. balance between benefits 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. **WHO considers that, under programmatic conditions, only these medicines (Groups A–C) have a role in longer MDR-TB treatment regimens**. In addition to agents from Groups A–C, the potential role for clavulanic acid and high-dose isoniazid was discussed (see "Other medicines" in this section).

The most notable differences between the classification of longer regimen components used before 2018 and the current guidelines 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 *p*-aminosalicylic acid, relative to other treatment options. Several agents that were featured previously in these groups are no longer included because they are:

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

The classification facilitates design of the treatment regimen for patients with DR-TB who are not eligible for the BPaLM/BPaL or 9-month treatment regimens. **Table 2.6.1** summarizes the general steps to take when including agents for the longer MDR-TB regimen according to the latest WHO guidance, with more details provided for some of the most common situations and patient subgroups that clinicians and NTPs may encounter.

Table 2.6.1. 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: individual patient data; LPA: line probe assay; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

[a] This table is intended to guide the design of individualized, longer MDR-TB regimens. Medicines in Group C are ranked by decreasing order of usual preference for use, subject to other considerations. The 2018 IPD meta-analysis for longer regimens included no patients on thioacetazone and high-dose isoniazid, 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 *(1)*.

[b] Bedaquiline is usually administered 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally thrice weekly for 22 weeks (total duration of 24 weeks). As a result of multiple reviews following new data gradually becoming available, the use of bedaquiline is not restricted by age of the patient. Evidence on the safety and effectiveness of bedaquiline use beyond 6 months was insufficient for review in 2018. Therefore, the use of bedaquiline beyond 6 months was implemented following best practices in "off-label" use *(78)*. New evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG in 2019, but the GDG was not able to 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 bedaquiline 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. In relation to safety, the GDG concluded that the data suggested no additional safety concerns regarding concurrent use of bedaquiline and delamanid. More evidence was added to that regard between 2020 and 2022 *(79)*. Both medicines may be used concurrently in 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 in 2019, but owing 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 linezolid for at least 6 months was shown to increase effectiveness, although toxicity may limit its use. The analysis suggested that using linezolid for the whole duration of treatment would optimize its effect (about 70% of patients on linezolid 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 linezolid could be inferred from the IPD subanalysis.

[e] Evidence on the safety and effectiveness of delamanid beyond 6 months was insufficient for review. The use of delamanid beyond these limits should follow best practices in "off-label" use *(78)*. As a result of multiple reviews following new data gradually becoming available throughout the years the use of delamanid is not restricted by age of the patient.

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

[g] Every dose of imipenem–cilastatin or meropenem should be preceded by the oral administration of oral clavulanic acid 30–60 minutes beforehand; oral clavulanic acid is only available in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

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

[i] These agents only showed effectiveness in regimens without bedaquiline, linezolid, clofazimine or delamanid and are thus only proposed when other options to compose a regimen are not possible.

Group A

Group A includes FQ (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 the WHO guidelines *(1)*, and it is strongly recommended that they be 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

Levofloxacin and moxifloxacin are later-generation FQ, 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, 8, 80, 81)*. Levofloxacin and moxifloxacin appear to be equally effective in FQ-susceptible patients receiving longer regimens, and either of these drugs can be considered for MDR/RR-TB treatment using these regimens. Ciprofloxacin and ofloxacin are less effective in MDR-TB treatment and are no longer recommended.

Reliable rapid molecular DST is available for levofloxacin and moxifloxacin (including Xpert MTB/XDR and second-line LPA). Not all point mutations present the same resistance profile. Despite some mutations having consistently high minimum inhibitory concentrations (MICs) (i.e. *gyr*A D94N or D94Y), most mutations present a range of phenotypic resistance that may cross critical concentration (CC) and clinical breakpoint (CB) levels. Therefore, once FQ resistance has been detected by molecular methods and treatment has started, a phenotypic method may be used as a reference test for distinguishing between high-level (>CB) and low-level (>CC and <CB) resistance mutations, possibly allowing for the use of a high-level FQ dose. Where these mutations are detected, the composition of the longer regimen should be re-evaluated based on phenotypic DST results at the CB *(82)*.

If DST for moxifloxacin confirms high-level resistance, or if the patient's history suggests that moxifloxacin has not been effective (e.g. if used in a failing regimen for more than 15–30 days), moxifloxacin should not be used. Work is ongoing to optimize the use of moxifloxacin related to sequencing, CC in phenotypic DST and clinical correlation *(82–84)*.

Bedaquiline

In the IPD meta-analysis used as evidence for the WHO guidelines, bedaquiline use resulted in significantly fewer episodes of treatment failure, relapse and death *(1)*. There is growing experience of its use in children, adolescents and older people, patients with extrapulmonary TB disease and PLHIV *(85, 86)*. Currently, there is no age restriction for the use of bedaquiline, including in longer regimens *(56)*.

Analyses of observational study data highlighted the improved survival of patients treated with regimens containing bedaquiline *(56)* and the favourable safety profile of bedaquiline when the drug is used alongside other TB medicines, including medicines with a QT prolongation effect (e.g. moxifloxacin, clofazimine and delamanid) *(87–92)*. The recent data review for the WHO consolidated guidelines *(1)* suggested no additional safety concerns for the use of bedaquiline beyond 6 months, used concurrently with delamanid or in pregnancy *(89)*. The available data suggested that the concurrent use of bedaquiline and delamanid does not increase the risk of clinically meaningful QT prolongation *(93)*.

Some inconclusive evidence is emerging; for example, some published data on the rapid advent of bedaquiline resistance in settings where it is used may suggest a possibility of bedaquiline being a low genetic barrier drug (i.e. causing resistance to emerge rapidly) as a result of frequent natural mutations. Also worth considering is the long half-life of the drug (5.5 months), which may lead to the drug acting as monotherapy in patients lost to follow-up. FQ resistance testing should be performed to prevent bedaquiline resistance acquisition, and the levels of resistance should be monitored when possible. Bedaquiline presents cross-resistance with clofazimine in cases of *Rv0678* gene mutation (which lead to upregulation of efflux pumps) and *pepQ* mutations. Resistance may occur spontaneously, even without prior exposure to bedaquiline or clofazimine (4.1% in some studies) *(94, 95)*. Mutations at the *atp*-E gene may confer high-level resistance to bedaquiline.

Linezolid

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, 96–100)*.

Linezolid is associated with considerable toxicity, which necessitates close monitoring for signs of bone marrow suppression and neuropathies. The 2018 IPD meta-analysis informing the WHO guidelines 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, LTFU and death. This analysis also suggested that the optimal duration of use would be about 20 months, corresponding to the usual total duration of a longer MDR-TB regimen; however, the analysis did not account for survivorship bias (i.e. 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, 101)*.

The evidence from the WHO consolidated guidelines *(1)* suggests that linezolid should be used for as long as it is tolerated. There may be improved outcomes if linezolid is used for the full duration of treatment. However, it probably 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 *(102)*. If toxicity develops, dosing of linezolid should be reduced or replaced by another bactericidal drug *(15)*.

Linezolid is not affected or metabolized by the cytochrome p450; however, it is an inhibitor of monoamine oxidase (IMAO), leading to an increase in serotonin and tyramine levels. Serotonergic syndrome, which can be serious and life threatening, can result when linezolid is given concomitantly with other IMAO drugs that are often used in clinical practice in TB patients (e.g. antidepressants, opioid pain killers such as tramadol, common cold medications or antitussives such as dextromethorphan) *(103)*.

Group B

Group B medicines include 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 the 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 antileprosy medicine that has shown in vitro activity against *Mtb* 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, FQ and delamanid), clofazimine may cause additive QT prolongation. ECG monitoring should be implemented when several QT-prolonging drugs are also part of the regimen. Non-TB drugs that cause QT prolongation should be avoided if possible.

Common AEs associated with clofazimine are brown-orange or purple-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 within a few months (sometimes more) of the drug being stopped and are not considered dangerous. These skin changes can be quite concerning to patients and reassurance is required. Clofazimine can be used during pregnancy or breastfeeding owing to limited data 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

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, and 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 (**Section 3.1**). Patients should be well informed of the potential AEs of cycloserine. A major drug AE is CNS toxicity, including inability to concentrate, depression, behaviour change (e.g. violence and aggressiveness, and suicidal ideation), frank psychosis, seizures and lethargy.

Cycloserine may exacerbate preexisting neurologic or psychiatric conditions. Situations of stigma, extreme poverty and social vulnerability are not infrequent among MDR/RR-TB patients, and these also affect mental health. Depression and anxiety are also highly prevalent and can lead to a worse prognosis and LTFU, especially in programmes without patient-centred systems. In these situations, management of cycloserine toxicity is critical to obtain good clinical outcomes and to avoid serious AEs.

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

Ethambutol is a TB medicine that is used in the treatment of DS-TB and may be added to longer MDR-TB regimens. At recommended dosages, the safety profile of ethambutol is good. Owing

to difficulties in interpreting its DST, ethambutol should only be considered when other criteria of likelihood of effectiveness are met (e.g. evidence on a population level of low prevalence of drug resistance in circulating MDR/RR-TB strains and no prior use of ethambutol based on a reliable clinical history).

Delamanid

Based on current evidence on its effectiveness and safety, delamanid is recommended for use as a Group C agent *(1)*. Delamanid has a potent in vitro bactericidal activity and potential sterilizing activity; it is thought that nitroimidazooxazole derivatives generate reactive nitrogen species, including nitrogen oxide, which are responsible for cell poisoning in low metabolic states. There is no age restriction for use of delamanid and there are currently dispersible formulations that are preferred over crushing and dispersing adult tablets *(56, 104)*. Delamanid is strongly bound to plasma proteins, resulting in low CNS penetration; however, studies in humans and animals with CNS TB suggest that delamanid could potentially play a beneficial role when other options are not available *(105)*.

The recent data review for the WHO guidelines *(1)* suggested that there are no additional safety concerns for concurrent use of delamanid with bedaquiline. The combined QT effects, compared with bedaquiline or delamanid alone, were evaluated in an RCT of 75 patients (>3000 ECGs) *(90)*. Studies undertaken between 2020 and 2022 had shown no increased toxicity with the use of delamanid beyond 6 months; they showed safety on the concomitant use of delamanid with bedaquiline, while increasing rates of survival of patients with restricted therapeutic options *(79, 93)*.

Animal data show no evidence of teratogenicity. Although the case series of pregnant women on delamanid are small, all children had excellent birth outcomes, suggesting that pregnant women in need should not be denied access to delamanid. It can be considered for the treatment of DR-TB in pregnant women with restricted therapeutic options *(106)*.

Pyrazinamide

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 AE 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 (in such cases it is counted as one of the effective agents); in any other cases, if pyrazinamide is included in the regimen, it is not counted as one of the four effective drugs *(107, 108)*. There are synergies between pyrazinamide and other medicines such as bedaquiline, through complex mechanisms of action targeting dormant bacteria.

Imipenem–cilastatin and meropenem

Imipenem–cilastatin (not used in patients aged <15 years) and meropenem are the only carbapenems that have an established role in MDR-TB regimens. They are administered intravenously – a major drawback that limits their more widespread use outside hospitals, especially in resource-constrained settings *(109–113)*. Daily IV injections are not usually feasible unless there is a surgically fitted port (a port-a-cath) or a peripherally inserted central catheter connected to a major vein. Meropenem with clavulanate as part of regimens (usually also containing linezolid) for patients with MDR-TB and XDR-TB has been shown to improve culture conversion and survival *(114–116)*. Clavulanic acid (as co-amoxyclav) is not a TB medicine but is an adjunct agent that is given orally each time a carbapenem dose is administered, about 30 minutes before the IV 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

Amikacin and streptomycin are the only two aminoglycoside antibiotics that can be used when options for composition of the treatment regimen are limited. Based on the evidence reviewed in 2018, amikacin and streptomycin were associated with lower rates of treatment failure or relapse and death when used in people with *Mtb* strains susceptible to amikacin or streptomycin. However, these drugs 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). 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. Apart from the low bactericidal profile, use of ethionamide and prothionamide is limited because of poor gastrointestinal tolerance, which could be potentially linked to bad adherence. In pregnant women, these drugs are usually not recommended owing to poor tolerance, decrease in thyroid-stimulating hormone (TSH) levels (which are fundamental for the development of the fetus) and concerns raised by effects in animal reproductive studies.

P-aminosalicylic acid

P-aminosalicylic acid (PAS) can be considered as the last resource for treatment of MDR/RR-TB. It is often poorly tolerated and has a modest bacteriostatic activity. 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)*. Use of PAS is limited owing to poor gastrointestinal tolerance.

Other medicines

Some medicines previously recommended as potential components of MDR-TB longer treatment regimens do not feature in Groups A–C.

High-dose isoniazid

High-dose isoniazid is not included in Groups A–C given the rarity of its use in longer regimens for adults. It is considered 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 *(117)*. Other evidence suggests that high-dose isoniazid 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% CI: 1.7–20.5, *P*=0.007) *(118, 119)*. 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) *(120)*. Third, a more recent early bactericidal activity study among patients with MDR-TB – in which the isoniazid resistance was mediated by isolated *inh*A mutations – 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 DS-TB *(121)*. 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. In the absence of information on isoniazid mutation patterns for an individual patient, knowledge of the prevalence of both mutations among locally circulating RR-TB strains (e.g. from DRS in the relevant epidemiological setting) may also inform decisions as to which treatment regimens would be most appropriate.

6.2.3 Duration of the regimen

The total length of a long treatment regimen is 18 to 20 months.

Three evidence-based recommendations guide the duration of the longer MDR-TB regimens:

No.	Recommendation
3.15	In MDR/RR-TB patients on longer regimens, a **total treatment duration of 18–20 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.16	In MDR/RR-TB patients on longer regimens, a **treatment duration of 15–17 months after culture conversion** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.17	In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, **an intensive phase of 6–7 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*

The all-oral longer MDR-TB regimens have no intensive phase. The duration of use of different medicines will depend on their clinical indication, patient tolerability (e.g. linezolid used for as long as no serious AE emerges) and individual treatment response (e.g. culture negativity), until completion of the expected total duration of treatment or time after culture conversion.

Although the total length of treatment is expected to be about 18–20 months in most patients, it may be modified based on the patient's clinical situation and response to treatment.

The evidence assessed using the IPD[24] demonstrated that there was a marginally increased risk of treatment failure or relapse when the duration of MDR-TB treatment was 20–22 months (compared with 17.5–20.0 months), and 18–20 months was determined to be an optimal treatment duration to maximize treatment success (1). In practice, NTPs may choose a fixed duration (e.g. 18 months) for implementation purposes.

[24] Data used for analysis to support these recommendations were from patients who did not receive two or more Group A medicines. However, a small proportion of patients included in the analysis were on all-oral regimens, and in these patients the same optimal treatment duration was observed using identical parameters.

6.3 Key subgroups

6.3.1 People living with HIV

Currently, there are no specific changes in using longer regimens in PLHIV. However, there can be cumulative risk factors for clinical complications, toxicities and DDIs (**Annex 1** and **Annex 2**); hence, these patients may need close follow-up and support.

6.3.2 Children

WHO recommendations on longer MDR/RR-TB regimens apply to children as well as adults. Currently, there is no age restriction on the use of bedaquiline, so children of all ages should receive it in longer regimens unless there is a specific contraindication. Most medicines in longer regimens have been part of MDR/RR-TB regimens for many years, in similar combinations, for both adults and children. Second-line TB medicines are also available in child-friendly formulations. The dosage for children is available in the **Annex 4**, including regular and dispersible medication. The duration of treatment using longer regimens in children depends on the site and severity of disease, and the extent of resistance. Children with non-severe disease can usually be treated for much less than 18 months. Children with extensive disease may require longer treatment durations, depending on clinical progress or site of the disease.

6.3.3 Pregnant and breastfeeding women

Dosing and safety data to support the optimal use of second-line TB medicines during pregnancy are generally sparse. There have been case reports and observational data reporting successful treatment and pregnancy outcomes among women who received treatment (including bedaquiline-containing regimens) for MDR/RR-TB during pregnancy and postpartum, but pregnant and breastfeeding women are usually excluded from clinical drug trials and early access programmes. Even less is known about the effects of MDR/RR-TB treatment on the infant in-utero and after birth; however, in general, the benefits (to both parent and child) of providing effective MDR/RR-TB treatment to the parent far outweigh the potential risks posed to the fetus in-utero or the breastfed infant.

Ethionamide is usually contraindicated in pregnancy because animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans. The adverse effects of linezolid may be exacerbated by the physiological effects of pregnancy, which lead to a relatively low Hb (due to the dilutional effect of increased blood volume) and a higher risk of peripheral neuropathies at treatment baseline compared with non-pregnant patients. Nevertheless, linezolid may be considered for pregnant and breastfeeding patients. More compelling evidence on the dosing and safety of specific anti-TB drugs among pregnant and breastfeeding women is needed to guide decision-making on the most appropriate regimen for treatment of MDR/RR-TB during pregnancy and postpartum. Amikacin and streptomycin are considered teratogenic and should be avoided during pregnancy. They should be considered only if there is no other option and the lives of the pregnant person and fetus are at risk.

Pregnant and breastfeeding women require considerable adherence support and monitoring of proper administration of MDR/RR-TB treatment, along with other chronic medications, to ensure successful treatment outcomes and minimal risk of TB transmission from mother to infant postpartum. Care providers must also pay particular attention to seamless continuity of care between antenatal and TB services; such services are rarely integrated in TB-endemic settings *(106)*.

Considerations on the use of TB medication during pregnancy are given in **Annex 1**.

6.3.4 Patients with diabetes mellitus

Currently, there are no specific changes in patients with diabetes; however, such patients may present cumulative risk factors for clinical complications, toxicities and DDIs. Good glycaemic control is considered essential while on TB treatment because such control optimizes the chance of cure and limits complications. The concomitant use of metformin at high doses and linezolid may increase the risk of lactic acidosis. Also, the long-term use of linezolid, high doses of isoniazid and cycloserine in patients with diabetes can lead to an increased risk of peripheral neuritis. Baseline optic nerve or retinopathy or maculopathy may worsen after linezolid use; hence, eye evaluation is recommended before and during treatment. Regarding potential baseline renal damage, amikacin and streptomycin should be used with caution. Patients with DR-TB and diabetes may need close follow-up and support, with quick identification of DDIs and AEs.

6.3.5 Patients with extrapulmonary TB

The WHO recommendations on longer MDR-TB regimens also apply to patients with extrapulmonary disease. Adjustments may be required, depending on the specific location of disease. Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by the ability of TB medicines to cross the blood–brain barrier. Group A FQ (e.g. levofloxacin, moxifloxacin and linezolid) have good penetration across the blood–brain barrier (i.e. the CNS), as do ethionamide (or prothionamide), cycloserine (or terizidone) and imipenem–cilastatin *(122–124)*. Seizures may be more common in children with meningitis treated with imipenem, and meropenem is preferred for cases of TB meningitis and in children *(125–127)*. High-dose isoniazid and pyrazinamide can also reach therapeutic levels in the CSF and may be useful if the strains are susceptible. Neither PAS nor ethambutol penetrate the CNS well and they should not be considered effective agents for MDR-TB meningitis. Amikacin and streptomycin only penetrate the CNS in the presence of meningeal inflammation. Data are sparse on the CNS penetration of clofazimine, bedaquiline or delamanid.

6.4 Implementation considerations and treatment in special situations

6.4.1 Extensive DR-TB disease

Extensive (or advanced) TB disease in adults is defined as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, extensive (or advanced) disease is usually defined by the presence of cavities or bilateral disease on chest radiography. This highlights the importance of chest radiography as part of the diagnostic work-up for patients, along with bacteriological tests. Patients with extensive disease tend to have a higher bacterial burden, especially in cases of parenchymal lung destruction (e.g. lobe collapse, fibrotic tracts or atelectasis), where drug concentration might be low due to decreased tissue perfusion. These patients tend to benefit from longer regimens to decrease the chances of relapse on shorter regimens. Patterns of lung destruction tend to present a higher risk of negative outcomes such as treatment failure and clinical complication (e.g. bacterial, fungal or mycobacterial superinfections, bronchiectasis and respiratory failure). Disability after cure is frequent. Close follow-up is needed during and after TB treatment.

6.4.2 Severe extrapulmonary TB

A longer treatment regimen may be more suitable in cases of severe extrapulmonary TB, owing to the high risk of negative outcomes including relapse. All such cases have in common the dispersion of *Mtb* through blood. Severe extrapulmonary TB is associated with lesions in multiple organs, potentially

leading to multiorgan failure. This is more frequently suffered by patients with frank or relative immunosuppression (PLHIV, children, pregnant people, older people, people with cancer, those with solid organ transplants, those on immunosuppressive medication and people with uncontrolled diabetes mellitus). The potential reasons for immunosuppression should be addressed and all potential complications managed. Corticosteroids should be considered case by case, but are recommended in TB meningitis and pericardial TB to reduce complications and disability.

6.4.3 DR-TB in different patient groups

DR-TB meningitis and brain tuberculomas

When TB affects the CNS it leads to several additional problems. For example, the concentrations of some drugs in the CNS can be reduced owing to low penetration through the blood–brain barrier. Therefore, drugs need to be selected on the basis of both susceptibility and specific CNS penetration. Drugs with high CNS penetration should be used.

Information on each drug's CNS penetration is given in **Annex 1**. Where options are limited, drug dosages can be increased to better reach the CNS, but with close monitoring of toxicity. Also, IV medication can be considered as the route of administration to optimize the drug concentration in blood while avoiding potential malabsorption problems. Patients with TB in the CNS may present with reduced consciousness and may require hospitalization, nutritional support (e.g. nasogastric tube and use of dispersible or IV medication) and, in advanced cases, intensive care. In all TB meningitis cases, the use of corticosteroids should be considered, to prevent disability and improve survival. Usually, when there is TB in the CNS, this is by haematogenous dissemination; therefore, it is important to search for the presence of TB in other organs such as lungs (e.g. bronchogenic or miliary TB), liver, spleen and bone marrow.

DR-TB in older patients

Patients with MDR/RR-TB who are aged 65 years and older are generally frailer and more vulnerable to the adverse effects of TB medications owing to the physiological changes of ageing (e.g. increase in QT interval, and baseline renal, eye or hearing damage). Also, they are more likely to present with other comorbidities (e.g. diabetes mellitus or hypertension) and therefore to be on other medications (i.e. to have a higher likelihood of polypharmacy), meaning there is a greater potential for additive drug toxicities and interactions. In addition, TB can be a consequence of a decline in the immune system due to age (immunosenescence), meaning that older patients may present with complicated forms of extrapulmonary TB.

DR-TB patients with renal failure

Patients with renal failure may be older, have diabetes or present with other comorbidities and use of multiple medications; thus, an in-depth evaluation is needed for each case. Patients with renal failure may present a baseline anaemia (possibly a clinical complication) that may be made worse by the use of linezolid or another myelotoxic drug. For many anti-TB drugs, dosage and administration may need to be adjusted according to levels of renal function. **Annex 1** has detailed information on the use of each specific drug in renal failure.

DR-TB in patients with anaemia

Patients with TB often have anaemia, and treatment with an effective drug regimen may lead to improvement or resolution of the anaemia once the disease is properly treated. In the case of disseminated TB, *Mtb* itself may be suppressing bone marrow function. Malnutrition is also associated with anaemia, which often presents as low Hb, iron deficiency and low iron stores. Iron

and multivitamins are recommended, but may interact with the absorption of important drugs such as FQ (requiring intake separated by >2 hours). In the case of severe anaemia, blood transfusion can be considered. Some of the drugs that are often used in patients with TB (e.g. linezolid, azidothymidine and co-trimoxazole) can also lead to bone marrow suppression and should be used with caution.

DR-TB in malnourished patients

Malnutrition is frequently found in children and adults with TB. Malnutrition can be a cause or a consequence of TB disease. A low BMI (<18 kg/m^2, and especially <14 kg/m^2) is considered a risk factor for negative outcomes. Immune system function is decreased in malnourished patients; thus, more complicated extrapulmonary TB affecting critical organs may develop. In a patient with malnutrition, many other complications and superinfections can coexist, making clinical management much more complex; such patients also then require more medication, with potential DDIs. Malnourished patients may have poor tolerance for the daily intake of medication (owing to gastrointestinal issues), with frequent nausea, vomiting and diarrhoea. In addition, malnourished patients tend to present with malabsorption; thus, even if the intake of the medication is correct, the concentrations of anti-TB medication in blood can be suboptimal. Malnourished patients require close monitoring and a nutritional approach while on TB treatment; they may even benefit from IV administration of TB medication for short periods until there is improvement (either clinical or nutritional). Close monitoring of side-effects and an in-depth clinical evaluation is needed, to identify additive superinfections or comorbidities. Nutritional supplements could help malnourished patients to recover by strengthening their immune system and improving weight gain.

DR-TB in patients with hepatitis B or C

There are limited data on the use of the longer treatment regimen among people with viral hepatitis or undergoing treatment for hepatitis C. It may be prudent to monitor closely for DDIs and hepatotoxicity among this patient group.

DR-TB in patients with depression

Mental suffering and depression is common in DR-TB patients, because of, for example, symptomatic and life-threatening disease, side-effects, stigma and social exclusion, inability to work and family catastrophic costs. Some TB medications such as cycloserine (and to a lesser extent isoniazid and ethionamide) can trigger depression and suicidal ideation. These circumstances need to be seriously considered, especially in longer regimens, because depression and the social and emotional circumstances around it are often linked to difficulties in treatment adherence. Linezolid could potentially interact with all antidepressant drug families, increasing the risk of serotonergic syndrome (**Annex 1** has more detailed information on linezolid DDIs). A balance between risk from TB and depression needs to be considered.

DR-TB in patients who present with alcohol or other substances abuse

Patients with DR-TB presenting with alcohol or other substances abuse is a situation that is often associated with the depression and social vulnerability that occurs particularly with TB in big cities. In addition to the negative emotional impact of DR-TB, anti-TB medication can have a negative effect on the patient. Cycloserine is associated with mood changes and potentially with craving and overconsumption of food, and methadone and psychiatric medication may interact with linezolid. A comprehensive patient-centred approach and harm reduction models that include psychosocial support are especially needed in these patients and had been shown to improve outcomes.

6.5 Treatment monitoring

Individuals prescribed the longer treatment regimen should be monitored to assess regimen effectiveness and safety, taking into account resistance patterns and challenging clinical conditions, while using less active and more toxic medicines. The WHO framework for aDSM needs to be applied to patients on any MDR-TB regimen, to ensure appropriate action and an acceptable level of monitoring for and prompt response to AEs – alongside monitoring for treatment outcomes, including early monitoring for treatment failure.

No.	Recommendation
5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. *(Strong recommendation, moderate certainty in the estimates of test accuracy)*

It is desirable for sputum culture to be repeated at monthly intervals.

Table 2.6.2. Summary algorithm for longer MDR-TB regimen composition in commonplace situations of resistance pattern or contraindication

Medicines to which there is resistance or contraindication of use		Consider adding medicines likely or confirmed to be effective			Examples of regimens
		Group A	Group B	Group C[b]	
1	Two Group A medicines	Remaining medicine	Both medicines	At least 1 medicine	18 $Bdq_{(6\ m\ or\ longer)}$-Cfz-Cs-$Dlm_{(6\ m\ or\ longer)}$-(Z or E) 18 Lzd-Cfz-Cs-$Dlm_{(6\ m\ or\ longer)}$-(Z or E) 18 Lfx-Cfz-Cs-$Dlm_{(6\ m\ or\ longer)}$-(Z or E) If there is a suspected resistance to E or Z, replace with Group C drugs
2	One Group B medicine	All 3 medicines	Remaining medicine	May not be needed	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Lzd-(Cfz or Cs)
3	Both Group B medicines	All 3 medicines	None	1 or 2 medicines	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Lzd – $Dlm_{(6\ m\ or\ longer)}$-(Z or E) If there is a suspected resistance to E or Z, replace with Group C drugs

Medicines to which there is resistance or contraindication of use		Consider adding medicines likely or confirmed to be effective			Examples of regimens
		Group A	Group B	Group C[b]	
4	One Group A and both Group B medicines	Remaining 2 medicines	None	At least 3 medicines	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-$Dlm_{(6\ m\ or\ longer)}$-Z-E _____ 18 (Lfx or Mfx)-Lzd-$Dlm_{(6\ m\ or\ longer)}$-Z-E _____ 18 $Bdq_{(6\ m\ or\ longer)}$-Lzd-$Dlm_{(6\ m\ or\ longer)}$-Z-E If there is a suspected resistance to E or Z, replace with Group C drugs
5	All Group A medicines	None[c]	Both	3 or more medicines	18–20 Cfz-Cs-Dlm-Z-E or other combinations of Group C drugs, depending on known or suspected resistance

CB: clinical breakpoint; m: months; MDR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or rifampicin-resistant TB; MIC: minimum inhibitory concentration; TB: tuberculosis; WHO: World Health Organization.

Drugs: Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Lfx: levofloxacin; Lzd: linezolid; Mfx: moxifloxacin; Z: pyrazinamide.

[a] The situations shown are not exhaustive. Other factors may influence choice, such as patient risk for poor outcome or drug–drug interactions, clinician and patient preference and availability of a medicine. More medicines may be added than the recommended minimum if there is limited confidence in the effectiveness of regimen components, or if the patient was exposed in a setting where second-line TB drug resistance is frequent and longer MDR-TB regimens perform poorly despite good programmatic management of MDR/RR-TB. For MDR-TB with confirmed FQ resistance, no FQ is used and, if Group C agents are needed, the recommended WHO grouping will be followed based on benefit versus risk and individual circumstances.

[b] The choice and number of Group C medicines to include depends on the confidence in the effectiveness of medicines in this group and the other components of the regimen, thus:

- if 4 Group A and B agents are included and there is confidence in all of them, then Group C agents are not needed;
- if 3 Group A and B agents are included and there is confidence in all of them, then at least one Group C agent is added; and
- if 2 Group A and B agents are included and there is confidence in all of them, then at least three Group C agents are added.

[c] Moxifloxacin, a later-generation FQ, may still be effective at a high dose when the FQ MIC is below the CB. If the MIC is elevated, then FQ are not used, and additional Group C agents will be needed.

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

This section refers to an Hr-TB treatment regimen that has a duration of 6 months and uses oral agents.

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:

No.	Recommendation
4.1	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 of evidence)*
4.2	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 of evidence)*

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)RZE-Lfx

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

7.1 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, to avoid the inadvertent treatment of MDR/RR-TB with an inadequate regimen. Ideally, rapid DST for FQ 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 2HRZE/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 PLHIV. Thus, HIV testing and treatment of PLHIV with 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) *(128)*. 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 is ruled out before TB treatment is started – in such cases, the 6(H)RZE-Lfx regimen is started immediately. If the diagnosis is strongly presumed (e.g. close contact 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 to complete a 2HRZE/4HR regimen.
- Hr-TB is discovered after the start of treatment with the 2HRZE/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 undertaken (or repeated). Once rifampicin resistance has been excluded, a full 6-month course of (H)RZE-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 6 months. 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 2.7.1** illustrates a typical situation that could arise.

7.2 Composition and duration of the regimen

The duration of Hr-TB treatment is driven by the need to complete 6 months of a FQ-containing regimen. This implies that, when Hr-TB is diagnosed *after* the start of the regimen for treatment of DS-TB, the companion medicines (HRZE) 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)RZE-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 FQ is given.

Levofloxacin is the preferred FQ for Hr-TB regimens. The exposure to moxifloxacin decreases markedly when it is combined with rifampicin *(129)*. This effect has not been reported in the case of levofloxacin; also, levofloxacin appears to cause less QT interval prolongation than moxifloxacin *(55, 130, 131)*.

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 FQ, and when there is preexisting prolongation of the QT interval and pregnancy. If a FQ cannot be used, a patient with Hr-TB can still be treated with 6(H)RZE; streptomycin is not required in such cases.

For patient convenience and ease of administration, the HRZE FDC may be used to treat Hr-TB (given that no RZE FDC is currently available). The dosage of other TB medicines in the Hr-TB regimen is the same as in the standardized DS-TB 2HRZE/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 increase the hepatotoxicity of pyrazinamide *(132, 133)*. 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 MIC, even in "fast acetylators" (i.e. individuals who metabolize isoniazid rapidly) *(134)*. 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 2.7.1. Evaluation of a typical scenario – a delayed DST result in a patient on a first-line regimen

Before starting the 2HRZE/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. The results are returned to the treating physician 3 months later; they show resistance to isoniazid. The patient has meanwhile adhered to their 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 (usually in FDC); however, the patient is effectively 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 **Section 5**, **Section 6** and **Section 7**).
- ➔ If rifampicin resistance is not detected, the patient should be switched to the (H) RZE-Lfx regimen for 6 months. Ideally, DST for FQ should be performed.

Patients with Hr-TB may have a higher risk of acquiring additional resistance and MDR-TB, which may manifest during 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.

7.3 Considerations for implementation

The regimens recommended for treatment of Hr-TB is not divided into 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, social support and the use of digital technologies should be considered to ensure favourable treatment outcomes *(17)*.

The cost of medicines to compose a full 6(H)RZE regimen with levofloxacin is slightly higher than the cost of a 2HRZE/4HR regimen used for DS-TB *(135)*. Nonetheless, the 6(H)RZE 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.

A new diagnostic platform has been approved for the detection of Hr-TB – the new Xpert MTB/XDR cartridge, which can detect isoniazid resistance in less than 90 minutes, matching the rapidity and convenience of Xpert MTB/RIF for rifampicin resistance. First-line LPA can also detect isoniazid resistance, and the infrastructure required 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 a 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 DST. First, such treatment will lead to unnecessary overtreatment with FQ and prolongation of pyrazinamide use in many patients. Most recurrent 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 FQ. Third, this policy would deflect the focus of the programme from testing new 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 Xpert MTB/XDR or LPA. Liquid culture may replace LPA, but the additional delay in obtaining results is a disadvantage.

7.4 Treatment monitoring

The clinical monitoring of patients on Hr-TB treatment follows similar principles to those that apply to other first-line TB regimens. Bacteriological monitoring of sputum generally follows the same schedule as DS-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. ECG for patients on 6(H)RZE-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 the **Annex 4**, even when taken for longer than 6 months. Dosage adjustment, in consultation with a specialist, is recommended if creatinine clearance is below 30 mL/min *(15)*. 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 *(113)*. The case may be retained in the TB register for the purposes of monitoring the treatment response and the interim or final outcomes. Cases without Hr-TB may be enumerated with the main DS-TB cases for the purposes of treatment outcome reporting. Hr-TB cases given FQ or other second-line agents in addition to 6(H)RZE may also be registered in the second-line TB register if the programme wishes to monitor how many patients are being given regimens containing second-line medicines *(15)*. If this is done, it is important that cases without RR-TB are not enumerated with the MDR/RR-TB cohort for treatment outcome monitoring purposes.

It will be helpful to monitor efforts to improve testing coverage, detection, enrolment and outcomes for Hr-TB separately from other TB or MDR/RR-TB cases. The indicators for MDR/RR-TB may be adapted for this purpose; outcome definitions are the same as for non-MDR/RR-TB *(113)*. Reporting can be at the same frequency as that recommended for standard monitoring of other TB cohorts.

Combining data for patients with different resistance patterns into a single cohort may complicate comparison of performance between centres and determination of trends over time, given that these patients may have different risks for treatment failure. However, treatment of TB patients who do not have rifampicin resistance with regimens discussed in this section should lead to a successful outcome in most patients, and maximizing the likelihood of success should be the end objective of TB programmes. The use of electronic case-based databases facilitates the grouping of patients by comparable resistance patterns or treatment episodes to undertake more advanced analyses, allowing adjustment for at least some covariates. Programmes are encouraged to follow good practices when collecting these data, and to participate in collaborative initiatives to share individual patient records for pooled reviews of global patient series *(136–139)*. Such data could be useful to guide future policy on the optimization of regimens for the treatment of DR-TB.

8. Adjuncts to DR-TB treatment and comorbidities

8.1 Surgery in the treatment of MDR/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 MDR/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 way 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 *(140, 141)*.

The 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 patients with resistance to additional medicines. The recommendation does not apply to radical pneumonectomy, which had no statistically significant effect *(140)*. The recommendation 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 *(140)*, and a systematic review and study-level meta-analysis *(142)*.

No.	Recommendation
7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*

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 *(8)* 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 MDR/RR-TB and resistance to FQ and injectable agents were significantly lower when they underwent surgery compared with other patients (aOR: 0.4, 95% CI: 0.2–0.9) *(140)*. This finding is likely to be biased, given that patients who underwent surgery would have had other factors predisposing them 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 4, 5, 6 and 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 AEs, surgical complications or long-term sequelae – some of which may be fatal – to allow for 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, 143)*:

No.	Recommendation
4.1	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 of evidence)*
4.2	In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used *(Conditional recommendation, very low certainty of evidence)*

The recommendations are limited to these two forms of extrapulmonary TB. In patients with TB meningitis, evidence from RCTs *(144–148)* 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. AEs and severe AEs, including severe hepatitis, were lower in patients receiving steroids. In patients with TB pericarditis, studies showed a benefit to steroid treatment in relation to death, constrictive pericarditis and treatment adherence *(149–156)*.

Although the evidence and the recommendations primarily relate to non-MDR-TB, these recommendations could also apply 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 Treatment of MDR/RR-TB patients with HIV

With regard to ***HIV infection***, a specific recommendation was made in 2011 on the use of ART in all patients with HIV and DR-TB *(80, 128)*:

No.	Recommendation
6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)*

Delaying ART increases the risk of dying among TB patients living with HIV; therefore, 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 *(157)*.

There may be a potential for overlapping, additive toxicities or DDIs 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. While no interactions are anticipated for the preferred first-line ARV, dolutegravir, it is not recommended to use bedaquiline and efavirenz in combination (**Annex 2**). **Annex 1** provides 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 *(158)*. Antiretroviral treatment regimens should be initiated early, in accordance with WHO recommendations *(15, 80)*. 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 *(15)*.

8.4 Treatment of MDR/RR-TB patients coinfected with HCV

This section refers to a treatment recommendation for people with confirmed MDR/RR-TB and infection with hepatitis C virus (HCV). The new recommendation in the updated 2024 guideline states:

No.	Recommendation (NEW)
8.1	In patients with MDR/RR-TB and HCV co-infection, WHO suggests the co-administration of HCV and TB treatment over delaying HCV treatment until after treatment of MDR/RR-TB is completed. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. This recommendation applies to people with confirmed MDR/RR-TB and HCV.
2. Treatment initiation should take into account potential DDI and other comorbidities.

8.4.1 Eligibility

Individuals with confirmed HCV and MDR/RR-TB can receive both treatments. The composition and duration should follow the current recommendation *(159)*.

8.4.2 Implementation considerations

Co-administration of MDR-TB and HCV treatments

Initiating co-administered treatment for HCV and MDR/RR-TB requires careful consideration of potential DDIs and other comorbidities. This is important because, globally, MDR/RR-TB treatment success rates remain low (only 63% in 2022). Coinfection with HCV further complicates treatment, because individuals are at increased risk of liver damage (hepatotoxicity) due to certain anti-TB medications *(160)*.

There is an overlap in the risk factors for both HCV and TB. Chronic viral hepatitis B or C can further negatively impact TB treatment by increasing the risk of drug-induced hepatotoxicity *(161)*. Fortunately, the development of short-course, oral DAAs has revolutionized HCV treatment, achieving cure rates exceeding 90%, with minimal side-effects *(161, 162)*.

A recent systematic review identified limited direct evidence on co-administration; however, expert analysis suggests potential benefits. Co-administering treatment for MDR-TB and HCV may improve MDR-TB treatment success, reduce treatment failures and decrease LTFU *(163)*. Although data on HCV treatment outcomes from co-administration are scarce, the potential advantages of MDR-TB treatment outweigh the uncertainties. Therefore, co-administration is conditionally recommended for MDR/RR-TB patients with confirmed HCV coinfection and delaying HCV treatment is discouraged *(163)*. The decision to administer both treatment regimens should be informed by knowledge of potential DDIs and patient preferences. Importantly, if HCV treatment is not available, this should not impede the initiation of MDR-TB treatment.

It is important to acknowledge limitations in the available data, particularly for pregnant women, PLHIV and children. Caution is advised when applying the findings to these groups. Currently, there are no official recommendations for HCV treatment in pregnancy; however, this is an evolving area, and emerging evidence will guide future development of treatment recommendations. Clinicians should make co-administration decisions based on individual patient factors, including a thorough understanding of potential DDIs and existing comorbidities. Transparency regarding the current evidence limitations is crucial when discussing treatment options with patients.

Supporting patient adherence is vital throughout treatment, particularly considering the potential for shorter regimens. Health care providers should prioritize strategies aimed at enhancing adherence and empowering patients to successfully complete both treatment courses.

In summary, co-administration of MDR-TB and HCV treatment is the suggested approach for individuals diagnosed with MDR/RR-TB and HCV. Although there are some data limitations, the potential benefits of improving MDR-TB treatment outcomes outweigh the risks. Effective implementation should prioritize patient support and clear communication.

Access to treatment for HCV and MDR-TB

The coordination of HCV and MDR-TB treatments necessitates access to both groups of medicines, with initiation of MDR-TB treatment not delayed if HCV treatment is not available. Programmes must also have access to reliable DST for MDR-TB medicines and bacteriological tests, as well as the ability to monitor the virological response for HCV.

8.4.3 Monitoring treatment response and outcome assignment

Close monitoring of the treatment response is critical throughout the entire duration of therapy.

HCV treatment progress is tracked through accurate viral load measurement; a sustained virological response at 12 weeks post-treatment indicates a successful cure. Given the potential impact of HCV treatment on liver health, regular LFT are essential to detect any signs of liver damage during treatment.

In MDR/RR-TB, the response to treatment is evaluated through bacteriological monitoring using regular sputum smear microscopy and culture, ideally monthly *(17, 164)*. Regular clinical monitoring ensures timely adjustments of treatment and informed decision-making.

The treatment outcome definitions and reporting framework for patients receiving both HCV and MDR-TB treatments align with those for all DS-TB and DR-TB regimens (see **Section 10, Chapter 1**). Beyond treatment completion, follow-up evaluations are critical to monitor for potential relapse (**Section 9.9**).

8.4.4 Monitoring safety

Treatment monitoring schedules should encompass relevant clinical and laboratory parameters, to promptly detect, manage and prevent common and serious AEs. Although no significant risks were identified in the available data, the active drug-safety monitoring (aDSM) framework should be used for promptly detecting, managing and reporting any suspected or confirmed drug toxicities.

There is a paucity of data on DDIs between HCV treatments that use DAAs and MDR-TB medicines. Based on the limited published data available, current evidence suggests minimal interactions; however, caution is still advised.

It is notable that bedaquiline, a key component of most MDR-TB regimens, may increase the risk of liver toxicity, particularly when co-administered with some HCV treatments. Additionally, some MDR-TB drugs (e.g. ethionamide/prothionamide and clofazimine) may interact with specific DAAs (e.g. daclatasvir) by affecting how the body processes them, although this has not been definitively proven *(72)*.

To address the paucity of published data on DDIs between anti-TB medications and HCV DAAs, health care professionals rely primarily on two key information sources:

- drug package inserts: these provide known DDIs for each medication; rifampin was the only anti-TB drug with established DDI studies, so the results of these studies were extrapolated to estimate potential DDIs for other anti-TB and HCV DAA combinations; and
- the University of Liverpool HEP drug interaction tool *(165)*: this online resource aided in further evaluation and confirmation of potential DDIs; however, some anti-TB drugs (kanamycin, cycloserine, clofazimine, ethionamide and para-aminosalicylic acid) were not included in this database *(162)*.

Using these resources, health care providers can assess potential DDIs by considering various HCV regimens and their predicted interactions with individual TB drugs used in the treatment of MDR-TB. This approach facilitates a more comprehensive understanding of possible DDIs, thereby informing treatment decisions and enhancing patient safety. As research in this area continues to evolve, it is crucial to approach concomitant treatment of TB and HCV with caution. Health care providers should remain vigilant and use available resources and emerging evidence to guide clinical decision-making, ensuring the best possible outcomes for patients with both conditions.

Potential DDIs were evaluated considering different HCV regimens and their predicted interaction with individualized TB drugs used for MDR-TB, as shown in **Table 2.8.1**.

Table 2.8.1. DDIs between MDR/RR-TB and HCV drugs

Hepatitis C treatment regimens[a]	TB medicines						
	Lfx/ Mfx	Am	Lzd	Cfz	PAS/ Cs/Eto	Bdq	Dlm
First-line drugs							
Glecaprevir, pibrentasvir *(159–164)*							
Sofosbuvir, velpatasvir *(159–164)*							
Elbasvir, grazoprevir *(159, 162)*							
Ledipasvir, sofosbuvir *(159, 162–164)*							
Alternative							
Paritaprevir, ritonavir, ombitasvir, dasabuvir, ribavirin *(159)*							
Paritaprevir, ritonavir, ombitasvir, ribavirin *(162)*							
Simeprevir, sofosbuvir *(159)*							
Daclatasvir, sofosbuvir *(159–161)*							
Elbasvir, grazoprevir, ribavirin *(162)*							

DDI: drug–drug interaction; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

Drugs: Am: amikacin; Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; Eto: ethionamide; Lfx: levofloxacin; Lzd: linezolid; Mfx: moxifloxacin; PAS: *para*-aminosalicylic acid.

Colour coding:

Orange		Potential clinically significant interaction
Green		No clinically significant interaction expected
Yellow		Potential weak interaction unlikely to be clinically significant

[a] As recommended in the hepatitis C treatment guidelines from the American Association for the Study of Liver Diseases/Infectious Diseases Society of America *(166, 167)*.

No TB medicines are advised for dosage adjustments in individuals with preexisting liver conditions (**Table 2.8.2**); nevertheless, it is crucial to conduct vigilant and regular monitoring of liver function, particularly for those with unstable or advanced liver disease, because certain studies indicate that such individuals may face an increased risk of drug-related liver damage *(168)*. Given that many TB medications are metabolized in the liver, it is important to consider the potential influence of liver disease severity on the pharmacokinetics of anti-TB drugs *(169)*.

Table 2.8.2. Characteristics of anti-TB drugs related to liver disease

Drug	Dosing adjustments for hepatic disease	Associated with hepatotoxicity
Levofloxacin *(170)*	None	No[a]
Moxifloxacin *(170, 171)*	None; use with caution secondary to risk of QT prolongation	No[a]
Amikacin *(172, 173)*	None	No
Ethionamide *(173, 174)*	None; use with caution	Yes
Cycloserine *(173, 174)*	None; use with caution in alcohol-related hepatitis	No
Linezolid *(175, 176)*	None; not evaluated in severe hepatic impairment	No; a single case has been reported
Clofazimine *(177)*	Not studied; use with caution, dose reduction may be warranted	No
Bedaquiline *(178, 179)*	None; use with caution in severe hepatic impairment (not studied)	Yes
Delamanid *(180, 181)*	None; not recommended in moderate and severe liver impairments	No

TB: tuberculosis.

[a] Although levofloxacin and moxifloxacin were associated with increased risk of acute liver injury compared to clarithromycin , they are generally not considered hepatotoxic drugs.

Given these potential interactions and characteristics of TB drugs related to liver disease, consulting with a specialist is essential. A specialist can assess individual patient factors and recommend the optimal treatment plan that minimizes DDIs and maximizes treatment success for both HCV and MDR-TB *(162)*.

9. Programmatic implementation of DR-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. This section summarizes some key considerations for those steps.

9.1 Policy and operational documents

Policy and operational documents that govern the main components of the programme will 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. Ideally, the type of regimen used by the patient would be indicated in the register and could be summarized for reporting. 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) *(16)*. Any changes should also cover the use of the regimen in private practice.

9.2 National DR-TB expert committee 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 and 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 levels, and at regional level through, for example, the regional Green Light Committee (rGLC). In making use of such support, it is important 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.

9.3 Electronic recording and reporting

There is a need to improve the quality of patient data using standardized variables, such as data on DST patterns, prescribed treatment, treatment outcomes and adverse drug reactions. The collection and utility of these data are important for future evidence-based recommendations, especially given the lack of RCTs on the management of DR-TB *(139)*. If digital patient records do not already exist, it

is important that the programme managers consider their introduction, at least for surveillance and possibly also for case management *(182)*. 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 (e.g. the development of the WHO consolidated guidelines benefited hugely from the experience of patient treatment within programmes) *(136, 137)*. The treatment outcome cohort reports for MDR/RR-TB do not need to 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 (app) that is available for download free of charge.[25] It is important to ensure that digital records can accommodate key measures in children that may differ from those for adults.

9.4 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/RR-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 in line with national and subnational plans. The programme first establishes the number of MDR/RR-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, Tuberculosis and Malaria). Then, based on knowledge from surveillance, eligibility and estimated rate of scale-up, the programme defines different patient groups; for example, those expected to receive different variants of the longer MDR/RR-TB regimens and those likely to receive a shorter MDR/RR-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/RR-TB regimens (e.g. treatment of AEs, 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.

9.5 Management of the supply chain and storage conditions for pharmaceuticals

Management of the supply chain and storage conditions for pharmaceuticals should be reviewed to ensure that TB drug orders are made in good time and are correctly quantified to avoid 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. Similarly, 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 *(183)*. The principles for the quantification of medicines needed for the longer and shorter MDR/RR-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

[25] Available at https://siapsprogram.org/tools-and-guidance/quantb/.

weight of the patients; whether children will also be enrolled; the expected losses (from interruptions, deaths and transfers to another regimen); and current stock on hand, including expiry dates and orders of medicines already in the pipeline and not yet delivered. It is best to split an order of medicines, the first part being for the patients expected to be started within 6 months, and the second part adjusted 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 secretariats of the Global Drug Facility (GDF) and rGLC (which are housed in WHO regional offices) or via the WHO country offices. GDF provides support to many NTPs on the procurement and supply chain aspects of phase-in and phase-out plans of products or regimens and can procure child-friendly formulations. Child-friendly formulations allow more accurate paediatric dosing and are more acceptable to children and parents; they should be provided as the SoC wherever possible.

9.6 Preparation for the introduction of new treatment regimens

When planning important changes for the national TB treatment policy to align with the latest WHO recommendations, the NTP needs to balance the will to provide the best possible options for patients according to the latest evidence against the programmatic circumstances and the implications of such changes (e.g. the need to re-train staff or obtain funds for reprogramming). The programme must 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.

Given the increased use of newer and repurposed medicines in combination MDR-TB regimens, aDSM is particularly important. 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 *(16)*. It applies the principles of active pharmacovigilance to the specific needs and context of NTPs, 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 AEs as a priority requirement, but any AE during treatment administration (whether or not it is related to drug toxicity) needs to be managed to limit harms to patients. MDR-TB treatment sites may also monitor nonserious AEs that are of clinical significance or of special interest to the programme, as part of more comprehensive aDSM. In aDSM, in addition to the spontaneously reported reactions, AEs are elicited as part of a patient monitoring plan that comprises a set of questions and often an array of laboratory or clinical tests at defined periods of time, before, during and after treatment (**Annex 3**).

To ensure rapid uptake of the WHO-recommended shorter treatment regimens for TB, NTPs should take the lead on gathering a technical working group (TWG) from the representatives of affected communities and partners organizations to develop an introduction plan that defines all necessary measures and organizations responsible for implementation. Subsequently, the TWG, in collaboration with NTP, needs to coordinate the practical implementation of the planned activities. **Table 2.9.1** presents a checklist of activities for considerations by the programme manager when planning and implementing the DR-TB regimens that are newly recommended.

For the successful introduction of a new regimen, the following needs to be achieved at the different levels of the NTP.

National level:

- Updated regulatory approval of the new regimen and the updated national policy;
- Funding available for all necessary steps and requirements; note that eventually, the use of the new regimen may lead to reduced costs;

- Tools for the nationwide introduction of the new regimen are available (e.g. updated national guidelines, training of trainers and training materials for all relevant cadres, needs assessment of clinical and laboratory services, funded nationwide scale-up plan);
- Updated surveillance and monitoring and evaluation system (including active drug-safety monitoring and management [aDSM] if required), revised treatment outcome indicators;
- An adequate drug procurement system, with the proper quantification and forecasting of new drugs for the new regimen; and
- Partnership with clear roles and responsibilities (Ministry of Health [MoH]/NTP, technical partners, donors, patient organizations).

Health facility level in adopting areas

- Clinical Expert Committee/Consilia oriented on the updated/new guidelines and role ensured, especially the provision of clinical advice;
- Personnel are trained in clinical and programmatic implementation of the new regimen, including aDSM (if required), and roles and responsibilities clearly laid out;
- Facilities at the institutional level using updated national guidelines, and meeting requirements of the new regimen (e.g. people-centred approach, social support in place);
- Access to the relevant laboratory (clinical and bacteriological) tests is secured, and facilities equipped with the tools for conducting of clinical assessment for AEs (e.g neurological examination, visual acuity and colour vision tests, ECG, etc.); and
- The surveillance system, programmatic standard operating procedures (SOP) and patient management protocols are adequately implemented.

Table 2.9.1. List of activities and corresponding responsible organizations

Activities	Responsible organizations
Preparatory Phase and initial introduction of the new regimen	
Advocacy • To present latest international evidence, trial results etc. to MoH and NTP, regulatory authorities, donors, technical partners, civil society and patient organizations	
Policy documents and regulatory framework • Drug registration, local requirements for the use of new drugs and/or new treatment regimens, update of national treatment guidelines, national strategic plan for TB, the essential medicines list, etc.	
Needs assessment for introduction and scale-up plan • Conduct situational assessment to identify the needs for programmatic introduction and national scale-up. The results will help NTP and partners in preparation and planning towards the regimen implementation and national scale-up.	

Activities	Responsible organizations
Development of initial adopting site and national scale-up plan (e.g. activities, timelines, budget) • Design the introduction approach highlighting the activities and timelines for the selected initial adopting sites with a budget plan to support training, supportive supervision, dissemination of lessons learned and best practice, etc. The lessons learned and best practices identified will support NTP and partners towards a nationwide programmatic scale-up of the new regimen	
Access to diagnostics • Access to necessary diagnostics (e.g. DST capacity for FQ, bedaquiline, linezolid, delamanid and/or pretomanid; new generation sequencing), specimen transportation, link with treatment (e.g. reporting of test results via diagnostic connectivity system, clinical interpretation of test results, use of data including that obtained via the diagnostic connectivity network for estimation of drug/regimen needs)	
Drug quantification, procurement and supply chain • Estimation of needs for drugs and consumables, adjustment of drug procurement plans and estimation of needs for laboratory consumables • Ensure an uninterrupted supply of TB drugs and consumable through proper quantification and quarterly monitoring, with an early warning system • Revision of indications for different regimens for TB patients (adults and children) and estimation of number of patients for different regimens	
National policy/guideline documents, clinical protocols, SOP and job aids updated for introduction of the new regimen • Updating of national policy/guideline documents, development of clinical protocols, SOPs, and job aids for the introduction of new regimen, including algorithm for safety monitoring	
Recording and reporting • Revision of recording and reporting forms to include the new regimen	
Capacity-building • Establish training plans, supportive supervision, mentoring for clinical staff and treatment supporters for all staff involved	
Digital health solutions • Introduction of innovative treatment adherence support technologies, use of digital health tools for blended learning (e.g. webinars, video-instructions, job aids, digital patient support tools). Scaling up utilization of existing diagnostic connectivity for notification and data extraction/analyses	
Monitoring • Monitoring of adherence to protocols, analysis of patient enrolment progress and interim treatment outcomes, drug safety, adjustment of Policy/Guideline documents, clinical protocols and drug forecasting as needed	

Activities	Responsible organizations
Nationwide scale-up	
Advocacy (dissemination of lessons learned from early introduction) • Sharing results of initial adopting sites and updates on latest international evidence, updated guidelines, trial results etc. with MoH/NTP, regulatory authorities, donors, technical partners, civil society and patient organizations	
Updating national scale-up plan • Update national scale-up plan as required based on results from initial adopting sites (e.g. activities, timelines, budget), sharing data in international forums	
Re-estimation of needs for drugs and consumables • Re-estimation of number of patients for the different regimens; adjustment of drug procurement plan as required, and re-estimation of needs for laboratory consumables	
Adjustment of National policy/Guideline documents, clinical protocols and SOP • Adjustment of National Policy/Guidelines, adjustment of clinical protocols, SOPs and job aids as required based on the experiences in the initial adopting sites	
Capacity-building • Cascade trainings (blended trainings) for all regions / laboratories involved	
Ongoing capacity-building and monitoring of the clinical care quality • Regular supportive supervision visits, clinical mentoring, distant virtual consultations, experience sharing visits including to laboratory facilities	
Digital health solutions • Expanding access to innovative treatment support technologies, use of digital health for blended learning (e.g. webinars, video-instructions, job aids)	
Monitoring • Regular data collection and analysis (enrolment progress, cohort analysis) and reassessment of needs for drugs and consumables, adjustment of procurement plan if needed. Sharing data in national and international forums (e.g. publications, conferences) and contributing to global policy update	

Costing

Funding sources for the introduction of the new regimen should be identified and funds secured at the time of preparation. In addition to the expected cost of planned activities, the confirmed or possible sources of funding should be noted in the budget plan. This will allow for targeted fund raising and advocacy to ensure that the costs of implementation will be covered. The budget should include the following items:

- Costs of medicines and pharmaceutical products (e.g. component drugs in the new regimen and ancillary drugs);
- Supply and management costs (procurement, storage, distribution);

- Costs of preparation activities (e.g. task force meetings, TWG meetings, sensitization workshops, situational assessment, communication materials, development of national plan, administration, technical assistance);
- Costs of system strengthening to meet the minimum requirements (e.g. upgrading/renovating infrastructure, maintenance, equipment needed for laboratory and for patient monitoring including for aDSM such as ECG, tuning forks, Ishihara test), costs of referral to laboratories and specialists;
- Costs of implementation (e.g. human resources including non-TB specialists, technical and management assistance, printing of materials, including job aids, training, laboratory reagents and consumables costs, aDSM, supportive supervision and monitoring visit to implementing sites, patient transport, or incentives); and
- Costs for enhanced monitoring and evaluation (M&E) during the initial adopting sites period and technical assistance for analysis and publication and dissemination of results in local, national, regional and international forums.

Monitoring and evaluation

Recording and reporting of the use of the new regimen should be part of the routine surveillance system established at country level for programmatic management of TB, including:

- Standardized definitions of cases and treatment outcomes;
- Standardized registration of cases;
- Generation of interim results and treatment outcome indicators; and
- Generation of data on the occurrence of serious AEs.

All the above need to adhere to the latest WHO recommendations and definitions.

Information on enrolment, results of treatment and AEs for all patients diagnosed and treated in the initial adopting sites, and subsequently in all sites of the country, should be collected; all patient related data should be disaggregated for sex and age groups (children 0–4, 5–14, adults). This will allow for assessment of experiences of patients and health workers, the implementation of the diagnostic and treatment algorithms (triage) and will allow for assessment of treatment outcomes in either cohort of DS-TB or DR-TB patients receiving different treatment regimens.

To ensure appropriate introduction of the new treatment regimen, a schedule for regular on the job support needs to be realized. National M&E protocols need to be adjusted for the new treatment regimen and used to generate the required information for the country to fine tune its implementation model.

The experiences of the initial adopting sites should be documented by collecting key data related to M&E results and programmatic implementation to inform the subsequent nationwide expansion of the new regimen. The interim cohort review will also allow to evaluate treatment response of individual patient during treatment and take timely action at patient and programmatic levels to prevent unfavourable treatment outcomes.

9.7 Monitoring treatment response and safety

Individuals undergoing MDR/RR-TB treatment require close monitoring throughout treatment, using appropriate clinical and laboratory testing schedules. Regular assessments should include medical history reviews, physical examinations, specialized tests (e.g. visual acuity assessments, peripheral neurological exams and electrocardiography) and laboratory monitoring (**Table 2.9.2**).

9.7.1 Monitoring the treatment response

The treatment response should be monitored through monthly sputum smear microscopy and culture, ideally conducted at the same frequency. Regular clinical assessments are critical to evaluate improvements in TB signs and symptoms, assess regimen effectiveness and prevent LTFU.

It is not always necessary to repeat radiological assessment during treatment because some radiological abnormalities may persist throughout and beyond treatment completion; hence, they may not indicate poor response or failure of treatment. However, radiological deterioration and new abnormalities (compared with baseline) may assist in identifying a poor treatment response. Therefore, radiological assessment should be repeated if clinically indicated.

There is growing evidence of resistance to both bedaquiline and linezolid in *Mtb* strains, particularly in patients who have been previously exposed to these medications. Reliable DST for bedaquiline, linezolid and all medicines included in the treatment regimen is crucial to understand the reasons behind a lack of bacteriological and clinical improvement. Ideally, DST for all medicines used in regimens should be accessible. However, this must not delay the initiation of life-saving treatment.

Before beginning a 9-month regimen, it is essential to have the patient's bacteriological status, including confirmation of TB disease, MDR/RR-TB (at a minimum) and FQ susceptibility. FQ DST is also critical for tailoring appropriate 6-month regimens such as BPaLM/BPaL, BDLLfxC, BDLLfx or BDLC. This ensures efficacy while minimizing unnecessary toxicity. However, the lack of immediate FQ DST should not hinder the initiation of treatment, because regimens can be started with combinations that allow flexibility pending FQ DST results.

NTPs should prioritize establishing baseline DST capacity for bedaquiline and linezolid, especially in patients with FQ resistance. Additionally, DST should be conducted on samples from patients with no bacteriological conversion after 4 months of treatment or in cases of recurrence while using 6-month regimens. Collecting strains for sequencing should also be considered as part of this effort.

All patients, and particularly children, should be followed up for clinical reassessment beyond treatment completion (ideally over a 12-month period) to monitor for potential relapse.

Treatment monitoring for special populations

For children, monitoring should also include regular assessments of weight, height and BMI using age-appropriate growth charts. Radiological assessments are not routinely required in children, but may help to identify poor treatment response in cases of clinical deterioration or when new abnormalities arise compared to baseline.

Monitoring treatment in pregnant and breastfeeding women with MDR/RR-TB requires close attention to both safety and efficacy; for this population, the 6-month regimen BDLLfxC or 9-month regimens, BLMZ or a linezolid variation, may be used (see **Section 5**). The modified 9-month regimen, BLMZ, is preferred over the 9-month regimen with linezolid owing to its limited drug count and history of use in pregnancy. Regular assessments should include fetal development monitoring, maternal health checks and drug-specific AE screening.

For breastfeeding women treated with shorter regimens, extra vigilance is needed to monitor infant health and potential drug exposure through breast milk. In both cases, adherence support and proper administration of MDR/RR-TB treatment are crucial. Care providers must ensure continuity of care between antenatal and TB services, which are often poorly integrated in high TB burden settings. Good communication between providers and the patient is critical to avoid unnecessary treatment modifications, reduce stigma and prevent LTFU.

For PLHIV, there are limited data but some promising results from current research. Monitoring should focus on regular viral load and CD4 count assessments, vigilant screening for DDIs between

TB medications and ART, close observation for overlapping toxicities, and adherence support for both TB and HIV treatments.

Treatment outcome definitions and reporting frameworks for DR-TB regimens, whether short or long, are consistent with those used for DS-TB regimens (see **Section 10, Chapter 1**).

9.7.2 Monitoring safety

Active surveillance for AEs is essential for all DR-TB regimens, to ensure patient safety and minimize both short-term and long-term morbidity. The WHO framework for aDSM (**Annex 3**) should be applied to patients receiving DR-TB regimens.

The recommended schedule for baseline, routine and post-treatment monitoring examinations (**Table 2.9.2** and **Annex 2**) applies to all DR-TB regimens, including 6-month, 9-month and longer regimens. This guidance ensures comprehensive patient monitoring, including monitoring of the treatment response and safety. The schedule should also consider specific situations where more frequent assessments may be necessary; for example, in cases of electrolyte disturbances, haematologic abnormalities or ECG irregularities. Additionally, closer monitoring is advised for high-risk groups, including older adults; PLHIV; and people with hepatitis caused by HBV or HCV, diabetes mellitus, moderate to severe hepatic or renal impairment, baseline anaemia or visual disturbances (e.g. glaucoma, cataracts or colour blindness). Audiometry and specific biochemical tests should also be made available whenever certain agents are included in regimens.

Generating additional evidence on AEs will further strengthen the safety profile of the shorter regimens across a variety of implementation settings. NTPs should actively monitor drug safety to ensure proper patient care, report AEs to the relevant drug-safety authority within the country, and contribute to informing both national and global policy.

Table 2.9.2. Recommended schedule of baseline, routine and post-treatment monitoring examinations for patients on DR-TB treatment[a]

Examination	Baseline	2nd week from start of treatment (for Lzd containing regimens)	Monthly	End of treatment	6 and 12 months post-treatment
Clinical evaluation by physician including weight/BMI	✓	✓	✓	✓	✓
Bacteriological tests					
Smear microscopy	✓		✓	✓	✓
TB culture	✓		✓	✓	✓
DST: Xpert MTB/XDR or First- and second-line LPA Phenotypic DST	 ✓ ✓		If culture remains positive at month 4 of treatment in cases of culture reversion or culture positivity during post-treatment follow-up		

Examination	Baseline	2nd week from start of treatment (for Lzd containing regimens)	Monthly	End of treatment	6 and 12 months post-treatment
Diagnostic tests					
Chest X-ray (Conduct every 6 months while on treatment)	✓			✓	✓
ECG (If regimen contains Bdq, Dlm, Pa, Mfx, Lfx or Cfz)	✓		In patients with preexisting cardiac disease and if the patient has any symptoms e.g. palpitations, dizziness or syncope	✓	
Visual acuity and colour vision tests (If regimen contains Lzd or E)	✓	✓	✓	✓	
Brief peripheral neuropathy screening (If regimen contains Lzd, H, Cs, Trd, Lfx, Mfx, or Am)	✓	✓	✓	✓	
Mental health screening (PHQ-9)	✓		✓ (If Cs or Hh containing)	✓	
Blood chemistry/Haematological/Immunological tests					
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (If regimen contains Z, H, Pa, Bdq, Eto/Pto, Cs/Trd, and PAS)	✓		✓	✓	
CBC with platelet count (If regimen contains Lzd, Mpm, H and Pa)	✓	✓	✓	✓	
Fasting blood sugar and/or glycosylated Hb (HbA1C)	✓				

Examination	Baseline	2nd week from start of treatment (for Lzd containing regimens)	Monthly	End of treatment	6 and 12 months post-treatment
Serum potassium	✓				
Creatinine	✓		✓ (If Am or S containing)		
Thyroid-stimulating hormone	✓ (If Pto/ Eto or PAS containing and 3 monthly)				
Albumin (If regimen contains Dlm)	✓				
Pregnancy test (For women of reproductive age)	✓				
HIV screening	✓				
CD4 count (latest test if PLHIV)	✓				
HBsAg and anti-HCV	✓				

BMI: body mass index; CBC: complete blood count; DR-TB: drug-resistant TB; DST: drug susceptibility testing; ECG: electrocardiogram; Hb: haemoglobin; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LPA: line probe assay; MDR/RR-TB: multidrug- or rifampicin-resistant TB; PHQ-9: Patient Health Questionnaire; PLHIV: people living with HIV; TB: tuberculosis.

Drugs: Am: amikacin; Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Eto: ethionamide; H: isoniazid; Hh: isoniazid high dose; Lfx: levofloxacin; LPA: line probe assay; Lzd: linezolid; Mfx: moxifloxacin; Mpm: meropenem; Pa: pretomanid; PAS: *p*-aminosalicylic acid; Pto: prothionamide; Trd: terizidone; Z: pyrazinamide.

[a] Schedule is applicable to all the recommended MDR/RR-TB treatment regimens.

9.8 Treatment outcome definitions

The standardized treatment outcome definitions are summarized in **Section 10, Chapter 1**. The treatment outcome definitions allow all patients with either DS-TB or DR-TB to have a treatment outcome assigned when completing treatment (cure or treatment success) or when unfavourable events occur (e.g. LTFU, failure or death). Although the definitions of treatment outcomes have been harmonized since 2020, minor differences remain between those for DS-TB and DR-TB (e.g. treatment monitoring by sputum culture for DR-TB and by sputum smear microscopy for DS-TB) *(184)*. Although the role of new bacteriological tests was considered, treatment monitoring will continue to rely on the available tools (i.e. sputum culture for DR-TB and sputum microscopy for DS-TB), despite their limitations.

9.9 Post-treatment follow-up

Patients that have completed a DR-TB regimen with a successful treatment outcome, ideally need to be monitored for recurrence for a duration of at least 12 months after the end of treatment. Some programmes may have capacity to ensure post-treatment follow-up and record the additional, optional outcome that is described in the WHO standard treatment outcome definitions *(184)*.

A patient who presents with TB after treatment completion may be sick due to a relapse with the same TB strain or due to reinfection with a new strain. Genetic fingerprinting can compare the initial infecting TB strain to the recurrent TB strain. In many settings it is not possible because genetic fingerprinting is not available. In areas with access to genetic fingerprinting, documenting relapse from reinfection can be a piece of important evidence to guide the design of the retreatment regimen. If programmes have the capacity, they are encouraged to freeze the baseline specimen so that it can be used for future comparison should the patient relapse or acquisition of drug resistance is the reason for treatment failure or relapse.

Patients in whom a DR-TB regimen has failed to produce a successful outcome present unique challenge and often their next regimen may be their last opportunity for cure.

This handbook suggests the following post-end-of-treatment schedule, described in **Table 2.9.3**. Monitoring cultures are sent at month 6 and month 12 regardless of if the patient has symptoms of TB or not. A combined monitoring table for post-end-of-treatment follow-up is provided in **Table 2.9.3**.

The patient should be well informed to contact the programme should symptoms of TB reoccur or if any family members or close contacts develop symptoms of TB. At the end of 12 months of post-end-of-treatment follow-up, the patient will be given a post-end-of-treatment outcome: sustained successful treatment (no evidence of recurrence), recurrence, death or lost to follow-up.

Table 2.9.3. Post-end-of treatment schedule

Activity	3 months post-end-of-treatment	6 months post-end-of-treatment	9 months post-end-of-treatment	12 months post-end-of-treatment
In-person clinic visit* or telephone contact**	X	X	X	X
Monitoring smear and culture (done regardless of signs of recurrence being present)	If indicated	X	If indicated	X
Chest X-ray	If indicated	If indicated	If indicated	If indicated
Any positive culture in the post-treatment period	Conduct resistance testing for all drugs			

*The clinical visit should consist of the weight, BMI, and brief peripheral neuropathy screen as well as any other clinical and laboratory examination needed based on symptoms.

**Telephone contact is acceptable only when it is not feasible for the patient to come for an in-person clinic visit. Discuss directly with the patient only, unless permission has been granted to discuss the patient's illness with a family member or health proxy.

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Chapter 3
Tuberculosis care and support

1. Introduction

Tuberculosis (TB), including its drug-resistant forms, can affect people in all parts of society. However, its effects are often most devastating among the poorer and more marginalized members of a society. A person's quality of life, social status and financial situation can be made worse both by the disease and by its treatment, namely: adverse drug reactions produced by the treatment, the high costs he or she may have to pay while undergoing care and treatment, having to miss work due to illness, and the stigma and discrimination linked to the disease. People who are poorer or have less social support may suffer these effects the most because they may have fewer resources to help them through the illness. The delivery of person-centred care and social support is essential to the management of TB and should protect human rights and support ethical standards, reducing the patient's and family's social and economic costs and using the most effective methods to prevent and treat the disease. Person-centred care and social support also contribute to improving the treatment outcomes and quality of life of people with TB. In many cases it also makes a difference in enabling the patient and family to access health care.

This chapter addresses the person-centred care approach to treatment administration and the social support framework for programmatic management of TB – both aimed at improving the quality of life of patients, enabling their adherence to treatment and reducing social and economic costs. The scope of the social support recommended in this operational handbook chapter includes several elements of the social assistance recommended in forthcoming guidance on social protection for people affected by TB. This module, however, emphasizes the interventions recommended to improve TB treatment outcomes.

Key WHO recommendations on TB care and support

1. Care and support interventions for all people with TB	
1.1	Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment *(Strong recommendation, moderate certainty of evidence).*
1.2	A package of treatment adherence intervention[26] may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option[27] *(Conditional recommendation, low certainty of evidence).*

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

[27] Suitable treatment administration options include various forms of treatment support, such as video-supported treatment and regular community or home-based treatment support.

1.3 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[28] or digital medication monitor[29] *(conditional recommendation, very low certainty of evidence)*;

b. material support to patient[30] *(conditional recommendation, moderate certainty of evidence)*;

c. psychological support[31] to patient *(conditional recommendation, low certainty of evidence)*;

d. staff education[32] *(conditional recommendation, low certainty of evidence)*.

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

a. Community- or home-based treatment support is recommended over health facility-based treatment support or unsupervised treatment *(Conditional recommendation, moderate certainty of evidence)*.

b. Treatment support administered by trained lay providers or health care workers is recommended over treatment support administered by family members or unsupported treatment *(conditional recommendation, very low certainty of evidence)*.

c. Video-supported treatment (VST) can replace in-person treatment support 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 of evidence)*.

2. Models of care for people with drug-resistant TB

2.1 Patients with multidrug-resistant TB (MDR-TB) should be treated using mainly ambulatory care rather than models of care based principally on hospitalization *(conditional recommendation, very low certainty of evidence)*.

2.2 A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment *(conditional recommendation, very low certainty of evidence)*.

3. Models of care for children and adolescents exposed to TB or with TB disease

3.1 In TB high burden settings, decentralized models of care may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB *(conditional recommendation, very low certainty of evidence)*.

3.2 Family-centred, integrated models of care to deliver TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB, in addition to standard models of care *(conditional recommendation; very low certainty of evidence)*.

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

[29] 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 patient to take medications, along with recording when the pill box is opened.

[30] 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 consequences of income loss related to the disease.

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

[32] Staff education can be adherence education, chart or visual reminder, educational tools and desktop aids for decision-making and reminder.

2. People-centred approach

In view of the high burden of disease, death and suffering associated with TB, Standard 9 of the *International standards for tuberculosis care (1)* states: "A patient-centred approach to treatment should be developed for all patients in order to promote adherence, improve quality of life, and relieve suffering. This approach should be based on the patient's needs and mutual respect between the patient and the provider". In 2016, WHO advocated a people-centred care approach which is focused on, and organized around, the health needs and expectations of people and communities rather than focusing on patients or diseases *(2)*. As a result, a people-centred model of TB care was defined as "an efficient and integrated set of affordable, accessible and acceptable health services, provided in a supportive environment to prevent, diagnose and treat TB" *(3)*.

A people-centred (also referred as person-centred in this section) approach recognizes that TB care should be designed to address the needs, values and preferences – and protect the rights of – the people who suffer from TB in order to ensure successful treatment outcomes and improve their well-being and financial risk protection. People-centred or person-centred care "reflects care that is holistic, individualised, respectful and empowering, and considers the person as central to the process of care, encouraging informed, shared decision-making and self-determination. It means that a person and a health-care provider work together, discussing care options, treatment risks and benefits, to reach collaborative care decisions. Rather than being a passive recipient of health-care, the person is an active participant." *(4)*.

In contrast to a disease-centred approach where the focus was on medication treatment only, a people-centred approach also focuses on supporting people to overcome the social economic, cultural, legal and psychological difficulties that can affect their response to the diagnosis and treatment of TB. Through person-centred care, the patient with TB is the most important person in the care plan; therefore the social and personal needs and preferences of the patient – not just the immediate requirements of medical treatment – are also focused on. This approach should also allow people to know and use their patient rights and fulfil their treatment responsibilities while being treated with respect and dignity and having their values and needs reflected in their treatment and care whenever possible.

Person-centred care is defined as "providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions". Pillar 1 of the End TB Strategy *(5)* clearly endorses this approach which treats patients as the most important element when providing TB treatment.

A people-centred approach focuses on the overall well-being, choices, convenience and safety of the individual patient. Thus, it takes account of the social and personal circumstances of the person, and not just the immediate requirements of medical treatment *(6)*. A people-centred approach helps to build a partnership between the people suffering from TB and health care providers, allowing care to be adapted to individual patient needs with the goals of improving the ability of patients to take all their medications and curing them from TB. The ability of a person to take all their medications is influenced by a number of factors, namely: the person's knowledge, attitudes and beliefs about the disease, the treatment and the health care system; family experiences and beliefs; economic concerns (e.g. the ability of a patient to pay the costs associated with treatment); the health care system's ability to support the patient; and available community resources to deal with the stigma and discrimination

surrounding TB. These concerns can be resolved by making sure that patients have the support they need to complete their treatment. The types of support are described later in the module.

TB care is not just about the science of treatment but also about human rights and social justice. The ethical values recommended for TB programmes include equity, the common good, solidarity, reciprocity, the harm principle, trust and transparency, the duty to care, effectiveness, efficiency, proportionality, participation and community engagement, respect and dignity, autonomy, privacy and confidentiality *(7)*.

Frequently, TB most strongly affects people who are already marginalized and can worsen existing inequalities and discrimination. The marginalized include persons who are homeless, persons who use drugs, persons living with HIV, people who are incarcerated, indigenous persons and undocumented migrants. These persons experience stigma and discrimination in their day-to-day lives and care must be taken to ensure that this is not worsened in the context of TB. In addition, health care providers should keep in mind that gender may also be a driver of stigma in people with TB *(8)*.

The violation of human rights of people with TB is well recognized *(9, 10)*. Persons with TB often experience stigma and discrimination in many areas of life, including work, social activities and family life. They may also have difficulties in following medical advice due to social, economic, cultural and legal reasons. Consequently, it is important that the health care services are aware of all the barriers faced by people affected by TB and provide appropriate and comprehensive social support to help them cope successfully with the hardships of treatment. TB stigma can be defined as the negative labelling or rejection of people with TB, and often also their families, due to stereotyping or other negative traits associated with TB and the affected communities. As a result of a diagnosis of TB, people may experience feelings of shame, self-hatred, guilt or blame which may affect their ability to accept the diagnosis and to follow their care and treatment plans.

Health care workers may also be prejudiced against people with TB, and this may affect their interactions with patients with TB. They may do things that further stigmatize these patients, either through how they interact with the patient, the language they use or even the practices that are built into the health care system. If health care providers are not well supported and TB services lack resources, the health care workers may feel undervalued, which may reinforce stigma and prevent them from delivering quality care. Fear of infection can also serve as a driver of stigma in health care workers and may have an adverse impact on their relationships with people affected by TB.

In order to support people with TB during their treatment, health policies must reflect the fact that TB affects all aspects of peoples' lives. Caring for each person as an individual should be the basis of treatment and care. The following principles can be followed for person-centred care and support *(11, 12)*:

1. Focus on the patient's concerns and priorities.
2. Refer to the 5 A's aspects of care: Assess, Advise, Agree, Assist and Arrange.
3. Link the patient with a suitable TB treatment supporter.
4. Screen, assess and manage undernutrition.
5. Recognize and address poverty and food insecurity by linking TB patients to national social protection measures and ensure their inclusion in appropriate national legislation.
6. Organize proactive follow-up and maintain regular communication with the patient in order to work as a team.
7. Involve former patients, peer educators and health care workers providing support in health facilities or communities.
8. Link the patient to community-based resources and support.

9. Provide integrated care in collaboration with other public health programmes, such as those for HIV, diabetes care, maternal and child health, lung health and mental health services.
10. Assure continuity of care, including palliative and end-of-life care whenever needed.

Although building person-centred high-quality TB care as outlined in the *International standards for tuberculosis care* will often require additional human resources, a lot can be achieved by training health care providers to respect patients' rights and by developing communication skills to involve patients and their families actively in TB care *(5, 13, 14)*.

3. Care and support interventions to enable TB treatment adherence

Ensuring adherence to TB therapy is one of the important challenges for achieving a successful treatment outcome, particularly for patients with drug-resistant TB (DR-TB). This is because of the large number of medications, the frequent and serious adverse drug reactions, and the social and financial costs to patients related to TB treatment. Because DR-TB and extensively drug-resistant TB (XDR-TB) treatment are often the last chance for treatment for many patients, and because there are serious public health consequences if treatment fails, it is important that all patients are supported using a person-centred approach to ensure full adherence to treatment *(7)*.

Good adherence to TB treatment (taking all the medications at the correct time) is essential to prevent the development of resistance and increase the chances of cure. Taking all the medications for TB therapy is difficult, particularly for DR-TB, because treatment regimens can sometimes be long, the daily pill burden is high, there are frequent and serious adverse drug reactions, and access to care can cause social and economic costs to patients. A person-centred approach is needed to maximize treatment adherence and enable early intervention with patients who are not responding to treatment, who are not able to take their medications or who are having adverse effects from treatment. Optimal person-centred care consists of multiple interventions, including social support (informational/educational, psychological and emotional, and material support), treatment administration options and digital adherence technologies. Staff education and support that allow health care workers to provide health education and counselling on TB disease and treatment adherence are strongly recommended. It is also recommended that all patients receive medicines under an appropriate treatment administration option and that they benefit from social support interventions that ensure full adherence to treatment, with a person-centred approach based on sound ethics and with respect for human rights.

NTPs need to improve patient access to quality treatment adherence interventions and optimal treatment administration options. Although all people with TB should receive appropriate care and support interventions, particular attention should be paid to patients being treated for DR-TB because DR-TB treatment is often the last therapeutic option for many patients and there are serious public health costs if treatment fails.

The following recommendations from the WHO guidelines on TB care and support *(15, 16)* continue to apply to patients with drug-susceptible (DS) and drug-resistant (DR) TB.

No.	Recommendation
1.1	Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. *(Strong recommendation, moderate certainty of evidence)*
1.2	A package of treatment adherence interventions[33] may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option.[34] *(Conditional recommendation, low certainty of evidence)*
1.3	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[35] and/or digital medication monitor[36] *(Conditional recommendation, very low certainty of evidence);* b. material support[37] to patient *(Conditional recommendation, moderate certainty of evidence);* c. psychological support[38] to patient *(Conditional recommendation, low certainty of evidence);* d. staff education[39] *(Conditional recommendation, low certainty of evidence).*
1.4	The following treatment administration options may be offered to patients on TB treatment: a. Community- or home-based treatment support is recommended over health facility-based treatment support or unsupported treatment *(Conditional recommendation, moderate certainty of evidence).* b. Treatment support by trained lay providers or health-care workers is recommended over treatment support by family members or unsupported treatment *(Conditional recommendation, very low certainty of evidence).* c. Video-supported treatment (VST) may replace in-person treatment support when the video communication technology is available and it can be appropriately organized and operated by health-care providers and patients *(Conditional recommendation, very low certainty of evidence).*

3.1 Social support in TB management

TB causes suffering and even death. Despite highly effective treatment, there are many psychological, social, medical and economic factors that can prevent people from accessing diagnosis, following

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

[34] Suitable treatment administration options include various forms of treatment support, such as video-supported treatment and regular community or home-based treatment support.

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

[36] 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 may send an SMS to remind the patient to take the medications, along with recording when the pill box is opened.

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

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

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

care plans and successfully completing a course of treatment. The following is an adapted summary of how these factors may have an impact on psychological health, health-seeking behaviour and adherence *(8)*:

1. Stigma, fear of discrimination, social isolation and lack of social support can affect screening, access to care and the ability to complete a treatment plan.
2. The poorest and most marginalized communities that are at high risk of TB are also most likely to experience significant health and economic inequalities which further limit their access to care and treatment.
3. The diagnosis of TB may cause distress and have an impact on self-worth that may affect patients' sense of agency.
4. Financial worries and limitations on everyday activities associated with TB (e.g. time off work) and its treatment (e.g. diagnostic and treatment costs, transport costs) add to the burdens on the patients.
5. Long treatment duration may cause frustration and possible side-effects may make treatment intolerable or unpleasant, leading people to interrupt treatment.
6. Life situations (e.g. financial challenges, a death in the family or marital difficulties) may have a negative impact on psychological health and on patients' ability to take their medication.
7. TB often presents with comorbidities (e.g. diabetes, HIV/AIDS) which may cause further difficulties for the patient.
8. People with TB may also have mental disorders – such as opioid or alcohol use disorders or depression – that may complicate their ability to adhere to treatment or tolerate medication without additional support. Similarly, some TB medications may also worsen mental health conditions.
9. Poor-quality medical care without rights-based, people-centred and respectful care can also add to the psychological burden of illness and treatment.
10. When treatment fails, people grieve and may suffer and feel hopeless.
11. Lack of support from services, friends and family may harm the patient's emotional health.
12. TB and its long-term treatment affect families and caregivers. Their anxieties and burden of work taking care of the patient can make it difficult to support treatment adherence, infection control and the patient's needs over time.

Several populations are particularly vulnerable to TB and at higher risk of having poor outcomes, namely: children, miners, migrant populations, people who are incarcerated, and people who suffer from opioid or alcohol use disorders. Health care providers who deal with vulnerable populations need to have skills to assess and respond to the psychological and social needs of these people when TB is detected *(17)*.

Social support is very important to a people-centred approach to improve the well-being of people infected with TB and to support treatment plans by addressing the barriers described above. Social support must be available for people throughout TB treatment, from diagnosis to the conclusion of the treatment.

Social support refers to the amount of perceived and practical care received from family, friends and/or the community *(18)*. It aims to provide care to patients to show that they are part of a social network that cares for them. Social support improves health outcomes and reduces death. Adding social support to the medication treatment regimens can improve treatment outcomes for people suffering from TB *(15, 16)*.

Social support is made up of four resources, namely *(11)*:

1. Informational support is information or education that helps a person to solve problems and reduce stress; it includes training and education on the medications a person is taking, their possible side-effects, how treatment is monitored, and how the success of treatment is determined.

2. Psychological (emotional) support refers to all types of care that strengthen self-esteem through understanding, trust, encouragement and care, and that help to deal with the psychological challenges in life.
3. Material support includes financial support which could be money (e.g. grants from the government), food support, travel support or anything that helps the patient with the financial costs of TB disease and its treatment.
4. Companionship support is help that makes a person feel that he or she belongs to the social system, and that he or she can rely on it for certain needs.

Creating a way for the TB programme to deliver these four social support resources to patients, taking into consideration any specific age- or gender-sensitive concerns, is necessary for a person-centred approach that makes sure patients are doing well and can complete their TB treatment. The principles of social support described here should be ensured for vulnerable populations, including older persons, people who are incarcerated, internally displaced persons or refugees, people with substance use disorders, indigenous communities and ethnic minorities.

Many programmes use a multidisciplinary "support to adherence" team (social workers, nurses, health educators, community treatment supporters and doctors). Support may focus on problems related to different stages of treatment, social stigma of the illness, treatment adherence, side-effects, financial and social difficulties, other comorbidities or special situations and death.

The type of support should be selected on the basis of an assessment of the patient's needs, the health provider's resources and conditions in the community. A single type of support or a combination of different types of social support can be chosen for each patient according to the individual needs. Social support should be available to people in inpatient or outpatient care, including home- or community-based treatment and care, peer support and community TB support programmes.

3.1.1 Informational and educational support

This support includes all information necessary to help patients and their caregivers understand TB, including the biological and social determinants of the disease, and agree on the steps for following the treatment plan and participating in local activities to engage communities in the response to TB. As an example, the guide on the standardized package of community-based support services to improve TB outcomes describes many of the possible services for adherence support in detail *(19)*. Provision of information and education should begin as soon as diagnosis is made and should continue throughout the course of treatment. Patient information and education take place over several visits with different health care providers, including physicians, nurses and community health workers. Materials should be appropriate to the literacy levels of the patient, available in local languages and should be gender-, age- and culturally sensitive. Information and educational pamphlets with reminders of the main points, in the local language, are helpful. For patients with literacy limitations, efforts should be made to use e-health tools based on audio or visual support.

Patients should also be provided with material to help them understand their rights in their local language *(9, 10)*. The Patients' Charter for Tuberculosis Care also describes the responsibilities of patients and will help the provider to educate the patient about the disease, the treatment and the overall response of the government and civil society to the TB epidemic.

The NTP and all health care providers should use methods of "communicating with" (and not "talking at") patients and their caregivers in a way that builds a positive partnership towards successful improved quality of life and treatment completion. For patients with literacy limitations, e-health tools based on audio or visual support should be used.

Although implementing patient-centred high-quality TB care as outlined in the *International standards for tuberculosis care (1)* will often require additional time to be spent by health care workers, a lot can

be achieved with simple changes in the attitudes and language used by health care providers and by communicating key information about the disease.

The ethical and person-centred approach of the End TB Strategy is to be reflected as well in the language used by all TB stakeholders, including health care providers. Language is a well-known method of exerting power and control. Words such as "defaulter", "suspect" and "control" contribute to disempowering TB patients despite the good intentions of the health care providers. It is still not uncommon to find expressions such as "patient failed treatment", which puts the blame only on the patient as if he or she were the only person responsible for failure of treatment. WHO has recommended replacing such language with words that are more respectful of patients and reflect better the values of the patient-centred approach to care that is now widely accepted in the TB community. Some examples include replacing "defaulter" with "person lost to follow-up", "TB suspect" with "person with suspected TB" or "person to be evaluated for TB"; and "control" with 'prevention and care'. This handbook and future TB documents of WHO are taking note of this suggestion to prevent derogatory and judgemental tones in the language used with patients and within TB prevention, diagnosis, treatment and care *(20)*. For further details, see **Section 4.2** on Effective communication skills and **Section 4.3** on Counselling to provide information.

3.1.2 Psychological and emotional support

Dealing with TB and its treatment can be emotionally devastating for patients and their families. As a result, there is immense distress that affects the quality of life of patients and that may also interfere with the way they follow their treatment.

Emotional support usually refers to having close relationships with family and friends, with whom one can talk and feel loved and cared for. Psychological support is based on a skill set whereby trained personal can help alleviate distress. Psychological support tries to help with thought, emotional and behavioural concerns that may arise because of the stress of being diagnosed with TB, because of the treatment, or because of other life situations or stresses caused by TB. Informal psychological support can be provided by physicians, nurses, treatment supporters, family or community members by building a relationship with patients based on understanding and compassion to help them deal with psychological challenges in life, solve problems and lessen sources of stress. This kind of support may also help patients to follow their treatment plans and gain the skills needed to deal with stigma and discrimination. Details of techniques to provide psychological support are further discussed in **Section 4.5**.

For formal psychological support – particularly if informal support is not successful, the impact of the challenges is severe or mental health problems are suspected (e.g. depression, substance and alcohol misuse, and persons experiencing post-traumatic stress disorder) – some TB patients may need to be referred to mental health services. There is also a close association between common mental disorders, including substance use disorders, which is described in **Section 4.5**. Therefore, it is essential to have a comprehensive assessment and referral system between TB, mental health services and community support.

Formal methods of providing psychological support can be one-to-one counselling sessions or support groups assisted by counsellors. Support groups may allow patients with TB to meet and socialize with other patients, including those who have recovered from TB, and provide support to each other as well. Further details are discussed in **Section 4.5** on Counselling to provide psychological support.

Support group

A support group should be guided by a counsellor, social worker or someone trained in guiding support groups. A trained community nurse or health worker may also help with the group.

- Some groups may be for patients with specific needs or concerns (e.g. women, young people).
- Psychological support is important for patients who may still be infectious, and infection control measures should be established to enable such persons to gather in support groups safely or in a way that minimizes the risk of TB transmission to other patients or health care staff (e.g. outdoor or virtual meetings).
- Patients who have recovered may also be invited to support groups as they provide hope to patients who are still on treatment.
- Support groups may need help in inviting participants or finding a safe meeting place and may face other organizational challenges.
- At the end of each support group meeting, the facilitator and co-facilitator should stay behind to discuss and evaluate the lessons learned in the process and to plan the next session.

For patients with serious psychological problems, the group may require to be facilitated by an appropriately trained mental health professional.

3.1.3 Material support

Socioeconomic problems should be addressed to enable patients and their families to be able to complete TB treatment and reduce the impact that the disease and treatment have on their quality of life. These challenges can be successfully tackled through socioeconomic interventions, such as food baskets or transportation vouchers, that enable patients to complete the treatment and which usually work best when they are adapted to a patient's specific needs. Some NTPs and health care providers have used these as enablers – i.e. as a means to help patients to address hurdles in taking medication and completing therapy. While enablers may improve outcomes, it is most important to use material support to overcome barriers that otherwise would be impossible for patients to overcome without some form of support.

Material support can be services or commodities – e.g. financial support, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing enablers or cash transfer. This support helps patients or caregivers with the costs they face in order to obtain health services and tries to lessen the stress of income loss related to TB. At the beginning of treatment, the financial resources of the patient should be evaluated in order to support those in need of assistance using material support. The most support should be given to patients with the most need. Health care workers, treatment supporters, social workers or other professionals can help evaluate needs and make sure the material support reaches the patient. Cash transfers and microfinance support can improve household food security, which has been shown to increase access to health care. When prolonged hospitalization is necessary, supporting the patient and their family financially with a minimum "living-allowance" would be a helpful step under the patient-centred care approach.

Nutritional support is particularly important and can be part of material support. Not only does nutritional support help to lessen the financial stress of TB disease, but malnutrition/undernutrition can

make TB disease worse, and TB can cause malnutrition. People who are malnourished/undernourished and who have TB disease are more likely to have worse outcomes and are more likely to die of TB than others. Children and pregnant/breastfeeding women are at particular risk from malnutrition. Treatment of malnutrition/undernutrition through material support should be considered just as important as other TB medications when managing patients with TB. Indeed, nutritional support should be included as part of a standard treatment and care plan for TB. Further details on nutritional care and support can be found in the *Guideline: nutritional care and support for patients with tuberculosis (21)* and *WHO framework for collaborative action on tuberculosis and comorbidities (22)*.

The involvement of civil society – such as patient support groups and nongovernmental organizations, as well as community- or faith-based organizations – is necessary to provide social support services. A more long-term way to provide material support to TB patients is to include all patients who qualify in the social protection programmes (such as unemployment benefits if the patient cannot work) that many countries have for vulnerable populations.

3.1.4 Companionship support

On-site social support for patients, their families and friends through peer counselling can improve the effectiveness of TB programmes. TB programmes can develop support activities that identify patients who have been cured ("community champion" or "ex-patient") and provide them with training to be a peer supporter. This worker engages in support, treatment literacy and communication with other patients under treatment. These community champions or ex-patients should follow each patient from diagnosis through to cure, and they should act as both friend and educator. From the patient's perspective, having this companion available reduces the psychological burden of the long duration of treatment and provides them with skills to cope with TB stigma and discrimination.

Peer support groups, community champions or ex-patients and trained health workers can offer information-sharing sessions to educate patients, help with better detection of risk factors for default (e.g. understanding adverse effects of medication) and identify other warning signs that can affect treatment outcome.

Companionship support provides the basis for developing a social network within the care facility, which can play an essential role in improving rates of treatment completion. Working together, a health worker, a peer supporter and the patient can build a spirit of collaboration and innovation aimed at reducing stigma and can reaffirm that TB can be successfully treated within an environment of mutual respect among all involved.

3.2 Treatment administration and digital adherence technologies

3.2.1 Treatment support

Treatment administration options that are effective and suitable should be considered for each patient at the start of the patient's treatment. Treatment support (an updated adaptation of directly observed treatment) is defined as another person (either a health care worker or a lay person) helping a patient with TB take his/her TB medications, providing emotional support and medically intervention (or recognizing when medical intervention is necessary) in the case of non-response to therapy or adverse effects from treatment. However, some subgroups of patients with factors affecting treatment adherence are more likely or less likely to benefit from certain forms of treatment support than other patients are; or certain types of delivery of treatment support (e.g. location of treatment support or type of treatment support provider) are likely to work better than others. Consequently, an assessment is required at the start of treatment in order to choose the most appropriate treatment administration

option for each patient. Treatment provided closer to the patient normally offers convenience for the patient and, therefore, achieves better outcomes. Treatment support delivered at home or in the community, near the patient's home or workplace, should be considered as the preferred options as they have shown better outcomes than treatment support provided at a health care facility, which is normally further away from the patient than the other options *(15, 23)*.

The TB treatment supporter should maintain strict confidentiality regarding the patient's disease and treatment. In some cases, this may require working out a system whereby the patient can receive medication without the knowledge of others. The TB treatment supporter should be someone whom the patient is comfortable with. The TB treatment supporter should have the appropriate training and skills. Although evidence shows that treatment support by a health care worker, trained lay provider and family member displays advantages compared to unsupervised treatment, treatment support provided by trained lay providers and health care workers are the preferred options and the least preferred treatment support provider is a family member *(15)*.

In some settings and circumstances treatment support may be provided by health workers and in others by community members trained to deliver treatment for all forms of TB. While family-based treatment support has shown effectiveness in several settings, health care workers should be aware that family relationships can be complicated for the TB patient, and as a result either the patient or the family TB treatment supporter may encounter subtle manipulation or abuse that can jeopardize adherence to treatment, management of adverse drug reactions and access to social support services. Training and education for health care workers and treatment support providers are necessary to ensure the quality of treatment administration. Training and education can be done through many types of educational sessions, charts or visual reminders, educational tools and desktop aids for decision-making and reminders.

When in-person treatment support is not possible for the patient and treatment provider, digital adherence technologies, such as video-supported treatment (VST), short message service (SMS), telephone calls or other means of communication can be considered when they are available and can be used by both health care providers and patients.

3.2.2 Digital adherence technologies

Various digital health products are being used to support different elements of TB programmes, such as electronic health records, direct data transfer from diagnostic systems and e-Learning modules on mobile applications *(24)*. Digital adherence technologies fit into the larger landscape of information technologies and are intended to help improve communication between patients and health care workers *(25)*. Three technologies have been studied in TB patients and are used to support treatment on a large scale, namely SMS or mobile text, event monitoring devices for medication support (EMMs) and VST for TB *(26, 27)*.

SMS is a standard, built-in function found in all types of mobile telephones worldwide and is generally inexpensive and easy to use. It is thus widely applied for communicating with outpatients. SMS can provide regular, automated message reminders to patients to take their medications, can provide information related to their health or condition (unidirectional) or provide opportunities to interact as well (bidirectional). Most RCTs of SMS reminders in TB care in different geographical settings failed to show improved patient outcomes when compared with standard care. However, the control groups in these trials achieved high levels of adherence through varying scales of in-person support. The results also suggest that SMS could, to some degree, support adherence at times during treatment when in-person treatment support by a health care provider is not possible, thus increasing efficiency if not effectiveness. SMS could also be used when there is less necessity to see the patient face to face but there is still a need to keep in contact with the patient in case any concerns arise, such as during the continuation phase of treatment or when a patient has been on stable treatment for a long time without any problems. Research has yet to look more creatively at how SMS can influence

adherence behaviour other than just by reminding people to take their pills, such as by channelling cash transfers when treatment milestones are achieved, by combining SMS reminders with other digital solutions and by targeting other points along the patient pathway. The popularity and affordability of SMS present a compelling case for further studies to investigate its potential more exhaustively. Instant messaging via installed mobile software may be used instead of SMS.

EMMs aim to provide more patient flexibility when following up treatment; to support patients with dosing and refill reminders and instructions; and to compile patient-specific dosing histories to enable counselling and differentiated care. EMM boxes consist of automated electronic devices that record and inform the health care provider about the regularity with which a medicine container is opened. Older devices recorded usage on the container itself, but mobile telephones now allow patient reminders and alerts to be sent to the caregiver when medicine boxes remain unopened for a day or more. A large cluster-randomized trial showed a statistically significant effect of EMM boxes on adherence relative to the SoC; however, the effect on successful treatment completion was less clear *(28)*. Various technological advances with EMMs, such as requiring patients to dial in (to toll-free numbers) codes revealed when daily blister packs of medications are opened can be used to verify adherence. Under trial, a prototype brand of this technology – 99DOTS *(29)* – showed similar treatment completion rates when compared to the traditional adherence monitoring and support used by the sites, suggesting that this EMM could be a viable alternative to more labour-intensive forms of medication adherence monitoring *(30)*. Nonetheless, more evaluation is needed of the feasibility and utility of this technology *(31)*.

VST is the form of digital adherence technology that most closely replicates human interaction. The increasing availability of Internet-enabled smartphones and tablet computers equipped with free or customized video communication software has increased options for both real-time (synchronous) and recorded (asynchronous) interactions. Observational studies and trials of VST for TB treatment from different settings suggest that the technique can produce similar outcomes to those produced by in-person monitoring and can improve efficiency *(32–35)*. Given the potential benefits of VST, studies are needed to evaluate it against different standards of care, including self-administered treatment, and to evaluate the acceptability of VST in different population subgroups and in more resource-limited geographical settings.

The advantages of using VST are its potential to provide treatment support from a distance – and even when people travel and cannot visit or be visited by a TB treatment supporter. VST could help achieve better levels of patient interaction at a much lower cost and less inconvenience when compared with in-person treatment support. VST can be used in addition to, or interchangeably with, in-person treatment support or other treatment administration options.

Another option for providing care to patients when face-to-face visits are difficult is to schedule appointments to talk with them by telephone. Questions regarding treatment can be answered, symptoms can be monitored and counselling can be provided. Care should be taken to make sure that patients are able to find a place to talk where they have privacy. Also, if airtime is expensive, the length of time needed for these discussions may be too costly for the patient.

The performance of digital adherence technology under study conditions needs to be translated into programmatic realities. Health care practitioners and patients require practical aids that can adapt to a patient's treatment course across a wide variety of different treatment conditions and at distinct time points when treatment interruption is more likely to happen. Technologies for treatment adherence support should be part of an integrated approach that complements the delivery of quality care. For instance, it is unrealistic and undesirable for patients on a longer DR-TB regimen to be placed on exclusive VST for 18–20 months. The risk of interruption is not uniform between patients or even during the treatment of the same patient. Treatment support therefore needs to be flexible throughout a patient's course of treatment. Special attention is needed when there is a change in the treatment regimen which increases the risk of developing adverse medication reactions when: 1) the patient questions the need to continue the prescribed treatment as symptoms disappear and when she or

he feels better; 2) conversely, when the patient may not be feeling better and may feel that treatment is hopeless; 3) when the patient travels far away from the usual treatment centre; or 4) when other events affect a patient's daily routine and make daily treatment more difficult.

The three digital approaches discussed have specific strengths and weaknesses, which may make them work better in some circumstances rather than in others, as well as differing preferences of the patient and health care workers. On the basis of the different characteristics of each of the adherence support technologies and the patient's individual situation, multiple options might be suitable. Two additional issues to consider are access to smartphones and to broadband Internet via mobile subscriptions. Smartphones and tablet computers, given their computing power and storage space, could be a valuable resource for multiple aspects of TB care. These can be useful even when broadband Internet is unavailable or erratic (e.g. recording of asynchronous VST, storage of patient medical records and e-Learning applications). SMS and EMM – which can operate without mobile broadband Internet coverage – are currently the most accessible, affordable and easily expandable treatment support approaches in resource-limited settings. Where mobile Internet is reliable and computer hardware available, solutions with more connectivity requirements can be considered as options.

The increasing range of technologies available for treatment support helps improve person-centred care. Nonetheless, digital technologies are still to be regarded as tools and should not replace face-to-face interactions when these are more appropriate. Another important consideration is that digital adherence technologies depend on the regular observation of a person's behaviour in order to follow up adherence. This poses a number of ethical issues *(7)*. Some technologies may affect a patient's privacy more than others – such as receiving a daily SMS text message that asks for a reply, the automated monitoring of the opening of a medicine box, or a video recording of a medicine being swallowed. The benefits of having recordings of patients taking their medications and the ability to text or speak with patients have to be balanced against potential downsides – such as patients feeling they are being controlled, a sense of being tracked and distrusted, loss of empowerment and concerns about confidentiality. These issues need to be discussed at length with the patients (see **Section 4.1** on Guiding principles for health education and counselling). Further issues to consider when determining which treatment support technology may be best for a patient include the ability and willingness to learn to use the technology. Visual impairment and literacy may make it difficult for patients to use mobile telephones correctly. Another concern is that the cost of airtime or data may be too expensive for patients to use some of these technologies. Acceptability and preferences should be explored with each patient as part of her or his adherence plan.

3.3 Selecting a suitable package of care and support for a patient

To support people with TB during their treatment, health policy-makers and practitioners must appreciate that TB affects all aspects of patients' lives. A focus on caring for each patient as an individual should underlie all aspects of treatment and care. Overall, the principles for person-centred care and support (described in **Section 2**) should be followed.

The evidence reviewed and WHO recommendations suggested that a combination of appropriate care and support interventions improves outcomes for patients *(15, 23)*. Selecting appropriate interventions for each patient is very important and requires proper assessments and consultation with each patient to identify her or his needs and preferences. This should be done both prior to the start of the TB treatment and during the treatment. All the recommended interventions should be considered as part of this process – including social support, treatment administration options, digital adherence technologies and the model of TB care.

Box 1 describes the use of the 5 A's (Assess, Advise, Agree, Assist and Arrange) that help to facilitate a process for identifying the best treatment plan together with the most appropriate package of care and support interventions that best suits the patient.

Box 1. The 5 A's: Assess, Advise, Agree, Assist and Arrange

ASSESS

- Assess the patient's knowledge, beliefs, concerns and daily behaviours related to TB and its treatment.
- Assess the patient's goals at the start of any consultation.
- Assess the patient's clinical status, identify relevant current or previous TB treatments or other diseases and provide education on TB disease and treatment and infection control.
- Assess the patient's ability to take medication.
- Assess factors associated with the patient's lifestyle that might prevent them from taking their medications (e.g. opioid or alcohol use disorders).
- Assess for any comorbidities that may need special attention or may affect treatment (in particular HIV, diabetes, hepatitis or other liver disease, kidney disease, tobacco use, mental health illnesses).
- Assess for the presence of adverse effects from medications.
- Assess the financial situation (job, education, dependents, patient's living conditions (if s/he has a stable place to live).
- Assess the patient's capacity and available conditions for using digital adherence technologies.

ADVISE

- Use neutral and nonjudgemental language. Speak in a language that the patient understands and use words the patient understands (avoid complex medical terms).
- Correct any inaccurate knowledge (as assessed above) and complete gaps in the patient's understanding of his/her conditions and/or risk factors and treatments.
- Discuss the treatment plan options (including different treatment regimens, different medication delivery/pick up options, treatment administration options, treatment adherence support options, palliative care) that are available to the patient to help them complete treatment.
- Discuss any proposed changes in the treatment plan, relating them to the patient's concerns (as assessed above).
- Evaluate the importance the patient gives to the indicated treatment.
- Advise on the social protection schemes the patient is eligible to benefit from.
- Evaluate the patient's confidence and readiness to adopt the indicated treatment.

AGREE

- ➔ Negotiate a treatment and care plan from the different options.
- ➔ Agree upon treatment options that reflect the patient's priorities.

ASSIST

- ➔ Provide a written or pictorial summary of the plan.
- ➔ Provide or identify a TB treatment supporter.
- ➔ Provide TB treatments/medication.
- ➔ Provide other medical treatments to help manage side-effects.
- ➔ Provide psychological support.
- ➔ Provide skills and tools to assist with self-management and with completing treatment.
- ➔ Provide a sickness certificate to facilitate access to social protection schemes.
- ➔ Provide equipment to help patients take their medications (e.g. pill box).
- ➔ Provide self-monitoring tools (e.g. a calendar or other ways to remind and record the treatment plan and next appointment).
- ➔ Address obstacles.
- ➔ Help patients anticipate barriers to completing treatment and identify strategies to overcome them.
- ➔ If the patient is depressed, treat the depression; if the patient has substance use disorder, link with appropriate care services.
- ➔ Link to available support:
  - TB treatment supporter
  - friends and family
  - expert patients/community champions
  - peer support group
  - community services.

ARRANGE

- ➔ Arrange follow-up care to monitor treatment progress and to reinforce key message.
- ➔ Arrange a way for the patient to contact a health care provider if problems arise before the next patient visit.
- ➔ Schedule for group appointments or relevant support groups, if available.
- ➔ Record what happened during the visit.
- ➔ Refer to existing social services for enablers and other social support measures.
- ➔ Ensure that patients receive their preferred treatment options to help them take all their medications.

4. Health education and counselling for people affected with TB

This section focuses on a key recommendation on patient care and support by providing health education and counselling on the disease and treatment adherence to TB treatment *(15, 16)*.

No.	Recommendation
1.1	Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. *(Strong recommendation, moderate certainty of evidence)*

This recommendation is based on evidence from extensive literature which shows better rates of treatment adherence and completion, and lower rates of LTFU, in patients who received health education and counselling prior to and during the course of TB treatment *(15, 23, 36–41)*. Health education and counselling on TB and its treatment should be provided to all patients.

The goal of health education is to provide accurate information so that patients have the information to make the best choice for themselves. Education can be provided by talking with the patient, distributing written materials, sharing video recordings, or through arts and performance with participation of people affected by TB. The education should discuss TB as a disease, its treatment and the services for which the patient is eligible. The education can and should be given at multiple times during TB treatment both to remind patients of information and also to provide specific information for treatment changes that may be coming up. Education could occur right before or at the start of treatment, when finishing the intensive phase of therapy, or at each presentation or interaction for follow-up care. It can be provided by different types of health care workers or pharmacists. Educational sessions might include the patient alone or might involve the patients' family members and/or friends. *(15, 16)*.

While health education aims to equip people with the right knowledge, counselling helps them to apply that knowledge by changing their attitude and behaviour. The term "counselling" refers to a two-way interaction between the patient and the health care provider. It is an interpersonal, dynamic communication process that involves a kind of contractual agreement between a patient and a health care provider who is trained in counselling skills and who is bound by a code of ethics and practice. It requires understanding and concern for the patient without any moral or personal judgement. To achieve this, health care providers should be taught interpersonal skills in order to build a partnership with patients and to have good communication skills in order to talk with them and strengthen their understanding of TB. The goal is to make the patients feel strong enough to do what they need to do for treatment of their TB disease.

4.1 Guiding principles for health education and counselling

With regard to the rights of patients outlined in the declaration of the rights of people affected by TB *(9)*, the following are particularly pertinent as the guiding principles for patient education and counselling:

- the right to be treated with respect and dignity;
- the right to information;
- the right to confidentiality.

People have a right to complete and correct information related to TB and the suggested treatment's risks and benefits explained in simple language that patients can easily understand. If possible, written information should also be shared. The goal of counselling is to make sure that people have understood the information and to answer any questions they might have. The health care provider should also correct any commonly held misconceptions or myths about TB.

A person's independence and right to choose should be respected. The health care providers should respect the patient's choices and beliefs and not make decisions for the patient. All efforts should be made to involve the patient in making a treatment plan. WHO clearly states that every person affected by TB has the right to liberty and security of person and that involuntary detention, hospitalization or isolation of a person with TB is a deprivation of liberty and violation of the security of the person *(9)*. WHO also narrowly defines the circumstances in which this right can be overridden but makes clear that this must be for the shortest duration possible and in accordance with strict guidelines.

Section 2 on the people-centred approach described how people suffering from TB might face stigma, prejudice or discrimination from the community as well as from health care providers. All efforts should be made to protect people from discrimination and to engage them in the most inclusive way. They should be treated with respect and dignity no matter what their age, gender, financial status, social situation, religion, sexuality or any other factors. In order to reduce stigma and discrimination, patients should be reminded that TB is not the result of any wrong behaviour and that most people completely recover after completing treatment.

People suffering from TB should have personal privacy and confidentiality. It is important that they are seen in a private space for health counselling. They should be assured that information about their care is confidential and that it will not be shared with another person without the patient's permission. Other family members should be invited to join the discussion only after receiving permission from the patient.

4.2 Effective communication skills to provide health education and counselling

Communication is best when it is a discussion between the patient and the health care provider, and not just the health care provider giving instructions or information to the patient. Good communication skills are very important for the treatment of TB. Not only can good communication help patients to understand the disease and treatment, but it can also help the community to better understand TB and correct misinformation that contributes to stigma *(42)*.

Some important elements of communication needed for health education and counselling are discussed below.

4.2.1 Forming a therapeutic alliance

The first step of counselling is to build a partnership with the patient and, if present, with his/her family. This partnership is the foundation that encourages people not just to participate in health education meetings, but also to engage in all aspects of treatment and care. Developing a trusting and caring environment is needed for this partnership, so that people are more likely to talk about their situation and concerns and receive necessary information. Forming a partnership allows for the sharing of information which is important to the process of counselling. Trust and a feeling of understanding should develop between the patient and the health care provider.

Understanding is one of the most important elements in forming a partnership. A health care provider should try to understand a patient's problems and feelings in a particular situation and should be able to communicate that understanding back to the patient. In order to build understanding, the health care provider should: 1) listen and observe carefully, without making judgements, in order to gather information; 2) focus and understand how the patient feels; and 3) talk with the patient to make sure he/she has been understood correctly. This is particularly important because it shows the health care provider's sincere desire to help, develops a full understanding and provides an opportunity for the patient to explain further. This can be achieved by statements such as "it sounds as if the pain is unbearable..". or "have I got it right that you are unable to sleep because of the cough" or "let me just check that...".

Empathy is not the same as sympathy. Sympathy means, for instance, that a health care provider feels sad or becomes tearful when a person starts to cry. Understanding does not mean that a health care provider has to actually "feel" like the person. Instead, the health care provider has to "understand" how the person might feel *(43)*. For a complete understanding, health care providers should understand the cultural values and health beliefs of the patients they treat. They need to constantly check that they have understood what the patient explained. This might be a reason why patients continue to seek health advice from faith healers who share a better understanding of the patients' experiences.

Many of the skills of good communication are important when providing counselling – including active listening, the language used, gestures and body language, and showing genuine interest and care.

4.2.2 Active listening

Actively listening is a specific communication skill which involves giving undivided attention to both verbal and non-verbal cues. It requires intense concentration; the health care provider should show a deep interest in and respect for patients and should not interrupt them. In health counselling it is very important to listen to patients carefully so that the conversation can be adjusted to their individual needs.

Active listening is more than just hearing someone else's words; it means paying attention and showing that you have heard and understood what is being said to you. If health care providers can show that they really are listening, this increases the patient's trust and confidence in the health care provider and the patient will feel more comfortable. This will make it easier to form a partnership.

To show that the health care provider has understood what has been said, it helps to repeat to the patient or summarize what has been said using different words. Paraphrasing or summarizing a patient's responses or questions may also help to verify information. Some helpful examples of summarizing a conversation are:

> *"Let me check if I have understood you correctly. You understand what TB is; you also understand about the treatment that has been recommended for you and why this treatment is so important for you. But you are worried about the side-effects of the medicines, especially because you will be taking these medicines for a few months, is that right?"*

These skills also show the participation of the health care provider in the conversation. Another communication skill is called reflection. For example, if a patient is describing his or her concerns, the health care provider should observe the patient's emotional reaction and then comment *"It looks as if you are very worried about these symptoms."* Acknowledging a patient's feelings also shows understanding and helps build an effective relationship.

4.2.3 Using non-verbal communication

Non-verbal communication includes eye contact, facial expressions, gestures, looking attentive, posture, nodding one's head and other movements.

Non-verbal communication also involves both the patient and the health care provider. The behaviour of the health care provider can give strong messages to show respect for and interest in the patient: It also builds a relationship, shows that the health care provider is listening carefully and shows that they want to help the patient understand about TB and treatment. Health care providers should use non-verbal communication to show that they are actively listening; this includes eye contact, smiling, nodding and sitting down while talking. The health care provider should avoid doing things like looking at their watch or fidgeting.

A patient's expressions also communicate emotions. Movements of eyes, mouth, eyebrows, forehead or even nostrils in different combinations signal happiness, sadness, anger, surprise, disgust, fear and interest. A slightly furrowed forehead will usually mean that the person either disagrees with what is being said or does not understand. That simple expression alone can show that they need more explanation. Because tension and anxiety may be reflected in body language, a reasonable guess at a person's state of mind can be made simply from looking at their posture. People who are anxious or worried about something tend to adopt characteristically tense positions of the hands, which may be clasped tightly together, or of legs, which may be wrapped around each other or the feet may tap repeatedly on the floor. Often without the need for any words, these clues can alert an observant health care provider to investigate further.

4.2.4 Asking questions

Asking questions appropriately is an important technique that can help to:

- identify what is already known and reveal any information gaps;
- identify specific needs;
- explore the attitudes and beliefs of a patient;
- generate discussions and options for problem-solving;
- help to understand the reasons behind decisions or actions.

An understanding of a patient's existing knowledge about TB and its treatment is important before giving further information. In this situation, asking questions is important. A balance between "closed" and "open" questions can help to collect the necessary information in a short time.

A closed question is one to which the only answer is "Yes" or "No". Some examples are: Do you have a cough? Do you have fever? The trouble with using closed questions is that "Yes" or "No" often does not describe fully what the person wants to say.

That is where the "open" question has value. This type of technique lets people describe their experience in their own words. Open questions are short and suggest no specific answer. They begin with words like "What", "Why", "How" and are very short. Some examples are: How do you feel after you take your medicines? Why do you have trouble taking your medicines every day?

Ideally, a problem should be explored with open-ended questions and then closed-ended questions should be asked in order to complete the information. Sometimes, however, people may go into

unnecessary details and health care providers need to maintain some control over the interaction by gently moving on.

4.2.5 Providing information

Health education and counselling must be given in very simple and clear language. Even medical information should avoid technical terms and medical jargon. Sometimes a limited amount of information is shared in one meeting so that the patient can understand it and then can think about it and is prepared for further information at the next meeting. Sometimes, important information needs to be repeated to help the patient understand it.

Health care providers should use language that is respectful towards patients and caregivers. It is important to not use derogative or judgemental language. Terms such as "defaulter", "suspect" and "control" are disrespectful and disempowering. These are best replaced with "person lost to follow-up", "person with suspected TB" or "person to be evaluated for TB". The term "control" can be replaced by "prevention and care". Similarly, expressions such as "patient failed treatment" or "failed to comply" reflect the view that the patient is to blame for the failure of treatment *(44)*.

The volume and tone of the voice of the health care provider is also important during health counselling. A very loud volume might be intimidating, and a very low volume may be difficult to hear or may give the impression that the health care provider is unsure of him/herself. Similarly, if the health care provider is speaking too fast, it seems as if they are in a rush and can also be difficult to understand. **Table 1** summarizes effective communication skills for a clinical encounter *(45)*.

Table 1. Effective communication skills

1	**Create an environment that helps with communication**	Meet the person in a private space, if possible.
		Be welcoming and conduct introductions in a culturally appropriate manner.
		Use culturally appropriate body language, facial expressions and eye contact to help to build trust.
		Explain that information discussed during the visit will be kept confidential and will not be shared without permission.
		If caregivers are present, suggest speaking with the person alone (except for young children) and obtain consent to share clinical information.
		If a male health care provider is interviewing a young woman, consider having another female staff member or caregiver present.
2	**Involve the person**	Include the patient (and with their consent, their caregivers and family) in all aspects of assessment and management as far as possible. This includes children, adolescents and older adults.
3	**Start by listening**	Actively listen. Avoid distractions.
		Be understanding and sensitive.
		Use non-verbal communication to show that you are listening.
		Allow the person to speak without interruption.
		If the history is unclear, be patient and ask for explanations.

		For children, use language that they can understand. For example, ask about their interests (toys, friends, school).
		For adolescents, show that you understand their feelings and situation.
4	**Be friendly, respectful and nonjudgemental at all times**	Always be respectful.
		Do not judge people by their behaviours and appearance.
		Stay calm and patient.
5	**Use good verbal communication skills**	Use simple language. Be clear and concise.
		Use open-ended questions, summarizing and clarifying statements.
		Summarize and repeat key points.
		Allow the person to ask questions about the information provided.
6	**Respond with sensitivity when people disclose difficult experiences**	Show extra sensitivity with difficult topics.
		Remind the person that what they tell you will remain confidential.
		Acknowledge that it may have been difficult for the person to talk with you about their thoughts and concerns.

4.3 Counselling to provide information about TB and the responsibilities of affected individuals and communities

This section focuses on *what* information about TB needs to be provided to patients and *how* that information should be provided.

The sharing of information with patients and their families should begin as soon as the diagnosis of TB is made. If the patient is being treated for DR-TB, another good time to have an educational meeting is when finishing the intensive phase of treatment. Educational talks should continue over several visits throughout the treatment course. Education can be provided by physicians, nurses, community health workers and other health care providers.

It can be difficult to provide patients with the information they need. A lot of new information, much of which may be technical, has to be given to someone who may not understand medical language well. The patient may not feel well and may also be emotionally distressed because of the diagnosis. The patient may also have health beliefs that contain incorrect information about TB.

4.3.1 What information must be provided?

1. Factual information about TB as a disease and its treatment

Information about TB and its treatment should be explained to the patient. This includes:

- what causes TB, how it is spread, the symptoms of TB and what can happen if TB is not treated;
- an explanation that TB is treatable and curable, and how to access treatment for TB;
- how TB is treated: how long the treatment lasts, the types of medicines that are used to treat TB and the possible side-effects of the medications;

- the effects of TB treatment on other comorbidities (e.g. alcohol, illicit drugs etc.);
- what could happen if a patient stops taking TB medications against the advice of the health care provider;
- why starting treatment quickly after diagnosis reduces the risk of transmission to others;
- the infection control practices that help to reduce the risk of spread of TB;
- what the available support services are and how to make a referral plan and/or organize integrated care at an early stage in case of other comorbidities.

2. The rights of people affected by TB

The Patients' Charter for Tuberculosis Care *(10)* outlined the rights and responsibilities of people with TB. The charter encouraged a person-centred approach in the treatment of TB, and encouraged collaboration between patients, communities and health care providers in order to improve TB care. In 2019, WHO also declared the rights of people affected by TB *(9)*. These are outlined in **Table 2**.

Table 2. The rights of people affected by TB and obligations of state and non-state actors

Rights of people affected by TB	
Article 2	The right to life.
Article 3	The right to be treated with dignity and respect.
Article 4	The right to the highest attainable standard of physical and mental health (right to health).
Article 5	The right to freedom from torture and other cruel, inhuman or degrading treatment.
Article 6	The right to equality and freedom from discrimination.
Article 7	The right to liberty and security of person.
Article 8	The right to freedom of movement.
Article 9	The right to privacy and family life.
Article 10	The right to confidentiality.
Article 11	The right to information.
Article 12	The right to informed consent.
Article 13	The right to education.
Article 14	The right to work.
Article 15	The right to adequate food.
Article 16	The right to housing.
Article 17	The right to water and sanitation.
Article 18	The right to social security.
Article 19	The right to freedom of expression.

Article 20	The right to freedom of assembly and association.
Article 21	The right to participation.
Article 22	The right to justice and due process.
Article 23	The right to enjoy the benefits of scientific progress (right to science).
Obligations and responsibilities	
Article 24	State obligations under international and regional human rights law.
Article 25	Non-state actor responsibilities under international and regional human rights law.

4.3.2 How should this information be provided?

Effective communication skills are described in **Section 4.2**. These need to be practised by health care providers before they can share the information outlined above as part of health education and counselling.

1. It is important to form a partnership with the patient before sharing any information. All efforts should be made to have a two-way conversation, rather than the health care provider just telling the patient facts. Patients should be encouraged to ask questions, information should be repeated to help them understand, and health care workers should check whether the patients have understood the information by asking short questions. Taking time to make sure that patients understand leads to better treatment outcomes.

2. The first question should be: *"What do you already know about TB?"*

Once a health care provider has found out what a patient already knows about TB, the health care provider can focus the discussion on what the patient still needs to know.

3. The next question should be: *"What questions do you have about TB?"*

The information about TB can then be personalized to the patient. For instance, it is quite possible that a patient is more interested in treatment options than the cause of TB. Once patients' questions have been answered, they may be more ready to discuss other important TB subjects. Sometimes, it might be difficult to give all the necessary information during one meeting, so the health care provider needs to prioritize the information so that the most important questions are answered first.

4. Next the health care providers need to ask themselves: *"What is the most important information that the patient must understand?"*

The health care provider should focus on this most important information during the first educational talks with the patient. The health care provider should still encourage questions from patients and help them understand information by repeating it or asking them short questions.

Questions like *"What do you know about your rights?"* will communicate better with patients instead of reading them a list of their rights.

5. Finally, health care providers should summarize the gaps and mistakes in the patient's knowledge about TB.

While respecting a patient's religious beliefs, it is important to explore their health beliefs – particularly those that might make it difficult for the patient to finish treatment. These questions also help to the health care provider to understand what patients think about their illness or treatment, especially in

their cultural context. Most people already have some understanding of TB because it is a common illness. They might also be anxious about their diagnosis or have some worries about the health care provider and the treatment. These concerns, beliefs and worries must be dealt with as part of health education and counselling. Families may also have their own ideas which might or might not be shared by the patient. Since families have a strong influence on patients' behaviour, their views also need to be taken into account. This helps to avoid confusion within families with regard to medical advice. The importance of exploring a person's health beliefs is also relevant to **Section 5.4** on counselling for treatment adherence.

In addition to sharing information during visits, educational pamphlets that clearly state facts about TB and its treatment are very helpful. The educational material should be appropriate for all ages, culturally sensitive, presented in local languages and in reader-friendly formats. Digital tools with audio or visual aids are also likely to help patients who may have difficulty reading. Additionally, specific marginalized populations may require special educational efforts.

4.4 Counselling to provide information about TB treatment and to ensure adherence to treatment

This section discusses how to counsel patients about TB treatment to help prevent them from stopping their treatment without medical advice.

4.4.1 Counselling to provide information about TB treatment

Patients and their caregivers should be prepared for TB treatment by giving them information (see **Table 3**) about:

- the treatment administration options; length of treatment; importance of adherence to treatment;
- pharmacological treatment: drug regimen; side-effects; monitoring side-effects;
- infection control at home and in the community;
- follow-up plan: routine appointments; emergency contact;
- support mechanisms: social support and social protection;
- palliative and end-of-life care.

Table 3. Information about TB treatment

About the treatment	The treatment setting	Where will the treatment start? If at a hospital, estimate the approximate length of stay and other important things the patient should know about when being in the hospital. If at home, involve the treatment supporter (preferably a community health volunteer) and discuss any changes in the home environment, if needed.
	Length of treatment	Explain how it may differ according to the regimen selected – often 4–6 months for TB without drug resistance.
	Adherence to treatment	Point out the complications of interrupting or not completing treatment.

About the pharmacological treatment	Medicines	Give basic information about different anti-TB medicines used in the treatment regimen, formulations (e.g. tablet or capsule, single dose or fixed-dose combination), preferably by showing each medicine and formulation.
	Side-effects	Give details about potential side-effects (including those that can be serious) and the need and how to report these immediately.
	Monitoring	Explain requirements for treatment monitoring by clinical examinations, radiology, smear, culture or other tests for early detection of side-effects.
Follow-up plan	Routine	Outline the process of routine follow-up and how to make an appointment when needed.
	Emergency	Explain how patients can contact their health care providers urgently. Explain what to do in case of an emergency (such as severe shortness of breath).
	Referral to other medical services	Show how to make a referral plan and/or organize integrated care at the early stage for comorbid medical (including mental health or substance use) conditions.
Infection control	Principles of transmission	In transmission of TB, when is the highest risk of infectivity?
	Household infection control measures	Note precautions to be taken at home. Note precautions to be taken in the community.
Support mechanisms	Social support and social protection options	Draw attention to existing services and laws in the country, including disability grants etc.
Palliative and end-of-life care		Describe services, laws, mechanisms etc.

As already noted, participate and completely understand that treatment should not be stopped without medical advice.

4.4.2 Counselling to ensure adherence to treatment

The most common challenge in TB care is when a patient discontinues taking medicines or misses treatment appointments. For this reason, it is extremely important to have a plan to quickly follow up with the patient. If possible, this plan should involve a member of the TB treatment centre team (community nurse, doctor, TB treatment supporter) who will visit the patient at home the same day, if the patient has given you permission to visit their home. If they have not given you permission, another plan should be in place to contact the patient (e.g. by mobile telephone or through a trusted friend of the patient who the patient has given you permission to contact).

The following steps should be taken *(11)*:

1. Make a home visit to engage with the patient, if they have given you permission to visit their home.

2. Assess the reasons for discontinuing the treatment.
3. Discuss the concerns that caused the patient's non-adherence.
4. Educate the patient about the need to continue treatment.
5. Counsel and support the patient.
6. Involve family members/caregivers to ensure treatment.

1. Home visit to engage with the patient

The member of the TB treatment centre – such as community nurse, doctor or supervisor – should visit the home (if given permission) of the patient together with, or in addition to, the TB treatment supporter. During the home visit it may be possible to identify more clinical problems than during the monthly clinic evaluation. The patient should be treated in a friendly and sympathetic way by showing that he/she is respected and valued. The guidelines discussed in **Section 5.2** on effective communication skills should be followed.

2. Assess the reasons for discontinuing treatment

- Every effort should be made to listen carefully to the patient's reasons for missing treatment.
- The health care provider should make a list of problems that contributed to the patient being unable to follow treatment.
- The health care provider should explore the patient's understanding of the illness.
- The health care provider should be sympathetic and should recognize the difficulties faced by the patient.
- The health care provider should not just speak *at* the patient but should have a discussion with him/her.

3. Discuss the patient's concerns that caused non-adherence

The health care provider needs to discuss some of the common reasons why patients are unable to follow up with treatment or take their medications. For instance:

a. Manage side-effects

The most common reason for stopping treatment is difficulty in tolerating medicines. This is particularly important when people are on second-line medicines for the treatment of DR-TB. It is extremely important to inquire about possible side-effects and to refer to the guide on managing these *(46)*.

b. Explore the person's health beliefs

People can hold a number of beliefs and ideas – for instance, on what has caused their illness or how can it be treated, which are quite different from those held by the health professionals. If patients believe that there is no cure for TB, or that when symptoms get better it is not necessary to continue treatment, or that cure might be offered by alternative or traditional medicine, they may not continue their treatment.

Some examples of questions that can help explore a patient's health beliefs are:

- *What do you think has caused your illness?*
- *How does your illness affect your body?*
- *How severe do you think it is?*
- *What kind of treatment do you think might help?*
- *What are the major problems caused by your illness?*
- *What are you afraid of most about your illness?*

In such cases, the TB treatment supporter, along with a nurse, doctor or community supervisor, should explore ways to correct the misunderstandings and discuss with the patient how to restart treatment.

c. Address economic problems

Many people are unable to work when they are ill and may be the primary wage-earners for their family. Housing, food and clothing needs should be assessed to find out what types of material support can help (see **Section 3.2** for more details).

d. Address substance use or other mental health conditions

Alcohol and drug use are known to affect treatment adherence. People should be encouraged to reduce or stop consumption if it interferes with their treatment. If this is difficult or other mental health conditions are suspected, consultation with a mental health or other relevant specialist should be considered.

e. Problems with the health care service

People may have problems with health care providers who might arrive late, might not listen carefully, or might make the patient feel not respected or not valued. These issues are also known to affect adherence and must be addressed. The health care provider should recognize any service problems, apologize and offer a solution.

f. Address social problems

If there are other social problems, the patient should be referred for appropriate support. This would also include homeless people, or patients who might be shunned by their family or who have to re-locate for immigration, work or economic reasons, in which cases they should be linked to services in the new location.

4. Educate the patient about need to continue treatment

The health care provider should:

- *Assess if there are gaps in the patient's understanding of the disease and its treatment.*
- *Correct any misunderstandings or misinformation.*
- *Encourage the patient to ask additional questions.*
- *Summarize the diagnosis, treatment and recommended steps in simple terms.*
- *Ask the patient to repeat or describe the treatment terms.*

5. Counsel and support the patient to resume treatment promptly

Once the reasons for discontinuing medication have been discussed, have been dealt with to the best of the health care provider's ability and the patient has been educated about the need to continue treatment, the health care provider should reassure the patient and provide realistic encouragement. Follow-up plans should be confirmed with the patient.

Further guidelines for psychological support are discussed in **Section 5.5**.

6. Engage community health workers, family members and caregivers to ensure treatment adherence

Engagement of community health workers has been demonstrated to be effective in securing favourable treatment outcomes. Family can also be an important source of support for the patient. If

it is not possible for a family member to care for the patient, another caregiver should be identified and should also be educated about the need to continue treatment so that they can make sure the patient takes the treatment correctly at home. Information about measures to prevent the spread of infection, and that a person is usually no longer infectious within 2 weeks of the start of treatment, is also extremely important.

Community opinion and religious leaders can be helpful if there are community-wide issues – such as stigma towards patients dealing with TB. This option is possible only if the patient allows the health care providers to share information about his or her TB diagnosis.

4.5 Counselling to provide psychological support

Section 3.2.2 describes factors that can affect a person's psychological health, cause distress, decrease their quality of life, prevent them from following their treatment plan and cause them not to be able to complete a course of treatment.

Being diagnosed with TB and worrying about its impact on what a patient needs to do daily – employment, income, family and taking treatment as prescribed – can be an extremely stressful experience. A stress response can manifest in psychological symptoms, physical symptoms and changes in behaviour (see **Table 4**).

Table 4. Symptoms of stress

Psychological symptoms	Physical symptoms	Changes in behaviour
Constant worry	Headaches, migraine, dizziness	Feeling irritable/aggression
Depression/anxiety	Muscle tension, spasm or cramp	Changes in sleeping pattern (too much or too little sleep, inability to sleep)
Difficulty concentrating	Changes in breathing/panic attacks	Changes in diet (eating too much or too little, loss of appetite)
Feeling overwhelmed	Chest pain/faster heartbeat	Use of alcohol, drugs, tobacco to cope with stress
Forgetfulness	Digestive problems (upset stomach, nausea, constipation, diarrhoea)	Avoiding dealing with difficult situations
Difficulty making decisions	Lethargy/tiredness	Lack of motivation
Feeling disconnected	Increase in blood pressure	Crying

People with TB may be more vulnerable to developing severe stress responses. Common mental disorders and TB are both associated with greater social vulnerability, inadequate living conditions and socioeconomic inequality *(17, 47–49)*. People with mental illness may find it very difficult to take the long treatment course required for TB *(50)*. People with mental illness and TB would particularly benefit from psychiatric care *(51)*. Additionally, some of the TB medications are associated with psychiatric side-effects *(52)*.

It is extremely important to recognize and deal with the stress reactions in people who are at risk by finding out what their worries and concerns are and by offering support. They should be referred to specialist services if necessary. This section focuses on providing basic psychological support, strengthening social support, problem-solving technique and providing support to caregivers and dependent family members.

4.5.1 Basic psychological support

Basic psychological support tries to help people deal with emotional distress and help them recover from stress responses *(53)*. In addition to following the principles of effective communication in **Section 5.2**, these guidelines should be followed:

1. Distressed people may not always give a clear account of their situation or may take longer to explain themselves. They should be listened to patiently, without interrupting or rushing them. Asking for clarification usually helps. Sometimes, they might find it difficult to open up their feelings; being there and reassuring them is important. If they describe their feelings or difficult experiences, responding with empathy and sensitivity can help. Some examples of responses are:

   That sounds like a very challenging experience.

   I understand how painful this has been for you.

   I can see why you are so worried (or frightened).

2. Sources of stress should be identified. After actively listening and allowing the person to speak without interruption, following questions may be needed:

   What is your biggest worry these days?

   How do you deal with this worry?

   What are some of the things that give you comfort, strength and energy?

3. Their basic needs should be assessed. If they need more information or additional services, simply establishing contact with their family and providing other social support is important.
4. Education should be provided about the normal stress reactions of people diagnosed with TB or experiencing difficulties with treatment or services.
5. If the stress reaction is long or severe, specific stress management techniques should be offered *(54)*.
6. The health care provider should look for potential signs of sexual or physical abuse (including domestic violence) in women, children and older people (e.g. unexplained bruises or injuries, excessive fear, overly withdrawn behaviour, reluctance to discuss matters when a family member is present, malnourishment in a family with access to sufficient food). When signs of abuse or neglect are present, the patient should be interviewed in a private space and asked if anything hurtful is going on. If abuse or neglect is strongly suspected or confirmed, help should be requested from colleagues with experience of dealing with this. If the patient gives consent, he/she should be referred to relevant community resources for protection (e.g. trusted legal services and protection networks).

4.5.2 Strengthen social support

Strengthening social support is important to reduce the many of the harmful effects of stress *(45)*.

1. The first step is to ask about support mechanisms that the patient has now or those that might have helped the patient in the past.
2. Some example questions are:

   What comforts you when you are upset?

   Do you talk to anyone about your problems and what you are going through?

   Is there any person who you feel can give you support?

   Who do you feel most comfortable sharing your problems with? When you are not feeling well, who do you turn to for help or advice?

How is your relationship with your family? In what way do your family and friends support you and in what way do you feel stressed by them?

3. Then identify people who could provide support, such as trusted family members, friends and community members, and talk about how each one can be involved in helping.
4. If the patient is willing, he/she should be referred to other community resources for companion or material support. These include: social or protection services; community centres; self-help and support groups; employment and or other income-generating activities; formal/informal education; shelter, food and non-food items; child-friendly spaces. When making a referral, the patient should be helped to access them (e.g. provide directions to the location, operating hours, telephone number) and provide the patient with a short referral note.

4.5.3 Problem-solving technique

Stress can affect a patient's ability to respond well to problems. Patients may feel helpless or lack confidence in managing their problems, or possibly their feelings of anxiety or grief will get in the way of managing their day-to-day problems well. Problem-solving is a step-by-step strategy that may help distressed patients to solve and manage their problems *(55)*.

In general, direct advice should not be offered. Instead, patients should be helped to explore their own solutions (see **Box 2**).

Box 2. Problem-solving technique

1. List problems as solvable (can be influenced or changed) and unsolvable (cannot be influenced or changed).
2. Choose an easier (solvable) problem to start with.
3. Choose the part of the problem for which the solution is practical in nature and in your control.
4. If a problem has many parts, break it down and deal with each part separately.
5. Make a list of possible solutions to the problem. Think of what you can do by yourself and also think of people who can help you to manage parts of the problem.
6. From the list of potential solutions, choose those that have most helpful strategies (those that have very few disadvantages and are easier to carry out).
7. Develop a detailed plan (step by step) of how and when you will carry out the solution.
8. After trying to solve the problem, review to see what has been solved and what the next step should be.

4.5.4 Provide support to the caregivers

It is important to realize how stressful it can be to care for people with TB and how important the caregiver is in helping the patient to recover completely from TB. Caregivers need to be respected even if they find it difficult to support the patient with TB; if the patient allows, the caregiver should be involved in making decisions about treatment. Providing support to the caregivers is an important psychosocial element of treatment for chronic conditions *(45)*.

Some areas that may help assess the stress in caregivers are:

- worries and anxiety around caring for the person with TB;
- practical challenges (e.g. burden on the caregivers' time, freedom, money);
- ability to carry out other daily activities, such as work or participation in community events;
- physical fatigue;
- social support available to the caregivers;
- psychological well-being.

Once their needs have been assessed, the health care provider can help by:

- providing information;
- linking the caregiver with community services and supports;
- discussing respite care, which is when another family member or appropriate person can take over the care of the patient temporarily while the main caregiver takes a rest or does other things they need to do;
- offering problem-solving or stress management counselling;
- referring the caregiver to mental health services, if needed.

4.5.5 Refer to mental health services

If a mental health condition is suspected or identified, refer the patient to appropriate mental health services.

4.6 Counselling on nutritional care and support

In view of a strong bidirectional causal link between TB and undernutrition, WHO recommends that all persons with active TB should receive appropriate counselling based on their nutritional status at diagnosis and throughout treatment *(21)*.

Undernutrition can present in children, adolescents or adults, including pregnant women. In case of young children (under the age of 10), their parents need to be part of counselling and support. In case of adolescents (ages 10–19), the health care providers should make an effort to develop a therapeutic alliance with the young person as well as his/her parents (**Section 4.2.1**).

4.6.1 Treat the underlying cause

An assessment of the cause of undernutrition is essential. If the cause is primarily poverty or food insecurity related, these socioeconomic issues will need to be addressed. If underlying medical causes are suspected, then an appropriate medical referral should be considered. In cases of comorbid medical (e.g. diabetes) or psychiatric conditions (e.g. alcohol use), again the individual should be referred appropriately.

Irrespective of these causes, the person should be offered the counselling techniques already described: basic psychological support (4.5.1), strengthen social support (4.5.2), Problem-solving technique (4.5.3), and provide support to the family/caregivers (4.5.4).

4.6.2 Educate the person

In cases where the health care providers feel that the person does not understand the nature of undernutrition, potential harm and need for diet modification or nutritional supplements, the health care providers should follow the principles of 'health education and counselling' described in **Section 3** to educate the person.

4.6.3 Assess 'readiness' of the person to change diet/lifestyle

The basic principle of a health behaviour change is that people hold a range of beliefs about their problems and behaviours. They range between those who do not acknowledge that there is a problem, those who acknowledge that there is a problem but are not ready to act and those who understand and make efforts to act but are unable to persist with desired actions. A careful assessment of an individual's readiness or preparedness to change can help a healthcare provider plan further intervention.

4.6.4 Motivate the person

Health care providers are trained to 'advise' and have an inherent desire to set things right for their patients. This rarely helps to bring a change in behaviour. Instead, the aim should be to explore people's difficulties about changing their behaviour and help them find their own solutions. A therapeutic alliance (**Section 4.2.1**) is important to understand the person's point of view and identify the conflicts between how the person behaves and what he/she aims to achieve. The health care providers should encourage the person with whatever efforts he/she is able to make towards a desired change in diet/ taking supplements, without any confrontation or external pressures.

4.6.5 Rewarding desired behaviour (in children)

It can be very helpful if children are rewarded for implementing a desired behaviour (e.g. eating nutritious food or taking supplements) to reinforce those habits. The most effective reward is attention from the parents.

4.7 Counselling at the end of TB treatment and on palliative care

4.7.1 Counselling at the end of TB treatment and post-TB treatment

After completing TB treatment, some people have to deal with the possibility of post-TB symptoms or sometimes respiratory disability or sequelae. TB recurrence may happen in a small proportion of patients including those successfully treated. Counselling at the end of TB treatment is necessary to provide people with necessary information on the possibilities of post-TB symptoms, disability or sequelae, or the recurrence of TB; they need to access health care services for follow-up examinations when necessary. The process of counselling should continue to support people to adjust to their health challenges until they are emotionally stable. Counselling aims to provide a safe and trusted space to help people to work through their inner fears and apprehensions.

Patients and family members often need emotional support to face the losses associated with post-TB disability. People who suffer from post-treatment debilitating complications may also experience adverse psychological, social and financial impacts. It is extremely important to monitor their adjustment to compromised health status. It may take up to several months before they are able to completely recover their emotional health. During this period, counselling and other forms of social and occupational support can be of tremendous help.

4.7.2 Counselling on palliative care

As discussed in **Section 6**, assessment and relief of psychological, social and spiritual distress of patients and family caregivers are critical parts of palliative care for people affected by TB.

When patients learn that they are likely to die from their illness, they may experience any or all of the following emotions or thoughts in no particular order *(56, 57)*:

- Denial: inability to believe, understand or accept the terminal prognosis.
- Anger: blaming others or God for the situation.
- Bargaining: desperately searching for a way out of the terminal situation.
- Depression: feelings of despair, worthlessness, guilt or shame.
- Acceptance: finding peace.

In addition to the counselling techniques already described – providing basic psychological support (**Section 4.5.1**), strengthening social supports (**Section 4.5.2**), problem-solving (**Section 4.5.3**), supporting the family/caregivers (**Section 4.5.4**) – health care providers can do the following *(57)*:

1. Allow the patient to express strong emotions such as sadness, tearfulness or anger without interrupting or judging.
2. Express the wish that there were some means to treat the illness.
3. Assure patients that they will continue to be cared for, that they will be accompanied throughout the illness and that any discomforts will be treated.
4. Ask whether the patient would like spiritual support and arrange for an appropriately trained spiritual supporter if requested by the patient.
5. Assess the patient for symptoms of anxiety or depression. If these symptoms are in excess of what would normally be expected in this situation, consider treating. Refer for mental health services only if such services are easily and quickly accessible by the patient.
6. Prior to the patient's death, assess family members for bereavement risk (e.g. history of mental illness, difficult and emotionally charged relationship with the patient) *(58)*.
7. Make bereavement support available to the family via the palliative care team, a community-based bereavement support group, or a social worker *(59)*.
8. In the course of bereavement support, watch for signs and symptoms of prolonged grief disorder (e.g. more than 12 months of difficulty in accepting the death and clinically significant impairment in social or occupational functioning). Refer to a mental health specialist if suspected *(58)*.
9. Implement resilience-promoting programmes within palliative care or DR-TB teams such as regular sharing of difficult cases, memorial ceremonies for deceased patients, regular social activities.

Provide information and education to patients, as follows:

1. Educate the patient about common reactions to disability or terminal conditions. The following statements are some examples:

   People in similar situations may react in different ways. Some people show strong emotions while others do not.

   It is all right to feel sad and even cry; it does not mean you are weak.

   People who do not cry may feel the emotional pain just as deeply as others but have different ways of expressing it.

   There are no right or wrong feelings. Sometimes you might feel very sad, and at other times you might feel better.

2. People who suffer from debilitating complications after treatment may also experience adverse psychosocial and financial impacts. It is extremely important to monitor their adjustment to compromised health status; it may take up to 6 months before they are able to recover their emotional health completely. During this period, other forms of social and occupational support can be of tremendous help.

3. Health care providers also need to be mindful of patients' cultural and religious beliefs. Spiritual distress and existential concerns should be treated with the same level of priority as psychosocial distress and physical pain. Support may involve a spiritual caregiver.
4. If a person presents with severe symptoms of distress, or is unable to sleep or eat, or there are signs of mental disorders (e.g. substance use disorders or depressive disorders) he/she should be referred to mental health services.
5. Patients and family members often need emotional support to face the losses associated with disability, dying and bereavement. In cases where a patient dies, the family may need to be supported through the bereavement periods. Some bereaved family members may develop complicated grief requiring specialist treatment. Community support can also be mobilized to sustain bereaved family members.
6. Providing support to people facing disability or death can be extremely distressing for health care providers themselves. They also need to be supervised and supported within their teams. NTPs should encourage self-care and staff support strategies, such as regular sharing of difficult cases, memorial ceremonies for patients who have died, regular social activities for palliative care team members, regular exercise and other supports.

5. Models of care for TB services

5.1 Models of care for all TB patients

Although traditionally patients with DR-TB were hospitalized for portions of, and sometimes all of, their treatment, recommendations on this have changed. With the increasing use of all-oral DR-TB treatment, patients with DR-TB should be treated whenever possible in an outpatient-based treatment programme similar to patients with DS-TB *(60–62)*. Additionally, for both patients with DR-TB and those with DS-TB, treatment should move towards a decentralized, ambulatory care setting in order to make it easier for all patients to access medications and treatment support and for TB treatment to be less disruptive to their lives.

The following recommendations from WHO's guidelines *(15)* apply to patients with DR-TB.

No.	Recommendation
2.1	Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization. *(Conditional recommendation, very low certainty of evidence)*
2.2	A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment. *(Conditional recommendation, very low certainty of evidence)*

However, sometimes patients do require treatment in the hospital (inpatient). These may be patients with DR-TB, but they may also be patients with DS-TB with severe disease or treatment complications. The following discussion addresses some of the concerns regarding strategies for decentralized (outpatient/ambulatory) care models – which apply to majority of TB patients – and inpatient or hospital-based treatment for patients who need special treatment and care.

5.1.1 Outpatient model of TB treatment: decentralized care

Decentralized care means care that is provided in smaller, ambulatory, non-specialized health care centres closer to where a patient lives, often by community health workers or nurses, non-specialized doctors, community volunteers or TB treatment supporters. Care could occur at local centres (e.g. community centres), or at the patient's home or workplace. Having treatment and care provided in decentralized health care centres is a good way to improve access to treatment and increase the number of patients who receive regular, community-based treatment and support. Decentralized care is often less disruptive to patients' lives, allowing them to access treatment, care and counselling more easily and with less cost. It may also allow them to continue to work (therefore lessening the financial burden of TB disease) and to remain with their families. Decentralized care can be used for patients with either DS-TB or DR-TB. According to the WHO guidelines, all-oral regimens are preferred for TB treatment *(61 –63)*; however, if the patient must receive injectable medication, it should be investigated whether the injectable can be given at a decentralized location *(60–62)*.

Decentralized care may not be best for all patients. Of particular concern would be patients with severe TB disease or severe comorbidities or very infectious forms of TB. However, studies have shown

higher rates of treatment success and fewer patients lost to follow-up when patients were treated with decentralized care versus hospital-based care *(64)*. There were no higher risks of death or treatment failure among patients who were treated with decentralized care. Before a patient begins decentralized care, the health care provider needs to make sure that all required safety monitoring (e.g. laboratory tests, ECG) can still be done in the decentralized system or that, when needed, a patient can travel to a clinic or hospital with a higher level of care that can do this monitoring. There should always be a plan to get patients to a hospital if they need inpatient treatment. This may be necessary in certain patient groups at particular risk, such as children with severe forms of TB or people who also have advanced HIV. These patients may need close monitoring in a hospital for a certain period of time.

The backbone of community-based TB care is often a community TB treatment supporter, who may belong to the neighbourhood where the patient lives *(53)*. Community TB treatment supporters, like all health care workers, must respect and preserve patient confidentiality at all times. They can also play an important role in educating the community about TB and can help reduce stigma around the disease. Community-based TB providers need to be properly trained and supervised by qualified health care workers *(65)*. In some settings, and where there are no other alternatives, a community-based TB treatment supporter can even be a family member who has undergone proper training and is supervised by a health care worker or qualified community member. However, family relationships can be complex, and so the nature of family relations should be evaluated beforehand to ensure that the patient receives fully supportive care.

Decentralized care requires staff at the clinics to receive extra training and for the clinics to be able to support TB patients. This is likely to require additional help from the NTP. Clinic staff must be aware of the early detection and management of adverse drug reactions and should be familiar with social support services. When patients are on good medical treatment, the bacterial load rapidly falls and the risk of transmission of TB drops. Nevertheless, infection control measures need to be put in place at the clinic. The patients also need to be educated on infection control measures they can do at home, particularly if they live with someone who is at a particular risk from TB infection, such as a young child or someone living with HIV. These infection control measures will decrease the risk of transmission in households, the community and clinics. In the case of a patient with DR-TB, it may be illegal in some countries to treat DR-TB patients in a decentralized setting, especially when the treatment involves injections. Such legal concerns need to be considered when making plans for decentralized versus hospital-based care (see **Box 3**).

This decentralized model of care may require the patient to travel from home and receive medicines under person-centred treatment support at the clinic. Long daily travel times or cost of travel could lead to LTFU. Patients may need financial support to help with their travel costs.

Box 3. Basic conditions to be met by an optimum community-based model of decentralized TB care

- The public health legal framework should allow community members to deliver the required health care functions.
- The patient has no medical indication for receiving long-term care in hospital.
- The patient's household/living situation can allow for basic standards for respiratory infection control.
- All health care workers and community TB treatment supporters are trained, follow the rules of TB infection control and have access to masks and respirators at all times.
- There are sufficient community TB treatment supporters to provide person-centred treatment support to all patients as needed and required by NTPs.
- A team consisting of a physician, a nurse, a pharmacist and a social worker supervises, monitors and supports community-based TB treatment supporters and can provide rapid care to patients if needed.
- Plans are in place for good and rapid communication with laboratories providing the tests in order to monitor the response to treatment and detect adverse drug reactions.
- All community-based TB treatment supporters are trained in patient confidentiality and in methods to decrease stigma.
- All community-based TB treatment supporters are fully covered for all out-of-pocket costs associated with their work. The TB treatment supporters also receive fair compensation for the services being provided to the patients (Note: compensation is more than just reimbursement of the out-of-pocket costs of doing the job and needs to be included in the budget of all TB programmes that use community-based TB treatment supporters).

5.1.2 Inpatient model of TB treatment and care

Some patients may need to stay in hospital to receive treatment for TB. This is the case, for instance, if a patient has a severe form of DS-TB or DR-TB disease (e.g. meningitis, vertebral bone infection, pericarditis, miliary TB or severe TB lung disease with signs of respiratory distress/failure or sepsis), has serious comorbidities (e.g. severe malnutrition, untreated HIV, uncontrolled diabetes mellitus), is either very young or quite old, or has serious adverse reactions to medication *(66)*. In these cases, the patients may need to be hospitalized until these conditions stabilize. In the past, patients with DR-TB, were routinely kept in hospital until the end of the intensive phase of treatment or until conversion to smear/culture-negative status. Long hospitalization should not be routinely required for patients on DR-TB treatment unless it is absolutely medically necessary. The treatment regimen should rarely require a patient with DR-TB to be hospitalized because every attempt should be made to put the patient on an all-oral regimen that they can receive as an outpatient. Additionally, a patient should be kept in isolation while hospitalized only when no other options remain.

Box 4 lists things to consider when a patient must be hospitalized. Hospitalized patients should have access to all the social support services they need (see **Section 3.1**). Patients should be hospitalized for the shortest amount of time that is medically safe, and this duration of time should regularly be reassessed by the health care providers. Every effort should be made to transfer the patient's care to outpatient clinics as soon as it possible.

Good communication and coordination need to be in place between the hospital(s) and outpatient care providers. This should include: 1) notification to appropriate outpatient teams several days ahead of the planned discharge of the patient from the hospital; and 2) supplying all clinical information about the patient, including all prescribed drugs needed for the first 2–4 weeks of treatment as an outpatient.

An assessment of the risks for a patient who is not able to take his/her medicines and a plan to reduce the risks with social support should be discussed with patient and the outpatient care providers well ahead of the patient's discharge from hospital.

Box 4. Basic conditions to be considered when a TB patient needs hospital care (inpatient)

- Basic standards for respiratory infection control are in place.
- Respiratory isolation rooms are available for all patients who remain smear- or culture-positive.
- All staff are properly trained in TB infection control.
- Treatment support teams are available to provide all recommended and necessary services to all patients.
- An open and safe space is available for patients to socialize and conduct occupational therapy activities.
- Friendly administrative procedures are in place to allow family members to visit patients regularly.
- There is good communication with the laboratories providing services during treatment, and with the health care centres that will take over the patient's care after discharge from hospital.
- Social support should be provided to patients to pay for hospital-related costs, which may include transport to and from the hospital of relatives or family caregivers living close by.

5.1.3 Deciding on the best suited model for a situation

It is important to remember that: 1) decisions on the model of care for a particular situation should not be made in the belief that only one model serves the needs of all patients in a particular setting; and 2) in some settings, allowing community health care workers to do more and different types of jobs to relieve staff shortages and to encourage more meaningful community participation may be important to allow services to be available to all patients. Therefore, in real-life circumstances, multiple models of care may be used depending on the needs of the patient and the resources of the health care system.

Some patients may need hospital-based care (inpatient model) either while receiving complicated treatment or when on end-of-life care. This is because hospitals play a very important role in the clinical management of severe TB disease and DR-TB. This includes: treatment of TB comorbidities (such as HIV or noncommunicable diseases (e.g. diabetes, severe mental health disorders); surgical treatment of selected TB patients; management of severe adverse drug reactions (particularly to second-line anti-TB drugs); treatment of pulmonary complications in patients with severe TB disease; medical support during palliative and end-of-life care; and the initial care of patients who are homeless, have

difficult family situations, or who live in remote areas where TB care is difficult or DR-TB care is not yet available.

However, in some settings, depending only on an inpatient model of care may result in problems, namely: it may slow down or even make it impossible to get all patients into treatment due to the high costs of hospital care; create long patient waiting lists due to the lack of hospital beds; cause longer than necessary suffering of patients with TB; and create catastrophic costs for patients. An outpatient system must be in place to support patients upon discharge even in settings that rely mainly on a hospital-based model. Thus, the ability to provide ambulatory TB care has to be built into whatever model is used.

When comparing different treatment models, a number of issues have to be considered (see **Box 5**) and ethical concerns need to be respected. While outpatient care is often socially more acceptable to patients and reduces health system costs, the creation of outpatient person-centred treatment support is challenging. It requires access to a primary health care network, strong social support and community-based care. However, in some settings, the community-based decentralized model of care is the only way to achieve universal access to treatment.

Whichever model is chosen to provide treatment for TB, a multidisciplinary team of providers – including physicians, nurses, psychologists, social workers and community health workers or volunteers – should be involved in care. The roles and responsibilities of each of these groups of providers will vary depending on the needs and resources available in specific settings.

Adherence to TB treatment – particularly DR-TB treatment – is challenging and therefore social support and social protection measures to improve adherence should be used, whichever model is chosen (see **Section 3.1**).

The risk of TB (with particular concern for DR-TB) transmission when proper infection control measures are not being used occurs in all models of care whenever the patient remains sputum smear-/culture-positive. However, the risk is particularly serious in the hospital-based model where the adverse effects of transmission could be higher (hospitals are crowded so it is easier to infect more people, and those people are likely to have other serious illnesses as well). This is a critical factor to consider when selecting a model of care for a DR-TB patient.

Person-centred treatment support is the method recommended to deliver treatment and support patients in each of the models of care. New ways to deliver person-centred treatment include VST, which can also be considered in any of the models of care presented above. More specific and detailed WHO guidance on how to implement VST and other digital based technologies to monitor adherence to treatment are presented elsewhere *(25)*.

Box 5. Factors to consider when selecting the model of care for TB patients

- Patients' needs, values and preferred options for treatment.
- Attitudes of caregivers, patients and their families to the different options of care.
- Local laws and ethical standards.
- The availability of care (of particular concern for DR-TB care).
- Quality of infection control measures used in the hospital or clinic.
- The ability to teach patients and family about hygiene and infection control measures at the household level.
- Comorbidities (e.g. HIV, mental health illnesses, diabetes mellitus, liver disease, kidney disease, malnutrition and substance use disorders (particularly alcohol and opioids).
- Funding to support health care workforce delivery of person-centred treatment support.
- Availability of private sector and public hospitals to provide DR-TB management.
- Training requirements for the different models.
- Capacity to train and supervise TB treatment supporters, with special attention to the more complex DR-TB treatment.
- Social support networks to assist person-centred treatment support.
- Costs of a specific model of care.
- Political commitment from the government to implement and sustain the model of care most convenient to the needs of the patient and health system.

5.2 Decentralized and integrated family-centred models of TB care for children and adolescents

In high TB burden countries, the capacity to manage TB in children and adolescents is often centralized at the tertiary or secondary level of health care rather than being decentralized at the primary health care level where children and adolescents with TB or TB exposure commonly seek care *(67, 68)*. Care at higher levels in the health system is often managed in a vertical, non-integrated way. Children and adolescents with TB may go undetected because of missed opportunities for contact investigation, TB prevention, detection and care, and as a result of weak integration of child and adolescent TB services with other programmes and services – especially the integrated management of childhood illness (IMCI), malnutrition and HIV services. If not addressed, such access challenges contribute to preventable delays in diagnosis and treatment, which may lead to increased disease severity, suffering and mortality *(69)*.

An important step towards improving access to TB prevention and the management of TB in children and adolescents is the provision of decentralized, family-centred integrated care *(67)*. Integrated, person-centred care and prevention is a key pillar of WHO's End TB Strategy and aims to ensure that all people with TB have access to affordable high-quality services according to their needs and preferences *(5)*. This is further underpinned in the 2018 WHO roadmap towards ending TB in children

and adolescents *(67)*, which calls for the implementation of integrated family- and community-centred strategies.

This section focuses on models of care to increase access to TB services for children and adolescents through family-centred, integrated care. Family-centred models of care refer to interventions selected on the basis of the needs, values and preferences of the child or adolescent and their family or caregiver. This can include health education, communication and material or psychological support. Integrated services refer to approaches to strengthen collaboration, coordination, integration and harmonization of child and adolescent TB services with other child health-related programmes and services. This can include integration of models of care for TB screening, prevention, diagnosis and treatment with other service delivery platforms for maternal and child health (e.g. antenatal care, integrated community case management, IMCI) and other related services (e.g. HIV, nutrition, immunization). Other examples include the evaluation of children and adolescents with common comorbidities (e.g. meningitis, malnutrition, pneumonia, chronic lung disease, diabetes, HIV) for TB and community health strategies that integrate child and adolescent TB awareness, education, screening, prevention and case-finding into training and service delivery activities.

The following are the WHO recommendations on decentralized and integrated family-centred models of care for TB services for children and adolescents *(70)*.

No.	Recommendation
3.1	In TB high-burden settings, decentralized models of care may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB. *(Conditional recommendation, very low certainty of evidence)*
3.2	Family-centred, integrated models of care to deliver TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB, in addition to standard models of care. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. These recommendations relate to TB services along the full range of care with a focus on case detection and provision of TPT.
2. The recommendations apply to children and adolescents with signs and symptoms of TB in terms of the impact on case detection. They also concern children and adolescents who are exposed to TB (i.e. TB contacts), and who are eligible for TPT, in terms of the impact on provision of TPT. Children and adolescents with signs and symptoms who need evaluation for TB disease may also have a history of exposure to TB (i.e. TB contacts). Children and adolescents who are TB contacts and who do not have signs and symptoms should be evaluated for TPT eligibility.
3. The recommendation on decentralized services refers to enhancing child and adolescent TB services at peripheral levels of the health system where they are closer to the community, and not to replacing specialized paediatric TB services at higher levels of the health system.
4. Decentralization should be prioritized for settings and populations with poor access to existing services and/or in high TB-prevalence areas.
5. Family-centred, integrated approaches are recommended as an additional option to standard TB services (e.g. alongside specialized services that may have a limited level of integration with other programmes or links to general health services).
6. Family-centred care is a cross-cutting principle of child care at all levels of the health system.

These approaches on decentralization and family-centred integrated care aim to bring TB services closer to where children, adolescents and families live. As the recommendations were published in 2022 *(70)*, evidence on the best ways to implement these recommendations is emerging, and national programmes are encouraged to document examples of best practice in this area.

Decentralization includes the provision of access to or capacity for child and adolescent TB services at a lower level of the health system than the lowest level where it is currently routinely provided. In most settings, decentralization applies to the district hospital level (first referral level), the primary health care level or the community level. Interventions to facilitate decentralization include capacity-building of various cadres of health care workers, access to diagnostic services, availability of TB medicines for children and adolescents, and follow-up of children and adolescents with TB or on TPT.

Since children and adolescents who are unwell commonly seek care at the primary health care level, where TB services are not always available, decentralization and integration of such services using a family-centred approach has the potential to improve access to care, especially for children and adolescents who do not need referral to a higher level facility. The objectives of decentralization are closely linked to the aspirations of universal health coverage (all people have access to the health services they need, when and where they need them, without financial hardship), which is a strategic priority for Sustainable Development Goal (SDG) target 3.8 *(71)*.

Decentralization of care at the community level has the following advantages:

- increased equity via improved access to health services;
- provision of TB care at the same time and in the same place for all family members;
- savings in time and money when care is provided closer to home;
- continuity of care between the person's home, community and local health centre;
- increased community support, which may lead to better adherence to treatment and can be instrumental in overcoming barriers to long-term care, including treatment adherence, transportation costs, missing school and loss of wages during sickness and clinic visits.

Other potential benefits of decentralization in the context of TB include increased treatment coverage in children and adolescents, reduced time to diagnosis and time to treatment, improved treatment success among children and adolescents started on TB treatment and TPT initiation, and reduced transmission *(72–75)*.

Regarding family-centred integrated care, many opportunities exist for the integration of TB services. For instance, opportunities for the integration of TB services at the health facility level exist in outpatient departments; nutrition, HIV, maternal and child health clinics (e.g. prevention of mother-to-child transmission, antenatal care, immunization clinics); general paediatric, adult TB and chest clinics; and inpatient departments. If resources are available, the NTP may consider implementing provider-initiated TB screening in relevant child health entry points, and linkages to diagnosis or treatment. If resources are limited, entry points or services designed to care for sick children could be prioritized.

The WHO policy on collaborative TB/HIV activities recommends the delivery of integrated TB/HIV services, preferably at the same time and location *(76)*. The policy further recommends that HIV programmes and NTPs should collaborate with other programmes to ensure access to integrated and quality-assured services, including for children and adolescents. Quality statement 1.8 of the *Standards for improving the quality of care for children and young adolescents in health facilities* recommends that all children at risk for TB or HIV are correctly assessed and investigated and receive appropriate management according to WHO guidelines *(77)*.

Many health care providers at the primary health care level in high TB burden countries have been comprehensively trained on assessing and caring for children with pneumonia, diarrhoea and malnutrition using IMCI and integrated service delivery packages on community case management. These packages are centred on the most common childhood illnesses, such as pneumonia and malnutrition, which have a clinical presentation similar to TB *(78, 79)*. Therefore, they offer an

opportunity to strengthen integrated symptom-based screening for TB in sick children aged under 5 years. Specifically, the 2014 *WHO IMCI chart booklet (79)* caters for referral of children with a cough for more than 14 days, assessment of TB infection among children with acute malnutrition, and TB assessment and TPT among children living with HIV *(78, 79)*.

Several considerations for the implementation of decentralized and integrated family-centred models of care for children and adolescents are included in the *WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents (69)*.

Treatment support

Implementation of the recommendations related to treatment support should enable the provision of people-centred TB services. Treatment adherence interventions that may be offered for people on TB treatment may include material support (e.g. food, financial incentives, transport fees), psychological support, tracers such as home visits or digital health communication (e.g. SMS, telephone) and medicine monitoring *(15, 16)*. Interventions should be selected on the basis of assessment of the individual's needs and preferences as well as available resources. It is important to involve local schools, including educating teachers and other staff about TB and providing accurate information about infectiousness, the needs of children and adolescents with TB or TB/HIV coinfection, the necessity for frequent visits to clinics, and the importance of taking medicines regularly. This may help to reduce stigma in schools and minimize time out of education. Faith-based organizations and other community groups can also be involved in supporting children and adolescents with TB and their families.

Socioeconomic impact of TB on children, adolescents and families

TB commonly affects people of lower socioeconomic status and worsens poverty through high costs related to treatment and reduced household income. Most children with TB develop it after contact with an adult family member with active infectious pulmonary TB (PTB). A high number of TB notifications in children indicates an ongoing adult epidemic *(80)*. TB in the family threatens household income and financial security.

Some examples of the impact of TB on children include dropping out of school following parental bereavement from TB or leaving school to go to work to maintain household income *(81)*. TB in childhood or adolescence may also disrupt or delay schooling and impair growth *(82)*. A recent scoping review reported that time spent caring for a child with TB had impacts on family spending, nutrition and education, and overall reduced household income – all of which were associated with lowered family well-being.[40] In addition, perceived and enacted stigma had practical implications for TB diagnosis, clinic attendance and treatment, and other psychosocial impacts beyond stigma, including breakdown of parental relationships. School disruption, food insecurity and a lack of social protection have also been reported for children and adolescents with TB based on an analysis of national TB patient cost surveys.[41]

5.3 Models of service delivery for people with TB, HIV and comorbidities

Models of service delivery for people with TB and comorbidities range from the least integrated, where stand-alone disease-specific providers refer patients to the relevant specialist services for comorbidities, to the most integrated, where all services across the cascade of care for TB and key

[40] Atkins S et al., unpublished, 2022.

[41] Nishikiori N et al., unpublished, 2022.

comorbidities are provided in a "one-stop-shop" by one health care worker *(83, 84)*.[42] Services may be provided at different levels of the health system, depending on the availability of comprehensive primary care and the degree of decentralization of the respective services. In some settings, TB services may be decentralized to the primary care level, while services for comorbidities such as diabetes and mental disorders may be available only at the secondary care level. In this situation, the degree of integration can be increased only if diabetes and mental health services are also decentralized closer to the end user *(22)*. The provision of integrated care and comprehensive services for people with HIV-associated TB as close as possible to where they live has long been a focus of WHO policy documents. Such efforts should include integrating services for the prevention, diagnosis, treatment and care of TB and HIV into maternal and child health services, including the prevention of parent-to-child transmission of HIV, and treatment centres for drug dependency where applicable *(76)*.

Within these models, care may be provided by separate specialist health care workers who refer patients to different services according to established pathways. Alternatively, multidisciplinary teams comprising professionals with a mix of skills, including medical and nonmedical, that are required to meet the needs of the end user, may provide coordinated care *(85)*. Care can also be provided by one health care worker for both TB and comorbidities, where the expertise is available (e.g. for TB and HIV) *(84)*. All models of care may be strengthened by the engagement of community health care workers, outreach teams and peer supporters.

5.4 Private-sector involvement in TB care

In many high TB burden countries, the majority of people seek treatment from private providers not linked to the public health care system *(86)*. Private health care providers are an entry point to TB care and treatment *(86–88)*. However, people with TB may not have good-quality TB services if the NTP does not cooperate with the private sector. Health care providers in the private sector may not be provided with information about TB or trained in the up-to-date guidance on TB diagnosis and treatment, including the use of child-friendly formulations. Additionally, patients managed in private health facilities and services are often not notified to the NTP. A wide range of private health care providers exist in different settings, and the services they provide vary. It is important for NTPs to recognize the different private health care providers in the community and work with them to improve the services TB patients are receiving. Private health care providers should particularly be educated on TB – including TB prevention, screening, diagnosis, treatment and care – and should understand the importance of mandatory reporting *(67)*. Working with professional organizations and nongovernmental organizations who also work with the private sector may help to build relationships with the private sector in providing TB care.

5.5 TB and health emergencies

Health emergencies, such as the COVID-19 pandemic, are associated with a disruption in health service delivery, either directly due to the focused attention given to the emergency or indirectly due to the actions taken to control the emergency.

The COVID-19 pandemic has reversed years of progress in providing essential TB services and reducing the disease burden of TB. There has been a large global drop in the number of people newly diagnosed with TB. Reduced access to TB diagnosis and treatment has resulted in an increase in the number of TB-related deaths.

[42] The models of care described here are categorized according to where a person first seeks care, and according to the degree of integration. They are not prescriptive; national programmes should define the models that best enable the provision of quality-assured comprehensive services as close as possible to the end-user.

Indirect impacts of health emergencies, such as reduced household income, increased poverty, food insecurity, malnutrition, missed health checks, missed vaccinations and missed work or schooling, may affect TB diagnosis and care.

In May 2021, WHO updated its information note on *COVID-19 – considerations for tuberculosis (TB) care* to guide countries on approaches to maintaining TB services *(89)*. For instance, both COVID-19 and TB have respiratory symptoms, which provides an opportunity to diagnose both COVID-19 and TB *(90)*.

Programmes should make sure that there are enough stocks of TB preventive therapy for the predicted increased need for this therapy resulting from people with undiagnosed TB and increased associated exposure because of COVID-19-related lockdowns. NTPs should ensure that supplies of TB medicines are not interrupted and that people with TB are provided with adequate refills to enhance treatment completion and minimize frequent trips to health facilities, where there may be an increased risk of infection from COVID-19. This may be achieved via multi-month dispensing or community delivery of TB medicines. Efforts should be made to ensure that neonatal and infant Bacillus Calmette–Guérin (BCG) vaccination continues uninterrupted.

6. Palliative care

Palliative care is the preventing and relieving of the suffering of people affected by TB during and after treatment and at the end-of-life.

Many people with TB, and most with DR-TB, suffer in multiple ways: from physical symptoms such as pain or dyspnoea, from psychological symptoms such as anxiety or depression, and from social problems such as discrimination or homelessness. This suffering may be due to the disease, its treatment, physical or psychological comorbidities such as HIV/AIDS, diabetes, or mental health/substance use disorders, stigma and discrimination, or extreme poverty *(91, 92)*. People continue to die from both DR-TB and DS-TB *(93)*, and their family members may suffer from the stress of caregiving, financial challenges, further stigma and grief *(91)*.

6.1 What is palliative care?

Palliative care is the prevention and relief of the physical, psychological, social and spiritual suffering of adults and children with serious illnesses and psychosocial support for their families *(94, 95)*. The prevalence, types and severity of suffering of people with TB vary by geopolitical situation, socioeconomic conditions, culture, accessibility of primary and specialized health care, and the susceptibility of their TB to anti-TB medicines. Attention to local needs is necessary for palliative care services to be person-centred: tailored to local needs and to the needs of individual patients and families *(94, 96)*.

6.1.1 Why is palliative care an essential part of comprehensive TB care?

WHO's End TB Strategy has a vision of zero suffering *(13)*. Based on this vision alone, palliative care is an essential part of comprehensive care for people with TB *(13, 91, 94, 97)*. In addition, World Health Assembly Resolution WHA67.19 from 2014 and the WHO Ethics Guidance for the implementation of the End TB Strategy state that palliative care is "an ethical responsibility of health systems and that it is the ethical duty of health-care professionals to alleviate pain and suffering, whether physical, psychosocial or spiritual, irrespective of whether the disease or condition can be cured". *(16)*. They also state explicitly that palliative care is a core component of the human right to health, and of comprehensive care for people with DR-TB *(16, 94)*. Palliative care not only can alleviate the suffering of patients with TB but also may improve treatment outcomes and protect the community by helping patients adhere fully to treatment *(91, 92)*.

6.1.2 When and where should palliative care be provided for people with TB?

An initial assessment for suffering related to TB should be done at the time of diagnosis. Palliative care should be initiated immediately as needed and should be combined with TB treatment to relieve any suffering due to the disease, to the adverse effects of treatment, to comorbidities or to social problems. It is especially important for people with DR-TB *(98)*. Tailored to the patient's needs, palliative care

should continue regardless of whether the cure is expected or whether treatment fails. It should be available at all levels of the health care system *(94–96)*, namely:

- TB and lung disease hospitals and general hospitals with TB units;
- district hospitals;
- TB clinics in the community;
- patients' homes.

Even when a patient recovers from TB disease, all the medical effects of TB may not be resolved. People that survive TB may have long-term impairment from TB disease *(99–102)*. People who had bone or neurological infections may continue to have problems related to bone damage or neurological issues. It is also becoming more and more recognized that even people who had pulmonary TB may have serious long-term medical problems resulting from lung damage resulting from TB. Studies find that a majority of patients report respiratory symptoms after completing TB treatment. Patients may have continued shortness of breath, cough, decreased lung function, bronchiectasis and recurrent bacterial pneumonia. They may also develop heart failure due to lung damage. These symptoms often continue to affect their daily lives. Although many people improve with time, a significant number continue to have symptoms, and their symptoms may even worsen with time.

It is important to continue to monitor the health of TB patients even after they have finished their medications for TB disease. They may need to be followed by a lung or heart doctor to help treat ongoing symptoms. They may benefit from palliative care which can offer treatments to help with their symptoms such as shortness of breath, swelling from heart disease, pain and psychiatric care to help patients who are facing long-term health problems.

6.1.3 Who should provide palliative care for people with TB?

Most palliative care can and should be provided by TB and lung disease specialists, primary care doctors and nurses with at least basic palliative care training (30–40 hours of training), TB treatment supporters and community health workers trained to recognize and report uncontrolled suffering, and by social workers and psychologists *(91, 92, 94–96)*. Ideally, specialist palliative care doctors should be available to treat patients with refractory or complex suffering and also as supervisors, consultants and teachers.

6.1.4 What is end-of-life care for people with TB?

End-of-life care is palliative care for patients whose curative treatment options have been completely exhausted. When failure of all curative options is suspected, it is imperative that careful plans be made both:

- to suspend all non-beneficial anti-TB therapy, and
- to commence end-of-life care combined with infection control.

These plans are crucial to maximize the patient's comfort and quality of life, help prevent transmission and protect public health.

6.2 Planning and implementing palliative care for people affected by TB

6.2.1 Integration of palliative care into NTPs

Most people with DR-TB, and many with DS-TB, have palliative care needs. Yet palliative care is in general not widely accessible in high TB burden countries *(103)*. Wherever palliative care services are

not yet accessible, the NTP may need to take the lead in planning and implementing them *(16)*. If possible, official collaboration should be established between an existing palliative care programme and the NTP *(104)*. Plans for TB palliative care should include the following:

- a list of palliative care interventions (**Table 5**);
- an essential package of palliative care (medicines, equipment, social supports, human resources) (**Table 6**);
- the estimated number of patients to be served;
- models of care that are responsive to the needs of patients;
- regulations to assure access to essential medicines for palliative care;
- M&E; and
- sustained funding to cover the costs of the operation *(91)*.

Table 5. Palliative care interventions needed for people with TB

General intervention	Specific examples
Physical suffering relief	• Assessment and treatment of pain, dyspnoea and other physical symptoms due to TB. • Assessment and treatment of pain and other physical symptoms due to comorbidities, adverse drug reactions or AEs.
Psychological suffering relief/ psychological support	• Assessment and treatment of psychological symptoms or mental illnesses such as anxiety, depression, delirium or hallucinations. • Assessment and treatment of substance use disorders such as alcohol use disorders. • Counselling to promote coping and treatment adherence. • Counselling to assist patients to prepare for death when appropriate. • Bereavement counselling as needed for family members.
Social suffering relief/ social support	• Counselling to mitigate stigma and discrimination. • Specific supports for patients or family caregivers living in extreme poverty (Table 6). • Referral for legal counselling as needed.
Spiritual suffering relief/ spiritual support	• Enable access to local volunteer spiritual supporters.

6.2.2 Essential package of palliative care for people affected by TB

The essential package of palliative care for people affected by TB consists of a set of medicines, simple equipment, social supports and human resources (**Table 6**). Adapted from the WHO essential package of palliative care for primary care *(95)*, it is designed to be safe and effective for preventing and relieving all types of suffering associated with TB (**Box 6**). The package includes only inexpensive and readily available medicines and equipment, and its use requires only basic palliative care training (30–40 hours). Consequently, this package can and should be made accessible everywhere, including for the rural poor. The medicines include: at least one non-opioid analgesic, opioid analgesic, anti-pyretic, anti-emetic, anxiolytic, antidepressant, antihistamine, anticholinergic, antifungal and anti-diarrhoeal agent; as well as a bronchodilator, corticosteroid, diuretic, expectorant, laxative, neuroleptic and proton pump inhibitor.

Table 6. Essential package of palliative care for people affected by TB *(91, 105)*

Medicines*
Albuterol metered-dose inhaler
Amitriptyline, oral
Bisacodyl (Senna), oral
Dexamethasone, oral and injectable
Diazepam, oral and injectable
Diphenhydramine (chlorpheniramine, cyclizine or dimenhydrinate) oral and injectable
Fluconazole, oral
Fluoxetine (sertraline and citalopram), oral
Furosemide, oral and injectable
Guaifenesin, oral
Haloperidol, oral and injectable
Hyoscine butylbromide, oral and injectable
Ibuprofen (naproxen, diclofenac or meloxicam), oral
Lactulose (sorbitol or polyethylene glycol), oral
Loperamide, oral
Metoclopramide, oral and injectable
Metronidazole, oral – to be crushed for topical use
Morphine, oral fast-acting and injectable
Naloxone, injectable
Omeprazole oral
Oxygen
Paracetamol, oral
Petroleum jelly
Equipment
N-95 respirator masks
Surgical masks
Antimicrobial hand wash
Spacers for metered-dose inhalers
Pressure-reducing mattress
Nasogastric drainage & feeding tube

Urinary catheters
Opioid lock box, only for hospitals & clinics
Flashlight with rechargeable battery (if no access to electricity)
Adult diapers/cotton and plastic
Social supports**
Cash payment monthly for housing or school tuition
Food package monthly
In-kind support once per patient or caregiver, including blanket, sleeping mat, shoes, soap, toothbrush, toothpaste
Transportation costs to receive health care
Funeral costs, once, only if patient & caregiver in extreme poverty
Human resources for palliative care***
Doctor with at least basic training in palliative care (specialist or general practitioner)
Nurse with at least basic training in palliative care (specialist or general)
Social worker, psychologist or counsellor
Pharmacist
Community health workers/TB treatment supporters

* Based on *WHO Model List of Essential Medicines, 2019*. In parentheses () are acceptable substitutes where the primary recommended medication is not available or is expensive.

** For patients who qualify on the basis of financial need.

*** Staffing will vary depending on the level of the health care system (referral hospital, provincial hospital, district hospital, community health centre, or home). Staff members of palliative care centres or wards may provide palliative care full-time. Others may provide relief of suffering combined with TB treatment most of the time and may provide end-of-life care only when needed. All staff members should be trained to practise and teach infection control.

6.2.3 Oxygen for relief of mild dyspnoea

Oxygen therapy may provide relief from mild dyspnoea and sometimes at least partial relief from moderate dyspnoea. It should be accessible at least in TB hospitals and wards. Whenever possible, it also should be accessible in the home.

6.2.4 Morphine for safe relief of chronic or refractory dyspnoea

Strong opioids such as morphine have been proven to relieve safely and effectively not only pain but also dyspnoea that is refractory to oxygen therapy and treatment of the underlying cause *(106–112)*. Morphine is the most studied and least expensive strong opioid and is widely available on the world market. Consequently, morphine, in both oral fast-acting and injectable preparations, is the most essential of the essential palliative medicines for people with TB *(106, 107)*. Misconceptions about the use of opioids held by health care workers and caregivers result in unnecessary suffering from pain and chronic or refractory dyspnoea and perpetuate unethical medical practices *(108)*. NTPs should work with the officer responsible for controlled medicines at the health ministry to ensure that these

morphine preparations are accessible for TB palliative care at least in TB hospitals and wards, and ideally also at TB clinics, according to international standards *(91, 94, 106, 107, 109–112)*.

6.2.5 Palliative care teamwork

Palliative care is best provided by a multidisciplinary team whenever possible *(104)*. The ideal palliative care team includes a physician, nurse and psychologist or social worker. TB treatment supporters, community health workers or volunteers can be trained and supervised to visit patients at home, to provide emotional support, to recognize and report inadequately controlled suffering or inappropriate use of opioids, and to practise and teach strict infection control *(91)*.

6.2.6 Management of substance use disorders and other comorbidities

People affected by TB are often also affected by other medical conditions such as HIV/AIDS, diabetes, hepatitis, chronic lung disease, neurological disease, substance use disorders and other mental health problems. Some of these illnesses and disabilities may by themselves contribute to an increased risk of death among people with TB while on treatment and afterwards. When creating TB palliative care services, the prevalence of serious comorbidities in the target population and the associated types of suffering should be estimated and preparations should be made to address them. Mental health disorders may worsen when TB patients learn of a poor prognosis. Therefore, all TB patients in need of palliative care should undergo an assessment for mental health disorders.

Alcohol use disorder and injection drug use are risk factors for poor DS-TB and DR-TB treatment outcomes and many other problems *(113–115)*. Treatment of alcohol use disorder and opioid use disorder can and should be integrated with comprehensive TB care and treatment *(116, 117)*. WHO guidance on task-shifting, training and supervision of human resources for palliative care is provided elsewhere *(104)*. Task-shifting to enable effective community-based treatment of alcohol use disorder has also been demonstrated *(118, 119)*.

6.2.7 M&E of palliative care for people affected by TB

Palliative care for people affected by TB should be monitored and evaluated to help assure its accessibility and quality *(104, 120, 121)*. The following two outcome indicators are recommended:

- Number of patients with TB in the previous reporting period/year for whom all attempts at curative treatment were deemed to have failed.
- Number of patients with TB in the previous reporting period who received morphine (oral fast-acting or injectable) for symptom relief.

The following process indicators are optional but also suggested:

- Is there a national TB policy strategic plan that includes palliative care? (Yes / No / NA)
- Is morphine (oral fast-acting or injectable) available in public TB hospitals or wards (Yes / No / Unknown) (available in over 50% of TB hospitals or wards)?

6.2.8 Cost savings from palliative care integration into TB programmes

The essential palliative care package need not increase the cost of the routine TB care and treatment significantly, if at all. There is growing evidence that palliative care integrated into health care systems and including home care can save money for these systems by reducing hospital admissions near the end of life and the length of stay in hospitals *(92, 105, 122–125)*. For patients not expected to survive,

a one-time expense may be necessary to refurbish rooms either in institutions or in the home to ensure infection control. Palliative care has also been shown to provide financial risk protection for patients and families *(92, 126, 127)*.

6.3 End-of-life care for people with TB

6.3.1 When should suspension of TB treatment be considered?

TB treatment often consists of an initial treatment cycle and, if no response is seen, it is necessary to reassess the regimen and treatment plan as well as to formulate a new plan of action. Suspension of drug therapy is recommended in cases where the medical personnel involved are confident that the patient has been adherent to the prescribed regimen, the patient is on the correct regimen with respect to drug sensitivities (e.g. the patient is not on a DS-TB regimen if they may have DR-TB) and there is no possibility of offering another effective therapy *(61)*. In patients who have no therapeutic options, there is a medical, moral and public health obligation to continue providing care to the end of life with proper infection control *(91, 103)*.

6.3.2 Important considerations in suspending TB treatment

There are at least three important considerations in suspending anti-TB therapy:

- **Doing no harm:** The medicines used to treat TB, and especially DR-TB, have significant adverse effects. Continuing them while the treatment is failing may cause additional unnecessary suffering and create false expectations in patients and families.
- **Public health:** Patients in whom DR-TB regimens fail are likely already to have highly resistant strains, and ongoing therapy can result in resistance to even more medications. The resultant highly resistant strains could subsequently infect others and be extremely difficult to treat. In addition to the creation of further resistance, continued treatment in this situation also uses resources that may be very scarce. Thus, in general, treatment should be discontinued in this situation. However, if there is no clinical deterioration and the clinician prefers to continue the regimen, strict respiratory infection control is critical.
- **Non-abandonment:** Provision of palliative and end-of-life care is imperative to optimize the quality of life with proper TB infection control *(16, 91)*.

6.3.3 Decision-making about suspension of TB treatment

If suspension of DR-TB therapy is considered, there should be discussion with the entire clinical team – including the patient and all physicians, nurses and health workers or TB treatment supporters involved in the patient's care. If the clinical team decides together that treatment should be suspended, a clear plan should be prepared for approaching the patient and the family. This process usually requires personal interaction with patient and family, ideally including home visits, and may take several weeks. It is not recommended to suspend therapy before the patient understands and accepts the reasons to do so, agrees with a change in goals of care to optimizing quality of life and comfort, and accepts palliative care. It is crucial that care continues and that the patient not be abandoned.

Box 6. Checklist of essential palliative and end-of-life care

- **Is relief from dyspnoea offered?** Oxygen may be used to alleviate shortness of breath in some cases, but there is no significant evidence to generalize its practice. Bronchospasm can be controlled with a metered-dose inhaler with a spacer or mask. Morphine and other strong opioids provide effective relief from chronic or refractory dyspnoea and should be offered according to established clinical protocols available in the medical literature *(106–111)*. Morphine also relieves cough refractory to bronchodilators, guaifenesin or non-opioid cough suppressants.
- **Is relief from pain and other symptoms offered?** Paracetamol typically gives relief from mild pain. A strong opioid such as morphine should be used to treat moderate or severe pain *(110–112)*. Antiemetics and antipyretics may be needed.
- **Is psychological support being offered?** Psychological counselling for the patient and family caregivers is critical for providing emotional support and assisting patients with end-of-life decision-making. Patients should be assessed for anxiety or depression and treated whenever the assessment is positive. Any doctor with basic palliative care training should be able to diagnose and treat uncomplicated anxiety disorders, depression, and delirium *(91, 95)*. Patients with complex mental health problems should have virtual or in-person psychiatric evaluation.
- **Are infection control measures being applied thoroughly?** A patient who is taken off anti-TB treatment because of failure often remains infectious. Infection control measures should be continued with reinforcement of environmental and personal measures, including N95 mask use for caregivers and surgical masks for patients.
- **Is there respect for patient's beliefs and values?** Every patient is different, and an acceptable quality of life for one patient would not be acceptable to another. As much as possible, the patient's wishes for the location and type of care should be respected *(10, 16, 91)*. Also, it is common for patients and family caregivers to develop or increase their interest in spirituality or religion once they perceive that the end of life is approaching. Health care providers should respect those beliefs and not impose personal values and practices.
- **Has the patient received nutritional assessment and support?** Small and frequent meals are often best for a person at the end of life. Nausea and vomiting should be treated, but it should be accepted that appetite and intake will decline as the patient's condition deteriorates and during end-of-life care. Artificial nutrition, either enteral via gastric tube or parenteral, typically provides no longevity benefit and often worsens suffering from dyspnoea or oedema.
- **Is the patient being visited regularly by the TB programme?** When TB treatment stops, regular visits by health care providers and the support team should continue in order to address medical needs and to ensure that infection control practices are being followed.
- **Are all basic hygiene and preventive measures being given?** Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important except in the last hours of life. Encourage patients to move their bodies in bed if able to do so. Keeping beds dry and clean is also important.

6.3.4 Providing end-of-life care for people with TB

End-of-life care can be provided either in an inpatient setting (hospital or hospice) or in the home depending on: the preference of the patient; the willingness of the relatives and community to provide home care; the presence of a medical need for inpatient care; and the existing capacity for proper infection control in each setting *(91, 122)*. Palliative home care combined with strict infection control may be preferred by many patients and may be less expensive than institutional care for health care systems. Patients could be with family and friends rather than isolated in an institution that may be far from home. Those who are well enough may be able to engage with family in income-earning activities such as crafts or Internet-based businesses. However, adherence to infection control measures should be a prerequisite for remaining at home. TB programmes should explore opportunities to collaborate with local palliative care programmes to provide palliative home care for people with TB. In addition, TB programmes should build basic capacity for the estimated number of patients in need of institutionally-based end-of-life care either for medical reasons or because of the lack of relatives or community members willing to provide home care.

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Annex 1. Tuberculosis medicine information sheets

Sources of information

These information sheets on drugs for the treatment of tuberculosis (TB) represent an update of the sheets first published in the World Health Organization (WHO) document, *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (1)*, which was based on an adaptation of the publication *Drug resistant tuberculosis: a survival guide for clinicians (2)*. The information has been updated and expanded through a review of multiple sources, including available information on new drugs, recent trials, pharmacokinetics, pharmacodynamics and safety studies. Formulations and dosages have been updated and are in line with the Annex 4 of the *WHO operational handbook on tuberculosis. Module 4: Treatment –tuberculosis treatment and care, 2024 update*. These formulations are available in quality-assured forms, and have been approved by Stringent Regulatory Authorities, prequalified by WHO or approved by the Expert Review Panel of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). WHO recommends using formulations that have been quality assured based on international standards.

Information on drug interactions was sourced primarily from online resources from the United States Food and Drug Administration and the European Medicines Agency.

Bedaquiline (B or Bdq)

Bedaquiline (B or Bdq) Drug class: diarylquinoline	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target**: *M. tuberculosis* inner metabolism. Inhibits ATP synthesis, leaving the bacteria without sources of energy that are needed for replication and for latency. **Activity**: High bactericidal activity, but it may take 7–14 days to manifest a bactericidal effect. **Sterilizing activity**: Significant; able to support reduction in duration of treatment. **Half-life and excretion**: has a 5.5-month half-life, with slow release of bedaquiline from peripheral tissues, which may have implications in toxicity and in cases of loss to follow-up (sustained monotherapy). Is hepatically metabolized by CYP3A4 (cytochrome p450) leading to the formation of its main metabolite M2, which does not contribute significantly to antimycobacterial activity compared with the parent compound. Bedaquiline is mainly eliminated in faeces. The renal clearance of the unchanged drug is insignificant.
Cross-resistance	Cross-resistance has been reported between bedaquiline and clofazimine, through efflux pump-mediated resistance and other mechanisms.
Dose[a]	• **Adults:** 400 mg once daily for 2 weeks, followed by 200 mg once daily, thrice weekly for 22 weeks. The maximum daily dose is 400 mg. For patients treated with the BPaLM/BPaL regimen (>14 years), bedaquiline can also be administered 200 mg once daily for 8 weeks, followed by 100 mg once daily until the end of treatment. • **Children:** There is no age restriction (see the handbook **Annex 4** for weight bands). • **Renal failure or dialysis:** No dose adjustment is needed for mild-to-moderate renal insufficiency. It should be used with caution in patients requiring renal dialysis (see the handbook **Annex 4** for weight-based dosing in adults and children).
Administration	Oral. In children, 100 mg tablets can be administered whole, or crushed and suspended in water without affecting bioavailability. Vigorous stirring or shaking is needed before administration. The 20 mg tablets can be administered whole or crushed and dispersed in <1–3 mL of water per tablet (maximum of 5 tablets in 5 mL of water) or crushed and mixed with food.
Formulation and preparation	20 mg scored, dispersible tablet. 100 mg uncoated tablets.
Storage	Tablets can be stored at room temperature (15–30 °C). Tablets removed from the original packaging should be stored in a tightly sealed, light-resistant container and labelled with an expiration date that should not exceed 3 months.
Oral absorption	Administration with food (ideally high-fat meals) leads to a twofold increase in bioavailability.

Bedaquiline (B or Bdq) Drug class: diarylquinoline	
CSF penetration	Studies[b] involving a small number of participants indicate that bedaquiline and M2 (main metabolite) penetrate well into the CSF of patients with pulmonary TB with a presumably intact blood–brain barrier.
Special circumstances	**Use in pregnancy or breastfeeding:** No fetal harm was found in animal studies. The drug accumulates significantly in breast milk, and breastfed infants receive doses of bedaquiline equivalent to maternal doses.[c] **Use in renal disease:** No dosage adjustment is required in patients with mild-to-moderate renal impairment. It should be used with caution in patients requiring peritoneal dialysis or haemodialysis. Therapeutic drug monitoring may be useful, if available. **Use in hepatic disease:** Bedaquiline should be used with caution because it is metabolized in the liver. No dosage adjustment is required in patients with mild-to-moderate hepatic impairment. It has not been studied in patients with severe hepatic impairment and should be used with extreme caution in such patients, and only when benefits outweigh risks. Clinical monitoring for bedaquiline-related adverse reactions is recommended.
Adverse reactions	**Overall tolerance:** Well tolerated. **Occasional:** Nausea, arthralgia (joint pain) and headache (~10%). QTc prolongation (estimated QTc increased by 10–15 msec, maximal at week 15). Overall QTc prolongation in cohorts using bedaquiline and other QTc-prolonging drugs was 2.7%, with median appearance at 2.5 months. **Uncommon:** Hyperuricaemia, phospholipidosis (accumulation of phospholipids in the body tissues) and elevated transaminase are an early signal for increased risk of pancreatitis.
Contraindications	Hypersensitivity to bedaquiline. Taking other medications that are strong inducers of CYP3A (e.g. rifamycins and carbamazepine). **Use with caution in potential situations that may increase QT interval:** Such situations are patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, concomitant use of other QT-prolonging drugs. Any syncopal event (such as fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase was modest, and no arrhythmias or related deaths were reported even when bedaquiline and delamanid were co-administered. **Discontinue or do not use in the presence of:** • clinically significant ventricular arrhythmia; • a QTcF interval of >500 msec (confirmed by repeat ECG); • severe liver disease; or • abnormal electrolytes.

Bedaquiline (B or Bdq) Drug class: diarylquinoline	
Drug interaction	Metabolized by CYP3A4 (cytochrome p450). • Co-administration with rifamycins (e.g. rifampicin, rifapentine and rifabutin) significantly reduces concentrations of bedaquiline (<50%). Other strong CYP3A4 inducers (e.g. efavirenz, phenytoin and glucocorticoids) may also require caution and dose adjustment.[d] • CYP3A4 inhibitors (e.g. azole antifungal drugs, some macrolides and PIs) can increase the level of bedaquiline. Substitution of the PI with an integrase inhibitor (e.g. dolutegravir or raltegravir) is suggested. If a ritonavir-boosted PI must be used, an ECG should be performed every 2 weeks for the first 8 weeks. • Use with other medicines that direct or indirectly prolong the QT interval may cause additive prolongation that requires caution and monitoring. Such medicines include TB drugs (fluoroquinolones, clofazimine and delamanid) and ancillary and common drugs (azoles, macrolides, metoclopramide, efavirenz, furosemide, hydrochlorothiazide, citalopram, escitalopram, methadone, antiarrhythmics and others).
Food interactions	Administered with food; ideally, with high-fat meals (which increases the oral bioavailability).
Monitoring	Ideally, an ECG should be obtained before initiation of treatment, monthly during treatment and at the end of treatment for a DR-TB treatment regimen, or as required based on specific regimens. Bedaquiline should be stopped if the QTc >500 msec, and ECGs and potassium levels should be monitored regularly until the QTc returns to normal. More frequent monitoring is recommended if cardiac conditions, hypothyroidism or electrolyte disturbances are present. Liver function tests should be done at baseline, then monthly.
Patient instructions and alerting symptoms	Medication is to be taken with food. Alcohol should be avoided. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • baseline heart problems, fast or irregular heartbeat, or if the patient faints; or • liver problems (hepatotoxicity): nausea or vomiting, stomach pain, jaundice, fever, weakness, itching, unusual tiredness, loss of appetite, light-coloured stool, dark-coloured urine, and yellowing of the skin or the whites of the eyes.

ATP: adenosine triphosphate; BMI: body mass index; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CSF: cerebrospinal fluid; ECG: electrocardiograph; HIV: human immunodeficiency virus; *M. tuberculosis*: *Mycobacterium tuberculosis*; PI: protease inhibitor; TB: tuberculosis; TdP: torsade de pointes.

[a] See the handbook **Annex 4** for weight bands.

[b] Upton CM, Steele CI, Maartens G, Diacon AH, Wiesner L, Dooley KE. Pharmacokinetics of bedaquiline in cerebrospinal fluid (CSF) in patients with pulmonary tuberculosis (TB). J Antimicrob Chemother. 2022;77:1720–4. doi: https://doi.org/10.1093/jac/dkac067.

[c] Court R, Gausi K, Mkhize B, Wiesner L, Waitt C, McIlleron H et al. Bedaquiline exposure in pregnancy and breastfeeding in women with rifampicin-resistant tuberculosis. Brit J Clin Pharm. 2022;88:3548–58. doi: https://doi.org/10.1111/bcp.15380.

[d] Sirturo (bedaquiline) label. Maryland: United States Food and Drug Administration; 2012 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf). (See Section 7).

Clofazimine (C or Cfz)

Clofazimine (C or Cfz) Drug class: iminophenazine	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall; clofazimine is highly lipophilic and it interferes with the proton-motive force, leading to membrane-destabilizing effects and, ultimately, ATP production. **Activity:** Studies suggest bactericidal and sterilizing effect. **Half-life and excretion:** Tissue half-life is estimated to be around 25–70 days. Metabolized by the liver and very slowly eliminated, mainly by bile in the faeces.
Cross-resistance	Cross-resistance has been reported between bedaquiline and clofazimine through efflux pump-mediated resistance and others.
Dose[a]	• **Adults:** 100 mg daily (upper daily dose is 100 mg). • **Children:** See handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** No adjustment required. See handbook **Annex 4** for weight-based dosing in adults and children.
Administration	Oral. Capsules should be taken whole. Tablets can be taken whole or dispersed. Clofazimine tablets dissolve slowly (~5 minutes) in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred before administration.
Formulation and preparation	50 mg tablets or capsules. 100 mg tablets or capsules.
Storage	Should be stored below 30 °C. Capsules should be protected from moisture.
Oral absorption	70% absorption after an oral dose.
CSF penetration	There are limited data available regarding CNS penetration.
Special circumstances	**Use during pregnancy or breastfeeding:** There are limited data; recommended during pregnancy when benefits outweigh risk. The drug passes into human breast milk. Infants exposed to it in utero or during breastfeeding may appear more deeply pigmented. **Use in renal disease:** No dosage adjustment required. **Use in hepatic disease:** Partially metabolized by the liver; use caution or adjust the dose for severe hepatic impairment.

Clofazimine (C or Cfz) Drug class: iminophenazine	
Adverse reactions	**Overall tolerance**: Poorly tolerated. **Common:** In 75–100% of patients receiving clofazimine there will be an orange, pink or brownish-black discolouration of the skin, conjunctivae and bodily fluids (owing to deposits, primarily in fatty tissues). The drug is often rejected by adolescents or in societies where body image or skin colour is highly important. Also causes dry skin (ichthyosis and xerosis) and itching. **Frequent:** QT prolongation (10–20 msec). **Uncommon:** Photosensitivity, abdominal pain and obstruction or bleeding, due to the deposition of drug and formation of crystals in the intestinal mucosa.
Contraindications	Allergy to clofazimine. Cfz should be used with caution in potential situations that may increase QT interval: Such situations are patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, concomitant use of other QT-prolonging drugs. Any syncopal event (such as fainting) or palpitations should prompt an immediate medical evaluation and ECG.
Drug interactions	Use with other medicines that direct or indirectly prolong the QT interval may cause additive prolongation that requires caution and monitoring: • anti-TB drugs: fluoroquinolones, bedaquiline and delamanid; and • ancillary and common drugs: azoles, macrolides, metoclopramide, efavirenz, furosemide, hydrochlorothiazide, citalopram, escitalopram, methadone, antiarrhythmics and others.
Food interactions	To be administered with a meal, to avoid stomach upset and improve absorption.
Monitoring	Monitor clinical signs and symptoms. Where it is possible, perform ECG at every schedule visit if other QT interval-prolonging agents are given concomitantly.
Patient instructions and alerting symptoms	To be taken with food to avoid stomach upset and improve absorption. May discolour skin and body secretions to orange, pink or brownish-black. This effect goes away after stopping the medicine but may take a long time to do so (months to years). Patients should avoid the sun and use strong sunscreens. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • abdominal pain, severe nausea, vomiting, or diarrhoea; • baseline heart problems, fast or irregular heartbeat, or if the patient faints

ATP: adenosine triphosphate; CNS: central nervous system; CSF: cerebrospinal fluid; ECG: electrocardiography; *M. tuberculosis*: *Mycobacterium tuberculosis;* TB: tuberculosis.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Cycloserine (Cs) or terizidone (Trd)

Cycloserine (Cs) or terizidone (Trd) Drug class: analogue of D-alanine	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Cycloserine (Cs) or terizidone (Trz)** are considered equivalent drugs and are commonly used interchangeably. Terizidone is formed by two molecules of cycloserine combined. There is no significant safety difference between the two drugs. **Target:** *M. tuberculosis* cell wall. These drugs block the formation of the peptidoglycan layer (which has a structural role, especially in the Gram-positive cell wall). **Activity:** Bactericidal or bacteriostatic (low bactericidal activity), depending on concentration. **Half-life and excretion:** Has a half-life of 10 hours. Renally excreted.
Cross-resistance	There is no cross-resistance with other drugs.
Dose[a]	• **Adults:** 10–15 mg/kg/day (upper daily dose is 1 g). • **Children:** See handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** 250 mg once daily or 500 mg, thrice weekly; monitor drug concentrations, if possible, to keep peak concentrations <35 mcg/mL. **Pyridoxine (vitamin B6):** commonly used to limit cycloserine toxicity but there are insufficient data to support systematic administration of vitamin B6 to adults or children on these drugs. See the handbook **Annex 4** for weight-based dosing in adults and children**.**
Administration	Oral. Capsules should be taken whole. However, dissolving the content of the capsules in 10 mL of water and administering the volume corresponding to the correct milligram dose may facilitate administration in younger children, although bioavailability is uncertain.
Preparation	125 mg mini capsule (only available for cycloserine). 250 mg capsule.
Storage	Should be stored at room temperature (15–25 °C) in an airtight container. Protect from moisture.
Oral absorption	Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids or orange juice.
CSF penetration	Concentrations in CSF approach those in serum.
Special circumstances	**Use during pregnancy or breastfeeding:** Not well studied; there is exposition in utero and these drugs are present in milk, but no teratogenicity has been documented. **Use in renal disease:** Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see under Dose section, above). Use with caution. **Use in hepatic disease:** These drugs are considered to be liver friendly, but hepatotoxicity and jaundice have been reported.

Cycloserine (Cs) or terizidone (Trd) Drug class: analogue of D-alanine	
Adverse reactions	**Overall tolerance:** Variable; poorly tolerated by many patients due to common neuropsychiatric toxicity. **Common:** Inability to concentrate, lethargy, neuropathy (30%) and depression (10%). **Frequent:** Psychosis (7.6%). **Occasional:** Seizures (3%), jaundice, suicidal ideation and skin problems. Severe CNS side-effects can be associated with peak concentrations >35 mcg/mL but may also be seen in the normal therapeutic range, especially in patients with pre-existing mental health conditions.
Contraindications	Pre-existing significant neurological or mental health conditions including seizure disorders, depression, anxiety, psychotic disease, personality disorder or alcohol and other substance abuse.
Drug interactions	Increased risk of CNS toxicity when given with isoniazid. Co-administration with delamanid or efavirenz may increase the risk of neuropsychiatric adverse events, especially in children (for delamanid) *(3, 4)*.
Food interactions	Best taken on an empty stomach, with juice or antacids. If food is taken, large high-fat meals should be avoided, as should alcohol, which increases the risk of convulsions.
Monitoring	Baseline and monthly monitoring for depression should be done using a tool (e.g. the Beck Depression Index). If therapeutic drug monitoring is possible, peak concentrations should be obtained within the first 1–2 weeks of therapy and monitored serially during therapy. The peak concentration should be kept at <35 mcg/mL. When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important. These events should be reported through the national pharmacovigilance system.
Patient instructions and alerting symptoms	**Patients and family members should be instructed to inform their health care provider immediately if any of the following occur:** • seizures; • shakiness, trouble talking or thinking or loss of memory; • depression or thoughts of hurting themselves or others; and • anxiety, confusion or personality changes (e.g. aggressive behaviour).

CNS: central nervous system; CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Delamanid (Dlm)

Delamanid (Dlm) Drug class: nitro-dihydro-imidazooxazole (nitroimidazole)	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall. Inhibits the synthesis of methoxy-mycolic and keto-mycolic acid, which are mycobacterial cell wall components. **Activity:** Bactericidal, potent in vitro activity. Potential sterilizing activity as nitroimidazooxazole derivatives are thought to generate reactive nitrogen species, including nitrous oxide, which causes cell poisoning. **Half-life and excretion:** The prodrug is activated by mycobacterial nitroreductase and binds tightly to plasma proteins. It is metabolized mainly by albumin and to a lesser extent by the CYP3A4 isoenzyme in the liver (cytochrome P450). The half-life is 30–38 hours. It is excreted primarily in the faeces, with less than 5% excretion in the urine.
Cross-resistance	There is limited published information about resistant mutations, frequencies and their correlation with clinical relevance.
Dose[a]	• **Adults:** 200 mg daily (upper daily dose is 200 mg). • **Children:** No age restriction. Dispersible tablets are the preferred option. See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** No dose adjustment needed for mild-to-moderate renal insufficiency; there are no data regarding use in patients with severe renal impairment. Initially, delamanid is not recommended for patients with severe renal impairment.
Administration	Oral. The use of the 25 mg dispersible tablet formulation is preferred in children. Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole, and they can be used in young children or people who cannot swallow tablets whole if the dispersible tablet formulation is not available.
Formulation and preparation	25 mg dispersible tablet. 50 mg film-coated tablets.
Storage	Should be stored at room temperature (15–25 °C) and in the original package, to protect from moisture.
Oral absorption	Absorption is increased with a standard meal (about 2.7-fold compared with fasting); 25–47% of the delamanid dose is absorbed following oral administration with food.
CSF penetration	One study suggests that, despite relatively low total CSF drug levels, delamanid achieves adequate concentrations in brain tissue and the oral formulation may be sufficient to have a role in treating TB meningitis.[b]

Delamanid (Dlm) Drug class: nitro-dihydro-imidazooxazole (nitroimidazole)	
Special circumstances	**Use during pregnancy or breastfeeding:** Data on the use of delamanid in pregnancy are limited. Animal data show no evidence of teratogenicity. The manufacturer allowed its use in pregnant women in their compassionate-use protocol. Although the case series of pregnant women on delamanid is small, all neonates had good birth outcomes, suggesting that pregnant women in need should not be denied access. In animals, delamanid and its metabolites appeared in breast milk. **Use in renal disease:** No dosage adjustment is required in patients with mild-to-moderate renal impairment, but delamanid is not recommended for patients with severe renal impairment. **Use in hepatic disease:** No dosage adjustment is required in patients with mild hepatic impairment, but delamanid is not recommended in patients with moderate-to-severe hepatic impairment. **Use in cardiac disease:** Patients with various cardiac risk factors, including QTc interval prolongation, should not receive delamanid unless the potential benefits of treatment are expected to outweigh the possible risks. For all patients, an ECG is recommended before starting treatment, and then monthly throughout treatment. Patients with serum albumin levels <3.4 g/mL (but at least 2.8 g/mL) or with cardiac risk factors should receive more frequent ECG monitoring. Serum electrolytes should be checked and corrected as needed. **Use beyond 6 months and in combination with bedaquiline is considered safe**.
Adverse reactions	**Overall tolerance**: Well tolerated, low toxicity profile. **Occasional:** QTc prolongation (5–15 msec average, peak at 8 week). Overall QTc prolongation in cohorts using delamanid, bedaquiline and other QTc-prolonging drugs was 2.7%, with median appearance at 2.5 months, with no cardiac deaths reported. Other effects are nausea, vomiting, dizziness, insomnia, anxiety, hallucinations, night terrors commonly in children and upper abdominal pain. Delamanid is reported to cause neuropsychiatric adverse effects, particularly in children *(5)*. The most frequent are sleep disturbance and vivid nightmares, but insomnia, hallucinations and others have been reported. Most of these events are mild and self-limited, resolving without any intervention or change to the delamanid. The evidence of hallucinations in children, although reported, is uncertain as the potential of misclassifying 'night terrors' and 'nightmares', which are common in child development, as 'hallucinations' *(6)*.

Delamanid (Dlm) Drug class: nitro-dihydro-imidazooxazole (nitroimidazole)	
Contraindications	Hypersensitivity to delamanid. Use with caution in patients sensitive to lactose. **Discontinue or do not use in the presence of:** • clinically significant ventricular arrhythmia; • QTcF interval of >500 msec (confirmed by repeat ECG); • severe liver disease; or • abnormal electrolytes. **Use with caution in situations that may increase QT interval:** In patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism and concomitant use of other QT-prolonging drugs. Any syncopal event (e.g. fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase is modest and no arrhythmias or related deaths were reported, even with bedaquiline and delamanid co-administration.
Drug interactions	Low potential for drug–drug interactions. Concomitant administration of strong CYP3A inducers (e.g. rifampicin and carbamazepine) should be avoided. Co-administration with strong CYP3A inhibitors (e.g. ritonavir and ketoconazole): frequent monitoring of ECG should be considered. No interactions have been found between delamanid, dolutegravir and the main antiretroviral drugs. Delamanid may attenuate vitamin K-dependent blood clotting,and increase prothrombin time and activated partial thromboplastin time. Use with other medicines that directly or indirectly prolong the QT interval may cause additive prolongation, which requires caution and monitoring: • anti-TB drugs: fluoroquinolones, clofazimine and bedaquiline; and • ancillary and common drugs: azoles, macrolides, metoclopramide, efavirenz, furosemide, hydrochlorothiazide, citalopram, escitalopram, methadone, antiarrhythmics and others. Co-administration with cycloserine may increase the risk of neuropsychiatric adverse events, especially in children.
Food interaction	Delamanid should be taken with food, and alcohol should be avoided.
Monitoring	ECG and baseline electrolytes should be obtained whenever possible before the initiation of treatment, and repeated if necessary (e.g. documented QTc prolongation or multiple QTc-prolonging risk factors). When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important.

Delamanid (Dlm) Drug class: nitro-dihydro-imidazooxazole (nitroimidazole)	
Patient instructions and alerting symptoms	**Patients should be instructed to inform their health care provider immediately if any of the following occur:** • history of heart problems, heart attack, congenital long QT syndrome or problems with heart rhythm; • liver or kidney disease; or • pregnancy or planning to get pregnant.

BMI: body mass index; CSF: cerebrospinal fluid; ECG: electrocardiography; HIV: human immunodeficiency virus; *M. tuberculosis*: *Mycobacterium tuberculosis*; PD: pharmacodynamic; PK: pharmacokinetic; TB: tuberculosis; TdP: torsades de pointes.

[a] See the handbook **Annex 4** for revised weight-based dosing.

[b] Tucker EW, Pieterse L, Zimmerman MD, Udwadia ZF, Peloquin CA, Gler MT et al. Delamanid central nervous system pharmacokinetics in tuberculous meningitis in rabbits and humans. Antimicrob Agents Chemoth. 2019;63:e00913–19. doi: https://doi.org/10.1128/AAC.00913-19.

Ethambutol (E)

Ethambutol (E) Drug class: unspecified	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall. It inhibits the synthesis of arabinogalactan and lipoarabinomannan (special cell wall layer typically from *Mycobacterium* species), preventing division. **Activity:** Low bactericidal activity (bacteriostatic; bactericidal only at the high end of the dosing range). At doses used over long periods of time, ethambutol protects against further development of resistance to other drugs. **Half-life and excretion:** has a half-life of 3.3 hours; mainly renal excretion (20–22% of a dose is eliminated unchanged in the faeces).
Cross-resistance	Not reported.
Dose[a]	• **Adults:** 15–25 mg/kg/day. • **Children:** See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** 15–25 mg/kg/dose, thrice weekly (not daily). See the handbook **Annex 4** for weight-based dosing in adults and children.
Administration	Oral.
Formulation and preparation	100 mg dispersible tablets. 400 mg film-coated tablets. Crushing and dissolving 400 mg tablets in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole, and avoids fractioning solid formulations, although the bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should be stored below 30 °C.
Oral absorption	Has 80% bioavailability, independent of food intake.
CSF penetration	Penetrates meninges poorly.
Special circumstances	**Use during pregnancy or breastfeeding:** Ethambutol is considered safe in pregnancy; it can be used while breastfeeding but may appear in breast milk. **Use in renal disease:** Should be used with caution; ethambutol is cleared by the kidneys. Dose adjustment is required (see under Dose section, above) because there is an increased risk of toxicity. **Use in obesity:** Risk of chronic overdose; dose adjustment is required (see under Dose section, above). **Use in hepatic disease:** Considered safe.

Ethambutol (E) Drug class: unspecified	
Adverse reactions	**Overall tolerance**: Well tolerated; side-effects are commonly related to chronic overdose (e.g. wrong prescription, renal failure or overdose in obesity). **Occasional**: Decrease in visual acuity and colour vision (retrobulbar neuritis). The effect may be related to dose and duration of treatment; ethambutol should be stopped in cases of optic neuritis because irreversible blindness has been reported. **Uncommon**: Liver toxicities.
Contraindications	Pre-existing optic neuritis or severe visual problems; visual changes after ethambutol use.
Drug interactions	Low potential for drug–drug interactions. No major interactions with CYP450. Concomitant use with aluminium hydroxide-containing antacid should be avoided for at least 4 hours after ethambutol administration.
Food interactions	No interaction; food may reduce gastrointestinal irritation.
Monitoring	Patients should be counselled to report any changes in vision. Baseline and monthly visual acuity and colour discrimination monitoring should be performed; particular attention should be given to individuals on higher doses or with renal impairment. Each eye must be tested separately and both eyes tested together.
Patient instructions and alerting symptoms	Can be taken with food or on an empty stomach. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** Any problems with vision changes, blurring, colour blindness, trouble seeing or eye pain.

CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Ethionamide (Eto) or prothionamide (Pto)

Ethionamide (Eto) or prothionamide (Pto) Drug class: carbothionamides group, derivatives of isonicotinic acid	
Activity against *M. tuberculosis*, mechanism of action and metabolism	Ethionamide and prothionamide (a propyl-analogue of ethionamide) are both thioamides; they have similar efficacy and are considered interchangeable; however, ethionamide is more widely available. As with pyrazinamide, they are nicotinic acid derivatives related to isoniazid. **Target:** *M. tuberculosis* cell wall. Ethionamide and prothionamide are pro-drugs. Following enzymatic activation by mycobacterial EthA, the active metabolite inhibits the inhA enzyme, which is responsible for mycolic acid synthesis (mycolic acid is an essential part of mycobacterium cell wall), with a similar mechanism to isoniazid. **Activity:** Weak bactericidal (depending on the concentration of the drug attained in tissues, mostly bacteriostatic). **Half-life and excretion:** Has a half-life of 2–3 hours. Excreted via hepatic metabolism.
Cross-resistance	There is complete cross-resistance between ethionamide and prothionamide. In the case of mutation in the *inhA* gene, there is cross-resistance with isoniazid (high-level ethionamide and prothionamide resistance, but low-level resistance to isoniazid).
Dose[a]	• **Adults:** 15–20 mg/kg/day; upper daily dose is 1 g. Once-daily dosing is advised but clinicians can use 2 divided doses if tolerance is a problem, or until tolerance improves. Many individuals require gradual ramping up of the dose and treatment due to gastrointestinal upset. • **Children:** See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** No change. • **Pyridoxine (vitamin B6):** There are insufficient data to support the systematic administration of vitamin B6 to adults or children receiving ethionamide and prothionamide. See the handbook **Annex 4** for weight-based dosing in adults and children.
Administration	Oral. Crushing and dissolving 250 mg tablets in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; this avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Formulation and preparation	125 mg dispersible tablet (only ethionamide). 250 mg film-coated tablets (ethionamide and prothionamide).
Storage	Should be stored below 30 °C in a dry place.
Oral absorption	Has almost full oral bioavailability but there is potential for erratic absorption, possibly owing to associated gastrointestinal disturbances.
CSF penetration	Concentrations approach those in the serum; one paediatric study evaluating drug concentrations in the CSF suggested that ethionamide should be dosed at the higher end of the dose range for patients with meningitis.

Ethionamide (Eto) or prothionamide (Pto) Drug class: carbothionamides group, derivatives of isonicotinic acid	
Special circumstances	**Use during in pregnancy or breastfeeding:** These drugs are generally avoided during pregnancy owing to increased nausea and vomiting, risk of decreased TSH (fundamental for pregnant woman and the fetus) and limited reports of teratogenicity. TSH levels should be monitored and supplemented if necessary to prevent congenital hypothyroidism. There are few data about the use of these drugs during breastfeeding: it is estimated that 20% of the infant therapeutic dose will be passed on to the baby in breast milk (the infant should be supplemented with vitamin B6 if breastfed). **Children:** TSH levels should be monitored, and supplemented if necessary to avoid growth failure and permanent intellectual disability. **Use in renal disease:** No precautions are required for renal impairment. **Use in hepatic disease:** These drugs can cause hepatotoxicity similar to that seen with isoniazid; they should be used with caution in liver disease.
Adverse reactions	**Overall tolerance:** Poorly tolerated. **Common**: Most patients (adults and children) will experience dose-related gastrointestinal intolerance with ethionamide and prothionamide, resulting in nausea, vomiting, metallic taste, anorexia, abdominal discomfort, diarrhoea and weight loss. Symptoms are moderated by food or by taking the drugs at bedtime. Many individuals require gradual ramping up of the dose and treatment due to gastrointestinal upset. Premedication with an antiemetic is often helpful. Gastrointestinal upset may increase with concomitant use of para-aminosalicylic acid. **Occasional:** Hypothyroidism in adults is usually subclinical and reversible but has potential important consequences in pregnant woman and children, requiring monitoring of TSH and supplementation with levothyroxine. The risk of hypothyroidism increases when the drugs are used with para-aminosalicylic acid. Hepatotoxicity may occur, and the risk is increased by the concomitant use of rifampicin. Neurological side-effects (e.g. convulsions) may be exaggerated in patients also taking cycloserine. **Uncommon**: Gynaecomastia, hair loss, acne, impotence and menstrual irregularity.
Contraindications	Resistance to ethionamide and prothionamide or isoniazid.
Drug interactions	Temporarily raises serum concentrations of isoniazid. No major drug–drug interactions have been found but there is the potential for increased side-effects in the presence of other anti-TB medication (para-aminosalicylic acid, cycloserine, isoniazid and rifampicin).
Food interactions	Can be taken with or without food. Taking ethionamide and prothionamide with food may reduce gastrointestinal upset. Alcohol ingestion should be avoided because it may increase the risk of psychotic reactions.
Monitoring	TSH should be monitored for evidence of hypothyroidism requiring replacement therapy; therapeutic drug monitoring is required if malabsorption is suspected. Liver function tests should be monitored.

Ethionamide (Eto) or prothionamide (Pto) Drug class: carbothionamides group, derivatives of isonicotinic acid	
Patient instructions and alerting symptoms	Should be taken with food. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • convulsions, personality changes such as depression, confusion or aggression; • severe nausea and vomiting or dehydration; • yellowing of skin or eyes or dark-coloured urine; or • swollen breasts.

CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; TSH: thyroid-stimulating hormone.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Imipenem–cilastatin (Imp–Cln)

Imipenem–cilastatin (Imp–Cln) Drug class: beta-lactam – carbapenem	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall. Imipenem is a beta-lactam antibiotic belonging to the subgroup of carbapenems. It needs to be used in combination with clavulanic acid to block the β-lactamase secretion present in bacteria such as *M. tuberculosis*, which otherwise inactivates most penicillins. Carbapenems have several mechanisms of action, including inactivating the penicillin-binding proteins and transpeptidases, inhibiting the biosynthesis of the peptidoglycan layer of the bacterial cell wall (creating lysis) or interfering with cell wall formation. **Activity:** Bactericidal and probably sterilizing activity. **Half-life and excretion:** Imipenem is rapidly degraded by renal proximal tubule dipeptidases; therefore, it is used in combination with the dipeptidase inhibitor cilastatin. Following IV injection, imipenem has a half-life of 1 hour; following IM injection, it has a half-life of 1.3–5.1 hours. Cilastatin is partially metabolized renally. Imipenem is mainly excreted in the urine (70%).
Cross-resistance	Imipenem and meropenem may have cross-resistance, but evidence about *M. tuberculosis* is limited.
Dose[a]	These drugs should not be used in children aged <15 years. **Adults: 1000 mg twice daily**. Upper daily dose 2000 mg. **Renal failure or dialysis:** Adjustment in dose based on severity of renal failure; for example, 750 mg every 12 hours for creatinine clearance of 20–40 mL/min or 500 mg every 12 hours for creatinine clearance <20 mL/min. See the handbook **Annex 4** for weight-based dosing in adults.
Administration	No oral absorption. It can be administered IV or IM. Every dose is to be preceded by 30–60 minutes of administration of clavulanate (see amoxicillin–clavulanic acid medicine information sheet for dosing). **IV:** The infusion must be given slowly and can take 20–60 minutes to complete (or even longer in case of nausea). For long-term use as part of TB treatment, consider insertion of a peripherally inserted central catheter line.
Formulation and preparation	Powder for injection, 500 mg/500 mg in 10 mL vial.
Storage	The powder should be kept at room temperature (15–25 °C); the reconstituted product should be used within 2 hours and not frozen. Any unused product or waste material should be disposed of in accordance with local requirements.
Oral absorption	–
CSF penetration	Good CSF penetration. Meropenem is usually preferred for TB meningitis and for children because of the increased risk of seizures associated with use of imipenem.

Imipenem–cilastatin (Imp–Cln) Drug class: beta-lactam – carbapenem	
Special circumstances	**Use during pregnancy or breastfeeding:** There is limited information regarding the use of this medicine in pregnancy; safety during breastfeeding is unknown. **Use in renal disease:** Dose adjustment is required (see under Dose section above); dose after dialysis. **Use in hepatic disease:** Elevated liver function test levels have been noted in up to 6% of patients, but no definite liver damage has been documented.
Adverse reactions	**Overall tolerance**: Poorly tolerated, owing to the disruption of daily life from lengthy infusions and the care of a peripherally inserted central catheter line, which may be needed for many months. **Frequently**: Diarrhoea, nausea or vomiting; yeast infection (thrush). **Occasional**: Pseudomembranous colitis (overgrowth of *Clostridioides difficile*). **Uncommon**: Seizures (noted with CNS infection), palpitations.
Contraindications	Carbapenem intolerance. **Meningitis** (use meropenem rather than imipenem–cilastatin).
Drug interactions	Low potential for drug–drug interactions. Ganciclovir: Increased risk of convulsions. Valproate: Imipenem reduces serum concentrations of valproate. Avoid concomitant use.
Food interactions	None.
Monitoring	Monitor clinical signs and symptoms.
Patient instructions and alerting symptoms	Ask patient about concomitant medication with ganciclovir or history of allergy to penicillins or cephalosporins. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • severe diarrhoea (watery or bloody); • seizures or epilepsy; or • fast or irregular heartbeat.

CNS: central nervous system; CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Isoniazid high dose (Hh)

Isoniazid high dose (Hh) Drug class: isonicotinic acid hydrazide	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** The *M. tuberculosis* cell wall. Isoniazid is a prodrug that after activation by the enzyme katG (bacterial catalase), blocks the action of the inhA enzyme that is responsible for the biosynthesis of mycolic acids, a major component of mycobacterial cell walls. Isoniazid is a first-line TB medicine that may be an effective as a second-line agent if used at high doses in the absence of high-level resistance. **Activity:** Strongly bactericidal against actively growing intracellular and extracellular *M. tuberculosis*. To date, isoniazid is considered the most bactericidal of the first-line and second-line drugs. **Half-life and excretion**: Primarily hepatic metabolism (*N*-acetyl transferase). The half-life is 0.5–1.6 hours in fast acetylators and 2–5 hours in slow acetylators (the acetylation rate in humans is genetically determined). Isoniazid is 50–70% excreted in the urine.
Cross-resistance	Mutations in the *inhA* promoter region may cause low-level resistance to isoniazid and resistance to thionamides.
Dose[a]	In DR-TB, a higher dose of isoniazid may be used as part of a shorter 9-month regimen. • **Adults**: 10–15 mg/kg/day. Standard daily dose is 300 mg/kg; high dose is 600 mg. • **Children:** See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** 300 mg once daily. • **Pyridoxine (vitamin B6):** Should be used when high-dose isoniazid is administered. Pregnant and postpartum women and exclusively breastfed infants should always receive vitamin B6 while taking isoniazid. See the handbook **Annex 4** for weight-based dosing in children.
Administration	Oral.
Formulation and preparation	50 mg/5 mL oral solution. 100 mg dispersible tablets. 100 mg scored and unscored tablets. 300 mg scored and unscored tablets. Crushing and dissolving uncoated tablets (100 mg and 300 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; it also avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	The oral solution should be stored below 25–30 °C. Tablets should be stored below 30 °C and protected from light. The dispersible tablets should be protected from moisture.
Oral absorption	Well absorbed orally or intramuscularly. Best absorbed on an empty stomach (there is a >50% reduction in peak concentration if taken with a high-fat meal).

Isoniazid high dose (Hh) Drug class: isonicotinic acid hydrazide	
CSF penetration	Being a moderately lipophilic small molecule, the concentration in CSF is equivalent to that in plasma in inflamed meninges, but to only 20% of plasma concentrations in noninflamed meninges.
Special circumstances	**Use during pregnancy or breastfeeding:** Such use is not contraindicated. When breastfeeding, both infant and mother should receive pyridoxine supplementation. **Use in renal disease:** No dose adjustment is necessary in cases of renal failure, but pyridoxine supplementation should be used. **Use in hepatic disease:** It may exacerbate liver failure and should be used with caution.
Adverse reactions	**Overall tolerance:** Well tolerated. **Frequently:** Peripheral neuropathy: numbness, weakness, tingling, or burning pain in the hands or feet; nausea, vomiting and upset stomach; and abnormal liver function test results (transaminitis). **Occasional:** Hepatitis (higher risk in older age, alcohol misuse, pregnancy, viral hepatitis, fatty liver disease or nonalcoholic steatohepatitis and liver TB); and fever, chills, joint pain (arthralgia) and mild CNS effects (enhanced by concomitant use of cycloserine). **Uncommon:** Severe hypersensitivity (allergic) reaction; serious and sometimes fatal liver problems (more frequent in isoniazid monotherapy, less in rifampicin–isoniazid concomitant use); and drug-induced lupus.
Contraindications	Patients with high-level isoniazid resistance for whom an isoniazid-containing regimen has failed. History of allergic reaction to isoniazid or ethionamide or prothionamide.
Food interactions	Should be taken on an empty stomach (1 hour before or 2 hours after meals); absorption and bioavailability are reduced when administered with food. In case of stomach upset, isoniazid can be taken with a snack. Should be taken separately from antacids (which reduce absorption). Alcohol should be avoided because it may increase the risk of induced hepatitis and neuropathy. Caffeine and chocolate intake should be avoided, as should foods and supplements containing histamine and tyramine.
Drug interactions	Low potential for drug–drug interactions. Isoniazid is a weak CYP3A4 inhibitor and may increase the concentration of certain cytochrome P450 enzyme substrates such as phenytoin (increase concentration) and carbamazepine (risk of hepatotoxicity). Alcohol can lead to an increased risk of convulsions. There is an increased risk of CNS toxicity when isoniazid is given concomitantly with cycloserine.
Monitoring	Clinical monitoring and liver function testing should be undertaken, ideally monthly. For patients receiving multiple TB drugs or other hepatotoxic drugs, or with underlying liver disease (including viral hepatitis), baseline liver function testing is recommended. Follow-up liver function testing is determined by baseline concerns and symptoms of hepatotoxicity.

Isoniazid high dose (Hh) Drug class: isonicotinic acid hydrazide	
Patient instructions and alerting symptoms	The medication should be taken on an empty stomach for better absorption. It should not be taken with a large fatty meal. In the case of stomach upset, isoniazid can be taken with a snack. The liquid suspension should not be refrigerated. Patients should avoid alcohol, antacids, chocolate, caffeine, and foods and supplements containing histamine and tyramine while taking this medicine. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • convulsions (seizures) or behavioural change; • flushing, sweating or headaches; • numbness, pain or tingling or burning of fingers or toes; • blurred vision or eye pain; • loss of appetite, tiredness, weakness, yellow skin or eyes or dark-coloured urine; or • fever and skin rash that spreads and causes blistering and peeling.

CNS: central nervous system; CSF: cerebrospinal fluid; DR-TB: drug-resistant tuberculosis; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Levofloxacin (Lfx)

Levofloxacin (Lfx) Drug class: fluoroquinolone	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** Inner *M. tuberculosis* cell metabolism. A third-generation fluoroquinolone (along with moxifloxacin), it inhibits enzymes that are crucial for bacterial DNA replication. In *M. tuberculosis* it appears that DNA gyrase is the sole topoisomerase targeted. DNA gyrase is a tetrameric A_2B_2 protein (two A subunits and two B subunits). Inhibiting DNA gyrase (in any subunit) results in a blockade of DNA replication, inhibiting cell division and resulting in cell death of replicative and nonreplicative *M. tuberculosis*. The antimycobacterial activity of this fluoroquinolone depends on the molecule's affinity to target enzyme and efflux pumps, and the naturally low permeability of the *M. tuberculosis* cell wall. **Activity:** Levofloxacin is considered both highly bactericidal (excellent early bactericidal activity) and highly sterilizing. **Half-life and excretion:** The half-life of levofloxacin is 6–8 hours. It is mainly excreted unchanged in the urine.
Cross-resistance	In general, there is a class effect of cross-resistance among fluoroquinolones in vitro. Data suggest that levofloxacin and moxifloxacin may continue to demonstrate some activity, even against strains that have in vitro resistance to second-generation fluoroquinolones. The pattern of resistance or susceptibility to the different fluoroquinolones depends on specific point mutation and is the subject of ongoing research.
Dose[a]	• **Adults:** 750–1125 mg/day (oral or IV); usually at least 750 mg/day, and the standard upper daily dose is 1.5 g. • **Children**: See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** 750–1000 mg/dose, thrice weekly for creatinine clearance <30 mL/min. See the handbook **Annex 4** for weight-based dosing in adults and children.
Administration	Oral.
Formulation and preparation	100 mg dispersible tablet. 250 mg, 500 mg, 750 mg tablets film coated (may be scored in some markets). Crushing and dissolving film-coated tablets (100 mg and 300 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; it also avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should be stored below 30 °C, in a dry place, protected from light.
Oral absorption	Excellent oral absorption. Absorption can be reduced by ingestion of aluminium or magnesium antacids, sucralfate, metal cations (e.g. iron and multivitamin preparations with zinc). When use of these products is necessary, they should be administered at least 2 hours before or 2 hours after the fluoroquinolone.

Levofloxacin (Lfx) Drug class: fluoroquinolone	
CSF penetration	In general, fluoroquinolones achieve an effective concentration in the brain and meninges. Levofloxacin concentrations are at least 65% of the concentration in serum. Levofloxacin is also widely bioavailable in other organs and body fluids. It has been successfully used in the treatment of TB meningitis.
Special circumstances	**Use during pregnancy or breastfeeding:** It has been associated with arthropathy in canine models. There have been multiple case reports of fluoroquinolones being used safely in humans during pregnancy and breastfeeding. **Use in renal disease:** Dosage adjustment is recommended if creatinine clearance is <50 mL/min. The drug is not cleared by haemodialysis; supplemental doses after dialysis are not necessary. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease. It is presumed to be safe in severe liver disease. **Marfan syndrome, Ehlers–Danlos syndrome or steroid use:** Increased risk of tendon or aorta lesions **Diabetes:** Increased risk of hypoglycaemia. **Long QT syndrome (patient or family member), hypokalaemia, malnutrition, hypothyroidism in those aged >60 years, multiple QT-prolonging drugs:** Increased risk of QTc prolongation.
Adverse reactions	**Overall tolerance**: Generally well tolerated, with low potential for acute toxicity. **Common**: Diarrhoea, nausea and bloating, and arthralgia. **Occasional:** QTc interval prolongation (levofloxacin is considered safer than moxifloxacin); may decrease or alter glycaemia (this is true of all third-generation fluoroquinolones); and tendon rupture, especially Achilles tendon. **Uncommon**: Peripheral neuropathy, mood or behaviour changes, insomnia, and aortic dissection patients with in Marfans.
Contraindications	Fluoroquinolone intolerance. It should be used with caution in situations that may increase the QT interval: patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection and concomitant use of other QT-prolonging drugs. Any syncopal event (e.g. fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase was modest, and no arrhythmias or related deaths were reported even with co-administration of bedaquiline and delamanid. **Discontinue or do not use in the presence of:** • clinically significant ventricular arrhythmia; • a QTcF interval of >500 msec (confirmed by repeat ECG); or • abnormal electrolyte levels.

Levofloxacin (Lfx) Drug class: fluoroquinolone	
Drug interactions	Low potential for drug–drug interactions. Concomitant steroid use may increase risk of tendon rupture. Multivalent cation-containing products including antacids and metal cations may decrease absorption. The intravenous formulation should not be co-administered through the same IV line as a multivalent cation, such as magnesium. Warfarin: The effect of this drug may be enhanced. Prothrombin time and INR should be monitored, and the patient should be monitored for bleeding. Antidiabetic agents: Carefully monitor blood glucose.
Food interactions	Can be taken with or without food, without a clinically significant impact on absorption or bioavailability. There are no major interactions between milk or dairy products and third-generation fluoroquinolones. Antacids (especially those containing aluminium), mineral supplements (e.g. iron or magnesium) or multivitamins should be taken more than 2 hours before or after this medication.
Monitoring	No specific laboratory monitoring is required. Ideally, an ECG should be obtained before initiation of treatment, and at least 2, 12 and 24 weeks after starting treatment. Levofloxacin should be stopped if the QTc >500 msec, and ECGs and potassium should be monitored frequently until the QTc returns to normal. More frequent monitoring is recommended if cardiac conditions, hypothyroidism or electrolyte disturbances are present.
Patient instructions and alerting symptoms	This medication should be taken with or without food. Antacids (especially aluminium-containing ones), mineral supplements (e.g. iron or magnesium), or multivitamins should be taken more than 2 hours before or after of this medication. This medicine may cause sun sensitivity; sunscreens should be used. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • pain, swelling or tearing of a tendon (such as the back of the ankle, elbow), or muscle or joint pain; • severe diarrhoea (watery or bloody); • seizures, epilepsy, change in mood or behaviour; or • low blood sugar symptom (i.e. headache, hunger, sweating, irritability, dizziness, nausea, fast heart rate, or feeling anxious or shaky).

BMI: body mass index; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; ECG: electrocardiography; HIV: human immunodeficiency virus; INR: international normalized ratio; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; TdP: *torsade de pointes*.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Linezolid (L or Lzd)

Linezolid (L or Lzd) Drug class: oxazolidinones	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** Bacterial ribosome. Linezolid blocks protein synthesis at the bacterial ribosome. It interferes with translation of the bacterial mRNA into proteins by binding to the 23S ribosomal RNA component (part of the large ribosome subunit). Without the capacity to synthesize proteins, bacterial reproduction and subsistence is not possible. **Activity:** Has modest early bactericidal activity in vitro, and probable sterilizing and excellent bioavailability in tissues. **Half-life and excretion**: Maximum plasma concentrations are reached in about 1–2 hours after dosing. The half-life is estimated as 5–7 hours. About 31% binds to plasma proteins (mainly albumin). It is primarily metabolized by the liver (biotransformation routes are unclear) and subsequently eliminated by the kidneys, with minor faecal elimination.
Cross-resistance	Cross-resistance between linezolid and other oxazolidinones in *M. tuberculosis* is not fully documented.
Dose[a]	• **Adults:** 600 mg, once daily, upper daily dose is 1.2 g. • **Children:** See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** No dose adjustment is required. However, accumulation of the two primary metabolites may occur; hence, it should be used with caution. See the handbook **Annex 4** for weight-based dosing in adults and children
Administration	Oral.
Formulation and preparation	100 mg/5 mL powder for oral liquid. Following reconstitution, the solution should be mixed gently before administration; it should not be shaken. 150 mg dispersible tablet. 600 mg coated tablet. Crushing and dissolving film-coated tablets (600 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; also, it avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	The powder for the oral liquid should be stored below 25 °C, protected from light and moisture. The reconstituted suspension may be stored at room temperature for 21 days. Tablets should be stored below 25 °C, protected from light and moisture.
Oral absorption	It is extensively absorbed following oral administration and has an absolute bioavailability of about 100%.
CSF penetration	It has excellent CSF and brain penetration.

Linezolid (L or Lzd) Drug class: oxazolidinones	
Special circumstances	In patients with pre-existing haematological conditions, it should be used with extreme caution. **Use during pregnancy or breastfeeding:** Studies in animals have shown evidence of an increased occurrence of fetal damage. There are limited data in humans but no reports of increased malformation or other direct or indirect harmful effects on the human fetus. Drug levels appear in breast milk at lower than the usual infant dose. **Use in renal disease:** No dose adjustment is recommended, but metabolites may accumulate. **Use in hepatic disease:** Despite hepatic metabolism, it is rarely associated with increased transaminases. **Use in diabetes mellitus:** There is increased risk of lactic acidosis in patients being treated with metformin. Hypoglycaemia has been reported in patients receiving insulin or oral hypoglycaemic agents and linezolid. **Use in patients with cerebrovascular or cardiovascular disease, pheochromocytoma, carcinoid syndrome or untreated hyperthyroidism:** Linezolid may exacerbate symptoms of those conditions. **Use in patient with depression:** Administration of linezolid concurrently with even common SSRIs can lead to serious reactions such as serotonin syndrome or neuroleptic malignant syndrome-like reactions. See the sections on Adverse reactions and Drug interactions.
Adverse reactions	**Overall tolerance:** Poorly tolerated. **Frequently/common:** – Nausea, vomiting and diarrhoea. – **Myelosuppression**, which may manifest within the first 2 months of treatment with decreased platelet or white blood cell counts and anaemia. – **Optic nerve toxicity and peripheral neuropathy** tend to develop after several weeks of treatment and may lead to irreversible blindness or disabling permanent neuropathy. Nerve toxicity is usually a reason to stop linezolid. **Occasional:** Pseudomembranous colitis, vaginal candidiasis, hypoglycaemia, serotonin syndrome and lactic acidosis; and arrhythmia (tachycardia), transient ischaemic attacks, pancreatitis, seizures. **Uncommon:** Stevens–Johnson syndrome, angioedema and alopecia.

Linezolid (L or Lzd) Drug class: oxazolidinones	
Contraindications	• Hypersensitivity to oxazolidinones. • If patient is taking another MAO inhibitor medication or has used one in the past 14 days, linezolid should not be taken. • Should be used with extreme caution with antidepressants, antimigraine and other medications (see section on Drug interactions, and balance risk of serotonin syndrome versus benefit). • Should not be used concomitantly with stavudine or didanosine. • Should be used with extreme caution with zidovudine. • Should be used with extreme caution if metformin is used at a high dose; in such cases, it is best to consider a change to other oral antidiabetic medication or insulin to limit the risk of lactic acidosis. • Should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis or carcinoid syndrome.
Drug interactions	There is a high potential for drug–drug interactions. There are no CYP450 enzyme system interactions but linezolid is an MAO inhibitor, and combination with other drugs may increase the risk of severe clinical conditions and linezolid-induced toxicities. **Increased risk of pancytopenia:** Zidovudine and co-trimoxazole. **Increased risk of lactic acidosis:** Metformin, lamivudine, zidovudine and abacavir. **Increased risk of serotonin syndrome:** Because linezolid is an MAO inhibitor, there is increased risk with SSRIs, SNRIs, TCAs, serotonin 5-HT1 receptor agonists, bupropion, anti-seizure medication, opioid analgesics, buspirone, antiemetics, anti-Parkinson's medication, sympathomimetic agents, vasopressive agents, dopaminergic agents and common medications used for influenza or congestion and bought over the counter such as dextromethorphan, pseudoephedrine, diphenhydramine or guaifenesin.
Food interactions	Oral absorption is not significantly affected by co-administration with food; thus, it may be taken with or without food, but taking with food may alleviate stomach irritation. **Increased risk of tyramine toxicity:** Patients should avoid tyramine-containing foods and supplements such as aged cheese, fava beans, cured foods, dried meats, pickled foods, sauerkraut, kimchi, soy sauce, teriyaki sauce, fish sauce and red wine, tap beers and liquors.
Monitoring	Patients should be monitored for: • peripheral neuropathy and optic neuritis, through visual eye acuity (both eyes) and Ishihara tests on every schedule visit or, if symptoms develop, clinical examination for peripheral neuropathy monthly; • complete blood count weekly during the initial period, then monthly, and thereafter as needed based on symptoms; and • pH, anion gap and lactate levels in case of suspected lactic acidosis (hyperlactatemia, if lactate >2.0 mmol/L and confirmed lactic acidosis at >4.0 mmol/L), hypotension, lethargy or clinical worsening without a clear explanation.

Linezolid (L or Lzd) Drug class: oxazolidinones	
Patient instructions and alerting symptoms	The medication can be taken with or without food but patients should avoid tyramine-containing foods (see list in Food interactions section, above). Patients should be asked about any medicines or supplements taken, especially metformin, antidepressants and common cold medications (see Drug interactions section above). **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • pain, numbness, tingling or weakness in the extremities; • unusual tiredness, weakness, hypotension; • black, tarry stools or severe diarrhoea; • unusual bleeding or bruising; • changes in vision; or • headache, nausea or vomiting, sweating, rigidity, tremor, or change in mood, behaviour or consciousness.

CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*; MAO: monoamine oxidase; mRNA: messenger ribonucleic acid; RNA: ribonucleic acid; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Meropenem (Mpm)

Meropenem (Mpm) Drug class: beta-lactam – carbapenem	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall. Meropenem is a beta-lactam antibiotic belonging to the subgroup of carbapenems. It must be used in combination with clavulanic acid to block the β-lactamase secretion present in bacteria such as *M. tuberculosis*, which otherwise inactivates most penicillins. Carbapenems, through several mechanisms (e.g. inactivation of the penicillin-binding proteins and transpeptidases), inhibit the biosynthesis of the peptidoglycan layer of the bacterial cell wall, causing lysis or interfering with cell wall formation. **Activity:** Has bactericidal and probably sterilizing capacity. One study found a better efficacy profile with meropenem than with imipenem. **Half-life and excretion:** Meropenem is stable to renal dipeptidases and does not require cilastatin. It is mainly excreted in the urine (70%) and has a half-life of about 1–1.5 hours in adults and children.
Cross-resistance	Imipenem and Meropenem may have cross-resistance, but evidence with *M. tuberculosis* is very limited.
Dose[a]	• **Adults:** 1 g (20 mL) IV thrice daily or 2 g twice daily. Each dose is preceded by 125 mg clavulanate (administer clavulanic acid 60 minutes before each dose of meropenem). Upper daily dose is 6000 mg. • **Children:** See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** The adjustment to the dose is based on the severity of renal failure; for example, 750 mg every 12 hours for creatinine clearance of 20–40 mL/min or 500 mg every 12 hours for creatinine clearance <20 mL/min. See the handbook **Annex 4** for weight-based dosing in adults and children.
Administration	IV only (no IM recommended); there is no oral absorption. Clavulanate should be given orally 30–60 minutes before an IV dose of meropenem (every 8 hours) For long-term use in TB, insertion of a peripherally inserted central catheter line should be considered.
Formulation and preparation	Powder for injection or infusion (1 g) is to be reconstituted (1 g in 20 mL) with water for injection or 0.9% sodium chloride or 5% glucose solution for infusion before administration.
Storage	Powder should be stored below 25–30 °C. Reconstituted solution storage conditions vary; hence, the specific product label should be checked.
Oral absorption	Not applicable
CSF penetration	Has adequate CSF penetration and is recommended in case of TB meningitis (where meropenem is preferred over imipenem).

Meropenem (Mpm) Drug class: beta-lactam – carbapenem	
Special circumstances	**Use during pregnancy or breastfeeding:** It is considered safe but there is little information regarding lengthy use in TB use during pregnancy. Meropenem is excreted into human milk, and its safety during breastfeeding is unknown. **Use in renal disease:** Dose adjustment is required in renal disease (see under Dose section, above); dose after dialysis. **Use in hepatic disease:** Liver disease does not alter the pharmacodynamics of meropenem.
Adverse reactions	**Overall tolerance:** It is poorly tolerated because of important disruption to daily life owing to IV administration and the need to care for a peripherally inserted central catheter line, sometimes for many months. **Frequently:** Headache, diarrhoea, nausea or vomiting, and yeast infection (thrush). **Occasional:** Anaemia and pseudomembranous colitis (overgrowth of *Clostridioides difficile*). **Uncommon:** Seizures (noted with CNS infection), but rare compared with imipenem; and elevated liver enzymes, haematologic toxicity and hypersensitivity.
Contraindications	Carbapenem intolerance.
Drug interactions	Low potential for drug–drug interactions. Co-administration of probenecid inhibits renal excretion of meropenem. Co-administration of valproic acid or divalproex sodium reduces the serum concentration of valproic acid, potentially increasing the risk of seizures.
Food interactions	None.
Monitoring	Monitoring of clinical signs and symptoms.
Patient instructions and alerting symptoms	The patient should be asked about concomitant medication with valproic acid and whether they are allergic to penicillins or cephalosporins. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • severe diarrhoea (watery or bloody); • skin rash, hives or itching; • pale skin, unusual tiredness; or • swelling in the face, throat or lips, wheezing or trouble breathing.

CNS: central nervous system; CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Moxifloxacin (M or Mfx)

Moxifloxacin (M or Mfx) Drug class: fluoroquinolone	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** Inner *M. tuberculosis* metabolism. A third-generation fluoroquinolone (the other is levofloxacin), which inhibits enzymes that are crucial for bacterial DNA replication. In *M. tuberculosis* it appears that DNA gyrase is the sole topoisomerase targeted. DNA gyrase is a tetrameric A_2B_2 protein (two A subunits and two B subunits). Inhibiting DNA gyrase (in any subunit) results in blockade of DNA replication, inhibiting cell division and resulting in cell death of replicative and nonreplicative *M. tuberculosis*. The particular antimycobacterial activity of the third-generation fluoroquinolones depends on their molecule affinity to target enzymes and efflux pumps, and the naturally low permeability of the *M. tuberculosis* cell wall. **Activity:** Moxifloxacin is considered both highly bactericidal (it has excellent early bactericidal activity) and highly sterilizing. Based on in vitro data, moxifloxacin anti-TB activity is higher than the other current fluoroquinolones. **Half-life and excretion:** The half-life of moxifloxacin is 11.5–15.3 hours. It is mainly metabolized via glucuronide and sulfate conjugation, and 45% is excreted as the unchanged drug in urine and faeces.
Cross-resistance	In general, there is a class effect of cross-resistance among fluoroquinolones in vitro. Data suggest that levofloxacin and moxifloxacin may continue to demonstrate some activity, even against strains that have in vitro resistance to second-generation fluoroquinolones. The pattern of resistance or susceptibility to particular fluoroquinolones depends on specific point mutations, which is the subject of ongoing research.
Dose[a]	• **Adults:** 400 mg daily (oral or IV). High dose is 600–800 mg daily, depending on weight band. • **Children:** See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** No dose adjustment is required. See the handbook **Annex 4** for weight-based dosing in children and adults.
Administration	Oral.
Formulation and preparation	100 mg dispersible tablet (poor palatability; taste-masking studies are ongoing). 400 mg film-coated tablet. Crushing and dissolving film-coated tablets (400 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; also, it avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should be stored below 30 °C, protected from light. Dispersible tablets should be stored in a dry place.

Moxifloxacin (M or Mfx) Drug class: fluoroquinolone	
Oral absorption	Has good oral absorption (90% bioavailable). It should be administered at least 4 hours before or 8 hours after antacids or other medications (e.g. iron, magnesium, calcium, zinc, vitamins and sucralfate), because they may interfere with absorption.
CSF penetration	In general, fluoroquinolones achieve an effective concentration in the brain and meninges. Moxifloxacin has good penetration in animal model studies and humans with TB meningitis, reaching high concentrations in the CSF in the presence and absence of meningeal inflammation. It has been used successfully in TB meningitis.
Special circumstances	**Use during pregnancy or breastfeeding:** Associated with arthropathy in canine models. there are multiple case reports of fluoroquinolones being used in humans safely during pregnancy and breastfeeding. **Use in renal disease:** Excretion is unchanged during renal failure; there are no data on the effect of dialysis. **Use in hepatic disease:** Moxifloxacin is rarely associated with hepatotoxicity, but should be used with caution. No dose adjustment is required for mild-to-moderate liver disease. **Marfan syndrome, Ehlers–Danlos syndrome or steroids use:** In these situations, there is increased risk of tendon or aorta lesions. **Diabetes:** Increased risk of hypoglycaemia. **Long QT syndrome (in the patient or a family member), hypokalaemia, malnutrition, hypothyroidism in patients aged >60 years or taking multiple QT prolonging drugs:** Increased risk of QTc prolongation.
Adverse reactions	**Overall tolerance**: Generally well tolerated, with a low potential for acute toxicity **Common**: Diarrhoea, nausea and bloating, and arthralgia. **Occasional:** QTc interval prolongation (it is considered the most QTc-prolonging of the fluoroquinolones, causing an estimated QTc increase of 10–20 msec). Headache and dizziness. All third-generation fluoroquinolones may cause dysglycaemia. Tendon rupture, especially Achilles tendon. **Uncommon**: Peripheral neuropathy; mood or behaviour changes; insomnia; disturbances in mental abilities; aortic aneurysm rupture, and aortic dissection in patients with Marfans.

Moxifloxacin (M or Mfx) Drug class: fluoroquinolone	
Contraindications	Fluoroquinolone intolerance. **Use with caution in situations that may increase QT interval:** Patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection, concomitant use of other QT prolonging drugs. Any syncopal event (e.g. fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase was modest and no arrhythmias or related deaths were reported, even with co-administration of bedaquiline and delamanid. **Discontinue or do not use in the presence of:** • clinically significant ventricular arrhythmia; • a QTcF interval of >500 msec (confirmed by repeat ECG); or • abnormal electrolyte levels.
Drug interactions	Low potential for drug–drug interactions (the cytochrome P450 system is not involved in metabolism). Concomitant steroid use may increase the risk of tendon rupture. Multivalent cation-containing products (including antacids and metal cations) may decrease absorption. Warfarin: The effect of moxifloxacin may be enhanced. Prothrombin time and INR should be monitored, as should bleeding. Antidiabetic agents: Blood glucose should be carefully monitored. Concomitant use with antiarrhythmics Class IA (e.g. quinidine, ajmaline and disopyramide) and Class III (e.g. amiodarone, dronedarone and sotalol) should be avoided because the proarrhythmic effect may be enhanced.
Food interactions	Can be taken with or without food; food has little effect on absorption. There are no major interactions with milk or dairy products in third-generation fluoroquinolones. Antacids (especially those containing aluminium), mineral supplements (e.g. iron or magnesium) or multivitamins should be taken more than 2 hours before or after of this medication.
Monitoring	Symptomatic monitoring. Ideally, an ECG should be obtained before initiation of treatment, and at least 2, 12 and 24 weeks after starting treatment. Moxifloxacin should be stopped if QTc >500 msec, and ECGs and potassium should be monitored frequently until the QTc returns to normal. More frequent monitoring is recommended if cardiac conditions, hypothyroidism or electrolyte disturbances are present.

Moxifloxacin (M or Mfx) Drug class: fluoroquinolone	
Patient instructions and alerting symptoms	Can be taken with or without food. Antacids (especially those containing aluminium), mineral supplements (e.g. iron or magnesium) or multivitamins should be taken within 2 hours of this medication. **Patients should be instructed to inform their health care provider Immediately if any of the following occur:** • pain, swelling or tearing of a tendon (such as the back of the ankle, elbow), or muscle or joint pain; • severe diarrhoea (watery or bloody); • seizures, epilepsy, change in mood or behaviour; or • low blood sugar symptom (e.g. headache, hunger, sweating, irritability, dizziness, nausea, fast heart rate, or feeling anxious or shaky).

BMI: body mass index; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; ECG: electrocardiography; HIV: human immunodeficiency virus; INR: international normalized ratio; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; TdP: torsade de pointes.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Para-aminosalicylic acid (PAS)

Para-aminosalicylic acid (PAS) Drug class: salicylic acid – anti-folate	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall and inner metabolism. Probably inhibits folic acid synthesis and thus slows cell growth and multiplication. Para-aminosalicylic acid may inhibit the synthesis of mycobactin (a cell wall component) leading to a reduction of iron uptake by *M. tuberculosis* and inhibiting cell wall synthesis. **Activity:** Very low bactericidal (bacteriostatic) activity. It is used as a companion drug to prevent resistance to other medicines. **Half-life and excretion**: the half-life of PAS is 1.5 to 2 hours, within 24 hours, more than 80% is excreted in the urine. More than 50% of the excreted PAS is acetylated.
Cross-resistance	No data available.
Dose[a]	• **Adults:** 8–12 g/day in 2–3 divided doses; upper daily dose is 12 g. Doses are given twice daily; however, if tolerated, the same dose can also be administered at one time. • **Children:** See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** No dose modifications. See the handbook **Annex 4** for weight-based dosing in children and adults.
Administration	Oral. The powder should be reconstituted in water (100 mL) before administration. It should be taken with food to limit gastrointestinal disturbances.
Formulation and preparation	Sodium powder is used for the oral solution: 5.52 g sachet (equivalent to 4 g para-aminosalicylic acid).
Storage	Para-aminosalicylic acid sodium salt may be stored at room temperature.
Oral absorption	Absorption is incomplete, and sometimes requires increased doses to achieve therapeutic concentrations. Absorption is unaffected by food.
CSF penetration	Para-aminosalicylic acid poorly penetrates the meninges, but penetrates better when the meninges are inflamed.
Special circumstances	**Use during pregnancy or breastfeeding:** The safety profile is unknown; however, it is used during pregnancy. There is limited information on its use while breastfeeding (a proportion goes into human milk). **Use in renal disease:** The inactive metabolite is cleared by the kidneys. It should be avoided in severe renal failure. **Use in hepatic disease:** It should be used with caution.

Para-aminosalicylic acid (PAS) Drug class: salicylic acid – anti-folate	
Adverse reactions	**Overall tolerance:** It is poorly tolerated. **Common:** Most patients experience gastrointestinal upset (although this is less with the Paser® formulation than with older preparations); nausea, vomiting, diarrhoea and abdominal pain. **Frequently:** Hypothyroidism in adults is usually subclinical and reversible but the consequences may be important in pregnant woman and children, necessitating TSH monitoring and levothyroxine supplementation. The risk of hypothyroidism increases when it is used with ethionamide and prothionamide. It reduces the absorption of vitamin B12; if significant erythrocyte abnormalities develop, vitamin B12 supplements should be considered. **Uncommon**: Hepatotoxicity and coagulopathy.
Contraindications	Allergy to aminosalicylic acid.
Drug interactions	There is a low potential for drug–drug interactions. Antacids cause fast dissolution of the acid-resistant coating, resulting in early release of para-aminosalicylic acid into the stomach. Ethionamide and prothionamide: If these are co-administered with para-aminosalicylic acid, it may intensify hypothyroidism and gastrointestinal effects (e.g. jaundice, hepatitis or hepatotoxicity, nausea, vomiting, diarrhoea, abdominal pain or anorexia). Rifamycins: Para-aminosalicylic acid reduces the absorption of rifamycins, and these drugs should be given 8–12 hours apart. Diphenylhydramine decreases the gastrointestinal absorption of para-aminosalicylic acid and should not be administered concomitantly.
Food interactions	The absorption is unaffected by food. Taking para-aminosalicylic acid with food may reduce gastrointestinal upset. To improve tolerance, it should be given sprinkled onto or stirred into yogurt or similar food.
Monitoring	Should monitor TSH, electrolytes, blood counts and liver function tests.
Patient instructions and alerting symptoms	It is better tolerated when taken with food. Gastrointestinal discomfort and diarrhoea usually improve over time. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • skin rash, severe itching or hives; • severe abdominal pain, nausea or vomiting; • unusual tiredness or loss of appetite; or • black stools or bleeding.

CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*; TSH: thyroid stimulating hormone.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Pretomanid (Pa)

Pretomanid (Pa) Drug class: nitro-dihydro-imidazooxazole	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall and inner cell metabolism. Pretomanid is a prodrug that is metabolically activated by the Ddn enzyme or F420 co-enzyme, producing various active metabolites responsible for its anti-TB effects: • A des-nitro derivative is responsible for the induction of nitric oxide, leading to cell poisoning even in anaerobic conditions, and thus killing active and also dormant or latent bacteria. • Other metabolites inhibit mycolic acid biosynthesis, resulting in the inhibition of the bacterial cell wall biosynthesis. This mechanism is not yet fully understood, but data suggest that it involves the *fasI* and *fasII*, *efpA* and *iniBAC cyd* genes. **Activity:** It is bactericidal and has potent in vitro activity to kill actively replicating bacteria. **Half-life and excretion:** It is a prodrug that requires bioactivation. It binds tightly to plasma proteins (86.4%). It has a half-life of 18 hours. Hepatic metabolism is by different routes, and no single major metabolic pathway has been identified. CYP3A4 (cytochrome P450) is responsible for 20% of its metabolism. About 53% is excreted in urine and 38% in faeces.
Cross-resistance	To date, there is limited published information about mutations that may lead to cross-resistance, their frequency, distribution and correlation with clinical relevance.
Dose[a]	**Adults:** 200 mg once daily with food (upper daily dose is 200 mg). See the handbook **Annex 4** for weight-based dosing in the BPaLM/BPaL regimens. **Pretomanid is not recommended by WHO for use in those aged <14 years.**
Administration	Oral (it is better absorbed with food). Tablets should be taken whole; they should not be broken, crushed or chewed. Currently, Pa is recommended only for use in combination with Bdq, Lzd, and moxifloxacin in the BPaLM or BPaL regimens.
Formulation and preparation	200 mg tablet.
Storage	Should be stored below 30 °C and in the original package.
Oral absorption	Absorption is increased when it is taken with high-calorie and high-fat food.
CSF penetration	No data.

Pretomanid (Pa) Drug class: nitro-dihydro-imidazooxazole	
Special circumstances	**Use during pregnancy or breastfeeding:** There are no studies available on pretomanid use in pregnant women, and no pregnancy category has been assigned. Animal studies (of prenatal and postnatal development) showed changes in the fetus at toxic doses but not at equivalent doses used in humans. Pretomanid passes into breast milk. It is currently not recommended during pregnancy or breastfeeding. **Use in renal disease:** Safety, effectiveness and pharmacokinetics are unknown. **Use in hepatic disease:** Safety, effectiveness and pharmacokinetics are unknown. **Use in cardiac disease:** It is a QTc prolonging drug; hence, it should be used with caution in patients with predisposing factors for QTc interval prolongation. **Use in malnourished patients:** Unknown. **Use beyond 6 months**: Unknown. Use with caution in case of confirmed or suspected resistance to delamanid (potential cross-resistance).
Adverse reactions	**Overall tolerance:** Well tolerated. In combination with bedaquiline and linezolid, the most common toxicities reported related to pretomanid were headache (32%), nausea (12%), contact dermatitis (11%), decreased haemoglobin level (11%), diarrhoea (9%) and dizziness (8%). **Adverse events of special interest:** In animal studies, toxic effects attributable to pretomanid were ocular disorders and male reproductive toxicity; however, a recent review of available evidence reported no changes in male hormones in four clinical trials, suggesting no association between pretomanid-containing treatment and testicular toxicity *(7, 8)*. Additional data from a reproductive safety study focused on sperm count *(9)* suggest that pretomanid does not have negative effects on the reproductive function of male humans. [1] Other adverse events include: • convulsions; • ECG QT prolongation: 5 msec average, without significant clinical consequences; • hepatotoxicity (increase in GGT); and • myelosuppression (anaemia). There are several studies ongoing to further evaluate the efficacy and safety of pretomanid alone or in combination with other medicines.
Contraindications	It is currently contraindicated in patients for whom bedaquiline or linezolid is contraindicated. Pa should not be used in combination with Z as rarely fatal hepatotoxic events have been observed in trials.

[1] Howell, Pauline. Results of studies on pretomanid: side effects on male fertility and PK/PD in female children. Presented during: WHO BPaLM Accelerator Virtual Meeting on 28 May 2024.

Pretomanid (Pa) Drug class: nitro-dihydro-imidazooxazole	
Drug interactions	There is low potential for drug–drug interactions. No major interactions had been reported but data are limited. If possible, concomitant administration of strong CYP3A inducers should be avoided. In studies, rifampicin decreases the pretomanid AUC by 66%, and nevirapine decreases the pretomanid AUC by 35%. It should be used with caution with other QTc-prolonging medicines.
Food interaction	It should be taken with food; alcohol should be avoided owing to increased risk of hepatotoxicity.
Monitoring	Signs and symptoms of hepatotoxicity should be monitored, and liver function tests monitored at baseline, at 2 weeks and then monthly as needed. The BPaL regimen has been associated with hepatic adverse reactions. ECG and baseline electrolytes should be obtained whenever possible before the initiation of treatment and repeated if needed (e.g. documented QTc prolongation or multiple QTc-prolonging risk factors).
Patient instructions and alerting symptoms	It should be taken with food. The tablet should be swallowed whole and should not be crushed, chewed or broken. Alcohol should be avoided. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • history of heart problems, heart attack, congenital long QT syndrome or problems with heart rhythm; • liver or kidney disease; • HIV; or • pregnancy or planning to get pregnant.

AUC: area under the curve; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CSF: cerebrospinal fluid; Ddn: deazaflavin-dependent nitroreductase; ECG: electrocardiography; GGT: gamma-glutamyl transferase; HIV: human immunodeficiency virus; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; WHO: World Health Organization.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Pyrazinamide (Z)

Pyrazinamide (Z) Drug class: synthetic derivative of nicotinamide	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** Inner *M. tuberculosis* metabolism with potential multiple mechanisms. Pyrazinamide is a prodrug that, via the pyrazinamidase enzyme, is activated into pyrazinoic acid (active form); it is highly active in acidic conditions in which most drugs become inactive and bacilli enter into nonreplicating, or latent or dormant forms. Pyrazinamide is the prototype for drugs that specifically targets dormant or latent *M. tuberculosis* forms. Under acidic conditions (found inside macrophages and in inflammation and caseum), pyrazinoic acid enters the cell wall and may destroy *M. tuberculosis* by: • accumulating intracellularly, leading to acid bacterial cytoplasm; • accelerating energy consumption: bacilli efflux pumps on the cell wall are constantly pumping pyrazinoic acid out of the cell; • disrupting membrane potential and interfering with energy production of bacilli in acid medium; • potentially inhibiting fatty acid synthesis; and • binding to the ribosomal protein S1 (RpsA) and inhibiting trans-translation. **Activity:** Pyrazinamide has potent sterilizing capacity; it is able to kill dormant or latent bacilli; however, it has weak or no bactericidal activity, because the drug is only active against bacilli in acid media. **Half-life and excretion**: Peak plasma concentrations are attained within 2 hours, and the half-life is 9–10 hours (under normal conditions). About 10% binds to plasma proteins. It undergoes hepatic metabolism and 70% is excreted in the urine (mainly by glomerular filtration within 24 hours).
Cross-resistance	None reported.
Dose[a]	• **Adults:** 20–30 mg/kg/day. Upper daily dose 2000 mg. • **Children:** See the handbook **Annex 4** for weight bands. • **Renal failure or dialysis:** 25 mg/kg/dose, thrice weekly (not daily). See the handbook **Annex 4** for weight-based dosing in adults and children
Administration	Oral.
Formulation and preparation	150 mg dispersible tablet. 400 mg tablet. 500 mg tablet. Crushing and dissolving uncoated tablets (400 mg and 500 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; also, it avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should not be stored above 25–30 °C. Dispersible tablets should be protected from moisture.
Oral absorption	Well absorbed from the gastrointestinal tract.

Pyrazinamide (Z) Drug class: synthetic derivative of nicotinamide	
CSF penetration	Being a moderately lipophilic small molecule, concentrations in the CSF are equivalent to those in serum in patients with inflamed meninges.
Special circumstances	**Use during pregnancy or breastfeeding:** Has no known teratogenicity. It is distributed into breast milk but is commonly used while breastfeeding. **Use in renal disease:** It is cleared by the kidneys; dosage adjustment may be needed; for example, when changing to thrice weekly dosage and after dialysis. **Use in hepatic disease:** It should be used with caution. Patients with pre-existing liver disease (alcohol abuse, nonalcoholic steatohepatitis, chronic viral hepatitis or TB hepatitis) should be carefully monitored. It is associated with hepatotoxicity in about 1% of patients. Hepatotoxicity can be severe and can worsen treatment outcomes. **Use in patients with gout:** The drug to be avoided if the patient has frequent or ongoing gout. **Use in diabetes mellitus:** It should be used with caution.
Adverse reactions	**Overall tolerance:** Variable. **Common (>10%):** Asymptomatic hyperuricemia is an expected effect and should not be treated or considered pathologic. The drug should be discontinued only if hyperuricemia is accompanied by an acute gout-associated arthritis. Arthralgia (pain in large and small joints) and gastrointestinal effects (nausea, vomiting and anorexia). **Frequently (5–10%):** Arthralgia (pain in large and small joints that are not inflamed) and gastrointestinal effects (nausea, vomiting and anorexia). **Occasional (>1%):** Hepatotoxicity can occur at any time and appears to be dose related. Transient increase in ALT/AST (<4 times the ULN) is the most frequent presentation. However, severe liver injuries, including some fatalities, have been reported. The drug should be discontinued in symptomatic or asymptomatic patients with an ALT concentration >4–5 times the ULN, and in patients who have serum bilirubin concentrations above the ULN. Gout is described as sudden, severe attacks of pain, swelling, redness and tenderness in one or more joints, most often in the big toe, with or without hyperuricaemia. It may cause photosensitivity and dermatitis. **Rare (<1%):** Sideroblastic anaemia, hypersensitivity reactions and effects on blood clotting.
Contraindications	Hypersensitivity to pyrazinamide. Severe hepatic damage. Acute gout or frequent flares. Pa should not be used in combination with Z as rarely fatal hepatotoxic events have been observed in trials.
Drug interactions	There is low potential for drug–drug interactions. If used with other hepatotoxic drugs, the effects can accumulate.
Food interactions	The absorption is unaffected by food.

Pyrazinamide (Z) Drug class: synthetic derivative of nicotinamide	
Monitoring	Liver function (AST, ALT, and bilirubin) should be monitored at baseline and monthly if possible. Patients should be closely monitored if they are at risk for drug-related hepatitis (e.g. alcohol abuse, nonalcoholic steatohepatitis or chronic viral hepatitis) and if signs or symptoms of hepatotoxicity occur.
Patient instructions and alerting symptoms	May be taken with or without food. Pyrazinamide may cause a rash after sun exposure (so sun exposure should be limited). It should not be used if there is active gout with frequent flares or if the patient presents with severe liver disease (e.g. alcohol abuse, nonalcoholic steatohepatitis or chronic viral liver infections). **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • skin rash, severe itching or hives; • pain or swelling in the joints; • yellowing of the skin or eyes or dark urine; or • unusual tiredness or loss of appetite.

ALT: alanine transaminase; AST: aspartate transaminase; CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; ULN: upper limit of normal.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Rifampicin (R)

Rifampicin Drug class: Rifamycin	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** Inhibits ribonucleic acid synthesis. Rifampicin is a semi synthetic derivative of rifamycin, a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. **Activity:** It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extra cellular locations. **Excretion and half-life:** Rifampicin is lipid-soluble, following oral administration it is rapidly absorbed, about 80% protein bound, and widely distributed throughout the cellular tissues and body fluid including cerebrospinal fluid. It reaches a peak serum concentration within two to four hours after oral administration. After absorption, rifampicin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampicin undergoes progressive deacetylation so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite has antibacterial activity. Intestinal reabsorption is reduced by deacetylation, and elimination is facilitated. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.
Cross-resistance	Organisms resistant to rifampicin are likely to be resistant to other rifamycins.
Dose	150 mg and 300 mg capsule Child under 30 kg: 15 mg/kg once daily, on an empty stomach Child 30 kg and over and adult: 10 mg/kg once daily, on an empty stomach Maximum daily dose of 600mg
Administration	Oral administration
Formulation and preparation	150 and 300 mg capsules; contents of capsules can be mixed with liquid or semi-soft vehicles. Extemporaneously prepared oral solutions have unproven homogeneity and shelf life. Immediate administration of the dose after mixing capsular contents in a vehicle is ideal.
Storage	Capsules and tablets should be kept in tightly closed containers, protected from light at room temperature (15–25 °C) Powder suspended in saline is stable for 24 hours. Powder suspended in dextrose solutions is stable for 4 hours.
Oral absorption	Usually, absorption is rapid but may be delayed or decreased by high-fat meals.
CSF penetration	Rifampicin CSF penetration is variable and typically achieves only 10–20% of serum concentrations in CSF (significant amounts enter the cerebrospinal fluid in inflamed meninges), but this may still be an important contribution to the regimen. Some authors recommend increased doses of rifampicin in patients with TB meningitis.

Rifampicin Drug class: Rifamycin	
Special circumstances	**Pregnancy:** no contra-indication. Risk of maternal and neonatal bleeding disorders when the mother receives rifampicin in late pregnancy: administer phytomenadione (vitamin K) to the mother and the neonate to reduce the risk. **Breast-feeding:** no contra-indication **Use in renal disease:** Can be used without dose adjustment. **Use in hepatic disease:** Use with caution as it can be associated with hepatotoxicity.
Adverse reactions	Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe (can be taken with a small amount of food to increase gastrointestinal tolerance). • Rifampicin may cause harmless orange-red discoloration of body secretions (urine, tears, saliva, sputum, sweat, etc.); and • Other adverse effects (headache, drowsiness, hepatotoxicity; influenza-like symptoms; thrombocytopenia, systemic hypersensitivity reactions; severe cutaneous adverse reactions e.g. Stevens-Johnson syndrome; isolated porphyria exacerbation). • Hepatic adaptation occurs in most patients with low level increases in AST and ALT less than 3 times the upper limit of normal. In the absence of symptoms, do not interrupt treatment.
Contraindications	Do not administer to patients with jaundice, hypersensitivity to rifamycins or history of severe haematological disorders (thrombocytopenia, purpura) during a previous treatment, or in patients who are also receiving ritonavir-boosted saquinavir (increased risk of severe hepatocellular toxicity). Avoid or administer with caution to patients with hepatic disorders
Drug interactions	Rifampicin reduces the effect of many drugs (antimicrobials, some antiretrovirals, some hormones, antidiabetics, corticosteroids, phenytoin, direct-acting antivirals for chronic hepatitis C, warfarin, etc.): • in patients taking lopinavir/ritonavir, atazanavir/ritonavir, use rifabutin in place of rifampicin; • Rifampicin reduces the effectiveness of the oral contraceptive pill, in women using contraception, use injectable medroxyprogesterone or an intrauterine device; • in the event of concomitant fluconazole administration, administer each drug 12 hours apart (rifampicin in the morning, fluconazole in the evening); • for the other drugs, adjust dosage if necessary; • Antiretroviral drugs (non-nucleoside reverse transcriptase inhibitors and protease inhibitors) interact with rifampicin. This may result in the ineffectiveness of antiretroviral drugs, ineffective treatment of TB or an increased risk of drug toxicity; and • Concomitant antacid administration may reduce the absorption of rifampicin. Daily doses of rifampicin should be given at least 1 hour before the ingestion of antacids.

Rifampicin Drug class: Rifamycin	
Food interactions	Absorption of rifampicin is reduced by about 30% when the drug is ingested with food
Monitoring	Baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count, and a platelet count (or estimate) are advised. Baseline tests unnecessary in paediatric patients unless a complicating condition is known or clinically suspected. Liver function monitoring during treatment if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.
Patient instructions and alerting symptoms	Best taken without food; if it irritates the stomach, try taking it with a small amount of food. It is normal for urine, tears, and other secretions to turn an orange colour when taking this medicine. Soft contact lenses may become discoloured while on this medicine. Make sure your doctor knows all the medicines you take because many drugs can interfere with this one. Avoid the use of oral hormone-contraceptive pills because rifampicin may decrease their effectiveness. Instruct patients to inform their health care provider right away if any of the following occurs: • Unusual tiredness or loss of appetite • Severe abdominal upset • Fever or chills

Rifapentine

Rifapentine (Rpt) Drug class: Rifamycin	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** Rifapentine is an antibacterial medicine indicated in combination with other tuberculosis medicines in patients aged 12 years or more for the treatment of tuberculosis caused by Mycobacterium tuberculosis (*M.tb)*, and is also indicated together with other medicines for the prevention of tuberculosis in persons at risk. It inhibits DNA-dependent RNA polymerase activity in susceptible strains of *M.tb* and acts via the inhibition of DNA-dependent RNA polymerase, leading to a suppression of RNA synthesis and cell death. **Activity:** Rifapentine has shown higher bacteriostatic and bactericidal activities against intracellular bacteria growing in human monocyte-derived macrophages. Excretion and half-life: Rifapentine is primarily eliminated in faeces and partial excretion in urine. It has a relatively long half-life (14–25 hours).
Cross-resistance	*M.tb* strains resistant to rifamycins are likely to be resistant to rifapentine. A high level of cross-resistance between rifampicin and rifapentine has been demonstrated.
Dose	Given to patients aged 12 years and above once daily for a period of 4 months, as part of a regimen with isoniazid, moxifloxacin, and pyrazinamide (HPMZ) for the treatment of drug-susceptible TB. Maximum daily dose of 1,200 mg (4 tablets). For prophylaxis, it may be given together with isoniazid (H) daily for 28 days (1HP) or once a week on the same day for a period of 12 weeks (3HP).
Administration	Oral administration Administration of rifapentine with a meal increases oral bioavailability and may reduce the incidence of gastrointestinal upset, nausea, and/or vomiting.
Formulation and preparation	150 mg or 300 mg film coated tablets.
Storage	Store under 25°C. Protect from excessive heat and humidity and avoid temperature excursions (below 15°C or above 30°C)
Oral absorption	Rifapentine is highly lipophilic, and absorption is improved by about 50% when it is taken with a fat-containing meal. The drug is highly (98%) bound to plasma proteins, and this contributes to a long half-life (14–25 hours) which renders it suitable for intermittent use.
CSF penetration	

Rifapentine (Rpt) Drug class: Rifamycin	
Special circumstances	Children: Due to a lack of evidence of the safety of rifapentine in children, rifapentine is not recommended in children less than 12 years of age in the treatment of active TB or less than 2 years of age for the prevention of TB. Pregnancy: There are no adequate and well controlled studies of rifapentine use during pregnancy. Further evidence is required before it can be recommended during pregnancy. People living with HIV: The 4-month treatment regimen with rifapentine, isoniazid, moxifloxacin and pyrazinamide has been shown to be effective in patients with drug-sensitive TB who are also HIV-positive. However, the evidence on the use of this 4-month regimen in people with HIV was limited to those with a CD4 count of above 100 cells/mm^3. Elderly people: Caution should be exercised in such patients, especially if there is evidence of hepatic impairment. Hepatic impairment: Use should be carefully monitored in patients with chronic liver disease as Rpt can cause ALT and AST levels to be elevated. Renal impairment: There are no pharmacokinetic data for rifapentine in patients with renal impairment.
Adverse reactions	Rifapentine may cause side effects such as hypersensitivity reactions which has been reported in both clinical trials and programmatic use for treatment of active TB and preventative treatment. These reactions are sometimes called systemic drug reactions and often characterized by flu-like symptoms. Hypersensitivity episodes are uncommon and usually resolve quickly after the medication is stopped, without any long-term effects. Gastrointestinal related problems such as nausea, upper stomach pain, loss of appetite and jaundice (yellowing of the skin or eyes) have been observed. It can also cause headache, joint pain, itching or rash and elevated liver transaminases. Severe cutaneous adverse reactions such as Stevens-Johnson syndrome and drug reaction with eosinophilia and systemic symptoms syndrome have been reported in association with the use of rifapentine treatment regimens in patients with active and latent tuberculosis. Rifapentine may cause red-orange appearance of the skin, tears, sweat, saliva, urine, or stools, teeth, tongue, or the inside of the mouth may also appear red orange. Dentures and contact lenses may be permanently stained.
Contraindications	Do not administer Rifapentine to patients with hypersensitivity to any of the rifamycin class of drugs such as rifampicin and rifabutin.

Rifapentine (Rpt) Drug class: Rifamycin	
Drug interactions	Rifapentine induces CYP450 enzymes and its concomitant use with drugs metabolized by CYP450 (e.g. digoxin, azole antifungal agents, phenytoin, warfarin) may cause a significant decrease in plasma concentrations and loss of therapeutic effect of these drugs. These also include protease inhibitors, reverse transcriptase inhibitors, and hormonal contraception. Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment.
Food interactions	Absorption is improved by about 50% when it is taken with a fat-containing meal.
Monitoring	Rifapentine is an analogue of rifampicin with a longer half-life that makes it attractive for shortening the duration of treatment and for intermittent treatment. It induces hepatotoxicity with ALT and AST level elevations during combination TB therapy, but slightly less than rifampicin. Baseline measurements of hepatic enzymes are necessary. Liver function monitoring during treatment if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.
Patient instructions and alerting symptoms	It is best taken with fatty foods, and rifapentine may cause urine, sweat, saliva, or tears to turn reddish. This effect is harmless and will disappear when the drug is stopped. However, dentures and contact lenses may be permanently stained. Make sure your doctor knows all the medicines you take because many drugs can interfere with this one. Avoid the use of oral hormone-contraceptive pills because rifapentine may decrease their effectiveness. Instruct patients to inform their health care provider right away if any of the following occurs: • Unusual tiredness or loss of appetite; • Yellowing of the skin or whites of the eyes; • Severe abdominal upset; or • Fever or chills.

Amikacin (Am)

Amikacin (Am) Drug class: aminoglycosides	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* inner metabolism. Inhibits protein synthesis. Irreversibly binds to bacterial 30S ribosomal subunits. Leads to misreading of t-RNA (meaning that bacteria are unable to synthesize proteins) and hence interferes with bacterial growth. **Activity**: Mainly bactericidal, high early bactericidal activity. **Half-life and excretion:** Half-life is usually 2–3 hours. Primarily excreted unchanged through the kidney by glomerular filtration.
Cross-resistance	Cross-resistance with capreomycin and kanamycin has been reported.
Dose[a]	**Amikacin is recommended by WHO only in adults aged >18 years.** • **Adults:** 15–20 mg/kg/day in a single daily dose, 6–7 days per week (upper daily dose is 1 g). • **Adults > 60 years old:** Lowering of amikacin dosage is advised. A lower starting dose of 10 mg/kg/day (max 750 mg) 5–7 times a week may be used. Alternatively, a 15 mg/kg/dose may be administered thrice weekly. • **Renal failure or dialysis:** Consider replacing amikacin with another agent. Otherwise, a 12–15 mg/kg/dose after dialysis, twice or thrice weekly (not daily) may be considered. Amikacin should be used with caution.
Administration	IV or IM. Intraperitoneal and intrathecal administrations have been reported; however, intrathecal administration is not advised provided there are oral TB medications with high CSF penetration.
Formulation and Preparation	Available as 500 mg/2 mL solution for injection, ampoules and vials. For **IV solution**, mix with 100 mL or 200 mL of sterile diluent (e.g. D5W) or any other compatible solution. In paediatric patients, the volume of diluent used will depend on the amount of amikacin tolerated by the patient. The solution should be infused over 30–60 minutes for adults. It should not be mixed with any other parenteral medicine administered concurrently. **IM** absorption is complete within 4 hours and peak concentrations are achieved in 1–2 hours; however, absorption can be delayed if the same site is used repeatedly.
Storage	The solution in the original vial is stable at room temperature (15–25 °C). Reconstituted solutions can be stored at 2–8 °C for not more than 12 hours. Once at room temperature, it should be used within 24 hours.
Oral absorption	There is no significant oral absorption.
CSF penetration	Penetration is more effective in inflamed meninges.

Amikacin (Am) Drug class: aminoglycosides	
Special circumstances	**Use during pregnancy or breastfeeding:** Should be avoided during pregnancy because of documented cases of congenital deafness. It is excreted into human milk; it is considered compatible with breastfeeding but should be used with caution (i.e. monitor for infant thrush and diarrhoea). **Use in renal disease:** Should be used with extreme caution; where possible, concentrations should be monitored in patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis (see under Dose section, above). The drug is variably cleared by haemodialysis. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease (except a larger volume of distribution for patients with ascites due to cirrhosis). It is presumed to be safe in severe liver disease; however, it should be used with caution because patients with severe liver disease may progress rapidly to hepato-renal syndrome. **Diuretic use:** Co-administration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity. **Older people:** There is increased risk of ototoxicity and nephrotoxicity owing to potential baseline damage in both organs.
Adverse reactions	**Overall tolerance:** It is badly tolerated, giving local pain or inflammation with IM injections or lengthy infusions. Toxicity is associated with prolonged use and dose accumulation. **Common:** Proteinuria. **Occasional:** Nephrotoxicity (9% for general population, may be lower with thrice weekly administration), ototoxicity (hearing loss, increased risk with advanced age and prolonged use) and vestibular toxicity (vertigo, ataxia and dizziness); and electrolyte abnormalities, including hypokalaemia (which may prolong the QTc interval), hypocalcaemia and hypomagnesaemia. **Uncommon:** Neuropathy and rash.
Contraindications	**Hypersensitivity to aminoglycosides.** **Renal, hepatic, vestibular or auditory impairment**: In such cases, it should be used only with extreme caution and safety monitoring in place.
Drug interactions	**Loop diuretics:** Co-administration of furosemide and aminoglycoside antibiotics carries an increased risk of ototoxicity and hypokalaemia.
Food interactions	None.

Amikacin (Am) Drug class: aminoglycosides	
Monitoring	Monitoring of renal function should include: • creatinine at least monthly (more frequently if there is renal or hepatic impairment); • creatinine clearance if there is baseline renal impairment or any concerns; and • electrolytes: baseline follow-up with monthly minimum potassium, magnesium and calcium if possible. Audiology examination: document baseline and monthly results. Vestibular examinations: question patient regularly about vestibular symptoms and perform serial vestibular exams. If possible, in patients aged over 60 years or with altered renal function, peak serum concentrations should be monitored.
Patient instructions and alerting symptoms	**Patients should be instructed to inform their health care provider immediately if any of the following occur:** • problems with hearing, dizziness or vertigo; • rash or swelling of the face; • trouble breathing; • swelling, pain or redness at the IV site; or • muscle twitching or weakness.

CSF: cerebrospinal fluid; D5W: dextrose 5% in water; IM: intramuscular; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; t-RNA: transfer ribonucleic acid; WHO: World Health Organization.

[a] See the handbook **Annex 4** for revised weight-based dosing.

Streptomycin (Sm)

Streptomycin (Sm) Drug class: aminoglycosides	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* inner metabolism. Streptomycin binds to the bacterial ribosome small subunit (30 S or 16 S rRNA), leading to mistranslation of proteins and also disruption of the cytoplasmic membrane. **Activity:** It has important bactericidal activity (medium–high early bactericidal activity) and the potential for sterilizing activity. **Excretion and half-life:** Reaches peak serum concentration within 1 hour after IM administration, and 50% is eliminated in the urine within 24 hours after IV or IM administration.
Cross-resistance	Mutations at the *eis* gene may confer resistance to amikacin but not to streptomycin.
Dose[a]	**Streptomycin is recommended by WHO** only in adults aged >18 years. • **Adults:** 12–18 mg/kg/day in a single daily dose, upper daily dose is 1 g**.** • **Renal failure or dialysis:** 12–15 mg/kg/dose, twice or thrice weekly (not daily). It should be used with caution. See the handbook **Annex 4** for weight-based dosing. • **Markedly obese individuals (e.g. BMI >35):** The dose should be adjusted because of decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. For dosing in obese adults who conform to weight bands corresponding to the following adjusted weights: – ideal body weight (men): 50 kg plus 0.9 kg/cm >1.52 m; and – ideal body weight (women): 45 kg plus 0.9 kg/cm >1.52 m. Serum concentrations should be monitored closely, if possible.
Administration	It is not absorbed orally. Aminoglycosides (amkacin and streptomycin) are administered parenterally as an IM injection, and in some cases may be administered IV. IM absorption may be delayed if the same site is used consistently. Intrathecal and intraperitoneal administration have been tried in the past.
Formulation and preparation	The powder for injection (1 g, vial) requires reconstitution with water for injection (at 200 mg/mL, 250 mg/mL or 400 mg/mL) before administration. For IV use, the concentration may be decreased.
Storage	The powder for injection should be stored below 30 °C. The reconstituted solution may be stored at room temperature for 1 week, protected from light.
Oral absorption	There is no significant oral absorption.
CSF penetration	Penetration is better in inflamed meninges.

Streptomycin (Sm) Drug class: aminoglycosides	
Special circumstances	**Use during pregnancy or breastfeeding:** The drug should be avoided during pregnancy owing to documented cases of congenital deafness. It is excreted into human milk, and is considered compatible with breastfeeding but should be used with caution (the infant should be monitored for thrush and diarrhoea). **Use in renal disease:** It should be used with extreme caution. Concentrations should be monitored in patients with impaired renal function, if possible. Interval adjustment is recommended for renal impairment or dialysis (see under Dose section above for dosage under renal disease or dialysis). Clearance by haemodialysis is variable. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease (except for a larger volume of distribution for patients with ascites due to cirrhosis). It is presumed to be safe in liver disease; however, it should be used with caution because patients with severe liver disease may progress rapidly to hepato-renal syndrome. **Diuretic use:** Co-administration of loop diuretics and aminoglycoside antibiotics increases the risk of ototoxicity. **Older people:** There is increased risk of ototoxicity and nephrotoxicity due to potential baseline damage in both organs. **Children:** It should be used with extreme caution. There is a risk of ototoxicity with important consequences (e.g. effects on verbal communication, cognitive and emotional development linked to school performance and future disability).
Adverse reactions	**Overall tolerance:** Generally, it is poorly tolerated, due to local pain from IM injections or lengthy infusions. **Common:** IM injection pain, permanent hearing loss (10–12%) and vestibular toxicity including nausea, vomiting and vertigo. **Frequently:** Electrolyte abnormalities, including hypokalaemia, hypocalcaemia and hypomagnesaemia. Watery or bloody diarrhoea may occur months after the last dose; vaginal itching or discharge; and eosinophilia. **Occasional:** Nephrotoxicity (typically transient), paraesthesia of face and neuropathy, weakness and neuromuscular blockage.
Contraindications	Hypersensitivity to aminoglycosides. Pregnancy: Congenital deafness can occur with streptomycin and kanamycin use during pregnancy. Children: Owing to the important consequences of ototoxicity. Older people or adults with renal, vestibular or auditory impairment.
Drug interactions	There is low potential for drug–drug interactions. It should be used with caution with other drugs that might be nephrotoxic or may change the electrolyte balance (e.g. loop diuretics) or in clinical conditions such as dehydration. The ototoxic effects of aminoglycosides, including streptomycin, are potentiated by the co-administration of ethacrynic acid, furosemide, mannitol and other diuretics.
Food interactions	No alcohol or food interactions.

Streptomycin (Sm) Drug class: aminoglycosides	
Monitoring	Patients should be carefully monitored for early signs of hearing loss and vestibular dysfunction, to prevent permanent damage to sensorineural cells. Baseline and monthly audiology exams should be documented. Renal function should be monitored by documenting creatinine at least monthly (and more frequently if there is renal or hepatic impairment). Serum concentrations should be monitored serially for patients with impaired renal function, if possible.
Patient instructions and alerting symptoms	The patient should be informed of the potential harm to the fetus, so should be advised on contraception methods and a pregnancy test should be administered before drug initiation. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • problems with hearing, dizziness or balance; • decreased urination; • watery or bloody diarrhoea; • swelling, pain or redness at IV site; or • muscle twitching or weakness.

BMI: body mass index; CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; WHO: World Health Organization.

[a] See the handbook **Annex 4** for revised weight-based dosing.

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Annex 2. Monitoring and management of adverse events in treatment of drug-resistant tuberculosis

A2.1 Introduction

Early identification, ongoing monitoring and proper management of adverse events (AEs) associated with anti-tuberculosis (TB) medications are crucial for relieving suffering and improving the quality of care for patients undergoing treatment for all forms of drug-resistant TB (DR-TB). Awareness and optimal management of AEs are essential parts of a holistic approach to supporting patients to adhere to various treatment regimens. A holistic approach requires comprehensive education and training for health care workers, and provision of appropriate information and counselling for patients and their treatment supporters. From the early stages of DR-TB treatment, patients and their care providers must be aware of the potential AEs associated with anti-TB drugs; how to prevent, manage or cope with common but non-serious AEs; how to recognize serious or severe signs and symptoms; and when and where to seek medical assistance or psychosocial support. Health care workers must be prepared to anticipate, prevent, monitor and manage common AEs, particularly those that may affect patients' adherence to treatment; rapidly identify serious or potentially serious AEs and respond appropriately; record details of all AEs associated with DR-TB treatment; and know when to notify the responsible authorities.

National TB programmes (NTPs) should have established systems for active TB drug-safety monitoring and management (aDSM). Such systems involve the active and systematic clinical and laboratory assessment of patients being treated with new TB medicines or novel DR-TB regimens, with the aim of detecting, managing and reporting suspected or confirmed drug toxicities *(1)*. The details of the aDSM framework are described in **Annex 3**.

A2.2 AEs and drug–drug interactions associated with DR-TB treatment

AEs associated with DR-TB treatment

Several systematic reviews have summarized AEs associated with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) treatment over the past decade; however, most of these reviews could not assign causal relationships between specific anti-TB drugs and the reported AEs. Furthermore, most meta-analyses were conducted at a time when injectable drugs were commonly used in MDR/RR-TB treatment regimens. Other systematic reviews have focused on specific drugs and the AEs commonly

associated with their use, but patients with MDR/RR-TB are usually treated with multidrug regimens; hence, attribution of causality can be difficult.

In 2020, the Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB Treatment used the individual patient data (IPD) MDR database (created for the meta-analysis of MDR-TB treatment and outcomes that was published in 2018) to obtain IPD from studies published between 2009 and 2016 on AEs that led to permanent discontinuation of anti-TB drugs *(2)*. The group also obtained patient-level data that were shared with the World Health Organization (WHO) in response to a public call in 2018. Thus, the combined data from more than 9000 patients with MDR/RR-TB in 28 countries were used to conduct an IPD meta-analysis to estimate the frequency of AEs that led to permanent discontinuation of 20 different anti-TB drugs. The analysis did not include high-dose isoniazid, rifabutin, gatifloxacin or delamanid because too few patients received these drugs across the included studies. Almost one quarter of patients had at least one drug permanently stopped because of an AE, and stopping of one or more drugs was significantly more likely among female patients, older people and those receiving treatment in high-income countries. Fluoroquinolones, clofazimine and bedaquiline had the lowest incidence of AEs leading to permanent drug discontinuation, whereas second-line injectable drugs, aminosalicylic acid and linezolid had the highest incidence *(2)*. **Table A2.1** outlines the types of AEs associated with each of the key drugs in this analysis.

Table A2.1. Types of AEs resulting in permanent discontinuation of TB drugs

TB drug	AEs[a]/ patients using the drug	Pooled incidence of AEs, random effect[b] (95% CI)	AE types reported[c]	Type of AE[d]				
				Type 1	Type 2	Type 3	Type 4	Type 5
Levofloxacin	22/1012	1.3% (0.3–5.0)	14	Musculoskeletal (9, 64%)	Peripheral neuropathy (2, 14%)	Rash (2, 14%)	Hypoglycaemia (1, 7%)	–
Clofazimine	12/1712	1.6% (0.5–5.3)	12	Cardiovascular (4, 33%)	Hyperpigmentation (5, 42%)	Rash (2, 17%)	Gastrointestinal (1, 8%)	–
Bedaquiline	9/464	1.7% (0.7–4.2)	9	Cardiovascular (5, 56%)	Hepatotoxicity (2, 22%)	CNS toxicity (1, 11%)	Musculoskeletal (1, 11%)	–
Ethambutol	124/6089	1.8% (1.0–3.3)	59	Visual impairment (41, 70%)	Gastrointestinal (10, 17%)	Musculoskeletal (2, 3%)	Rash (2, 3%)	Hepatotoxicity (1, 2%)
Linezolid	140/783	14.1% (9.9–19.6)	137	Peripheral neuropathy (87, 64%)	Myelosuppression (30, 22%)	Optic neuritis (7, 5%)	Gastrointestinal (3, 2%)	Rash (3, 2%)
Moxifloxacin	30/904	2.9% (1.6–5.0)	24	Cardiovascular (5, 21%)	Hepatotoxicity (4, 17%)	Gastrointestinal (3, 13%)	Peripheral neuropathy (3, 13%)	Musculoskeletal (2, 8%)
Imipenem and meropenem	9/158	4.9% (1.0–20.5)	6	Hepatotoxicity (3, 50%)	Rash (1, 17%)	Fatigue (1, 17%)	Pneumonia (1, 7%)	–
Pyrazinamide	410/5141	5.1% (3.1–8.4)	142	Musculoskeletal (47, 33%)	Gastrointestinal (33, 23%)	Hepatotoxicity (29, 20%)	Rash (18, 13%)	Hyperuricaemia (8, 6%)

TB drug	AEs[a]/ patients using the drug	Pooled incidence of AEs, random effect[b] (95% CI)	AE types reported[c]	Type of AE[d]				
				Type 1	Type 2	Type 3	Type 4	Type 5
Cycloserine and terizidone	337/7547	5.7% (4.1–7.8)	140	Psychiatric (92, 66%)	CNS toxicity (35, 25%)	Gastrointestinal (5, 4%)	Peripheral neuropathy (2, 1%)	Rash (1, 1%)
Ethionamide or prothionamide	376/4627	6.5% (4.1–10.1)	108	Gastrointestinal (52, 48%)	Hepatotoxicity (24, 22%)	Psychiatric (6, 6%)	Gynaecomastia (5, 5%)	Musculoskeletal (5, 5%)
Amikacin	235/4106	10.2% (6.3–16.0)	211	Ototoxicity (183, 87%)	Nephrotoxicity (22, 10%)	Gastrointestinal (2, 1%)	Intolerance (2, 1%)	Musculoskeletal (1, 1%)
Aminosalicylic acid	532/2929	11.6% (7.1–18.3)	120	Gastrointestinal (95, 79%)	Hypothyroidism (6, 5%)	Hepatotoxicity (5, 4%)	Rash (5, 4%)	Nephrotoxicity (4, 3%)

AE: adverse event; CI: confidence interval; CNS: central nervous system; TB: tuberculosis.

[a] AEs were defined as those that resulted in permanent discontinuation of a drug.

[b] Pooled incidence of AEs was estimated through meta-analysis of proportions.

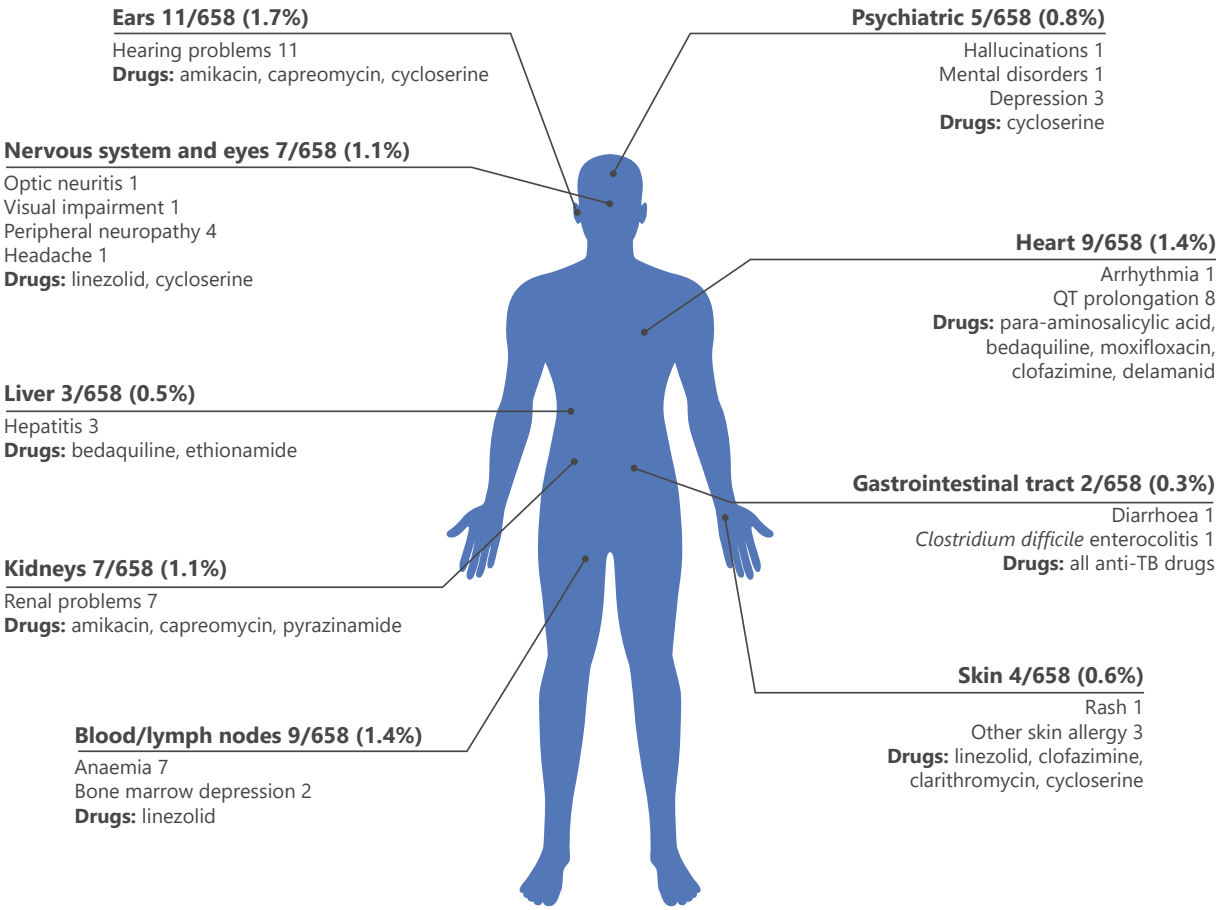
[c] This analysis included only studies that reported AE types.

[d] For each drug, simple pooling was done to calculate the number of each type of AE; the five most common AE types with the corresponding proportions are presented.

Source: Table modified from Lan et al. (2020) (2).

In addition to the IPD-MDR analysis, the first global report from the WHO global aDSM database presented an interim analysis of safety data reported between July 2017 and August 2019; it covered 658 patients receiving regimens based on bedaquiline or delamanid (or both) for treatment of MDR/RR-TB at participating centres in 26 countries *(3)*. Because the data were prospectively collected, it was possible to assign causal attribution of AEs to specific drugs through external assessment of reported events, discussion with reporting clinicians and consideration of the scientific evidence available for each drug during the study period. The drugs most often used in treatment regimens for this cohort, in addition to bedaquiline or delamanid, were linezolid, moxifloxacin, levofloxacin, clofazimine, capreomycin, amikacin and carbapenems. **Fig. A2.1** illustrates the distribution of reported serious AEs by organ or system.

Fig. A2.1. Summary of the distribution of 57 SAEs, by organ or system, among 658 patients treated for MDR/RR-TB in 26 countries between 2017 and 2019



MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; SAE: serious adverse event; TB: tuberculosis.

Source: Borisov et al. (2019) (3).

Longer, individualized treatment regimens for MDR/RR-TB often contain many drugs with overlapping toxicities; hence, the frequency of AEs will depend on the combination of drugs in the regimen. The drug information sheets in **Annex 1** outline clinically significant AEs associated with each of the WHO-recommended anti-TB drugs.

For the shorter regimens, the frequency of specific AEs may be more predictable because these regimens are standardized. The most common AEs associated with the 9-month all-oral regimens are anaemia (among patients receiving the linezolid-containing regimen), hepatotoxicity, QT prolongation,

nausea and vomiting *(4)*. The most common AEs for the BPaLM (bedaquiline, pretomanid, linezolid and moxifloxacin) regimen (e.g. peripheral neurophathy, anaemia, optic neuritis and hepatotoxicity) are mostly associated with linezolid. AEs associated with the BDLLfxC (bedaquiline, delamanid, linezolid, levofloxacin and clofazimine) regimen are also mostly attributed to linezolid, with anaemia being the most commonly reported serious AE in the Building Evidence to Advance Treatment of TB (BEAT) Tuberculosis trial in South Africa *(5)* and the BEAT-India study in India *(6)*. In both of these studies, skin hyperpigmentation and acneiform rashes were the most commonly reported AEs among people receiving clofazimine-containing regimens.

Children generally experience fewer AEs from second-line TB treatment than adults, and most of the AEs are mild or moderate; however, treatment-related AEs appear to be more common among children who are HIV-positive *(7)*. Furthermore, monitoring and timely detection of AEs (e.g. through repeated blood sampling, clinical assessment of vision and neuropathies, and identification of emergent neuropsychiatric events) can be more challenging in children than in adults.

Data on AEs among women who are pregnant or breastfeeding and receiving shorter standardized treatment regimens for DR-TB are relatively limited because pregnant women continue to be excluded from clinical TB research trials. However, many of the AEs often associated with MDR/RR-TB treatment, as outlined above (e.g. anaemia, peripheral neuropathy, nausea and vomiting), may be masked or exacerbated by physiological changes and common symptoms of pregnancy. Women who are pregnant or breastfeeding should continue to be monitored for the same AEs at least as frequently as non-pregnant patients receiving the same treatment *(8)*.

Common drug–drug interactions associated with DR-TB treatment

Drug–drug interactions (DDIs) are common with many of the medications used in MDR-TB regimens, especially those involving bedaquiline. For each possible DDI, if the clinician determines that the potential benefits outweigh the risks (considering alternative treatment options), treatment may proceed with caution. Details of interactions for individual drugs used in all WHO-recommended TB regimens are provided in **Annex 1**.

Vigilance or, preferably, drug substitution should be considered when certain medications are prescribed concurrently with a DR-TB regimen; for example:

- TB treatments and antiretroviral therapy (ART) can have DDIs and overlapping toxicities, including these common ones:
  - zidovudine and linezolid can lead to an increased risk of myelosuppression;
  - boosted protease inhibitors can elevate bedaquiline levels;
  - efavirenz can induce the metabolism of bedaquiline and thus lower bedaquiline concentrations (hence, alternative ART should be considered for patients who are prescribed efavirenz);
- linezolid is known to be associated with serotonin syndrome; therefore, caution should be taken with using other serotonergic drugs (e.g. sertraline and fluoxetine);
- concomitant drugs that prolong QT interval should be avoided if possible – such drugs require extra vigilance and monitoring with electrocardiography (ECG) if prescribed with bedaquiline and moxifloxacin; for example:
  - ondansetron, methadone, amitriptyline, clarithromycin, and neuroleptics-phenothiazines (e.g. thioridazine, haloperidol, chlorpromazine, trifluoperazine, pericycline, prochlorperazine, fluphenazine, sertindole and pimozide);
  - quinoline antimalarial drugs (e.g. halofantrine, chloroquine, hydroxychloroquine and quinacrine);
  - anti-arrhythmic drugs (e.g. quinidine, procainamide, encainide, disopyramide, amiodarone, flecainide and sotalol);
- CYP3A4 inhibitors and CYP3A4 inducers can interact with bedaquiline:

  - CYP3A4 inhibitors include the azole antifungal medications (ketoconazole, voriconazole and itraconazole), ketolides, such as telithromycin, and macrolide antibiotics other than azithromycin; in general, the azole antifungals can safely be used for less than 2 weeks, whereas fluconazole can potentially be used for more than 2 weeks;
  - CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, St John's wort (*Hypericum perforatum*), rifamycins and glucocorticoids;
- drugs inducing myelosuppression (e.g. azathioprine, cytotoxic agents and zidovudine) should be used with caution; and
- DDIs between DR-TB and drugs for hepatitis C are detailed in Chapter 2, Section 8.4.

A2.3 Monitoring AEs of interest associated with DR-TB treatment

Treatment monitoring schedules must include relevant clinical and laboratory parameters to detect, manage and prevent common and serious AEs in a timely manner (**Table A2.2**). Many AEs are easy to recognize (e.g. skin hyperpigmentation due to clofazimine), and most adults, adolescents and older children can largely describe the symptoms they experience. However, some patients or caregivers may be reticent about reporting symptoms or might only remember them when asked about specific problems; thus, it is important to have a systematic approach when screening for potential AEs. Safety monitoring requirements will vary depending on the chosen treatment regimen, because some parameters apply to specific drugs (e.g. complete blood counts [CBCs] during exposure to linezolid), whereas others (e.g. liver function tests [LFTs]) measure AEs associated with a wider variety of anti-TB drugs. The frequency of evaluation of specific safety monitoring parameters for various treatment regimens is outlined in **Table A2.2**. Further information on key monitoring parameters is given below.

Brief peripheral neuropathy screen

All patients should be assessed every 2 weeks for a month, then monthly, for symptoms suggesting neuropathic pain, using the brief peripheral neuropathy screen (BPNS), which allows for subjective grading of the symptoms. Although neuropathic pain is difficult to define and varies from one person to another, it is often described as "burning", "electric", "tingling" and "shooting" in nature, and can vary from a constant pain to intermittent sharp, shooting pains. As described, the pain is most often present without associated stimulation, but it can be exacerbated by stimuli. The BPNS is a non-invasive, fast, cheap, easy-to-do diagnostic clinical tool that was developed by the AIDS Clinical Trials Group *(9)*.

Other common causes of peripheral neuropathy include alcohol use, certain other medications, HIV infection, pregnancy and diabetes, and these causes should also be assessed in any patient found to have peripheral neuropathy while receiving DR-TB treatment.

For a definitive diagnosis of peripheral neuropathy, patients with symptoms should be examined, including deep tendon ankle reflexes, light touch perception with a cotton swab or monofilament, or vibration testing with a 128-Hz tuning fork.

Haematological assessment

Because of the risk of myelosuppression associated with even relatively short exposures to linezolid, pretreatment assessment of haemoglobin (Hb), neutrophil and platelet levels is crucial for patients considering treatment with a linezolid-containing regimen. Severe anaemia in patients with TB is a significant risk factor for poor treatment outcomes *(10)*, and patients with a low baseline Hb level may be at higher risk of severe linezolid-induced haematological toxicity *(11)*. Linezolid should be administered with caution to patients with a pretreatment serum Hb level below 80 g/L that cannot be rapidly corrected (i.e. with a blood transfusion) before starting DR-TB treatment. Similarly, owing to the

morbidity associated with severe neutropenia and thrombocytopenia, treatment with linezolid should be administered with caution to patients with neutrophil levels below 0.75 × 10^9/L or platelet levels below 50 × 10^9/L before starting treatment. Owing to the high risk of anaemia posed by linezolid, even among people with normal blood counts before starting treatment, Hb level must be checked every 2 weeks at least for the first month, then monthly for the duration of linezolid exposure. CBCs should be performed more often if clinically indicated (i.e. if there are signs and symptoms of myelosuppression, particularly if levels of Hb, neutrophils or platelets were relatively low at the start of treatment).

Other causes of anaemia (e.g. iron deficiency, other nutritional deficiencies or occult gastrointestinal bleeding) should be considered and appropriately managed, although these are less likely to occur in the middle of treatment, especially if the patient's condition is improving. Additional work-up and management of anaemia involve the following:

- review of CBC, including the red blood cell (RBC) indices, white cell differential counts and platelet levels, and other investigations to determine possible etiology of anaemia;
- review of other medications that could possibly be associated with anaemia; and
- assessment for other infections, including parasites and viral pathogens (i.e. parvovirus).

The RBC indices, including the mean corpuscular volume of the CBC, can be used to assess whether the anaemia is microcytic or macrocytic. Microcytic anaemia is often caused by iron deficiency, for which iron supplements are indicated; macrocytic anaemia is usually caused by vitamin B12 or folate deficiency.

Visual acuity and colour vision tests

The first sign of optic neuritis is usually the loss of red–green colour distinction. This is best tested using the Ishihara test for colour vision *(12)*. Optic neuritis can also manifest as decreased visual acuity, which can be tested using the Snellen chart *(13)*. These tests should be undertaken every 2 weeks for 1 month after starting a linezolid-containing regimen, then monthly until the end of treatment. Results should be compared with the baseline or previous test results to establish a change in colour vision or visual acuity.

LFTs

It is advisable to screen for viral hepatitis B and C in patients who are due to receive regimens with multiple hepatotoxic drugs (e.g. BPaLM or BPaL [bedaquiline, pretomanid and linezolid]), because these patients require monthly liver function monitoring throughout treatment. All patients starting treatment for DR-TB must have serum liver enzyme levels (at least alanine aminotransferase [ALT]) checked at baseline, and liver enzyme tests should be repeated for all patients who experience signs and symptoms of hepatotoxicity through treatment.

QT interval monitoring

The absolute QT interval is measured from the onset of the Q-wave to the termination of the T-wave. Either limb lead II or precordial lead V5 is best for measuring the QT interval; alternative leads may be used if T-wave termination is poorly visualized. The normal QT interval changes physiologically (e.g. depending on time of day, level of activity and emotional state). Several formulae may be used to correct the absolute QT interval for an individual's heart rate *(11)*. The Fridericia correction (QTcF) measures the QT interval in milliseconds divided by the cubed root of the RR (interval between two consecutive R waves) in seconds; a corrected QT interval between 450 ms and 500 ms is considered borderline, and a QTcF of more than 500 ms in adults or more than 450 ms in children warrants closer ECG monitoring. A QTcF of more than 500 ms would be an indication for interrupting QT-prolonging drugs (see **Table A2.3**).

Other factors that may trigger a requirement for closer ECG monitoring are symptoms of palpitations, dizziness, chest pain and syncope; however, these are not in themselves reliable indicators of increased risk of torsades de pointes (TdP) – a specific type of abnormal heart rhythm that can lead to sudden death. A corrected QT interval of more than 500 ms is considered dangerous and increases the risk of TdP with possible arrhythmic death. This level of QT prolongation typically occurs when multiple QT-prolonging drugs are used, particularly in individuals with additional risk factors, such as cardiac disease, hypokalaemia, hypomagnesaemia, hypocalcaemia or hypothyroidism.

Neuropsychiatric assessment

Several TB medications (e.g. cycloserine or terizidone, delamanid and high-dose isoniazid) are known to be associated with neuropsychiatric AEs, whereas other TB medications (e.g. clofazimine) have side-effects that may be socially unacceptable or stigmatizing in some settings. Furthermore, some patients may experience depression, anxiety or even psychosis during DR-TB treatment that is not directly related to specific drug AEs but may be due to underlying psychiatric disorders or other psychosocial stressors and catastrophic costs associated with the diagnosis and treatment of DR-TB. Additionally, the consumption of alcohol or other psychotropic substances can complicate the neuropsychiatric presentation. Screening for unsafe substance use should be performed using a validated tool, such as the *ASSIST-linked brief intervention for hazardous and harmful substance use (14)*. The psychosocial aspects of DR-TB must not be ignored because they may have a considerable impact on patients' mental health and adherence to treatment.

The nine-question Patient Health Questionnaire (PHQ-9) is a validated tool that was developed to assess the degree of depression in an individual *(15)*. Ideally, PHQ-9 is done at baseline and then monthly, especially when cycloserine or high-dose isoniazid (or both) are part of the DR-TB regimen, or ad hoc when the patient is showing signs of depression.

Delamanid is reported to cause neuropsychiatric adverse effects, particularly in children *(16)*. The most frequent are sleep disturbance and vivid nightmares, but insomnia, hallucinations and others have been reported. It is important to provide anticipatory guidance to patients and their families, so they can monitor for these adverse effects and follow-up with their health care providers if these occur. Most of these events are mild and self-limited, resolving without any intervention or change to the delamanid. If the events are not disruptive to the child or family, then continuing delamanid and monitoring is appropriate. If they are impacting the child and family more substantially, are persistent, or are more severe, then it is reasonable to temporarily hold the delamanid and observe. The events appear to resolve quickly after discontinuation. For mild-to-moderate events, re-introduction of delamanid after resolution can be done; often there will not be recurrence. If the event was more severe initially or recurs after reintroduction and remains disturbing to the child or family, then the delamanid should be permanently discontinued, although this is not commonly needed. It is important to consider other causes of these events as well, including central nervous system TB or other TB drugs like cycloserine or terizidone.

Signal of hallucinations in children treated with delamanid was reported and evaluated by the WHO advisory committee on safety of medicinal products, which suggested that the evidence of hallucinations in children is uncertain as the potential of misclassifying 'night terrors' and 'nightmares', which are common in child development, as 'hallucinations' *(17)*. Given that the product label of delamanid has been modified by the market authorization holder to include hallucinations as an adverse event, further monitoring and assessment are required.

Renal assessment

It is important to assess kidney function at baseline to determine whether a patient requires renal dosing of selected anti-TB drugs (e.g. levofloxacin, cycloserine or terizidone, pyrazinamide, ethambutol, carbapenems, para-aminosalicylic acid and amikacin), if used. Patients with a history of renal disease

(including comorbidities such as HIV and diabetes), advanced age or any renal symptoms, or with a low baseline glomerular filtration rate, should be monitored monthly or more often as necessary during treatment. If baseline renal function is normal, re-assessment of renal function during DR-TB treatment is only required if clinically indicated or if the patient starts taking nephrotoxic drugs, such as tenofovir.

Thyroid function assessment

Para-aminosalicylic acid or ethionamide/prothionamide (or both) can cause hypothyroidism, which may be suspected during clinical assessment and should be confirmed by testing levels of serum thyroid-stimulating hormone (TSH). Goitres can develop owing to the toxic drug effects, but symptoms can often be subtle and may be masked by TB symptoms or other AEs; hence, it is recommended that patients be screened for hypothyroidism (via serum TSH levels) every 3 months, or sooner if symptoms arise, for the duration of exposure to either of these drugs. Dosing of thyroid replacement therapy should be guided by serum TSH levels every month until a stable dose of the thyroid replacement hormone is reached, at which point 3-monthly monitoring may resume. In areas where iodine deficiency goitres are endemic, treatment with iodine is indicated, in addition to assessment and treatment for hypothyroidism.

Table A2.2. Recommended schedule of baseline, routine and post-treatment monitoring examinations and tests for patients receiving DR-TB treatment (applicable to all recommended MDR/RR-TB treatment regimens)

Examination	Baseline	2nd week from start of treatment (for Lzd-containing regimens)	Monthly	End of treatment	6 and 12 months after treatment
Clinical evaluation by physician, including weight and body mass index	✓	✓	✓	✓	✓
Bacteriological tests					
Smear microscopy	✓		✓	✓	✓
TB culture	✓		✓	✓	✓
Drug-susceptibility testing: Xpert® MTB/XDR or first- and second-line LPA	✓		If culture remains positive at Month 4 of treatment, in cases of culture reversion, or in cases of culture positivity during post-treatment follow-up		
Phenotypic DST	✓				

Examination	Baseline	2nd week from start of treatment (for Lzd-containing regimens)	Monthly	End of treatment	6 and 12 months after treatment
Diagnostic tests					
Chest X-ray (conduct every 6 months while receiving treatment)	✓			✓	✓
Electrocardiogram (if regimen contains Bdq, Dlm, Pa, Mfx, Lfx or Cfz)	✓		For patients with pre-existing cardiac disease and with any symptoms (e.g. palpitations, dizziness or syncope)	✓	
Visual acuity and colour vision tests (if regimen contains Lzd or E)	✓	✓	✓	✓	
Brief peripheral neuropathy screen (if regimen contains Lzd, H, Cs, Trd, Lfx, Mfx or Am)	✓	✓	✓	✓	
Mental health screening (PHQ-9)	✓		✓ (if regimen contains Cs or Hh)	✓	
Blood chemistry, haematological and immunological tests					
ALT and AST (if regimen contains Z, H, Pa, Bdq, Eto/Pto, Cs/ Trd or PAS)	✓		✓	✓	
CBC with platelet count (if regimen contains Lzd, Mpm, H or Pa)	✓	✓	✓	✓	
Fasting blood sugar and/or glycosylated haemoglobin	✓				

Examination	Baseline	2nd week from start of treatment (for Lzd-containing regimens)	Monthly	End of treatment	6 and 12 months after treatment
Serum potassium	✓				
Creatinine	✓		✓ (if regimen contains Am or S)		
TSH	✓ (if regimen contains Pto/Eto or PAS; then 3-monthly)				
Albumin (if regimen contains Dlm)	✓				
Pregnancy test (for women of reproductive age)	✓				
HIV screening	✓				
CD4 count (latest test for PLHIV)	✓				
HBsAg and anti-HCV	✓				

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBC: complete blood count; DR-TB: drug-resistant TB; DST: drug-susceptibility testing; HbsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LPA: line probe assay; MDR/RR-TB: multidrug-resistant and rifampicin-resistant TB; PHQ-9: nine-question Patient Health Questionnaire; PLHIV: people living with HIV; TB: tuberculosis; TSH: thyroid-stimulating hormone.

Drugs: Am: amikacin; Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Eto: ethionamide; H: isoniazid; Hh: high-dose isoniazid; Lfx: levofloxacin; Lzd: linezolid; Mfx: moxifloxacin; Mpm: meropenem; Pa: pretomanid; PAS: para-aminosalicylic acid; Pto: prothionamide; S: streptomycin; Trd: terizidone; Z: pyrazinamide.

A2.4 Management of AEs associated with DR-TB treatment

Most patients receiving DR-TB treatment experience one or more AEs associated with the TB medications. Therefore, ongoing education of patients and their caregivers or family members is crucial, to empower patients to anticipate and prepare for common AEs, and to be aware of signs and symptoms that may be serious and require urgent medical attention. Too much information at the start of treatment, especially just after receiving the diagnosis of DR-TB (a potentially life-threatening disease that the patient may not have heard of), can be overwhelming for the patient; therefore, information should be shared with as much detail and as often as the patient can cope with, in ways

that the patient can understand. Some people may request information leaflets to read in their own time, or referral to relevant websites and other sources of accurate information; others may prefer to receive the information through individual counselling sessions or patient support groups, where they can also learn helpful coping strategies.

Acknowledgement of a patient's experiences and reassurance by the health care provider is sometimes all that the patient needs to cope with the AEs associated with treatment, particularly if the patient understands the importance of completing a full course of effective treatment. Patients who feel negated, belittled or unheard may decide to stop taking their TB medications, particularly if the AEs outweigh the perceived benefit of their treatment (e.g. as they start feeling better and TB symptoms resolve). Some AEs may disappear or diminish over time, even without intervention, and patients may be able to continue taking their medication if they are sufficiently motivated to tolerate the non-serious AEs. Some AEs (e.g. skin hyperpigmentation) may be completely unacceptable to some patients, despite health care providers not considering the AE to be clinically serious enough to withhold the responsible agent from an otherwise effective treatment regimen. Additional medications to treat AEs can add to patients' already heavy pill burden, and these ancillary medications come with their own side-effects. Clinicians must take patients' preferences into account and, wherever possible, involve patients or their caregivers in decisions about whether to treat AEs with additional medications and when to withdraw TB medications in response to AEs, particularly if this might compromise the efficacy of their treatment regimen.

AE management strategies

Table A2.3 summarizes the common AEs associated with DR-TB treatment, the TB medications likely to be responsible for those AEs, suggested management strategies and other potentially useful information. In general, clinicians should avoid lowering doses of TB medications to reduce the incidence or severity of AEs. It may be possible to split doses or change the frequency of some drugs; however, this needs to be considered carefully for regimens based on BPaL. In the case of linezolid specifically, dose reduction, interruption and discontinuation, if absolutely necessary, may be done at certain points in the treatment course (see **Chapter 2, Section 4** for further details). It is sometimes helpful to change the timing of administration of certain drugs, to help patients to cope with certain AEs, especially in relation to food intake and sleeping. Weight-banded dosing guidelines may allow for some medications (e.g. terizidone or cycloserine, ethionamide/prothionamide, pyrazinamide and ethambutol) to be administered at the lower end of the recommended dose range for people in a specific weight band. Pharmacokinetic studies of TB medications are helpful in determining an acceptable dosing range and frequency that balance safety and tolerability without compromising efficacy.

Overlapping toxicities between TB medications and ART drugs must be considered for patients who are coinfected with HIV; for example, efavirenz, as a CYP4A inducer, could lower levels of bedaquiline and pretomanid, and thus should not be given together with these anti-TB drugs. Also, zidovudine should be avoided in patients receiving linezolid because of the increased risk of myelosuppression.

Table A2.3. AEs, suspected agents and management strategies

AE	Suspected agent	Suggested management strategies	Comments
Allergic reaction, anaphylaxis and rashes	**Any drug**	• For severe rashes (i.e. peeling skin, mucous membrane involvement and the patient being systemically unwell) and serious allergic reactions, stop all therapy pending resolution of reaction. Manage anaphylaxis as per standard emergency protocols. • Eliminate other potential causes of allergic skin reactions (e.g. scabies and other environmental agents). • For non-severe skin reactions, continue TB medications and manage symptoms with relevant ancillary agents: – antihistamines and calamine lotion; – hydrocortisone cream (localized rash); – oral prednisone (low dose, short course); – sunscreen (to prevent phototoxicity); – moisturizing lotion for dry skin (common with Cfz, and in patients with diabetes); – topical benzoyl peroxide for acneiform rashes. • After resolution of severe adverse cutaneous drug reactions, reintroduce drugs one at a time, with the drug most likely to have caused the reaction being given last. Where applicable, consider avoiding or substituting drugs that are highly likely to have caused a severe reaction – this may necessitate a change in regimen if a standardized regimen has been used. • Permanently withdraw any drug confirmed to be the cause of a serious drug reaction, and counsel the patient about avoiding the drug in future.	• History of previous drug allergies should be carefully reviewed and noted on the treatment card. • A flushing reaction to Z is usually mild and resolves with time; it can be managed with antihistamines. • Hot flushes, itching and palpitations can be caused by interaction of tyramine-containing foods (e.g. cheese and red wine) with H or Lzd – counsel the patient about avoiding these foods while taking these drugs. • Although rarely reported, patients (particularly adolescents) receiving MDR/RR-TB treatment regimens containing novel or repurposed agents sometimes experience a non-serious acneiform papular rash. Topical benzoyl peroxide may be helpful, but this rash eventually resolves without intervention. • Any drugs can cause urticaria (hives). Reintroduce each of the drugs one at a time to identify the causative agent. Desensitization can be attempted if necessary. • Some antihistamines (e.g. diphenhydramine) are associated with QT prolongation; this risk must be balanced with the benefits to the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required. • Do not consider rechallenging any drugs that resulted in anaphylaxis or Stevens–Johnson syndrome.

AE	Suspected agent	Suggested management strategies	Comments
Alopecia	**H, Eto/Pto**	• Reassure the patient that hair loss related to TB medications usually resolves after completing treatment. • It may be helpful to educate the patient on other causes of hair loss because these could also be investigated and addressed.	• Alopecia occurs more often after prolonged exposure (>18 months) to TB medications. • Other possible causes of hair loss include childbirth, stressful life events, use of abrasive hair products, polycystic ovary syndrome, psoriasis, thyroid disease, mineral deficiencies, hereditary hair loss and ageing.
Arthritis and arthralgia	**Z, Bdq, Lfx, Mfx, Amx/ Clv**	• Initiate therapy with an NSAID (indomethacin or ibuprofen) for symptomatic relief. • Rule out other causes of arthralgia (e.g. trauma or injury). • If possible, decrease the dose of the suspected agent (probably Z) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. Dosing of drugs with standard fixed-dosing recommendations should not be altered. • In severe cases where there is no abatement of symptoms, withdraw the suspected agent or agents and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen has been used.	• Symptoms of drug-induced arthralgia often diminish over time, even without intervention. • If a joint is acutely swollen, red and warm, consider aspiration for diagnosis of gout, infection, autoimmune diseases and other causes. • Uric acid levels may be elevated in patients taking Z. There is little evidence to support the addition of allopurinol, although it may be helpful if gout is confirmed.
Candidiasis	**Lfx, Mfx**	• Common types of yeast infection are usually easily treated with a topical antifungal agent or a short course of an oral systemic medication. • Presentation among individuals with immunosuppression can be severe and may require treatment with more potent agents. Patients presenting with severe symptoms should be retested for HIV.	• The most common types of yeast infection associated with antibacterial treatment include vulvovaginal and penile candidiasis, oral thrush and cutaneous candidiasis. • Other common risk factors for yeast infection include pregnancy and uncontrolled diabetes.

AE	Suspected agent	Suggested management strategies	Comments
CNS toxicity (dizziness, insomnia and headaches)	**Lfx, Mfx, Dlm, Am, Trd/Cs, Mpm, Bdq, Eto/Pto, H**	• Consider other causes of CNS symptoms (e.g. arrhythmias, H2 receptor antagonists, local anaesthetics, cancer, recreational substance use, stress and hyperventilation) and manage appropriately. • Rule out more serious causes of headaches (e.g. raised intracranial pressure, pre-eclampsia, meningitis and other CNS infections) and investigate thoroughly in patients coinfected with HIV. • Manage drug-related headaches with analgesic agents (e.g. paracetamol or ibuprofen) and encourage good hydration. Consider low-dose TCAs for refractory headaches, with consideration of their QT-prolonging effect. • Administer medications at a different time of day (e.g. before sleeping or early in the morning) to reduce the impact of specific CNS symptoms on daily activities. • For other CNS symptoms, consider decreasing the dose of the suspected agent (aside from Bdq and Dlm) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. Also consider starting Cs or PAS (or both) at a low dose and gradually building up to the full dose over 2 weeks. • In severe cases where there is no abatement of symptoms, withdraw the suspected agent or agents and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen has been used.	• Dizziness and syncope can be symptoms of QT prolongation; closer ECG monitoring may be indicated. • Drug-related headaches and dizziness are often self-limiting and ease over time. • Pyridoxine (vitamin B6) can help to prevent neurotoxicity during exposure to Trd/Cs and H. • High doses of TCAs are associated with QT prolongation; this risk must be balanced with the benefits to the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required. • Fullness and intermittent ringing in the ears are early symptoms of vestibular toxicity associated with an injectable agent, and symptoms generally do not resolve on withholding medications; in such cases, counsel patients to report these symptoms early, and withdraw the drug. • Dlm has been associated with insomnia and sleep disturbance due to nightmares – this may become intolerable and require drug withdrawal, particularly for children.

AE	Suspected agent	Suggested management strategies	Comments
Depression and suicidal ideation	**Trd/Cs, Dlm, H, Eto/Pto, Lfx, Mfx**	• Acknowledge and assess the patient's psychological and socioeconomic circumstances, emotional issues and level of control of other chronic conditions. Refer patients to available services for counselling and social support. • Screen patients for substance use and other mental illness using validated screening tools (e.g. PHQ-9 for depression) and refer them to relevant services for intervention and support. • In cases where depressive symptoms are affecting a patient's adherence to treatment and other activities of daily living, antidepressant therapy may be indicated. SSRIs and TCAs may be considered, but DDIs with these are common. • If possible, decrease the dose of the suspected agent (e.g. Cs) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. • In severe cases with no abatement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen has been used. • Always screen patients with depressive symptoms for symptoms and signs of suicidal ideation – if indicated, withdraw all suspected agents and hospitalize the patient with 24-hour surveillance until stable.	• Although depressive symptoms may be expected after a diagnosis of MDR/RR-TB, and some TB medications may be associated with psychiatric AEs, do not underestimate the contribution of underlying psychological, emotional and socioeconomic conditions and chronic illness as contributing factors to depression. Some patients may require medical intervention for depression even after completing treatment for MDR/RR-TB, and they should be referred and followed up appropriately. • A history of previous depressive illness is not a contraindication to the use of these agents, but this might increase the likelihood of depression developing during MDR/RR-TB treatment. If a patient has significant depressive symptoms at the start of treatment, avoid the use of Cs and Dlm, if possible. • SSRIs and TCAs are associated with QT prolongation; this risk must be balanced with the benefits to the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required.

AE	Suspected agent	Suggested management strategies	Comments
Diarrhoea and flatulence	**PAS, Eto/ Pto, Mpm, Amx/Clv, Lzd**	• Counsel patients that some degree of loose stools and flatulence is inevitable with these medications, but that these symptoms are likely to resolve over time without having to withhold medication. • Encourage sufficient fluid intake. • Administer the total daily dose of PAS only once a day, if tolerated. • Treat persistent uncomplicated diarrhoea (i.e. no blood in stool and no fever) with loperamide. • If diarrhoea is severe, check serum electrolyte levels and dehydration status and manage accordingly. For children with acute diarrhoea, supplement zinc (20 mg per day) for 10–14 days to improve water and electrolyte absorption. • In severe cases with no abatement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required.	• Fever and diarrhoea or blood in stool suggest causes other than simple side-effects of TB medications: – Pseudomembranous colitis related to broad-spectrum antibiotics (including FQs) is serious and can be life threatening. Warning signs include fever, bloody diarrhoea, intense abdominal pain and increased white blood cells. – Infection with parasites and common waterborne pathogens should be investigated and treated. – Consider lactose intolerance. • Loperamide must not be used for children aged below 2 years.

AE	Suspected agent	Suggested management strategies	Comments
Electrolyte disturbances	**Am**	• Consider other causes of electrolyte imbalance (e.g. vomiting, diarrhoea, burns, diabetes and use of insulin, cardiac failure and use of diuretics) and manage accordingly. • Assess renal function and check levels of other electrolytes (i.e. potassium, magnesium, calcium and phosphate) if possible. • Rehydrate and replace electrolytes as needed – if unable to check magnesium levels, consider magnesium supplementation for patients with refractory hypokalaemia. • Amiloride or spironolactone may help to reduce potassium and magnesium wasting. • Patients with severe hypokalaemia (potassium level <2.5 mmol/L) should be hospitalized for IV electrolyte replacement and cardiac monitoring.	• Clinical symptoms (e.g. muscle weakness and cramps, dizziness, nausea and impaired concentration) may not be evident until the potassium level is <3 mmol/L. • Hypokalaemia, hypomagnesaemia and hypocalcaemia can prolong the QT interval; closer ECG monitoring is warranted until electrolyte levels are corrected. • Oral potassium replacements may cause nausea and vomiting, and oral magnesium may cause diarrhoea.

AE	Suspected agent	Suggested management strategies	Comments
Gastritis and abdominal pain	**Eto/Pto, PAS, Cfz, Lfx, Mfx, H, E, Z, Mpm**	• Abdominal pain may be associated with serious AEs such as pancreatitis, lactic acidosis and hepatitis. If any of these conditions is suspected, the most likely causative agent or agents should be withheld while awaiting further investigations and appropriate management. • If symptoms are consistent with gastritis (e.g. epigastric burning or discomfort, sour taste in mouth associated with reflux), initiate medical therapy with H2 blockers or proton pump inhibitors. Avoid the use of antacids if possible, because they reduce absorption of FQs and, to a lesser extent, H and E. • If possible, decrease the dose of the suspected agent to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. • In severe cases with no abatement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if Cfz or an FQ is withdrawn.	• Consider other causes of gastritis, such as NSAIDs or *Helicobacter pylori* infection, and manage accordingly. • Gastritis must be acknowledged and managed appropriately to provide relief to patients and facilitate their adherence to TB treatment. • Proton-pump inhibitors can induce hypomagnesaemia and lead to QT prolongation; this risk must be balanced with the benefits to the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required. • If antacids must be used, time their administration to avoid interference with TB medications (e.g. take antacid 2 hours before or 3 hours after TB medications). • Gastritis is common during pregnancy, but pregnant patients with persistent or severe abdominal pain must be investigated for other non-drug-related causes. • Severe abdominal distress has been reported with the use of Cfz, and the drug should be withdrawn if it is considered to be the most likely cause.
Gynaecomastia	**Eto/Pto, H**	• Consider other causes (e.g. obesity, older age, puberty in boys, use of recreational substances and other drugs) and educate the patient on possible causes. • Reassure the patient that changes in breast tissue that are related to TB medications are temporary and that the tissue will return to normal after completing treatment.	• Other drugs that can cause gynaecomastia include spironolactone, cimetidine, ketoconazole, risperidone, omeprazole and efavirenz.

AE	Suspected agent	Suggested management strategies	Comments
Hepatitis	**Z, H, Pa, Bdq, Mpm, Amx/Clv, Eto/Pto, Cfz, Trd/Cs, PAS**	• Stop all drugs if liver enzyme levels are >5 times the upper limit of the normal range (regardless of symptoms), or if they are >3 times the upper limit and combined with symptoms and signs of drug-induced liver injury. • Investigate and treat other potential causes of hepatitis (e.g. viral hepatitis, alcohol-induced hepatitis and use of other hepatotoxic drugs). • Wait for liver enzyme levels to return to <3 times the upper limit of normal. Reintroduce three of the least hepatotoxic TB drugs first (e.g. Lzd, Dlm and an FQ). All three drugs can be started together to provide a backbone regimen, if applicable. • Introduce potentially hepatotoxic drugs one by one, every 5–7 days, while monitoring liver enzyme levels to identify the responsible drug. • Withdraw the most likely causative agent – depending what this is, withdrawal of the drug may necessitate a change in treatment regimen.	• Symptoms and signs of liver injury include nausea, vomiting, fatigue, malaise, pruritus, fever, right upper quadrant pain, tender liver and jaundice. • Hepatocellular drug-induced liver injury with jaundice (and raised total bilirubin levels) indicates a serious reaction (Hy's law) and presents a high risk of acute liver failure. • Viral serological testing should be carried out to investigate for hepatitis A, B and C. • A history of previous drug-related hepatitis may suggest a likely causative agent or agents – counsel the patient and document in their file that these drugs must be avoided in future treatment. • Patients with alcohol or substance use problems may benefit from additional psychosocial intervention and adherence support. • Do not rechallenge with Z after a drug-induced liver injury.

AE	Suspected agent	Suggested management strategies	Comments
Hypothyroidism	**Eto/Pto, PAS**	• Exclude other causes (e.g. use of lithium or amiodarone, previous radioiodine therapy, pregnancy-associated thyroid dysfunction and Hashimoto's disease). • Consider thyroxine supplementation if the TSH level is >5 mIU/L and free T4 level is decreased or the patient has symptoms of clinical hypothyroidism. • If the TSH level is >10 mIU/L, start levothyroxine at 50 mcg daily (start at a lower dose for older patients and those with significant cardiovascular disease). • Monitor TSH monthly and increase the dose by 12.5–25 mcg until the TSH level normalizes. • Continue levothyroxine supplementation for the duration of exposure to the causative agent.	• Symptoms of hypothyroidism include fatigue, drowsiness, cold intolerance, dry skin, coarse hair, constipation, depression and inability to concentrate. These can be difficult to distinguish from TB symptoms and drug side-effects; hence, routine TSH monitoring is recommended for patients receiving PAS or Eto/Pto. • Hypothyroidism can lead to QT prolongation; these patients may require closer ECG monitoring, depending on their exposure to QT-prolonging drugs. • The combination of PAS and Eto/Pto increases the likelihood of hypothyroidism, but it is completely reversible upon discontinuation of these drugs.
Lactic acidosis	**Lzd, H**	• Suspect lactic acidosis in patients presenting in shock or acutely ill while being treated with Lzd or H. • Check electrolyte levels and measure serum lactate level and pH if the anion gap is >12 mmol/L, or if there are other reasons to suspect lactic acidosis. • Withhold Lzd and H, and do not rechallenge if lactic acidosis occurs.	• Clinical signs of lactic acidosis may include severe hypotension, altered mental state, tachypnoea and oliguria, abdominal pain, nausea and vomiting. • The calculated anion gap = sodium – (chloride + bicarbonate).

AE	Suspected agent	Suggested management strategies	Comments
Metallic taste	**Eto/Pto, H, Lfx, Mfx**	• Consider other causes (e.g. pregnancy, upper respiratory infections, underlying medical conditions and use of other drugs) and educate the patient on possible reasons for the change in their taste. • Advise the patient that sucking hard candy or chewing gum can be helpful. • Reassure the patient that changes in taste that are related to TB medications will return to normal after completing treatment.	• Other drugs leading to metallic taste include metformin, lithium and phenytoin. • Underlying conditions that can cause metallic taste include diabetes, zinc deficiency and Crohn's disease.

AE	Suspected agent	Suggested management strategies	Comments
Myelosuppression	**Lzd, Mpm, H**	• Do not initiate or continue Lzd when the patient's serum haemoglobin level is <80 g/L, neutrophil count is $<0.75 \times 10^9$/L or platelet count is $<150 \times 10^9$/L. Do not continue treatment with Lzd when serum haemoglobin <8 g/dL, neutrophils $<0.75 \times 10^9$/L or platelets $<50 \times 10^9$/L (i.e. <50 000/mm3). Referral for hospitalization and blood transfusion may be required in these cases. • Investigate other causes of anaemia (e.g. TB and other chronic diseases, nutritional deficiencies such as iron deficiency, pregnancy and blood loss), neutropaenia (HIV and other viral infections, leukaemia and lymphoma) or thrombocytopenia (pregnancy, other drugs and autoimmune disorders) and manage appropriately. • Lzd may be introduced at the full dose if the haematological parameters improve with blood transfusion at the start of treatment. • Lzd-induced myelosuppression tends to recur with ongoing exposure to Lzd after blood transfusion; Lzd should not be continued long term in these cases. • Wherever possible, avoid dropping the Lzd dose to subtherapeutic levels in response to this AE.	• Lzd-induced myelosuppression usually affects red blood cells, but sometimes it affects only neutrophils or platelets in isolation. • In rare cases, Mpm and H can cause haemolytic anaemia. • Effective TB treatment, including with Lzd, usually leads to improvement of anaemia that is due to chronic disease; initial blood transfusion at the start of treatment may improve haematological parameters enough to allow Lzd to be initiated as part of an effective regimen. Blood transfusions should be undertaken according to local guidelines. Lzd-induced anaemia is reversible, and patients will recover over days to weeks. • During treatment, blood transfusions might also facilitate completion of the recommended duration of Lzd treatment, to avoid substituting with other medications or changing treatment regimens (see the relevant sections on Lzd-containing regimens). • Iron supplements are unlikely to be useful in the acute management of Lzd-induced anaemia unless there is concomitant iron deficiency. • Unless indicated for severe confirmed iron deficiency anaemia, iron supplementation can be delayed until later in TB treatment, when the pill burden and side-effects of ferrous compounds can be better tolerated.

AE	Suspected agent	Suggested management strategies	Comments
Nausea and vomiting	**Eto/Pto, PAS, Amx/Clv, Bdq, Lfx, Mfx, Mpm, H, E, Z, Cfz, Dlm**	• Assess for danger signs (e.g. dehydration, electrolyte disturbances and hepatitis). Initiate rehydration therapy if indicated and correct electrolyte disturbances. Check haemoglobin level and treat patients for bleeding ulcers in those with haematemesis. • Exclude and manage other causes of new-onset nausea and vomiting (e.g. hepatitis, pancreatitis, raised intracranial pressure, pregnancy or pre-eclampsia, and gastroenteritis). • Counsel the patient that these symptoms are common and usually worse at the start of TB treatment, and that they often abate over time without having to withhold medication. • Encourage the patient to try different ways of taking the medication in relation to food and the timing of usual daily activities, such as: – taking Eto/Pto or PAS at a different time of day (e.g. just before going to sleep); – eating a light snack before or after taking medication, or trying different foods; and – taking Eto/Pto or PAS 2 hours after other TB medications. • Consider antiemetic(s) if nausea and vomiting persist: – metoclopramide – administer 30 minutes before TB medications; or – ondansetron (or promethazine) – administer 30 minutes before TB medications and again 8 hours later; can be used on its own or with metoclopramide, but with caution because of their QT-prolonging effects. • If possible, decrease the dose of the suspected agent to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen.	• Nausea is common in the early weeks of TB treatment; it usually abates with time, although some patients need adjunctive therapy. • Ongoing information, education and peer support may help patients to anticipate and cope with common symptoms. • Absorption of TB medications is often affected by the type and timing of food intake; however, the "ideal" administration of TB medications with or without food may have to be altered if it is not tolerated by the patient. • Monitor renal function and replace electrolytes and fluids, as necessary, in patients with severe persistent vomiting. • Consider temporarily withholding the most likely causative agent and reintroduce it gradually by slowly increasing the dose over 2 weeks. • Ondansetron is a serotonin 5-HT3 receptor antagonist and has strong antiemetic properties. Different antiemetics, even from the same class, may be worth trying for some patients. • Ondansetron can prolong the QT interval; this risk must be balanced with the benefits to the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required. • Patients with "anticipatory nausea and vomiting" may benefit from a small dose of an anxiolytic (e.g. diazepam) 30 minutes before taking TB medications.

AE	Suspected agent	Suggested management strategies	Comments
		• For non-remitting symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen has been used.	• Antihistamines may be useful for nausea associated with CNS or vestibular toxicity.
Nephrotoxicity	**Am**	• Investigate and manage other causes of nephrotoxicity (e.g. NSAIDs, diabetes, other medications, dehydration, congestive cardiac failure and urinary obstruction). • Discontinue the injectable agent and replace it with another effective TB medication if required. • Adjust doses of renally excreted TB medications according to creatinine clearance. • Monitor creatinine and electrolyte levels every 1–2 weeks until they are normal or stabilized.	• A history of diabetes or renal disease is not a contraindication to using Am; however, patients with either or both of these comorbidities may be at increased risk of renal failure after exposure to this injectable agent; renal impairment may be permanent. • Renal dosing of selected TB medications is recommended for patients with creatinine clearance <30 mL/min.
Optic neuritis	**Lzd, E**	• Withhold Lzd and E immediately in patients experiencing symptoms of optic neuritis. • Consider other causes of optic neuritis (e.g. autoimmune conditions, exposure to toxic substances such as methanol, and other bacterial or viral infections). All patients with suspected optic neuritis should be referred to an ophthalmologist for immediate evaluation and management. • Patients with diabetes are at increased risk of optic neuritis. Check their blood sugar levels and control of diabetes. • Do not reintroduce Lzd and E if optic neuritis is confirmed. • Only consider reintroducing Lzd if other DR-TB treatment options are severely limited and optic neuritis has been definitively ruled out.	• Symptoms of optic neuritis include ocular pain, loss of vision, and seeing flashing lights; symptoms are often unilateral. • All patients receiving Lzd and E must be counselled at the start of therapy to recognize the early symptoms of this potentially sight-threatening AE and to seek urgent medical assistance if they occur. • Drug-induced optic neuritis is usually reversible with early cessation of the agent responsible.

AE	Suspected agent	Suggested management strategies	Comments
Ototoxicity (hearing loss, tinnitus and vertigo)	**Am**	• Withdraw the injectable agent if there is new or worsening tinnitus, dizziness, fullness in the ears or evidence of hearing loss; replace it with another effective agent. • Check renal function because nephrotoxicity is also an AE associated with injectable agents, and a reduced creatinine clearance may lead to increased exposure to ototoxic medications, with exacerbation of symptoms. • Vestibular symptoms (e.g. dizziness and nausea) may abate with use of an antihistamine such as meclizine or dimenhydrinate.	• Audiology screening, to detect early changes and high-frequency hearing loss, is essential for patients requiring treatment with the injectable agent. • Aspirin and loop diuretics are also ototoxic and may exacerbate the effects of aminoglycosides.

AE	Suspected agent	Suggested management strategies	Comments
Peripheral neuropathy	**Lzd, H, Trd/Cs, Lfx, Mfx, Am, Amx/Clv, Eto/Pto**	• Manage baseline risk factors – correct and prevent vitamin or nutritional deficiencies, obtain better control of diabetes, and educate the patient about possible causes of peripheral neuropathy. • Lzd-containing regimens should be avoided for patients with Grade 3 or 4 peripheral neuropathies at baseline. • For patients who have H or Trd/Cs included in their treatment regimen, pyridoxine doses of 50 mg for adults (25 mg for children) should be administered for peripheral neuropathy prophylaxis; however, pyridoxine doses must not be increased beyond 100 mg for adults because, paradoxically, this may contribute to worsening peripheral neuropathy symptoms. • Neuropathic pain relief may be achieved with pregabalin, gabapentin, carbamazepine or TCAs *(18)*. • If possible, decrease the dose of the suspected agent (e.g. Trd/Cs) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. • For worsening or non-remitting symptoms, withdraw the suspected agent (e.g. Lzd) or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen has been used. • Linezolid-containing regimens may need to have linezolid dose adjusted downward or stopped early for Grade 1 and 2 peripheral neuropathies.	• The risk of peripheral neuropathy is increased in patients with malnutrition, diabetes, heavy alcohol use, HIV, pregnancy or co-administration of multiple suspected drugs; these conditions are not contraindications to these agents. • H inhibits the metabolic action of vitamin B6, and Trd/Cs increases its renal excretion; therefore, pyridoxine supplementation can protect against drug-induced vitamin B6 deficiency, which leads to peripheral neuropathy. Pyridoxine does not appear to protect against the development of Lzd-induced peripheral neuropathy *(19–21)*. • Peripheral neuropathy can manifest in various ways and be difficult to assess properly, especially in young children – ask about crying at night, pulling at their feet, kicking off bed covers, weakness, clumsiness and changes in gait or balance. • TCAs are associated with QT prolongation; this risk must be balanced with the benefits to the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required.

AE	Suspected agent	Suggested management strategies	Comments
			• Caution should be applied if using pregabalin because its serotonergic action may cause serotonin syndrome. Gabapentin increases serotonin concentrations in the human body. • Carbamazepine is a strong CYP3A4 inducer and should not be used with Bdq (the DDI is likely to lead to subtherapeutic Bdq levels). • Many patients report abatement of symptoms when the responsible agent is withheld; however, drug-induced peripheral neuropathy is common after prolonged drug exposure and may become irreversible (particularly with Lzd). Good communication and joint decision-making with the patient is crucial when considering ongoing treatment with the suspected agent or agents.

AE	Suspected agent	Suggested management strategies	Comments
Psychotic symptoms (hallucinations and delusions)	**Dlm, Trd/Cs, H, Lfx, Mfx**	• Consider other causes of psychotic symptoms (e.g. fever, CNS infections, head injury or trauma, recreational substance use, and psychological and neurological conditions) and manage appropriately. • In severe cases – particularly if the patient is a potential risk to themselves or others – initiate antipsychotic therapy (e.g. haloperidol) and refer the patient for hospitalization. Use haloperidol with caution, as it has a QT-prolonging effect. • Check the patient's renal function because this may lead to reduced excretion of, and increased exposure to, toxic drugs – amended dosing of TB medications may be required. • Increase pyridoxine dosing to the maximum daily dose (100 mg daily for adults) if Trd/Cs or H is used. • If possible, decrease the dose of the suspected agent (e.g. Trd/Cs or H) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. • In severe cases with no abatement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required.	• A prior history of psychotic symptoms or psychiatric disease is not a contraindication to using these drugs, but it may increase the likelihood of psychotic symptoms developing during treatment with these drugs. • Drug-induced psychotic symptoms are generally reversible upon withdrawal of the agent responsible. • Renal dosing of selected TB medications is recommended for patients with creatinine clearance <30 mL/min. • Some patients who experience psychosis can tolerate these drugs along with an antipsychotic agent throughout MDR/RR-TB treatment, but this should only be considered in consultation with a psychiatrist and if treatment options are limited.

AE	Suspected agent	Suggested management strategies	Comments
QT prolongation	**Cfz, Bdq, Mfx, Dlm, Pa, Lfx**	• Obtain a thorough drug history and establish any family history of heart conditions. • Ask about history of cardiac symptoms (i.e. chest pain, palpitations, dizziness or syncope). • Repeat ECG when the patient is relaxed and at rest. • Measure levels of serum electrolytes (potassium, magnesium and calcium) and TSH, and correct these if necessary. • For children weighing <20 kg, consider reducing the dose of Cfz. • For patients with a QTcF >500 ms, perform close ECG monitoring, and withhold all QT-prolonging TB medications and refer for hospitalization if the patient has cardiac symptoms or in some cases e.g. children, even without cardiac symptoms. • QT-prolonging drugs that are essential to the TB regimen may be rechallenged sequentially, with close ECG monitoring, once the QTcF improves to ≤500 ms. • Withdraw the most likely QT-prolonging agent in cases of recurrent or persistent severe QT prolongation – this may necessitate a change in treatment regimen.	• The QT interval is a physiological parameter that fluctuates throughout the day and is affected by emotional state, hunger, anxiety, exercise, endocrine and metabolic disturbances, and exogenous substances. • Patients with prolonged QTc are at risk of developing cardiac arrhythmias such as TdP, which can lead to sudden death – this risk increases substantially with QTcF >500 ms. • Cfz exposure is relatively high in young children receiving recommended doses; in this population, a reduction in dose may reduce the risk of QT prolongation while maintaining drug efficacy. • Many drugs have the potential to prolong the QT interval. • Risk of QT prolongation may be additive with multiple QT-prolonging drugs and additional risk factors (electrolyte and thyroid disturbances). • Patients with QT prolongation are at risk of developing cardiac arrhythmias such as TdP, which can lead to sudden death – this risk increases substantially with a QTcF >500 ms.

AE	Suspected agent	Suggested management strategies	Comments
Seizures	**H, Trd/Cs, Mpm, Lfx, Mfx**	• Consider other causes of seizures (e.g. fever, CNS infections, recreational drug use, hypoglycaemia, hyperglycaemia, head injury and epilepsy) and manage appropriately. • Check the patient's blood sugar and serum electrolyte levels and correct as needed. • Check the patient's renal function because this may lead to reduced excretion of, and increased exposure to, toxic drugs – amended drug dosing may be required. • Increase pyridoxine dosing to the maximum daily dose (100 mg daily for adults) if Trd/Cs or H is used. • Anticonvulsant therapy (e.g. sodium valproate) may be needed to control seizures. • Withhold all suspected agents until seizures have stabilized, then reintroduce TB medications one at a time. Do not reintroduce H.	• Seizures are a common complication of tuberculous meningitis. • Renal dosing of selected TB medications is recommended for patients with creatinine clearance <30 mL/min. • A prior history of seizures is not a contraindication to using these drugs, provided the patient's seizures are under control or the patient is receiving anticonvulsant therapy (or both); however, such patients may still be at increased risk of developing seizures during MDR/RR-TB treatment, and these agents should only be used if treatment options are severely limited. • Phenytoin and carbamazepine are strong CYP3A4 inducers and should not be used with Bdq or Pa (or both), because the DDI is likely to lead to subtherapeutic Bdq or Pa levels.
Skin and scleral hyperpigmentation	**Cfz**	• Some degree of skin hyperpigmentation is inevitable with prolonged use of Cfz, and patients should be informed of this at the start of treatment. • Occasionally, patients experience staining of the whites of their eyes; this may be mistaken for conjunctivitis. • Some patients may also complain of skin rashes and dry, itchy skin. These can be managed conservatively with moisturizing lotions and other topical agents. All will resolve with no need to modify the TB regimen. • Reassure the patient that drug-induced skin and scleral changes are temporary, and their skin and eyes will return to normal after completing treatment with Cfz.	• This AE can be distressing and stigmatizing for some patients (particularly adolescents), and they may require extra psychological counselling and peer support. • This effect is likely to be exacerbated by prolonged sun exposure.

AE	Suspected agent	Suggested management strategies	Comments
Tendonitis or tendon rupture	**Lfx, Mfx**	• Mild to moderate tendonitis or partial tendon tears may be managed conservatively with rest, ice, compression, elevation, immobilization of the affected joint or tendon, and therapy with NSAIDs. • Patients with complete tendon rupture should be referred for surgical assessment and physiotherapy-led rehabilitation. • Unless MDR/RR-TB treatment options for the individual are severely limited, ongoing treatment with FQs should be avoided for patients with tendinopathy.	• Prolonged exposure to FQs (>1 week) increases the risk of tendonitis and tendon rupture. • Tendon rupture associated with FQ use is more common among people with diabetes and people aged over 30 years; men are at higher risk than women. • Patients who participate in sports that involve running, jumping or sudden movements should be counselled about the higher risk of tendon rupture while taking FQs. • Exposure to corticosteroids, both systemic and locally applied, contributes to tendon weakening and increases the risk of tendon rupture.

AE: adverse event; CNS: central nervous system; DDI: drug–drug interaction; ECG: electrocardiography; FQ: fluoroquinolone; H2: histamine type 2; HIV: human immunodeficiency virus; IU: international units; IV: intravenous; MDR/RR-TB: multidrug-resistant and rifampicin-resistant TB; NSAID: non-steroidal anti-inflammatory drug; PHQ-9: nine-question Patient Health Questionnaire; QTcF: corrected QT interval per Fridericia's formula; SSRI: selective serotonin reuptake inhibitor; TB: tuberculosis; TCA: tricyclic antidepressant; TdP: torsades de pointes; TSH: thyroid-stimulating hormone.

Drugs: Am: amikacin; Amx: amoxicillin; Bdq: bedaquiline; Cfz: clofazimine; Clv: clavulanic acid; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Eto: ethionamide; H: isoniazid; Lfx: levofloxacin; Lzd: linezolid; Mfx: moxifloxacin; Mpm: meropenem; Pa: pretomanid; PAS: para-aminosalicylic acid; Pto: prothionamide; Trd: terizidone; Z: pyrazinamide.

Ancillary medications

Clinical management of people receiving treatment for DR-TB often requires the use of ancillary medications to prevent, lessen or eliminate the AEs associated with TB medications. NTPs may choose to make ancillary medications available for health care providers to prescribe to patients free of charge, to reduce the burden of catastrophic costs on patients and their households. **Table A2.4** presents a list of commonly used ancillary medications and their indications for use; this list may be adapted by countries according to best practices in their settings.

Table A2.4. Commonly used ancillary medications for treating AEs associated with TB medications

Indication	Drugs	Notes
Anaemia	Folate, vitamin B12, ferrous compounds and anthelmintics (mebendazole and albendazole)	Deworming medicines may assist in reducing anaemia, particularly in children. Iron supplements are to be given only for anaemia with iron deficiency; caution the patient against injudicious use of such supplements because it can lead to iron overload that can deposit to major organs (e.g. deposition to the liver can lead to cirrhosis).
Bronchospasm	Inhaled beta-2 receptor agonists (e.g. albuterol and salbutamol), inhaled corticosteroids (e.g. beclomethasone), oral steroids (e.g. prednisone and prednisolone) and injectable steroids (e.g. dexamethasone and methylprednisolone)	Spacers are useful to ensure adequate administration of inhaled medications in children and some adults.
Candidiasis (oral, genital or cutaneous)	Topical miconazole, nystatin suspension (mouthwash), clotrimazole lozenges, oral fluconazole, and nystatin, miconazole or clotrimazole creams and suppositories	Azole antifungal drugs inhibit the CYP3A4 pathway and increase exposure to bedaquiline and pretomanid; co-administration should be limited to <2 weeks. Fluconazole is a less potent inhibitor and could be used for longer than 2 weeks, with closer monitoring for AEs associated with bedaquiline.
Cutaneous reactions and itching	Hydrocortisone cream, calamine and caladryl lotions, antihistamines, oral prednisone, sunscreen, moisturizing lotions, and topical benzoyl peroxide	Some antihistamines (e.g. diphenhydramine, but **not** levocetirizine or cetirizine) are associated with QT prolongation.
Depression	SSRIs (e.g. fluoxetine and sertraline) and TCAs (e.g. amitriptyline)	There is a risk of serotonin syndrome with concurrent use of SSRIs and linezolid. TCAs are associated with QT prolongation.
Diarrhoea	Loperamide and zinc supplements	Do not use loperamide in children aged <2 years.

Indication	Drugs	Notes
Electrolyte wasting	Potassium, magnesium and calcium replacement therapy (oral and intravenous formulations), vitamin D supplements, amiloride and spironolactone	Oral potassium and magnesium cause nausea, vomiting and diarrhoea. Vitamin D assists the absorption of calcium.
Gastritis	H2 blockers (e.g. cimetidine), proton pump inhibitors (e.g. lansoprazole) and antacids	Proton pump inhibitors are associated with QT prolongation. Antacids reduce absorption of fluoroquinolones.
Hypothyroidism	Levothyroxine	Monitor TSH monthly and adjust dose until TSH level is stable in normal range.
Insomnia	Sedating antidepressants (e.g. low-dose amitriptyline), antihistamines (e.g. dimenhydrinate) and melatonin	TCAs are associated with QT prolongation.
Nausea and vomiting	Metoclopramide, ondansetron, dimenhydrinate, prochlorperazine, promethazine and benzodiazepines (e.g. diazepam and lorazepam)	Some antiemetics, such as ondansetron (known risk) and metoclopramide (conditional risk), are associated with QT prolongation.
Pain (musculoskeletal, arthralgia and headaches)	Paracetamol/acetaminophen, NSAIDs (e.g. indomethacin and ibuprofen) and codeine	–
Peripheral neuropathy	Pregabalin, gabapentin, amitriptyline and carbamazepine	TCAs are associated with QT prolongation. Carbamazepine induces metabolism of bedaquiline.
Prophylaxis of neuropathic complications of isoniazid and terizidone or cycloserine	Pyridoxine (vitamin B6)	Usual dose is 50 mg daily for adults, 25 mg daily for children aged ≥5 years, and 12.5 mg daily for children aged <5 years. Do not exceed double these doses daily because (paradoxically) doing so may worsen symptoms.
Psychosis	Haloperidol and risperidone	Haloperidol and risperidone may prolong the QT interval.
Systemic hypersensitivity reactions	Antihistamines (e.g. diphenhydramine, chlorpheniramine and dimenhydrinate) and corticosteroids (e.g. prednisone, prednisolone and dexamethasone)	Some antihistamines (e.g. diphenhydramine) are associated with QT prolongation.
Vestibular symptoms	Antihistamines (e.g. meclizine, dimenhydrinate and promethazine)	Some antihistamines are associated with QT prolongation.

AE: adverse event; H2: histamine type 2; NSAID: non-steroidal anti-inflammatory drug; SSRI: selective serotonin reuptake inhibitor; TB: tuberculosis; TCA: tricyclic antidepressant; TSH: thyroid-stimulating hormone.

Management of AEs associated with the BPaLM regimen

Among 109 participants enrolled in the Nix-TB trial who received the BPaL (1200 mg/day) regimen, 57% experienced a Grade 3 or 4 AE and 17% experienced serious AEs. More than 80% of all participants experienced peripheral neuropathy, with most reporting mild or moderate symptoms, and 37% had anaemia *(22)*. Twelve participants (11%) had an elevation in ALT level, and 11 (10%) had an elevation in AST to a level three times higher than the upper limit of normal (ULN); no participants had QT prolongation beyond 480 ms *(22)*. In the ZeNix study, peripheral neuropathy of Grade 3 or lower was reported in 11 of 45 participants (24%) in the group that had received 600 mg of linezolid for 26 weeks. Laboratory-confirmed myelosuppression was reported in one of the 45 participants (2%) who had received 600 mg of linezolid for 26 weeks. Across the treatment groups, 47 of 181 participants (26%) had one or more liver-related AEs, with similar numbers in each group *(23)*. In TB-PRACTECAL, 17% (26/151) of the BPaLM group experienced Grade 3 or higher AEs or serious AEs during or within 30 days after treatment, compared with 47% (71/151) in the standard of care group *(24)*.

In a multicountry operational research study using the BPaL regimen,[2] 32 linezolid-associated AEs of special interest (AESI) occurred in the cohort of 53 patients using a linezolid dose of 600 mg/day, and two of these AESI (6.3%) were classified as severity Grade 3 or 4. In the group of 297 patients using a linezolid dose of 1200 mg/day, 308 AESI occurred; among them, 79 (25.6%) were classified as severity Grade 3 or 4: peripheral neuropathy (39/79), myelosuppression (38/79) or optic neuritis (2/79). In the LIFT-TB initiative, the rate of serious AEs reported among patients treated with BPaL was 24% (*n*=323) *(25)*.

Regardless of AEs, more than 90% of participants in the Nix-TB, ZeNix and TB-PRACTECAL trials were able to complete more than 75% of the maximal intended dose and duration of linezolid *(22)*. In the LIFT-TB initiative, 46% of patients receiving the BPaL regimen (148/323) experienced AEs that led to treatment modification *(25)*. Among patients using linezolid 600 mg/day, the rate of permanent discontinuation of linezolid owing to peripheral neuropathy or optic neuritis was 7.5% (4/53). In the group of patients using linezolid 1200 mg/day (*n*=297), 42 patients (14%) had to permanently discontinue linezolid owing to peripheral neuropathy (30/42), optic neuritis (7/42) or myelosuppression (5/42).[2]

Table A2.5 provides general definitions of the severity of AEs from Grade 1 to Grade 4. Table A2.6 suggests how AEs associated with the BPaLM regimen could be managed, according to their severity grading.

Peripheral neuropathy

Peripheral neuropathy is extremely common in patients taking linezolid 1200 mg/day, and it was experienced by 81% of the patients in the Nix-TB study. The ZeNix and TB-PRACTECAL trials, which used the BPaLM or BPaL regimen with lower doses or a shorter duration of linezolid than 1200 mg for 6 months, showed high efficacy and improved safety, including in relation to peripheral neuropathy. In the ZeNix study, peripheral neuropathy occurred in 38% of those given linezolid 1200 mg/day and in 24% of those given linezolid 600 mg/day.

In the BPaL operational research study, 32.1% (17/53) of individuals receiving linezolid 600 mg developed peripheral neuropathy, with none being of Grade 3 or higher. In the linezolid 1200 mg group, 58.6% (174/297) of the patients experienced peripheral neuropathy, of which 22.4% (39/174) were Grade 3 or higher.[2]

Peripheral neuropathy generally occurs around 3 months after treatment initiation , with onset occurring after several weeks of drug exposure, depending on both the dose and duration of treatment with

[2] Multi-country operational research on the effectiveness and safety of the BPaL regimen for drug-resistant tuberculosis: Unpublished partial cohort analysis (350 individuals enrolled from Indonesia, Kyrgyzstan, the Philippines, Uzbekistan, Viet Nam [LIFT-TB initiative], and Nigeria. 2020–2023. KNCV Tuberculosis Foundation (KNCV TB Plus). 2024.

linezolid. Among patients who develop a mean score on the BPNS scale indicating moderate to severe neuropathy, the median time to return to a score indicating no or mild neuropathy was 3 months. After dose reduction, interruption or discontinuation of linezolid, the symptoms may disappear or significantly improve. However, in some cases, discomfort persisted, highlighting the importance of careful monitoring throughout treatment.

Myelosuppression

In the NiX-TB study, where linezolid was dosed at 1200 mg/day, myelosuppression occurred in 52 patients (48%); among the 40 of these patients (37% of the study population) who had anaemia, seven had decreases in Hb level to less than 80 g/L. In most of the patients who experienced this AE, it occurred during the first 2 months of treatment, with results being similar in HIV-coinfected and uninfected patients, and in patients who received different starting doses of linezolid. In the ZeNix study, myelosuppression occurred in 22% of those given linezolid 1200 mg/day versus 2% of those given 600 mg/day.

In the BPaL operational research study, 13 patients (24.53%) receiving linezolid 600 mg/day experienced myelosuppression, with none being of Grade 3 or higher. In the linezolid 1200 mg group, 125 patients (42.1%) experienced myelosuppression, 38 (30.4%) of which were Grade 3 or higher. Myelosuppression generally occurred within the first 3 months of treatment and was resolved in most of the patients with this AE.[3]

Optic neuritis

Among all the TB drugs, linezolid is the most common cause of optic neuritis, with the condition mostly developing after 3 months of treatment. Patients may develop painless, progressive, bilateral, symmetrical visual disturbances.

In the Nix-TB study, optic nerve disorders were reported in 11% of patients, with most AEs being of Grade 1 or Grade 2. Two cases were reported as serious AEs with confirmed optic neuritis or neuropathy; both cases resolved after discontinuation of linezolid, with visual acuity returning to baseline levels. In comparison, in the ZeNix trial, optic neuritis occurred in four patients (9%) receiving linezolid 1200 mg/day and none in the group receiving 600 mg/day. All four cases resolved after withdrawal of linezolid.

In the operational research study, optic neuritis was reported in 11 individuals from the cohort of 350 receiving the BPaL regimen. In the linezolid 600 mg daily group, two of 53 patients (3.8%) developed optic neuritis, and both cases were resolved or improved by the end of treatment. In the linezolid 1200 mg daily group, nine of 297 patients (3%) experienced optic neuritis, which had resolved or improved by the end of treatment for all of them, including two cases that resolved with sequelae.[3]

Hepatotoxicity

In patients receiving the BPaLM regimen, drug-induced liver injury can result from pretomanid or bedaquiline, and less often from other drugs. Chronic liver disease, secondary to alcoholic liver disease or infection with hepatitis B or C virus, increases the risk of drug-induced liver injury among patients receiving treatment for DR-TB *(26)*.

[3] Multi-country operational research on the effectiveness and safety of the BPaL regimen for drug-resistant tuberculosis: Unpublished partial cohort analysis (350 individuals enrolled from Indonesia, Kyrgyzstan, the Philippines, Uzbekistan, Viet Nam [LIFT-TB initiative], and Nigeria. 2020–2023. KNCV Tuberculosis Foundation (KNCV TB Plus). 2024.

QT prolongation

In patients receiving the BPaLM regimen, bedaquiline and moxifloxacin are known to be associated with prolonged QT intervals, as recorded by ECG.[4] However, QT prolongation of Grade 3 or higher is rarely reported among patients receiving the BPaLM or BPaL regimen.

Table A2.5. General definitions of severity scale of adverse events

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life threatening
Mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated	Severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions, with intervention indicated to prevent permanent impairment, persistent disability or death

Source: US Department of Health and Human Services, 2017 *(27)*.

[4] The website https://crediblemeds.org/ lists drugs that have a QT-prolonging effect.

Table A2.6. Management of common AEs associated with the BPaLM regimen, according to severity grading

AE	Severity grade Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening
Peripheral neuropathy				
Paraesthesia (burning, tingling, etc)	Mild discomfort, no treatment required, and/or brief peripheral neuropathy screening (BPNS) subjective sensory neuropathy score of 1–3 on either side	Moderate discomfort, non-narcotic analgesia required, and/or BPNS subjective sensory neuropathy score of 4–6 on either side	Severe discomfort, narcotic analgesia required (with symptomatic improvement), and/or BPNS subjective sensory neuropathy score of 7–10 on either side	Incapacitating, or not responsive to narcotic analgesia
Action	Closely monitor the patient for any progression of symptoms. Instruct the patient to return to the clinic immediately if pain, numbness, or tingling worsens. Educate the patient that if symptoms progress, a dose adjustment may be necessary to prevent permanent nerve damage.	Management depends on regimen used, BPaLM or BPaL, fluoroquinolone (FQ) susceptibility status, and time on treatment. When there is Moxifloxacin resistance or FQ resistance is unknown, the consequences of holding the linezolid are greater because the patient may be left with	May require permanent suspension of Lzd; however, in some cases after pausing the drug for 2–4 weeks and reversion to Grade 2 AE, Lzd can be restarted and tolerated, often at a lower dose, provided the AE does not revert to Grade 3 or 4	May require permanent suspension of Lzd; however, in some cases after pausing the drug for 2–4 weeks and reversion to Grade 2 AE, Lzd can be restarted and tolerated, provided the AE does not revert to Grade 3 or 4
		If AE occurs during the initial 9 weeks, close clinical monitoring as described in Grade 1. Support patients through the first 9 weeks and avoid decreasing the dose	If AE occurs in first 9 weeks, change the regimen	If AE occurs in first 9 weeks, change the regimen

AE	Severity grade Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening
		If AE occurs after first 9 weeks, pause Lzd for 1–2 weeks and restart at normal dosing if tolerated or reduce the dose 300mg daily	If AE occurs after first 9 weeks, pause Lzd for 2–4 weeks, then may reduce the dose to 300 mg daily	If AE occurs after first 9 weeks, pause Lzd for 2–4 weeks, then may reduce the dose to 300 mg daily
		If AE occurs in last 8 weeks, consider stopping Lzd and continuing the remaining regimen	If AE occurs in last 8 weeks, stop Lzd and continue the remaining regimen	If AE occurs in last 8 weeks, stop Lzd and continue the remaining regimen
Myelosuppression (anaemia, thrombocytopenia or neutropenia)				
Anaemia (Hb level)	95–105 g/L	80–94 g/L	65–79 g/L or significant drop in Hb: 25% or more from a patient's baseline	< 65 g/L
Platelets decreased (because low platelets can be transient, repeat the test within a week before making any decisions)	75–99.999 × 10^9/L	50–74.999 × 10^9/L	20–49.999 × 10^9/L	< 20 × 10^9/L

AE	Severity grade Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening
Absolute neutrophil count low (because neutropenia can be transient, repeat the test within a week before making any decisions)	1.0–1.5 × 10^9/L	0.75–0.999 × 10^9/L	0.5–0.749 × 10^9/L	<0.5 × 10^9/L
Action for anaemia	Monitor carefully at least every 2 weeks	Consider hospital admission, repeat CBC at least weekly	Consider hospital admission, repeat CBC at least weekly	Consider hospital admission, repeat CBC at least weekly
Action for all types of myelosuppression (anaemia, thrombocytopenia, or neutropenia)	Monitor carefully	If AE occurs in initial 9 weeks, hold the drug for 1 – 2 weeks, then restart at full dose if tolerated, or reduce the dose 300mg daily if full dose is not tolerated	If AE occurs in first 9 weeks, change the regimen	If AE occurs in first 9 weeks, change the regimen
		If AE occurs after initial 9 weeks, hold the drug for 1–2 weeks then may reduce the dose 300mg daily	If AE occurs after first 9 weeks, pause Lzd for 1–2 weeks, then may reduce the dose to 300 mg daily; consider a blood transfusion of at least one pint or packed cell volume	If AE occurs after first 9 weeks, pause Lzd for 1–2 weeks, then may reduce the dose to 300 mg daily; consider a blood transfusion of at least one pint or packed cell volume
		If AE occurs in last 8 weeks, stop Lzd and continue the remaining regimen	If AE occurs in last 8 weeks, stop Lzd and continue the remaining regimen; take measures to correct thrombocytopenia	If AE occurs in last 8 weeks, stop Lzd and continue the remaining regimen; take measures to correct thrombocytopenia

AE	Severity grade Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening
Prolonged QT interval				
Prolonged QT interval (QTcF)	450–480 ms	481–500 ms	>500 ms without signs or symptoms of serious arrhythmia	>500 ms and one of the following: TdP or polymorphic ventricular tachycardia, or signs or symptoms of serious arrhythmia
Action			Repeat ECG after allowing the patient to rest for at least 10 min; hospitalize if possible and replete electrolytes as necessary; if QTcF remains >500 ms, stop the regimen and repeat ECG within 2–5 days; ensure that the patient is not taking any other QT-prolonging drugs; exclude hypothyrodism; and reintroduce BPaLM once QTcF ≤500 ms	The whole regimen needs to be stopped (e.g. interupt BPaLM); hospitalize and replete electrolytes as necessary; ensure that the patient is not taking any other QT-prolonging drugs; and exclude hypothyrodism
Optic neuritis				
Optic nerve disorder (this depends on what the patient's visual acuity was before Lzd)	Asymptomatic, clinical or diagnostic observations only (usually considered a two-line drop on the Snellen chart)	Limiting vision of the affected eye (20/40 [6/12] or better)	Limiting vision of the affected eye (worse than 20/40 [6/12] but better than 20/200 [6/60])	Blindness (20/200 [6/60] or worse) in the affected eye

AE	Severity grade			
	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life threatening**
Action	Stop Lzd immediately if there are any suspicions of optic neuritis and do not restart it; refer to ophthalmologist (for the BPaL/BPaLM regimen, see drug modification guidelines for Lzd)	Stop Lzd immediately if there are any suspicions of optic neuritis and do not restart it; refer to ophthalmologist (for the BPaL/BPaLM regimen, see drug modification guidelines for Lzd)	Stop Lzd immediately if there are any suspicions of optic neuritis and do not restart it; refer to ophthalmologist (for the BPaL/BPaLM regimen, see drug modification guidelines for Lzd)	Stop Lzd immediately if there are any suspicions of optic neuritis and do not restart it; refer to ophthalmologist (for the BPaL/BPaLM regimen, see drug modification guidelines for Lzd)
Hepatitis				
ALT	1.1–3.0 × ULN	>3.0–5.0 × ULN	>5.0–20.0 × ULN	>20.0 × ULN
AST	1.1–3.0 × ULN	>3.0–5.0 × ULN	>5.0–20.0 × ULN	>20.0 × ULN
Action (exclude other causes of hepatotoxicity; e.g. alcohol, viral hepatitis, hepatotoxic drugs for comorbidities)	Continue the treatment regimen; follow patients until resolution (return to baseline) or stabilization of AST/ALT levels	Continue the treatment regimen; follow patients until resolution (return to baseline) or stabilization of AST/ALT levels	Stop all drugs, including anti-TB drugs; repeat LFTs weekly; treatment may be reintroduced after toxicity is resolved (for the BPaL/BPaLM regimen, see drug modification guidelines for Lzd)	Stop all drugs, including anti-TB drugs; repeat LFTs weekly; treatment may be reintroduced after toxicity is resolved (for the BPaL/BPaLM regimen, see drug modification guidelines for Lzd)

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; BPNS: brief peripheral neuropathy screen; CBC: complete blood count; ECG: electrocardiography; Hb: haemoglobin; LFT: liver function test; Lzd: linezolid; MWF: Monday, Wednesday, Friday; QTcF: corrected QT interval per Fridericia's formula; TB: tuberculosis; TdP: torsades de pointes; ULN: upper limit of normal.

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Annex 3. Active TB drug-safety monitoring and management for treatment of drug-resistant tuberculosis

A3.1 Background

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". It is a fundamental public health surveillance activity designed to inform the management of patient safety measures in health care. Pharmacovigilance is a facet of programme monitoring, and is similar to the way many countries operate routine surveillance of tuberculosis (TB) drug resistance based on diagnostic testing.

Patients can be better served if monitoring of drug safety is implemented in tandem with management of adverse events (AEs) and adverse drug reactions (ADRs). Many of the second-line anti-TB drugs are more likely to cause toxic reactions in patients than first-line drugs, making pharmacovigilance more important in programmatic management of drug-resistant TB (PMDT). By recording the occurrence of ADRs for patients on treatment, many programmes are already collecting basic data inherent to pharmacovigilance. However, the collection of such data and the measurement of indicators on pharmacovigilance are not part of the standard parameters used in the monitoring of TB patients on treatment. Consequently, in most programmes, the nature and frequency of harm caused by the drugs themselves are poorly profiled, and they can only be inferred indirectly, from interruption or failure of treatment. As programmes start to incorporate newly released drugs into treatment regimens, WHO recommends that capacity to undertake pharmacovigilance also be improved, because this is fundamental in ensuring the safety of patients and the updating of patient safety standards, drug-safety profiles and TB treatment guidelines.

In November 2014, a WHO workshop with broad representation from stakeholders and experts was held in Viet Nam, to define methods for active surveillance of drug-safety concerns in TB programmes *(1)*. To improve understanding and arrive at a broad consensus on ways to address patient safety, the WHO Global TB Programme (WHO/GTB) convened a consultation meeting in Geneva, Switzerland, for key technical partners on 28–29 July 2015. The technical partners discussed essential requirements for the implementation of active pharmacovigilance and proper management of AEs and ADRs, which is one of the conditions included in the WHO interim policies on the use of new anti-TB medicines or novel multidrug-resistant TB (MDR-TB) regimens. The consensus reached during this meeting and in subsequent discussions is presented in the framework for the implementation of active TB drug-safety monitoring and management (aDSM) *(2)*. The framework outlines the agreed essential requirements for aDSM in patients on treatment for drug-resistant TB (DR-TB), and proposes key terms that were adapted to the specific context of TB drug-safety monitoring. This section provides advice on implementing the WHO policy on aDSM for the treatment of MDR-TB. TB practitioners,

health officials, planners, public health teams, drug regulatory authorities and others should become familiar with other publications relating to the subject *(3, 4)*.

A3.2 Definitions used in aDSM[5]

Active TB drug-safety monitoring and management (aDSM) is the active and systematic clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR-TB regimens or extensively drug-resistant TB (XDR-TB) regimens to detect, manage and report suspected or confirmed drug toxicities. Although all detected AEs need to be managed, the core package of aDSM requires the reporting of serious AEs (SAEs) only. MDR-TB and XDR-TB treatment sites with additional resources may also monitor other AEs that are of clinical significance or of special interest to the programme, as part of comprehensive aDSM.

Adverse drug reaction (ADR) is a response to a TB medicine that is noxious and unintended, and that occurs at doses normally used in humans.

Adverse event (AE) is any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but does not necessarily have a causal relationship with this treatment.

Serious adverse event (SAE) is an AE that leads to death or a life-threatening experience, hospitalization or prolongation of hospitalization, persistent or significant disability, or a congenital anomaly. The definition includes SAEs that do not immediately result in one of these outcomes but may require an intervention to prevent it from happening. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event.

Adverse event of special interest is an AE documented to have occurred during clinical trials and for which the monitoring programme is specifically sensitized to report, regardless of its seriousness, severity or causal relationship to the TB treatment. The centres that offer intermediate and advanced packages of aDSM will include all AEs of special interest in their reporting.

Adverse event of clinical significance is an AE that is serious, is of special interest, leads to a discontinuation or change in the treatment, or is otherwise judged as being clinically significant by the clinician. The centres that offer the advanced package of aDSM will include all AEs of clinical significance in their reporting.

Adverse event leading to treatment discontinuation or change in drug dosage is an event that leads a clinician to stop, interrupt temporarily or change the dosage of one or more drugs, regardless of its seriousness, severity or causal relationship to the TB treatment.

Causal relationship is a relationship between an exposure (A) and an event (B) in which A precedes and causes B. This may refer to the causal association between an exposure to a TB medicine and the occurrence of an adverse reaction.

Causality assessment is the evaluation of the likelihood that a TB medicine was the causative agent of an observed adverse reaction.

Drug-safety profile is a description of the benefits, risks and toxicity of a given TB drug or regimen, specifying any known or likely safety concerns, contraindications, cautions, preventive measures and other features that the user should be aware of to protect the health of a TB patient.

Sentinel sites are centres that, in addition to the core package of aDSM, also undertake intermediate or advanced levels of drug-safety monitoring.

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[5] The definitions of some terms have been modified from those in general usage, to fit better in the context of national TB programmes (NTPs).

Signal is reported information on a possible causal relationship between an AE and a TB medicine, the relationship being unknown or incompletely documented previously or representing a new aspect of a known association. It covers information arising from one or multiple sources that is judged to be of sufficient likelihood to justify verification *(5)*.

A3.3 What to monitor for aDSM

WHO recommends aDSM for all MDR/RR-TB patients treated with new medicines (e.g. bedaquiline, delamanid or pretomanid), repurposed medicines (e.g. linezolid, clofazimine) or novel regimens (e.g. 6-month BPaLM/BPaL regimen, 9-month all-oral regimen or other regimens that include multiple new and repurposed drugs). The appropriate and timely management of all AEs and ADRs is an integral component of aDSM and patient care.

A priority for monitoring is the detection of SAEs that lead to hospitalization or prolongation of hospitalization, a persistent significant disability, a congenital anomaly, a life-threatening condition or death. It is necessary to report SAEs as per the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline definition *(6)*. All deaths are to be reported and as much relevant information as possible on the cause of death should be consistently collected. This may require recovering information from vital registration coding. Reporting of AEs and other events (e.g. pregnancy and lactation exposure) may be required, primarily based on what is known about the safety profile of the new agent and also for other possible harms that have not yet been described.

All reasonable measures are thus needed to ensure that patient safety is monitored alongside the effectiveness of treatment. In this situation, spontaneous reporting is not expected to represent an appropriate level of care, and active and cohort-based drug-safety monitoring approaches are considered necessary to improve early and systematic detection, and management of harms. It is also important to collect safety data accurately, to ensure that any AE is properly investigated and no hasty conclusions about the causative medicine are drawn. A cohort approach is essential to avoid bias in the selection of patients or in the measurement of events; it is also the best way to infer the potential association of an event with the given exposure, and it provides denominators and baseline data for analysis. Many TB practitioners are unfamiliar with the concept of "cohort event monitoring" and other conventional terminology of pharmacovigilance, making it difficult for them to follow recent recommendations for introduction of a drug-safety monitoring component in PMDT programmes. The aDSM approach therefore outlines the agreed "essential requirements for active drug-safety monitoring and management in patients on treatment for drug-resistant TB". It proposes key terms that have been adapted to the specific context of active TB drug-safety monitoring. This adaptation should help the TB community to speak a common language while implementing the required drug-safety activities.

The recording and reporting of aDSM primarily target SAEs as a core requirement. PMDT sites with additional resources may also monitor other AEs that are of clinical significance or of special interest to the PMDT programme as part of an extended aDSM approach.

aDSM is important when patients are treated with a medicine for which the drug-safety profile is not yet complete. This does not depend on the number of patients enrolled. Monitoring needs to be closely associated with early action to prevent and manage any serious consequences to the individual patient. A national programme should also strive to capture data in the private sector and through public–private partnerships.

aDSM is intended to pick up not only known reactions associated with a drug but also any unexpected effect of treatment (some of these may actually be beneficial to the patient). For aDSM, a non-severe event may be the early manifestation of a more consequential process (e.g. a dose-dependent effect).

Where it is feasible for the programme, such events should be captured on data collection forms. To reduce the workload, entering of this information into the aDSM database should be optional.

A3.4 Objectives of aDSM

The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second-line treatment for DR-TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines. To achieve these objectives, the aDSM includes four essential activities:

- Patients targeted for aDSM should undergo active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs.
- All AEs detected should be managed in a timely manner, to deliver the best possible patient care (as described in **Annex 2**).
- Standardized data should be systematically collected and reported for any SAE detected:[6] these data will eventually be used to characterize the types of SAEs, assess the safety of treatment and inform future policy on the use of these medicines.
- Improving the evidence base for global policy on new and repurposed medicines.

For the evidence base to improve, AE data collected by national authorities need to be shared to permit global monitoring and data pooling. This approach is also useful to detect previously unrecognized or poorly documented AEs. A global database for active TB drug-safety monitoring and management has been launched by WHO and the Special Programme for Research and Training in Tropical Diseases (TDR). The aDSM website provides details on how countries can submit data. Close coordination of aDSM activities with the main pharmacovigilance structures at the country level is essential to avoid overlap and duplication. Any future recommendation of WHO on off-label use of new anti-TB medicines (e.g. delamanid or bedaquiline) for more than 6 months will depend on the availability of good-quality safety data – proper implementation of aDSM is paramount for such data.

A3.5 Levels of monitoring in aDSM

There are three levels of monitoring in aDSM:

- core package – which requires monitoring for and reporting of all SAEs;
- intermediate package – which includes SAEs as well as AEs of special interest; and
- advanced package – which includes all AEs of clinical significance.

All PMDT sites treating eligible patients with new anti-TB drugs or novel MDR-TB regimens, or treating patients for XDR-TB, require the core package. These treatment centres should, as a minimum, also take part in spontaneous reporting of ADRs, as required by local regulations. Expansion of aDSM should be implemented in a phased approach as and when resources permit.

All SAEs detected should be reported to the national authority responsible for pharmacovigilance according to individual country requirements (including time limits for reporting) and should be regularly assessed for causality.

A3.6 Implementing aDSM

The implementation of aDSM will require the following eight essential steps:

1. Create a national coordinating mechanism for aDSM.
2. Develop a plan for aDSM.
3. Define management and supervisory roles and responsibilities.

[6] Countries and stakeholders may also monitor other AEs of special interest or clinical significance (see next section).

4. Create standard materials for data collection.
5. Train staff on the collection of data.
6. Define schedules and routes for data collection and reporting.
7. Consolidate aDSM data electronically.
8. Develop (or use existing) capacity for signal detection and causality assessment.

Ideally, all eight steps should be in place before patients are enrolled on treatment with new drugs, novel MDR-TB regimens or XDR-TB treatment. Where this is not feasible, Step 4 (Create standard materials for data collection) and Step 5 (Train staff on the collection of data) are considered essential ahead of any patient enrolment.

A fully functional aDSM is not required at the time of ordering drugs or starting patients on treatment. However, certain key elements need to be in place so that essential safety data are collected for all patients as soon as they are started on a new drug or new regimen. The capacity for aDSM can then be built over the following months.

The aDSM plan would clearly define the activities and standard operating procedures (SOPs), including the plan for data collection, reporting of indicators, analysis and communication. The final document would be incorporated within the national TB or PMDT guidelines. Local or international experts in drug safety as well as the national pharmacovigilance centre (if functional) should be engaged.

Some of the data collection tools for aDSM are separate from those used for routine PMDT monitoring; nevertheless, the process could be integrated with other cohort-based monitoring for bacteriological response and outcomes that have been a standard feature of the PMDT component of TB control programmes for several years (see Section 2 of the guidelines and the corresponding annexes). WHO is working closely with partners towards further integration of aDSM within routine PMDT monitoring.

In the core package of aDSM, clinical and laboratory test records at baseline and during regular reviews (e.g. monthly intervals) would be integrated with an expanded version of the programmatic MDR-TB (second-line TB) treatment card.

Before enrolling any patients, staff at the different levels of health services would be informed and trained on the use of new anti-TB drugs or novel regimens (including instruction on the completion of aDSM forms). This activity should be completed ahead of any patient enrolment, to ensure timely identification of AEs that need to be managed, and proper and complete collection of information.

All AEs detected during routine clinical patient care should lead to an appropriate and timely management response to limit potential harms to the patient. In terms of monitoring, the minimum requirement for aDSM is that all SAEs be registered and reported, regardless of their severity or whether they were caused by any of the medicines to which the patient was exposed.

Some centres with sufficient resources may be designated as "sentinel sites" and undertake monitoring additional to that required by the core package of aDSM (e.g. the reporting of AEs of special interest or AEs of clinical significance, as described above). In many countries, the law mandates the reporting of ADRs to the national pharmacovigilance centre. In all public and private health services, TB practitioners should comply with the national legal requirements for such reporting.

A standard form (in paper or electronic format) will need to be developed to alert the programme when any SAE occurs; the content of the form should be similar to that used by the national pharmacovigilance centre for spontaneous reporting. The creation of an electronic database – or preferably the adaptation of an existing TB patient database to accommodate the additional data fields required – is an important step in aDSM implementation. It will ensure the standardization and safekeeping of data. If data are collected on paper forms, these need to be entered regularly into the electronic database. The management of data in electronic format is indispensable for facilitating data sharing and data analysis, and for generating indicators.

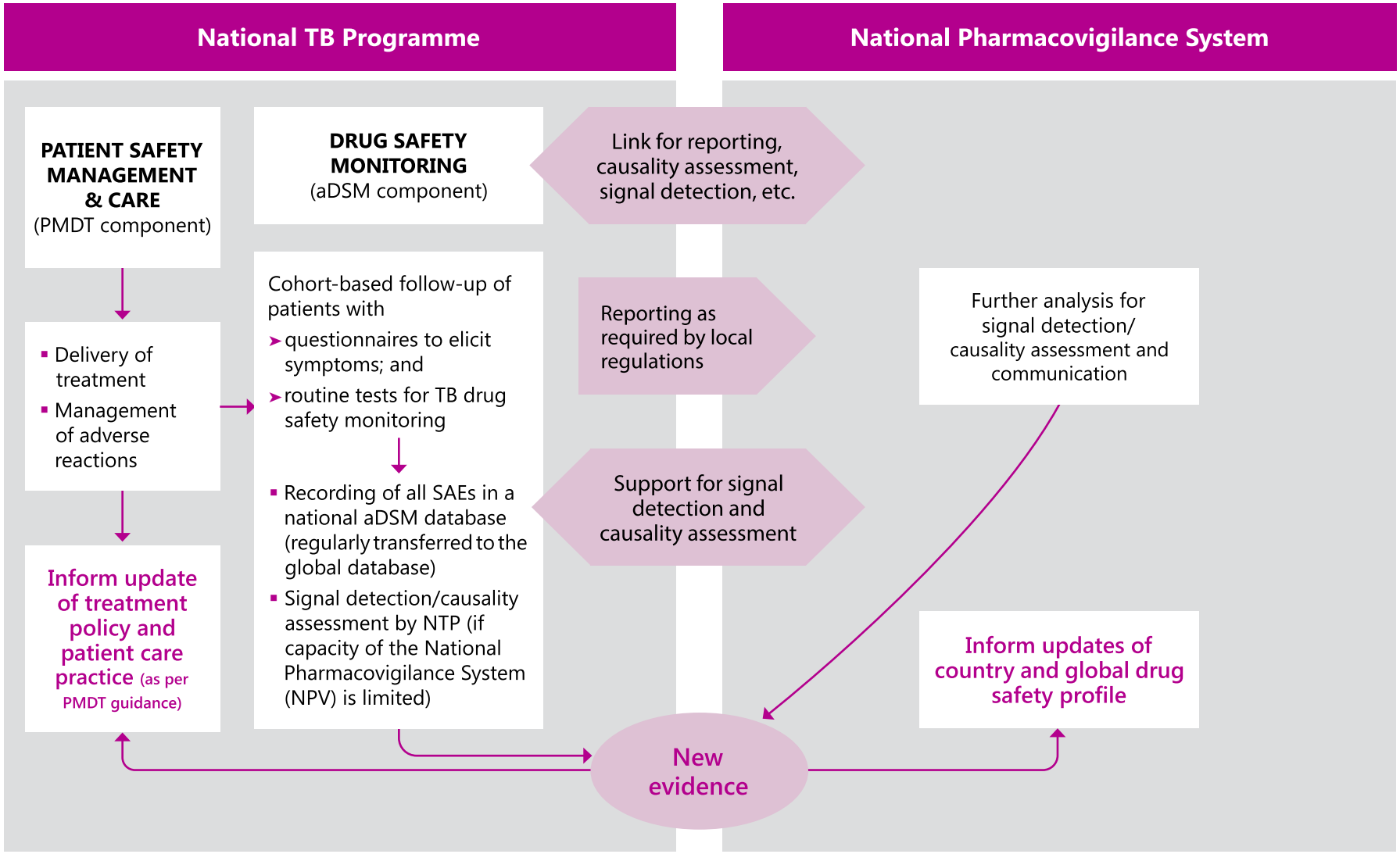
Measures would be taken to avoid duplication of work by revising existing databases, ensuring interoperability of data management systems, consulting with local pharmacovigilance authorities and granting access rights to users for different data as needed (**Fig. A3.1**). The roles and responsibilities for data management and analysis would be specified in the aDSM plan, to avoid the creation of parallel systems of ADR reporting and to make use of the best possible expertise on drug safety in the country.

Fig. A3.1 outlines the main lead responsibilities for the different components of aDSM; it could be useful in assigning complementary functions and associated funding needs. This construct is subject to adjustment based on local circumstances; for example, if the national pharmacovigilance centre has limited capacity for running an aDSM project in the country, it may be agreed that the national TB programme (NTP) or a technical agency will lead certain functions. Technical agencies could, for instance, catalyse the establishment of a committee or the protocol, organize training or provide technical assistance. Donors could have a role in supporting grant proposals for pharmacovigilance and facilitating the process for accessing the resources at country level.

In addition to the identification of signals and causality assessment, indicators will be useful for assessing the coverage of aDSM activities and summarizing the overall AE experience of monitored patients. For these purposes, **Table A3.1** presents the indicators and **Table A3.2** a "drug-safety profile" *(1)*. The essential laboratory tests and examinations that need to be conducted will be determined by the programme protocol.

Development of a schedule for screening of AEs and for laboratory, clinical and radiological testing is also recommended. Both the list of data elements and the frequency of testing would be validated and customized based on local needs before they are integrated in the programme's aDSM protocol.

Fig. A3.1. Generic model of aDSM within drug-safety structures at the national level



aDSM: active TB drug-safety monitoring and management; NPV: national pharmacovigilance centre; NTP: national TB programme; PMDT: programmatic management of drug-resistant TB; SAE: serious adverse event; TB: tuberculosis.

Source: WHO (2014) *(7)*.

A3.7 Roles, responsibilities and support for the implementation of aDSM

Responsibility for the coordination of aDSM at the national level should be assigned to an existing TB expert body, such as the MDR-TB committee (or consilium) or the technical working group on new drugs. These committees should primarily have scientific and clinical expertise for MDR-TB care and drug-safety monitoring, but could also include expertise important for coordination and advocacy (e.g. funding, communication and patient representation). Until such a group is tasked with this role, the NTP needs to assign someone to coordinate the necessary aDSM activities and ensure that the key steps mentioned above are in place before patient enrolment.

The ultimate purpose of systematic data collection within aDSM is to enable causality assessment for SAEs, determine the frequency (rates) of SAEs and detect signals. Physicians skilled in MDR-TB management already attempt to assess relationships between drugs and ADRs and take appropriate clinical action. However, formal causality assessment is a separate process that requires involvement of other experts. In several countries, the capacity of national pharmacovigilance centres to conduct formal causality assessment is limited, but where such capacity exists it should be used.

NTP staff need to acquire the skills to undertake essential activities related to aDSM. This is a long-term goal but needs to be started as part of the plan to introduce new anti-TB drugs and novel MDR-TB regimens. To carry out such capacity-building, the NTP should seek local or international expertise in causality assessment; WHO is also working with partners to accelerate these efforts.

The implementation of aDSM at the NTP level will be greatly facilitated by familiarity with the concept of cohort-based follow-up of patients, which is the foundation for the monitoring and evaluation of TB and MDR-TB treatment programmes. The testing schedules used in these projects have largely followed those generally recommended when second-line TB drugs are used.

Experience from observational studies of shorter regimens for MDR-TB has shown that active drug-safety monitoring can be implemented within programmes if dedicated funding is provided. Most of the additional resources are needed to undertake clinical testing (e.g. electrocardiography and audiometry) and laboratory analyses, and to collect drug-safety data.

Once the right skills have been acquired and links have been established with appropriate experts in drug safety, it is envisaged that causality assessment and signal detection could be organized within the PMDT programme, with appropriate capacity-building and support from drug-safety experts (if such capacity is missing at the national pharmacovigilance system). More work is needed to quantify the costs of aDSM, and these will eventually be reflected in the tools that will be provided to help users with budgeting.

Clinicians treating patients with second-line anti-TB drugs are usually familiar with clinical monitoring for AEs; however, this knowledge may not be available to many other health care workers within the programme. The monitoring component of aDSM is also likely to be novel to many health care workers. WHO/GTB and technical partners will be supporting NTPs to build such capacity and to integrate aDSM into routine PMDT monitoring.

Table A3.1. Programmatic indicators for aDSM

Class	Importance	Indicator number and name	Calculation	Stratification	Expressed as	Data sources	Level	Period of assessment	Notes
Coverage (process)	Essential	1) Target MDR/RR-TB patients included in cohort event monitoring	Numerator: Number of TB cases started on target treatment included in aDSM during the period of assessment Denominator: Number of TB cases started on target treatment during the period of assessment and eligible for aDSM	None	Absolute numbers, proportion	Numerator: aDSM register Denominator: Second-line TB treatment register	National; NTP and NPV	3 months	To be computed during the period of recruitment but not in the post-treatment observation phase
Completeness (process)	Optional	2) Time to stopping target drug	The difference in days between the date of start of treatment with a target drug and the date of stopping the target drug; the calculation is done for each member of the cohort	Reason for stopping	Number of patients included in the calculation; median interval and IQR in days	aDSM register	National; NTP and NPV	12 months	Stratify by reason for stopping (e.g. success, died, treatment failed, loss to follow-up, exclusion criterion developing after start of treatment such as pregnancy)
SAE	Essential (but stratification optional)	3) MDR/ RR-TB patients included in aDSM with any SAE	Numerator: Number of TB cases included in aDSM during the period of assessment with one or more SAEs Denominator: Number of TB cases included in aDSM during the period of assessment	By organ group; by outcome	Absolute numbers, proportion	Numerator: aDSM register Denominator: aDSM register	NTP and NPV	3 months	To be computed during the period of patient recruitment and during the post-treatment observation phase Indicate outcome (deaths, hospitalizations or disability)

Class	Importance	Indicator number and name	Calculation	Stratification	Expressed as	Data sources	Level	Period of assessment	Notes
ADRs associated with target treatment	Optional	4) Frequency of ADRs associated with target treatment	Numerator: Number of ADRs attributed to target treatment among patients on aDSM Denominator: Number of TB cases included in aDSM during the period of assessment	By organ group; by seriousness or severity	Absolute numbers, proportion	aDSM register	NTP and NPV	3 months	To be computed during the period of patient recruitment and during the post-treatment observation phase Only to be reported after causality assessment (e.g. dechallenge and rechallenge) suggests target treatment as the causative agent (certain, probable or possible) The same patient may have several ADRs (therefore, the unit of measurement is the ADR and not the number of patients)
ADRs associated with target treatment	Optional	5) Time to development of ADRs associated with target treatment	The difference in days between the date of start of the target treatment and the date of the first detected onset of the ADR attributed to it	By organ group	Number of ADRs included in the calculation; median interval and IQR in days	aDSM register	aDSM centre	6 months	To be computed during the period of patient recruitment and during the post-treatment observation phase The calculation is done for each reaction attributed to the target treatment; the same patient may have several ADRs computed (the unit of measurement is the ADR and not the number of patient); if a particular ADR recurs in the same patient during the aDSM it is not calculated again Only to be reported after causality assessment (e.g. dechallenge and rechallenge) suggests target treatment as the causative agent (certain, probable or possible)

ADR: adverse drug reaction; aDSM: active TB drug-safety monitoring and management; IQR: interquartile range; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; NPV: national pharmacovigilance centre; NTP: national TB programme; SAE: serious adverse event; TB: tuberculosis.

Adapted from WHO (2014) *(7)*.

Table A3.2. Elements for a summary profile of drug safety or toxicity

Dimension	Additional notes
The benefit: toxicity profile of the baseline MDR-TB regimen	The MDR-TB regimen, which constitutes the most widely used standard of care, is described in terms of its effectiveness and associated harms; this dimension of the profile uses information originating from the published literature; trials (unpublished or published); observational studies and cohorts (including nested case–controls); prospective aDSM data; and other pharmacovigilance findings based on spontaneous reporting
Safety concerns associated with a specific drug or regimen	The characteristics (organ class), risk, severity, drug–drug interactions and other safety concerns are summarized from the literature as well as local data (including aDSM)
Quantifying risk and benefit	As far as possible, the safety concerns are also expressed in terms of risk (e.g. per 100 or 1000 exposures and as relative risk); the effectiveness is generally expressed in terms of % successful outcome or cure
Risk factors	These include host-related predispositions to harms, such as comorbidities, severity of TB disease, drug–drug interactions or subpopulations (e.g. age group and sex); these could form the basis of contraindications or caution in use of the regimen or drug
Signal detection	The procedure followed for relationship and causality assessments and detection of signals in the cohort is explained, and any departures from agreed methodologies are described; signal detection is attempted both at country and supranational levels; any preliminary signals are discussed with the regulators and manufacturer before widespread communication
Preventive measures	Advice on avoidance of harm or toxicity, precautions and contraindications

aDSM: active TB drug-safety monitoring and management; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

Adapted from the *Draft framework for the harmonized and standardized summarization of both added benefit and risk associated with an intervention (7)*.

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Appendix 2. Adverse events of clinical significance or special interest for aDSM

See **Section A3.2** (Definitions used in aDSM) for the definitions of types of adverse events (AEs) mentioned in this appendix. AEs of clinical significance or special interest for active TB drug-safety monitoring and management (aDSM) are as follows:[7]

1) All serious adverse events (SAEs).

2) All AEs of special interest (suggested list):[8]

- peripheral neuropathy (paraesthesia);
- psychiatric disorders and central nervous system toxicity (e.g. depression, psychosis, suicidal intention and seizures);
- optic nerve disorder (optic neuritis) or retinopathy;
- ototoxicity (hearing impairment and hearing loss);
- myelosuppression (manifested as anaemia, thrombocytopenia, neutropenia or leukopenia);
- prolonged QT interval (Fridericia correction; see *(7)*);
- lactic acidosis;
- hepatitis (defined as increases in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥5× the upper limit of normal [ULN], or increases in ALT or AST ≥3× ULN with clinical manifestations, or increases in ALT or AST ≥3× ULN with concomitant increase in bilirubin ≥1.5× ULN);
- hypothyroidism;
- hypokalaemia;
- pancreatitis;
- phospholipidosis; and
- acute kidney injury (acute renal failure).

3) AEs leading to treatment discontinuation or change in drug dosage.

4) AEs not listed above but judged as otherwise clinically significant by the clinician.

[7] List adapted from *Pharmacovigilance guideline for endTB projects outside interventional clinical trial, version 0.7 (8).*

[8] The list shown here is provisional; it may be modified according to the composition of the regimen or the patient cohort.

Appendix 3. Alert for serious adverse events to the TB programme *(Example)*

Confidential – to be sent even when there is suspicion of a serious adverse event (SAE).

Is this report a new event?	Yes	No	Give date when previous SAE form was sent: (DD/MMM/YYYY)

1. Patient details

Surname		First name	
Sex	Male / Female	Date of birth	☐☐ DD / ☐☐☐ MMM / ☐☐☐☐ YYYY
			Age in years if DOB unknown
Pregnancy	No / Yes		

ID number _____ Phone no. _____

Address _____

_____

_____

2. Suspected and concomitant medicine(s)

Name (generic name)	Total daily dose	Date started	Date stopped	Continues
				❑
				❑
				❑
				❑
				❑

3. Details of SAE

Date event started		Date event stopped	
Description of event			

Why is the event considered serious?	❑ Death ❑ Life-threatening event (specify……) ❑ Hospitalization or prolongation of hospitalization ❑ Persistent or significant disability (specify……) ❑ Congenital anomaly ❑ Other (specify……)

4. Action taken

- ❑ Medicine withdrawn
- ❑ Dose increased
- ❑ Dose reduced
- ❑ Dose not changed
- ❑ Unknown

5. Outcome of SAE

- ❑ Recovered / resolved
- ❑ Recovering / resolving
- ❑ Recovered with sequelae
- ❑ Not recovered / not resolved
- ❑ Died
- ❑ Unknown

6. Reporter

Name		Position			
Facility or clinic					
Address					
Email		Phone no.			
Signature		Date sent	☐☐ DD	☐☐☐ MMM	☐☐☐☐ YYYY

Explanatory note – to be adapted according to the local situation:

- This form is intended for the core package of active tuberculosis (TB) drug-safety monitoring and management (aDSM). For more details, please refer to other documents on aDSM. The spontaneous reporting form in use by the national pharmacovigilance authorities may be adapted for the purposes of alerting the TB programme of SAEs and avoiding parallel reporting structures.
- The completed form can be sent electronically, via email or fax to <address> and the responsible authority alerted by phone.
- The report should be sent within <number> hours after it is detected, even when there is a suspicion of seriousness.
- The report should be sent even when not all details are available and the association with any particular medicine is uncertain. The essential details are the identifiers of the patient and the reporter; the name of the suspected medicine(s); and basic details on the SAE.
- If the report relates to a previously notified event, indicate this under Section 3 of the form; if more than one SAE occurs in the same individual, send separate forms for each event.

- All health care professionals are encouraged to report; patients and relatives may also report.
- Upon receipt of the information, the responsible authority will review the information and contact the reporter or the facility (or both) for more details. All information, including the identity of the patient and reporter, must be handled in strict confidence. Apart from action to protect public health, anonymized statistics from these reports will be used to improve drug safety.
- When reporting, use the format DD/MMM/YYYY to report dates. Under "Description of event" in Section 3 of the form, provide a single diagnosis and include anatomical location if applicable. If the diagnosis is unknown, describe the clinical picture.

References (Annex 3)

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Annex 4. Dosing of medicines used in TB regimens, adults and children

A4.1. Dosages of anti-TB medicines by weight band for treatment of DS-TB

Medicine	Weight-based dose	Formulation (mg)	Formulation type	25 to <30 kg	30 to <35 kg	35 to <50 kg	50 to <65 kg	65 kg +
				tablets	tablets	tablets	tablets	tablets
FDC (HR)		75/150	FDC	2	3	4	4	5
FDC (HRE)		75/150/275	FDC	2	3	4	4	5
FDC (HRZE)		75/150/400/275	FDC	2	3	4	4	5
Isoniazid (H)	4–6 mg/kg	300	Loose	0.5	1	1	1	1.25
Rifampicin (R)	8–12 mg/kg	300	Loose	1	1.5	2	2	2.5
Ethambutol (E)	15–25 mg/kg	400	Loose	1.5	2	3	3	4
Pyrazinamide (Z)	20–30 mg/kg	400	Loose	2	3	4	4	5
Pyrazinamide (Z)	20–30 mg/kg	500	Loose	1.5	2.5	3	3	4
Rifapentine (P)	Fixed	150	Loose			8	8	8
Rifapentine (P)	Fixed	300	Loose			4	4	4
Moxifloxacin (M)	Fixed	400	Loose			1	1	1

Adult FDCs (mg)	H	R	Z	E
FDC (HRZE)	75	150	400	275
FDC (HRE)	75	150		275
FDC (HR)	75	150		

DS-TB: drug-susceptible TB; FDC: fixed-dose combination; TB: tuberculosis

A4.2. Weight-based dosing of medicines used in multidrug-resistant TB regimens, adults and children[a]

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Levofloxacin (Lfx)	**100 mg dt (10 mg/mL)**	5 mL (0.5 dt)	1	1.5	2	3	–						–
	250 mg tab (25 mg/mL)	2 mL[b]	5 mL (0.5 tab)[b]		1	1.5	2	3		4			
	500 mg tab	–					1	1.5		2			
	750 mg tab	–						1		1.5			
Moxifloxacin (M or Mfx)	**100 mg dt (10 mg/mL)**	4 mL	8 mL	1.5	2	3	4			–			–
	400 mg tab (40 mg/mL) Standard dose	1 mL[b]	2 mL[b]	3 mL[b]	5 mL (0.5 tab)[b]	7.5 mL	1						
	400 mg tab high dose[c]	–						1 or 1.5	1.5	1.5 or 2	2		
Bedaquiline (B or Bdq)	**20 mg dt**	0 to <3 months: 1.5 od (2 weeks); then 0.5 od M/W/F (22 weeks) ≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks		0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥6 months: 4 od for 2 weeks; then 2 od M/W/F	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F	10 od for 2 weeks; then 5 od M/W/F		20 od for 2 weeks; then 10 od M/W/F		–			–

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Bedaquiline (B or Bdq)	**100 mg tab** (10 mg/mL)[d]	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F[b] ≥3 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b]		0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F[b] 3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b] ≥6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F[b]	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b] ≥6 months: 12 mL od for 2 weeks; then 6 mL od M/W/F[b]	2 od for 2 weeks; then 1 od M/W/F		4 od for 2 weeks; then 2 od M/W/F					–
	100 mg tab (alternative dosing strategy)	–						2 od for 8 weeks followed by 1 od					Dosing scheme for adults and adolescents >14 years.
Linezolid (L or Lzd)	**20 mg /mL susp**	2 mL	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	–			–
	150 mg dt (15 mg/mL)	2.5 mL	5 mL (0.5 dt)	1		2[e]		2	3	–			
	600 mg tab (60 mg/mL)	–	1.25 mL[b]	2.5 mL[b]		5 mL (0.5 tab)[b, e]		5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1			
	600 mg tab (alternative dosing strategy for modified 9 months regimens)	–					0.5	1 od for 16 weeks followed by 0.5 od or 1 M/W/F until the end of treatment					This applies to modified 9-month regimens (BLMZ, BLLCZ, BLLfxCZ).

Group B medicines	Formulation	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Clofazimine (C or Cfz)	**50 mg cap or tab**[f]	1 M/F	1 M/W/F		1		2						For children <24 kg, the use of the 50 mg tab is preferred.
	100 mg cap or tab[f]	–	1 M/F		1 M/W/F		1						
Cycloserine or **terizidone** (Cs/Trd)	**125 mg mini cap (Cs) (12.5 mg/mL)**	2 mL[b, g]	4 mL[b]	1	2	3	4			–			Pyridoxine is usually given to limit Cs toxicity.
	250 mg cap (25 mg/mL)	1 mL[b, g]	2 mL[b]	5 mL[b]	1	2				3			–
Group C medicines	**Formulation**	**3–<5 kg**[a]	**5–<7 kg**[a]	**7–<10 kg**	**10–<16 kg**	**16–<24 kg**	**24–<30 kg**	**30–<36 kg**	**36–<46 kg**	**46–<56 kg**	**56–<70 kg**	**≥70 kg**	**Comments**
Ethambutol (E)	100 mg dt (10 mg/mL)	5 mL (0.5 dt)	1	2	3	4	–						–
	400 mg tab (40 mg/mL)	1.5 mL[b]	3 mL[b]	4 mL[b]	6 mL	1	1.5	2		3		4	
Delamanid (D or Dlm)	25 mg dt	1 od	<3 months: 1 od ≥3 months: 1 bd		1 bd	2 morning 1 evening		2 bd		–			–
	50 mg tab[h] (5 mg/mL)	5 mL (0.5 tab) od[b]	<3 months: 5 mL (0.5 tab) od[b] ≥3 months: 5 mL (0.5 tab) bd[b]		5 mL (0.5 tab) bd[b]	10 mL (1 tab) morning 5 mL (0.5 tab) evening		1 bd		2 bd			
Pyrazinamide (Z or PZA)	150 mg dt (15 mg/mL)	5 mL (0.5 dt)	1	2	3	5	–						–
	400 mg tab (40 mg/mL)	2.5 mL[b]	5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	2	2.5	3	4			5	
	500 mg tab (50 mg/mL)	2 mL[b]	5 mL (5 mL)[b]		1	1.5	2	2.5	3			4	
Imipenem–cilastatin (Ipm/Cln)	500 mg + 500 mg powder for injection, vial (10 mL)	Not used in patients aged <15 years (use meropenem)						2 vials (1 g + 1 g) bd					Only to be used with clavulanic acid.
Meropenem (Mpm)	1 g powder for injection, vial (20 mL)	1 mL tid	2 mL tid	4 mL tid	6 mL tid	9 mL tid	11 mL tid	1 vial tid or 2 vials bd					Only to be used with clavulanic acid.

Group C medicines	Formulation	3–<5 kg[a]	5–<7 kg[a]	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Amikacin (Am)	500 mg/2 mL solution for injection, ampoule	–[i]								3–4 mL	4 mL		Recommended only in adults aged >18 years.
Streptomycin (S)	1 g powder for injection, vial	–[i]								Calculate according to the dilution used			Recommended only in adults aged >18 years.
Ethionamide or Prothionamide (Eto/Pto)	125 mg dt (Eto) (12.5 mg/mL)	3 mL[b]	7 mL[b]	1	2	3	4			–			Although once daily dose advised, two divided doses can be also given to improve tolerance.
	250 mg tab (25 mg/mL)	–	3 mL[b]	5 mL (0.5 tab)[b]	1	2				3		4	
***P*-aminosalicylic acid** (PAS)	PAS sodium salt (equivalent to 4 g PAS acid) sachet	0.3 g bd	0.75 g bd	1 g bd	2 g bd	3 g bd	3.5 g bd	4 g bd				4–6 g bd	Usually given in divided doses. Fully dose may be given once daily if tolerated.

Other medicines	Formulation	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Isoniazid[j] (INH or H) **(high dose)**	50 mg/5 mL soln	5 mL	9 mL	15 mL	20 mL	–							Pyridoxine is always given with high-dose isoniazid in children (1–2 mg/kg) and in people at risk of side-effects (e.g. those with HIV or malnutrition). In infants, pyridoxine may be given as part of a multi-vitamin syrup.
	100 mg dt or tab (10 mg/mL)	5 mL (0.5 dt)	1	1.5	2	3	4		4.5	–			
	300 mg tab	–				1	1.5			2			–
Clavulanic acid[j] **(as amoxicillin/ clavulanate)** (Amx/clav)	62.5 mg clavulanic acid as amoxicillin/ clavulanate (250/62.5 mg), powder for oral solution, 5 mL	1.5 mL tid	2 mL tid	3 mL tid	5 mL tid	8 mL tid	10 mL tid	10 mL bd or tid		–			Only available in combination with amoxicillin. To be given with each dose of imipenem/ cilastatin (bd) or meropenem (tid).
	125 mg clavulanic acid as amoxicillin/ clavulanate (500/125 mg) tab	–					1 tid	1 bd or tid					
Pretomanid (Pa)	200 mg tab	–						1					Currently only used as part of the BPaLM/ BPaL regimens.

bd: two times a day; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; cap: capsule; DR-TB: drug-resistant TB; dt: dispersible tablet; g: gram; GDG: Guideline Development Group; HIV: human immunodeficiency virus; kg: kilogram; MDR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or rifampicin-resistant TB; mg: milligram; mL: millilitre; M/F: Monday and Friday; M/W/F: Monday, Wednesday and Friday; od: once daily; soln: solution; susp: suspension; tab: tablet; TB: tuberculosis; tid: three times a day; WHO: World Health Organization.

[a] Dosing guidance is based on currently available data and may be revised once additional data are available. Dosages were established by the GDGs for the WHO guidelines on DR-TB treatment (2018 and 2020 updates), the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and the expert consultation on dosing convened by WHO in October 2021, following the GDG meeting on child and adolescent TB in June 2021.

Doses for children and young adolescents weighing <46 kg were revised according to Annex 6 of the 2022 *WHO operational handbook on tuberculosis – Module 5: Management of tuberculosis in children and adolescents (153)*, which was informed by an expert consultation on dosing convened by WHO in October 2021 *(154)*. They are based on the most recent reviews and best practices in the treatment of (paediatric) MDR/RR-TB. For certain medicines the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling and maturation *(155)*. 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. The guidance for the 3–<5 kg weight band and for bedaquiline and delamanid is based on currently available data and may be revised when new data become available.

[b] Dissolving of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide. This avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (use of dispersible tablets is preferred).

[c] 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.

[d] Bedaquiline adult tablets (100 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole. Vigorous stirring/shaking is needed prior to administering the 100 mg tablet crushed and suspended in water.

[e] When using the 600 mg tab and the 150 mg dt to dose children weighing 16 to <24 kg, the dose in mg/kg will exceed 10–12 mg/kg and clinicians may opt to administer 1.5 dt or 4 mL of the 600 mg tab dispersed in 10 mL water.

[f] Clofazimine tablets are technically not dispersible but they do dissolve slowly (this takes approximately 5 minutes) in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred prior to administration. The 50 mg and 100 mg soft gel capsules are difficult to swallow for young children and therefore countries are strongly encouraged to make the 50 mg tablet formulation available.

[g] In children weighing 3 to <7 kg doses are lower than previously recommended. This is because of relatively high exposures associated with risk of neuropsychiatric adverse events, which is especially concerning when co-administering cycloserine with delamanid.

[h] Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole.

[i] 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. If used, the weight-based daily dose for amikacin is 15–20 mg/kg and for streptomycin it is 20–40 mg/kg for children aged 2 years and older. To determine the dosing for infants and children aged below 2 years, a paediatric DR-TB expert should be consulted and a lower mg/kg dose used to compensate for immature clearance. Co-administration with lidocaine is advised to reduce pain at the injection site *(156)*.

[j] These medicines are only recommended as a companion agent (amoxicillin/clavulanic acid) or are not included in Groups A, B and C, because of a lack of data from the latest analysis on longer MDR-TB regimens in adults (isoniazid).

Specific comments on dosing children with medicines used in second-line MDR-TB regimens:

- For dosing of premature and low birth weight infants weighing <3 kg, advice should be sought from a paediatric DR-TB expert.
- For dosing of infants weighing 3 to <5 kg, a paediatric DR-TB expert should be consulted whenever possible.
- The use of child-friendly, dispersible tablets in infants and young children is preferred over manipulating adult tablets or administering or manipulating capsules. Where applicable, the dosing provided is based on dissolving the dispersible formulation in 10 mL of water and administering the number of mL (aliquots). The number of mL in the table reflects the dose to provide. The dissolved solution should be used immediately and the remainder of the 10 mL should be discarded.
- For some weight bands, dosing is indicated with both child-friendly, dispersible formulations and adult formulations. If adult formulations are used, the table provides the dose using aliquots in mL and tablet fractions where applicable (if the fraction is 0.5 or more). Aliquots refer to the volume to administer after crushing and dissolving the tablet in 10 mL of water.

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