

WHO operational handbook on tuberculosis

Module 4: Treatment

Drug-susceptible
tuberculosis treatment



World Health
Organization

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Abbreviations and acronyms

ART	Antiretroviral therapy
AUC	Area under the curve
BMI	Body mass index
CALHIV	Children and adolescents living with HIV
CI	Confidence interval
CLD	Chronic liver disease
CLHIV	Children living with HIV
CRF	Chronic renal failure
CTP	Child–Turcotte–Pugh
CXR	Chest radiography
DR-TB	Drug-resistant tuberculosis
DS-TB	Drug-susceptible tuberculosis
DST	Drug susceptibility testing
ECG	Electrocardiogram
FDC	Fixed-dose combination
GDG	Guideline Development Group
HIV	Human immunodeficiency virus
IRIS	Immune reconstitution inflammatory syndrome
MDR/RR-TB	Multidrug- or rifampicin-resistant tuberculosis
MDR-TB	Multidrug-resistant tuberculosis
NTM	Non-tuberculosis mycobacteria
NTP	National tuberculosis programme
PLHIV	People living with HIV
RCT	Randomized controlled trial
RR-TB	Rifampicin-resistant tuberculosis
SAM	Severe acute malnutrition
TB	Tuberculosis
TPT	Tuberculosis preventive treatment
VST	Video-supported treatment
WHO	World Health Organization

TB medicines

E	Ethambutol
H	Isoniazid
M or Mfx	Moxifloxacin
Z	Pyrazinamide
R	Rifampicin
P or Rpt	Rifapentine

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).

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 cavitory 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.

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.

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

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.

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: The presence of disseminated (miliary) TB or tuberculous meningitis. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe.

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".

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

Executive summary

Tuberculosis (TB), with an estimated incidence of 10 million people every year (range 8.9–11.0 million), is a major cause of ill health and one of the leading causes of death worldwide. Until the coronavirus disease (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV, with an estimated 1.2 million TB deaths among people who are HIV-negative (range, 1.1–1.3 million), and an additional 208 000 deaths among people who are HIV-positive (range, 177 000–242 000). Of the estimated 10 million cases, about 70% are diagnosed and treated, and reported to the World Health Organization (WHO), resulting in 7.1 million TB notifications by national TB programmes (NTPs). Of the 7.1 million people notified in 2019, 5.9 million (84%) had pulmonary TB.²

For several decades, WHO has developed and issued recommendations for the treatment of TB. WHO published recommendations for treating people suffering from drug-susceptible TB (DS-TB) in 2010,³ with updates in 2017⁴ and 2022. A focus of the 2010 and 2017 guidelines was a 6-month treatment regimen comprising four first-line TB medicines (i.e. isoniazid, rifampicin, pyrazinamide and ethambutol) recommended for treatment of DS-TB. This regimen is well known and has been widely adopted worldwide for decades; about 85% of patients on this regimen have a successful treatment outcome. The regimen is based on seminal TB treatment studies conducted by the Medical Research Council of the United Kingdom of Great Britain and Northern Ireland in the second half of the 20th century.⁵ The 2010 WHO guidelines and the 2017 update also included several recommendations on the modalities and formulations used for treatment, frequency of treatment administration, special situations and patient care during treatment. The 2022 *WHO consolidated guidelines on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment* consolidates all valid and evidence-based recommendations from the 2010 guidelines and the 2017 guideline updates; it also includes a new section stemming from the most recent round of guidelines development – the recommendation for two 4-month regimens for the treatment of DS-TB.^{6,7,8}

This document, the *WHO operational handbook on tuberculosis Module 4: Treatment – drug-susceptible TB treatment*, has been developed in the context of the End TB Strategy, which recommends treatment and care for all people with TB.⁹ It aims to use the best available evidence on the treatment of DS-TB to inform policy decisions made by NTP managers, national policy-makers and medical practitioners in all geographical, economic and social settings.

² Global tuberculosis report 2021. Geneva: World Health Organization; 2021 (<https://www.who.int/publications/i/item/9789240037021>).

³ Treatment of tuberculosis: guidelines – 4th ed. (WHO/HTM/TB/2009.420). Geneva: World Health Organization; 2010 (<https://apps.who.int/iris/handle/10665/44165>).

⁴ Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/255052>).

⁵ Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. *Int J Tuberc Lung Dis*. 1999;3(10 Suppl 2):S231–79 (<https://pubmed.ncbi.nlm.nih.gov/10529902/>).

⁶ WHO consolidated guidelines on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022.

⁷ WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/i/item/9789240046764>).

⁸ WHO operational handbook on tuberculosis Module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/bitstream/handle/10665/352523/9789240046832-eng.pdf>).

⁹ The End TB Strategy (WHO/HTM/TB/2015.19). Geneva: World Health Organization; 2015 (<https://www.who.int/publications/i/item/WHO-HTM-TB-2015.19>).

Key WHO recommendations on DS-TB

Treatment of DS-TB using the 6-month regimen

1. **New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR.**
(Strong recommendation, high certainty of evidence)
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)
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)
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)
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

6. **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) – new recommendation
7. **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) – new recommendation

DS-TB treatment and antiretroviral therapy in people living with HIV

8. **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)

9. **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

10. **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*)
11. **In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.**
(*Conditional recommendation, very low certainty of evidence*)

1. Introduction

This operational handbook on the treatment of drug-susceptible tuberculosis (DS-TB) complements the World Health Organization (WHO) publication *WHO consolidated guidelines on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment (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 handbook 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 a dedicated module: *WHO operational handbook on tuberculosis Module 4: Treatment – tuberculosis care and support (2)*.

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 (3). 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.

2. Key considerations in DS-TB treatment

2.1 TB diagnostics and drug susceptibility testing

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 (4). 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 (5). 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% (4). The highest proportions (>50% in previously treated cases) are found in countries in Eastern Europe and Central Asia (5).

Resistance to fluoroquinolones 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%) (6–10). 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 (5, 11). 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 (12–14).

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 (15–17).

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 (4, 18).

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 fluoroquinolones 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 fluoroquinolones. 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 fluoroquinolones. 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 re-treatment at, or before, the start of that re-treatment – at least for isoniazid and rifampicin resistance. Whenever rifampicin resistance is confirmed, testing for resistance to fluoroquinolones 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 (18).

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 (7). 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 trial¹⁰ and one based on the SHINE trial¹¹ (7).

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)/ 4 HR, 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,¹² in settings with isoniazid resistance or in children living with HIV (CLHIV), but can otherwise be omitted, resulting in the 2HRZ/4HR regimen (20).

¹⁰ Study 31 is a Phase III trial: TBTC Study 31/ACTG A5349 (7), also referred to as S31/A5349.

¹¹ 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.

¹² 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% (19).

- 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 resistance¹³ or in children and adolescents living with HIV (CALHIV).

Choice criteria for regimens in different age groups are summarized in [Table 2.1](#).

Table 2.1. Guide for regimen selection for DS-TB

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

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 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.

¹³ 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 2.1](#)).

In patients who require TB re-treatment, 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 (7).

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 (21), 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, although the success rate varies among WHO regions and is lower in PLHIV (7, 5). This regimen is estimated to have averted 66 million deaths during the 20 years from 2000 to 2020.

The core WHO recommendations included in the 2022 WHO guidelines for treatment of DS-TB are summarized below, with remarks.

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:

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 (7). 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:

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)

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

The use of FDC tablets is recommended over separate drug formulations in the treatment of patients with DS-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:

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 (18).

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 (7). 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 (20).

As a general rule, WHO does not recommend prolonging the regimen beyond 6 months (7), 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 (22).

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. (Web annex 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 (4). 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 difficulty 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 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 (7).

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 (7). 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 (7).

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 (7).

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) (7).

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 PLHIV

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. Key considerations for managing concomitant TB and HIV therapy were published by WHO in 2016 (23). 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) (23). 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 (24).

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 1. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in infants (20).

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 adverse events.

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 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 (25). Section 9 provides additional details on clinical monitoring in cases of adverse events 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 (26-28). The recent Phase III trial Study 31 (1) assessed the safety and efficacy of two 4-month regimens for the treatment of DS-TB (29). 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 (29).

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 adverse events 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 adverse events were noted in 18.8% of participants in the rifapentine-moxifloxacin arm compared with 19.3% in the standard 2HRZE/4HR regimen (29).

The slight difference in all-cause mortality and adverse events 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:

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) – new recommendation.

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/mm³ 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/mm³;
- children and adolescents aged under 12 years; and
- pregnant, breastfeeding and postpartum women.

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 1). The study was based on the regimen with moxifloxacin; therefore, replacement of moxifloxacin by another fluoroquinolone 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 fluoroquinolones, is rapidly expanding. WHO recommends rapid genotypic testing for TB and RR-TB as an initial test at diagnosis; if DST for the fluoroquinolones 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 fluoroquinolones would not be necessary for patients with confirmed rifampicin-susceptible TB by a reliable, WHO-recommended rapid molecular diagnostic test. The prevalence of fluoroquinolone resistance in patients without confirmed rifampicin resistance is usually low (6-10) but can reach 15% in patients with documented DR-TB (5). In settings where the prevalence of resistance to fluoroquinolones in patients with DS-TB is higher because of their widespread use for other conditions, DST for the fluoroquinolones would be highly recommended at baseline to exclude fluoroquinolone resistance (5).

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/m²) 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 (7).

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 (7).

PLHIV

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/mm³.

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 (30). 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 (7). 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 adverse events related to moxifloxacin that are common to other fluoroquinolones (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) (7, 37).

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) – new recommendation

5.1 Eligibility

The eligibility criteria in children and adolescents are summarized in Box 5.1 (30).

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

In children and adolescents who have undergone bacteriological testing and CXR, a 4-month treatment regimen should be started if all of the following criteria are met:

- CXR findings are consistent with non-severe TB; for example:
 - intrathoracic lymph node TB without significant airway obstruction;
 - pulmonary TB confined to one lobe with no cavities and no miliary pattern; or
 - uncomplicated pleural effusion (without pneumothorax or empyema);

- TB is negative, trace, very low or low by Xpert MTB/RIF or Ultra, or sputum smear negative (if Xpert MTB/RIF or Ultra are not available); and
- the child or adolescent has mild TB symptoms that do not require hospitalization.^a

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

- TB is negative, trace, very low or low by Xpert MTB/RIF or Ultra or smear negative; and
- the child or adolescent has mild TB symptoms that do not require hospitalization.^a

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

- there is isolated extrathoracic (peripheral) lymph node TB, without involvement of other extrapulmonary sites of disease; or
- the child or adolescent has mild TB symptoms that do not require hospitalization.^a

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 CALHIV in the SHINE trial received ethambutol in the first 2 months of treatment (regardless of which regimen they received). It is therefore preferred that CALHIV 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 1).

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 (7). 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 (78). 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 (30). 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 (20).

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).

CALHIV

CALHIV were eligible for enrolment in the SHINE trial; 65 (11%) CALHIV were enrolled in the 16-week arm and 62 (10%) in the 24-week arm, with 49% of CALHIV in the 16-week arm and 43% in the 24-week arm being on ART at the time of enrolment. Among CALHIV, 20% in both arms had a CD4 count of less than 200 cells/mm³, and 51% of CALHIV 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 CALHIV 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)¹⁴ 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.

¹⁴ Defined as weight-for-height Z-score below -3 or mid-upper-arm circumference below 115 mm (33).

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
- *CALHIV* – 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.

Symptomatic improvement and weight gain are the most valuable markers of treatment success or failure (30). 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 (30):

- incorrect dosage;
- adherence being compromised by adverse events; 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 (30), but this does not mean they are not responding to treatment.

6. Treatment of DS-TB in PLHIV

Worldwide, a total of 375 963 cases of TB among PLHIV were notified in 2020, equivalent to 9% of the 4.2 million people diagnosed with TB who had an HIV-positive test result. Overall, the percentage of people diagnosed with TB who are HIV-positive has fallen globally over the past 10 years.

The coverage of ART among people diagnosed with TB and known to be HIV-positive was 88% in 2020, the same level as in 2019. By 2020, most people provided with TPT were living with HIV.

Treatment success rates remain lower among PLHIV (77% globally in 2019 – the latest annual patient cohort for which data are available) although there have been steady improvements over time. TB treatment and provision of ART to HIV-positive people diagnosed with TB are estimated to have averted 66 million deaths between 2000 and 2020 (5). Patients with HIV infection and TB have an increased risk of death, treatment failure and relapse (5). 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 (23, 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 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/mm³.

6.2 Composition and duration of the regimen

All PLHIV 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 (7, 36). The 4-month regimen with rifapentine and moxifloxacin has also been shown to perform well in patients who are also HIV-positive (7). The evidence on the use of this 4-month regimen in PLHIV was limited to those with a CD4 count of above 100 cells/mm³; hence, the CD4 count value below 100 cells/mm³ is currently used in excluding PLHIV from the shorter regimen. For PLHIV with a CD4 count above that threshold, both regimens can be used.

CALHIV were eligible for enrolment in the SHINE trial. In view of the limited evidence available from the trial, clinicians may consider treating CALHIV 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 PLHIV (especially those with TB) should receive ART. PLHIV who are responding to ART should not expect a less favourable outcome to a treatment episode than those who are HIV-negative. Therefore, PLHIV 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* (23) and *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders* (37).

6.3 Considerations for implementation

There are no new implementation considerations beyond the current standards of care for PLHIV. 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 PLHIV with tuberculous meningitis, because immediate ART is significantly associated with more serious adverse events. Thus, delaying ART for 4–8 weeks after initiation of TB treatment might be considered in these situations (38). In patients commencing ART with a CD4 count of less than 100 cells/mm³, giving steroids may reduce TB-related IRIS.

6.4 Treatment monitoring

There are no new monitoring and evaluation considerations beyond the current standard of care for PLHIV. 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 (5). The WHO European Region is facing an increasing notification rate of extrapulmonary TB: in this region seven countries (Finland, the Netherlands, Norway, Sweden, Turkey, the United Kingdom and Uzbekistan) reported more than 30% of cases (39).

Overall, among both adults and children, about two of every three extrapulmonary TB cases are represented by pleural and lymph node TB (40). In settings with a high prevalence of HIV infection, lymph node TB represents about 10% of all TB cases (41). Osteoarticular, urogenital, intra-abdominal, pericardial and meningeal TB are less frequent (40). 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 (42).

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 (40). 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 CALHIV.

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) (40), and 9 months of treatment for osteoarticular TB (given the difficulties in assessing treatment response) (40, 43–45).

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) (20). 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) (20). 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 (7).

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 (7). 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, 23, 37, 43, 46).

In patients with tuberculous meningitis, evidence from RCTs (47–51) 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 adverse events and severe adverse events, 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 (52–59) 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 (54). 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 PLHIV 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 (55). 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 (54). 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 (38). 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 (5). Diabetes was estimated to account for more than 10% of global TB deaths among HIV-negative individuals (60).

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 (61). 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 (61).

Diabetes has a negative effect on the pharmacology of some anti-TB drugs (e.g. rifampicin), with higher risk of development of drug-resistance (61). 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 drug–drug interactions (61).

A higher proportion and sometimes a greater severity of adverse events has been described in TB patients with diabetes (e.g. peripheral neuropathy due to isoniazid and ocular neuropathy due to ethambutol) (61).

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 adverse events 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 (62).
- 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 (63).

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 (64). 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 (65). 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 (66). Disseminated TB in the mother can cause congenital TB in the infant, but this is a rare condition (67). 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 (68). 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 (69, 70). 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 (71). 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 (7). 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 (72).

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 adverse events to the mother and the child, monitoring of adverse events 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 (62, 73).
- 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 (5, 74). Outbreaks in nursing homes are frequently described, particularly in countries with a low incidence of TB (75, 76). 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 (77).

The main challenges to successful treatment among older patients include poor drug tolerance, adverse events 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 (43, 74). 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 (72).

Gastrointestinal upset and hepatitis are reported as the most frequent adverse events in older people (78, 79). 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 (80).

Clinical attention should be paid to older patients undergoing pyrazinamide treatment, to rapidly identify and manage any adverse events that eventually appear. Guidelines from the American Thoracic Society consider the option of excluding pyrazinamide in patients aged over 80 years (43).

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 (81). 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 (82).

Older individuals are likely to have several comorbidities and are therefore likely to be taking other medicines; hence, there is potential for drug–drug interactions (83). 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 (72).

Among older people, particular care is also necessary to ensure correct adherence to the prescribed treatment within a multidisciplinary and patient-centred approach (43, 84).

Implementation considerations

- Although the drugs used to treat DS-TB are generally well tolerated and are unlikely to cause adverse events among older people, monitoring of adverse events 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 (62).
- 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 adverse events 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 (85).

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 (61, 85). 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 (78, 86).

Experts recommend close monitoring of creatinine every week or every 2 weeks, and adequate hydration (70). 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 (70).

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 (62, 73).

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 (70).

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 re-challenge with pyrazinamide may be hazardous. In this situation, pyrazinamide may be permanently discontinued, with treatment eventually extended to 9 months (70). In patients with advanced CLD, coagulation factors should be carefully monitored (43, 87–89).

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 fluoroquinolones (70). Given their important bactericidal and sterilizing action, where possible, isoniazid or rifampicin (or both) should be included (70).

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 (90).

Table 8.1. CTP score parameters

	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 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 (90).

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 (70, 85). 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 (43, 62).

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 chapter 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 adverse events 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 adverse events; 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 (91). A chest radiograph at the end of treatment is also useful to optimally manage TB pulmonary sequelae after treatment (91).

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); and
- 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 (73).

Sputum culture can be used for treatment monitoring. Although monthly culture is recommended for MDR/RR-TB cases (18, 73, 92, 93), 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 (97).

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 (94).

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 9.1 summarizes the activities involved in and the frequency of monitoring.

Table 9.1. Summary of activities for monitoring treatment response

Monitoring evaluation	Suggested frequency
<p>Evaluation by clinician and monitoring for adverse events</p>	<p><i>During the first 2 months of treatment:</i> 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.</p> <p><i>After the second month of treatment:</i> 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.</p> <p><i>For monitoring for adverse events:</i> Daily at every encounter by the treatment supporter, or when possible when performing VST.</p>
<p>Sputum smears and culture</p>	<p>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.</p>

Monitoring evaluation	Suggested frequency
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.

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 (43).

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 (ARDS). 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 (95). 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 (96). 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 (97-99).

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 (100).

The new treatment outcome definitions are summarized in [Table 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, 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 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 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.
<i>An optional definition was also proposed for use in operational research only</i>	
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.

^aReasons 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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Annex. 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.

Web annexes

Web annex 1

Clinical outcomes and pharmacokinetics of first-line drugs (rifampicin, isoniazid, ethambutol and pyrazinamide) in children (aged <18 years) treated for drug-susceptible tuberculosis: systematic review and meta-analysis.

Web annex 2

Optimization of dosage of the first-line medicines rifampicin, isoniazid, ethambutol and pyrazinamide in treatment of drug-susceptible tuberculosis: summary of evidence from four systematic reviews.



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