WHO consolidated guidelines on tuberculosis

Module 4: Treatment

Drug-resistant tuberculosis treatment

World Health Organization

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Recommendations for the management and care of drug-resistant tuberculosis, 2020 update

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Guideline Development Group

The chairs of the GDG were Holger J. Schünemann (Chair, Grading of Recommendations Assessment, Development and Evaluation [GRADE] methodologist: Cochrane Canada & McMaster University, Canada) and Rafael Laniado-Laborin (Co-chair, clinician, national TB programme [NTP], end-user: NTP and Regional Green Light Committee [rGLC], Mexico). The following experts served as members of the GDG: Susan Abdel-Rahman (pharmacology, pharmacodynamics, pharmacokinetics: Children's Mercy Hospital Kansas City, United States of America [USA]); Erlina Burhan (clinician, end-user: Department of Respiratory and Pulmonology, Persahabatan Hospital, Indonesia); Daniela Cirillo (laboratory specialist: San Raffaele TB Supranational Reference Laboratory, Italy); Charles Daley (pulmonologist, MDR-TB expert: National Jewish Health, USA); Geraint (Gerry) Rhys Davies (trials expert, pharmacologist: University of Liverpool, United Kingdom of Great Britain and Northern Ireland [United Kingdom]); Fernanda Dockhorn Costa Johansen (NTP, end-user, clinician: Ministry of Health MDR-TB Referral Centre, Brazil); Kelly Dooley (clinical pharmacologist, researcher: Johns Hopkins University School of Medicine, USA); Bernard Fourie (clinical trials expert: University of Pretoria, South Africa); Agnes Gebhard (technical agency, end-user, clinician: KNCV Tuberculosis Foundation, Netherlands); Elmira Gurbanova (rGLC, clinician, end-user: Lung Clinic, University of Tartu, Estonia, WHO Collaborating Centre on TB in Prisons, Azerbaijan); Muhammad Amir Khan (civil society representative; Association for Social Development, Pakistan); Yuhong Liu (clinician, end-user: Clinical Center on TB, Chinese Center for Disease Control and Prevention [China CDC], Beijing Chest Hospital, WHO Collaborating Centre on TB Research and Training, China); Marian Loveday (specialist scientist, maternal health medicine: South African Medical Research Council, South Africa); Barend (Ben) Marais (paediatrician: The University of Sydney School of Medicine, Australia); Iqbal Master (clinician, MDR-TB physician, end-user: King George V Hospital, South Africa); Alberto Mendoza (clinician, end-user: NTP, Peru); Beatrice

Mutayoba (programme manager, end-user: National TB and Leprosy Programme, United Republic of Tanzania); Payam Nahid (clinician, clinical trials expert: University of California San Francisco & American Thoracic Society, USA); Mahshid Nasehi (programme manager, end-user: National TB and Leprosy Control Programme, Iran); Alberto Piubello (clinician, MDR-TB physician, end-user: International Union Against Tuberculosis and Lung Disease, Niger); Maria Rodríguez (clinician, NTP, end-user: Ministry of Health MDR-TB Referral Centre, Dominican Republic); Rohit Sarin (technical agency, end-user: National Institute of TB & Respiratory Diseases, India); Ingrid Schoeman (former MDR-TB patient: TB PROOF, South Africa); Alena Skrahina (NTP, MDR-TB physician, end-user: Republican Research and Practical Centre for Pulmonology and Tuberculosis, Belarus); Carrie Tudor (nursing specialist, technical agency, end-user: International Council of Nurses, South Africa); Debrah Vambe (NTP, end-user: NTP, Eswatini); Andrew Vernon (trials expert, technical agency, end-user: United States Centers for Disease Control and Prevention [US CDC], USA); and Nguyen Viet Nhung (NTP, end-user: NTP, Ministry of Health, Viet Nam).

External Review Group

We thank the External Review Group (ERG), which had the following members: Heather Alexander (federal agency, technical partner: International Laboratory Branch, Division of Global HIV and Tuberculosis, US CDC, USA); Giovanni Battista-Migliori (clinician, researcher: European Respiratory Society (ERS) liaison officer, ERS TB Collaborating Centre, Maugeri Institute, Italy); Anuj K. Bhatnagar (clinician, researcher: Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, India); Lisa Chen (researcher: Curry International Tuberculosis Center, USA); Farhana Amanullah (paediatrician, paediatric nephrologist: Interactive Research and Development, Pakistan); Mildred Fernando-Pancho (civil society, former MDR-TB patient, Philippines); Anna Marie Celine Garfin (end-user, clinician: NTP, Philippines); Edwin H. Herrera-Flores (clinician, end-user: Hospital Nacional MDR-TB referral centre, Arzobispo Loayza, Lima, Peru); Mathilde Jachym (clinician, pneumologist: Sanatorium, France); Guy Marks (technical agency, end-user, clinician, researcher: International Union Against Tuberculosis and Lung Disease, Australia); Andrei Maryandyshev (clinician: Northern State Medical University Arkhangelsk, Russian Federation); Lawrence Mbuagbaw (epidemiologist, biostatistician: McMaster University, Canada); Thato Mosidi (civil society, former MDR-TB patient, South Africa); Bhabana Shrestha (clinician, end-user: Nepal Anti-TB Association, Nepal); Welile Sikhondze (clinician, researcher: NTP, Eswatini); Sarabjit Singh Chadha (technical agency: Global Drug Initiative Working Group, Foundation for Innovative New Diagnostics [FIND], India); Ivan Solovic (clinician, end-user: National Institute for TB, Lung Diseases and Thoracic Surgery, Slovakia); Carlos Torres (technical agency, end-user, clinician: Latin American Thoracic Society, Colombia); and Zarir Udwadia (clinician, end-user: Hinduja Hospital MDR-TB Referral Centre, Breach Candy Hospital and Parsee General Hospitals, Mumbai, India).

Evidence reviewers

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Observers and external partners

Draurio Barreira Cravo Neto (technical manager, TB: Unitaid, Switzerland); Dan Everitt (vice president and senior medical officer: TB Alliance, USA); Christopher Gilpin (global laboratory coordinator: International Organization for Migration, Switzerland); Anisa Hajizadeh (GRADE methods trainee: McMaster University, Canada); Brian Kaiser (technical officer: Stop TB Partnership's Global Drug Facility, Switzerland); Blessi Kumar (civil society representative: Global Coalition of TB Activists, India); Tamara Lotfi (GRADE methodologist: American University of Beirut, Lebanon); YaDiul Mukadi (technical advisor: United States Agency for International Development [USAID], USA); Norbert Ndjeka (director, Drug-Resistant TB, TB & HIV: Department of Health of the Republic of South Africa, South Africa); Eugene Sun (head of Research & Development: TB Alliance, USA); Kitty Van Weezenbeek (executive director: KNCV TB Foundation, Netherlands); Francis Varaine (project lead, EndTB Project: Médecins Sans Frontières, France); and Mohammed Yassin (senior disease advisor, TB: The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland).

WHO Guideline Steering Committee

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Abbreviations and acronyms

aDSM	active TB drug safety monitoring and management
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
aIPD	adult individual patient data
aOR	adjusted odds ratio
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATS	American Thoracic Society
BID	twice a day
BPaL	bedaquiline, pretomanid and linezolid
CI	confidence interval
CL	confidence limits
CNS	central nervous system
DALY	disability adjusted life year
DELIBERATE	DELamanId Bedaquiline for ResistAnt TubErculosis (trial)
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
ECG	electrocardiogram
EDRWeb	Electronic Drug-Resistant Tuberculosis Register (South Africa)
FDC	fixed-dose combination (medicines)
GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
HR	isoniazid–rifampicin
HREZ	isoniazid–rifampicin–ethambutol–pyrazinamide
(H)REZ	(isoniazid optional)–rifampicin–ethambutol–pyrazinamide
Hr-TB	rifampicin-susceptible, isoniazid-resistant tuberculosis
IPD	individual patient data (or dataset)
IPD-MA	individual patient data meta-analysis
IQR	interquartile range
LPA	line probe assay
LTBI	latent tuberculosis infection

MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug- or rifampicin-resistant tuberculosis
MIC	minimum inhibitory concentration
MSF	Médecins Sans Frontières
NTP	national TB control programme
PICO	population, intervention, comparator and outcomes
PLHIV	people living with HIV
QD	once a day
QTcF	corrected QT interval by Fridericia
RCT	randomized controlled trial
REZ	rifampicin–ethambutol–pyrazinamide
RR-TB	rifampicin-resistant TB
SAT	self-administered therapy (also meaning unsupervised treatment)
SMS	short message service (mobile phone text message)
SRL	TB Supranational Reference Laboratory
STREAM	Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (trial)
TB	tuberculosis
USA	United States of America
USAID	United States Agency for International Development
US CDC	United States Centers for Disease Control and Prevention
US FDA	United States Food and Drug Administration
VOT	video-observed treatment
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Definitions

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]

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

Extensively drug resistant TB (XDR-TB): TB that is resistant to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.[2]

Longer multidrug-resistant TB (MDR-TB) regimens: used for treatment of multidrug- or rifampicin-resistant TB (MDR/RR-TB), these regimens last 18 months or more, and are designed using a hierarchy of recommended medicines, including a minimum number of medicines considered to be effective based on drug-resistance patterns or patient history. The features and indications of these regimens are further elaborated in the Recommendations in these guidelines.

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

New case: a newly registered episode of TB in a patient who has never been treated for TB or has taken anti-TB medicines for less than 1 month.

Operational research or **implementation research:** "the use of systematic research techniques for programme decision-making to achieve a specific outcome".[3] In the context of this document, it is also applied research that aims to develop the critical evidence base that informs the effective, sustained and embedded adoption of interventions within a health system, to improve health or patient outcomes. Such research deals with the knowledge gap between efficacy, effectiveness and current practice to produce the greatest gains in disease control.[4] Operational research also provides decision-makers with information to enable them to improve the performance of their health programmes.[5]

Previously treated: patients who have received 1 month or more of anti-TB medicines in the past. Previously treated cases may have been treated with a first-line regimen for drug-susceptible TB or a second-line regimen for drug-resistant forms (e.g. shorter MDR-TB regimen).

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1 Implementing tuberculosis diagnostics: a policy framework. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.11; http://apps.who.int/iris/bitstream/10665/162712/1/9789241508612_eng.pdf, accessed 15 February 2019).

2 The current definition of XDR-TB will probably need to be changed, given the phasing out of injectables, anticipated patterns of resistance that are more relevant to current and future regimens, and advances in diagnostic methods and drug susceptibility testing (DST). Changes to the definition of XDR-TB will be the subject of future expert consultation, and will be included in revised WHO surveillance and reporting guides. Choosing appropriate regimens for patients with strains showing multidrug-resistant TB (MDR-TB) plus additional resistance to fluoroquinolones (so-called "pre-XDR") are becoming more important and feasible, thanks to rapid advances in molecular DST.

3 Allotey P, Reidpath DD, Ghalib H, Pagnoni F, Skelly WC (2008) Efficacious, effective, and embedded interventions: implementation research in infectious disease control. BMC Public Health 8: 343.

4 The Global Fund and World Health Organization. Guide to operational research in programmes supported by the Global Fund. Geneva: The Global Fund; 2007.

5 Expanding capacity for operations research in reproductive health: summary report of a consultative meeting, World Health Organization, Geneva, Switzerland, December 10–12, 2001. Geneva: World Health Organization; 2003.

Rifampicin-resistant TB (RR-TB): TB caused by *M. tuberculosis* strains resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line or second-line TB medicines. In these guidelines and elsewhere, MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB and are eligible for treatment with MDR-TB regimens.

Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB): caused by *M. tuberculosis* strains resistant to isoniazid and susceptible to rifampicin.

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

Serious adverse events: is an adverse event that leads to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly. Serious adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included. Serious adverse events may require a drastic intervention, such as termination of the drug suspected of having caused the event.

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

Shorter MDR/RR-TB regimen: a course of treatment for MDR/RR-TB lasting 9–12 months, which is largely standardized, and whose composition and duration follows closely the one for which there is documented evidence from different settings.

Treatment outcomes and relapse: the categories for treatment outcomes used in these guidelines and the term relapse were applied according to the definitions agreed for use by TB programmes, unless otherwise specified.[6]

[6] Definitions and reporting framework for tuberculosis – 2013 revision. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.2; http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf, accessed 15 February 2019). Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005;9(6):640–5.

Executive summary

Tuberculosis (TB) strains with drug resistance are more difficult to treat than drug-susceptible ones, and present a major challenge for patients, health care workers and health care services. In addition, the increase of drug-resistant TB threatens global progress towards the targets set by the End TB Strategy[7] of the World Health Organization (WHO). Thus, there is a critical need for the continual development of evidence-based policy recommendations on the treatment and care of patients with drug-resistant TB, based on the most recent and comprehensive evidence available.

In the past decade, WHO has developed and issued evidence-based policy recommendations for the treatment and care of patients with drug-resistant TB, published in a range of documents (see **Box 1**). More recently, WHO has started to consolidate guidelines, in response to requests from Member States to facilitate policy transfer at the country level. The first integrated recommendations for the management and care of multidrug- or rifampicin-resistant TB (MDR/RR-TB) were released in 2019 as the WHO consolidated guidelines on drug-resistant tuberculosis treatment.[8] The consolidation of WHO recommendations on TB and drug-resistant TB has now been expanded to better outline the path that a patient will take following exposure to resistant strains of *Mycobacterium tuberculosis*, once infection has progressed to TB disease, and the patient has been identified by the health system and referred for drug-resistant TB treatment.

The guidance provided in this module outlines specific WHO recommendations on the overall treatment management, care and monitoring of patients with MDR/RR-TB. It brings forward recommendations developed by various WHO-convened Guideline Development Groups (GDGs), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the evidence, and formulate policy recommendations and accompanying remarks. However, it also incorporates new recommendations that were made in November 2019, based on new evidence that was available to WHO on the following: shorter regimens for MDR/RR-TB; the use of the bedaquiline, pretomanid and linezolid (BPaL) regimen for patients with MDR/RR-TB and additional fluoroquinolone resistance; the use of bedaquiline beyond 6 months; the use of bedaquiline in pregnancy; and the use of bedaquiline and delamanid together. In particular, this module focuses on public health recommendations on the use of effective treatment regimens for drug-resistant TB; specifically, regimens for isoniazid-resistant TB, all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting antiretroviral therapy (ART) in patients on second-line anti-TB regimens, surgery for patients on MDR-TB treatment, and care and support measures for patients with MDR/RR-TB. Additionally, in an effort to inform the global community of the major gaps and research areas to be addressed to help inform the development of evidence-based recommendations, this document outlines the research priorities that will help us generate knowledge on evidence-based and attainable standards of health.

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[7] End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization; 2014 (https://www.who.int/tb/strategy/en/, accessed 20 March 2020).

[8] WHO consolidated guidelines on drug-resistant tuberculosis treatment (WHO/CDS/TB/2019.7). Geneva: World Health Organization; 2019 (https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/, accessed 6 March 2020).

Box 1. WHO treatment recommendations incorporated into the present module on management and care of drug-resistant TB treatment

- Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2011.6).
- The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.6).
- The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.23).
- The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.14).
- WHO treatment guidelines for drug resistant tuberculosis: 2016 update. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.4).
- Guidelines for the treatment of drug-susceptible tuberculosis and patient care: 2017 update. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.05).
- WHO treatment guidelines for isoniazid-resistant tuberculosis. Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.7).
- WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.15).
- WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.7).

The objective of the present update is to provide evidence-based information on critical areas that will help to inform the use of novel all-oral regimens and potential label expansion for new TB medicines – for example, concomitant bedaquiline and delamanid use, extended bedaquiline use, and assessment of bedaquiline use in special populations – and that will supersede earlier guidance. In this updated document, stakeholders will be able to distinguish between previous recommendations that remain valid, those that have been updated, and those that have been newly developed based on additional studies, considering the range of known benefits and potential harms, modelling exercises and other data to inform the decision-making process.

The recommendations included herein are a component of the WHO consolidated guidelines on tuberculosis, and are primarily intended for use by national TB control programmes (NTPs), public health agencies, and other key constituencies involved in the planning, implementation and monitoring of activities for the programmatic management of drug-resistant TB.

The methods used to develop and formulate the recommendations complied with WHO standards for guideline development, and were based on up-to-date evidence reviews, complemented with additional information on values and preferences, feasibility and acceptability, and cost. The GRADE approach was used to rate the certainty in the estimate of effect (i.e. quality of evidence) as high, moderate, low or very low; it was also used to determine the strength of the recommendations, rating them as strong or conditional.

Current WHO recommendations on treatment and care for drug-resistant TB

The present recommendations for the treatment and care of drug-resistant TB have been derived from earlier WHO guideline documents (**Box 1**), and a recent WHO guideline development exercise conducted at the end of 2019. The current recommendations supersede the WHO consolidated guidelines on drug-resistant tuberculosis treatment that were published in 2019.[9]

This module contains policy recommendations on treatment regimens for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB) and MDR/RR-TB, including all-oral shorter and longer regimens for MDR/RR-TB, monitoring of patients on treatment, the timing of ART in MDR/RR-TB patients infected with HIV, the use of surgery for patients receiving MDR-TB treatment, and models of patient support and care. The recommendations are presented below.

1. Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis

1.1 In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.
(Conditional recommendation, very low certainty in the estimates of effect)

1.2 In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.
(Conditional recommendation, very low certainty in the estimates of effect)

2. Shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant tuberculosis

2.1 A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.
(Conditional recommendation, very low certainty in the evidence)

3. Longer regimens for multidrug- or rifampicin-resistant tuberculosis

3.1 In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.
(Conditional recommendation, very low certainty in the estimates of effect)

[9] WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, Switzerland: World Health Organization; 2019 (https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1, accessed 20 March 2020).

3.2 Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.
(Conditional recommendation, very low certainty in the estimates of effect)

3.3 Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.
(*Strong recommendation, moderate certainty in the estimates of effect*)

3.4 Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more.
(*Strong recommendation, moderate certainty in the estimates of effect*)
Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.
(*Conditional recommendation, very low certainty in the estimates of effect*)

3.5 Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.
(Strong recommendation, moderate certainty in the estimates of effect)

3.6 Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.
(Conditional recommendation, very low certainty in the estimates of effect)

3.7 Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.
(Conditional recommendation, very low certainty in the estimates of effect)

3.8 Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens.
(Conditional recommendation, moderate certainty in the estimates of effect)

3.9 Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens.
(Conditional recommendation, very low certainty in the estimates of effect)

3.10 Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.
(Conditional recommendation, very low certainty in the estimates of effect)[10]

3.11 Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.
(Conditional recommendation, very low certainty in the estimates of effect)

3.12 Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.
(Conditional recommendation against use, very low certainty in the estimates of effect)

3.13 *P*-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.
(Conditional recommendation against use, very low certainty in the estimates of effect)

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

3.14 Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens.
(Strong recommendation against use, low certainty in the estimates of effect)

3.15 In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.
(Conditional recommendation, very low certainty in the estimates of effect)

3.16 In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy.
(Conditional recommendation, very low certainty in the estimates of effect)

3.17 In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.
(Conditional recommendation, very low certainty in the estimates of effect)

4. The bedaquiline, pretomanid and linezolid (BPaL) regimen for multidrug-resistant tuberculosis with additional fluoroquinolone resistance

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

5. Monitoring patient response to MDR-TB treatment using culture

5.1 In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response *(Strong recommendation, moderate certainty in the estimates of test accuracy)***. It is desirable for sputum culture to be repeated at monthly intervals.**

6. Starting antiretroviral therapy in patients on second-line anti-TB regimens

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

7. Surgery for patients on multidrug-resistant TB treatment.

7.1 In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen.
(Conditional recommendation, very low certainty in the evidence)

8. Care and support for patients with multidrug- or rifampicin-resistant tuberculosis

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

8.2 A package of treatment adherence interventions[11] may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option.[12]
(Conditional recommendation, low certainty in the evidence)

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

a) tracers[13] and/or digital medication monitor[14] *(Conditional recommendation, very low certainty in the evidence);*

b) material support[15] to the patient *(Conditional recommendation, moderate certainty in the evidence);*

c) psychological support[16] to the patient *(Conditional recommendation, low certainty in the evidence);*

d) staff education[17] *(Conditional recommendation, low certainty in the evidence).*

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

a) Community- or home-based directly observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment *(Conditional recommendation, moderate certainty in the evidence).*

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

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

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

[12] Treatment administration options include DOT, non-daily DOT, VOT or unsupervised treatment.

[13] "Tracers" refer to the communication with the patient, including home visits or via SMS or telephone (voice) call.

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

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

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

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

8.5 Patients with multidrug-resistant TB (MDR-TB) should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.
(Conditional recommendation, very low quality evidence)

8.6 A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment.
(Conditional recommendation, very low certainty in the evidence)

Main changes to the guidance in the current update
(see also Supplementary table)

- One recommendation on shorter regimens to treat MDR/RR-TB has been updated. The shorter regimen conditionally recommended in this update comprises 6 Bdq with 4–6 Lfx/Mfx-Cfz-Z-E-Hh-Eto/ 5 Lfx/Mfx-Cfz-Z-E (in previous guidance, the shorter regimen comprised 4–6 Am-Mfx-Cfz-Eto-Z-E-Hh/ 5 Mfx-Cfz-Z-E). The new shorter regimen is recommended as a standardized package. New information has been included in these guidelines (Recommendations – Section 2) on the use of this shorter regimen, including implementation considerations for national TB programmes.
- A new 6–9-month regimen composed of bedaquiline, pretomanid and linezolid (BPaL) has been conditionally recommended for use in patients with MDR/RR-TB and additional fluoroquinolone resistance, under operational research conditions only. A new section (Recommendations – Section 4) has been added to these guidelines to describe the evidence that was assessed in relation to this regimen, the eligible population and the conditions of use as part of operational research studies.
- Additional guidance on the safety of extended bedaquiline use (beyond 6 months), the concurrent use of bedaquiline and delamanid, and the use of bedaquiline during pregnancy has been provided in the section on longer regimens for MDR/RR-TB (Recommendations – Section 3). The grouping of medicines into Groups A, B and C has not changed since the previous guidelines were issued by WHO in 2018.
- The content of the guidelines has been updated, citing current references and the latest available evidence, including unpublished data on cost–effectiveness, safety and patient preferences for treatment.
- The research gaps have been updated to reflect the latest evidence reviewed.

Introduction

Drug-resistant tuberculosis (TB) continues to be a public health problem, taking a heavy toll on patients, communities and health care systems. Recent global estimates indicate that there were about half a million new cases of multidrug- or rifampicin-resistant TB (MDR/RR-TB) in 2018, with less than 40% of the estimated burden being notified and 32% reported to have started second-line treatment *(1)*. Current treatment regimens for MDR/RR-TB patients are far from satisfactory. Compared with treatments for drug-susceptible TB forms, these regimens require a longer course of treatment, a higher pill burden and the use of medicines with a higher toxicity profile; in addition, patients may develop significant adverse events and have poorer treatment outcomes. Globally, although treatment success rates have increased, almost 15% of MDR/RR-TB patients die from the disease, and 26% of those deaths are in patients with extensively drug-resistant TB (XDR-TB) *(1)*.

The Global TB Programme of the World Health Organization (WHO) is now combining all current recommendations into one overall set of consolidated guidelines on TB. The guidelines will contain recommendations pertaining to all areas related to the programmatic management of TB (e.g. screening, preventive treatment, diagnostics, patient support, and the treatment of drug-susceptible and drug-resistant TB). The consolidated guidelines will contain modules specific to each programmatic area. This current module is on the treatment of drug-resistant TB; it presents WHO recommendations that have been newly developed and are published here for the first time, and existing recommendations that have been previously published in other WHO guidelines that applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Structure of the document

The Recommendations part of this document has eight main sections that cover aspects of the treatment of drug-resistant TB. The aspects covered are:

- the treatment of rifampicin-susceptible and isoniazid-resistant TB (Section 1);
- the shorter all-oral bedaquiline-containing regimen for MDR/RR-TB (Section 2);
- the composition and duration of longer regimens for MDR/RR-TB (Section 3);
- the bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance (Section 4);
- monitoring of the patient response to MDR-TB treatment (Section 5);
- the use of antiretroviral therapy (ART) for people living with HIV infection (Section 6);
- the role of surgery for patients on MDR-TB treatment (Section 7); and
- the vital role of care and support for patients with MDR/RR-TB (Section 8).

Each section starts with the current WHO recommendations for that aspect, then gives information on the evidence used to inform that recommendation, a summary of the analyses that were carried out based on the evidence, considerations for specific subgroups, and considerations for monitoring and evaluation and implementation. Research gaps identified for each of the sections are presented at the end of this document, while online annexes provide more details on the methods, the Guideline Development Groups (GDGs), the analyses, unpublished data and statistical analysis plans. Each section reflects discussions held at GDG meetings over recent years. Additional information on the management of MDR/RR-TB is presented in the relevant chapter of the *WHO operational handbook on tuberculosis*, a separate document that is designed to aid implementation efforts. Eventually,

the operational handbook will replace the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (2)*.

Background

Effective treatment of TB, including its drug-resistant forms, relies on the use of several medicines administered in combination for an adequate duration. Significant progress has been made in recent years in identifying more efficacious, safer medicines and shorter treatment regimens. The development of new TB drugs and the use of repurposed drugs such as linezolid and clofazimine has set a positive course; however, regimens for drug-resistant TB continue to present safety concerns, require long duration and put a significant burden on health care systems. Since the 1990s, WHO has regularly evaluated evidence on the use of specific drug compositions and combinations of different regimen durations *(3–12)*. Patients with drug-resistance patterns were often treated for 20 months or longer. In 2016, a standardized shorter treatment regimen (9–12 months) was recommended for patients with MDR/RR-TB strains not resistant to fluoroquinolones or second-line injectable agents, while longer regimens (18–20 months) continued to be an option for patients who were not eligible for the shorter option. Subsequent modifications to these treatment regimens led WHO to assess new evidence, which in turn resulted in revised recommendations, balancing effectiveness and harms on, for example:

- the use of all-oral longer treatment regimens; and
- the replacement of drugs associated with increased risk of treatment failure and relapse in the standardized shorter regimen.

Rationale for the update

The latest WHO evidence-based guidelines for the treatment of drug-resistant TB were released in December 2018 and incorporated into consolidated guidelines published in March 2019 *(11)*. Subsequently, new evidence on treatment for MDR/RR-TB and XDR-TB became available to WHO through national programmes, researchers and technical partners, and from a public call for data from WHO in August 2019 *(13)*. New data from patients on both longer (>18 months) and shorter (<12 months) MDR-TB regimens were validated and incorporated into the set of individual patient data (IPD) that had been established earlier to help inform development of WHO guidelines on drug-resistant TB (this dataset covers patients who have been treated for MDR/RR-TB, as of November 2019 it contains >13 000 patient records from 55 different studies or centres in 38 countries overall). International standards for meta-analysis were followed to assess the relative contributions of treatment regimens or combinations of medicines to patient treatment outcomes. WHO convened an independent GDG on 12–14 November 2019, to assess the results of these analyses using the GRADE system. The detailed recommendations presented here replace all previous and current WHO guidelines on the treatment of drug-resistant TB.

Scope of the 2020 update

This current module on drug-resistant TB management and care provides specific recommendations on the management and care of drug-resistant TB, including use of regimens for isoniazid-resistant TB, all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting ART in patients on second-line anti-TB regimens, surgery for patients on MDR-TB treatment, and care and support measures for patients with MDR/RR-TB.

These updated recommendations resulted from the 2019 GDG meeting, convened by WHO to review and discuss results on the following:

- use of all-oral shorter regimens (9–12 months duration);
- use of BPaL in combination for patients with MDR/RR-TB with additional fluoroquinolone resistance;

- use of bedaquiline for longer than 6 months;
- concurrent use of bedaquiline and delamanid; and
- use of bedaquiline-containing regimens in pregnant women.

Access to these data was achieved through close collaboration and engagement with national TB control programmes (NTPs), researchers, and a not-for-profit product-development partnership (TB Alliance) investigating the effectiveness and safety of these interventions (see **Annex 1**).

The text clearly indicates where recommendations are new.

Target audience

These guidelines are primarily targeted at policy-makers in ministries of health, or managers of NTPs who formulate country-specific TB treatment guidelines or who are involved in the planning of TB treatment programmes. It is expected that these updated recommendations will also be used by health professionals, including doctors, nurses and educators working in governmental and nongovernmental organizations, and by technical agencies involved in treating patients and organizing treatment services.

Recommendations

Section 1. Regimen for rifampicin-susceptible, isoniazid-resistant tuberculosis

1.1 Recommendations

No.	Recommendation
1.1	**In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.** *(Conditional recommendation, very low certainty in the estimates of effect)*
1.2	**In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.** *(Conditional recommendation, very low certainty in the estimates of effect)*

1.2 Justification and evidence

The recommendations in this section address one PICO (population, intervention, comparator and outcomes) question:

> ***PICO question 1*** *(Hr-TB, 2018): In patients with isoniazid-resistant TB (other than MDR-TB), which treatment regimen composition and duration, when compared with 6 months or more of rifampicin–pyrazinamide–ethambutol, leads to a higher likelihood of success with least possible risk of harm?*

Treatment with rifampicin, ethambutol and pyrazinamide – with or without isoniazid – has been used for the treatment of patients with rifampicin-susceptible, isoniazid-resistant TB (Hr-TB) *(14–16)*. The evidence reviewed for this guideline compared treatment regimens with isoniazid, rifampicin, ethambutol, pyrazinamide ((H)REZ)[18] of different durations (e.g. 6-month regimens versus longer duration ones). Additionally, the review of evidence focused on determining whether treatment outcomes in Hr-TB patients receiving (H)REZ treatment regimens of variable duration could be improved with the addition of a fluoroquinolone or streptomycin.

The evidence used to determine the composition and duration of regimens relied primarily on an analysis of IPD that comprised 33 databases with an analysable population of 5418 Hr-TB patients. All data used to develop these recommendations were derived from observational studies conducted in various settings (33% in Europe, 31% in the Americas, 26% in Asia and 6% in Africa) *(17)*.[19] In the IPD

[18] "(H)" indicates that isoniazid is optional.

[19] The number of patients highlighted in this section refers to the sample size of each study. However, the analysable sample size was later modified, depending on the availability of IPD for each analysable outcome (success and mortality).

analysed, patient treatment regimens contained rifampicin, ethambutol, pyrazinamide, streptomycin, isoniazid and fluoroquinolones; thus, recommendations could be made only for regimens containing these anti-TB agents. Based on an assessment of the certainty of the evidence, carried out using predefined criteria, the certainty of the evidence was rated as very low.

Duration of (H)REZ. The analysis comparing (H)REZ treatment regimens for 6 months (6(H)REZ) and more than 6 months (>6(H)REZ) demonstrated that a 6(H)REZ regimen had a higher likelihood of treatment success than a >6(H)REZ regimen. Further analyses determined that there was no statistically significant difference in the treatment outcomes of patients receiving regimens of 6-month REZ (6REZ) and those receiving more than 6 months REZ (>6REZ). Since data were not included on intermittent dosing of the 6(H)REZ and >6(H)REZ regimens, no inferences could be drawn about the use of alternating versus daily regimens. The effect of length of pyrazinamide use in the (H)REZ regimen was assessed, to investigate whether the use of this medicine could be minimized to the shortest possible duration. The reduction in treatment with pyrazinamide to less than 3 months was associated with a worse treatment outcome, even with the addition of streptomycin (adjusted odds ratio [aOR]: 0.4; 95% confidence limits [CL]: 0.2–0.7). In 118 patients on fluoroquinolone-containing regimens who received pyrazinamide for less than 4 months, the odds of treatment success were higher than in those who received a 6(H)REZ regimen, although the difference was not statistically significant.

Duration of levofloxacin use. In a subsample of 241 patients on an (H)REZ plus fluoroquinolone regimen, the median duration of fluoroquinolone use was 6.1 months (interquartile range [IQR]: 3.5; 8.4), and for REZ it was 9 months (IQR: 7; 11). Hence, in the observational studies that informed the IPD, it seems that treatment length was based on the completion of 6 months of treatment with a fluoroquinolone.

Acquisition of drug resistance. The analysis suggested that amplification of resistance to rifampicin was lower in patients receiving the 6(H)REZ regimen (0.6%) than in those receiving >6(H)REZ (4.3%). This observation could be due to the effect of selection and allocation of patients into specific regimens; for instance, the number of patients with extensive disease was slightly larger in those receiving >6(H)REZ. However, overall, the number of observations for each comparison was small and the effect was not statistically significant (aOR: 0.2; 95% CL: 0.02–1.70).

Adverse events. Data on adverse events were not evaluated owing to a of lack of standardization (dissimilar reporting). The GDG also considered two reports containing data from patients from the United States of America (USA) in whom a detailed assessment of adverse events suggested a risk of excess hepatotoxicity with the 6(H)REZ combination *(18)*. Drug-induced hepatotoxicity is not uncommon with anti-TB drugs. It has also been reported in individuals receiving rifampicin and pyrazinamide for 2 months for the treatment of latent TB infection (LTBI) – in such individuals, a much higher occurrence of hepatotoxicity has been observed than in those receiving only isoniazid preventive therapy *(19)*. It is not known whether the risk of hepatotoxicity differs between 6REZ and 6HREZ.

Addition of a fluoroquinolone. In patients with Hr-TB, treatment success rates were higher when fluoroquinolones were added to (H)REZ regimens than when patients were treated with 6(H)REZ or >6(H)REZ without the addition of fluoroquinolones (aOR: 2.8; 95% CL: 1.1–7.3). With the addition of fluoroquinolones in patients receiving (H)REZ, the number of deaths was reduced (aOR: 0.4; 95% CL: 0.2–1.1). Acquisition of additional resistance with progression to MDR-TB was also reduced when fluoroquinolones were added to a ≥6(H)REZ regimen (aOR: 0.10; 95% CL: 0.01–1.2), albeit with small absolute numbers: 0.5% (1/221) of patients on ≥6(H)REZ plus fluoroquinolones acquired resistance to rifampicin compared with 3.8% (44/1160) of patients who did not receive fluoroquinolones. Residual confounding could have increased this observed effect. The directness of the evidence was therefore downgraded because it was unclear whether fluoroquinolones were used at the beginning of treatment or only once drug susceptibility testing (DST) results were available (in the second month or later).

Addition of streptomycin. The analysis showed that the addition of streptomycin (up to 3 months) to an (H)REZ regimen with less than 4 months of pyrazinamide decreased the likelihood of treatment success (aOR: 0.4; 95% CL: 0.2–0.7), an effect that may in part be due to confounding. Addition of streptomycin did not reduce mortality significantly (see **Annex 3** and **Annex 4**). There were no data on the use of other injectable agents (i.e. kanamycin, amikacin and capreomycin) for the treatment of Hr-TB.

Treatment outcomes. When analysing the overall treatment outcomes for each one of the regimens assessed for this review, other limitations related to the characteristics of patients included in these studies were evident and could not be controlled for. Those limitations were patient selection, allocation to treatment with specific regimens and their relationship with disease severity. Outcomes appeared to be worse in patients with cavitary disease, persistence of sputum smear positivity and previous history of TB treatment, who received a 6(H)REZ or >6(H)REZ regimen with an additional 3 months of pyrazinamide and 1–3 months of streptomycin (see Hr-TB, 2018 in **Annex 3**). However, the limited number of observations made it difficult to draw definitive conclusions based on the severity of TB disease or the effect of other comorbidities on this regimen.

In formulating the recommendations, the GDG assessed the overall balance between benefits and harms of an (H)REZ–levofloxacin regimen; they also considered values and preferences (paying special attention to considerations of equity, acceptability and feasibility), in addition to clinical outcomes and the potential risks of increasing toxicities (see **Annex 3** and **Annex 4** for more details). The conclusions of the GDG were that a regimen composed of 6 months of REZ plus fluoroquinolones was associated with higher treatment success rates (with or without the addition of isoniazid). The difference between the 6(H)REZ and >6(H)REZ regimens was modest, slightly favouring the 6-month regimen (not statistically significant). The GDG acknowledged that it was not possible to control for all possible confounding by indication when comparing the 6(H)REZ and >6(H)REZ regimens. As an example (although data on the extent of disease were not systematically captured for all patients), it is possible that a larger number of cases with extensive disease received >6(H)REZ regimens, resulting in poor outcomes for this group of patients (given the extent of disease) and possibly favouring the 6(H)REZ regimen.

The GDG acknowledged the safety implications of (H)REZ–levofloxacin, particularly for hepatotoxicity associated with prolonged use of pyrazinamide-containing multidrug regimens. However, reducing the duration of the treatment with pyrazinamide to 3 months or less was associated with worse treatment outcomes, at least in Hr-TB regimens without a fluoroquinolone. Furthermore, the use of streptomycin in these regimens was associated with no significant added benefit. The use of streptomycin and other injectable agents has also been associated with increased serious adverse events *(20–22)*. On this basis, the GDG agreed that current data supported the use of the (H)REZ–levofloxacin regimen without streptomycin or any other injectable agent in Hr-TB cases, unless there is a compelling reason to do so (e.g. certain forms of polydrug resistance).

The GDG also noted that patients were likely to place a high value on a 6-month regimen, the likelihood of a relapse-free successful outcome and, especially, the implementation of a regimen without the use of injectable agents. GDG members agreed that the use of the 6(H)REZ regimen would probably increase health equity, given that the cost of the components is relatively low (compared with the recommended regimens for MDR/RR-TB) and the increased probability of cure in a substantial number of patients. In addition, the exclusion of streptomycin and other injectable agents reduces potential barriers to regimen administration.

Although patient costs were not factored into the analysis, the GDG agreed that improving diagnostic capacity to detect isoniazid resistance would be beneficial. A modelling analysis performed for the 2011 update of the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* estimated that the best strategy for averting deaths and preventing acquired MDR-TB was to undertake DST in all patients before treatment using a rapid test that detects resistance to isoniazid and rifampicin *(23)*. The modelling work also showed that rapid testing for resistance to both isoniazid

and rifampicin at the time of diagnosis was the most cost-effective testing strategy for any patient group or setting, even at very low levels of resistance among TB patients (MDR-TB in >1% and isoniazid resistance [other than MDR-TB] in >2%).

In general, the GDG considered that the use of the 6(H)REZ–levofloxacin regimen would be feasible in most drug-resistant TB treatment settings, and that the use of a regimen based on medicines that are fully administered orally may increase feasibility. Altogether, based on present evidence, when discussing the balance between benefits and harms, preferences and values for patients and other end-users, the GDG reached overall agreement on the beneficial effect that the Hr-TB regimen may have, if used in conformity with these policy recommendations. Although there was no clear evidence to suggest that the addition of isoniazid to this regimen would be beneficial, the four-drug (H)REZ fixed-dose combination (FDC) may be more convenient for the patient and the health service because it removes the need to use single drugs.

Consistent with the overall framework for the management and care of patients diagnosed with drug-resistant TB, careful selection of patients is a fundamental principle. Ahead of starting the (H)REZ–levofloxacin regimen, it is essential that resistance to rifampicin be excluded, using WHO-recommended genotypic or phenotypic methods *(24, 25)*. Ideally, resistance to fluoroquinolones (and, if possible, to pyrazinamide) should be similarly excluded before treatment, to help avert the acquisition of additional drug resistance (see Section 1.4).

Empirical treatment of Hr-TB is generally not advised. In cases where a diagnosis of Hr-TB is strongly presumed (e.g. close contacts of Hr-TB cases with active TB but without laboratory confirmation of Hr-TB), (H)REZ–levofloxacin may be introduced pending laboratory confirmation of isoniazid resistance, provided that rifampicin resistance has been reliably excluded. Should DST results eventually indicate susceptibility to isoniazid, levofloxacin is stopped, and the patient completes a 2HREZ/4HR regimen (i.e. 2 months of HREZ followed by 4 months of HR). For patients in whom Hr-TB is detected after the start of treatment with the 2HREZ/4HR regimen, the (H)REZ component drugs are continued (or pyrazinamide and ethambutol are reintroduced) and levofloxacin added, once rifampicin resistance has been excluded.

The duration of an (H)REZ–levofloxacin regimen is usually determined by the need to complete 6 months of a levofloxacin-containing regimen. Thus, in cases where the diagnosis of Hr-TB is made after first-line TB treatment has already been initiated, the patient may receive more than 6 months of (H)REZ by the end of treatment. When the confirmation of isoniazid resistance arrives late into treatment with a 2HREZ/4HR regimen (e.g. 5 months after start during the continuation phase), the clinician would need to decide, based on an assessment of the patient's condition, whether a 6-month course of (H)REZ–levofloxacin needs to be started at that point or not.

The addition of levofloxacin to (H)REZ is recommended in all patients with Hr-TB, with the exception of the following situations: resistance to rifampicin cannot be excluded; known or suspected resistance to levofloxacin; known intolerance to fluoroquinolones; known or suspected risk for prolonged QT interval; pregnancy or during breastfeeding (not an absolute contraindication). In Hr-TB cases in whom a fluoroquinolone cannot be used, the patient may still be treated with 6(H)REZ.

When additional resistance (especially to pyrazinamide) is suspected or confirmed, appropriate treatment regimens will have to be designed individually. The data reviewed for this guideline could not provide separate evidence-based recommendations for such cases.

Where possible, isoniazid resistance testing should also include information on the specific mutations associated with resistance to isoniazid (*katG* or *inhA*). In addition, knowledge about overall host acetylator[20] status at country or regional level will be useful, given that these may have implications for regimen design *(26)*.

[20] Decreased efficacy and toxicity of isoniazid have been related to its increased metabolism (acetylation) in certain individuals, as determined by mutations in the *N*-acetyltransferase type 2 (NAT2) gene.

Under development are high-throughput diagnostic platforms (as an alternative to line probe assay [LPA]) that can simultaneously detect TB, and resistance to rifampicin and isoniazid. Evaluation studies of these diagnostics are underway.

1.3 Subgroup considerations

Children. In the IPD review, only 2% of Hr-TB patients were children; thus, a separate estimate of effect for paediatric patients was not possible. However, there is no reason why the results and recommendations cannot be extrapolated from adults to children, considering that the regimen components have been standard paediatric TB medicines for many years.

Patients with extensive disease. Although the IPD analysis did not provide evidence for duration of treatment extension, the prolongation of the 6(H)REZ–levofloxacin regimen to more than 6 months could be considered on an individual basis for patients with extensive disease *(27)*. Prolongation of treatment may increase the risk of adverse events in some cases (see Section 1.5).

HIV-positive individuals. The effect of longer duration TB treatment among HIV-positive patients with and without ART has been studied among patients with drug-susceptible TB *(28)*. In these cases, relapse has been reported to be 2.4 times higher in HIV-infected patients who were not on ART and who received 6 months of treatment than in patients in whom treatment was prolonged (up to 9 months). In patients with drug-susceptible TB initiated on ART, no significant benefit from prolonging rifampicin-containing regimens for over 6 months has been observed *(29)*. In the current analysis, only a limited number of patients received ART; nonetheless, in TB patients with HIV coinfection, the first priority is to ensure that they are started on ART within 8 weeks of TB treatment initiation (regardless of CD4 count), in accordance with WHO guidelines *(30)*. The 6(H)REZ–levofloxacin regimen is therefore recommended in HIV-positive patients.

Extrapulmonary disease. No data were available for patients with exclusive extrapulmonary Hr-TB. The regimen composition proposed is likely to be effective even in these patients. However, the treatment of patients with extrapulmonary TB should be designed in close consultation with appropriate specialists (e.g. infectious disease physicians and neurologists), to decide upon individual variations in treatment duration and supportive care as needed.

1.4 Implementation considerations

Case scenarios. Implementing these recommendations requires the (H)REZ–levofloxacin regimen to be administered only in patients in whom resistance to isoniazid has been confirmed and resistance to rifampicin has been excluded. Preferably, testing for resistance to fluoroquinolones (and, if possible, to pyrazinamide) is also done ahead of starting treatment. It is envisaged that the treatment regimen for Hr-TB will apply in the following situations:

- *Hr-TB and rifampicin susceptibility are confirmed before TB treatment is started.* Treatment with (H)REZ–levofloxacin is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be introduced. Should the DST results taken at the start eventually show susceptibility to isoniazid, then levofloxacin is stopped, and the patient continues treatment in order to complete a 2HREZ/4HR regimen.
- *Hr-TB is confirmed after the start of treatment with the 2HREZ/4HR regimen.* This includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance later while on treatment with a first-line regimen. In such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance has been excluded, a full 6-month course of (H)REZ–levofloxacin is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this.

If rifampicin resistance is detected, the patient needs to be started on a recommended MDR-TB treatment regimen, as described in subsequent sections of these guidelines.

Diagnostic capabilities. The overall aim of TB treatment is to achieve cure without relapse in all patients, interrupting *Mycobacterium tuberculosis* transmission and preventing the acquisition (or amplification) of additional drug resistance. Globally, Hr-TB is more prevalent than MDR-TB. Thus, all countries need to move towards universal testing of both isoniazid and rifampicin resistance at the start of TB treatment, and to ensuring careful selection of patients eligible for the (H)REZ–levofloxacin regimen.[21] The minimum diagnostic capacity to appropriately implement these recommendations is rapid molecular testing for rifampicin resistance before the start of treatment with the Hr-TB regimen and, preferably, the ruling out of fluoroquinolone resistance using WHO-recommended tests.

Rapid molecular tests such as Xpert® MTB/RIF and LPAs are preferred, to guide patient selection for the (H)REZ–levofloxacin regimen *(25, 31)*.

Drug-resistant TB surveillance indicates that fluoroquinolone resistance among patients with rifampicin-susceptible TB is generally low worldwide *(32)*. However, national data on the prevalence of fluoroquinolone resistance – including targeted or whole-genome sequencing to detect specific mutations associated with resistance to fluoroquinolones *(33)* – could help to guide testing policies when countries implement the Hr-TB treatment recommendations.

When additional resistance (e.g. to both fluoroquinolones and pyrazinamide) is suspected or confirmed, treatment regimens that include other second-line TB medicines may have to be designed individually. The current review could not provide further evidence on effective regimens in patients with polyresistant disease.

Support and close monitoring of patients are needed in order to maximize treatment adherence and enable early detection of patients who are not responding to treatment (e.g. those with persistent sputum culture or smear positivity). In the presence of non-response to treatment, DST for rifampicin and the fluoroquinolones should be repeated, preferably with Xpert MTB/RIF or LPA, is indicated. Documented acquisition of resistance to rifampicin or a fluoroquinolone while on the Hr-TB treatment regimen should alert the clinician to the need to review the entire clinical and microbiological status of the patient, and change the regimen accordingly.

Levofloxacin is proposed as the fluoroquinolone of first choice in the Hr-TB treatment regimen for several reasons. First, the safety profile of this medicine is better characterized than that of other fluoroquinolones, and levofloxacin was the fluoroquinolone most frequently used in the studies reviewed for this guidance. Second, in comparison to moxifloxacin, levofloxacin has fewer known drug interactions with other medications. For example, although both plasma peak concentration and exposure to moxifloxacin decrease significantly when the drug is combined with rifampicin *(34)*, the same effect has not been reported for levofloxacin, possibly because levofloxacin undergoes limited metabolism in humans and is excreted unchanged in the urine *(35)*. Third, although levofloxacin may interfere with lamivudine clearance, in contrast to moxifloxacin, there are no contraindications for its use with other antiretroviral agents *(36)*.

The addition of levofloxacin to (H)REZ is recommended in patients with Hr-TB, with the exception of the following situations:

- resistance to rifampicin cannot be excluded (i.e. unknown susceptibility to rifampicin, or indeterminate or error results on Xpert MTB/RIF);
- known or suspected resistance to levofloxacin;
- known intolerance to fluoroquinolones;

[21] The association between previous TB treatment history and Hr-TB is less strong than that of MDR-TB. As a result, previous TB treatment is less reliable as a proxy for Hr-TB and a laboratory diagnosis is therefore important.

- known or suspected risk for prolonged QT interval;[22]
- if possible, in pregnancy or during breastfeeding (not an absolute contraindication).

Sometimes, the confirmation of isoniazid resistance arrives late (e.g. 5 months into a 2HREZ/4HR regimen). In such cases, a decision to start 6 months of (H)REZ–levofloxacin depends on the patient's clinical condition and microbiological status.

If levofloxacin cannot be used because of toxicity or resistance, the patient may be given 6(H)REZ as an alternative. Based on the results of the evidence review for these guidelines, replacement of levofloxacin with an injectable agent is NOT advised. The evidence review could not inform on the effect of other second-line TB medicines on treatment effectiveness.

Addition of isoniazid. There was no clear evidence that the addition of isoniazid affects patients (i.e. adding benefit or harm). For patient convenience and ease of administration, the four-drug HREZ FDCs[23] may be used to deliver the Hr-TB treatment regimen alongside levofloxacin.

The use of high-dose isoniazid (10–15 mg/kg per day in adults) was not evaluated in this review because there was insufficient data. However, the GDG discussed the effect of increasing isoniazid dosing beyond that provided in weight-banded FDCs, depending on the type of molecular mutations identified. In vitro evidence suggests that when specific *inhA* mutations are detected (and when *katG* mutations are absent), increasing the dose of isoniazid is likely to be effective; thus, additional isoniazid up to a maximum dose of 15 mg/kg per day could be considered. In the case of *katG* mutations, which usually confer a higher level resistance, the use of isoniazid even at a higher dose is less likely to be effective *(37)*.[24]

Dosage. Although the IPD analysis did not provide evidence to address the frequency of dosing, it is best to avoid intermittent or divided dosing of the 6(H)REZ–levofloxacin regimen *(29, 38, 39)*. In the absence of full information about optimal drug doses, a weight-band dosing scheme for levofloxacin is recommended.[25]

Drug–drug interactions. Levofloxacin may interfere with lamivudine clearance (increasing the levels of lamivudine) but it is not contraindicated with other antiretroviral agents, and no drug dosing adjustments are needed *(36)*. Co-administration of levofloxacin with oral divalent cation-containing compounds (e.g. antacids) may impair its absorption and should be avoided *(9)*. Restriction of concomitant use of milk products is not necessary.

Treatment prolongation beyond 6 months. This may be considered for patients with extensive disease or in those slow to convert to smear or culture negative. In the latter, acquisition of additional resistance to rifampicin must be ruled out, as must resistance to fluoroquinolones and pyrazinamide, if possible. Such patients require careful monitoring and follow-up.

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[22] Baseline-corrected QT. Prolongation of the QT interval and isolated cases of *torsade de pointes* have been reported. Avoid use in patients with known prolongation, those with hypokalaemia, and with other drugs that prolong the QT interval.

[23] Although most countries currently procure the four-drug FDC via the Stop TB Partnership's Global Drug Facility (GDF), in settings where only the three-drug combination FDC (i.e. HRZ) is available, ethambutol has to be administered separately.

[24] An isolated *kat*G or *inh*A mutation can correspond to variable minimum inhibitory concentration (MIC) levels. This implies that *inh*A mutations do not always indicate low-level isoniazid resistance, or that *kat*G mutations are not necessarily correlated with high-level isoniazid resistance. The presence of both mutations is usually an indication of high-level resistance *(37)*.

[25] Studies included in this IPD analysis involved the use of regimens containing levofloxacin (usually at a dose of 750–1000 mg/day), moxifloxacin (400 mg/day) or gatifloxacin (400 mg/day), as well as early generation fluoroquinolones (ciprofloxacin and ofloxacin), which are no longer recommended for the treatment of drug-resistant TB. Gatifloxacin is currently unavailable in quality-assured formulations, and ciprofloxacin and ofloxacin are no longer recommended for use in drug-resistant TB care.

Cost. Cost–effectiveness analysis was not performed for this review. **Table 1.1** presents approximate prices for a full course of medicines with the different regimens in adults, based on the cost of products available from the Global Drug Facility (GDF) *(40)*. Use of FDCs, even for part of the regimen, reduces costs. Medicines needed for a 6HREZ–levofloxacin regimen cost about twice as much as a 2HREZ/4HR regimen when using the HREZ FDC. The treatment of Hr-TB according to these guidelines is not expected to significantly increase operational costs.

Adherence. The IPD analysis contained limited data on the treatment adherence strategies used, such as directly observed treatment (DOT) and self-administered therapy (SAT). Improved treatment success rates appeared to be associated with increased patient support, including medication adherence support (e.g. by means of digital technologies) or other means, as recommended by WHO *(29)*. In contrast to regimens for drug-susceptible TB and MDR-TB, the recommended Hr-TB treatment regimen does not have an intensive phase and a continuation phase, simplifying the delivery and monitoring of treatment.

Table 1.1. Illustrative costs of regimens used to treat Hr-TB compared with the 6-month first-line TB regimen

Regimen	Average weighted prices, US$[a]
2HREZ/4HR	36
6HREZ	55
6REZ–Lfx	99
6HREZ–Lfx	76
9HREZ–Lfx	113

HR: isoniazid, rifampicin; HREZ: isoniazid, rifampicin, ethambutol, pyrazinamide; Lfx: levofloxacin; REZ: rifampicin, ethambutol, pyrazinamide.

[a] Prices are as of 15 March 2020 for a 60 kg adult, and reflect the use of FDCs whenever possible. Average weighted prices are based on prospective market share allocation and are indicative only. For budgeting purposes, it is recommended to use the budgeting prices from the Stop TB Partnership *(40)*.

Source: Stop TB Partnership (2020) *(40)*.

1.5 Monitoring and evaluation

Patients who receive the (H)REZ–levofloxacin regimen need to be monitored during treatment, using schedules of clinical and laboratory testing. The definitions to use when assigning outcomes are the same as those used for drug-susceptible TB *(41)*. Signs of non-response or treatment failure should be followed up with DST for rifampicin resistance and, if possible, for fluoroquinolones and pyrazinamide. To limit the risk of acquisition of additional resistance, the addition of single TB medicines should be avoided in patients who remain smear positive or culture positive after month 2 of treatment, those who do not show a favourable clinical response and those without recent DST results.

As with any other TB medicine and regimen, safety precautions are required to ensure the rapid identification and proper management of any serious adverse event. Close clinical monitoring is essential for all patients receiving this regimen, particularly liver function tests, given the hepatotoxic potential of prolonged pyrazinamide use. If possible, all patients should be tested each month for levels of aspartate aminotransferase (AST, also known as serum glutamic oxaloacetic transaminase, SGOT). If resources are not available to monitor all patients on the Hr-TB treatment regimen, monthly monitoring of patients at high risk (e.g. patients coinfected with viral hepatitis or with a history of heavy alcohol use) is strongly advised. Additionally, to prevent and manage the potential toxic effects of ethambutol in children (e.g. retrobulbar neuritis), it is necessary to adhere to the correct doses recommended for paediatric populations. Early signs of ethambutol toxicity can be tested in older children through red–green colour discrimination. Monitoring for retrobulbar neuritis can be undertaken early when appropriate *(42)*.

17. The following options are recommended for the treatment of LTBI regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3 month regimen of daily isoniazid plus rifampicin. *(Strong recommendation, moderate to high certainty in the estimates of effect)*. A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives. *(Conditional recommendation, low to moderate certainty in the estimates of effect)*.

18. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive treatment (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities. *(Conditional recommendation, low certainty in the estimates of effect)*

Regimens containing isoniazid or rifamycins

Both recommendations already featured in WHO guidance from 2015 (13),(25). A strong recommendation for TB preventive treatment alternatives to 6H, based on evidence of low to high certainty, featured in previous WHO guidance (12),(13),(16). In 2019 the GDG made edits to the text of this recommendation to add the two new conditional recommendations for daily rifapentine plus isoniazid for 1 month (1HP) and daily rifampicin monotherapy for 4 months (4R) in all settings. These new recommendations are based, respectively, on low to moderate certainty in the estimates of effect. In addition, instead of a previous range of 3–4 months, the GDG now recommends a duration of 3 months for daily isoniazid plus rifampicin (3HR) and of 4 months for daily rifampicin alone (4R) to reflect the usual length of time for which these regimens are currently employed. Moreover, three previous recommendations on the use of 6H, 3HR in people <15 years and 3HP in high TB prevalence settings that featured separately in previous guidance are now proposed as alternative options. The revised recommendation makes all LTBI options applicable to all settings.

Justification and evidence

Daily isoniazid monotherapy

The efficacy of daily isoniazid monotherapy for six months (6H) or more in different populations and settings has been shown in a number of systematic reviews (18),(66),(67). A systematic review of RCTs in PLHIV showed isoniazid monotherapy reduces the overall risk for TB by 33% (RR 0.67; 95% CI 0.51; 0.87), and the that preventive efficacy reached 64% for people with a positive TST (RR 0.36; 95% CI 0.22; 0.61) (18). Furthermore, the efficacy of the 6-month regimen was not significantly different from that of 12 months' daily isoniazid monotherapy (RR 0.58; 95% CI 0.3; 1.12). A recent systematic review of RCTs also showed a significantly greater reduction in TB incidence among participants given the 6-month regimen than in those given a placebo (Odds ratio [OR] 0.65; 95% CI 0.50; 0.83)(68). No controlled clinical trials were found of daily isoniazid monotherapy for 9 months (9H) versus 6H. Re-analysis and modelling of the United States Public Health Service trials of isoniazid conducted in the 1950s and 1960s, however, showed that the benefit of isoniazid increases progressively when it is given for up to 9–10 months and stabilizes thereafter (69). For this reason, 9H is retained as an alternative regimen to 6H in the recommended TB preventive treatment options.

Regarding the second recommendation above, a systematic review and meta-analysis of three RCTs of PLHIV in settings with high TB prevalence and transmission showed that continuous IPT can reduce the risk for active TB by 38% more than 6 months' isoniazid (70). The effect was greater in people with

a positive TST (49% for active TB and 50% for death). In those with a negative TST, neither effect was significant, although the point estimate indicated a reduction in TB incidence of 27%. In two of the studies reviewed ART was not used and in the third ART coverage was low at baseline but increased during the period of observation.

Daily rifampicin plus isoniazid for 3 months (3HR)

A systematic review updated in 2017 showed that the efficacy and the safety profile of 3–4 months' daily rifampicin plus isoniazid were similar to those of 6 months' isoniazid (68),(71). A previous GDG therefore strongly recommended that daily rifampicin plus isoniazid could be used as an alternative to isoniazid in settings with a TB incidence <100 / 100,000 population (13). A new review to compare the effectiveness of rifampicin plus isoniazid daily for 3 months with isoniazid for 6 or 9 months in children identified one RCT and two observational studies (72),(73),(74) (see also GRADE evidence summaries for PICO 5 in **Annex 2**). The RCT (73) reported no clinical disease in either group and used new radiographic findings suggestive of active TB as a proxy for clinical disease. Fewer participants given daily rifampicin plus isoniazid than those given 9 months of isoniazid developed radiographic changes (RR 0.49, 95% CI 0.32; 0.76). The authors also reported a lower risk for adverse events (RR 0.33, 95% CI 0.20; 0.56) and a higher adherence rate (RR 1.07, 95% CI 1.01; 1.14) among children given daily rifampicin plus isoniazid. Similar findings were reported in the observational studies (72),(74).

Daily rifampicin monotherapy for 4 months (4R)

A previous systematic review conducted for the 2015 LTBI guidelines and updated in 2017, found similar efficacy for 3–4 months' daily rifampicin and 6H (odds ratio, 0.78; 95% CI, 0.41;1.46) (68),(71). The review also showed that individuals given rifampicin daily for 3–4 months had a lower risk for hepatotoxicity than those treated with isoniazid monotherapy (OR 0.03; 95% CI 0.00;0.48).

In 2019, the GDG discussed the implications of using 4R in high TB burden settings based on findings from RCTs of 4R vs 9H that included adults and children from such countries(75),(76),(77),(78). In study participants >17 years, the difference in rate of confirmed TB between 4R and 9H (4R arm minus 9H arm) was <0.01 cases per 100 person-years (95%CI, −0.14; 0.16); the difference in treatment completion was 15.1% (95% CI, 12.7; 17.4); the difference for Grade 3–5 adverse events was −1.1% (95% CI, −1.9; -0.4). In individuals <18 years, the difference in rate of active TB between 4R and 9H was -0.37 cases per 100 person-years (95% CI, −0.88; 0.14); the difference in treatment completion was 13.4% (95% CI, 7.5; 19.3); the difference in risk for adverse events attributed to the medicine used and resulting in discontinuation was −0.0 (95% CI, −0.1; 0.1). The evidence underpinning this revised recommendation is summarised in the GRADE tables for PICO 6 in **Annexes 2** and **3**.

Daily rifapentine plus isoniazid for 1 month (1HP)

In 2019, the GDG considered data from the only known published study of the 1HP regimen: a randomized, open-label, phase 3 non-inferiority trial comparing the efficacy and safety of 1HP with 9 months of isoniazid alone ("9H") in PLHIV who were in areas of high tuberculosis prevalence or who had evidence of LTBI (79). Enrolment was restricted to individuals ≥13 years old who were not pregnant or breastfeeding. Noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the number of events per 100 person-years was less than 1.25. Among all study participants, the difference in incidence rate of TB (including deaths from any cause) between 1HP and 9H (i.e. 1HP arm minus 9H arm) was −0.02 per 100 person-years (95% confidence interval [CI], −0.35; +0.30); the relative risk (RR) for treatment completion of 1HP over 9H was 1.04 (95% CI, 0.99; 1.10); the RR for Grade 3–5 adverse events was 0.86 (95% CI, 0.58; 1.27); hazard ratio of death from any cause was 0.75 in favour of 1HP (95% CI, 0.42; 1.31); RR for emergence of resistance to isoniazid and rifampicin were, respectively, 1.63 (95% CI, 0.17; 15.99) and 0.81 (95% CI, 0.06; 11.77). Overall non-inferiority as defined by the study protocol was thus shown in the modified intention to treat (mITT) population. Non-inferiority was also shown for the sub-group with confirmed

LTBI infection (incidence rate difference per 100 person-years = 0.069 [-0.830 to 0.690]), as well as in males and females, and among those on or without ART at start of study. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority or noninferiority of 1HP was shown in this stratum. The evidence underpinning this new recommendation is summarised in the GRADE tables for PICO 7 in **Annexes 2** and **3**.

Weekly rifapentine plus isoniazid for 3 months (3HP)

A systematic review was conducted for the 2018 guidelines update to compare the effectiveness of a 3-month weekly regimen of rifapentine plus isoniazid (3HP) with that of isoniazid monotherapy. The review covered four RCTs (80),(81),(82),(83), which were analysed for three subgroups: adults with HIV infection, adults without HIV infection and children and adolescents, who could not be stratified according to HIV status because the relevant studies were lacking. The evidence underpinning this revised recommendation is summarised in the GRADE tables for PICO 8 in **Annexes 2** and **3**.

Two of the RCTs involved adults with HIV from South Africa, Peru and a number of countries with a TB incidence <100 / 100,000 population. No significant difference was found in the incidence of active TB between participants given a 3HP and 6H or 9H (RR 0.73, 95% CI 0.23; 2.30). Furthermore, the risk for hepatotoxicity was significantly lower with 3HP in adult PLHIV (RR 0.26, 95% CI 0.12; 0.55) and in those without HIV (RR 0.16, 95% CI 0.10; 0.27). The 3HP regimen was also associated with a higher completion rate in all subgroups (adults with HIV: RR 1.25, 95% CI 1.01; 1.55; adults without HIV: RR 1.19, 95% CI 1.16; 1.22; children and adolescents: RR 1.09, 95% CI 1.03; 1.15). One RCT included a comparison between 3HP and continuous isoniazid monotherapy in adult PLHIV (80). No significant difference in TB incidence was found in an intention-to-treat analysis; however, a per-protocol analysis showed a lower rate of TB infection or death in participants given continuous isoniazid. In all the studies, 3HP was given under direct observation. In a study of 3HP in 112 pregnant women, the rates of spontaneous abortion and birth defects were similar to those in the general US population (84).

Implementation considerations

The decision on which treatment to offer should not be confined to the manner in which it was studied in a trial (e.g. 1HP to replace 9H). The GDG agreed that the benefits of all the treatment options being recommended outweigh the potential harm. The programmes and clinicians should also consider the characteristics of the individual concerned to maximise the likelihood that treatment is completed as expected. Regimen choice is determined by considerations such as age, risk of toxicity or interaction, co-morbidity, drug susceptibility of the strain of the most likely source case, availability and the individual's preferences.

On the basis of existing practice, albeit in the absence of a direct comparison, the GDG judged that 9H is an equivalent option to 6H in countries with a strong health infrastructure. It noted, however, that 6H is preferable to 9H from the point of view of feasibility, resource requirements and acceptability to patients.

All recommended treatment options are possible in PLHIV. The recommendation to give at least 36 months of daily isoniazid monotherapy in PLHIV in high TB transmission settings is conditional and based on evidence that longer-term IPT significantly adds benefit to ART. The efficacy, safety and convenience of repeated treatment with shorter rifapentine regimens is being studied in PLHIV in such settings. The definition of a high TB transmission setting should be established by the national authorities (see also **Definitions**). Testing for LTBI is not a prerequisite for TB preventive treatment in PLHIV but its use is encouraged because people who are TST positive have a greater protective benefit from TB preventive treatment. PLHIV with a negative TST should not receive 36 months of daily IPT.

The GDG agreed unanimously that the benefits of 3HR for infants and children < 15 years of age outweigh the harm, given its safety profile, the higher rate of completion as compared with isoniazid monotherapy and the availability of child-friendly, fixed-dose combinations of rifampicin and isoniazid.

The GDG therefore made a strong recommendation despite the low quality of the evidence. There are no or very limited data on the performance and pharmacology of rifapentine in children < 2 years. The 3HP regimen is only recommended for use in children aged 2 years and more while the 1HP regimen in individuals aged 13 years and more.

The 2019 GDG considered that there was moderate certainty that 4R is not inferior to 9H, and when also considering the good safety profile of the 4R regimen and its reduced length, it recommended that this regimen may also be used in high TB-burden settings. When deciding to make a conditional recommendation the GDG considered that most people would value a shorter regimen, but raised concerns regarding variability in acceptability, uncertainty in resource requirements given its higher cost, and potential for reducing equity should it deflect resources and decrease treatment coverage of more vulnerable individuals. The GDG agreed that the introduction of 4R needs to be accompanied by mobilization of appropriate resources from the start to avoid shortages in other programmatic needs. The GDG also observed that impact on equity could change if the price and policy of use of 4R also change (see also **Annex 3** for more details on the GDG decisions).

With respect to 1HP, the 2019 GDG concluded that there was low certainty that its effectiveness would be non-inferior to 9H when used under programmatic settings in different populations at risk. When taking also into account the good safety profile of 1HP and its much shorter length when compared with other approved LTBI regimens, the GDG recommended that this regimen may also be used in high TB-burden settings and in people without HIV infection. The GDG considered that most people would value its much shorter duration than other options, that its implementation would be feasible, but raised concerns regarding uncertainty in resources requirements and the potential for reducing equity, leading to a conditional recommendation (see also **Annex 3** for more details on the GDG decisions).

In the current update, the GDG considered that all regimens could be used in any setting, regardless of TB burden, provided that the health infrastructure can ensure the treatment is given correctly without creating inequities, and that active TB can be excluded reliably before the initiation of treatment.

The GDG noted that all the treatment options can be self-administered. An RCT showed that self-administered treatment of the 3HP is not inferior to directly observed treatment (85); however, there is little further evidence on self-administration of this regimen. The GDG noted that a requirement for a direct observation could be a significant barrier to the implementation. People receiving TB preventive treatment should also be supported through access to advice on treatment and management of adverse events at their encounters with the health services. The GDG further noted that individuals receiving treatment, clinicians providing treatment and programme managers would prefer shorter to longer regimens.

Drug-drug interactions

Rifamycins induce certain cytochrome P-450 enzymes and may therefore interfere with medicines that depend on this metabolic pathway, accelerating their elimination. These include ART as well as many other medicines such as anticonvulsants, antiarrhythmics, quinine, oral anticoagulants, antifungals, oral or injectable contraceptives, corticosteroids, cyclosporine, fluoroquinolones and other antimicrobials, oral hypoglycaemic agents, methadone, and tricyclic antidepressants. Such medicines may therefore need to be avoided when rifampicin or rifapentine containing regimens are given, or that their dosages are adjusted.

Regimens containing rifamycins should be prescribed with caution to PLHIV who are on ART because of potential drug–drug interactions. These regimens should not be administered to people receiving protease inhibitors or nevirapine, including HIV-exposed infants on preventive treatment. Rifampicin can decrease the concentrations of other antiviral agents: atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir and tipranavir. It should not be used with saquinavir/ritonavir. No dose adjustment is required when rifampicin is co-administered with efavirenz. The dose of dolutegravir however

needs to be increased to 50 mg twice daily when given together with rifampicin (86), a dose that is usually well tolerated and gives equivalent efficacy in viral suppression and recovery of CD4 cell count compared with efavirenz.

The 3HP regimen can be administered to patients receiving efavirenz-based antiretroviral regimens without dose adjustment, according to a study of pharmacokinetics (87). Administration of rifapentine with raltegravir was found to be safe and well tolerated (88). A drug interaction study in healthy volunteers of dolutegravir with once weekly HP reported toxicities in 2 of 4 participants (89). However results released more recently from a Phase 1/2 trial of 3HP and dolutegravir in adults with HIV reported good tolerance and viral load suppression, no adverse events of Grade >3 related to the HP, and did not indicate that rifapentine reduced dolutegravir levels sufficiently to require dose adjustment (90). The GDG stressed however the continued need for studies of the pharmacokinetics of 3HP concomitantly with other medicines, particularly ART.

Concurrent use of alcohol needs to be avoided with TB preventive treatment.

Pregnancy

In preparation for the current update, a systematic review was conducted in 2019 to assess evidence in support or against recent reports from one RCT of adverse pregnancy outcomes associated with the use of IPT (91),(92). In addition to this RCT, three non-randomized, comparative observational studies provided data on at least one of the pregnancy outcomes in women with HIV (93),(94),(95) (see PICO 9 in **Annex 2**). While the RCT showed a higher risk of adverse pregnancy outcomes in women who initiated IPT during pregnancy (Mantel-Haenszel OR stratified by gestational age, 1.51 95%CI 1.09; 2.10), all three other studies reported an overall OR <1 suggesting the opposite (I^2=80%, p=0.002). A meta-analysis from two observational studies that cited adjusted estimates and whose data could be pooled suggested lower risk for composite adverse pregnancy outcomes (OR 0.40, 95%CI 0.20; 0.74) (93),(94). The observational studies did not reproduce the associations with IPT reported by the RCT for *individual* adverse outcomes such as foetal/neonatal death, prematurity, low birth weight, and congenital anomaly. No statistically significant risks for maternal hepatotoxicity, Grade 3 or 4 events or death were reported by any of the four studies. Based upon these findings the GDG concluded that there were insufficient grounds to change previous guidance or to develop a separate recommendation for the use of IPT in pregnant women with HIV. The GDG considered that systematic deferral of IPT to the postpartum would deprive women from its protective effect at a point when they are more vulnerable to TB. Appropriate care during the antenatal and postnatal periods and during delivery may reduce risk of adverse pregnancy outcome. While obtaining baseline liver function tests when IPT is given in pregnancy is strongly encouraged when feasible, it is not required, and routine liver function testing when IPT is given in pregnancy is not indicated unless there are other risk factors for liver toxicity are present. Vitamin B6 supplementation should however be considered. The GDG agreed that this is an area requiring more research, such as on pharmacokinetics and pharmacovigilance of IPT and other preventive treatment regimens. Rifampicin is generally considered safe in pregnancy. There are limited data on the pharmacokinetics and safety of rifapentine in pregnancy and therefore the use of 1HP in pregnancy would best await more data to ensure appropriate dosing and at least preliminary safety data for this regimen in pregnant women.

Table 3. Recommended dosages of medicines for TB preventive treatment

Regimen	Dose by weight band
6 or 9 months of daily isoniazid monotherapy (6H, 9H)	Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg)
Four months of daily rifampicin (4R)	Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)
Three months of daily rifampicin plus isoniazid (3HR)	Isoniazid: Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg) Rifampicin: Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)

Three months of rifapentine plus isoniazid weekly (12 doses) (3HP)

Age 2–14 years

Medicine, formulation	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg
Isoniazid, 100 mg*	3	5	6	7	7
Rifapentine, 150 mg	2	3	4	5	5

Age >14 years

Medicine, formulation	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
Isoniazid, 300 mg	3	3	3	3	3
Rifapentine, 150 mg	6	6	6	6	6

* 300mg formulation can be used to reduce pill burden

One month of rifapentine plus isoniazid daily (28 doses) (1HP)	Age ≥13 years (regardless of weight band) Isoniazid, 300 mg/day Rifapentine, 600 mg/day
Six months of levofloxacin daily (preventive treatment of MDR-TB)	Age >14 years, by body weight: < 46 kg, 750 mg/day; >45 kg, 1g/day Age <15 years (range, approx. 15–20 mg/kg/day), by body weight: 5–9 kg: 150 mg/day; 10–15 kg: 200–300mg/day; 16–23 kg: 300–400mg/day; 24–34 kg: 500–750mg/day

Other subgroups and settings

The recommended dosages for TB preventive treatment regimens in adults and children are shown in **Table 3**. Regimens based on isoniazid and rifampicin can be used in individuals of all ages. There are no or very limited data on the efficacy and safety of rifapentine in children < 2 years and the 3HP regimen is only recommended for use in children aged 2 years and more. The data from the 1HP trial relates only to individuals aged 13 years and more. The GDG considered that extrapolation of effects to children aged 2–12 years is reasonable, although the dosage of *daily* rifapentine in this age group has yet to be established. The suitability of this regimen in people <13 years needs to be

reviewed once results from studies of pharmacokinetics and safety in children of all ages become available in a near future.

In candidates for transplantation or anti-TNF treatment it may be particularly important to complete TB preventive treatment fast and therefore shorter regimens like 1HP and 3HP could have an advantage over longer treatments. Likewise, in homeless people and in people being released from prison, in whom there is limited opportunity for repeated encounters during treatment, shorter treatment could be more suitable than longer regimens.

In addition to PLHIV on ART, other populations who may be more commonly at risk of drug-drug interactions from rifampicin include women of childbearing age on contraceptive medicines (who need to be counselled about potential interactions and consider nonhormonal birth control while receiving rifampicin) and opiate users on substitution therapy with methadone.

Contacts of patients with laboratory confirmed isoniazid-resistant, rifampicin-susceptible TB (Hr-TB) may be offered a four-month regimen of daily rifampicin.

Other considerations

Given the widespread use of rifampicin-containing fixed dose combinations to treat drug-susceptible TB, single dose rifampicin has become less available to disease programmes. If the 4R regimen will be used more often the demand for loose tablets of rifampicin will increase and programmes would need to procure it. Quality-assured supplies of rifampicin should be used. The provision of 4R outside the TB programme centres (e.g. primary care facilities, HIV programmes) should be accompanied by stepwise guidance on how to maximise the effect of rifampicin and avoid it being diverted for use as a broad-spectrum antibiotic.

Fixed-dose combinations (FDC) of HR should be used where possible to reduce the number of pills to be taken. FDCs of 3HP are expected to be released in a near future and will facilitate administration. Shorter regimens are also more likely to be completed. Concerns about adherence should not be a barrier to starting TB preventive treatment and support provided to enable better person-centred care. No data-supported recommendations exist on how to handle interruptions of TB preventive treatment, i.e. how many missed doses can be made up for by prolonging treatment without compromising efficacy?

Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, or who are pregnant or breastfeeding, should receive pyridoxine (vitamin B6) when taking isoniazid-containing regimens. A lowering of isoniazid dosage from the one proposed may be required to avoid toxicity if there is a high population prevalence of "slow acetylators". Combination tablets of co-trimoxazole, isoniazid and pyridoxine could be helpful in PLHIV. However, unavailability of pyridoxine should not be a reason to withhold TB preventive treatment.

Interventions to enhance adherence and completion of treatment should be tailored to the specific needs of risk groups and the local context. A systematic review conducted for the WHO 2015 LTBI guidelines provided heterogeneous results for interventions to improve treatment adherence and completion, and the evidence was considered inconclusive (14). The WHO guidelines for treatment of drug-susceptible active TB propose several interventions to support adherence, which could also be applied to TB preventive treatment (96).

In areas with high background resistance to rifampicin, such as countries in eastern Europe, it is particularly important to try to get the strain from the presumed source tested for drug susceptibility so that treatment given is more likely to work. If there is rifampicin monoresistance or other contraindications to rifampicin, then an isoniazid regimen of 6 or more months may be the most appropriate option. Unfortunately, in many settings, rifampicin resistance is often accompanied by isoniazid resistance – multidrug-resistant TB (MDR-TB) – requiring different preventive medication (see below).

Preventive treatment for MDR-TB

Justification and evidence

Evidence for effectiveness and safety of MDR-TB preventive treatment was reviewed and summarised in **Section 1.1**. The medicines used in these studies were mainly fluoroquinolones (e.g. moxifloxacin, levofloxacin) with or without other agents (e.g. ethambutol, ethionamide). The median proportion of participants who discontinued treatment because of adverse events in all the studies was 5.1% (interquartile range, 1.9–30.2%).

While ethambutol is considered safe in pregnancy, ethionamide was associated with teratogenic potential at high doses in preclinical animal studies, with minimal data in human pregnancy. Although there has been concern about the use of fluoroquinolones in children because of retardation of cartilage development shown in animals (97), similar effects have not been demonstrated in humans (98),(99). While the effects of fluoroquinolones on bone and cartilage in animals have not been observed in humans, available data and infant follow-up times are limited. One meta-analysis of observational studies including 2800 pregnant women exposed to fluoroquinolones found no differences in birth defects, spontaneous abortion or prematurity compared to unexposed pregnant women (100). Recent alerts have however highlighted the safety concerns associated with prolonged use of fluoroquinolones in humans (101),(102).

There is limited evidence for the optimal duration of MDR-TB preventive treatment, and this should be based on clinical judgement. Regimens used in the studies conducted so far were given for 6, 9 and 12 months. None of studies included data on pharmacokinetics and safety in pregnancy or a comparison of the risk for adverse events, although one reported that no serious adverse events could be attributed to fluoroquinolone-based preventive treatment (36).

Implementation considerations

The regimen of preventive treatment of MDR-TB contacts should be individualized and based on reliable information on the drug resistance profile of the presumed source. Later-generation fluoroquinolones (e.g. levofloxacin or moxifloxacin) may be used unless the strain of the presumed source shows resistance to these medicines. A dosing schedule for levofloxacin in children and adults is proposed in **Table 3**. Paediatric formulations of levofloxacin can be used for this purpose. For strains showing additional resistance other treatment regimens used in some of the studies may be used (37).

Contacts of people with rifampicin-resistant TB (RR-TB) are usually treated as for MDR-TB unless isoniazid-susceptibility in the index case is reliably confirmed, in which case IPT may be effective.

As the recommendation for preventive treatment in MDR-TB exposure is based on very low-quality evidence, people must be given detailed information about the potential benefits and harms of giving fluoroquinolones or other regimens. In view of uncertainties about the balance of benefit to harm, informed consent, preferably in writing, is required, based on the local context and practices in similar situations.

2. Monitoring and evaluation

Coverage of contact investigation and TB preventive treatment among child contacts and PLHIV are among the top 10 core indicators for monitoring implementation of the End TB Strategy (8). National TB and HIV programmes report data yearly to WHO and UNAIDS on progress in LTBI care in target populations. PMTPT should include monitoring and evaluation systems that are aligned with national patient monitoring and surveillance systems (103),(104). Appropriate recording and reporting tools should be developed and electronic case-based monitoring will facilitate LTBI management and individual care[10]. Standardized indicators should be measured to regularly inform decision-making for programme implementation. Some may require changes to national regulations or health policies (e.g. making LTBI a notifiable condition or mandating a reporting framework), which should be addressed according to the local and national context. It is important to engage the private health sector and to ensure proper recording and reporting from both the private and public sectors.

Most individuals who receive TB preventive treatment are healthy and adverse reactions to treatment are likely to influence their likelihood of completing it. Drug-related toxicity should therefore be minimized. Medicines used for TB preventive treatment regimens are generally safe and well tolerated but adverse reactions have been associated with isoniazid (asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity) and rifampicin and rifapentine (cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity). While most of these reactions are minor and occur rarely, specific attention should be paid to preventing drug-induced hepatotoxicity.

Individuals on TB preventive treatment should be monitored routinely at monthly encounters with healthcare providers, who should explain the disease process and the rationale of the treatment and emphasize the importance of completing it. They should also be advised to contact their healthcare provider at any time if they become aware of symptoms such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools, jaundice, confusion or drowsiness. If a healthcare provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately. This is one of the critical areas for frontline healthcare workers and students to receive training on.

There is insufficient evidence to support testing of baseline liver function (105). It is, however, strongly encouraged, where feasible, for individuals with the following risk factors: history of liver disease, harmful use of alcohol, chronic liver disease, HIV infection, age > 35 years, pregnancy or in the immediate postpartum period (within 3 months of delivery). For individuals with abnormal baseline test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks, and they should be tested routinely at subsequent visits. Appropriate laboratory testing should also be performed for patients who become symptomatic while on treatment (e.g. liver function tests for those with symptoms of hepatotoxicity). Trial criteria for when to stop a medicine – e.g. an increase in transaminases to 5 times the upper limit of normal or to 3 times plus symptoms in people on rifampicin – will need to be adapted to something more practical under field conditions.

There is no evidence of a significant association between anti-TB drug resistance and use of isoniazid or rifamycins for the treatment of LTBI (106),(107). Nonetheless, active TB disease must be excluded before TB preventive treatment is initiated (**Section 1.2**), and regular follow-up is required to ensure

[10] More detail will be provided in the practical operational guide that WHO is releasing with these guidelines.

early identification of people who develop active TB while receiving TB preventive treatment. National surveillance systems for anti-TB drug resistance may need to be strengthened in countries scaling up PMTPT.

Monitoring the adherence to TB preventive treatment and ensuring its completion are conducive to clinical benefit. An electronic application for mobile phones has been created by WHO to guide national programmes on critical data to collect along the LTBI care pathway, as an accessory to monitoring and evaluation (103). It could also be helpful to collect information about the occurrence of active TB in people who have received TB preventive treatment. This can be done by asking patients registered for TB treatment about any history of starting or completing TB preventive treatment or the cross linkage of registers (e.g. LTBI registers compared with TB treatment or mortality registers). In people who develop TB after or well into a TB preventive treatment it would be important to test for emergence of resistance.

In people on MDR-TB preventive treatment the close monitoring for adverse events and adherence to treatment is essential. The types of adverse reactions depend on the medicines used (for more details see (101),(102),(108)). Adverse events should be monitored according to the WHO framework for monitoring and managing the safety of medicines against active TB (109). Evidence for the effectiveness and safety of MDR-TB preventive treatment is urgently needed (see also **Section 3**). The GDG reiterated that strict clinical observation and close monitoring for active TB disease based on sound clinical practice and national guidelines is required for at least 2 years after MDR-TB exposure, regardless of whether preventive treatment was given or not. Consideration should also be given to interactions with ART, immunosuppressants and other medicines when providing MDR-TB preventive treatment.

3. Research gaps

The evidence reviewed ahead of the current update exposed additional knowledge gaps to the ones reported in other recent updates of the guidelines. Continued research on development and on implementation science remain critical for many aspects of the PMTPT. Some of this information may be collected as part of user feedback put in place by the implementing programme.

Risks for progression to active TB

Evidence on the likelihood of progression from infection to active TB in different at-risk populations will help determine the potential benefits of TB preventive treatment and for the design of appropriate public health interventions. In particular, strong evidence from clinical trials is lacking particularly for indigenous populations and people under the following circumstances: diabetes, harmful use of alcohol, tobacco smoking, underweight, silica exposure, on steroid treatment, rheumatological diseases, and cancer. Both direct measurement of the incidence of active TB and methods for measuring the risk for active TB disease could be explored, such as use of genotyping to investigate reactivation. Evidence is also required on differential harm and the acceptability of LTBI testing and TB preventive treatment in specific risk groups, including socially adverse effects such as stigmatization.

Defining the best algorithm for ruling out active TB

Operational and clinical studies should be conducted to exclude active TB before preventive treatment is given. The performance and feasibility of the algorithms proposed in these guidelines should be assessed. Data on children and pregnant women are particularly limited. Better evidence is needed to identify the best strategies to trace contacts and to save cost and improve feasibility (e.g. use of mobile chest radiography).

Improved diagnostic tests and performance of LTBI tests in at-risk populations

Diagnostic tests with improved performance and predictive value for progression to active TB are critically needed. In addition, the performance of LTBI tests should be evaluated in various risk groups, to assess reinfection, and to understand how best to use available tools in each population (e.g. combination or sequential use of TST and IGRA).

Treatment options for LTBI

Research to find shorter, better-tolerated TB preventive treatment regimens than those currently recommended remains a priority. Studies of efficacy and adverse events in certain risk groups (e.g. people who use drugs, people who engage in the harmful use of alcohol and older persons) are essential. There remain very limited data on the use of rifapentine in children < 2 years and in pregnant women. Trial data on 1HP in children and adults not infected with HIV and in PLHIV with low CD4 counts, under different settings, would also be desirable. A direct comparison of 1HP vs. 3HP for safety, effectiveness, and cost-effectiveness will be useful. Pharmacokinetics studies could help establish an

optimal daily dosage of rifapentine in children under 13 years, and interactions between rifamycin-containing regimens and other medicines, particularly ART in both adults and children. In addition, the durability of protection of different preventive treatment regimens, including long-acting injectables, need to be evaluated in settings in which TB is endemic, including the efficacy of repeated courses of preventive treatment. Studies of the preference of different stakeholders for different regimen characteristics would be helpful.

Monitoring of adverse events

Prospective randomized studies are required to determine the incremental benefits of routine monitoring of liver enzyme levels over education and clinical observation alone for preventing severe clinical adverse events, with stratification of the evidence by at-risk population. Programmatic data on maternal and pregnancy outcomes, inclusive of post-natal follow-up of the child, could supplement current knowledge about the safety of different LTBI regimens when used in pregnancy.

Drug resistance and TB preventive treatment

Programme-based surveillance systems and clinical studies are needed to monitor the risk for resistance to the medicines used in TB preventive treatment. Particular consideration should be given to rifamycin-containing regimens because of the dearth of data. Conversely the impact on preventive treatment efforts of high levels of resistance to isoniazid and/or rifamycins among prevalent TB strains would be useful to study.

Adherence to and completion of treatment

Carefully designed studies, including RCTs, are required to generate evidence on the effectiveness of context-specific interventions to enhance adherence and completion of treatment. The studies should include specific risk groups, depending on the available resources and the health system infrastructure and address questions about how to integrate TB preventive treatment into differentiated models of HIV service delivery. Use of digital technologies to improve adherence is an important area. Further research is required on the effectiveness of self-administration of the 3-month regimen of weekly rifapentine plus isoniazid.

Cost–effectiveness

Although a number of studies of the cost-effectiveness of TB preventive treatment are available, their wide heterogeneity obviates a comprehensive appraisal of the cost-effectiveness of LTBI management stratified by population group, and type of regimen or intervention. Cost-effectiveness analysis using parameters from different resource settings could allow better planning for the extension of a PMTPT strategy at national or local level.

Preventive treatment for contacts of people with MDR-TB

The WHO recommendation on MDR-TB preventive treatment should not signal a lesser need for continued studies or create ethical impediments. RCTs with adequate power are urgently needed to update the recommendation on preventive treatment for contacts of people with MDR/RR-TB. Trials should be performed with both adult and paediatric populations and with at-risk populations such as PLHIV. The composition, dosage and duration of preventive treatment regimens for MDR-TB should be optimized, and the potential role of newer agents with good sterilization properties should be

investigated. The effectiveness and safety of preventive treatment for contacts of people with MDR-TB should be evaluated under operational conditions. Further evidence on the risk of contacts of people with MDR-TB for progression to active TB will be important to understand the benefits of preventive treatment.

Programme management

Continued epidemiological research should be conducted to determine the burden of LTBI in various geographical settings and risk groups and as a basis for nationally and locally tailored interventions, including integrated community-based approaches. Implementation research on context-specific barriers and facilitators is needed for different LTBI regimens, to explore dimensions for which evidence is often sparse, such as acceptability, feasibility, equity and resource use. Research is also needed on service delivery models to improve management including the provision of additional interventions for smokers, harm reduction services for people who use drugs or who engage in the harmful use of alcohol and in prison. Household implementation models could increase the effectiveness and efficiency of delivery of interventions. Future trial evidence could guide better how to optimise contact tracing strategies in households and elsewhere. Tools should be developed and assessed to facilitate monitoring and evaluation of PMTPT efforts as an accessory to improving future global guidance.

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Supplementary Table

Summary of changes to the WHO TB preventive treatment recommendations between 2018 and current updates

Note: In the current update, two of the 2018 recommendations on LTBI testing (Section C) were incorporated into the remarks as implementation considerations; four recommendations on individual TB preventive treatment options have been merged into one recommendation (Recommendation 17). Recommendations 3, 6, 9, 17 and 18 may apply to specific settings in a country regardless of the overall national TB incidence (see text and Annexes for further explanation of the changes). Other recommendations from the 2018 update remain unchanged or else underwent language editing to enhance clarity (Recommendations 1, 2, 4, 5, 7, 8, 10–16).

Recommendations in the 2018 update	***Recommendations in the current update***
A. Identifying at-risk populations for LTBI testing and treatment	**1.1. Identifying populations for LTBI testing and TB preventive treatment**
People living with HIV	*People living with HIV*
Adults and adolescents living with HIV, with unknown or a positive tuberculin skin test (TST) and who are unlikely to have active TB should receive preventive treatment of TB as part of a comprehensive package of HIV care. Treatment should be given to these individuals irrespective of the degree of immunosuppression and also to those on antiretroviral treatment (ART), those who have previously been treated for TB and pregnant women.	1. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable. *(language editing)*
Infants aged < 12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive 6 months of isoniazid preventive treatment (IPT) if the investigation shows no TB disease.	2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment. *(language editing)*
Children aged ≥ 12 months living with HIV who are considered unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB should be offered 6 months of IPT as part of a comprehensive package of HIV prevention and care if they live in a setting with a high prevalence of TB.	3. Children aged ≥ 12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB. *(refers to setting with high TB transmission rather than prevalence)*

Recommendations in the 2018 update	***Recommendations in the current update***
All children living with HIV who have successfully completed treatment for TB disease may receive isoniazid for an additional 6 months.	4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment. *(language editing)*
HIV-negative household contacts	*Household contacts (regardless of HIV status)*
HIV-negative children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment.	5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable. *(language editing)*
In countries with a low TB incidence, children, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB should be systematically tested and treated for LTBI.	*Incorporated into the following recommendation and its accompanying commentary* 6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.
In countries with a high TB incidence, children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.	
In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification.	7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. *(no change)*
Other at-risk groups	*Other people at risk*
Patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated for LTBI.	8. People who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis should be systematically tested and treated for LTBI. *(language editing)*
In countries with a low TB incidence, systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs.	9. Systematic LTBI testing and treatment may be considered for prisoners, health workers, immigrants from countries with a higher TB burden, homeless people and people who use drugs. *(language editing; restriction by TB burden setting removed)*
Systematic testing for LTBI is not recommended for people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people unless they are already included in the above recommendations.	10. Systematic LTBI testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people unless they also belong to other risk groups included in the above recommendations. *(language editing)*

Recommendations in the 2018 update	***Recommendations in the current update***
B. Algorithms to rule out active TB disease	**1.2. Algorithms to rule out active TB disease**
Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status.	11. Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status. *(no change)*
Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases that cause such symptoms.	12. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases and offered preventive treatment if active TB is excluded. *(language editing)*
Chest radiography may be offered to people living with HIV and on ART and preventive treatment given to those with no abnormal radiographic findings.	13. Chest radiography may be offered to people living with HIV on ART and preventive treatment given to those with no abnormal radiographic findings. *(no change)*
Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a case of TB should be evaluated for TB and other diseases that cause such symptoms. If the evaluation shows no TB, these children should be offered preventive treatment, regardless of their age.	14. Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age. *(language editing)*
The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥ 5 years and other at-risk groups before preventive treatment.	15. The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥ 5 years and other risk groups before preventive treatment. *(no change)*
C. Testing for LTBI	**1.3. Testing for LTBI**
Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI.	16. Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI. *(no change)*
People living with HIV who have a positive test for LTBI benefit more from preventive treatment than those who have a negative LTBI test; LTBI testing can be used, where feasible, to identify such individuals.	*Incorporated into the implementation considerations*
LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged < 5 years.	

Recommendations in the 2018 update	***Recommendations in the current update***
D. Treatment options for LTBI	**1.4. TB preventive treatment options**
Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence.	*Incorporated into a single recommendation, applicable to all settings* 17. The following options are recommended for the treatment of LTBI regardless of HIV status : 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3 month regimen of daily isoniazid plus rifampicin. A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives.
Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence.	
Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence.	
The following options are recommended for treatment of LTBI in countries with a low TB incidence as alternatives to 6 months of isoniazid monotherapy: 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 1-month regimen of daily rifapentine plus isoniazid, or 3–4 months of daily isoniazid plus rifampicin, or 3–4 months of rifampicin alone.	
In settings with high TB incidence and transmission, adults and adolescents living with HIV who have an unknown or a positive TST and are unlikely to have active TB disease should receive at least 36 months of IPT, regardless of whether they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy.	18. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive therapy (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities. *(refers to setting with high TB transmission only)*

For further information, please contact:

World Health Organization
20, Avenue Appia CH-1211 Geneva 27 Switzerland
Global TB Programme
Web site: www.who.int/tb

World Health Organization

9 789240 001503