

WHO consolidated guidelines on drug-resistant tuberculosis treatment

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Note

These consolidated guidelines have been updated following Guideline Development Group (GDG) processes carried out between 2011 and 2018 in accordance with WHO requirements ([online Annexes 3–5](#)) (7). The document replaces other WHO recommendations relating to the treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) issued since 2011 (2–6) (as well as recommendations in other guidelines relevant to the care of drug-resistant TB (DR-TB); see Box 1). The PICO (Population, Intervention, Comparator and Outcomes) questions underlying the recommendations and the revised dosage of medicines used in second-line regimens and key references are included in this document (Annexes 1 and 2 and the References section, respectively). More details on the GDG processes and participants, the main methods used to develop the recommendations, the resultant Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence summaries and decision frameworks for each recommendation, and unpublished data, data analysis plans and reports of systematic reviews are available online ([online Annexes 3–9](#)). The recommendations and other practical information to support their implementation will be reproduced in a forthcoming update of the WHO TB programmatic management handbook (7).



Abbreviations and acronyms¹

aDSM	active TB drug safety monitoring and management
aIPD	adult individual patient data
AE	adverse event
AIDS	acquired immunodeficiency syndrome
aOR	adjusted odds ratio
aRD	adjusted risk difference
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATS	American Thoracic Society
CDC	(United States) Centers for Disease Control and Prevention
CL	(95%) confidence limits
CNS	central nervous system
DALY	disability-adjusted life year
DOI	WHO Declaration of Interest
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
ERG	External Review Group
FDC	fixed-dose combination (medicines)
GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADEPro	online tool to create guideline materials (see https://gradepro.org/)
GRC	WHO Guideline Review Committee
GTB	WHO Global TB Programme
HALT	Hepatitis and Latent TB infection study
HIV	human immunodeficiency virus
(H)REZ	(isoniazid)–rifampicin–ethambutol–pyrazinamide
Hr-TB	confirmed rifampicin-susceptible, isoniazid-resistant TB
IPD	individual patient data
IPD-MA	individual patient data meta-analysis
IQR	interquartile range
ITT	intention to treat

¹ See abbreviations of TB agents in separate list in page 5.

KNCV	KNCV Tuberculosis Foundation
LPA	line probe assay
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug/rifampicin-resistant tuberculosis
MTBDRs/	GenoType <i>Mycobacterium tuberculosis</i> drug-resistant second-line assay
OR	odds ratio
PICO	Population, Intervention, Comparator and Outcomes
PK/PD	pharmacokinetics/pharmacodynamics
PLHIV	people living with HIV
RCT	randomized controlled trial
RR-TB	rifampicin-resistant TB
SAE	serious adverse event
SAT	self-administered treatment or unsupervised treatment
SGOT	serum glutamic oxaloacetic transaminase
SMS	short message service (mobile phone text message)
TB	tuberculosis
UNION	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
US NIH(NIAID)	United States National Institutes of Health (National Institute of Allergy and Infectious Diseases)
VOT	video-observed treatment
WHO	World Health Organization
WHO/GTB	Global TB Programme of the World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Abbreviations of TB agents

Am	amikacin	Km	kanamycin
Amx-Clv	amoxicillin-clavulanic acid	Lfx	levofloxacin
Bdq	bedaquiline	Lzd	linezolid
Cfz	clofazimine	Mfx	moxifloxacin
Cm	capreomycin	Mpm	meropenem
Cs	cycloserine	PAS	<i>p</i> -aminosalicylic acid
Dlm	delamanid	Pto	prothionamide
E	ethambutol	R	rifampicin
Eto	ethionamide	S	streptomycin
Gfx	gatifloxacin	T	thioacetazone
Hh	high-dose isoniazid	Trd	terizidone
Imp-Cln	imipenem-cilastatin	Z	pyrazinamide

Key definitions²

Drug-susceptibility testing (DST) refers to in-vitro testing using either phenotypic methods to determine susceptibility or molecular techniques to detect resistance-conferring mutations to a medicine (7,8).

Extent or severity of disease in patients older than 14 years is usually defined by the presence of cavities or bilateral disease on chest radiography or smear positivity (see [online Annex 9](#)). In children under 15 years, severe disease is usually defined by the presence of cavities or bilateral disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) (adapted from (9)). In children, the occurrence of advanced malnutrition (defined by syndrome or by metrics) or advanced immunosuppression or positive tuberculosis (TB) bacteriology (smear, Xpert® MTB/RIF, culture) may also be considered when determining disease severity.

The **intensive (or injectable) phase**, as used in these guidelines and in the evidence reviews that informed the recommendations, is the initial part of a shorter or longer regimen for treating multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB). During this phase, an injectable agent – amikacin, capreomycin, kanamycin or streptomycin – is used. Regimens without an injectable agent are considered not to have an intensive phase.

Isoniazid-resistant TB (Hr-TB), refers to *Mycobacterium tuberculosis* strains in which resistance to isoniazid and susceptibility to rifampicin has been confirmed in vitro.

Longer MDR-TB regimens are those used for the treatment of MDR/RR-TB. These last 18 months or more and may be standardized or individualized. These regimens are usually designed to include a minimum number of second-line TB medicines considered to be effective based on patient history or drug-resistance patterns. The features and indications of these regimens are further elaborated in Sections 2 and 3 under [Recommendations and remarks](#) in these guidelines. The term “conventional” was previously used to refer to such regimens but was discontinued in 2016.

New case is defined as 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.

Polyresistance refers to resistance to more than one first-line anti-TB drug, other than isoniazid

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