



WHO treatment guidelines for isoniazid- resistant tuberculosis

**Supplement to the WHO treatment
guidelines for drug-resistant tuberculosis**



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**World Health
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Annexes 5 and 6 are **only available online** at:

http://www.who.int/tb/publications/2018/WHO_guidelines_isoniazid_resistant_TB/en/

Abbreviations & acronyms

aOR	adjusted odds ratios
ART	antiretroviral therapy
ATS	American Thoracic Society
DOI	WHO Declaration of Interest
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
E	ethambutol
ERG	External Review Group
FDC	fixed-dose combination medicines
GDF	Global Drug Facility
GDG	Guideline Development Group
Gfx	gatifloxacin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADEpro	online tool to create guideline materials (see http://gdt.guidelinedevelopment.org)
GRC	WHO Guideline Review Committee
GTB	WHO Global TB Programme
H	isoniazid
HALT	Hepatitis and Latent TB Infection study
HIV	human immunodeficiency virus
Hr-TB	confirmed rifampicin-susceptible, isoniazid-resistant TB
IPD	individual patient data
Km	kanamycin
KNCV	KNCV Tuberculosis Foundation
Lfx	levofloxacin
LPA	line probe assay
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
Mfx	moxifloxacin
M.tb	Mycobacterium tuberculosis
OR	odds ratio
PI	Principal Investigator
PICO	Patients, Intervention, Comparator and Outcomes
R	rifampicin
RCT	randomized controlled trial
RR-TB	rifampicin-resistant TB
S	streptomycin
SAE	serious adverse event
TB	tuberculosis
UNION	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
USD	United States dollars
WHO	World Health Organization
WHO/GTB	Global TB Programme of the World Health Organization
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

Glossary

The following definitions refer to common terms as used in these guidelines:

Isoniazid-resistant TB (Hr-TB), refers to *Mycobacterium tuberculosis* strains with resistance to isoniazid and susceptibility to rifampicin confirmed *in vitro*. Definitions and terms used herein have been described elsewhere.^{1,2}

Poly-resistance refers to resistance to more than one first-line anti-TB drug, other than isoniazid and rifampicin together.

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 particular medicine. Policy guidelines on the use of phenotypic and molecular tests for the detection of resistance to isoniazid has been published by WHO.^{3,4,5}

Previously treated refers to patients who have received one month or more of anti-TB medicines in the past.¹ **Previously treated cases** may have been treated with an individualized regimen including fluoroquinolones or injectable agents in addition to first-line TB medicines.⁶

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.

Treatment outcome definitions used in these guidelines, and the term **relapse**, refer to those used for patients without rifampicin-resistant tuberculosis, unless otherwise specified.¹

Serious adverse event (SAE) is defined as an adverse event which either leads to death or a life-threatening experience; to initial or prolonged hospitalization; to persistent or significant disability; or to a congenital anomaly. SAEs that do not immediately result in one of these outcomes but that require an intervention to prevent permanent impairment of a body function or damage to a body structure are included. The management of SAEs may require termination of the drug suspected of having caused the event.⁷

¹ Definitions and reporting framework for tuberculosis – 2013 revision (WHO/HTM/TB/2013.2). Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf. Geneva: World Health Organization. 2013.

² Guidelines for surveillance of drug resistance in tuberculosis - 5th ed [WHO/HTM/TB/2015.13]. Available from: http://apps.who.int/iris/bitstream/10665/174897/1/9789241549134_eng.pdf. Geneva: World Health Organization. 2015.

³ Policy statement: Liquid media for culture and DST. The use of liquid medium for culture and DST, 2007. Available from: http://www.who.int/tb/areas-of-work/laboratory/policy_liquid_medium_for_culture_dst/en/. Geneva: World Health Organization. 2007.

⁴ Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs. Available from: http://www.who.int/tb/publications/2008/whohtmtb_2008_392/en/. 2008.

⁵ WHO policy statement: molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis. Available from: http://www.who.int/tb/areas-of-work/laboratory/line_probe_assays/en/. Geneva: World Health Organization, 2008.

⁶ Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2014.11). Available from: http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf. Geneva: World Health Organization. 2014.

⁷ Active tuberculosis drug-safety monitoring and management (aDSM): framework for implementation (WHO/HTM/TB/2015.28). Available from: http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf?ua=1. Geneva: World Health Organization. 2015.

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Guideline Development Group

The chairs of the *Guideline Development Group* (GDG) were Nancy Santesso (GRADE Methodology specialist; Canada) and Kelly Dooley (Clinical Pharmacologist, Infectious Diseases specialist; United States). In addition, the following experts served as members of the GDG: Farhana Amanullah (Paediatrician, clinical practice; Pakistan), Tsira Chakhaia (Patient representative and civil society representative; Georgia), Daniela Cirillo (Laboratory specialist; Italy), Luis Gustavo Do Valle Bastos (Drug management and procurement; Switzerland), Philipp du Cros (Programme manager, clinician; United Kingdom), Raquel Duarte (Programme management, public health; Portugal), Christopher Kuaban (Programme management; Cameroon), Rafael Laniado-Laborin (Clinician (private sector), public health specialist; Mexico), Gary Maartens (Pharmacology; South Africa), Andrei Maryandyshev (Clinician; Russian Federation), Ignacio Monedero-Recuero (Clinician; Spain), Maria Imelda Josefa Quelapio (Clinician, programme implementation; Netherlands), Wipa Reechaipichitkul (Clinician, public health; Thailand), Michael Rich (DR-TB expert; United States), Radojka (Rada) Savic (Pharmacokinetics/pharmacodynamics specialist; United States), Welile Sikhondze (Programme manager; Swaziland), and Armand Van Deun (Microbiologist; Belgium).

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We thank the following members of the *External Review Group* (ERG) for reviewing the final guideline document and providing valuable inputs: Charles L. Daley (Clinical management; United States), Essam Elmoghazi (Programme management; Egypt), James Johnston (Clinical management; Canada), Enos Masini (Programme management, end-user; Kenya), Ingrid Oxley

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