World Health Organization

Report of a WHO expert consultation on dosing to enable implementation of treatment recommendations in the WHO consolidated guidelines on the management of TB in children and adolescents

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WHO also acknowledges the meeting participants for their contributions to the discussions summarized in this report (see annex 1 for a list of participants).

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Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
AUC	area under the concentration-time curve
BID	twice daily
C_{max}	maximum plasma concentration
CNS	central nervous system
CSF	cerebrospinal fluid
CYP	cytochrome P450
DM-6705	delamanid main metabolite (M1)
DS-TB	drug-susceptible tuberculosis
DT	dispersible tablet
ECG	electrocardiogram
EMA	European Medicines Agency
Eto	ethionamide
FDC	fixed-dose combination
GDF	Global Drug Facility
GDG	Guideline Development Group
H	isoniazid
HIV	human immunodeficiency virus
IQR	interquartile range
M1	delamanid main metabolite (DM-6705)
M2	bedaquiline N-desmethyl metabolite
MDR/RR-TB	multidrug- or rifampicin-resistant tuberculosis
MDR-TB	multidrug-resistant tuberculosis
MIC	minimal inhibitory concentration
PD	pharmacodynamic
PK	pharmacokinetic
QD	once daily
R	rifampicin
RR-TB	rifampicin-resistant tuberculosis
TB	tuberculosis
TBM	tuberculous meningitis
TIW	thrice weekly (Monday/Wednesday/Friday)
US FDA	United States Food and Drug Administration
Z	pyrazinamide

Executive summary

The World Health Organization's (WHO's) Global Tuberculosis (TB) Programme convened a Guideline Development Group (GDG) meeting in May–June 2021 to review questions on the management of TB in children and adolescents. Based on the evidence reviewed, WHO conditionally recommended the use of bedaquiline in children with multidrug- or rifampicin-resistant TB (MDR/RR-TB) aged below 6 years, as part of shorter and longer regimens, and the use of delamanid in children with MDR/RR-TB aged below 3 years, as part of longer regimens. In addition, a 6-month intensive regimen (6HRZEto) was conditionally recommended for use in children and adolescents with bacteriologically confirmed or clinically diagnosed tuberculous meningitis (TBM) (without suspicion or evidence of MDR/RR-TB), as an alternative to the currently recommended 12-month regimen (2HRZE/10HR).[1]

As a follow-up to the GDG meeting, an online expert consultation was convened by the WHO Global Tuberculosis Programme on 26–27 October 2021, to address dosing of bedaquiline, delamanid and the short intensive TBM regimen. At this meeting, decisions on the dosing of bedaquiline and delamanid in younger children were informed by finding a balance between efficacy (i.e. ensuring that high enough exposures are reached that approximate adult exposures, which have been found to be effective in treating MDR/RR-TB), safety (i.e. avoiding exposures that are too high, which may result in unacceptable toxicity) and implementation considerations (e.g. the availability of child-friendly formulations, acceptability and accessibility).

The meeting participants had expertise in clinical pharmacology, pharmacokinetics and pharmacodynamics, the clinical management of paediatric TB, research, policy, community engagement and programmatic implementation (see annex 1 for the list of participants annex 2 and for the meeting agenda). This meeting report summarizes the discussions and advice provided to WHO with respect to the dosing of bedaquiline, delamanid and the short intensive TBM regimen.

WHO has used the advice provided by meeting participants to update the dosing table for bedaquiline and delamanid used in MDR/RR-TB regimens in children and adolescents who weigh less than 46 kg, as part of a comprehensive update of the dosing table for second-line TB drugs. The advice also informed the development of a dosing table for the shorter 6-month intensive TBM regimen that has now been included in the 2022 WHO operational handbook on the management of TB in children and adolescents.[2]

Bedaquiline

Bedaquiline forms a core component of current MDR/RR-TB treatment, both as a Group A drug for use in longer regimens and as a component of the shorter regimen. Although available pharmacokinetic (PK) and safety data in children are limited, interim dosing guidance can be based on an analysis of existing data using population PK modelling and simulation tools. Dosing of bedaquiline in children is known to be affected by body weight and age.[3,4] The PK parameters of bedaquiline in adults have been well described and are informed by a larger body of evidence.[5] By accounting for age, body weight and other known covariates, an adult population PK model was used to simulate dose-exposure scenarios for a virtual representative paediatric population. In addition, individual paediatric data from various studies – the IMPAACT P1108 study, the Janssen TMC207-C211 trial and the MDR-PK2 observational study – were used to evaluate a virtual population and to inform doses, exposure, safety and the population PK model and assumptions. Using these population PK methods and current paediatric

[1] WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/rest/bitstreams/1414329/retrieve).

[2] WHO operational handbook on tuberculosis Module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/rest/bitstreams/1414333/retrieve).

[3] Holford N, Heo Y-A, Anderson B. A pharmacokinetic standard for babies and adults. J Pharm Sci. 2013;102(9):2941–52 (https://pubmed.ncbi.nlm.nih.gov/23650116/).

[4] Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25–36 (https://pubmed.ncbi.nlm.nih.gov/19252334/).

[5] Svensson EM, Dosne AG, Karlsson MO. Population pharmacokinetics of bedaquiline and metabolite M2 in patients with drug-resistant tuberculosis: the effect of time-varying weight and albumin. CPT Pharmacometrics Syst Pharmacol. 2016;5(12):682–91 (https://pubmed.ncbi.nlm.nih.gov/27863179/).

bedaquiline PK data, different dosing options were formulated and evaluated. Participants considered a combined age- and weight-based dosing approach for the use of bedaquiline in children aged below 6 years to be the most suitable option. The use of the 20 mg dispersible tablet (DT) formulation of bedaquiline is preferred for dosing young children; however, when that formulation is not available, or the pill burden is thought to be too high, the 100 mg adult formulation can be used (whole or after crushing and dispersing in water).[1] This interim dosing guidance will be reviewed by WHO in the future as new data become available.

The final dosing advice is summarized in table ES1.

Table ES1. Final dosing advice provided by the participants of the expert consultation for the use of bedaquiline in children who weigh less than 46 kg with MDR/RR-TB (with age- and weight-based dosing in children with MDR/RR-TB weighing <16 kg)

Weight range[a]	Age category	Dosing of bedaquiline[b]
3 to <5 kg	0 to <3 months	30 mg QD/10 mg TIW
	≥3 months	60 mg QD/20 mg TIW
5 to <7 kg	0 to <3 months	30 mg QD/10 mg TIW
	≥3 months	60 mg QD/20 mg TIW
7 to <10 kg	0 to <3 months	30 mg QD/10 mg TIW
	3 to <6 months	60 mg QD/20 mg TIW
	≥6 months	80 mg QD/40 mg TIW
10 to <16 kg	3 to <6 months	60 mg QD/20 mg TIW
	≥6 months	120 mg QD/60 mg TIW
16 to <24 kg	–	200 mg QD/100 mg TIW
24 to <30 kg	–	
30 to <35 kg[c]	–	400 mg QD/200 mg TIW
35 to <50 kg	–	
≥50 kg	–	

DR-TB: drug-resistant TB; MDR/RR-TB: multidrug- or rifampicin-resistant TB; QD: once a day; TB: tuberculosis; TIW: thrice weekly (Monday/Wednesday/Friday).

[a] For dosing of premature and low birth weight infants weighing <3 kg, advice should be sought from a paediatric DR-TB expert.

[b] Dosing is provided for the intensive phase (2 weeks) followed by dosing for the continuation phase (22 weeks).

[c] The cut-off for this weight band was adjusted in the final dosing table published in the 2022 operational handbook,[2] to align with the first weight band of the dosing table for patients aged 15 years and older (as in the *2020 WHO operational handbook on tuberculosis Module 4: Treatment – drug-resistant tuberculosis treatment*)

Delamanid

Delamanid is a Group C medication that is used in longer regimens to treat MDR/RR-TB. The participants considered different dosing options for delamanid in children aged below 3 years, through review of the