TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS IN CHILDREN / ADOLESCENTS <16 YEARS

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NEED HELP?

Contact the TOLL-FREE National HIV & TB Health Care Worker Hotline

0800 212 506 / 021 406 6782

Alternatively "WhatsApp" or send an SMS or "Please Call Me" to 071 840 1572

www.mic.uct.ac.za

NON-SEVERE TB, SEVERE PULMONARY TB AND EXTRAPULMONARY TB

excluding TB meningitis / central nervous system (CNS) TB / miliary TB

NON-SEVERE TB = intrathoracic lymph node TB without airway obstruction; simple TB pleural effusion, isolated perihilar opacities, consolidation involving less than an entire lobe with no cavities or miliary pattern, or isolated cervical lymph node TB. SEVERE PULMONARY TB = children & adolescents <16 years who do not meet the criteria for non-severe TB

TB DRUG DOSING CHART FOR CHILDREN/ADOLESCENTS <16 YEARS

WITH CONFIRMED OR CLINICALLY DIAGNOSED DRUG-SUSCEPTIBLE NON-SEVERE TB, SEVERE PULMONARY TB AND EPTB

excluding TB meningitis / central nervous system (CNS) TB / miliary TB

Treatment phase	Intensive phase Once daily, 7 days a week		Continuation phase* Once daily, 7 days a week			Treatment phase
Duration	2 months		Non-severe TB: 2 months	Severe PTB & most EPTB: 4 months	Bone & joint TB: 10 months	Duration
Target dose (range)	Isoniazid (H): 10 (7-15) mg/kg; Rifampicin (R): 15 (10 - 20) mg/kg; Pyrazinamide (Z): 35 (30 – 40) mg/kg; Ethambutol (E): 20 (15 – 25) mg/kg					Target dose (range)
Formulation Body weight (kg)	HRZ 50/75/150 mg dispersible tablet (scored) OR 50/75/150 mg/4 ml suspension[1]	+ E 400 mg tablet (not scored) OR 400 mg/8 ml suspension[2]	HR 50/75 mg dispersible tablet (scored) OR 50/75 mg/4 ml suspension[1]			Formulation Body weight (kg)
<2	Obtain expert advice					<2
2–2.9	½ tablet	1 ml	½ tablet			2–2.9
3–3.9	¾ tablet (3 ml)[1]	1.5 ml	¾ tablet (3 ml)[1]			3–3.9
4–7.9	1 tablet	2.5 ml	1 tablet			4–7.9
8–11.9	2 tablets	½ tablet or 4 ml	2 tablets			8–11.9
12–15.9	3 tablets	¾ tablet or 6 ml	3 tablets			12–15.9
16–24.9	4 tablets	1 tablet or 8 ml	4 tablets			16–24.9
≥25	HRZE (75/150/400/275 mg) tablet#		Choose one of the below options HR 75/150 mg tablet	HR 150/300 mg tablet		≥25
25 – 29.9	2 tablets		2 tablets	1 tablet		25 – 29.9
30 – 34.9	3 tablets		3 tablets	-		30 – 34.9
35 – 64.9	4 tablets		4 tablets	2 tablets		35 – 64.9
≥65	5 tablets		5 tablets	-		≥65

*The duration of the continuation phase depends on the eligibility for treatment shortening, the initial diagnosis and response to therapy - See *Eligibility Criteria for Shortened Regimen*; #Please note dosing bands for HRZE differ from adult dosing bands

*ASSESSING ELIGIBILITY OF CHILDREN AND ADOLESCENTS FOR SHORTENED TB TREATMENT REGIMEN

If not eligible for the shortened treatment regimen, treat for standard duration

SCENARIO 1: CXR AVAILABLE

DIAGNOSIS – Clinical Criteria

Eligible for treatment shortening if ALL OF THE BELOW CRITERIA ARE MET:
- Age 3 months to < 16 years at start of TB treatment
- DS-PTB or cervical TB lymphadenitis (presumed or confirmed with no evidence of EPTB other than lymphadenitis)
- First episode of TB (no previous TB treatment)
- No danger signs** indicating severe illness at presentation
- No severe acute malnutrition
- No asymmetric or persistent wheezing
- If living with HIV: viral load < 1,000 in the preceding 3/12 AND on ART for > 3/12
- No respiratory sample that is AFB smear positive[a]

DIAGNOSIS – Radiological Criteria

Eligible for treatment shortening if NONE OF THE FOLLOWING ARE PRESENT:
- Complicated intra-thoracic lymph node TB (i.e., airway compression or deviation and / or hyperinflation or collapse)
- Consolidation ≥ 1 lobe
- Complicated pleural effusion (loculated effusion, empyema or pneumothorax)
- Miliary pattern
- Cavities

FOLLOW-UP – Clinical Criteria

Eligible for shorter treatment if ALL BELOW CRITERIA ARE MET:
- Adherent to treatment
- **MONTH 1:** All TB signs & symptoms improved
- **MONTH 4:** All TB signs & symptoms resolved[b] and appropriate/improving weight trend

SCENARIO 2: NO CXR AVAILABLE

DIAGNOSIS – Clinical Criteria

Eligible for treatment shortening if ALL OF THE BELOW CRITERIA ARE MET:
- Age 3 months to < 8 years at start of TB treatment
- DS-PTB or cervical TB lymphadenitis (presumed or confirmed with no evidence of EPTB other than lymphadenitis)
- First episode of TB (no previous TB treatment)
- No danger signs** indicating severe illness at presentation
- No severe acute malnutrition
- No asymmetric or persistent wheezing
- Not living with HIV (HIV negative)
- No respiratory sample that is AFB smear positive[a]

FOLLOW-UP – Clinical Criteria

Eligible for shorter treatment if ALL BELOW CRITERIA ARE MET:
- Adherent to treatment
- **MONTH 1:** All TB signs & symptoms improved
- **MONTH 4:** All TB signs & symptoms resolved[b] and appropriate/improving weight trend

[a]Routine smears for AFB are not recommended as part of the diagnostic work-up. However, if there is an AFB smear positive result on any respiratory sample, the child is not eligible for treatment shortening. FNA smear positivity is not an exclusion. [b]If cervical peripheral lymph nodes did not decrease in size at month 4, continue to 6 months of treatment. If there was not a significant reduction in size of the lymph nodes, enlargement or complications, especially if TB was not bacteriologically confirmed, refer for further investigation (biopsy or aspiration) to exclude other diagnoses.

**DANGER SIGNS NEEDING URGENT ATTENTION:

Adapted from the WHO Operational Handbook on TB Module 5, SA National 2022 IMCI Guidelines and Chapter 15: Respiratory System of the STG and EML for paediatric hospitals in SA, 2023

General danger signs
- Unable to drink or breastfeed
- Vomiting everything
- Convulsions
- Unconscious or lethargic
- Any signs of shock

Signs of severe respiratory illness (any of the following)
- Chest indrawing
- Stridor in calm child
- Oxygen saturation <92% on room air
- Central cyanosis

Signs of severe dehydration (2 of the following)
- Unconscious or lethargic
- Sunken eyes
- Unable to drink or drinking poorly
- Skin pinch goes back very slowly

Signs of meningitis (any of the following)
- Neck stiffness
- Bulging fontanelle
- Restless, continuously irritable

Signs of severe anaemia (any of the following)
- Severe palmar pallor
- Hb <7 g/dl

TB MENINGITIS / CENTRAL NERVOUS SYSTEM TB / MILIARY TB

TB DRUG DOSING CHART FOR CHILDREN/ADOLESCENTS <16 YEARS

WITH CONFIRMED/PRESUMED DRUG-SUSCEPTIBLE TB MENINGITIS / CENTRAL NERVOUS SYSTEM TB / MILIARY TB

Single phase of treatment: 6-9 months[Δ] Once daily, 7 days a week

Target dose, range and maximum doses	Isoniazid (H): 15-20 mg/kg, maximum dose 450 mg Rifampicin (R): 22.5-30 mg/kg, maximum dose 900 mg	Pyrazinamide (Z): 35-45 mg/kg, maximum dose 2 g	Ethionamide (Eto)[#]: 17.5-22.5 mg/kg, maximum dose 1 g	Target dose, range and maximum doses
Formulation Body weight (kg)	HR 50/75 mg dispersible tablet (scored) OR 50/75 mg/4 ml suspension[1]	+ Z 500 mg tablet (scored) OR 500 mg/8 ml suspension[3]	+ Eto 250 mg tablet (not scored) OR 250 mg/8 ml suspension[4]	Formulation Body weight (kg)
<2	Obtain expert advice			<2
2 – 2.9	¾ tablet (3 ml)[1]	1 ml	1.5 ml	2 – 2.9
3 – 3.9	1 ½ tablets	2 ml	2 ml	3 – 3.9
4 – 4.9	**<3 months**: 1 ½ tablets **≥3 months**: 2 tablets	2.5 ml	2.5 ml	4 – 4.9
5 – 5.9	2 ½ tablets	3 ml	3 ml	5 – 5.9
6 - 7.9	3 tablets	½ tablet or 4 ml	½ tablet or 4 ml	6 – 7.9
8 - 8.9	3 ½ tablets			8 - 8.9
9 – 9.9		¾ tablet or 6 ml	¾ tablet or 6 ml	9 – 9.9
10 – 11.9	4 tablets			10 – 11.9
12 – 12.9		1 tablet or 8 ml	1 tablet or 8 ml	12 – 12.9
13 – 14.9	4 ½ tablets			13 – 14.9
15 – 15.9	5 tablets		1 ¼ tablets or 10 ml	15 – 15.9
16 - 16.9	6 tablets			16 - 16.9
17 – 17.9		1 ¼ tablets or 10 ml		17 – 17.9
18 – 19.9			1 ½ tablets or 12 ml	18 – 19.9
20 – 24.9	7 tablets	1 ½ tablets		20 – 24.9
25 – 29.9	HR 150/300 mg tablet 3 tablets	2 tablets	2 tablets or 16 ml	25 – 29.9
30 – 34.9		2 ½ tablets	2 ½ tablets or 20 ml	30 - 34.9
35 – 39.9		3 tablets	3 tablets or 24 ml	35 – 39.9
40 – 49.9		3 ½ tablets	3 ½ tablets or 28 ml	40 – 49.9
≥50		4 tablets	4 tablets or 32 ml	≥50

[#]If ethionamide is out of stock, phone the hotline (0800 212 506) for alternative regimens

[Δ]In children with complex disease, where treatment interruptions or changes occurred, or in children with other significant immune dysfunction (including HIV), it is recommended that treatment be extended to 9 months or longer. Discuss with an expert.

Note: A lumbar puncture (LP) should be done in all children <2 years with miliary TB. For older children, do LP if there are CNS symptoms.

Note: Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets so as to avoid large volumes of liquid medication if possible

TO MAKE ORAL SUSPENSION:

[1] **HRZ (50/75/150 mg) or HR (50/75 mg):** Disperse the required number of tablets and fractions of tablets in an amount of water (5-10 ml) and administer all of the suspension to the child orally or via nasogastric tube. If the recommended dose is 3 ml, disperse 1 tablet in 4 ml of water, administer 3 ml, discard unused suspension. Make a new suspension with each dose.

[2] **Ethambutol (400 mg/8 ml):** For each dose, crush 1 x ethambutol 400 mg tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 400 mg/8 ml (50 mg/ml). Administer required dose as indicated in chart, discard unused suspension. Make a new suspension with each dose.

[3] **Pyrazinamide (500 mg/8 ml):** Crush 1 x 500 mg pyrazinamide tablet to a fine powder, disperse in 8 ml water to prepare a concentration of 500 mg/8 ml (62.5 mg/ml). Administer required dose as indicated in above chart, discard unused suspension. Make a new suspension with each dose.

[4] **Ethionamide (250 mg/8 ml):** Crush 1 x 250 mg ethionamide tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 250 mg/8 ml (31.3 mg/ml). Administer required dose as indicated in above chart, discard unused suspension. Make a new suspension with each dose.

ORAL CORTICOSTEROID USE IN TB

Oral corticosteroids (prednisone 2 mg/kg orally - max 60 mg, daily for 4 weeks. Tapered to stop over 2 weeks. Total duration 6 weeks) are recommended in children with miliary TB, intrathoracic lymphadenopathy with significant airway compression, TB IRIS, TBM, tuberculoma or pseudo-abscess with surrounding brain oedema and TB pericarditis.

PYRIDOXINE PROPHYLAXIS IN CHILDREN ON DS-TB TREATMENT

CALHIV, malnourished children, breastfed infants, children and adolescents ≥ 8 years and children receiving high-dose INH (as with TBM/miliary TB) should receive pyridoxine for the duration of TB treatment.

Dose: Pyridoxine (vitamin B6) 1-2 mg/kg/day

<6 kg: 6.25 mg/d (¼ x 25 mg tablet); **≥6 kg but < 5 years:** 12.5 mg/d (½ x 25 mg tablet); **≥5 years:** 25 mg/d (1 tablet)

TREATMENT OF TB IN HIV CO-INFECTED CHILDREN

DTG-containing regimens are preferred for all patients, including those on TB treatment. All ART naïve patients and patients re-initiating ART after previously interrupting ART should be initiated on a DTG-containing regimen, if appropriate. Patients on ART who have not yet been transitioned to a DTG-containing regimen should be evaluated and transitioned as a matter of urgency—see ART guidelines

TB DIAGNOSED BEFORE STARTING ART:	TB DEVELOPS WHILE ON ANTIRETROVIRAL THERAPY (ART):
• **Start ART as soon as TB treatment is tolerated (ideally within 2 weeks)** • **If TBM/CNS TB: defer starting ART until 4 weeks after starting TB treatment**	ART should be continued throughout TB treatment. TB treatment should be started at standard doses. Assess adherence, do VL and do CD4 if VL not suppressed. Ensure patient is on cotrimoxazole prevention therapy. **On dolutegravir-based regimen:** Rifampicin decreases the concentration of DTG. Dose adjustment of DTG is required. DTG-boosting entails doubling the standard ("unboosted") dose of DTG by giving it twice daily rather than once daily. Refer to Antiretroviral Drug Dosing Chart for Children 2022 **On atazanavir/ritonavir or darunavir/ritonavir:** Do not use with rifampicin. Consult the hotline or an expert **On lopinavir/ritonavir-based regimen:** • Rifampicin reduces LPV/r concentration and dosage adjustment required • **LPV/r solution or pellets:** Super boosting with additional ritonavir powder: maintain standard LPV/r dose but add additional ritonavir twice daily as per Antiretroviral Drug Dosing Chart for Children 2022 • **LPV/r tablets:** Double dose LPV/r tablets only in children who can swallow whole tablets (tablets must not be crushed, broken or chewed) ***Boosted doses of ART should be continued for 2 weeks after completion of rifampicin-containing TB treatment*** **On nevirapine as part of HIV preventive therapy:** Rifampicin reduces nevirapine levels. Consult with an expert

MONITORING RESPONSE TO TREATMENT

TYPE OF MONITORING	FREQUENCY OF MONITORING	MONITORING PARAMETERS
Clinical (Children responding well will have resolution of symptoms and will gain weight)	Monthly for first 2 months, thereafter every 2 months until completion of TB treatment	• Presence (and change) of TB symptoms • Treatment adherence—review the patient treatment card, conduct pill count. At least 80% — ideally more—of all prescribed medication should be taken • Adverse events— see table below • Weight gain—measure, plot on chart, and assess/interpret • Review medication dosages and adjust according to weight • If vaccinations are not up to date, catch-up vaccinations should be given **Assessing treatment response in shortened regimen:** ***Adequate response in patients with PTB —*** *see follow-up criteria in Assessing eligibility for treatment shortening table:* stop TB treatment after 4 months ***Inadequate clinical response:*** extend treatment to a total of 6 months—also consider evaluation for DR-TB and non-TB related diseases (see section 14.5, p 70 of guideline)
Radiological	Not routinely recommended in children with non-severe TB or asymptomatic children during or at the end of TB treatment	Only repeat CXR if: • any clinical deterioration during TB treatment • if there is no clinical improvement • at the end of treatment for children with severe PTB, to assess for post-TB lung disease
Bacteriological (Not routinely recommended in children with good clinical response)		• If smear or culture positive at baseline, repeat smear and/or culture as for adults (i.e. smear at 7 weeks and 5 months. Culture and DST at 8 weeks if smear still positive at week 7. If follow-up tests are positive, discuss with the hotline) • If smear negative at baseline in older children, do not repeat unless there is clinical deterioration • TB-NAAT testing should not be used to monitor response to treatment • Consider smear and culture if there is clinical deterioration or a new exposure to a source patient with DR-TB

Note: Patients should be weighed regularly and the dose adjusted according to their current weight

MANAGEMENT OF COMMON ADVERSE DRUG REACTIONS

This list is not exhaustive. For more information phone the hotline 0800 212 506.

Adverse reaction	Drug involved	Management
Peripheral neuropathy *Signs and/or symptoms:* Pain in feet and/or gait abnormality	Isoniazid	Ensure patient is on pyridoxine and discuss the need for alternative treatment with an expert. ***Note:*** *Drug-induced peripheral neuropathy can be irreversible if the offending drug is not stopped promptly*
Hepatotoxicity or jaundice *Signs and/or symptoms:* Any jaundice, new onset vomiting, persistent nausea and vomiting, liver tenderness, enlarged liver or abdominal pain, evidence of liver failure (e.g. bleeding or encephalopathy)	Pyrazinamide, ethionamide, isoniazid, rifampicin	**If signs and/or symptoms:** Stop TB treatment (ART and other hepatotoxic drugs e.g. co-trimoxazole, if applicable) until the results of further investigations are available **Refer same day for assessment by a doctor:** • Check LFTs, INR and blood glucose • Exclude other causes e.g. viral hepatitis For more details see section 14.4.1, p 67—69 of the guideline: *Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa*, September 2024 and refer to the dosing chart in Annexure 1, p 47-52 in *Clinical management of rifampicin-resistant tuberculosis, updated clinical reference guide,* September 2023, or *Drug-resistant-TB treatment dosing table for children 2024* on MIC website (www.mic.uct.ac.za) or SA HIV/TB Hotline app • For cases of severe TB requiring stopping first-line TB drugs based on results of above investigations, start an adjusted TB treatment regimen with less hepatotoxic drugs usually a three-drug regimen of levofloxacin + ethambutol + linezolid (if Hb >8). If any of these drugs are contra-indicated or unavailable or if the child has TBM/CNS TB/miliary TB, call the hotline to discuss an alternative/s & ensure good CNS penetration. • Once LFTs have normalised and asymptomatic, rechallenge TB treatment in hospital. Discuss details with the hotline (0800 212 506) or a specialist
Gastrointestinal disturbances	Ethionamide, rifampicin, isoniazid, pyrazinamide, ethambutol	Symptomatic treatment.
Skin rash	Rifampicin, isoniazid, pyrazinamide, ethionamide	*Mild:* Symptomatic treatment *Severe (skin rash with blistering, mucosal involvement, systemic symptoms for example: feeling unwell, GIT symptoms, fever, respiratory symptoms, malaise, fatigue, achiness):* stop all medicines. Once resolved, consider rechallenge of TB drugs in hospital. Discuss with hotline 0800 212 506
Optic neuritis	Ethambutol	Rare side effect if dose remains <25 mg/kg/day. However, every complaint of visual disturbance should be taken seriously: stop ethambutol and refer for ophthalmologic evaluation. Optic neuritis is reversible if ethambutol is stopped promptly.
Joint pain	Pyrazinamide	Give paracetamol 15 mg/kg (up to 1 g) 6 hourly as needed up to 5 days

TREATMENT INTERRUPTION

If TB symptoms recur during interruption, reassess the child or adolescent with a rapid molecular test and culture/DST to assess for drug resistance

TREATMENT INTERRUPTION DETAILS	MANAGEMENT
Cumulative interruption <1 month on a four or 6-month regimen	Add missed doses to the end of the relevant treatment phase
Cumulative interruption >1 month on the 4-month regimen	Change to 6-month treatment. If the interruption is in the intensive phase, add missed doses to the end of the intensive phase and continue for 6 months in total
Cumulative interruption >1 month on 6-month regimen	Add missed doses to the relevant treatment phase
Interruption ≥2 months consecutively on the 4 or 6-month regimen	Assign outcome as 'loss to follow-up'. Repeat full clinical assessment of the patient (including radiology and bacteriological testing if available). Discuss with a clinician experienced in child and adolescent TB whether to restart a new treatment episode or monitor carefully for relapse. Factors to consider would be the clinical picture and overall adherence pattern. If unsure, restart a new treatment episode

Department: Health REPUBLIC OF SOUTH AFRICA

NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE 0800 212 506

MEDICINES INFORMATION CENTRE

Based on the National Guidelines for the Management of Tuberculosis in Children and Adolescents 2024, Department of Health, South Africa
Available online: https://knowledgehub.health.gov.za/elibrary/management-tuberculosis-children-and-adolescents

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AFB = acid-fast bacilli; ART = antiretroviral therapy; CALHIV = children and adolescents living with HIV; CNS = central nervous system; CXR = chest X-ray; CSF = cerebrospinal fluid; DR-TB = drug-resistant tuberculosis; DS = drug susceptible; DST = drug susceptibility testing; DTG = dolutegravir; E = ethambutol; EPTB = extrapulmonary tuberculosis; Eto = ethionamide; FNA = fine-needle aspirates; GIT = gastrointestinal tract; H = isoniazid; Hb = haemoglobin; HIV = human immunodeficiency virus; INH = isoniazid; IRIS = immune reconstitution inflammatory syndrome; INR = international normalized ratio; LFTs = liver function tests; LP = lumbar puncture; LPV/r = lopinavir and ritonavir; PTB = pulmonary TB; TB-NAAT = TB nucleic acid amplification test; R = rifampicin; TB = tuberculosis; TBM = TB meningitis; VL = viral load; Z = pyrazinamide