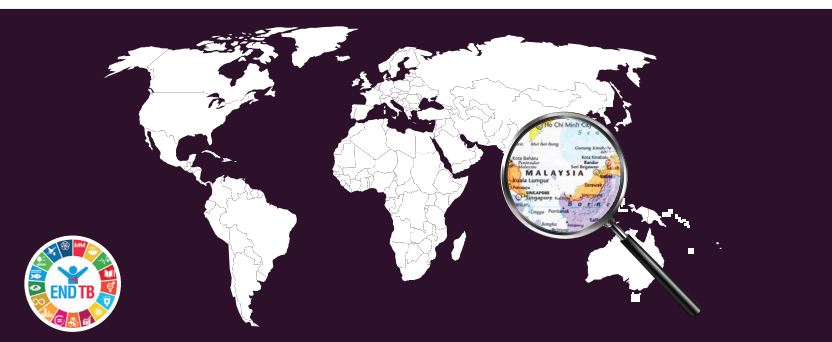


QUICK REFERENCE FOR  
HEALTHCARE PROVIDERS

# MANAGEMENT OF TUBERCULOSIS

(FOURTH EDITION)



Ministry of Health  
Malaysia



Academy of  
Medicine Malaysia

## Key Messages

1. The vision of the Malaysian Tuberculosis (TB) Control Programme is for Malaysia to be a TB-free country by 2035.
2. Adults with productive cough, haemoptysis, loss of appetite, unexplained weight loss, fever, night sweats & fatigue should be screened for pulmonary TB (PTB).
3. TB disease in children is mostly paucibacillary with non-specific signs & symptoms. It could be disseminated especially in young children. In children <5 years old, additional symptoms include anorexia, failure to thrive, poor feeding & decreased activities or playfulness. Therefore, a high index of suspicion is needed for the diagnosis.
4. Testing with Xpert Ultra & mycobacterial culture should be done as part of assessment for the diagnosis of smear negative & extrapulmonary tuberculosis (EPTB). Chest radiograph (CXR) should be done in people with suspected EPTB to rule out concomitant PTB.
5. The standard treatment regimens for drug susceptible TB are:
  - PTB - 2EHRZ/4HR (8 weeks of EHRZ, 18 weeks of HR)
  - TB meningitis - 2EHRZ/10HR
  - bone & joint TB - 2EHRZ/4 - 7HR
  - other forms of EPTB - 2EHRZ/4HRAdjunctive corticosteroids should be given in tuberculous meningitis & pericarditis.
6. Fixed-Dose Combination (FDC) tablets or flavoured, dispersible child-friendly FDC should be used to treat active TB.
7. Rifabutin should be used instead of rifampicin for HIV-TB co-infected patients on protease inhibitors or integrase strand transfer inhibitors.
8. Active TB must be ruled out before starting latent TB infection (LTBI) treatment. Shorter LTBI treatment regimens are preferred in eligible individuals without contraindications.
9. Adverse drug reaction (ADR) should be recognised early & managed well to reduce treatment-related morbidity & mortality, & to inspire confidence in the patient.
10. Isoniazid & rifampicin interact with a broad range of commonly used medications. These medications may need to be switched or have their dose adjusted.

This Quick Reference provides key messages & summarises the main recommendations in the Clinical Practice Guidelines (CPG) Management of Tuberculosis (Fourth Edition).

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:

Ministry of Health Malaysia: [www.moh.gov.my](http://www.moh.gov.my)

Academy of Medicine Malaysia: [www.acadmed.org.my](http://www.acadmed.org.my)

### **CLINICAL PRACTICE GUIDELINES SECRETARIAT**

Malaysian Health Technology Assessment Section (MaHTAS)

Medical Development Division, Ministry of Health Malaysia

Level 4, Block E1, Presint 1,

Federal Government Administrative Centre 62590

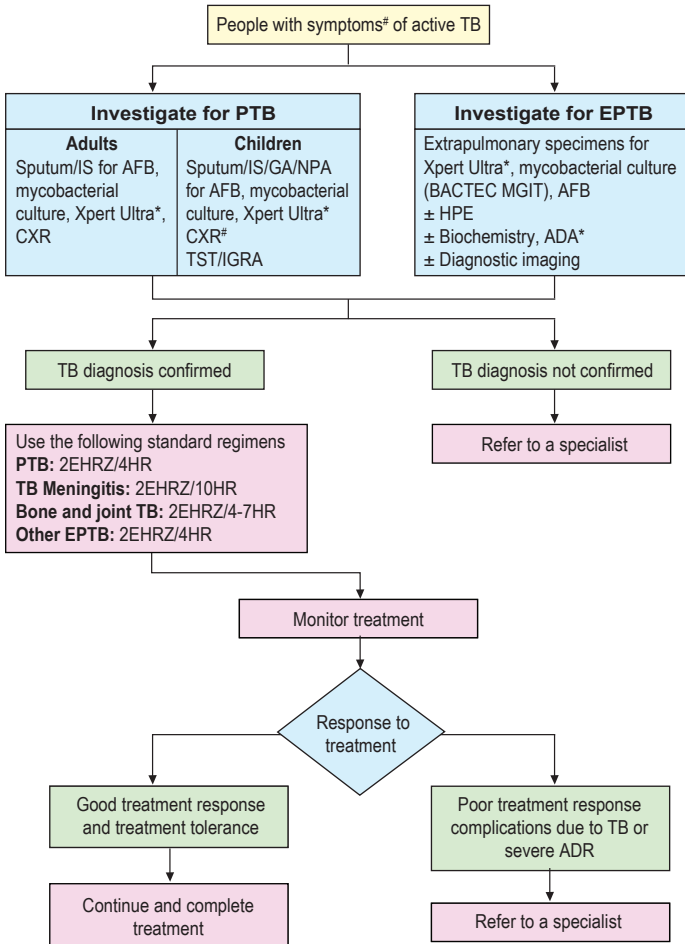
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## SECTION 1. ACTIVE TUBERCULOSIS

### Algorithm 1: Management of Active Tuberculosis



#Symptoms of TB and CXR findings in children may be different from adults

\*When indicated

**Important note:** Please refer to the texts in the relevant sections in the CPG for further details.

**Abbreviations:**

ADA=adenosine deaminase, ADR=adverse drug reaction, AFB=acid fast bacilli, CXR=chest radiograph, EPTB=extrapulmonary tuberculosis, GA=gastric aspirate, HPE=histopathological examination, IS=induced sputum, IGRA=Interferon Gamma Release Assay, NPA=nasopharyngeal aspirate, PTB=pulmonary tuberculosis, TB=tuberculosis, TST=tuberculin skin test

## **Active TB Treatment & Monitoring**

### **Recommended dose for FDC in adults**

Body weight (kg)	Number of FDC tablets daily
30 - 37	2
38 - 54	3
55 - 70	4
>70	5

### **Recommended dose of first-line anti-TB in adults**

Drug	Recommended doses	
	Dose (range) in mg/kg body weight daily	Maximum dose in mg daily
Isoniazid (INH)	5 (4 - 6)	300
Rifampicin (RIF)	10 (8 - 12)	600
Ethambutol (EMB)	15 (15 - 20)	1600
Pyrazinamide (PZA)	25 (20 - 30)	2000

\*Pyridoxine 10 - 30 mg daily needs to be added if INH is prescribed

### **Monitoring schedule of adults on PTB treatment**

Visit	Treatment duration	Regimen	Investigations
1*	0 month	EHRZ	FBC, RBS, RP, LFT, HIV screening Sputum smear for AFB Sputum mycobacterial culture & drug susceptibility testing CXR
2*	2 - 4 weeks	EHRZ	LFT Sputum smear for AFB**
3*	2 months	HR	Sputum smear for AFB CXR
4	5 months	HR	Sputum smear for AFB#
5*	6 months	Treatment complete	Sputum smear for AFB CXR

E=ethambutol, H=isoniazid, R=rifampicin, Z=pyrazinamide

\*requires in-person visit

\*\*for return to work/school purposes

#sputum smear for AFB should be done at the end of five months of standard anti-TB treatment

TB treatment should be observed directly (DOT). Alternatively, video observed treatment (VOT) may be used. Self-administered treatment should be reserved for patients who are unable to undergo DOT or VOT.

### **Recurrent TB**

- Patients exposed to anti-TB drugs are at risk of drug resistance. Hence, all patients who are suspected to have recurrent TB should be investigated using rapid molecular tests, e.g. Xpert Ultra & mycobacterial culture (BACTEC MGIT).
- If the rapid molecular test results are negative, the patients should be treated with a standard regimen for drug susceptible TB pending drug culture & susceptibility results.

### TB in Special Situations

- Patients having chronic kidney disease with GFR of <30 ml/min, & patients on hemodialysis should be treated with standard anti-TB regimen & have the dosage adjusted.
- Patients with liver cirrhosis should be managed at an experienced specialist centre.
- Pregnant & lactating women should receive the same treatment regimen for TB as for non-pregnant women.
- Women on rifampicin-based anti-TB treatment should use alternative contraception methods other than oral contraceptive pills.

### HIV-TB Co-infection

Timing for anti-retroviral treatment (ART) initiation in patients with HIV-TB coinfection:

Clinical conditions	Timing of ART initiation
CD4 >50 cells/mm <sup>3</sup>	Initiate within 8 weeks of anti-TB treatment
CD4 <50 cells/mm <sup>3</sup>	initiate within the first 2 weeks of anti-TB treatment
HIV with TB meningitis	Delay ART until 2 months after initiation of TB treatment

- Immune Reconstitution Inflammatory Syndrome typically occurs within 2 - 12 weeks after starting ART, especially in patients with CD4 count <50 cells/mm<sup>3</sup>, anaemia or EPTB.
- Co-trimoxazole prophylaxis should be given to patients with HIV-TB coinfection with an unknown CD4 count or a CD4 count <200 cells/mm<sup>3</sup>.

### TB in Children

The TB treatment regimen in children for both PTB & EPTB are the same as in adults. Anti-TB dose in children should be calculated in mg/kg & the total dose must not exceed the maximum dose.

#### Recommended dose of anti-TB drugs in children

Drug	Dose (range) in mg/kg body weight	Maximum dose (mg)
Isoniazid*	10 (7 - 15)	300
Rifampicin	15 (10 - 20)	600
Pyrazinamide	35 (30 - 40)	2000 (2 g)
Ethambutol	20 (15 - 25)	1000 (1 g)

\*Pyridoxine 5 - 10 mg daily needs to be added if INH is prescribed.

#### WHO recommended dose for FDC in children

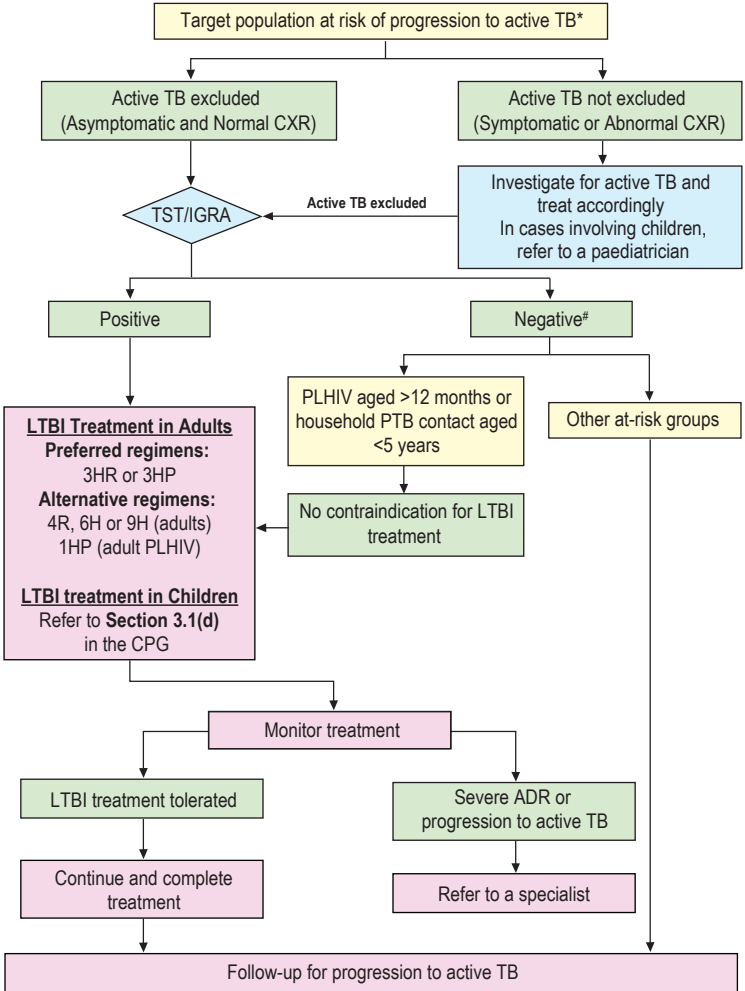
Weight band (kg)	Numbers of tablets daily	
	Intensive phase: RHZ 75/50/150*	Continuation phase RH 75/50
4 - 7	1	1
8 - 11	2	2
12 - 15	3	3
16 - 24	4	4
>25	Adult doses recommended	

\*EMB should be added in the intensive phase for children with extensive disease.

Newborns to mothers with active TB should be screened for active & latent TB before receiving BCG vaccination .

## SECTION 2. LATENT TUBERCULOSIS INFECTION

### Algorithm 2: Management of Latent Tuberculosis Infection



#IGRA/TST may be repeated if the initial testing has been done with <2 months of exposure to an index case, initiate LTBI treatment if repeat testing is positive. For children <5 years old, refer to a specialist to consider withholding the treatment if 2 consecutive IGRA/TST are negative.

\*Refer to page 6

**Abbreviations:**

ADR=adverse drug reaction, CXR=chest radiograph, IGRA=Interferon Gamma Release Assay, LTBI=latent tuberculosis infection, PLHIV=people living with HIV, PTB=pulmonary tuberculosis, TB=tuberculosis, TST=tuberculin skin test

### Systematic Screening & Treatment Of LTBI

The target population for LTBI screening & treatment are:

- household & close contact of bacteriologically-confirmed PTB
- PLHIV including children
- patients receiving dialysis
- patients preparing for organ/haematological transplant
- patients initiating anti-tumour necrosis factor treatment
- patients with silicosis

#### Recommended dosage for LTBI treatment in adults

Drug	Duration	Interval	Doses	Dosage
Isoniazid (6H/9H)	Six months/ nine months	Daily	180/270	5 mg/kg, max 300 mg
Isoniazid + rifampicin (3HR)	Three months	Daily	90	INH: 5 mg/kg, max 300 mg RIF: 10 mg/kg, max 600 mg
Rifapentine + isoniazid (3HP)	Three months	Weekly	12	INH: 15 mg/kg, max 900 mg RPT: <50 kg: 750 mg >50 kg: 900 mg
Rifampicin (4R)	Four months	Daily	120	10 mg/kg, max 600 mg

Pyridoxine 10 - 30 mg/day should be given to patients on isoniazid

#### Recommended LTBI regimen for children according to age\*

Age	Preferred	Alternative
28 days & below	6H	Nil
29 days to 2 years old	4R	3HR, 6H, 9H
More than 2 years old	4R or 3HP	3HR, 6H, 9H

P=rifapentine \*For children living with HIV, refer to the main CPG.

#### Recommended dosage for LTBI treatment in children

Drugs	Duration	Interval	Dose	
<b>Isoniazid (6H)</b>	6 months	Daily	1. Age 10 years & older: 5 mg/kg/day 2. Age <10 years: 10 mg/kg/day (range 7 - 15 mg/kg) <b>Maximum dose: 300 mg</b>	
<b>Rifampicin (4R)</b>	4 months	Daily	1. Age 10 years & older: 10 mg/kg/day 2. Age <10 years: 15 mg/kg/day (range 10 -20 mg/kg) <b>Maximum dose: 600 mg</b>	
<b>Isoniazid + rifampicin (3HR)</b>	3 months	Daily	Dose of INH & RIF same as above	
<b>Rifapentine + isoniazid (3HP)</b>	3 months*	Weekly	Isoniazid: 10 - 15 kg: 300 mg 16 - 23 kg: 500 mg 24 - 30 kg: 600 mg >31 kg: 700 mg <b>(For children age 2 - 14 years old)</b>	Rifapentine: 10 - 15 kg: 300 mg 16 - 23 kg: 450 mg 24 - 30 kg: 600 mg >31 kg: 750 mg <b>(For children age 2 - 14 years old)</b>

\*Given for total of 12 doses

Pyridoxine 5 - 10 mg/day should be given to patients on isoniazid.

Both adults & children on LTBI treatment should be monitored regularly for treatment compliance, ADR & progression to active TB.

### **SECTION 3. ANTI-TUBERCULOSIS DRUG ADVERSE REACTIONS & DRUG INTERACTIONS**

Anti-TB ADRs may affect any organ/system & they vary in severity.

#### **COMMON ADRs TO FIRST-LINE ANTI-TB DRUGS**

Drug	ADR
<b>INH</b>	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, burning/numbness/tingling sensation in hands or feet
<b>RIF</b>	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, orange/red urine, flu syndrome (fever, chills, malaise, headache, bone pain)
<b>EMB</b>	Visual impairment
<b>PZA</b>	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, joint pain

Drug induced liver injury (DILI) is one of the commonest serious ADRs due to first-line anti-TB drugs. Two criteria may be used to diagnose anti-TB DILI, after excluding other causes of abnormal liver enzymes:

1. The American Thoracic Society criteria for drug-induced hepatitis
  - i. an ALT  $\geq 3$  times the upper limit of normal (ULN) in patients with symptomatic hepatitis, or
  - ii. an ALT  $\geq 5$  x the ULN in patients without any symptoms
2. The international DILI expert consensus criteria:  
(any of the following, regardless of symptoms)
  - i. an ALT  $\geq 5$  x the ULN
  - ii. an ALP  $\geq 2$  x the ULN
  - iii. an ALT  $\geq 3$  x & total bilirubin 2x the ULN

Patients with suspected severe ADR, including DILI, should have their TB treatment stopped immediately or switched to an alternative anti-TB regimen. All patients with ADR should be treated compassionately, offered symptomatic treatment & given reassurance of getting good medical care. They should be referred to specialists for drug challenge/dechallenge or drug desensitisation when indicated.

The first-line anti-TB drugs, INH & RIF, interact with many commonly used medications shown below.

#### **DRUGS WITH POTENTIAL INTERACTIONS INVOLVING RIFAMYCINS & ISONIAZID**

Anti-TB	Potential interactions with these drugs
Rifamycins (Rifampicin, Rifabutin, Rifapentine)	Clarithromycin, moxifloxacin, doxycycline, fluconazole, itraconazole, voriconazole, caspofungin, dapsone, artemether/lumefantrine, hepatitis C direct-acting antivirals, immunosuppressive agents, protease inhibitors, integrase strand transfer inhibitors, hormone therapy, anticonvulsants, antidepressants, antipsychotics, barbiturates, benzodiazepines, opioid agonists, oral anticoagulants, antiplatelet agents, calcium channel blockers, beta-blockers, enalapril, losartan, digoxin, ivabradine, ranolazine, propafenone, antihyperlipidemics, methylxanthines, aprepitant, proton pump inhibitors, tyrosine kinase inhibitors, cyclin-dependent kinase inhibitors.
Isoniazid	Azole antifungal agents, rifampicin, clozapine, levodopa, paracetamol, warfarin, antihyperlipidemics, immunosuppressive agents, anticonvulsants, methylxanthines, benzodiazepines.

Therefore, health care workers should routinely check for drug-drug interactions when starting anti-TB treatment. It may be necessary to switch to other drugs or adjust the dose of these medications during TB treatment.