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CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TUBERCULOSIS

(FOURTH EDITION)

END TB

Ministry of Health Malaysia

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. The guidelines should not override the responsibility of the practitioners to make clinical decisions appropriate to the circumstances of the individual patient. This should be done in consultation with the patients and their families or guardians, taking into account the management options available locally.

UPDATING THE CPG

This CPG was issued in 2021 and will be reviewed in a minimum period of four years (2025) or sooner if new evidence becomes available. When it is due for updating, the Chairperson of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed, and the latest systematic review methodology used by MaHTAS will be employed.

Care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which will be the definitive version. This version can be found on the websites mentioned above.

TABLE OF CONTENTS

TABLE OF CONTENTS

LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

In this CPG the word ‘should’ is used to reflect a strong recommendation and ‘may’ to reflect a weaker recommendation.

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

Diagnosis and Treatment of Active TB

- Sputum should be sent for mycobacterial culture and drug susceptibility testing for patients with pulmonary tuberculosis (PTB).
- Sputum should be sent for Xpert Ultra if smear negative PTB is suspected.
- Sputum should be sent for both Xpert Ultra and mycobacterial culture (BACTEC MGIT) for individuals suspected to have recurrent PTB.

- Standard anti-tuberculosis regimen of 2EHRZ/4HR should be used in the treatment of pulmonary tuberculosis (PTB).
- Only daily anti-tuberculosis regimen should be used throughout the treatment of PTB.

- The following standard regimens should be used for extrapulmonary tuberculosis (EPTB):
  - 2EHRZ/4-7HR for tuberculosis of the bone or joint
  - 2EHRZ/10HR for tuberculous meningitis
  - 2EHRZ/4HR for other forms of EPTB
- Corticosteroids should be used in tuberculous meningitis and pericarditis.

- In HIV-tuberculosis (TB) co-infection, antiretroviral treatment (ART) should be initiated within eight weeks of anti-TB treatment.
  - However, for HIV-TB patients with a CD4 count <50 cells/mm^3, ART should be initiated within the first two weeks of anti-TB treatment.
- For people living with HIV with TB meningitis, ART should be delayed until two months after initiation of TB treatment.
- For HIV-TB co-infected patients on a protease inhibitor-based antiretroviral therapy, rifabutin should be used instead of rifampicin.
- Co-trimoxazole preventive therapy should be given during TB treatment in HIV-TB co-infection with an unknown CD4 count or a CD4 count <200 cells/mm^3.
- Directly observed treatment (DOT) should be done in patients on tuberculosis (TB) treatment.

- Video observed treatment (VOT) should be an alternative to DOT in selected patients where facilities are available.
- Self-administered treatment may be offered to patients who cannot perform VOT or DOT.

Diagnosis and Treatment of Latent TB Infection

- Interferon gamma release assay (IGRA) or tuberculin skin test (TST) should be used to test for latent tuberculosis infection (LTBI) for adults in the target groups.
- IGRA or TST should be used to test for LTBI in children at risk of progressing to active tuberculosis.

- In the treatment of all adults with latent tuberculosis infection (LTBI):
  - 3HR or 3HP regimens should be the first-line regimen unless contraindicated.
  - 4R may be used for patients who cannot tolerate or who are contraindicated for INH-based regimens.
  - 6H or 9H may be used for patients who cannot tolerate or who are contraindicated for rifamycin-based regimens.
  - 1HP may be considered for HIV-positive adults.

- In the treatment of children with latent tuberculosis infection (LTBI), the preferred regimens are:
  - 4R for all children >28 days of age or 3HP for children aged >2 years.
  - 6H for all newborns aged 28 days and below.
- Alternative regimes of LTBI in children are 3HR, 6H or 9H.
- In HIV-infected children with LTBI, 6H is the preferred regimen for:
  - children <2 years of age.
  - children ≥2 years of age on antiretroviral treatment with rifamycin drug interaction.

GUIDELINE DEVELOPMENT AND OBJECTIVES

GUIDELINE DEVELOPMENT

The members of the Development Group (DG) for this Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH) and Ministry of Higher Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. PubMed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published in English on studies conducted in humans, from year "2012 to Current". In addition, the reference lists of all retrieved literature and guidelines were searched, and experts in the field were contacted to identify relevant studies. All searches were conducted from 19 November 2018 to 26 February 2019. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 30 June 2021 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other CPGs on Tuberculosis e.g.:

- World Health Organization - WHO consolidated guidelines on tuberculosis. Module 1: Prevention - Tuberculosis preventive treatment (2020)
- National Institute for Health and Care Excellence (NICE) – Tuberculosis (updated September 2019)
- World Health Organization (WHO) - Treatment of Tuberculosis: Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 Update)
- American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America - Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis (2016)

These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to their use as references.

A total of 13 clinical questions (CQ) were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG

members met 21 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG was developed largely based on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to page i). The writing of the CPG strictly follows the requirement of AGREE II.

Upon completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid=634).

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on the management of tuberculosis (TB) in the following aspects:

a) diagnosis
b) treatment

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria

- Active TB and Latent TB

Exclusion Criteria

The following topics are covered by separate guidelines and hence have been excluded:

- Drug-resistant TB
- TB in healthcare workers

TARGET GROUP/USERS

This document is intended to guide those involved in the management of TB at any healthcare level including:

i. healthcare providers (doctors, pharmacists, allied health professionals)
ii. professional organisations
iii. policy makers
iv. patients and their advocates

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The draft guidelines were reviewed by a panel of experts. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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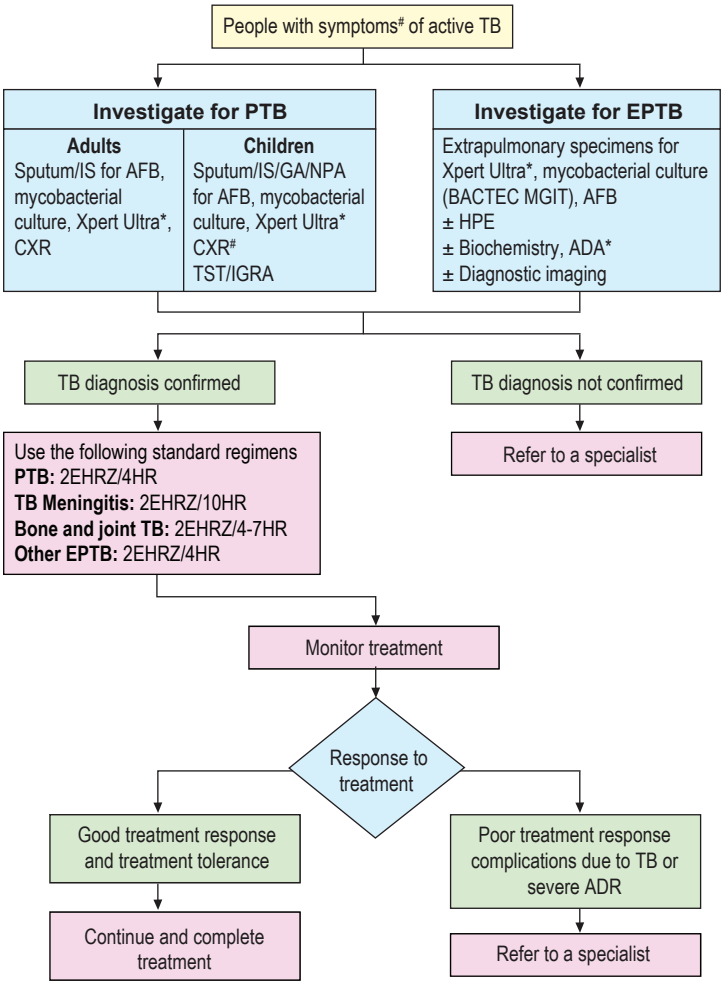
ALGORITHM 1: MANAGEMENT OF ACTIVE TUBERCULOSIS

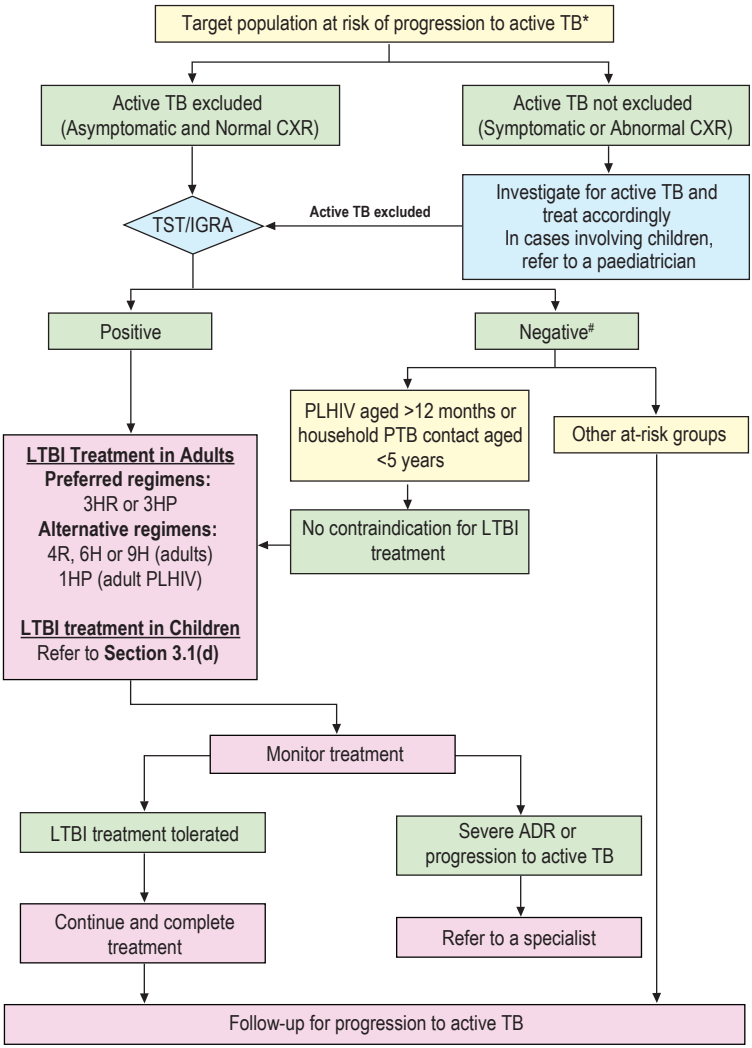


#Symptoms of TB and CXR findings in children may be different from adults
*When indicated

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

ALGORITHM 2: MANAGEMENT OF LATENT TUBERCULOSIS INFECTION



*Refer to **Section II** on **Latent TB Infection**

#IGRA/TST may be repeated if the initial testing was done with less than 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 consecutives IGRA/TST were negative

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

1. INTRODUCTION

The Global Tuberculosis Report 2020 estimated 10.0 million people contracted tuberculosis (TB) and 1.4 million people died of it in 2019.[1, level III] The World Health Organization (WHO) proposed the End TB Strategy to improve TB management with targets of a 90% decrease in TB incidence and 95% decrease in TB mortality by 2035 compared with 2015.[2, level III]

TB is endemic in Malaysia and continues to be a major public health concern. The TB incidence for Malaysia in 2015 was 79.0/100,000 population. In 2020, the TB incidence was reduced to 72.4/100,000 but it was still below the End TB Strategy target. There were 1,696 TB deaths (TB mortality rate of 5.5/100,000 population) in 2015 and this increased to 2,320 deaths (7.1/100,000 population) in 2020.[3, level III] By 2035, Malaysia aims to reduce TB death to fewer than 85 deaths per year.

In 2019, the number of people living with HIV (PLHIV) was estimated at 87,000 with 3,564 newly notified.[4, level III] The incidence of HIV-TB co-infection in Malaysia in 2020 was 1,700 (5.2/100,000 population). In terms of drug resistance, the occurrence of multi-drug resistant TB (MDR TB) among patients with TB infections was 0.34%.[5, level III] 221 cases of laboratory-confirmed rifampicin-resistant and MDR TB was reported in 2020.[6, level III]

The vision of the National Strategic Plan for TB Control (2016 - 2020) is for Malaysia to be a TB-free country by year 2035 (<1 case/1,000,000 population). To achieve this, it is vital to ensure timely universal access to quality-assured diagnosis and treatment for all forms of TB.[7, level III]

Malaysia faces many challenges in her TB control programme, from delays in the diagnosis of smear negative PTB, extrapulmonary TB (EPTB) and TB in children to treatment default and non-adherence. The newly launched programmatic management of latent TB infection (LTBI), also known as TB preventive treatment, will take time to mature and produce results. The socially disadvantaged still have difficulty accessing TB services due to various reasons e.g. transportation issues and poor social networking.

This CPG hopes to address some of these challenges and to provide updated information on diagnostic tests available in Malaysia since the previous edition in 2012. It will supersede all earlier MoH guidelines of drug-susceptible TB. The management of drug-resistant TB was addressed earlier in the CPG on Management of Drug Resistant Tuberculosis (1st Edition) 2016.

2. SECTION I: ACTIVE TUBERCULOSIS

The summary on the management of people with active TB is illustrated in **Algorithm 1** on **Management of Active Tuberculosis**.

2.1 Smear Positive Pulmonary Tuberculosis

a. Introduction

In Malaysia, 23, 644 cases of TB were notified in 2020, 91.7% of them new cases and 58.0% smear positive PTB.[3, level III]

Adult patients with active PTB typically present with a history of productive cough, haemoptysis, loss of appetite, unexplained weight loss, fever, night sweats and fatigue. However, typical symptoms may be absent in the immunocompromised or elderly patients.

When reviewing a patient with suspected TB, taking a full history and conducting a complete clinical examination is a must, followed by performing a chest radiograph (CXR) and sputum smear microscopy. In a centre where radiography facilities are not available, diagnosis of PTB can be made based on clinical findings and positive sputum smear results. All patients should be routinely screened for HIV and diabetes mellitus.

- All patients with clinically diagnosed or bacteriologically confirmed tuberculosis must be notified under the Prevention and Control of Infectious Diseases Act, 1988 (Act 342) to the District Health Office. TB notification is mandatory within seven days of diagnosis and failure to notify is compoundable.

b. Diagnosis

- **Laboratory investigations**

All patients suspected of having PTB should submit at least two sputum specimens for microscopic examination. When possible, at least one early morning specimen should be obtained as sputum collected at this time has the highest yield.[8] For patients who are unable to expectorate sputum spontaneously, sputum induction may be done. Refer to **Appendix 3** on **Procedure for Sputum Induction**.

Sputum should be sent for mycobacterial culture at the initiation of TB treatment to confirm the presence of *Mycobacterium tuberculosis (M. tuberculosis)* and to exclude drug-resistant TB. In a patient suspected of drug resistant TB, rapid molecular tests should be done prior to treatment for early confirmation of drug resistance. Refer to **Appendix 4** on **Specimen Collection for Diagnosis of Tuberculosis** for further information.

Recommendation 1
- Sputum should be sent for mycobacterial culture and drug susceptibility testing for patients with pulmonary tuberculosis.

- **Chest radiography**

Chest radiography should be used as the primary imaging modality to aid the diagnosis and management of PTB. Radiographic abnormalities are often seen in the apical and posterior segments of the upper lobe or in the superior segments of the lower lobe. However, lesions may appear anywhere in the lungs and may differ in size, shape, density and cavitation, especially in immunosuppressed patients.[8] The **Grading of Pulmonary Tuberculosis Severity Based on Chest Radiograph in Adults** is shown in **Appendix 5**.

- **Lateral Flow Urine Lipoarabinomannan Assay**

Lateral flow urine lipoarabinomannan assay (LF-LAM) is a new method for the diagnosis of TB. It detects lipoarabinomannan, a component of the mycobacterial cell wall, within one hour. Compared with sputum tests, LF-LAM is easier to perform and without the risk of laboratory TB transmission. Besides, urine is also easier to collect compared with sputum.

AlereLAM is the first commercially available LF-LAM recommended by WHO as an adjunct for the detection of TB in HIV-positive adults.[9] However, it is not recommended by WHO for use in HIV-negative adults due to its low sensitivity of 4 - 31%.[10, level II-2]

FujiLAM, a new LF-LAM, has been shown to be more sensitive than AlereLAM for the diagnosis of TB in HIV-positive adults.[11, level II-2; 12, level III] Its accuracy for the diagnosis of PTB in HIV-negative adults is still being studied.

In a cohort study involving 372 HIV-negative adults, both LF-LAMs showed low sensitivity for the diagnosis of PTB compared with sputum smear microscopy or Xpert MTB/RIF as shown in **Table 1**:[10, level II-2]

Table 1: Accuracy of AlereLAM, FujiLAM, sputum smear microscopy and sputum Xpert MTB/Rif for the diagnosis of PTB in HIV-negative adults

Test	Sensitivity	Specificity
AlereLAM	10.8% (95% CI 6.3 to 18.0)	92.3% (95% CI 88.5 to 95.0)
FujiLAM	53.2% (95% CI 43.9 to 62.1)	98.9% (95% CI 96.7 to 99.6)
Sputum smear microscopy	61.3% (95% CI 52.0 to 69.8)	100% (95% CI 98.5 to 100.0)
Sputum Xpert MTB/RIF	76.6% (95% CI 67.8 to 83.6)	100% (95% CI 98.5 to 100.0)

In smear positive PTB, the sensitivity of FujiLAM was only 68.4% (95% CI 57.3 to 77.8).[10, level II-2]

Recommendation 2
- Lateral flow urine lipoarabinomannan assay should not be used for the diagnosis of pulmonary tuberculosis in HIV-negative adults.

c. Treatment

The aims of TB treatment are to:
- reduce morbidity
- reduce mortality
- prevent relapse
- decrease transmission
- prevent emergence of drug-resistant TB

The current standard anti-TB regimen recommended by WHO consists of a 2-month (8-week) intensive phase with isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB), followed by a 4-month (18-week) continuation phase with INH and RIF (2EHRZ/4HR). Among the first-line anti-TB drugs, INH has the greatest early bactericidal activity, while RIF the greatest sterilising power.[13] EMB is bacteriostatic and is combined with other more potent drugs to prevent the emergence of resistant bacilli. The major justification for using this treatment regimen is to reduce TB relapse and to reduce emergence of drug-resistant TB. However, the long duration of TB treatment is associated with non-adherence and loss to follow-up. Therefore, more research is being carried out to shorten treatment with existing or repurposed drugs.

- **Anti-tuberculosis regimens**

A meta-analysis of three high-quality RCTs of adults with drug-susceptible PTB comparing 4-months moxifloxacin-based regimen with standard regimen (2EHRZ/4HR±E) found that the former was associated with higher relapse rate (RR=3.56, 95% CI 2.37 to 5.37). However, there were non-significant differences in treatment failure, acquired drug resistance, serious adverse events and death.[14, level I]

In a recently published RCT, a 4-month regimen containing rifapentine and moxifloxacin was non-inferior to standard 6-month regimen in terms of unfavourable treatment outcome and adverse effect at 12-months after randomisation. However, long-term follow-up results were not published yet.[15, level I]

International guidelines recommend the use of standard 2EHRZ/4HR regimen for the treatment of PTB.[13; 16; 17]

For further information on renal dosing and adverse drug reactions (ADR), please refer to **Appendix 6** on **First-Line Anti-Tuberculosis Drug Dosage and Adverse Drug Reactions**.

Recommendation 3
- Standard anti-tuberculosis regimen of 2EHRZ/4HR* should be used in the treatment of pulmonary tuberculosis.
  - Pyridoxine 10 mg/day should be given to patients on isoniazid. Those with high risk of neuropathy** should be given pyridoxine 30 mg/day.

*Two months of ethambutol, isoniazid, rifampicin and pyrazinamide followed by four months of isoniazid and rifampicin.
**Those at high risk of isoniazid induced neuropathy including pregnant women, PLHIV, elderly patients, patients with diabetes, alcoholism, malnutrition or chronic renal failure.

- **Fixed-dose combination of anti-tuberculosis treatment**

Fixed-dose combination (FDC) tablets are combinations of two or more anti-TB drugs in a tablet. They have been available since the 1980s. The aim of FDC tablets is to simplify TB treatment, to prevent monotherapy and to improve patient compliance as well as to prevent development of drug-resistant TB. The FDC tablets also simplify drug procurement, reduce storage space, and improve medicine distribution while reducing drug supply management and cost errors.

Two meta-analyses comparing FDC and separate-drug formulations showed no difference in the following outcomes:[18 - 19, level I]
- treatment failure and/or relapse
- sputum smear conversion at end of treatment
- adverse events leading to discontinuation of therapy
- serious adverse events
- acquired drug resistance
- death

The risk of bias of primary studies in both meta-analyses were heterogeneous.

In the first meta-analysis, FDC showed favourable patients' adherence and satisfaction although most results were non-significant.[19, level I] In the Cochrane systematic review, patients reported better taste tolerability (RR=1.39, 95% CI 1.27 to 1.51) and convenient number of tablets (RR=1.5, 95% CI 1.37 to 1.64) in FDC.[18, level I]

WHO recommends the use of FDC over separate drug formulations in the treatment of patients with drug-susceptible TB.[17] The recommended daily dosing for FDC is shown in the following table.

Table 2: 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

*FDC refers to either 2-, 3- or 4-anti-TB drug combinations.
A 4-drug FDC tablet contains isoniazid 75 mg, rifampicin 150 mg, ethambutol 275 mg and pyrazinamide 400 mg.
A 3-drug FDC tablet contains isoniazid 75 mg, rifampicin 150 mg and pyrazinamide 400 mg.
A 2-drug FDC tablet contains isoniazid 75 mg and rifampicin 150 mg.

Recommendation 4
- Fixed-dose combination is preferred over separate drug formulation in the treatment of pulmonary tuberculosis.

For patients who are unable to tolerate FDC tablets or who use separate drug formulations in alternative regimens, the recommended dose for first-line drugs is shown in **Table 3**.

Table 3: Recommended dose of first-line anti-TB in adults

Drugs	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

*High dose rifampicin for the treatment of TB is being evaluated.
**The maximum dose of anti-TB drugs may be adjusted according to the individual's pharmacokinetic/pharmacodynamic data.

Pyridoxine 25 - 50 mg/day is recommended by ATS for individuals receiving INH who are at high risk of neuropathy.[13] In Malaysia, pyridoxine has been given at 10 mg/day for all adult patients. The CPG DG now recommends a higher pyridoxine dose of 30 mg/day for individuals at high risk of neuropathy.

- **Intermittent vs daily dosing anti-tuberculosis regimens**

Intermittent therapy had been widely used in first-line TB treatment for over 30 years. It was used with directly observed treatment (DOT) to reduce costs of medication and healthcare worker workload, and improve treatment compliance. Unfortunately, it was noted to cause high rates of relapse and acquired drug resistance.

In a meta-analysis of 56 RCTs on newly diagnosed PTB patients treated with first-line drugs using RIF for >6 months, thrice weekly throughout regimen showed worse outcomes compared with daily treatment in terms of:[20, level I]

- failure (IRR=3.7, 95% CI 1.1 to 12.6)
- relapse (IRR=2.2, 95% CI 1.2 to 4.0)
- acquired drug resistance (IRR=10.0, 95% CI 2.1 to 46.7)

In another comparison, a twice-weekly regimen in the continuation phase after daily treatment in the intensive phase had higher risks of failure (IRR=3.0, 95% CI 1.0 to 8.8) and relapse (IRR=1.8, 95% CI 1.0 to 3.3) but the results were not statistically significant. There were also no significant difference in the outcomes with thrice weekly continuation phase after daily intensive phase.[20, level I]

This meta-analysis did not address adverse event outcomes and gave no report on risk of bias of the primary papers.

WHO recommends daily dosing treatment in all patients with drug-susceptible PTB. The use of thrice-weekly dosing is not recommended at all.[17]

Recommendation 5

- Only daily anti-tuberculosis regimen should be used throughout the treatment of pulmonary tuberculosis.

d. Follow-up and monitoring

All patients with anti-TB treatment should be monitored as shown in **Table 4**. Assessment of clinical response, adherence to treatment and monitoring of ADR must be done at every in-person visit. Sputum mycobacterial culture and drug susceptibility results should be traced two months after specimen collection to detect any positive result in a timely manner.

Table 4: Monitoring schedule of adult patients on PTB treatment

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

*for return to work/school purposes
**requires in-person visit
#sputum direct smear for AFB should be done at the end of five months of standard anti-TB treatment
FBC=full blood counts, FBS=fasting blood sugar, RP=renal profile, LFT=liver function test, HIV=Human immunodeficiency virus, AFB=acid fast bacilli, CXR=chest radiograph

- Patients with persistent smear positive PTB should be referred to specialists for further management.
- Patients who completed TB treatment should be asked to watch out for recurrence of TB symptoms and if present to contact their nearest health care providers.
- Patients who develop complications of PTB (e.g. bronchial stenosis or haemoptysis) need to be referred to respiratory physicians.
- For patients on ethambutol, visual acquity and Ishihara tests are required at baseline and subsequently if symptomatic.

The outcomes of TB patients treated should be reported to the National TB Control Programme according to **Appendix 7** on **Tuberculosis Treatment Outcome Definition**.

2.2 Smear Negative Pulmonary Tuberculosis

a. Introduction

Smear negative PTB accounts for 27.9% of all PTB cases in Malaysia in 2020.[3, level III] The reasons for a negative sputum smear in PTB are immunosuppression, early disease, or poor quality specimens. CXR is a sensitive tool for identifying and excluding PTB.[21] The accuracy of PTB diagnosis can be further increased with mycobacterial culture and/or Xpert Ultra.

b. Diagnosis

The symptoms of smear negative PTB are similar to smear positive PTB. However, smear negative results may delay PTB diagnosis. This may be related to the lack of knowledge or experience of healthcare providers in detecting the disease or the poor sensitivity of diagnostic methods to detect cases at an early stage. In patients suspected to have smear negative PTB, referral to a centre with experience in TB management is indicated.

- **Chest radiography**

In general, CXR is helpful in detecting PTB. Its sensitivity ranged from 87 to 98% when compared with mycobacterial culture.[21]

In a cross-sectional study comparing two community screening tests for TB, CXR was more sensitive in diagnosing PTB compared with Xpert MTB/ RIF sputum examination, 80% versus 34% respectively.[22, level III]

Thus, CXR is helpful to diagnose smear negative PTB. However, its use is limited by the need for experienced readers, quality of the CXR film, radiation exposure risk and logistic issues.

- **Xpert MTB/RIF and Xpert Ultra**

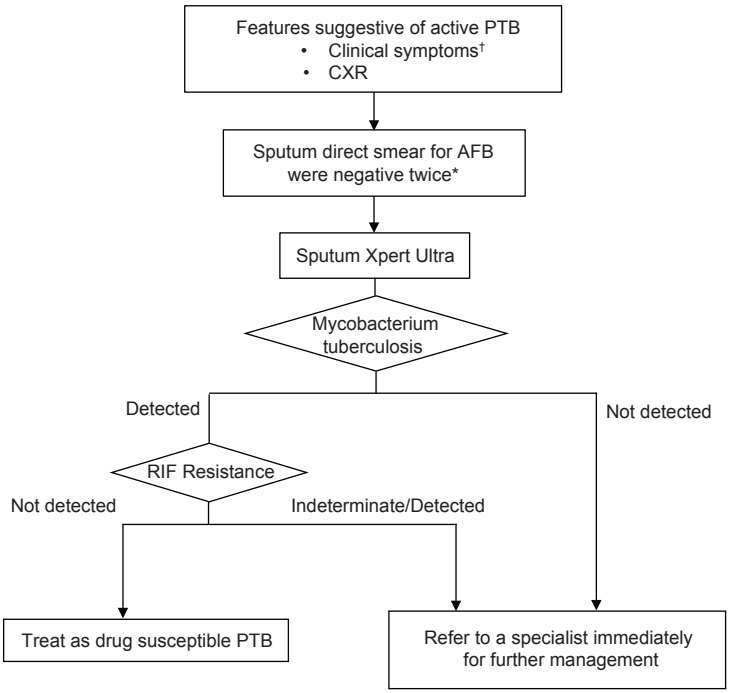
Sputum smear microscopy has poor sensitivity in the detection of PTB because a positive smear requires 5,000 - 10,000 AFB/ml from a sputum sample. Whereas, sputum mycobacterial culture, the gold standard for confirmation of PTB, requires only 10 - 100 AFB/mL.

Xpert MTB/RIF and Xpert Ultra are WHO recommended nucleic acid amplification tests for the detection of TB and RIF resistance.[9] The new Xpert Ultra, has a lower limit of detection for PTB (15.6 CFU/mL of sputum) compared with the older Xpert MTB/RIF (112.6 CFU/mL) in in-vitro studies.[23, level III] In MoH facilities, only Xpert Ultra is currently available. In a Cochrane systematic review of seven studies with low risk of bias, the pooled sensitivity and specificity of Xpert Ultra against culture were 90.9% (95% CI 86.2 to 94.7) and 95.6% (95% CI 93.0 to 97.4) respectively. For Xpert MTB/RIF, the pooled sensitivity and specificity were 84.7% (95% CI 78.6 to 89.9) and 98.4% (95% CI 97.0 to 99.3).[24, level III]

Recommendation 6

- Sputum should be sent for Xpert Ultra if smear negative pulmonary tuberculosis is suspected.

Figure 1 illustrates **Rapid diagnosis of smear negative PTB.**



†Clinical symptoms: current cough, haemoptysis, weight loss, fever or night sweats
*Sputum sample should be sent for mycobaterial culture and drug susceptibility testing in all cases of smear negative PTB but clinical decision should not be delayed by culture result.

Figure 1: Rapid diagnosis of smear negative PTB

- **Tuberculosis Loop-mediated Isothermal Amplification Test**

Eiken Tuberculosis Loop-mediated Isothermal Amplification Test (TB-LAMP) is the only commercially available TB-LAMP assay recommended for the diagnosis of PTB by WHO.[25]

In a meta-analysis of 13 studies with high risk of bias, Eiken TB-LAMP showed no significant difference in sensitivity and specificity compared with Xpert MTB/RIF in the diagnosis of PTB. It was also lower in sensitivity (42.2%, 95% CI 27.9 to 57.9), with no significant difference in specificity, compared with mycobacterial culture, for smear negative PTB.[26, level III]

Although it showed no significant difference in accuracy compared with Xpert MTB/RIF, Eiken TB-LAMP was not able to detect drug resistance.[9] Therefore, it is inferior to Xpert MTB/RIF for the diagnosis of smear negative pulmonary tuberculosis.

c. Treatment

The treatment and monitoring for smear negative PTB are the same as that for smear positive PTB.

The outcomes of TB patients treated should be reported to the National TB Control Programme according to **Appendix 7** on **Tuberculosis Treatment Outcome Definition**.

2.3. Extrapulmonary Tuberculosis

The incidence of EPTB cases reported in Malaysia had shown a general trend of proportionate increment from 13.3% in 2015 to 15.7% in 2020. These figures excluded EPTB occurring with PTB, which were classified under the latter.[3, level III] EPTB often presents as a diagnostic and therapeutic challenge due to difficulties associated with accessing the site of involvement and assessment of therapeutic response.

a. Diagnosis

In cases of suspected EPTB, a wide range of tests are employed to confirm the diagnosis. Microbiological tests, e.g. mycobacterial culture and molecular tests, are specific but not sensitive for the detection of EPTB. In these patients, work-up for possible concomitant PTB should also be done.

- **Xpert MTB/RIF and Xpert Ultra**

The use of Xpert MTB/RIF and Xpert Ultra for the diagnosis of EPTB has been practised because it gives faster results than culture. A large Cochrane systematic review of moderate quality primary papers compared Xpert MTB/RIF and Xpert Ultra with culture for various types of specimens in suspected EPTB. The sensitivity of Xpert MTB/RIF and Xpert Ultra varied across different extrapulmonary specimens, while specificity was high in most specimens.[27, level II-2] The results are summarised below.

Table 5: Summary accuracy of Xpert MTB/RIF and Xpert Ultra for detection of EPTB

Type of specimen	Test	Reference standard	Pooled sensitivity % (95% CI)	Pooled specificity % (95% CI)
CSF	Xpert Ultra	Culture	89.4 (79.1 to 95.6)	91.2 (83.2 to 95.7)
	Xpert Ultra	Composite	62.7 (45.7 to 77.0)	99.1 (96.6 to 99.9)
	Xpert MTB/RIF	Culture	71.1 (62.8 to 79.1)	99.1 (95.4 to 98.0)
	Xpert MTB/RIF	Composite	42.3 (32.1 to 52.8)	99.8 (99.3 to 100)
Lymph node aspirate	Xpert MTB/RIF	Culture	88.9 (82.7 to 93.6)	86.2 (78.0 to 92.3)
	Xpert MTB/RIF	Composite	81.6 (61.9 to 93.3)	96.4 (91.3 to 98.6)
Lymph node biopsy	Xpert MTB/RIF	Culture	82.4 (73.5 to 89.7)	80.3 (60.3 to 91.5)
Pleural fluid	Xpert Ultra	Culture	75.0 (58.0 to 86.4)	87.0 (63.1 to 97.9)
	Xpert MTB/RIF	Culture	49.5 (39.8 to 59.9)	98.9 (97.6 to 99.7)
	Xpert MTB/RIF	Composite	18.9 (11.5 to 27.9)	99.3 (98.1 to 99.8)
Bone/joint aspirate	Xpert MTB/RIF	Culture	97.9 (93.1 to 99.6)	97.4 (80.2 to 100.0)
Peritoneal fluid	Xpert MTB/RIF	Culture	59.1 (42.1 to 76.2)	97.6 (95.4 to 98.9)
Pericardial fluid	Xpert MTB/RIF	Culture	61.4 (32.4 to 82.4)	89.7 (74.9 to 99.0)
Urine	Xpert MTB/RIF	Culture	85.9 (71.4 to 94.3)	98.1 (93.1 to 99.7)

The sensitivity of Xpert MTB/RIF and Xpert Ultra compared with a composite reference standard was lower than that of mycobacterial culture as shown in **Table 5**. A composite reference standard might be based on the results of microbiological tests, culture or nucleic acid amplification test, imaging studies; histology and clinical characteristics. As expected, EPTB, which is paucibacillary by nature, is harder to diagnose using microbiological tests compared with a composite reference standard.

Recommendation 7

- In patients suspected to have extrapulmonary tuberculosis, the following specimens should be sent for Xpert Ultra when indicated:
  - cerebrospinal fluid
  - urine
  - lymph node aspirate or tissue
  - bone and joint tissue
  - pericardial fluid

- **Tuberculosis polymerase chain reaction**

TB Polymerase Chain Reaction (PCR) targeting IS6110 is an alternative diagnostic test for EPTB in Malaysia. A diagnostic study on extrapulmonary samples showed a sensitivity of 66.66% (95% CI 24.1 to 94) and specificity of 74.41% (95% CI 67.1 to 80.6). The positive and negative predictive values of IS6110 PCR were 8.33% (95% CI, 2.7 to 20.8) and 98.46% (95% CI 93.9 to 99.7) respectively.[28, level III]

- **Adenosine deaminase**

The measurement of adenosine deaminase (ADA) in pleural fluid is a useful diagnostic test for tuberculous pleural effusion. From the previous edition of this CPG, measurement of ADA level in pleural or cerebrospinal fluid may be considered as an adjunct in diagnosing pleural TB and tuberculous meningitis respectively.[8]

In a recent local cohort study of 93 participants, ADA values of 29.6 U/L gave a sensitivity of 97.6% and specificity of 90.4% in diagnosing TB pleural effusion.[29, level II-2]

A cohort study on the utility of ADA (clinical cut-off point of 30 U/L) vs Xpert Ultra when compared with composite reference standard in the diagnosis of pleural TB showed that:[30, level II-2]

- pleural fluid ADA was more sensitive (84.4% vs 28.6%, p<0.0001), but
- Xpert Ultra was more specific (98.8% vs 87.5%, p=0.004)

Recommendation 8

- In patients suspected to have pleural tuberculosis, pleural adenosine deaminase may be used as an adjunct in the diagnostic workup.

Refer to **Appendix 4** on **Specimen Collection for Diagnosis of Tuberculosis** for further information.

- **Central nervous system imaging**

Imaging is essential for the diagnosis of central nervous system (CNS) TB, although the radiological appearances do not confirm the diagnosis.

Computed tomography scan (CT scan) and magnetic resonance imaging (MRI) are commonly used imaging methods for CNS TB. The findings of CNS TB on CT scan are non-specific. In contrast, MRI could provide more diagnostic information. It can better define the neuroradiological features of CNS TB, particularly when evaluating brainstem and spinal disease.

CNS TB has various imaging appearances, including meningitis, tuberculoma, miliary TB, abscess, cerebritis and encephalopathy. In addition, the radiologic manifestations of this disease are not always typical and sometimes may be mistaken with other lesions. Familiarity with the various imaging presentations of CNS TB is of key importance for radiologists and clinicians to make a timely diagnosis, thereby reducing the morbidity and mortality of this potentially life-threatening disease.

NICE recommends the use of CT scan and MRI in patients with suspected CNS TB.[16]

Recommendation 9
- Computed tomography scan and/or magnetic resonance imaging should be used in the diagnosis of tuberculosis of the central nervous system.

b. Treatment

Duration of treatment in EPTB is not precisely known due to insufficient evidence and the governing principles with regards to treatment is mainly derived from evidence and experience from PTB treatment.

International guidelines recommend six months duration of treatment with standard anti-TB regimen for EPTB and 6 - 9 months of treatment (2EHRZ/4-7HR) for bone or joint tuberculosis.[13; 31] A recent open-labeled, RCT did not show significant difference in effectiveness between 6 and 12 months of anti-TB treatment in biopsy proven spinal TB.[32, level I]

A meta-analysis on different fluoroquinolones-based regimens in the treatment of TB meningitis showed fluoroquinolones and high dose RIF (20 mg/kg/day) compared with standard regimen had significantly higher rate of seizure and vision loss but no significant differences in overall ADR and death. However, the five RCTs in the meta-analysis were of low to moderate quality.[33, level I]

There was no significant difference in either ADR or death in the following comparison:[33, level I]
- fluoroquinolones plus standard regimen vs standard regimen alone
- fluoroquinolone substitution for EMB in standard regimen vs standard regimen alone
- fluoroquinolone substitution for RIF in standard regimen vs standard regimen alone

NICE recommends treating TB meningitis with 2 months of EHRZ followed by 10 months of HR (2EHRZ/10HR).[16]

Recommendation 10

- The following regimens should be used for extrapulmonary tuberculosis (EPTB):
  - 2EHRZ/4-7HR* for tuberculosis of the bone or joint
  - 2EHRZ/10HR** for tuberculous meningitis
  - 2EHRZ/4HR*** for other forms of EPTB

*two months of ethambutol, isoniazid, rifampicin and pyrazinamide, followed by four to seven months of isoniazid and rifampicin
**two months of ethambutol, isoniazid, rifampicin and pyrazinamide, followed by 10 months of isoniazid and rifampicin
***two months of ethambutol, isoniazid, rifampicin and pyrazinamide, followed by four months of isoniazid and rifampicin

- **Adjunctive corticosteroids regimen**

Corticosteroids are associated with improvement in TB symptoms and survival in HIV-negative patients with TB meningitis and TB pericarditis. Adjuvant corticosteroids treatment is recommended for TB meningitis and TB pericarditis.[8; 17]

A Cochrane systemic review of nine RCTs with mixed quality showed that corticosteroids use in TB meningitis reduced deaths by almost one quarter (RR=0.75, 95% CI 0.65 to 0.87) up to 18 months follow up.[34, level I]

A retrospective cohort study of 98 patients with TB meningitis treated with initial IV dexamethasone looked into the effectiveness of different regimens of corticosteroids. Oral prednisolone was introduced when patients had sustained improvement in headache and vomiting and, at least a two-point improvement in Glasgow Coma Score (GCS) for at least 48 hours. However, they will be put back on IV dexamethasone if they had reappearance of symptoms or deterioration in consciousness and later overlapped with oral prednisolone. Those who continued with oral prednisolone had shorter duration of hospitalisation compared with those receiving the overlapped treatment (6.97±3.20 days vs 20.05±12.98 days, $p<0.001$). There was also no significant difference in mortality, readmission rate and surgical complications between the two groups of patients.[35, level II-2] However, more evidence is warranted before early introduction of oral corticosteroids can be recommended.

The recommended corticosteroids regimen for TB meningitis is shown below.

Table 6: Corticosteroids regimen for TB meningitis

Stages of TB Meningitis*	Regimen (Dexamethasone dose)
Stage 1	Week 1: 0.3 mg/kg/day (IV) Week 2: 0.2 mg/kg/day (IV) Week 3: 0.1 mg/kg/day (oral) Week 4: 3 mg/day (oral) Week 5: 2 mg/day (oral) Week 6: 1 mg/day (oral)
Stage 2 and 3	Week 1: 0.4 mg/kg/day (IV) Week 2: 0.3 mg/kg/day (IV) Week 3: 0.2 mg/kg/day (IV) Week 4: 0.1 mg/kg/day (IV) Week 5: 4 mg/day (oral) Week 6: 3 mg/day (oral) Week 7: 2 mg/day (oral) Week 8: 1 mg/day (oral)
*According to the modified British Medical Research Council criteria for disease severity: Stage 1: GCS of 15 without focal neurological deficits; alert and oriented Stage 2: GCS of 14 - 11 or 15 with focal neurological deficits Stage 3: GCS of 10 or less, with or without focal neurological deficits	

Source: National Institute of Health and Care Excellence. Tuberculosis (NG 33). London: NICE; 2019.

A Cochrane systematic review evaluated the addition of corticosteroids to drug regimens of tuberculous pleural effusions. In the corticosteroids group, although there was evidence of benefit in terms of faster symptom and radiological responses, there was also high risk of ADRs and limited data on long-term respiratory function.[36, level I]

In an RCT assessing the role of add-on prednisolone in cervical lymph node TB, results showed that:[37, level I]

- at two months, significantly more patients with add-on prednisolone showed symptom relief compared with those without.
- at two months, complications in the form of abscess, sinus and/or appearance of new lymph nodes were significantly higher in patients without add-on prednisolone.
- at the end of therapy, complete resolution was significantly higher in patients with add-on prednisone.
- gastrointestinal side effects were higher in patients with add-on prednisolone but skin rashes and joint pain were higher in those without add-on prednisolone; the differences were not statistically significant.

Although clinical benefits were seen, this was a single-centre study with no post-treatment follow-up to monitor for possibility of higher TB relapse in the corticosteroids group. More evidence is warranted before oral corticosteroids can be recommended as an adjunct for treatment of TB lymphadenitis.

In another Cochrane systematic review:[38, level I]

- corticosteroids reduced death from tuberculous pericarditis (RR=0.39, 95% CI 0.19 to 0.80) but did not reduce need for repeat pericardiocentesis in non-HIV infected individuals.
- corticosteroids did not reduce death from tuberculous pericarditis or need for repeat pericardiocentesis in HIV-positive individuals.

The corticosteroids regimen used for the treatment of tuberculous pericarditis varied between studies. There was no study comparing the type or duration of corticosteroids used in terms of safety and efficacy.[38, level I]

Recommendation 11

- Corticosteroids should be used in tuberculous meningitis and pericarditis.

- Patients who develop complications of EPTB (e.g. hydrocephalus or constrictive pericarditis) need to be referred to specialists.

The outcomes of TB patients treated should be reported to the National TB Control Programme according to **Appendix 7** on **Tuberculosis Treatment Outcome Definition**.

- **Disseminated tuberculosis**

Disseminated TB is the term used to describe TB involving two or more organs/systems from hematogenous or lymphatic spread. All cases with positive mycobacterial blood culture should be referred to a specialist for further management.

The pharmacological treatment of disseminated TB is dictated by the organ/system involved. For example, when a patient is diagnosed with PTB and TB meningitis, the length of treatment is based on the duration of TB meningitis treatment (2EHRZ/10HR). In this case, adjunctive corticosteroid is used as per treatment for TB meningitis.

2.4. Recurrent Tuberculosis

TB recurs in a number of patients despite completion of treatment because of reactivation of TB (relapse) or a new episode of infection. Patients with relapsed TB have higher risk of drug-resistant TB compared to new cases. In high TB transmission areas, reinfection is relatively more common than reactivation. In these areas, intensified case finding measures are needed to bring TB under control.

a. Diagnosis

Microbiological tests should be done to confirm recurrent TB and rule out drug resistance. Xpert Ultra is recommended by WHO for confirmation of diagnosis and rifampicin resistance.[9] However, the specificity of Xpert Ultra for the diagnosis of active TB is reduced in patients with recurrent TB. The pooled sensitivity and specificity of Xpert Ultra in a meta-analysis of four cohort studies of patients with previously treated TB were only 84.2% (95% CI 72.5 to 91.7) and 88.2% (95% CI 70.5 to 96.6), respectively. These figures were low compared with the pooled sensitivity of 90.9% (95% CI 84.7 to 95.3) and pooled specificity of 94.9% (95% CI 91.3 to 97.2) in participants with newly diagnosed PTB from the meta-analysis of five cohort studies.[24, level III]

The reduction in specificity in patients with previously treated TB may be due to the presence of dead tuberculous bacilli which may remain detectable for years.[39, level II-2]

WHO gave a strong recommendation for Xpert Ultra as the initial test for patients with suspected recurrent TB if they had completed TB treatment >5 years because of high certainty of evidence for the test accuracy. For patients who had completed their TB treatment within the past 5 years, WHO gave a weak recommendation because of the low certainty of evidence.[9]

Only mycobacterial culture is able to differentiate live from dead tuberculous bacilli. Liquid media (BACTEC MGIT) for mycobacterial culture is the reference standard for bacteriological confirmation of TB.[40] Furthermore, it can provide a faster result compared to solid media. Therefore, mycobacterial culture using BACTEC MGIT should be sent for patients suspected of recurrent TB.

Recommendation 12

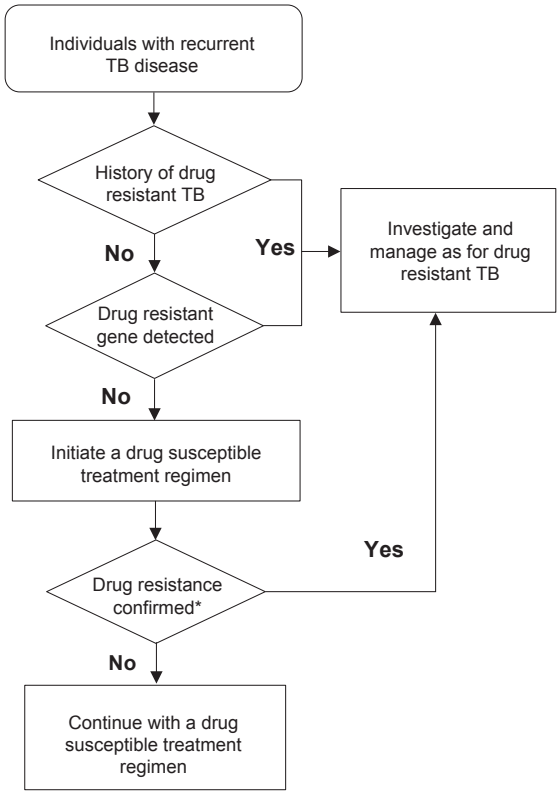
- Sputum should be sent for both Xpert Ultra and mycobacterial culture (BACTEC MGIT) for individuals suspected to have recurrent pulmonary tuberculosis.

b. Treatment

The initial treatment regimen for recurrent TB is determined by the earlier drug resistance pattern and results of current drug susceptibility testing.

- International guidelines no longer recommend a standard retreatment regimen for TB.[13; 16; 17]
- The drug resistance pattern of earlier episodes of TB should be used to guide initial treatment.
  - In patients with previous drug susceptible TB with no drug-resistant genes detected, a drug susceptible regimen should be initiated.
  - An initial drug-resistant TB regimen may be appropriate for patients with previous episode(s) of drug-resistant TB or detectable drug-resistant gene(s).
  - The final treatment regimen for patients with recurrent TB rests on the results of the mycobacterial culture and susceptibility test.

  These are summarised in **Figure 2** on **The initial treatment regimen for recurrent TB**.



*drug resistance confirmed on mycobacterial culture

Figure 2: The initial treatment regimen for recurrent TB

2.5. Tuberculosis in Special Situations

a. Tuberculosis in pregnancy and lactation

Prompt diagnosis and early treatment of maternal TB is crucial because it is associated with increased risk of maternal mortality and perinatal morbidity.[31] Successful treatment of TB is paramount in ensuring best outcome. The risk of untreated TB to pregnant women and their foetuses should be clearly explained.[13]

For pregnant and lactating women, standard anti-TB regimens can be administered safely.[8; 13; 31] The CPG DG opines that standard anti-TB regimen should be given to pregnant and lactating women and pyridoxine 30 mg/day is recommended in those taking INH.

RIF may cause yellow or orange coloured-milk, which is harmless.[41, level III] Breastfeeding should be continued in lactating mothers because the

amount of anti-TB drug in breastmilk is minimal. However, surgical mask should be used if the mother is infectious.[8; 13]

Patients on RIF taking oral contraceptive pills should use alternative contraception methods until one month after RIF is stopped.[8; 31]

Recommendation 13
- Standard anti-tuberculosis (TB) regimens should be used in pregnant and breastfeeding women with TB.
  - Pyridoxine 30 mg/day should be given to those taking isoniazid.
- Women on rifampicin-based anti-TB treatment should use alternative contraception methods other than oral contraceptive pills.

b. Tuberculosis with renal impairment

Patients with renal insufficiency or end-stage renal disease are immunocompromised. TB patients with chronic renal failure have worse clinical outcomes than those without renal failure and thus, they should be closely monitored.[13]

The clearance of ethambutol and pyrazinamide metabolites are impaired in patients with chronic renal failure when their creatinine clearance falls below 30ml/min, Hence, thrice weekly dosing is recommended in international guidelines. Conversely, RIF and INH do not require dose adjustment in renal failure as they are metabolized by the liver.[8; 13; 31] Refer to **Appendix 6** on **First-Line Anti-Tuberculosis Drug Dosage and Adverse Drug Reactions** for medication dosage in chronic renal failure.

A cross-sectional study looked at the safety and effectiveness of anti-TB treatment in 241 PTB patients with and without CKD. The results of the study showed that the renal dose adjusted regimen was safe and effective. There were no significant differences between the patients with CKD or without CKD in terms of:[42, level III]
- frequency of in-hospital TB-related death
- sputum conversion rate at two months
- any adverse events

Hence, renal dose adjusted standard anti-TB regimen should be used for patients with renal failure or severe renal insufficiency. All four anti-TB drugs may be administered after hemodialysis to facilitate DOT as well as to avoid premature drug removal.[8; 13]

Recommendation 14
- Standard anti-tuberculosis (TB) regimens should be used in patients with TB and renal failure.
  - Pyrazinamide and ethambutol should be given three times per week in patients with a creatinine clearance <30 ml/min or those receiving haemodialysis.

c. Tuberculosis with liver impairment

The management of TB in patients with chronic liver disease is challenging due to the risk of decompensated liver failure. These patients should be referred for specialist care.

2.6. Human Immunodeficiency Virus-Tuberculosis (HIV-TB) Co-infection

TB is one of the most important opportunistic infections and causes of death amongst PLHIV.

The number of patients with HIV-TB co-infection in Malaysia had fallen from 1,401 in 2015 to 1,205 in 2020. In 2020, PLHIV accounted for only 5.0% of all patients with TB. The majority (>97.5%) of HIV-TB coinfected patients from 2015 till 2020 were diagnosed with HIV prior to TB.[43, level III]

Smear negative PTB and EPTB are more common in PLHIV compared with HIV-negative individuals.[44, level III] PTB may show atypical features especially in advanced HIV infection. PLHIV with TB may not have cough, positive sputum smear microscopy or abnormal CXR.[8]

WHO recommends TB symptom screening (current cough, weight loss, night sweats and fever) for PLHIV. The four-symptom screening rule is more sensitive in untreated PLHIV than those on antiretroviral treatment (ART).[45]

PLHIV with any TB symptoms should be investigated with sputum smear microscopy, mycobacterial culture (BACTEC MGIT), Xpert Ultra and CXR. In addition, blood for mycobacterial culture and investigations for EPTB may be needed if disseminated TB is suspected.

- **LF-LAM in diagnosis of active TB in HIV-positive adults**

LF-LAM is a new urine test for the diagnosis of TB. Although it is not currently available in Malaysia, it has several advantages compared to sputum tests, namely:

i. urine can be collected any time of the day, whereas early morning sputum is preferred for TB diagnosis
ii. urine is easier to produce and collect compared with sputum
iii. it can detect disseminated TB

WHO recommends AlereLAM, the first commercially available LF-LAM, as an adjunct for the diagnosis of TB in selected hospitalised HIV-positive individuals with either:[9]

- signs and symptoms of TB (pulmonary and/or extrapulmonary)
- advanced HIV disease or who are seriously ill
- irrespective of signs and symptoms of TB and with a CD4 cell count of <200 cells/mm^3

FujiLAM, a newer LF-LAM, has been found in a number of studies to be more sensitive than AlereLAM for the diagnosis of TB in HIV-positive adults although it is not commercially available yet.

In a recent observational study involving 450 HIV-positive adults, FujiLAM was more sensitive than AlereLAM [sensitivity of 74.2% (95%CI 62.0 to 84.2) vs 53.0% (95%CI 40.3 to 65.4)] albeit at lower specificity [89.3% (95% CI 85.8 to 92.2) vs 95.6% (95% CI 93.0 to 97.4)] for PTB diagnosis.[11, level II-2] Both LF-LAMs did not meet the optimal diagnostic accuracy standard of WHO for PTB.[46, level III] Furthermore, although FujiLAM was more sensitive than AlereLAM, it was less accurate than Xpert Ultra, which had a sensitivity of 87.6% (75.4 to 94.1) and specificity of 92.8% (82.3 to 97.0).[24, level III]

FujiLAM was also found to be more sensitive than AlereLAM in the diagnosis of EPTB with or without PTB in a diagnostic study involving 553 HIV-positive participants.[12, level III]

- For EPTB, FujiLAM had a sensitivity of 67% (95% CI 59 to 75) and AlereLAM 41% (95% CI 33 to 49).
- For PTB with EPTB, FujiLAM had a sensitivity of 91% (95% CI 87 to 94) and AlereLAM sensitivity 61% (95% CI 55 to 67).

The sensitivity of FujiLAM varies depending on the type of EPTB. It has high sensitivity for bacteremic (94%, 95% CI 90 to 97) and urinary TB (88%, 95% CI 84 to 92) but low sensitivity for TB meningitis (47%, 95% CI 24 to 71) compared with mycobacterial culture/Xpert MTB/RIF.[12, level III]

- LF-LAM can be considered as an adjunct for the diagnosis of EPTB with or without PTB in hospitalised HIV-positive adults with either:
  - advanced HIV disease
  - serious illness
  - a CD4 cell count of less than 200 cells/mm^3

"Serious illness" is defined by WHO as having at least one of the following:[47]

- respiratory rate >30/minute
- temperature >39°C
- heart rate >120 beats/minute
- unable to walk unaided

False positive FujiLAM may occur from the presence of several bacteria, including non-tuberculous mycobacteria species, in the urine. Sterile urine collection method is needed to reduce this situation.

b. Treatment

Starting antiretroviral treatment (ART) during TB treatment reduces mortality and results in earlier conversion of sputum smear and cultures to negative.[8] In HIV-TB coinfected patients, ART should be initiated regardless of their CD4 cell count. However, TB treatment should be initiated first in ART-naïve patients.

Two meta-analyses that studied the timing of ART in HIV-TB coinfected patients showed that early ART initiation when compared with later initiation:

- reduced all-cause mortality with IRR of 0.75 (95% CI 0.59 to 0.95)[48, level I] and RR of 0.81 (95% CI 0.66 to 0.99).[49, level I]
- had fewer TB treatment failure with RR of 0.63 (95% CI 0.46 to 0.85).[49, level I]

However early ART was associated with a higher risk of immune reconstitution inflammatory syndrome (IRIS) (RR=1.83, 95% CI 1.24 to 2.70) and IRIS-related death (RR=6.05, 95% CI 1.06 to 34.59).[49, level I]

In HIV-TB co-infection, it is recommended that ART should be initiated within eight weeks of TB treatment. However, patients with a CD4 cell count <50 cells/mm^3 should receive ART within two weeks of TB treatment.[17]

For PLHIV with TB meningitis, ART should be delayed until two months after the start of anti-TB treatment to reduce the risk of severe ADRs associated with early ART.[13]

Recommendation 15

- In HIV-tuberculosis (TB) co-infection, antiretroviral treatment (ART) should be initiated within eight weeks of anti-TB treatment.
  - for HIV-TB patients with a CD4 count <50 cells/mm^3, ART should be initiated within the first two weeks of anti-TB treatment.
- For people living with HIV with TB meningitis, ART should be delayed until two months after initiation of TB treatment.

- **Antiretroviral treatment regimen for HIV-TB co-infection**

Drug-drug interactions (DDI) and overlapping drug toxicities are important issues when treating PLHIV with anti-TB and antiretroviral drugs (ARVs). Rifampicin interaction with ART is especially significant and thus requires special attention. Anti-TB drugs should be carefully chosen to avoid/minimise interactions with protease inhibitor (PI) and integrase strand transfer inhibitors (INSTI). Refer to **Table 7**.

Table 7: Preferred Anti-TB regimen in PLHIV on ART

Current ART regimen	Preferred anti-TB regimen
Non-nucleoside reverse transcriptase inhibitors (NNRTI)-based ART	Standard anti-TB regimen
Protease inhibitor (PI)-based ART	Rifabutin based anti-TB regimen
Integrase strand transfer inhibitors (INSTI)-based ART	Rifabutin based anti-TB regimen is preferred; however, if rifampicin-based regimen is to be chosen, the INSTI dose need to be adjusted

ART-naïve PLHIV with suspected ARV drug resistance need to be referred to Infectious Disease Physician/Paediatrician to discuss on anti-TB regimen. Otherwise, standard anti-TB regimen should be initiated.

A prospective cohort study among HIV-TB patients on ART compared RIF- and rifabutin (RFB)-based therapies, even though the RIF group showed better improvement in the immune and virological response, both groups of patients had no significant difference in the following outcomes:[50, level II-2]

- TB treatment default and cure rates
- interruption of therapy due to ADR
- IRIS
- mortality

Daily anti-TB regimen is recommended in HIV-TB co-infected patients as in non-HIV-TB population.[13; 16; 17; 51; 52]

Recommendation 16

- Daily anti-tuberculosis regimens should be used throughout the treatment of HIV-tuberculosis coinfected patients.

Further details on the interactions of ARV with anti-TB are discussed under **Subchapter 4.2** on **Anti-tuberculosis Drug Interactions**.

- **Immune Reconstitution Inflammatory Syndrome**

IRIS is an augmented inflammatory response in patients commenced on ART and anti-TB. It may cause clinical deterioration but does not primarily contribute to mortality.

While early initiation of ART in HIV-TB co-infection reduces all-cause mortality, it may also lead to IRIS which usually occurs within three months of TB treatment, typically within two to twelve weeks after the initiation of ART.

The major manifestations of IRIS are fever (40%), followed by lymphadenitis (38%).[8]

EPTB is the most significant risk factor associated with the emergence of IRIS. Other risk factors include baseline haemoglobin <100 g/L (OR=2.2, 95% CI 1.1 to 4.6) and baseline CD4 count <50 cells/mm^3 (OR=4.1. 95% CI 1.8 to 9.5).[8]

The severity of IRIS ranges from mild to life-threatening. Patients with severe IRIS should be referred to an Infectious Disease Physician for further management.

A 4-week course of prednisolone i.e. 1.5 mg/kg/day for two weeks, followed by 0.75 mg/kg/ day for two weeks improve symptoms and chest radiography findings as early as two weeks ($p<0.05$) in TB-associated IRIS.[8]

- Immune Reconstitution Inflammatory Syndrome should be suspected if there is paradoxical worsening of symptoms especially in patients with CD4 count <50 cells/mm^3, anaemia or extrapulmonary tuberculosis in HIV-TB co-infection on ART.

- **Co-trimoxazole prophylaxis**

WHO recommends co-trimoxazole preventive therapy be given as soon as possible and throughout TB treatment for all HIV-TB coinfected patients.[31] However, the ATS/CDC/IDSA recommends co-trimoxazole prophylaxis to be given only in HIV-TB coinfected patients with CD4 counts <200 cells/mm^3 (or less than 14%).[13]

In newly diagnosed HIV patients or those without baseline CD4 count, co-trimoxazole 960 mg daily should be initiated together with TB treatment.[8] Co-trimoxazole can be stopped once the CD4 count is >200 cells/mm^3 for two consecutive readings or CD4 count is 100- 200 cells/mm^3 and HIV viral load is undetectable at least once according to the Malaysia HIV consensus guidelines.[53, level III]

Recommendation 17

- Co-trimoxazole preventive therapy should be given during tuberculosis (TB) treatment in HIV-TB co-infection with an unknown CD4 count or a CD4 count <200 cells/mm^3.

2.7. Tuberculosis in Children

TB in children is common wherever adult TB is endemic. In 2019, WHO estimated 12% of the 10 million who had TB were children.[1, level I] In 2020, the proportion of registered TB cases among children in Malaysia was <5% of the total registered TB cases. Further analysis showed that the total TB cases among children <15 years old was 771 with an incidence rate of 9.9/100,000 population.[43, level III] Diagnosis of TB in children is challenging due to the paucibacillary and disseminated nature of the disease, and the wide range of clinical presentations mimicking common childhood illnesses. A positive TB contact history (usually an adult index TB case) would be a strong clue for TB in a symptomatic child. The risk factors for rapid TB progression in children are age <5 years old, malnutrition and HIV infection.

WHO recommends symptoms-based screening to exclude active TB based on the following scenarios:[54]

i. Non-HIV infected household contacts: any cough, fever, night sweats, haemoptysis, weight loss, chest pain, shortness of breath or fatigue. In children <5 years old, it should also include anorexia, failure to thrive, poor feeding, decrease activities or playfulness.
ii. Children living with HIV <10 years old: any current cough, fever, history of contact with TB, reported weight loss, confirmed weight loss >5% since last visit or growth curve flattening or weight for age < -2 Z-scores.
iii. Children living with HIV ≥10 years old: any current cough, fever, weight loss or night sweats.

a. Diagnosis

The expert consensus case definition classifies intrathoracic TB in children into the following categories:[55, level III]

Confirmed TB	*M. tuberculosis* confirmed by culture or Xpert MTB/RIF
Unconfirmed TB*	At least two of the following criteria in the absence of microbiological confirmation: • symptoms/signs suggestive of TB • CXR consistent with TB • close TB exposure or immunologic evidence of *M. tuberculosis* infection (TST and/or IGRA positive) • positive response to TB treatment
Unlikely TB	None of the criteria for confirmed or unconfirmed TB are met

TB=tuberculosis, CXR=chest radiograph, TST=tuberculin skin test, IGRA=interferon gamma release assay
*Unconfirmed TB: Clinically-diagnosed TB

CXR findings in children can be non-specific. Primary PTB findings include perihilar lymphadenopathy which is often missed by inexperienced clinicians. Post-primary PTB changes are not common in children. Absence of these changes do not exclude TB in children. Refer to **Appendix 8** on **Chest Radiograph Changes for Tuberculosis in Children**.

A good prospective cohort study using Xpert Ultra on 535 children demonstrated that induced sputum (IS) specimen was more sensitive than nasopharyngeal aspirate (NPA) in diagnosing intrathoracic TB. Sending two respiratory samples for Xpert Ultra improved the sensitivity and specificity of both IS and NPA. These findings are summarized in **Table 8**.[56, level II-2]

Table 8: Accuracy of Xpert Ultra using different respiratory specimen in diagnosis of TB in children

Specimen	Sensitivity	Specificity
1 sample of IS	74.3% (95% CI 56.7 to 87.5)	96.9% (95% CI 92.9 to 99.0)
1 sample of NPA	37.5% (95% CI 18.8 to 59.4)	98.0% (95% CI 93.4 to 99.8)
Repeated second NPA	54.2% (95% CI 32.8 to 74.4)	96.2% (95% CI 90.6 to 99.0)
1 IS and 1 NPA	80.0% (95% CI 63.1 to 91.6)	95.0% (95% CI 90.4 to 97.8)
1 IS and 2 NPA	87.5% (95% CI 67.6 to 97.3)	93.4% (95% CI 86.9 to 97.3)

IS=induced sputum, NPA=nasopharyngeal aspirate, CI=confident interval

A large Cochrane systematic review on children <15 years old with suspected TB showed that Xpert MTB/RIF from gastric aspirate (GA) had the highest pooled sensitivity, 73.0% (95% CI 52.9 to 86.7) followed by sputum, 64.6% (95% CI 55.3 to 72.9) and NPA, 45.7% (95% CI 27.6 to 65.1) compared with culture in diagnosing PTB. However, there was unclear risk of bias in the reference standard domain in 53% of the included studies.[57, level III]

In children who are symptomatic with more severe TB, GA and bronchoalveolar lavage (BAL) have significantly better yield than NPA in both smear for AFB and mycobacterial culture in a tertiary setting.[58, level III]

However, a good diagnostic study in primary care involving 119 children with TB contact or mild disease, IS, GA and NPA all have low yield for positive smear, Xpert MTB/RIF and TB culture. One limitation of the study was the small number of confirmed TB (four cases, study TB prevalence, 4.76%).[59, level III]

- This CPG DG advocates that two or three smears for AFB, and one sample each for Xpert Ultra and mycobacterial culture be obtained to increase the diagnostic yield in children with TB.

Recommendation 18
- In children suspected to have intrathoracic tuberculosis:
  - induced sputum should be performed in children who can expectorate.
  - gastric lavage/aspiration or nasopharyngeal aspirate should be performed in children who cannot expectorate.

The procedure for sputum induction is described in **Appendix 3** and the **Procedure for Gastric Aspiration and Nasopharyngeal Aspiration in Children** is described in **Appendix 9**.

- **Lateral Flow Lipoarabinomannan Assay in suspected intrathoracic tuberculosis**

Two small cohort studies compared the accuracy of AlereLAM and FujiLAM with Xpert MTB/RIF, Xpert Ultra or mycobacterial culture in children with intrathoracic TB. The sensitivity of FujiLAM ranged from 41.7% (95% CI 31.7 to 52.3) to 61.8% (95% CI 36.6 to 85.5) while its specificity ranged from 78.5% (95% CI 69.1 to 86.0) to 97.4% (95% CI 86.8 to 99.5). For AlereLAM, its sensitivity was between 38.8% (95% CI 0.4 to 98.9) and 50% (95% CI 39.5 to 60.5) while its specificity was between 74.4% (95% CI 58.9 to 85.4) and 80.5% (95% CI 68.3 to 89.4).[60 - 61,level II-2] The sensitivity and specificity for the diagnosis of intrathoracic TB in children in the studies were low. The two studies differ as to which of the LF-LAMs were more accurate in children.

Although LF-LAMs were not as accurate as Xpert MTB/RIF, Xpert Ultra or mycobacterial culture, they were able to detect intrathoracic TB missed by Xpert MTB/RIF, Xpert Ultra or mycobacterial culture.

- LF-LAM may be considered as an adjunctive test for the diagnosis of smear negative, Xpert Ultra negative intrathoracic TB in children.

Sterile method for urine collection is required to reduce false positive LF-LAM results from urine bacterial contamination.

The investigations for EPTB in children are similar to adults. Refer to **Subchapter 2.3** on **Extrapulmonary Tuberculosis**.

b. Treatment

- **Anti-tuberculosis regimens**

The TB treatment regimen in children for both PTB and EPTB are the same as in adults.

In children <5 years old, higher doses of anti-TB drugs are required to achieve effective bactericidal activity compared with older children and adults.[62, level III] Anti-TB dose in children should be calculated in mg/kg body weight and the total dose must not exceed the maximum dose. Refer to **Table 9** on **Recommended Dose of Anti-TB Drugs in Children**.

Medication dose requires recalculation every two to four weeks as children gain weight rapidly, particularly in neonates and young children.

Since the last edition of the CPG, there has been some revisions in the WHO recommendations on anti-TB dose for children. The revised dose has good safety profile and is not associated with increased risk of INH or PZA hepatotoxicity, or optic neuritis related to EMB.[63, level I; 64, level I]

Difficulty in serving anti-TB drugs by caregivers and vomiting after medication needs to be addressed during follow-up as these can lead to treatment failure in the children.

Table 9: Recommended dose of anti-TB drugs in children

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

[a]The higher end of the range for INH dose applies to younger children. As the children grow older the lower end of the dosing range becomes more appropriate.
Source: World Health Organization. Guidance for National Tuberculosis Programmes on The Management of Tuberculosis in Children (2nd Edition). Geneva: WHO;2014

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

For further information on renal dosing and ADR, refer to **Appendix 6** on **First-Line Anti-Tuberculosis Drug Dosage and Adverse Drug Reactions**

- **Fixed-dose combination of anti-tuberculosis regimen**

WHO recommends flavoured, dispersible child-friendly FDCs in treating children with TB. The new formulary contains anti-TB drugs according to the revised anti-TB dose for children (refer to **Table 10**).[65, level III]

Table 10: 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 FDC doses recommended	

*Ethambutol should be added in the intensive phase for children with extensive disease.
Source: Fixed-dose combinations for the treatment of TB in children. World Health Organization, 2018. Available from: https://www.who.int/tb/FDC_Factsheet.pdf.

The currently available adult anti-TB FDC tablet is not suitable for use in children <25 kg.

The benefits of the new anti-TB formulary include:[65, level III]

- avoidance of incorrect dosage due to broken pill and crushed tablets.
- patient- and caretaker-friendly (less pill burden, water dissolvable and palatable).
- easy storage and dispensing especially in remote areas.

Recommendation 19
- Child-friendly fixed-dose combinations* should be used to treat tuberculosis in children.

*The WHO recommended child-friendly FDC is not yet available in Malaysia.

The outcomes of patients treated for TB should be reported to the National TB Control Programme according to **Appendix 7** on **Tuberculosis Treatment Outcome Definition**.

c. BCG lymphadenitis

In Malaysia, BCG is given intradermally at birth. It is effective in preventing disseminated TB including TB meningitis in childhood. However, its effectiveness in preventing PTB is equivocal.

BCG lymphadenitis usually occurs two to four months after BCG vaccination (ranging from two weeks to six months) and 30 - 80% of cases can become suppurative. The most commonly involved lymph nodes are ipsilateral axillary lymph nodes, followed by supraclavicular or cervical lymph nodes.[66, level III]

Most non-suppurative BCG lymph nodes will regress without intervention in 4 - 6 months and can be managed conservatively. Once suppuration sets in, spontaneous rupture with chronic discharging sinus will occur. Healing will eventually take place by scarring.

A systematic review of five RCTs involving 237 children showed that fine needle aspiration shortens the resolution of BCG abscess at 6 months (RR=0.13, 95% CI 0.03 to 0.55). There is no evidence that oral antibiotics (e.g. erythromycin) or oral anti-TB prevent the progression of BCG abscess.[67, level I]

Children with unusually large, suppurative BCG lymphadenitis with constitutional symptoms, generalised lymphadenopathy and hepatosplenomegaly should be referred to the Infectious Disease Paediatrician for further management.

d. Congenital and neonatal tuberculosis

Congenital TB is caused by the transplacental spread of TB through umbilical vessels, or the aspiration or ingestion of infected amniotic or cervico-vaginal fluid in utero or intra-partum. Symptoms onset are usually within 3 weeks. Pulmonary, abdominal or disseminated TB are the usual manifestations.

Neonatal TB is TB acquired postnatally when a newborn is exposed to an infectious adult, usually the mother but sometimes other household members.

It is difficult to distinguish between the two conditions since clinical presentations are often non-specific. Both tend to be disseminated and have high mortality. Symptoms include poor feeding, failure to thrive, fever, respiratory distress, hepatosplenomegaly, lymphadenopathy, abdomen distension with ascites or “clinical sepsis” in disseminated TB. Identifying an infectious adult would be the key to the diagnosis of neonatal TB.

Investigations for both congenital and neonatal TB are similar to older children and adults. It is important to note that congenital TB tends to be disseminated involving the abdomen and central nervous system. Ultrasound abdomen or liver biopsy and lumbar puncture would need to be considered if there is clinical suspicion of TB. When congenital TB is suspected, the placental, vaginal and endometrial samples or biopsy should be sent for mycobacterial culture and HPE.[8]

The management of newborns of mothers with TB depends on the mothers' state of TB infectiousness. All newborns to mothers with active TB need to be screened for TB. Mothers whose current sputum smear is positive or who have received less than two months of PTB treatment are considered infectious. Refer **Figure 3** on **Management of newborn to mother with active infectious TB**.

For mothers diagnosed to have PTB post-partum, their newborns should be screened for active TB. Once excluded, LTBI treatment should be initiated (refer to **Subchapter 3.2** on **Latent TB Infection in Children**). The newborns should be managed by a paediatrician with experience in treating TB.

It is crucial to screen and treat other household members for active TB to prevent repeated exposure to the newborn or other children.

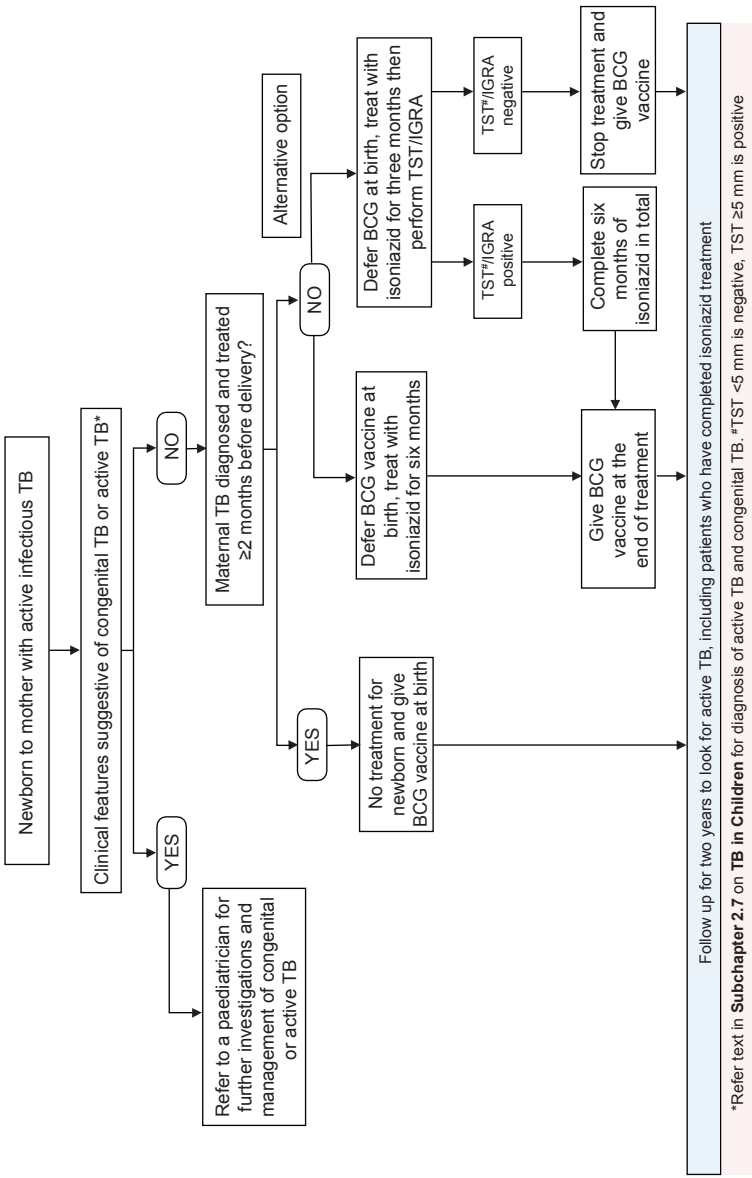


Figure 3: Management of newborn to mother with active infectious TB

2.8. Patient-Centred Care

Patient-centred care is one of the main pillars of the WHO End TB Strategy of ending TB by year 2035. In Malaysia, directly observed treatment (DOT) is supervised by healthcare providers, family members or community volunteers. DOT should be tailored to patient's preference and their risk of default. In 2015, the practice of DOT during intensive phase for TB cases in Malaysia was 89.6% while DOT during continuation phase was 87.9%. The DOT supervisor were healthcare providers in 59.6% of cases, family members in 39.8% and, non-governmental organisations and community volunteers in 1.2%.[7, level III]

A systematic review and meta-analysis of 22 RCTs comparing DOT with self-administered treatment in adults with active TB found that DOTS was superior in cure rate (RR=1.18, 95% CI 1.08 to 1.28) and default rate (RR=0.51, 95% CI 0.32 to 0.84).[68, level I]

Self-administered treatment is unavoidable for those who could not travel to a DOT centre and have no treatment supervisor at home.

Video-observed treatment (VOT) is recommended by WHO as a new form of DOT.[69] In Malaysia, VOT has been implemented in some healthcare facilities since 2019 and has been well received by patients and staff. VOT may be conducted by live streaming e.g. via Teleconsult in BookDoc App or recorded videos. It may be done in healthcare facilities with appropriate infrastructure. The major advantage of VOT is its ability to monitor patients from a distance. This will reduce visits by healthcare providers and travelling by patients. VOT also allows more flexibility for patients to manage their time. Patients should be educated on VOT and give consent for the procedure. A large RCT showed that VOT was more effective than DOT. A total of 70% of patients on VOT successfully completed ≥80% of a 2-month observation compared with only 31% of those on DOT (OR=5.48, 95% CI 3.10 to 9.68).[70, level I]

Besides DOT, patient adherence to anti-TB treatment could be achieved by combining several strategies e.g. patient education/counselling and financial incentives. A meta-analysis showed that patients given education/counselling had better cure rate (RR=1.16, 95% CI 1.05 to 1.29) and default rate (RR=0.87, 95% CI 0.77 to 0.98) compared with no education/counselling. In addition, financial incentives used during anti-TB treatment may help patients adhere to and complete treatment. The use of incentives compared with no incentive decreased default rate by 26% (RR=0.74, 95% CI 0.61 to 0.90).[68, level I] Financial incentives may be in the form of travel or phone allowances for DOT/VOT.

Recommendation 20

- Directly observed treatment (DOT) should be done in patients on tuberculosis (TB) treatment.
  - Video observed treatment (VOT) should be an alternative to DOT in selected patients where facilities are available.
  - Self-administered treatment may be offered to patients who cannot perform VOT or DOT.

3. SECTION II: LATENT TUBERCULOSIS INFECTION

LTBI is a state of persistent immune response to stimulation of *M. tuberculosis* antigen without clinical evidence of active TB.[8] About a quarter of the world population (approximately 1.7 billion people) are estimated to have LTBI.[71, level III]

An estimated 30% of individuals exposed to *M. tuberculosis* will develop LTBI and, if untreated, about 5% to 10% of will progress to active TB.[72] Identification and treatment of LTBI, the reservoir for *M. tuberculosis*, should be an effective strategy to prevent and reduce further transmission, morbidity and mortality of TB disease. This is in accordance with WHO End TB Strategy.[2, level III]

Under Pillar 1, Strategy 6 of the National Strategic Plan for TB Control (2016 - 2020), Malaysia aims to strengthen the programmatic management of LTBI.[7, level III]

The general approach to the management of people with LTBI is illustrated in **Algorithm 2** on **Management of Latent Tuberculosis Infection**.

3.1. Latent Tuberculosis Infection in Adults

a. At-risk groups for progression from latent TB to active TB

LTBI treatment should be targeted to the group of affected people at highest risk for progression to active TB, to be cost effective and minimise risk of treatment ADR.

The at-risk population that WHO recommends for systematic testing and treatment are:[54]

- household and close contacts of bacteriologically confirmed PTB
- PLHIV
- patients initiating anti-tumour necrosis factor (TNF) treatment
- patients receiving dialysis
- patients preparing for organ/haematological transplant
- patients with silicosis

While the following groups may be considered for LTBI testing and treatment:

- healthcare workers
- immigrants from high TB burden countries
- prisoners
- illicit drug users
- homeless people

- The CPG DG recommends the following target populations to be systematically tested and treated for LTBI:
  - household and close contact of bacteriologically confirmed PTB
  - PLHIV
  - patients initiating anti-TNF treatment
  - patients receiving dialysis
  - patients preparing for organ/haematological transplant
  - patients with silicosis
- The testing and treatment of LTBI in other at-risk populations as shown below can be considered on an individual basis:
  - healthcare workers
  - immigrants from high TB burden countries
  - prisoners
  - illicit drug users
  - homeless people

- **Household or close contacts**

Household or close contacts are individuals who live in the same household or share the same air space with the index case for a reasonable duration of time before the index patient received TB treatment.[73, level III] Contacts living in close proximity for prolonged periods of time with an infectious TB patient are at greater risk of being infected with the disease. A retrospective cohort study of 369 household contacts showed that the incidence of TB in contacts correlated with the amount of TB aerosolized by the index case.[74, level II-2] However, the minimum physical distance or duration of exposure has not been well-established.[75, level I]

- **People living with HIV**

PLHIV are 18 times more likely to develop TB disease than people without HIV. TB is also the leading cause of death among them.[1, level III] The annual risk of TB disease due to reactivation of LTBI for persons with untreated HIV infection has been estimated at 3% to 16% per year. The risk of TB begins in the first year of diagnosis of HIV infection. TB infection can occur at any CD4 cell count with the risk increasing with progressive immunodeficiency.[51] Even PLHIV on ART benefit from LTBI treatment.[54] All PLHIV should be screened for LTBI when diagnosed with HIV regardless of their epidemiologic risk factors or TB exposure history. However, testing is not a requirement prior to starting LTBI treatment as the benefits of treatment clearly outweigh the risks.[54]

- **Other at-risk groups**

Other at-risk groups for progression to active TB compared with general population are patients having anti-TNF treatment (RR range=1.6 to 25.1), dialysis (RR range=6.9 to 52.5), organ or haematological transplant (RR range=20 to 70) and silicosis (RR 2.8).[76, level III] These

groups of people are at risk due to their immunocompromised health status.

- **Diagnosis of LTBI**

Active TB must be ruled out before considering the diagnosis and treatment of LTBI. WHO recommends either a Tuberculin Skin Test (TST) or Interferon Gamma Release Assay (IGRA) be used for the diagnosis of LTBI.[54]

- The criteria for diagnosis of LTBI are:
  - **Absence of any clinical features suggestive of active TB** (productive cough, haemoptysis, loss of appetite, unexplained weight loss, fever, night sweats and fatigue).
  - **Normal or static CXR findings** (healed TB lesions are often characterised by nodules and fibrotic lesions that are well demarcated). If changes are present, consider repeating sputum induction, or bronchoalveolar lavage smear for AFB and mycobacterial culture. In the presence of any unexplained abnormal findings, consider sending the CXR for reporting.
  - **A positive TST or IGRA**.

- **Tuberculin skin test**

TST is performed via the Mantoux technique, which consists of intradermal injection of purified-protein derivative on the inner aspect of the forearm. This stimulates a delayed T-lymphocyte mediated hypersensitivity response in patients with prior mycobacterial exposure. The test must be read between 48 - 72 hours later.

There is no new evidence on the ideal cut-off value for TST in an intermediate to high TB burden country like Malaysia. Therefore, the CPG DG has decided to retain the existing Mantoux cut-off values from the previous guideline in **Table 11**.[8]

According to CDC and National Tuberculosis Controller Association (NTCA), the window period for TST and IGRA conversion (duration between infection and skin test reactivity) is 8 - 10 weeks after exposure to an infectious TB case. Consequently, a negative test result obtained <8 weeks after exposure is considered unreliable for excluding infection and the test should be repeated at the end of the window period.[77]

Table 11: TST cut-off value for different groups

Positive (TST) reaction	At-risk groups
≥5 mm	• PLHIV • Organ transplant recipients • Persons who are immunosuppressed for other reasons (e.g. those taking the equivalent of >15 mg/day prednisolone for ≥1 month or taking anti-TNF treatment)
≥10 mm	• All other high risk individuals including healthcare workers and children (except newborns and infants <3 months)
≥15 mm	• Individuals from countries with low incidence of TB

Source: Ministry of Health Malaysia. Management of Tuberculosis (Third Edition). Putrajaya: MoH Malaysia; 2012

Bacille Calmette-Guérin (BCG) vaccination has limited effect on the interpretation of TST results later in life as it is given at birth for most of the population in Malaysia.[54]

Refer to **Appendix 10** on **Procedure for Tuberculin Skin Test**

- **Interferon Gamma Release Assays**

IGRAs are blood tests that detect cell-mediated immune response. The test measure T-cell release of interferon gamma following stimulation by protein antigens secreted by *M. tuberculosis* and a few other mycobacteria. However, it does not detect *M. bovis*, BCG and most of the non-tuberculous mycobacteria.[78] IGRA does not require a follow-up visit for reading of results (in contrast with the TST).

IGRA cannot distinguish between LTBI and active TB. Thus, it should not be used to diagnose active TB.

All IGRAs are not affected by BCG vaccination which makes them useful for evaluating LTBI in BCG-vaccinated individuals.[79, level III]

In Malaysia, QuantiFERON-TB Gold Plus (QFTR-Plus) is currently the more widely used IGRA. It has two TB antigen tubes instead of one because it measures response of both CD8+ and CD4+ T cells. The test is positive when either tube containing the TB antigen shows a positive response.

A QuantiFERON assay may yield an indeterminate result. This may be due to in-vitro or in-vivo factors. Hence, proper handling of the QuantiFERON specimens is important. If the first result is indeterminate, the test may be repeated or TST can be performed. Refer to **Appendix 11** on **Procedure for QuantiFERON Specimen Collection.**

In a well conducted meta-analysis of 40 studies involving 50,592 adults and children comparing IGRA and TST, the former was better in predicting the progression of LTBI to active TB.[80, level II-2]

- The pooled RR for disease progression in untreated individuals:
  - IGRA positive vs IGRA negative was 9.35 (95% CI 6.48 to 13.49)
  - TST positive vs TST negative was 4.24 (95% CI 3.30 to 5.46)

  A positive IGRA has a significantly higher predictive ability than a positive TST (p=0.008).
- PPV for IGRA was 4.5% (95% CI 3.3 to 5.8) compared with 2.3% (95% CI 1.5 to 3.1) for TST (p=0.002).
- NPV for IGRA was 99.7% (95% CI 99.5 to 99.8) compared with 99.3% (95% CI 99.0 to 99.5) for TST (p=0.02).
- IGRA positive individuals who were untreated vs those who were treated was 3.09 (95% CI 2.08 to 4.60) compared with 1.11 (95% CI 0.69 to 1.79) for the same populations who were TST positive.

A retrospective cohort study of 416 HIV-infected adults found that a positive IGRA had substantial predictive ability for progression to active TB.[81, level II-2]

- The sensitivity, specificity, PPV and NPV of IGRA were 80.0% (95% CI 28.4 to 99.5), 85.9% (95% CI 82.1 to 89.1), 6.5% (95% CI 4.0 to 10.2) and 99.7% (95% CI 98.4 to 99.9) respectively.
- The progression to active TB was significantly more frequent in the IGRA positive vs IGRA negative group (p=0.001).

- LTBI testing is desirable but not required in PLHIV prior to initiation of LTBI treatment.

Recommendation 21

- Interferon gamma release assay or tuberculin skin test should be used to test for latent tuberculosis infection for adults in the target groups.

- All patients diagnosed with LTBI should be notified to the National TB Control Programme for surveillance purposes.

- **Treatment**

LTBI treatment is designed to prevent the progression of LTBI to active TB. Evidence show that treatment of LTBI can prevent 60 - 90% of cases from developing active TB.[45]

The benefit of treating individuals with LTBI should outweigh its harm. This is because safety is particularly important in LTBI treatment as the

patients are asymptomatic without active disease. To ensure treatment adherence and successful completion of treatment, an effective, safe and short regimen is preferred for both adults and children.

- **HIV-negative adults**

A local technology review showed the following LTBI treatment regimens were effective compared with placebo in preventing active TB:[82, level I]

- INH 6 months with OR=0.65 (95% CI 0.50 to 0.83)
- INH 12 - 72 months with OR=0.50 (95% CI 0.41 to 0.62)
- RIF 3 - 4 months with OR=0.41 (95% CI 0.19 to 0.85)
- RIF-INH 3 - 4 months with OR=0.53 (95% CI 0.36 to 0.78)
- RIF-INH-PZA 12 months with OR=0.35 (95% CI 0.19 to 0.61)
- RIF-PZA 12 months with OR=0.53 (95% CI 0.33 to 0.84)

In another comparison, the regimens containing rifamycin showed no difference in the risk of developing active TB compared with those containing INH.

In a well-designed RCT, 4R was non-inferior to 9H in HIV-negative adults with LTBI in preventing active TB. The 4R treatment arm had fewer grade 3 to 5 ADRs requiring treatment to be stopped permanently (RD in percentage points= -1.1, 95% CI -1.9 to -0.4) and better treatment completion rate (difference in percentage points=15.1, 95% CI 12.7 to 17.4).[83, level I]

The median rate of withdrawals from adverse events due to LTBI treatment regimens were as follows:[82, level I]

LTBI treatment regimen	Median withdrawal rate	Range
6H	5.8%	2.3% to 24.5%
3HP	4.3%	1.3% to 8.4%
9H	2.6%	0.4% to 26.8%
3-4HR	1.8%	0.5% to 5.1%
3-4R	0%	0% to 5.2%

In one small cross-sectional study, LTBI patients on 4R and 3HP were more likely to complete treatment than patients on 9H with RR of 1.39 (95% CI 1.07 to 1.81) and 1.67 (95% CI 1.27 to 2.19) respectively.[84, level III]

- **HIV-positive adults**

A large RCT on HIV-positive adults with LTBI comparing 1HP and 9H showed the following:[85, level I]

- lower treatment interruption due to liver toxicity in 1HP (OR=2.09, 95% CI 1.32 to 1.33)
- lower combined grade 3 and 4 serious adverse events in 1HP (2.9 vs 4.6 events per 100 person-years, p= 0.01)
- higher treatment completion rate in 1HP (97% vs 90%, p<0.001)
- no difference in development of active TB

In a systematic review of four RCTs, there was no significant difference between 3HP and 6H/9H or continuous INH (36 months) for LTBI treatment in HIV-positive adults on the following outcomes:[86, level I]

- development of active TB
- all-cause mortality

However, treatment completion rate was higher in the 3HP group compared with the other two groups:

- 3HP vs 6H/9H (RR=1.25, 95% CI 1.01 to 1.55)
- 3HP vs continuous INH (RR=1.59, 95% CI 1.40 to 1.80)

In the same review, 3HP was safer compared with its comparators:[86, level I]

- lower risk of any adverse events compared with 6H/9H (RR=0.63, 95% CI 0.43 to 0.92) or continuous INH (RR=0.20, 95% CI 0.12 to 0.32)
- lower risk of hepatotoxicity compared with 6H/9H (RR=0.26, 95%CI 0.12 to 0.55) or continuous INH (RR=0.05, 95% CI 0.02 to 0.13)

The above evidence supports the use of a short and effective LTBI treatment regimen with high treatment completion rate in adults with LTBI.

Recommendation 22

- In the treatment of all adults with latent tuberculosis infection (LTBI):
  - 3HR or 3HP* regimens should be the first-line regimen unless contraindicated
  - 4R may be used for patients who cannot tolerate or who are contraindicated for INH-based regimens
  - 6H or 9H may be used for patients who cannot tolerate or who are contraindicated for rifamycin-based regimens
  - 1HP* may be considered for HIV-positive adults

3HR=three months daily isoniazid and rifampicin, 3HP=three months weekly isoniazid and rifapentine, 4R=four months daily rifampicin, 6H=six months daily isoniazid, 9H=nine months daily isoniazid, 1HP=one month daily isoniazid and rifapentine

*rifapentine is not yet available in Malaysia

- The use of 3HR/3HP/4R:
  - is contraindicated in patients receiving protease inhibitor-based antiretroviral therapy
  - requires dose adjustment of dolutegravir and raltegravir

For further information on RIF-drug interaction, refer to **Subchapter 4.2** on **Anti-tuberculosis Drug Interactions**.

The dosing for LTBI treatment in adults is shown in **Table 12** below.

Table 12: 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

Adapted: World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Tuberculosis Preventive Treatment: Module 1: Prevention. Geneva: World Health Organization; 2020

Note: Pyridoxine 10 mg/day should be given for all adult patients on INH and a higher dose of 30 mg/day for individuals at high risk of neuropathy.

d. Monitoring

Ensuring treatment adherence in patients tolerating LTBI treatment is important to obtain maximum benefit. This can be achieved by providing health education and patient support. Patients should be advised to contact their healthcare providers whenever they have the following symptoms: loss of appetite, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools, jaundice, confusion or drowsiness. If a healthcare provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately.

Regular follow-up is needed to ensure early identification of active TB and treatment ADR in patients receiving LTBI treatment. A surveillance system for treatment outcome as well as resistance to TB drugs should be established. The CPG DG recommended monitoring schedule for individuals on LTBI treatment is shown in **Table 13** below.

Table 13: Recommended follow-up schedule for LTBI treatment monitoring

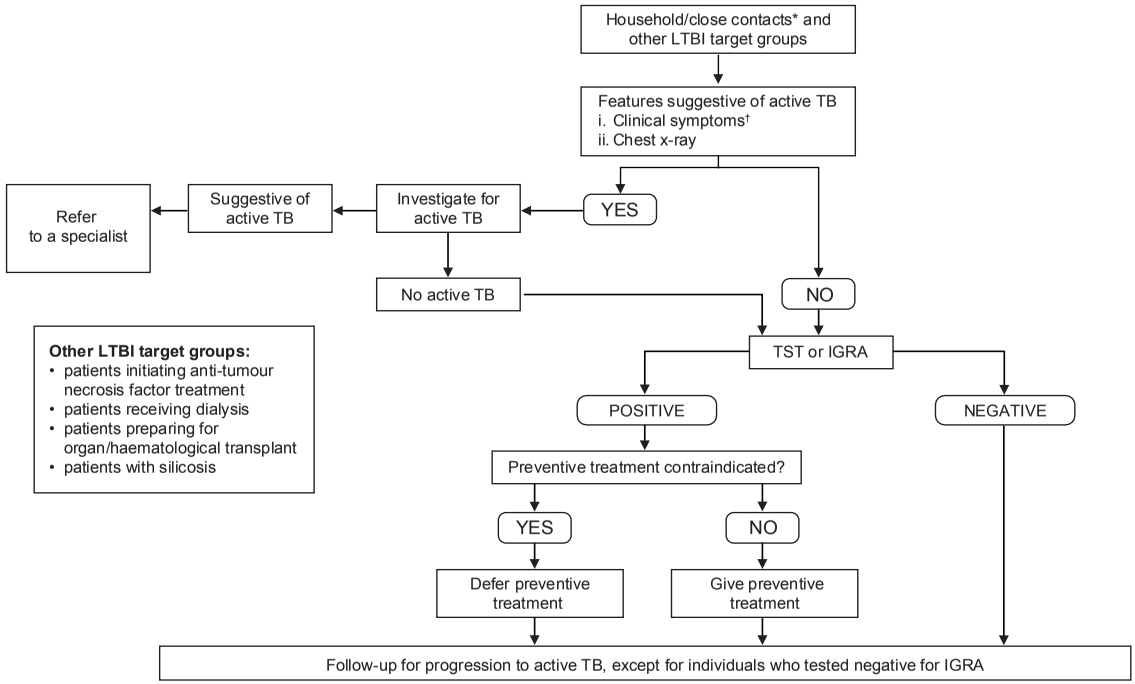
Time*	Management	
	Investigations	Other activities
Day 1	FBC, RP, LFT, HIV** CXR	Provide health education on: • Adherence • Side effects • Symptoms of active TB Initiate LTBI treatment
Week 2 - 4	LFT	Ensure treatment adherence Monitor for ADR and symptoms of active TB
End of LTBI treatment	CXR	
Three months after end of treatment	-	Monitor for symptoms of active TB
Nine months after end of treatment	-	
18 months after end of treatment	CXR	

FBC=full blood count, RP=renal profile, LFT=liver function test, HIV=human immunodeficiency virus, CXR=chest x-ray, TB=tuberculosis
*Day 1, week 2 - 4 and end of treatment monitoring is done by a medical officer/ specialist while the rest can be monitored by the paramedics
**With risk factors for HIV

Individuals with LTBI, whether or not they received treatment, are advised to be followed-up regularly for two years. Adults who developed active TB while on LTBI treatment or during follow-up should be referred to a specialist experienced in managing TB. TB drug resistance testing should be done to rule out acquired drug resistance.

WHO has not defined the treatment outcomes for LTBI. Patients started on LTBI treatment should have their outcomes reported. The LTBI treatment outcomes proposed by this CPG DG is shown in **Appendix 12**.

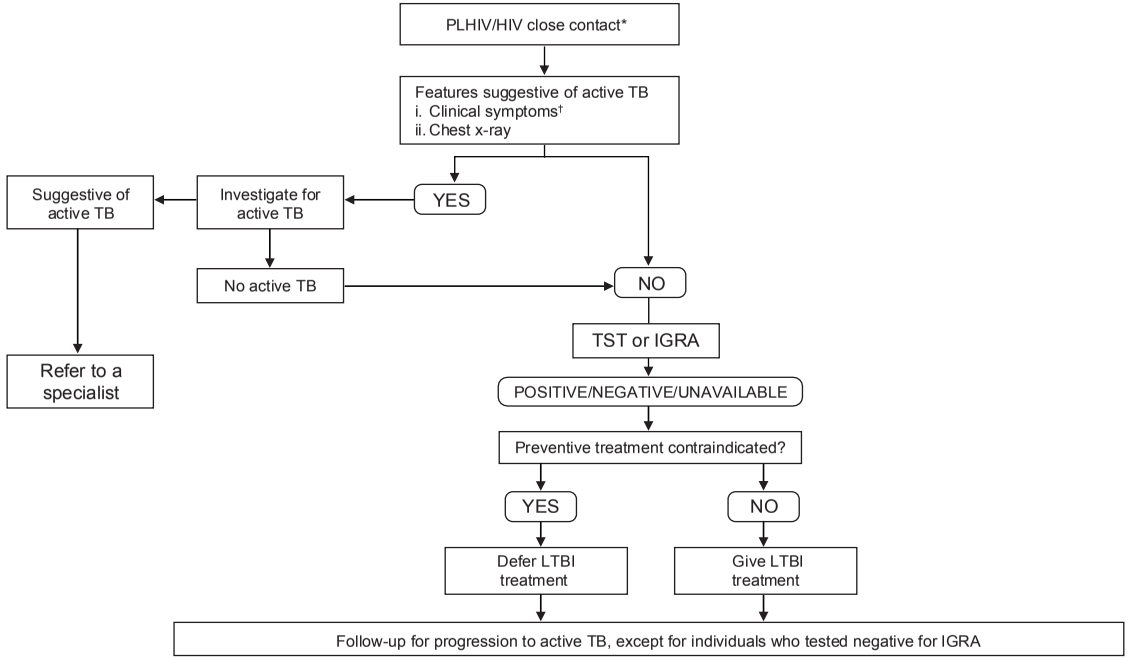
The management of LTBI in adults is shown in **Figure 4**.
The management of HIV-positive adults with LTBI is shown in **Figure 5**.



*Household or close contacts are individuals who live in the same household or share the same air space with an index case for a reasonable duration of time before the index patient started TB treatment. †Clinical symptom: current cough, fever, weight loss or night sweats

Adapted: World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Tuberculosis Preventive Treatment: Module 1: Prevention. Geneva: World Health Organization; 2020

Figure 4: LTBI testing and TB preventive treatment for adult household contacts and other targeted at-risk groups



*Close contacts are individuals who live in the same household or share the same air space with an index case for a reasonable duration of time before the index patient started TB treatment. †Clinical symptom: current cough, fever, weight loss or night sweats

Adapted: World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Tuberculosis Preventive Treatment: Module 1: Prevention. Geneva: World Health Organization; 2020

Figure 5: LTBI testing and TB preventive treatment for people living with HIV (PLHIV)

3.2. Latent Tuberculosis Infection in Children

Children below 2 - 4 years of age with LTBI have the highest risk of progression to active TB including disseminated and central nervous system TB.[87, level III] In a meta-analysis of 46 cohort studies in 34 countries involving 130,512 children, the 2 year cumulative TB incidence in untreated close contact with positive baseline TST or IGRA results was greatest among children below five years of age (19.0%, 95% CI 8.4 to 37.4). Most cases occurred within weeks of contact investigation initiation.[88, level II-2] Thus, early investigation and treatment for LTBI are necessary to prevent active TB especially in children below 5 years of age who are at higher risk for LTBI and/or progression to TB disease.

As in adults, LTBI in children is a clinical diagnosis established by:

- demonstrating prior TB infection using a LTBI test
- excluding active TB disease

a. LTBI tests

There is no gold standard for LTBI diagnosis in children; available tests include the TST and IGRAs. These tests measure immune response (type IV or delayed-type hypersensitivity) to mycobacterial protein antigens that might occur following exposure to mycobacteria. A negative TST or IGRA result is not reliable in infants younger than three months of age as their cell-mediated immune response may not be fully developed.

- **Tuberculin skin test**

The Interpretation of TST results in children is the same as for adults (refer **Table 11**, **Subchapter 3.1** on **Latent Tuberculosis Infection in Adults**). Children may take 8 - 12 weeks to develop a positive TST result after exposure to TB.

- **Interferon Gamma Release Assays**

IGRAs are in vitro blood tests of cell-mediated immune response to TB-specific antigens. The tests do not measure immune response to the antigens of the BCG vaccine and most nontuberculous mycobacteria. Compared to TST, IGRAs have a similar sensitivity but greater specificity for the diagnosis of TB infection. (A positive TST could be due to a recent BCG vaccination and nontuberculous mycobacterial infection).

For the diagnosis of LTBI in children ≥ 2 years old, either IGRA or TST may be used;[54] IGRA is preferred if available. In a study in the United States of America (USA) involving 3,593 children (25% of whom <5 years old and 92% born outside the USA) with risk for LTBI or progression to TB disease, the IGRAs (Quantiferon Gold In-Tube test [QFT-GIT] and T-SPOT) were found to have higher specificities [90.1% (95% CI 89.1 to 91.1) for QFT-GIT and 92.9% (95% CI 92.0 to 93.7) for T-SPOT] and

equally high NPVs (100 (95% CI 99.8 to 100) for QFT-GIT and 99.9 (95% CI 99.8 to 100) for TST-SPOT] compared to TST [specificity of 73.4% (95% CI 71.9 to 74.8) and NPV of 99.9 (95% CI 99.7 to 100)] at two years of follow-up. None of the 533 children (including 54 children <2 years old) with a TST-positive but IGRA-negative results developed TB disease although they were not treated for LTBI. The results of the study supported the use of IGRAs to screen for LTBI in children of any age, especially those who are born outside of the USA.[89, level II-2]

The use of IGRAs in children aged <2 years has been controversial and WHO cautions on their use in children <2 years old and children living with HIV because of concerns about the reduced sensitivity of the test.[54] However, a study in an USA-based health system involving 116 children <2 years (7 to 23 months), none of the untreated children who were TST positive, but IGRA negative developed TB disease.[90, level III] The American Academy of Paediatrics preferred TST for children <2 years but recommends the use of IGRA in combination with TST to improve the diagnosis of LTBI in certain clinical situations.[91, level III]

Either a positive IGRA or TST result should be considered indicative of M. tuberculosis infection. A negative IGRA or TST results cannot conclusively exclude the diagnosis of LTBI and should be interpreted in the context of other clinical data. An indeterminate or invalid IGRA result should not be used for clinical decision making.[92, level III]

- In immunocompromised children, both IGRAs and TST should be interpreted with caution.

b. Excluding active TB

Similar to adults, all treatment for LTBI in children should be initiated only after active TB has been ruled out. WHO recommends symptoms-based screening to exclude active TB (refer **Subchapter 2.7** on **Tuberculosis in Children**).[54] Evaluation for active TB must be pursued in all children with a positive TST or IGRA.

CXRs are usually normal in children with LTBI but may show dense nodules with calcifications, calcified non-enlarged regional lymph nodes, or pleural thickening (scarring).[93, level III] If there are any unexplained CXR abnormalities or diagnostic uncertainties, the child should be referred to a centre with a paediatrician experienced in managing TB disease in children.

WHO concludes that for household contacts, symptoms screening for active TB with or without addition of CXR should be acceptable. However, a normal CXR increases the confidence that active PTB has been excluded and reduces the risk of inadvertently treating active TB

with LTBI regimen. For adults and adolescents living with HIV, WHO reiterated that the requirement for CXR should not pose a barrier to LTBI treatment. However, there was no clear statement on the role of CXR for infants and children living with HIV.[54]

- CXR should be done prior to LTBI treatment. For children whose CXR cannot be done prior to treatment, it should be done within 14 days of treatment initiation.

c. Children at risk of progression to active TB and recommended for LTBI treatment

WHO makes the following recommendations for the high-risk group of children to be screened and given LTBI treatment.[54]

- Children <5 years (irrespective of HIV status) who are household contacts of people with bacteriologically confirmed PTB should be given TB preventive treatment even if LTBI testing is not available.
- Children ≥5 years (irrespective of HIV status) who are household contacts of people with bacteriologically confirmed PTB may be given TB preventive treatment.
- Children ≥12 months of age living with HIV in a setting with high TB transmission, should be offered TB preventive treatment regardless of contact with TB.
- Infants aged <12 months living with HIV who are in contact with a person with TB should receive TB preventive treatment.

The following are high-risk groups of children for progression to active TB:

- **Household contacts of bacteriologically confirmed PTB**

Child contact of bacteriologically confirmed PTB must be evaluated for active TB with history, physical examination, CXR, and TST or IGRA. Evaluation should be performed as soon as the contact is identified. Testing for TB infection with TST or IGRA shortly following exposure may be negative. If the initial TST or IGRA is negative, it should be repeated 8 to 12 weeks following the last known exposure to TB as immune response to TB may take up to 10 weeks (of window period) to develop.

i. Children aged <5 years

Treatment for LTBI should be initiated if there is no evidence for active TB, even in the absence of positive TST or IGRA results. This approach is known as "window prophylaxis".[94, level III] It is warranted because the child's cellular immune response to TB may not be fully developed at the time of testing, and children <5 years of age with recent TB exposure are at relatively high risk for progression to active TB (40% risk in infants <12 months and 25% in children 1 to 2 years of age).[95, level III] If the initial TST or IGRA is negative, the child may be retested at 8 to 12

weeks from the last date of contact with the index case. If the repeat test remains negative, treatment may be discontinued at the discretion of the clinician. In a setting where LTBI test is not available, all child contacts <5 years should be offered LTBI treatment as recommended by WHO.[54]

ii. Children aged ≥5 years

For immunocompetent child contacts ≥5 years of age with positive TST or IGRA without signs of active TB, LTBI treatment may be given.[54] However, if the initial LTBI testing is negative, decision regarding treatment may be deferred pending results of a second test, performed 8 to 12 weeks from the last date of contact with the index case. If the repeat test is negative, no treatment is warranted. If the repeat test is positive, a course of LTBI treatment may be completed.

- **Infant and children living with HIV**

All HIV-infected children should undergo annual screening for TB from 3 through to 12 months of age (for perinatal infected infant) or at the time HIV diagnosis (in older children and adolescents)

For HIV-infected children aged ≥12 months in a high TB transmission setting, treatment for LTBI should be offered regardless of CD4 cell count or if LTBI test is unavailable.[54] LTBI treatment administered in the absence of LTBI testing has been associated with a 40 - 50% reduction in active TB among HIV-infected male (employees of a South African gold-mining company with median age of 37 years) living in areas with very high TB incidence.[96, level I] WHO strongly recommends LTBI treatment for children aged ≥12 months living with HIV after excluding active TB despite the inconsistent/low quality evidence in the relevant studies. This is because of the clear benefits seen in adults with HIV and the high-risk of active TB among all PLHIV including children.[54]

If LTBI test is available and the result is negative for HIV-infected children aged ≥12 months, the decision on LTBI treatment should be made on an individual case basis, taking into account the potential benefits and harms of LTBI treatment.[54]

For HIV-infected infants <12 months old, the evidence of adult studies cannot be applied. WHO recommends that infants <12 months of age to be offered LTBI treatment only if there is history of contact with TB.[54]

- **Children in other risk groups**

For immunocompromised children or children in other high-risk groups for progression to active TB disease, the approach is the same as for adults. They should be tested for LTBI and if the result is positive, LTBI treatment should be offered after excluding active TB.

Recommendation 23

- Interferon gamma release assay or tuberculin skin test should be used to test for latent tuberculosis infection in children at risk of progressing to active tuberculosis

- All children diagnosed with LTBI should be notified to the National TB Control Programme for surveillance purposes.

d. LTBI treatment regimen

Similar to adults, this CPG DG prefers an effective but shorter regimen for LTBI treatment in children to ensure treatment adherence and treatment completion.

Current regimens used to treat LTBI in children include:

a. RIF daily for four months (4R)
b. INH and rifapentine weekly for three months (12 doses) (3HP)
c. INH and RIF daily for three months (3HR)
d. INH daily for six or nine months (6H/9H)

3HP should preferably be administered under DOT.

In a systematic review involving children below 15 years old with LTBI, 3- or 4-months of daily RIF and INH (3HR/4HR) was safe and showed better completion rate than 6 or 9 months of daily INH (6H/9H) based on the following outcomes:[97, level I]

- risk of active TB development based on radiological changes was lower in 4HR than 9H (RR=0.492, 95%CI 0.318 to 0.762)
- significantly higher GI-related ADR and transient increased liver enzyme in 9H than 4HR
- no significant difference in the rate of liver function impairment between 3HR and 9H
- treatment completion rate was higher in 3HR than 6H (RR=2.41, 95%CI 1.70 to 3.43)

Two recent good RCTs looked at alternative LTBI treatment regimens in children compared with 9H.

In the first RCT involving 884 non-HIV infected children <18 years old, 4R had better adherence with no significant difference in effectiveness and side-effects compared with 9H. Treatment completion with 4R showed an adjusted difference of 13.4 percentage points (95% CI 7.5 to 19.3).[98, level I]

The second RCT of 905 children aged 2 to 17 years showed that 3HP was non-inferior to 9H for LTBI treatment. Apart from that, 9H had lower overall treatment completion rate (OR= -7.2, 95% CI -2.0 to -2.5) and higher treatment discontinuation rate (OR=4.9, 95% CI 2.5 to 7.4). Neither arm had any hepatotoxicity, grade 4 ADRs or treatment-attributed death.[99, level I]

In a large retrospective cohort study of 1174 children <18 years old treated for LTBI, treatment completion was higher in the 4R group than in the 9H group (OR=1.64, 95% CI 1.07 to 2.52). ADR was uncommon in either group and there were no instances of symptomatic hepatotoxicity.[100, level II-2]

The choice of LTBI treatment regimen is based largely on the likelihood of adherence, the potential for adverse effects and preference of the patient, provider, and/or public health programme. The CPG DG recommends daily RIF for four months (for children of all ages except newborn 28 days and below) and weekly INH and RPT for three months (for children >2 years) as the preferred regimens, given the good safety profile and better completion rate. However, RPT is currently not available in Malaysia. Alternative regimens are 3HR and 6H if the preferred regimen is contraindicated or not available.

For children ≥2 years of age on ART, regimens should be reviewed carefully for compatibility of ART with the LTBI regimen. Children on ART incompatible with rifamycin-based regimens should be treated with INH monotherapy.

For children <2 years of age on ART, INH monotherapy is preferred as the potential for DDI with rifamycin-based regimens are high. WHO recommends six-month daily INH monotherapy for children aged <2 years in high-incidence settings (TB incidence rate ≥ 40 per 100,000 population).[54]

Pyridoxine 5 to 10 mg daily should be administered together with INH especially for infants who are being exclusively breastfed, children on meat and milk deficient diets, and those with conditions that can predispose to neuropathy (including diabetes, uraemia, malnutrition, and HIV infection).

The algorithm for LTBI testing and treatment recommendation for children at risk of progressing to active TB disease is summarised in **Figure 6**.

Recommendation 24

- In the treatment of children with latent tuberculosis infection (LTBI), the preferred regimens are:
  - 4R for all children >28 days of age or 3HP* for children aged >2 years.
  - 6H for all newborns aged 28 days and below.
- Alternative regimens of LTBI in children are 3HR, 6H or 9H.
- In HIV-infected children with LTBI, 6H is the preferred regimen for:
  - children <2 years of age.
  - children ≥2 years of age# on antiretroviral treatment with rifamycin drug interaction.

3HR=three months daily isoniazid and rifampicin, 3HP=three months weekly isoniazid and rifapentine, 4R=four months daily rifampicin, 6H=six months daily isoniazid

*Rifapentine is not yet available in Malaysia.

#for HIV-infected children ≥2 years old on ART without rifamycin drug interaction, follow the recommendation for HIV-negative children ≥2 years old.

The dosage of recommended LTBI regimen for children is as shown in **Table 14** below.

Table 14: Recommended dosage for LTBI treatment in children

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

*Given in total of 12 doses

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

Source: World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Tuberculosis Preventive Treatment: Module 1: Prevention. Geneva: World Health Organization; 2020

a. Monitoring and follow-up

- The objectives of follow-up during and after LTBI treatment in children are to:
  i. monitor progression to active TB
  ii. identify possible ADR
  iii. monitor and ensure adherence
  iv. adjust treatment dose according to the latest body weight
- In general, clinical monitoring every four to six weeks for the first three months is appropriate, followed by every two to three months thereafter, regardless of regimen used.
- The duration of follow-up is at least two years from initiation of treatment.

Breakthrough TB infection or LTBI treatment failure is still possible while a child is on LTBI treatment. Thus, signs and symptoms of active TB need to be monitored. Weighing and plotting serial weight in an age-gender appropriate growth chart is very important to ensure early detection of active TB.

Frequent dose adjustment for LTBI treatment will be needed for young infants due to relatively rapid weight gain, therefore 2 - 4 weeks follow up is required while for older children, 4 - 6 weeks follow-up would be adequate.

Baseline liver enzyme testing is not required for otherwise healthy children. However, it is warranted for children with malnutrition, pre-existing liver disease, obesity and HIV infection as well as those on potentially hepatotoxic drugs.[45; 93, level III] Children with deranged LFT should be referred to a specialist for initiation of LTBI treatment.

Routine LFT monitoring is not needed in children receiving LTBI treatment. However, laboratory evaluation is warranted for children who develop clinical symptoms of liver injury. Early signs of hepatitis include anorexia, nausea, vomiting and abdominal discomfort. Reduced activities and persistent fatigue/malaise/weakness that last for a few days, dark-coloured urine, pale stools, jaundice, confusion or drowsiness are late signs. Urgent LFT should be done, and if deranged the patient should be referred urgently to a paediatrician with experience in the management of TB.

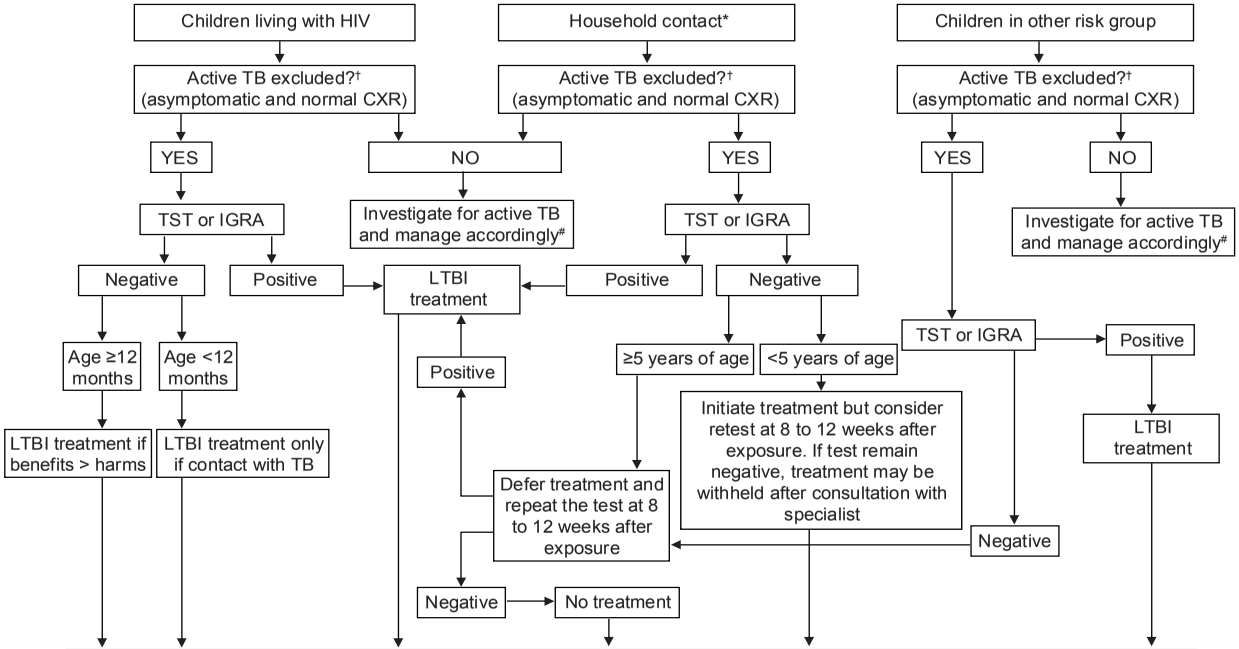
Counselling and support of patients and families on the importance of LTBI treatment will improve treatment acceptance and adherence. The child must complete the course to ensure the effectiveness of treatment. As LTBI treatment is given to a child who is otherwise well

and healthy, development of any unexpected ADR may affect the adherence and parents may default subsequent follow-up. Therefore, it is important to educate the patient and family about potential ADRs. They should understand the need to stop treatment and notify the healthcare provider immediately if signs or symptoms of drug toxicity are suspected. Refer to the **Subchapter 4.1** on **Anti-tuberculosis Adverse Drug Reactions** for the discussion on further management.

All children with TB contact, including those not given LTBI treatment, should be followed-up for two years with recommended interval as summarised in yellow box above. Children should be reinvestigated for active TB, including a CXR, if there is repeated TB exposure or presence of any signs and symptoms of active TB during follow-up. However, if the child has a positive TST or IGRA before, there is no clinical value to repeat the test unless a false positive result is suspected earlier. There is also no role of repeating a TST or IGRA to assess the effectiveness of LTBI treatment.[91, level III]

Children with breakthrough active TB while on LTBI treatment or who develop active TB within the two years of follow-up should be referred to a centre with a paediatrician experienced in managing TB. For all children who develop active TB during or after completing LTBI treatment, it is important to test for drug-resistant TB.

WHO has not defined the treatment outcomes for LTBI. Patients started on LTBI treatment should have their outcome reported. The LTBI treatment outcome proposed by this CPG DG is shown in **Appendix 12**.



¥Important notes: This algorithm should not be used alone for clinical decision. Refer to the text in the chapter for further details and discussions.
*Refer to **Glossary** for definition of "household contact". †Refer to **Subchapter** on **Excluding active TB** and **Subchapter** on **Diagnosis of TB in children**. #If active TB is confirmed, to treat accordingly. If no active TB detected after investigations, follow the pathway as active TB excluded.

Adapted: World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Tuberculosis Preventive Treatment:

Figure 6: LTBI testing and treatment in children at risk of progressing to active TB¥

4. SECTION III: ANTI-TUBERCULOSIS ADVERSE DRUG REACTIONS AND DRUG INTERACTIONS

4.1. Anti-tuberculosis Adverse Drug Reactions

a. Diagnosis

The rate of anti-TB ADR in Malaysia is unknown. Data from the Pharmacovigilance Section, Centre of Compliance and Quality Control National Pharmaceutical Regulatory Agency (NPRA), MoH indicates underreporting of these events, even for severe ADRs. Knowledge about anti-TB ADR rate is important to the national TB control programme, as recommendations on treatment regimen are partly based on adverse effects and treatment completion rates. Although reporting of these events is not mandatory, clinicians and their support staff should proactively report ADRs.

Risk factors for anti-TB ADR depend on the type of ADR. For anti-TB drug-induced liver injury (DILI), risk factors include abnormal baseline ALT, advanced liver disease, liver transplant, hepatitis C infection, advanced age, female gender, slow acetylator status, malnutrition and HIV infection.[13; 101, level III] For INH-induced neuropathy, risk factors include pregnancy, extremes of age, HIV infection, diabetes mellitus, alcoholism, malnutrition and chronic renal failure.[13]

Anti-TB ADRs present in a myriad of ways, with different frequency (common to rare) and severity (mild to severe). Hence, a high index of suspicion is required to make the diagnosis. Children are believed to experience less anti-TB ADR compared with adults.

Identification of the offending drug may be challenging in anti-TB ADR because of the use of combination antibiotic therapy. In such instances, the WHO-Uppsala Monitoring Centre causality assessment system may be used.[102, level III]

The use of skin or laboratory tests for the diagnosis of anti-TB ADRs are still experimental. Studies using skin or laboratory tests were small, isolated and used home-grown tests. Therefore, they cannot be recommended for the diagnosis of anti-TB ADRs.

In patients with suspected severe ADRs, full blood count, renal and liver function tests should be obtained. The presence of eosinophilia supports the diagnosis of drug hypersensitivity syndrome. While the presence of cytopenia, renal or liver impairment help to narrow the list of offending drugs. Additional investigations may be required as dictated by the clinical presentation.

The proper grading of ADR facilitates its management. Although there are many standards for the grading of ADRs the Common Terminology

Criteria for Adverse Events (CTCAE) is preferred because of its detailed description. The general description of an ADR by CTCAE is summarised below. It is worthwhile reiterating that patients who suffer from disabling symptoms despite appropriate treatment should be graded as severe.

CTCAE principle for grading severity of ADR	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to adverse event

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- **Anti-tuberculosis cutaneous adverse drug reactions**

Cutaneous ADRs are among the common ADRs due to anti-TB drugs in clinical practice. Their features are diverse and non-specific. Furthermore, they may occur in isolation or be a part of a drug hypersensitivity reaction.

Anti-TB cutaneous ADR range in severity from mild to severe. Maculopapular rash is a common cutaneous anti-TB ADR. Its severity is graded by the size of the rash, which is expressed as a percentage of the individual's body surface area. The CTCAE grading of maculopapular rash is shown in **Table 15**.

Table 15: Common Terminology Criteria for Adverse Events Severity of Maculopapular Rash Version 5

CTCAE term	Rash maculopapular
Grade 1	Macules/papules covering <10% BSA with or without symptoms (e.g. pruritus, burning, tightness)
Grade 2	Macules/ papules covering 10 -30% BSA with or without symptoms (e.g. pruritus, burning, tightness) limiting instrumental ADL; rash covering >30% BSA with or without mild symptoms
Grade 3	Macules/ papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

*CTCAE severity grade: 1 = mild ADR, 2 = moderate, 3 - 5 = severe
Source: U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017

Severe cutaneous adverse reaction (SCAR) is a term specifically used to describe drug-induced Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms, and Acute Generalised Exanthematous Pustulosis.[103, level III] SCARs are potentially life-threatening and hence patients with suspected SCAR should be referred to dermatologists for co-management.

- **Anti-tuberculosis drug-induced liver injury**

Anti-TB drugs may cause an elevation of ALT either through liver adaptation or liver injury. Liver adaptation to drugs is a benign process that is associated with transient, mild ALT elevation that resolves despite continuation of treatment. DILI, on the other hand, is more sinister and leads to serious complications if treatment is continued. Therefore, anti-TB treatment that contains RIF, INH or PZA must be stopped immediately when DILI is suspected.

Two criteria may be used to diagnose anti-TB DILI:

1. The American Thoracic Society criteria distinguishes between symptomatic and asymptomatic drug-induced hepatitis:[104]
   i. in patients with symptomatic hepatitis, an ALT ≥3 times the upper limit of normal (ULN).
   ii. in patients without any symptoms, an ALT ≥5 times the ULN.
2. The international drug-induced liver injury expert consensus criteria uses any of the following, regardless of symptoms.[105, level III]
   i. an ALT ≥5 times the ULN
   ii. an ALP ≥2 times the ULN
   iii. an ALT ≥3 times and total bilirubin 2 times the ULN

Elevation of liver enzymes are not specific for DILI. In order to diagnose DILI, other causes of abnormal liver function should be ruled out.

- In anti-TB DILI, liver function should be monitored closely, and anti-TB drugs be reintroduced when the liver function becomes normal. Physicians/paediatricians with experience managing TB should be consulted.

- **Drug challenge and de-challenge in anti-TB ADR**

Both drug challenge and de-challenge are used in the diagnosis of ADR. The drug most likely to cause the ADR is the last to be reintroduced and sometimes may be omitted in severe or life threatening ADRs.

i. Drug challenge

Drug challenge is the gold standard for diagnosing anti-TB ADR including drug hypersensitivity reaction.[106, level III] Drug challenge is used when multiple drugs may be responsible for the suspected ADR.

It is done by introducing the drug least likely to cause ADR first or the most important drug first. In severe or life-threatening ADR, drug challenge should be done in a graded manner when the patient has recovered.

The patient undergoing a drug challenge should be carefully monitored. Any ADR occurring during drug challenge should be treated promptly and effectively. Further drug challenge with the same drug should be stopped.

Continue drug challenge on other drugs once the patient recovers. If a drug is tolerated, it is continued even as drug challenge is done on other drugs as shown in **Table 16**.

Table 16: An example of a drug challenge schedule for severe ADR in an adult weighing 60 kg

Day	Drugs in daily dose			
	Rifampicin	Isoniazid	Pyrazinamide	Ethambutol*
1	150 mg	-	-	-
2	300 mg	-	-	-
3	600 mg	-	-	-
4	600 mg	50 mg	-	-
5	600 mg	100 mg	-	-
6	600 mg	300 mg	-	-
7	600 mg	300 mg	250 mg	-
8	600 mg	300 mg	500 mg	-
9	600 mg	300 mg	1500 mg	-
10	600 mg	300 mg	1500 mg	200 mg
11	600 mg	300 mg	1500 mg	400 mg
12	600 mg	300 mg	1500 mg	1200 mg

*EMB challenge may be omitted if the patient tolerated RIF, INH and PZA.

It is not necessary to challenge with all anti-TB drugs in the regimen. Drug challenge may stop once enough drugs are found to be safe to form a new regimen. A negative drug challenge provides assurance that the drug is safe to use.

Recurrence of an ADR during drug challenge identifies the offending drug. However, sometimes more than one drug may cause the same reaction. It is prudent to continue drug challenge with other suspected drugs in cutaneous drug reactions and DILI.

ii. Drug de-challenge

Drug de-challenge is done when one drug is suspected of causing an ADR and it is not safe to perform drug challenge. Examples include suspected RIF-induced-immune thrombocytopenia, -haemolytic anaemia or -acute renal failure.[107, level III]

Drug de-challenge is done by omitting the suspected offending drug from the anti-TB regimen and ruling out other causes. Resolution of the event and absence of alternative causes establishes the diagnosis.

b. Management of adverse drug reactions in active tuberculosis

The management of anti-TB ADR is determined by the:

i. severity of the reaction
ii. severity of the disease

In principle,

- symptomatic management and reassurance should be offered to all patients with ADR.[13]

- for mild to moderate ADR, treat the symptom and continue TB treatment.[13, 31]
- for severe ADR, withhold or switch the anti-TB regimen.[13; 16]

For a patient with severe TB and severe anti-TB ADR, switching to a bridging/interim regimen is preferred until an alternative regimen could be found.[13; 16] The bridging or alternative anti-TB regimen should contain at least three effective drugs in the intensive phase and two in the continuation phase. An example of such a regimen is the streptomycin-EMB-levofloxacin regimen used in EHRZ-associated DILI.

- **Drug desensitisation**

Drug desensitisation may be attempted in cutaneous ADR except for SCARs. A retrospective review of 34 drug desensitisation procedures in HIV-positive adults with anti-TB ADR showed:[108, level II-2]

- a success rate of 78.9%
- no severe ADR from failed desensitisation

The limitation of the study was its retrospective nature, a multiple drug hypersensitivity population and the small number of desensitisation procedures performed.

Recommendation 25

- In rifampicin- or isoniazid-induced cutaneous adverse drug reactions other than severe cutaneous adverse reactions (SCAR), drug desensitisation may be attempted.

Drug desensitisation may be started at 1:100 of the full dose of the offending drug. The dose is then doubled in subsequent doses until full dose is achieved.[109] Two drug desensitisation techniques are used.

- In rapid desensitisation, the drug is given in escalating doses at hourly intervals or less. The daily cumulative dose should not exceed the maximum daily dose for the drug.
- Slow desensitisation is done at a slower rate than rapid desensitisation. It is typically done daily or twice a day. It may also be attempted in patients who have failed rapid desensitisation.

Patients should be monitored closely during drug desensitisation for breakthrough reactions. Symptomatic treatment should be given immediately at the first sign of such a reaction. Further desensitisation for the day should be stopped. The same technique or principle of desensitisation can be applied on children with the help from a clinical pharmacist and after consultation with a paediatrician experienced in management of TB.

For severe cutaneous ADR and other ADR, anti-TB drugs that are tolerated during drug challenge or de-challenge are incorporated into an alternative treatment regimen.

- **Alternative anti-TB regimens**

The standard 2EHRZ/4HR regimen is the most effective regimen for PTB. It has the highest treatment success rate and lowest TB relapse rate compared with other regimens.[14, level I; 110, level I] Hence, alternative anti-TB regimens are only used when standard regimens are contraindicated or poorly tolerated.

Some of the alternative regimens using first-line drugs for the treatment of PTB include:

a. 2EHRZ/6HE[111]
b. 2HRZ/4HR[13]
c. 6RZE[13]
d. 2EHR/7HR[13]

- **New alternative anti-TB regimens**

There was no RCT that substituted rifamycins with other drugs for drug-susceptible TB.

In a meta-analysis of 2265 participants, four-month moxifloxacin-containing anti-TB regimens that replaced EMB or INH had higher relapse rate compared with standard regimen (RR 3.56, 95% CI 2.37 to 5.37).[14, level I]

New anti-TB regimens that do not include RIF or INH are mainly used in drug-resistant TB treatment. For patients who have absolute contraindication to INH or RIF, an INH- or RIF-resistant regimen may be used.[13] These patients should be referred to specialists for management.

c. Management of adverse drug reactions during latent tuberculosis infection

ADRs during LTBI treatment are rare but important events. Higher rates occur with combination therapy and longer regimens.[112, level I]

The principles of management for ADR are similar in both LTBI and active TB. Reassurance, symptomatic treatment, desensitisation and alternative regimens may be used when appropriate.

Individuals who develop severe ADR to 3HP or 3HR may switch to 4R or 6H once the patients recover.

4.2. Drug-Drug Interactions

Anti-TB drugs, particularly rifamycins and isoniazid, interact with many commonly prescribed drugs. These drug-drug interactions may lead to adverse events because of/resulting from the reduction in efficacy or the increase in toxicity of the affected drug. Popular drug interaction databases, such as Micromedex and Lexicomp provide searchable

information on drug-drug interactions. These databases are often used to advise clinicians on potential drug-drug interaction.

However, these databases differ in the way they classify and grade the seriousness of DDI, report the strength of evidence, and make their recommendation due to the lack of standards/guidelines for DDI reporting.[113, level III]

In general, the quality of evidence guiding DDI databases vary from low to high quality.[113, level III] The actual percentage of patients with potential DDI that manifested drug interactions was shown to be less than 10% in a recent systematic review.[114., level III]

It is advisable to check with several databases (to look for consistency) if there is uncertainty about potential drug-drug interactions. Potential DDIs are even more complicated in real life because patients may be on more than one drug that interacts with another.

a. Anti-tuberculosis drug interactions

Anti-tuberculous rifamycins (RIF, RFB and RPT) are key drugs in active and latent TB treatment. Rifamycins are enzyme inducers of a variety of metabolic pathways and hence they interact with many commonly used drugs. Rifamycins vary in their enzyme inducing potency with RIF being the strongest, and weekly RPT the weakest.[13] Clinicians managing TB must be familiar with rifamycin-drug interaction, particularly with new drugs. Refer to **Appendix 13** on **Drugs with Potential Interactions Involving Rifamycin** for the description and management of rifamycin drug interaction.

In contrast with the rifamycins, INH inhibits drug metabolism. It increases the toxicity of antiepileptic drugs (carbamazepine, phenytoin), and certain benzodiazepines (diazepam). Combining RIF with INH leads to a net drug metabolizing effect due to the stronger enzyme inducing effect of RIF.[13] Refer to **Appendix 14** on **Drugs with Potential Interactions Involving Isoniazid** for the description and management of INH drug interaction.

b. Antiretroviral and anti-tuberculosis drug interactions

Rifamycins affect the ARV classes differentially and may compromise the effectiveness of ART. But because of the importance of rifamycins in TB treatment, they are only replaced if there is an absolute contraindication. No clinically significant interactions are expected between ARVs with INH, EMB or PZA.

- **Nucleoside/nucleotide reverse transcriptase inhibitors**

There are no clinically significant interactions between NRTIs with either RIF or RFB.[8] However, there is limited evidence on the safety

of tenofovir alafenamide when used in combination with rifampicin and hence they should be used with caution. Tenofovir alafenamide should not be combined with rifabutin and rifapentine until more evidence is available.

- **Non-nucleoside reverse transcriptase inhibitors**

i. Efavirenz (EFV) and Nevirapine (NVP)

Two meta-analyses comparing EFV (600 mg daily) and NVP (200 mg twice daily) in patients on RIF-based anti-TB treatment showed no significant difference in mortality.[115 - 116, level I]

In the first meta-analysis, there was also no significant difference in virological success, progression to AIDS and discontinuation rate.[115, level I]

In the second meta-analysis, there was no significant difference in TB treatment outcomes. However, the EFV group was superior to NVP with:[116, level I]

- better virological response in terms of plasma viral load <400 copies/ml at the end of follow-up (RR=1.10, 95% CI 1.03 to 1.17) but not for plasma viral load <50 copies/ml.
- lower risk of ART discontinuation due to adverse events (RR=0.43, 95% CI 0.23 to 0.81).

The primary papers used in these meta-analyses were of mixed quality.

Recommendation 26

- Efavirenz is the preferred non-nucleoside reverse transcriptase inhibitor when combined with rifampicin-based anti-tuberculosis regimen.

- **Protease inhibitors**

RIF-based anti-TB regimen should not be used with PI-based ART.[8; 31] RFB 150 mg once daily is preferred in PLHIV on a PI-based ART.[31]

Recommendation 27

- For HIV-tuberculosis co-infected patients on a protease inhibitor-based antiretroviral therapy, rifabutin should be used instead of rifampicin.

- **Integrase strand transfer inhibitors**

i. Raltegravir

A recent large RCT on HIV-TB co-infected adults who were receiving RIF-based anti-TB treatment failed to show non-inferiority of raltegravir (RAL) 400 mg twice daily compared with EFV 600 mg once daily.[117, level I]

The recommended dose of RAL when co-administered with RIF is 800 mg twice daily.[118]

ii. Dolutegravir

A network meta-analysis of nine very low to moderate quality studies showed better outcomes for DTG relative to EFV in HIV-TB co-infected patients on RIF-based anti-TB treatment, in terms of:[119, level I]

- viral suppression at 4 weeks (OR=6.52, 95% CrI 2.44 to 17.40) and at 12 weeks (OR=2.98, 95% CrI 1.27 to 6.99).
- increase in CD4 cell count at 24 weeks (mean change=53.25, 95% CrI 15.06 to 89.30).

In the same network meta-analysis, DTG was comparable to EFV, NVP and RAL in terms of tolerability. DTG was also safer than EFV in treatment-emergent ADR (OR=0.29, 95% CrI 0.08 to 0.89). In terms of neuropsychiatric ADRs, the two drugs were comparable.[119, level I]

In an RCT with 113 participants, TB-associated IRIS was uncommon in both DTG and EFV groups, with no discontinuation of treatment due to it. DTG trough concentrations were similar between 50 mg twice daily (with anti-TB) and 50 mg once daily (without anti-TB).[120, level I]

In patients receiving INSTI-based ART, rifabutin-based anti-TB treatment may be used without adjusting INSTI dose.[118]

Recommendation 28

- In patients on rifampicin-based anti-tuberculosis treatment:
  - the dose of raltegravir should be increased to 800 mg twice daily.
  - the dose of dolutegravir should be increased to 50 mg twice daily.
- Alternatively, rifampicin may be substituted with rifabutin without increasing the dose of the integrase strand transfer inhibitors.

Refer to **Appendix 15** which summarises important DDI between ART and rifamycins.

5. IMPLEMENTING THE GUIDELINES

The management of TB should be guided by an evidence-based approach, in order to provide quality care to the TB patients. Several factors may affect the implementation of recommendations in the CPG.

5.1. Facilitating and Limiting Factors

Existing facilitating factors for application of the recommendations in the CPG include:

- the regular TB training activities conducted at state level
- an MoH CPG web site that is well known and easily accessible
- the widely available basic microscopic tests and radiology services for TB
- the availability of Xpert Ultra in almost all states and even some health clinics in Malaysia

Existing barriers for application of the recommendations of the CPG are:

- the inadequacy in frequency, breadth and depth of the current TB training programme, particularly on TB in children
- the lack of awareness and knowledge on LTBI among the healthcare providers and the public
- the lack of healthcare facilities and human resources in remote or high TB burden areas for TB control and management
- the unavailability of rifapentine at present in Malaysia

5.2. Potential Resource Implications

The recommendations in this CPG may require additional resources in terms of budget, healthcare infrastructures and human resources for their successful implementation as discussed below.

Although Xpert Ultra and radiological services for diagnosis of TB are available throughout the country, they are concentrated in hospitals and major health clinics. Other more specialised laboratory test like the ADA test is currently available only in the Sabah Public Health Laboratory. In order to diagnose TB early and prevent TB transmission, these diagnostic tests need to be expanded to more healthcare centres.

In terms of accuracy for the diagnosis of LTBI, IGRA is more specific than TST. However, it is not widely available, and testing can only be done by appointment. This is because the test is costly and the specimens need to be sent to reference laboratories for testing. At present, IGRA is recommended for testing only once in adult contacts of TB due to financial constraints.

Several drug formulations which are not currently in the national formulary need to be procured. These include child-friendly FDCs for the treatment of active TB; syrup INH (in health clinics) and RPT for LTBI treatment. These formulations are vital in ensuring treatment adherence.

The nationwide expansion of the programmatic management of LTBI since 2020 needs a strong surveillance system. Creation of dedicated TB teams for health clinics in high TB burden areas and the development of a web-based LTBI surveillance should be considered to facilitate the smooth running of the programme.

Online training modules on active TB and LTBI treatment need to be developed. The availability of such modules will rapidly increase the number of health care providers trained and improve the outreach of the training programme. This will enhance health care provider knowledge and skills in TB management.

Policy/decision makers should take the above issues into consideration when planning, implementing, monitoring and reviewing TB control activities.

5.3. Clinical Audit Indicators

Several MoH key performance indexes on TB management may serve as clinical audit indicators for the CPG. These clinical audit indicators are:

$$\text{TB treatment success rate} = \frac{\text{Number of successfully treated TB cases in a year}}{\text{Number of registered TB cases (all forms) in the same year}} \times 100\%$$

Target TB treatment success rate ≥ 90%

$$\text{TB mortality rate} = \frac{\text{Number of TB deaths in a year}}{\text{Estimated mid-year population in the same year}} \times 100{,}000$$

Target TB mortality rate ≤5 in 100,000 population

$$\text{LTBI treatment coverage for each of the three priority groups*} = \frac{\text{Number of people in each priority groups enrolled on LTBI treatment in a year}}{\text{Number of people in each priority groups eligible for LTBI treatment in the same year}} \times 100\%$$

Target LTBI treatment coverage for priority groups ≥ 90%

*1. People newly enrolled in HIV care; 2. Children aged <5 years who are household contacts of people with bacteriologically confirmed PTB; 3. People aged ≥5 years who are household contacts of people with bacteriologically confirmed PTB

Implementation strategies for the CPG, including the launching of the CPG; Quick Reference and Training Module, will be developed following the approval of the CPG by the MoH.

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APPENDIX 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: Are fixed-dose anti-TB combinations safer and more effective than separate drug formulations in:

- PTB

1. TUBERCULOSIS, PULMONARY/ (73851)
2. pulmonary tuberculos*.tw. (32391)
3. ptb.tw. (5261)
4. 1 or 2 or 3 (83602)
5. ANTITUBERCULAR AGENTS/ (35943)
6. ((antitubercular or tuberculostatic) adj1 (drug* or agent*)).tw. (2236)
7. Anti tb.tw. (3359)
8. Antitb.tw. (33)
9. 5 or 6 or 7 or 8 (38274)
10. DRUG COMBINATIONS/ (71218)
11. (drug adj1 combination*).tw. (13525)
12. fdc.tw. (2544)
13. Fixed-dose combination*.tw. (3226)
14. 10 or 11 or 12 or 13 (86654)
15. Single drug formulation*.tw. (28)
16. Separate drug*.tw. (186)
17. Sdf.tw. (6414)
18. separate drug regim*.tw. (1)
19. standard drug treatment*.tw. (87)
20. 15 or 16 or 17 or 18 or 19 (6714)
21. 14 and 20 (80)
22. 4 and 9 and 21 (10)
23. limit 22 to (english language and yr=”2012 -Current”) (5)

APPENDIX 2

CLINICAL QUESTIONS

Diagnosis

5.1 How accurate are the following diagnostic tools for the diagnosis of PTB?
- Xpert MTB/RIF, Xpert Ultra
- CXR vs Xpert MTB/RIF, Xpert Ultra in smear negative PTB
- LF-LAM
- TB LAMP

5.2 How accurate are the following diagnostic tools for the diagnosis of EPTB?
- Xpert MTB/RIF, Xpert Ultra
- LF-LAM
- ADA vs Xpert MTB/RIF for pleural TB
- CNS Imaging

5.3 What is the most accurate TST cut-off value for predicting progression from latent to active TB?

5.4 Is IGRA more accurate than TST in predicting progression of latent to active TB?

Treatment

5.5 Are there safer and more effective alternative anti-TB regimens than the current standard regimen in:
- PTB
- EPTB (TB meningitis/TB LN/pleural TB/TB spine)
- LTBI (adult & children/HIV adults & children)

5.6 Are fixed-dose anti-TB combinations safer and more effective than separate drug formulations in: (Standard dose vs higher dose)
- PTB
- EPTB

5.7 Is intermittent anti-TB dosing safer and more effective than daily dosing in PTB?

5.8 What is the most effective and safe corticosteroids dosing regimen in EPTB?

5.9 Is early initiation of ART safer and more effective than late initiation of ART in HIV and TB co-infection?

5.10 What are the safe and effective ARTs in HIV and TB co-infection?

5.11 What are the effective interventions to promote adherence to TB treatment?
- DOTs/modified DOTs vs SAT

5.12 How accurate are diagnostic tests compared with drug re-challenge in diagnosing anti-TB ADR?

5.13 Which alternative anti-TB regimens are safe and effective in patients with ADR to isoniazid and/or rifampicin?

APPENDIX 3

PROCEDURE FOR SPUTUM INDUCTION FOR CHILDREN AND ADULTS

1. Patients should rinse their mouth and gargle with boiled water.
2. Fill the nebuliser with 3% saline (5 ml for children, 20 - 30 ml for adults). Use an ultrasonic nebuliser if available.
3. Patients should sit upright. Apply the nebuliser mask or mouthpiece with a nose clip before turning on the nebuliser.
4. Inhale and exhale through the nebuliser mask or mouthpiece.
5. Gentle chest physiotherapy may be carried out during the procedure.
6. The procedure should be stopped when:
   - the patient has produced 1 - 2 ml of sputum for each test,
   - 15 minutes of nebulisation is reached, or
   - the patient develops dyspnoea, chest tightness or wheeze
7. Transport the specimen in a cool box to the laboratory for processing within 4 hours.
8. If the specimens need to be kept >4 hours, place them in a refrigerator at 4 - 8 °C until time for transportation.
9. The specimen should be labelled as “induced-sputum”.

The procedure should be done cautiously in patients with asthma or poor lung function (FEV1 <1 L) as sputum induction may induce bronchospasm. Patients with asthma should be premedicated with inhaled salbutamol to prevent asthma exacerbation.
Drugs and equipment for resuscitation should be available onsite.

Adapted: Ministry of Health, Malaysia. Management of Tuberculosis (Third Edition). Putrajaya MoH; 2012.

APPENDIX 4

SPECIMEN COLLECTION FOR DIAGNOSIS OF TUBERCULOSIS

Type of TB	Quantity and type of specimen	Recommended TB tests
PTB	• 3 - 5 ml of sputum	• AFB smear • Mycobacterial culture (MGIT for suspected drug-resistant TB and recurrent TB) • Xpert Ultra (when indicated) • GenoType MTBDRplus Line Probe Assay (when indicated)
Tuberculous meningitis	• 1 - 5 ml CSF; • tuberculoma tissue biopsy	• Xpert Ultra • Mycobacterial culture • AFB smear (if Xpert Ultra is not available)
Pleural TB	• 2 - 5 ml pleural fluid; • pleural tissue biopsy	• Mycobacterial culture • Xpert Ultra • ADA • HPE
Lymph node TB	• fine-needle aspirate; • lymph node biopsy specimen; • excised lymph node	• Mycobacterial culture • Xpert Ultra • HPE
Bone or joint TB	• 1 - 2 ml of joint fluid or periarticular pus; • periarticular tissue biopsy; • 3 - 5 ml of bone marrow aspirate	• Xpert Ultra (joint fluid or tissue biopsy only) • Mycobacterial culture in MycoF blood culture bottle • HPE
Genitourinary TB	• 50 ml of urine; • tissue biopsy of affected organs	• Xpert Ultra • Mycobacterial culture • AFB smear • HPE
Pericardial TB	• 1 - 2 ml of pericardial fluid; • pericardial tissue biopsy	• Xpert Ultra • Mycobacterial culture • AFB smear • HPE
Peritoneal TB	• 1 - 2 ml ascitic fluid; • peritoneal tissue biopsy	• Xpert Ultra • Mycobacterial culture • AFB smear • HPE
Disseminated (miliary) TB	• 5 ml of blood in plain tube for PCR; • 5 ml of blood in MycoF blood culture bottle	• TB PCR • Mycobacterial culture • AFB smear

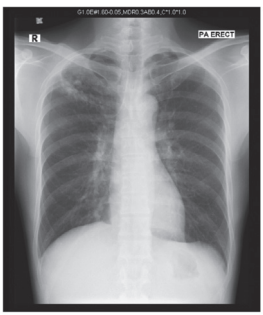
Further information can be obtained from Makmal Kesihatan Awam Kebangsaan website at: http://mkak.moh.gov.my/ms/

Adapted from:

1. Ministry of Health, Malaysia. The National Public Health Laboratory Test Handbook 2018: 1st Edition. Sg Buloh: National Public Health Laboratory; 2018.
2. Kohli M, Schiller I, Dendukuri N, et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults. The Cochrane database of systematic reviews. 2021;1(1):CD012768.

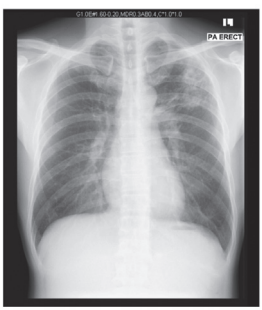
APPENDIX 5

GRADING OF PULMONARY TUBERCULOSIS SEVERITY BASED ON CHEST RADIOGRAPH IN ADULTS



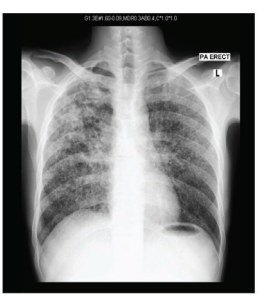
Minimal

- Minimal lesions without demonstrable cavitations and confined to a small part of one or both lungs. The total extent of the lesions should not exceed the volume of the lung on one side which lies above the second chondrosternal junction and the spine of the fourth or the body of the fifth thoracic vertebrae.



Moderately Advanced

- One or both lungs may be involved but the total extent of the lesions should not exceed the following limits:
  i. disseminated lesions of minimal to moderate density not exceeding the total volume of one lung or the equivalent in both lungs
  ii. dense and confluence lesions not exceeding one third of the volume of one lung
  iii. total diameter of cavitations, if present, must be <4 cm.



Far Advanced

- Lesions are more extensive than moderately advanced

Adapted:

1. Ministry of Health, Malaysia. Management of Tuberculosis (Third Edition). Putrajaya MoH; 2012.
2. Ministry of Health, Malaysia. Practice Guidelines for the Control and Management of Tuberculosis (Second Edition). MoH; 2002.

FIRST-LINE ANTI-TUBERCULOSIS DRUG DOSAGE AND ADVERSE DRUG REACTIONS

Drug	Adults			Children*			Common adverse drug reactions
	Dose range (mg/kg/day)	Maximum dose (mg/day)	Dose in renal impairment: CrCl <30 ml/min or HD	Dose range (mg/kg/day)	Maximum dose (mg/day)	Dose in renal impairment	
Isoniazid	5 (4 - 6)	300	No dose adjustment required	10 (7 - 15)	300 (200 mg/day if CrCl < 10ml/min/ CAPD/HD/ HDF/High Flux)	*No dose adjustment required*	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, burning/numbness/ tingling sensation in hands or feet
Rifampicin	10 (8 - 12)	600	No dose adjustment required	15 (10 - 20)	600	*No dose adjustment needed till CrCl <10 ml/min* CrCl <10 ml/min/CAPD/HD/HDF/High Flux: 50 - 100% of normal dose CAV/VVHD: Unknown drug dialysability Dose as in normal renal function	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, orange/red urine, flu syndrome (fever, chills, malaise, headache, bone pain)
Ethambutol	15 (15 - 20)	1600	20 - 25 mg/kg/dose 3 times/week	20 (15 - 25)	1000	CrCl 10 - 20 ml/min/CAV/VVUD: 50% of normal dose CrCl <10 ml/min/CAPD/HD/HDF/High Flux: 25% of normal dose. Give 4-6 hours before dialysis.	Visual impairment

Pyrazinamide	25 (20 - 30)	2000	25 - 35 mg/kg/dose 3 times/week	35 (30 - 40)	2000	CrCl <10 ml/min: 50 - 100% of normal dose CAPD: Drug not dialysed Dose as for CrCl < 10 ml/min HD: 50 - 100% dialysed Dose as for CrCl <10 ml/min or 25 - 30 mg/kg post dialysis HDF/High Flux: Drug dialysed Dose as for CrCl <10 ml/min or 25 - 30 mg/kg post dialysis CAV/VVHD: Unknown drug dialysability Dose as in normal renal function	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, joint pain

CrCl=creatinine clearance, HD=haemodialysis, CAPD=continuous ambulatory peritoneal dialysis, HDF=haemodiafiltration, High Flux=high-flux haemodialysis, CAV/VVHD= CAVHD(continuous arteriovenous haemodialysis)/CVVHD(continuous veno-venous haemodialysis)
*For paediatric patients, anti-TB dose should be calculated based on measured body weight except in obese patients where ideal body weight should be used.

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APPENDIX 7

TUBERCULOSIS TREATMENT OUTCOME DEFINITION

Outcome	Definition
Cured	A PTB patient with bacteriologically confirmed TB at the beginning of treatment who is smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Completed treatment	A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion are negative, either because tests are not done or because results are unavailable.
Treatment success	The sum of cured and treatment completed.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Loss to follow-up	A TB patient who does not start treatment or whose treatment is interrupted for two consecutive months or more.
Transferred out	A patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes case “transferred out” to another treatment unit as well as case for whom the treatment outcome is unknown to the reporting unit.

Source:

1. Ministry of Health, Malaysia. Management of Tuberculosis (Third Edition). Putrajaya, MoH; 2012.
2. World Health Organization. Definitions and reporting framework for tuberculosis - 2013 revision (Updated December 2014 and January 2020). Geneva: WHO; 2020.

APPENDIX 8

CHEST RADIOGRAPH CHANGES FOR TUBERCULOSIS IN CHILDREN

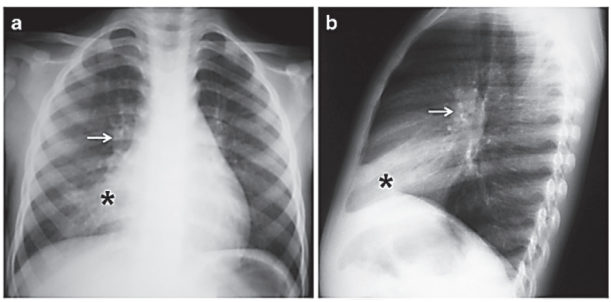


Fig. 1: Chest radiographs in a 5-year-old girl with primary tuberculous disease. Anteroposterior (a) and lateral (b) views show a middle lobe opacity (*) with right hilar lymphadenopathy (→).

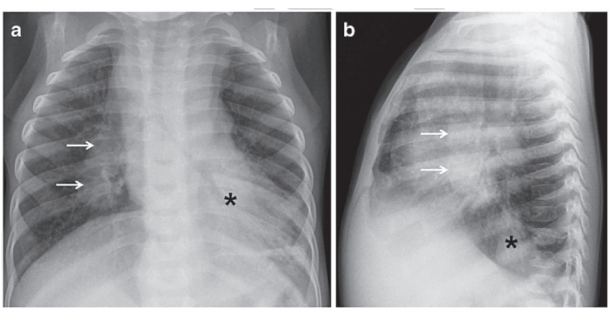


Fig. 2: Chest radiographs in a 1-year-old boy with primary tuberculous disease and lymphadenopathy. Anteroposterior (a) and lateral (b) views show hilar lymphadenopathy (→) on the right without ipsilateral lung abnormality. A left retrocardiac opacity (*) is noted.

Source: Concepcion NDP, Laya BF, Andronikou S, et al. Standardized radiographic interpretation of thoracic tuberculosis in children. Pediatr Radiol. 2017;47(10):1237-1248

APPENDIX 9

PROCEDURE FOR GASTRIC ASPIRATION AND NASOPHARYNGEAL ASPIRATION IN CHILDREN

Gastric Aspiration (Lavage)

Gastric aspiration should be performed on three consecutive mornings for each patient. The child must be fasted for at least four hours (three hours for infants) prior to the procedure. A child with a low platelet count or bleeding tendency should not undergo the procedure.

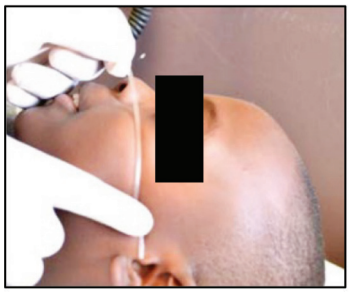
Gastric aspiration is generally not an aerosol-generating procedure, and can safely be performed at the child's bedside or in a routine procedure room.

1. Prepare the child and required equipment for nasogastric tube insertion.
2. Attach a syringe to the nasogastric tube.
3. Aspirate 2 - 5 ml of gastric contents.
4. If no fluid is aspirated, instil 5 - 10 ml sterile water or normal saline and repeat aspiration.
5. Transfer the gastric aspirate from the syringe into a sterile sputum container.

Nasopharyngeal Aspiration

1. Fasting is not necessary prior to nasopharyngeal aspiration.
2. Position the child on his/her back or side. Restrain the child by wrapping him/her in a piece of cloth.
3. Prepare the suction machine and mucous extractor (**Picture 1**).
4. Suction pressure used:
   - <12 months old: 80 - 100 mmHg/10 - 13 kPa
   - 1 - 5 years old: 100 - 120 mmHg/13 - 16 kPa
5. Measure the length of the suction tube by placing the end of the tube at the external opening of the ear and extend it to the tip of the nose (**Picture 2**). Mark the length on the tube.
6. Instil two drops of sterile saline into each of the child's nostrils.
7. Without applying suction, insert the tube through the nostril until the marked length is reached. (similar to performing a nasal suction)
8. Apply suction.
9. Using a rotating movement, collect respiratory secretion by slowly pulling out the tube. Do not push in the tube forward when aspirating
10. Collection should be >1 ml.

Picture 1: Mucus extractor



Picture 2: Measuring correct length of suction tube

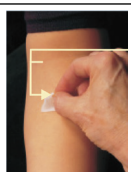
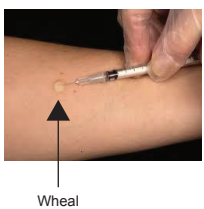
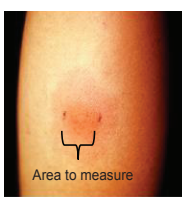
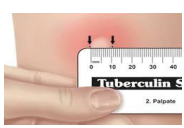
Adapted:

1. Ministry of Health, Malaysia. Management of Tuberculosis (Third Edition). Putrajaya MoH; 2012
2. Universite de Bordeaux. TB Speed Nasopharyngeal Aspirate (NPA) Collection. (Available at: http://www.tb-speed.com/wp-content/uploads/2020/09/TB-Speed_SOP_NPA.pdf)

APPENDIX 10

PROCEDURE FOR TUBERCULIN SKIN TEST

As with other medical procedures, TST should be explained to the patient and consent obtained verbally. Ensure that the correct patient information is written or printed in the form. Follow the steps below when performing the TST.

• Clean the area 2 - 4 inches below the elbow joint on the ventral aspect of the forearm for injection.	
• Make sure the area is free from scars or any infection. • Check the expiry date on the vial. • Use a 1 cc syringe to draw 2 tuberculin units of Purified Protein Derivative Statens Serum Institute RT23 in 0.1 ml solution. • Inject intradermally at 5° to 15° to the skin with the bevel pointing upwards. • A firm pale wheal about 6 - 10 mm in diameter usually appears. If it does not, then repeat the test at least two inches away from the original site.	
• The skin test should be read 48 - 72 hours after injection. • Feel the edges of the induration (hard, dense, raised area) and measure the longest diameter of the induration perpendicular to the long axis of the forearm. • The erythema surrounding the induration should not be measured. • Reading should be recorded in millimetres. • If there is no induration, record as 0 mm. • The interpretation and cut-off values for different populations is discussed in **Subchapter 3.1** on **LTBI in Adults**.	 

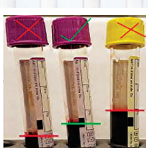
Adapted: Centre for Disease Control and Prevention. Mantoux Tuberculin SkinTesting Products. (Available at: https://www.cdc.gov/tb/education/mantoux/pdf/Mantoux_TB_Skin_Test.pdf)

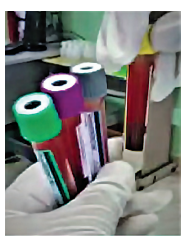
APPENDIX 11

QUANTIFERON SPECIMEN COLLECTION AND HANDLING

As with other medical procedures, explain to the patient and obtain verbal consent before drawing blood for a Quantiferon test. Ensure that the correct patient information is written or printed in the labels and form. Follow the steps below when drawing blood for a Quantiferon test.

<table>
<tr><td colspan="2">Collect 1 ml of whole blood into each four QFT-Plus blood collection tubes.
• The grey cap tube (Nil) serves as the negative control and adjust for background levels of IFN-γ.
• The green cap tube (TB1) and yellow cap tube (TB2) assess the interferon gamma (IFN-γ) response to TB-specific antigens.
• The purple cap tube (Mitogen) serves as a positive control, which can be useful to indicate the immune status of the person being tested and that correct blood handling has occurred.</td><td>  </td></tr>
<tr><td colspan="3">There are two options for collecting the sample</td></tr>
<tr><td>Option 1</td><td></td><td>Option 2</td></tr>
<tr><td>Blood collection
• Fill the Lithium heparin tube with >5 ml of the patient's blood.
• Gently mix the specimen by inverting the tube several times to dissolve the heparin. Label the tube appropriately including the time of blood collection.

Transport to laboratory
• Transport tube to laboratory at 22°C ± 5°C.
• Incubation of blood in QFT-Plus tubes must be initiated at the laboratory within 16 hours of blood collection.</td><td>  </td><td>Draw blood directly into QFT®-Plus blood collection tubes.</td></tr>
<tr><td>Transfer blood to QFT-Plus tubes in the laboratory.
• Gently invert the lithium heparin tube again at the laboratory.
• Transfer 1 ml into each four QFT-Plus tubes (to the centre of the black mark on the side of the QFT-Plus tube label). Replace the tube caps securely and mix as per QFT-Plus.</td><td> 
  </td><td>Blood collection
• Label QFT-Plus blood collection tubes appropriately. Tubes should be kept at room temperature (17 - 25°C).
• Collect 1 ml into each four QFT-Plus tubes (to the centre of the black mark on the side of the QFT-Plus tube label).</td></tr>
</table>

	Blood should be filled to the centre of black mark (indicated in green). **Shake 10x**  Invert the bottles 10 times to coat bottle like below to dissolve antigen on tube walls 	Replace the tube caps securely and mix as per QFT-Plus once the tube appears to have completed filling. • The black mark on the side of the tubes indicates the validated range of 0.8 to 1.2 ml. • New sample needs to be taken if blood level is outside the indicator mark. Tube handling • Immediately after filling the tubes, invert them 10 times just firmly enough to make sure the entire inner surface of the tube is coated with blood. This will dissolve antigens on tube walls. Important: Overly vigorous shaking may cause gel disruption and could lead to aberrant results. Transport and incubation • QFT-Plus tubes must be transferred to a 37°C ± 1°C incubator within 16 hours of collection (labelled as incubated). OR • Transport tubes to the testing laboratory at 22°C ± 5°C. Then proceed with incubation (labelled as not incubated).

Source: QuantiFERON-TB Gold Plus (QFT-Plus) ELISA Package Insert. (Available at: http://www.quantiferon.com/wp-content/uploads/2017/04/English_QFTPlus_ELISA_R04_022016.pdf)

APPENDIX 12

PROPOSED LATENT TB INFECTION TREATMENT OUTCOME DEFINITION

Outcome	Definition
Completed treatment	An LTBI patient who has completed treatment.
Died	An LTBI patient who dies for any reason during the course of treatment.
Treatment failed	An LTBI patient who has developed active TB during treatment or within 18 months post-treatment.
Loss to follow-up	An LTBI patient whose treatment is interrupted for ≥1 months.
Transferred out	A patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.
Treatment discontinued	An LTBI patient whose LTBI treatment is stopped prematurely.
Not evaluated	An LTBI patient for whom no treatment outcome is assigned. This includes a case “transferred out” to another treatment unit as well as a case for whom the treatment outcome is unknown to the reporting unit.

DRUGS WITH POTENTIAL INTERACTIONS INVOLVING RIFAMYCINS

Category of drugs	Type of drugs	Interactions	Suggestions
Anti-infectives	Clarithromycin	Rifamycins ↓ Clarithromycin, Clarithromycin ↑ Rifamycins	Clinical relevance uncertain
	Moxifloxacin	RIF ↓ Moxifloxacin	Clinical relevance uncertain
	Doxycycline	RIF, RPT ↓ Doxycycline	Clinical relevance uncertain
	Fluconazole	RIF, RPT ↓ Fluconazole, Fluconazole ↑ RFB	Be careful when combining drugs
	Itraconazole	Rifamycins ↓ Itraconazole, Itraconazole ↑ RFB	Avoid combination
	Voriconazole	Rifamycins ↓ Voriconazole, Voriconazole ↑ RFB	RIF, RFB: Avoid combination RPT: Be careful when combining drugs
	Caspofungin	RIF ↓ Caspofungin	Be careful when combining drugs
Antimycobacterials/ antiprotozoals	Dapsone	Rifamycins ↓ Dapsone	Be careful when combining drugs
Antimalarials	Artemether/ Lumefantrine	Rifamycins ↓ Artemether/ Lumefantrine	RIF, RPT: Avoid combination
Hepatitis C direct-acting antivirals	Daclatasvir, Sofosbuvir Glecaprevir/ Pibrentasvir, Sofosbuvir/ Ledipasvir, Sofosbuvir/ Velpatasvir	Rifamycins ↓ hepatitis C direct-acting antivirals	Avoid combination

Category of drugs	Type of drugs	Interactions	Suggestions
Immunosuppressive agents	Mycophenolate mofetil, Mycophenolate sodium	RIF ↓ Mycophenolate mofetil, Mycophenolate sodium	Avoid combination
	Dexamethasone, Fludrocortisone, Hydrocortisone, Methylprednisolone, Prednisolone, Triamcinolone	Rifamycins ↓ Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone RIF ↓ Fludrocortisone, Triamcinolone	Be careful when combining drugs
	Cyclosporine, Everolimus, Sirolimus, Tacrolimus	Rifamycins ↓ Cyclosporine, Everolimus, Sirolimus, Tacrolimus	Be careful when combining drugs
Hormone therapy	**Estrogens** Ethinyl estradiol, Estradiol, Estriol	Rifamycins ↓ estrogens	Be careful when combining drugs Alternative forms of contraception should be used during and for four weeks after completion of rifamycin therapy
	Progestogens Cyproterone, Desogestrel, Dienogest, Drospirenone, Dydrogesterone, Ethisterone, Etonogestrel, Gestodene,	Rifamycins ↓ progestogens	Be careful when combining drugs Alternative forms of contraception should be used during and for four weeks after completion of rifamycin therapy

Category of drugs	Type of drugs	Interactions	Suggestions
	Hydroxyprogesterone, Levonorgestrel, Medroxyprogesterone, Megestrol, Norelgestromin, Norethisterone, Norgestrel, Progesterone		
	Enzalutamide	Rifamycins ↓ Enzalutamide	Be careful when combining drugs
	Levothyroxine	RIF ↓ Levothyroxine	Be careful when combining drugs
	Tamoxifen	Rifamycins ↓ Tamoxifen	RIF: Avoid combination RFB, RPT: Be careful when combining drugs
Anticonvulsants	Carbamazepine, Lamotrigine, Phenytoin, Valproic acid	Rifamycins ↓ anticonvulsants	Be careful when combining drugs
Antidepressants	Mirtazapine	Rifamycins ↓ Mirtazapine	Be careful when combining drugs
Antipsychotics	Haloperidol, Quetiapine, Risperidone	Rifamycins ↓ antipsychotics	Be careful when combining drugs
Barbiturates	Phenobarbitone	RPT ↓ Phenobarbitone	Be careful when combining drugs
Benzodiazepines	Diazepam, Midazolam, Triazolam, Zolpidem	Rifamycins ↓ benzodiazepines	Be careful when combining drugs
Opioid agonists	Alfentanil, Codeine, Fentanyl, Morphine, Oxycodone,	Rifamycins ↓ Alfentanil, Codeine, Fentanyl, Oxycodone RIF ↓ Morphine	Be careful when combining drugs

Category of drugs	Type of drugs	Interactions	Suggestions
	Methadone	Rifamycins ↓ Methadone	Be careful when combining drugs
Oral anticoagulants	Warfarin	Rifamycins ↓ Warfarin	Be careful when combining drugs
	Direct oral anticoagulants Apixaban, Dabigatran, Edoxaban, Rivaroxaban	RIF ↓ direct oral anticoagulants	Avoid combination
Antiplatelet agents	Clopidogrel Ticagrelor	RIF ↑ Clopidogrel Rifamycins ↓ Ticagrelor	Be careful when combining drugs RIF: Avoid combination RFB, RPT: Be careful when combining drugs
Cardiovascular agents	**Calcium channel blockers** Verapamil, Diltiazem, Amlodipine, Felodipine, Nifedipine	Rifamycins ↓ calcium channel blockers	Be careful when combining drugs
	Beta-blockers Bisoprolol, Carvedilol, Metoprolol, Propranolol	RIF ↓ beta-blockers	Be careful when combining drugs
	Enalapril	RIF ↓ Enalapril	Be careful when combining drugs
	Losartan	RIF ↓ Losartan	Be careful when combining drugs

Category of drugs	Type of drugs	Interactions	Suggestions
	Digoxin	RIF ↓ Digoxin	Be careful when combining drugs
	Ivabradine, Ranolazine	Rifamycins ↓ Ivabradine, Ranolazine	Avoid combination
	Propafenone	Rifamycins ↓ Propafenone	Be careful when combining drugs
Antihyperlipidemics	Atorvastatin, Simvastatin	RIF ↓ Atorvastatin, Simvastatin	Be careful when combining drugs
Methylxanthines	Aminophylline, Theophylline	RIF ↓ Aminophylline, Theophylline	Be careful when combining drugs
Antiemetics	Aprepitant	Rifamycins ↓ Aprepitant	RIF: Avoid combination RFB, RPT: Be careful when combining drugs
Proton pump inhibitors	Esomeprazole, Omeprazole	RIF ↓ Esomeprazole, Omeprazole	Avoid combination
Tyrosine kinase inhibitors	Afatinib	RIF ↓ Afatinib	Be careful when combining drugs
	Nintedanib	RIF ↓ Nintedanib	Avoid combination
	Ceritinib, Crizotinib, Ibrutinib, Nilotinib	Rifamycins ↓ Ceritinib, Crizotinib, Ibrutinib, Nilotinib	RIF: Avoid combination RFB, RPT: Be careful when combining drugs
	Imatinib, Osimertinib	Rifamycins ↓ Imatinib, Osimertinib	Be careful when combining drugs

Category of drugs	Type of drugs	Interactions	Suggestions
Cyclin-dependent kinase inhibitors	Abemaciclib	Rifamycins ↓ Abemaciclib	Avoid combination
	Palbociclib, Ribociclib	Rifamycins ↓ Palbociclib, Ribociclib	RIF: Avoid combination RFB, RPT: Be careful when combining drugs

Abbreviations: INH=isoniazid, RIF=Rifampicin, RFB=rifabutin, RPT=rifapentine

Disclaimer:
The drugs and information listed above are not exhaustive. The suggestions above do not replace sound clinical judgement. Patients with complex medical issues and DDI should be discussed with an expert before therapy modification.

Note:
Be careful when combining drugs = monitor the patient clinically and with laboratory tests, including therapeutic drug monitoring when appropriate. Modify treatment if needed. Titrate drug dose according to clinical, laboratory or therapeutic drug monitoring.
Rifamycins = include RIF, RFB and RPT
↓ = reduces drug concentration
↑ = increases drug concentration

References:

1. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2016;63(7):e147-e95.
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3. UpToDate – Lexicomp® Drug Interactions (Available at: http://uptodate.com/drug-interactions)
4. Sparkes T, Lemonovich TL. Interactions between anti-infective agents and immunosuppressants – Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33:e13510.
5. The Sanford Guide to Antimicrobial Therapy, copyright 1969-2019 by Antimicrobial Therapy, Inc.
6. The John Hopkins POC-IT ABX Guide, copyright 2000-2021, The John Hopkins University.
7. IBM Micromedex Drug Interaction (electronic version).
8. ClinicalInfo.HIV.gov. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (Available at: https://clinicalinfo.hiv.gov/en/table/table-5-significant-pharmacokinetic-interactions-between-drugs-used-treat-or-prevent)

DRUGS WITH POTENTIAL INTERACTIONS INVOLVING ISONIAZID

Category of drugs	Type of drugs	Interactions	Suggestions
Azole antifungal agents	Itraconazole	INH ↓ Itraconazole	Be careful when combining drugs
Rifamycins	RIF	Additive hepatotoxicity with INH	
Antipsychotics	Clozapine	INH ↑ Clozapine	
Anti-Parkinsonian drugs	Levodopa	INH ↓ Levodopa	
Analgesics	Paracetamol	Additive hepatotoxicity with INH	
Oral anticoagulants	Warfarin	INH ↑ Warfarin	
Antihyperlipidemics	Simvastatin	INH ↑ Simvastatin	
Immunosuppressive agents	Sirolimus, Tacrolimus	INH ↑ Sirolimus, Tacrolimus	Be careful when combining drugs
Anticonvulsants	Carbamazepine (CBZ) Valproic acid (VPA) Phenytoin (PHT)	INH ↑ Carbamazepine, Valproic acid, Phenytoin Carbamazepine ↑ INH	
Methylxanthines	Aminophylline, Theophylline	INH ↑ Aminophylline, Theophylline	
Benzodiazepines	Alprazolam, Diazepam, Midazolam, Triazolam	INH ↑ Benzodiazepines	Be careful when combining drugs

Abbreviations: INH=isoniazid, RIF=rifampicin

Disclaimer:
The drugs and information listed above are not exhaustive. The suggestions above do not replace sound clinical judgement. Patients with complex medical issues and DDI should be discussed with an expert before therapy modification.

Note:
Be careful when combining drugs = monitor the patient clinically and with laboratory tests, including therapeutic drug monitoring when appropriate. Modify treatment if needed. Titrate drug dose according to clinical, laboratory or therapeutic drug monitoring.
↓ = reduces drug concentration
↑ = increases drug concentration

References:

1. Lexicomp Drug Interactions. UpToDate Inc. Accessed April 07, 2022. (Available at: http://uptodate.com/drug-interactions)
2. The Sanford Guide to Antimicrobial Therapy, copyright 1969-2019 by Antimicrobial Therapy, Inc.
3. The John Hopkins POC-IT ABX Guide, copyright 2000-2021, The John Hopkins University.
4. IBM Micromedex Drug Interaction (electronic version).
5. CLINICAL INFO.HIV.GOV. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (Available at: https://clinicalinfo.hiv.gov/en/table/table-5-significant-pharmacokinetic-interactions-between-drugs-used-treat-or-prevent)

ANTIRETROVIRAL AND RIFAMYCINS DRUG INTERACTIONS

Antiretroviral drug	Rifampicin	Rifabutin	Once weekly rifapentine
Nucleoside/nucleotide reverse transcriptase inhibitors			
Abacavir, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, zidovudine	May be combined		
Tenofovir alafenamide	May be combined	Do not combine	
Nucleoside/nucleotide reverse transcriptase inhibitors			
Efavirenz	May be combined	Avoid combination. If no alternative, ↑RFB 450mg once daily	May be combined
Nevirapine	Avoid combination. If no alternative, use NVP 200 mg twice daily with rifampicin (with no lead-in phase)	May be combined	Do not combine
Etravirine	Do not combine	May be combined but not with boosted PI	
Rilpivirine		RFB: 300mg once daily ↑RPV 50mg once daily	

Antiretroviral drug	Rifampicin	Rifabutin	Once weekly rifapentine
Protease inhibitors			
Lopinavir/ritonavir	Do not combine	↓RFB 150mg once daily LPR/r dose unchanged	Do not combine
Atazanavir/ritonavir		↓RFB 150mg once daily ATZ/r dose unchanged	
Darunavir/ritonavir		↓RFB 150mg once daily DRV/r dose unchanged	
Integrase strand transfer inhibitors			
Raltegravir	Rifabutin is preferred. If rifampicin is used, ↑RAL 800mg twice daily	May be combined	May be combined
Dolutegravir	Rifabutin is preferred. If rifampicin is used, ↑DTG 50 mg twice daily		

Abbreviations: NVP=nevirapine, RFB=rifabutin, RPV=rilpivirine, LPR/r=Lopinavir/ritonavir, ATZ/r=Atazanavir/ritonavir, DRV/r=Darunavir/ritonavir, RAL=raltegravir, DTG=dolutegravir
↓ = reduce drug to stated dosage
↑ = increase drug to stated dosage

Note: Certain ARV combinations may lead to complex drug-drug interactions, and it may be difficult to predict their significance. Always use other equally effective treatment options to avoid the interaction; but if unavoidable, seek expert advice.

References:

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11. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America, 2020. (Available at: http://clinicalinfo.hiv.gov/sites/default/files/inline-files/adult_oi.pdf)

GLOSSARY

Term	Definition
Adolescent	A person aged 10 to 19 years
Adult	A person over 19 years of age
At-risk group	Any group of people in which the prevalence or incidence of TB is significantly higher than in the general population
Bacteriologically confirmed TB	TB diagnosed in a biological specimen by smear microscopy, culture or a WHO-approved molecular test e.g. Xpert MTB/RIF®
Child	A person under 10 years of age
Close contact	Individuals who are sharing the same air space with the index case for a reasonable duration of time before the index patient starts TB treatment
Contact	Any individual who was exposed to a person with TB disease
High TB transmission setting	A setting with a high frequency of individuals with undetected or undiagnosed TB disease, or where infectious TB patients are present and there is a high risk of TB transmission
Household contact	Individuals who live in the same household or are sharing the same air space with the index case for a reasonable duration of time before the index patient starts TB treatment
Index case of TB	Initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed
Infant	A child under one year (12 months) of age
Latent tuberculosis infection	A state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest TB disease

LIST OF ABBREVIATIONS

ADA	adenosine deaminase
ADL	activities of daily living
ADR	adverse drug reactions
AFB	acid fast bacilli
AGREE II	Appraisal of Guidelines, Research and Evaluation II
ALT	alanine aminotransferase
ART	antiretroviral treatment
ARV	antiretroviral drug
BCG	Bacille Calmette-Guérin vaccine
CI	confidence interval
CNS	central nervous system
CPG	clinical practice guidelines
CQ	clinical question
CrI	credible interval
CXR	chest x-ray (it refers to chest radiograph/chest radiography in this CPG)
DDI	drug-drug interaction
DG	development group
DILI	drug induced liver injury
DOT	directly observed treatment
DTG	dolutegravir
EFV	efavirenz
EMB	ethambutol
EPTB	extrapulmonary tuberculosis
FDC	fixed-dose combination
GA	gastric aspirate
GCS	Glasgow Coma Score
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HIV	human immunodeficiency virus
HPE	Histopathological examination
IGRA	Interferon Gamma Release Assay
INH	isoniazid
INSTI	integrase strand transfer inhibitors
IRIS	immune reconstitution inflammatory syndrome
IRR	incidence rate ratio
IV	intravenous
kPa	kilopascal
LFT	liver function test
LF-LAM	lateral flow urine lipoarabinomannan assay
LTBI	latent tuberculosis infection
M. tuberculosis	*Mycobacterium tuberculosis*
max	maximum
MDR	multi-drug resistant
mg	milligramme
mg/kg	milligramme per kilogramme
ml	millilitre
mmHg	millimeter mercury
MoH	Ministry of Health
NICE	National Institute of Health and Excellence
NNRTIs	non-nucleoside reverse transcriptase inhibitors
NPA	nasopharyngeal aspirate

NPV	negative predictive value
NVP	nevirapine
OR	odds ratio
p	p-value
PI	protease inhibitor
PLHIV	people living with HIV
PPV	positive predictive value
PTB	pulmonary tuberculosis
PZA	pyrazinamide
QFT	quantiferon
RAL	raltegravir
RC	review committee
RCT	randomised controlled trial
RFB	rifabutin
RIF	rifampicin
RPT	rifapentine
RR	relative risk
SCAR	severe cutaneous adverse reaction
TB	tuberculosis
TDM	therapeutic drug monitoring
TST	tuberculin skin test
U/L	unit per liter
ULN	upper limit of normal
VOT	video-observed treatment
WHO	World Health Organization

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