CLINICAL PRACTICE GUIDELINES

2021 MOH/P/PAK/xxxxxx

MANAGEMENT OF TUBERCULOSIS
(FOURTH EDITION)

Ministry of Health
Malaysia

Academy of Medicine
Malaysia

Published by:
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre 62590
Putrajaya, Malaysia

ISBN:

Available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my

Also available as an app for Android and IOS platform: MyMaHTAS

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. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATING THE CPG

These guidelines were 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.

Every 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 at all time. This version can be found on the websites mentioned above.

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 the current development in CPG methodology, the CPG Unit of MaHTAS is in the process of 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 and 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

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

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

- 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
- Corticosteroids should be used in tuberculous meningitis and pericarditis.
  - Early use of oral corticosteroids is preferred in tuberculous meningitis when patients can tolerate orally.

- In HIV-tuberculosis (TB) coinfection antiretroviral therapy (ART) should be initiated within eight weeks of anti-TB treatment.
  - However, for HIV-TB patients with known CD4 <50 cells/mm^3, ART should be initiated within the first two weeks of anti-TB treatment.
- In HIV with TB meningitis, initiation of ART may need to be delayed until two months post-TB treatment.
- For HIV-TB co-infected patients on protease inhibitor-based anti-retroviral therapy, rifabutin should be used instead of rifampicin.
- Co-trimoxazole preventive therapy should be given during TB treatment in TB-HIV coinfection with unknown CD4 count or CD4 <200 cells/µL.

- Directly observed treatment (DOT) should be done in the intensive phase of 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 for latent tuberculosis infection (LTBI) diagnosis in adult 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 are contraindicated for INH-based regimens
  - 6H or 9H may be used for patients who cannot tolerate or are contraindicated for rifamycin-based regimens
- In HIV-positive adults with LTBI, 1HP may be considered for treatment.

- 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 and 6H.
- In HIV-infected children with LTBI, 6H is the preferred regimen for:
  - children <2 years of age
  - children ≥2 years on antiretroviral treatment not compatible with rifamycin-based regimen

GUIDELINES DEVELOPMENT AND OBJECTIVES
GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these 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 on humans, publication from year "2012 to Current" and English language. 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.:

- 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)
- World Health Organization - WHO consolidated guidelines on tuberculosis. Module 1: Prevention - Tuberculosis preventive treatment (2020)
- 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 them being used 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 follows strictly the requirement of AGREE II.

On 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

HEALTHCARE SETTINGS

Primary, secondary and tertiary care settings

DEVELOPMENT GROUP

Chairperson
Dr. Goon Ai Khiang
Respiratory Physician
Hospital Pulau Pinang, Pulau Pinang

Members (in alphabetical order)

Dr. Asmah Razali
Public Health Physician
TB/Leprosy Sector, Disease Control Division
Ministry of Health, Putrajaya

Dr. Azlina Samsudin
Respiratory Physician
Hospital Sultanah Nur Zahirah, Terengganu

Dr. Cheng Joo Thye
Consultant Infectious Disease Physician
Hospital Raja Permaisuri Bainun, Perak

Dr. Choo Chong Ming
Consultant Infectious Disease Paediatrician
Hospital Pulau Pinang, Pulau Pinang

Dr. Kartina Md Noor
Pathologist (Medical Microbiology)
Hospital Sultan Abdul Halim, Kedah

Ms. Khoo Ming-Yi
Pharmacist
Institut Perubatan Respiratori, Kuala Lumpur

Dr. Kumaresh Raj Lachmanan
Respiratory Physician
Hospital Raja Permaisuri Bainun, Perak

Ms. Koh Hui Moon
Pharmacist
Hospital Sungai Buloh, Selangor

Dr. Mohd Aminuddin Mohd. Yusoff
Public Health Physician
Malaysian Health Technology Assessment
Section, Ministry of Health, Putrajaya

Dr. Noor Ayuni Bazura Muhamad
Senior Principal Assistant Director
Malaysian Health Technology Assessment
Section, Ministry of Health, Putrajaya

Dr. Norlizah Paidi
Family Medicine Specialist
Klinik Kesihatan Bandar Mas, Johor

Dr. Rachael Shamini Danasamy
Family Medicine Specialist
Klinik Kesihatan Bandar Tasek Mutiara
Pulau Pinang

Dr. Rosminah Md Kassim
Consultant Radiologist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Sathya Rao Jogulu
Family Medicine Specialist
Klinik Kesihatan Ampang, Selangor

Dr. Tonnii Sia Loong Loong
Infectious Disease Physician
Hospital Umum Sarawak, Sarawak

Dr. Wong Chee Kuan
Respiratory Physician
Pusat Perubatan Universiti Malaya
Kuala Lumpur

Dr. Wong Ke Juin
Consultant Infectious Disease Paediatrician
Hospital Wanita & Kanak-kanak Likas, Sabah

Dr. Zamzurina Abu Bakar
Respiratory Physician
Institut Perubatan Respiratori, Kuala Lumpur

REVIEW COMMITTEE

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.

Chairperson

Dr. Irfhan Ali Hyder Ali
Head of Respiratory Services &
Consultant Respiratory Physician
Hospital Pulau Pinang, Pulau Pinang

Members

Professor Dato' Dr. Hj Abdul Razak Mutttalif
Senior Consultant Respiratory Physician
Professor and Head of Medicine
MAHSA University, Selangor

Associate Professor Dr. Pang Yong Kek
President
Malaysian Thoracic Society

Dr. Benedict Sim Lim Heng
Consultant Infectious Disease Physician
Hospital Sungai Buloh, Selangor

Dr. Rahela Ambaras Khan
Pharmacist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Iskandar Firzada Osman
Family Medicine Specialist
Klinik Kesihatan Jaya Gading, Pahang

Dr. Sathesh Kumar Periyasamy
Patient Advocate
Malaysian Association for the Prevention of Tuberculosis

Dr. Izzuna Mudla Mohamed Ghazali
Deputy Director & Public Health Physician
Malaysian Health Technology Section
Ministry of Health, Putrajaya

Dr. Suhaila Md. Hanapiah
Pathologist (Medical Microbiology)
Institut Kanser Negara, Putrajaya

Dr. Jeyaseelan P Nachiappan
Head of Department & Consultant Infectious Disease Paediatrician
Hospital Raja Permaisuri Bainun, Perak

Dr. Thilaka a/p Chinnayah@Nadarajah
Head of TB/Leprosy Sector & Consultant Public Health Physician
Disease Control Division
Ministry of Health, Putrajaya

Dr. Kuppusamy Iyawoo
Visiting Consultant Respiratory Physician
Assunta Hospital, Selangor

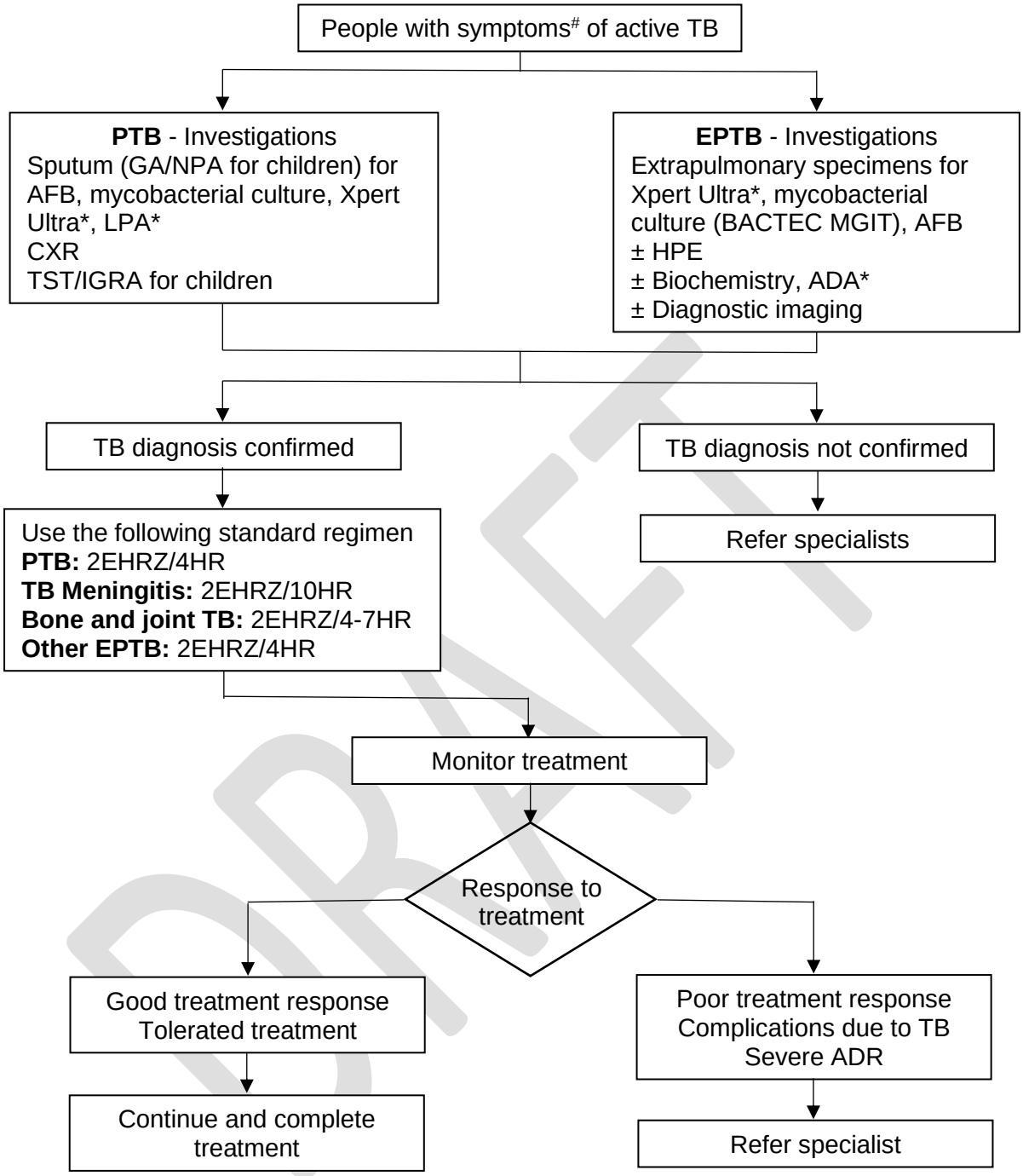
Dr. Yun Sii Ing
Head of Radiology Services &
Senior Consultant Radiologist
Hospital Sungai Buloh, Selangor

Associate Professor Dr. Nik Sherina Haidi Hanafi
Consultant Family Medicine Specialist
Universiti Malaya Medical Centre
Kuala Lumpur

EXTERNAL REVIEWERS (in alphabetical order)

The following external reviewers provided feedback on the draft:

Algorithm A: Management of Active Tuberculosis

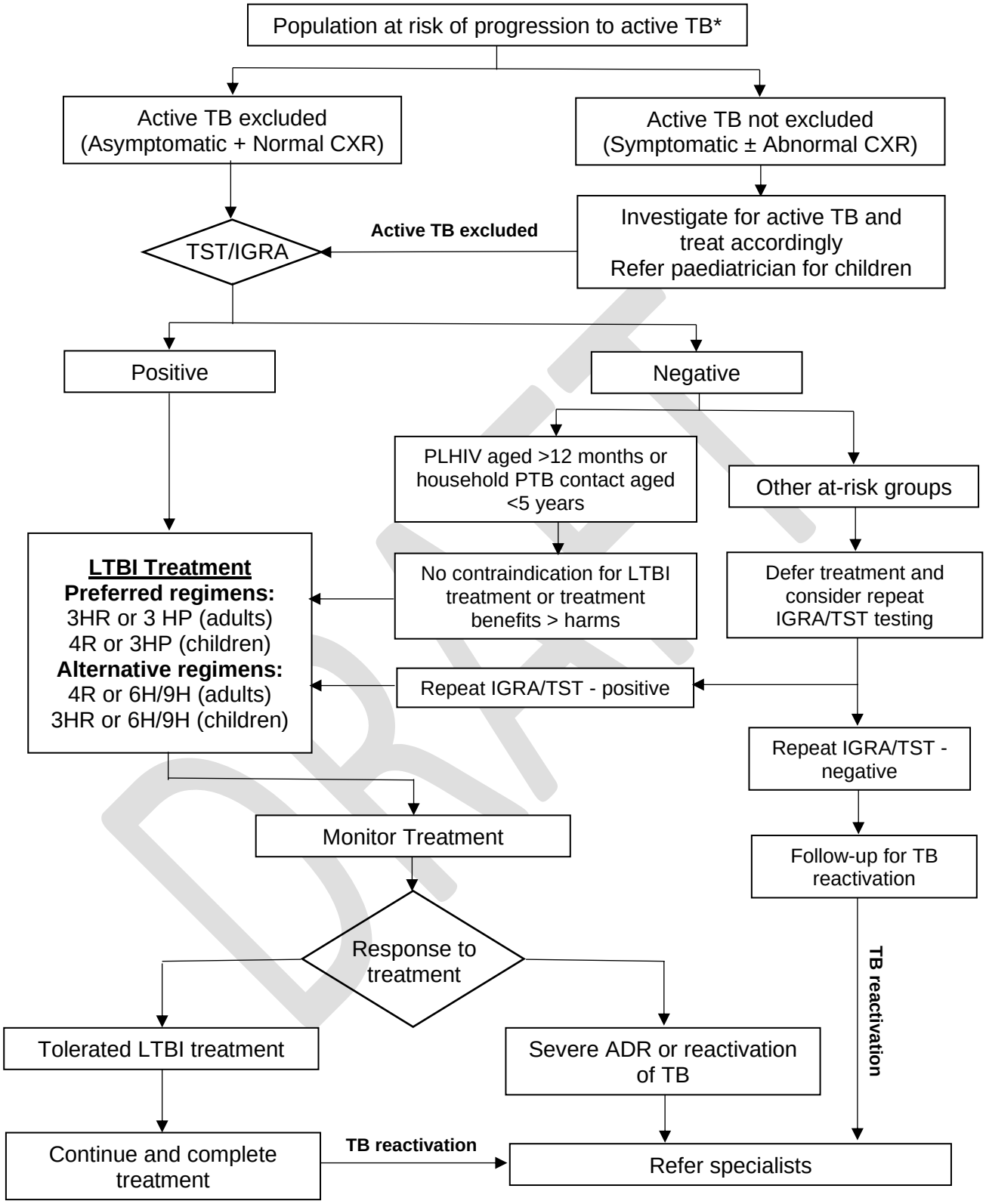


#Symptoms of TB in children may be different from adults
*When indicated

Important note: This algorithm **should NOT be used alone** for clinical decision. Refer to the texts in the relevant sections in the CPG for further details.

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

Algorithmn B: Management of Latent Tuberculosis Infection



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

Abbreviation:
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

Tuberculosis (TB) is endemic in Malaysia and continues to be a major public health concern. World Health Organization (WHO) has 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.[WHO, 2015]

TB incidence for Malaysia in 2015 was 79.0/100,000 population. There was a reduction of this incidence to 72.4/100,000 in 2020 but it was still below the End TB Strategy target of more than 20% reduction. By 2035, the aim is to reduce the incidence to less than 10/100,000 population. There were 1,696 TB deaths in 2015 and these increased to 2,320 deaths in 2020. By 2035, Malaysia aims to decrease it to fewer than 85 deaths.

The vision of National Strategic Plan for TB Control (2016 - 2020) is for Malaysia to be a TB-free country by year 2035. The burden of TB can be decreased by ensuring universal access to timely and quality diagnosis as well as treatment of all forms of TB.[MOH, 2018 (NSPTB)]

The challenges for TB management in Malaysia include delay in TB diagnosis and treatment especially in smear negative TB, extrapulmonary TB (EPTB) and TB in children. Treatment default and non-adherence to TB treatment continues to hamper the TB Control Programme. The programmatic management of latent TB infection (LTBI), also known as TB preventive treatment, is not fully established nationwide. Apart from that, socially disadvantaged population has difficulty in accessing TB services due to various reasons.

Since the previous CPG edition in 2012, there have been many advances in both diagnosis and treatment of TB. Xpert Ultra has replaced Xpert MTB/RIF in the diagnosis of active TB. Newer LTBI testing techniques including Quantiferon GIT is currently available in all states. Lateral-flow urine lipoarabinomannan assay (LF-LAM) is recommended by WHO as an adjunct to the diagnosis of TB in PLHIV. More evidence supporting the shorter regimen in LTBI treatment is now available.

Thus, this CPG update is timely and necessary to address some clinical issues and challenges in TB management in Malaysia. This CPG will supersede all earlier MoH guidelines of drug-susceptible TB. The management of drug-resistant TB has been addressed 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 A** on **Management of Active Tuberculosis.**

2.1 Smear Positive Pulmonary Tuberculosis

a. Introduction

Pulmonary tuberculosis (PTB) is one of the airborne infectious diseases with high mortality rate as reported by WHO which surpasses HIV mortality. It was reported in Global Tuberculosis Report 2020 that an estimated 10.0 million people contracted TB and 1.4 million people died of TB in 2019.[WHO, 2020a (GTR)] In Malaysia, 23,644 cases of TB were notified in 2020 with 91.7% of them were new cases and 58.0% were smear positive PTB.[TB & Leprosy Sector MoH, 2020] There were 2,320 cases of TB death cases giving a mortality rate of 7.1 per 100,000 last year which was above the WHO target for End TB Strategy.[TB & Leprosy Sector MoH, 2020]

For the targets to be achieved, early detection and diagnosis with shorter and more effective regimens which are tolerable with fewer side effects are required.

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, the typical symptoms may be absent in the immunocompromised or elderly patients.

Upon reviewing a patient with suspected TB, full history and 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 sputum smear results. All patients who are diagnosed as PTB must have sputum mycobacterial culture performed at the initial visit to look for susceptibility pattern.

- All patients with clinically diagnosed and/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.[MoH, 2012] For patients who are unable to expectorate sputum spontaneously, sputum induction may be done. Refer to **Appendix 3** on **Procedure for Sputum Induction**.

Mycobacterial culture must be sent at the initiation of TB treatment. It is to confirm the presence of *M. tuberculosis* and to exclude drug resistant TB. However, mycobacterial culture should not delay initiation of the treatment. In a patient suspected of drug resistant TB, mycobacterial culture must be sent. However, for early confirmation of diagnosis, rapid molecular test should be sent for initiation of treatment. Refer to **Appendix 4** on **Specimen Collection for Diagnosis of Tuberculosis** for further information.

- **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.[MoH, 2012] **Grading of Pulmonary Tuberculosis Severity Based on Chest Radiograph in Adults** is shown in **Appendix 5**.

- **Lateral Flow Lipoarabinomannan Assay**

Lateral flow 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.[WHO, 2021] However, it is not recommended by WHO for use in HIV-negative adults due to its low sensitivity of 4 - 31%.[Broger T et al., 2020, 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.[Bjerrum S et al., 2020, level II-2; Kerkhoff AD et al., 2020, 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-LAM showed low sensitivity as shown in **Table 1** below for the diagnosis of PTB compared with sputum smear microscopy or Xpert MTB/RIF:[Broger T et al., 2020, level II-2]

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

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 98.5-100.0%)
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).[Broger T et al., 2020, level II-2]

Recommendation 1
- Lateral flow lipoarabinomannan assay should not be used for the diagnosis of pulmonary tuberculosis in HIV-negative adults.

c. Treatment

The current standard anti-tuberculosis (anti-TB) regimen recommended by WHO consists of a 2-month intensive phase with isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB), followed by a 4-month continuation phase with INH and RIF (2EHRZ/4HR). INH and RIF are the drugs with the greatest early bactericidal activity, while RIF and PZA are the drugs with the greatest sterilising power. EMB is bacteriostatic and is combined with other more potent drugs to prevent the emergence of resistant bacilli.[Silva DR et al, 2020, level III] The major justification for using this longer treatment regimen is to reduce recurrence and 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-sensitive 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:[Grace AG et al., 2019, level I]

International guidelines recommend the use of standard 2EHRZ/4HR regimen for the treatment of pulmonary TB as shown in **Table 2**.[NICE, 2019; WHO, 2017; ATS, 2016 (Nahid P et al)]

Table 2: Recommended dosage 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

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 2
- Standard anti-tuberculosis regimen of 2EHRZ/4HR* should be used in the treatment of pulmonary tuberculosis.

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

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

Fixed-dose combination (FDC) tablets is a combination of two or more anti-TB drugs 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 make drug procurement simple, use less storage space, and ease 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:[Gallardo CR et al., 2016, level I; Albanna AS et al., 2013, level I]
- treatment failure and/or relapse with
- 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.[Albanna AS et al., 2013, 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.[Gallardo CR et al., 2016, level I]

WHO recommends the use of FDC over separate drug formulations in the treatment of patients with drug-susceptible TB.[WHO, 2017] The recommended daily dosing for FDC is shown in the following table.

Table 3: Recommended daily dosing for FDC* in adults

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

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

Recommendation 3

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

- **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. It was recommended in more than 130 countries worldwide. Unfortunately, it was noted to cause high rates of relapse and acquired drug resistant TB.

In a meta-analysis of 56 RCTs on newly diagnosed PTB patients treated with first-line regimens using RIF for >6 months, trice weekly throughout regimen showed worse outcomes compared with daily treatment in terms of:Johnston J et al., 2017, 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, twice weekly continuation phase after daily intensive had higher risk of failure (IRR=3.0, 95% CI 1.0 to 8.8) and relapse (IRR=1.8, 95% CI 1.0 to 3.3) although not significant. There was also no significant difference in the outcomes with thrice weekly continuation phase after daily intensive.Johnston J et al., 2017, 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.WHO, 2017

Recommendation 4

- 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** below. Assessment of clinical improvement, adherence to treatment and, monitoring medication side effect and ADR to the treatment must be done in every visits.

Table 4: Monitoring schedule of adult patients on PTB treatment

Visit	Treatment duration	Regimen	Investigations
1**	0 month	EHRZ	FBC, RBS, RP, LFT, HIV screening Sputum AFB direct smear Sputum MTB culture and sensitivity CXR
2**	2 - 4 weeks	EHRZ	LFT Sputum AFB direct smear*

3**	2 months	HR	Sputum AFB direct smear Trace sputum MTB culture and sensitivity CXR If persistent smear positive, for sputum mycobacterial C&S (BACTEC MGIT), LPA assay or Xpert Ultra
4	5 months		Sputum AFB direct smear[#]
5**	6 months	Completion of 6 months treatment and no more follow-up	Sputum AFB direct smear CXR Trace sputum MTB culture and sensitivity

*for return to work/school purposes
**requires in-person visit
[#]sputum AFB smear should be done at the end of five months of standard anti-TB treatment

FBC=full blood counts, RBS=random blood sugar, RP=renal profile, LFT=liver function test, HIV=Human immunodeficiency virus, AFB=acid fast bacilli, MTB=mycobacterium tuberculosis, CXR=chest radiograph, C&S=culture and sensitivity, LPA=line probe assay

- Patients with persistent smear positive 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.

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 32.1% of all PTB cases in Malaysia.[Liew SM et al., 2015, level III] The reasons for negative smear PTB are paucibacillary conditions e.g. immunosuppression and early disease, or due to poor quality specimens, even though collecting AFB direct smear three times can increase sensitivity of diagnosis.[WHO, 1998] CXR is a sensitive tool for identifying and excluding TB.[WHO, 2016a] The accuracy of PTB diagnosis can be further increased with combination of clinical symptoms, CXR and bacteriological testing [AFB direct smear, MTB culture and/or Nucleic Acid Amplification Test (NAAT)].

b. Diagnosis

Clinical symptoms of smear negative PTB is similar with smear positive PTB. However, smear negative results at initial presentation may delay PTB diagnosis. This may be related to the poor skill of healthcare providers in detecting the disease or poor sensitivity of diagnostic methods to detect cases at early stage.[Chen CC et al., 2015, level III] Therefore, a systematic diagnostic approach needs to be considered in smear negative cases with high suspicion of PTB.

- **Chest radiography**

In general, CXR is helpful in detecting PTB as it has high sensitivity of 87 to 98% regardless of smear status when compared with mycobacterial culture.[WHO, 2016a]

In a cross-sectional study comparing two community screening tests for TB, CXR was more sensitive in diagnosing PTB at 80% compared with Xpert MTB/ RIF sputum examination at only 34%.[Nguyen TBP et al., 2020, level III]

Thus, CXR is helpful to diagnose smear negative PTB. However, its use is limited by the need for experienced readers, good quality of 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. On the other hand, sputum mycobacterial culture, the gold standard for confirmation of PTB, requires only 10 - 100 AFB/µL to detect PTB. However, PTB may be smear negative in early disease or immunocompromised patients.

Xpert MTB/RIF and Xpert Ultra are WHO recommended nucleic acid amplification tests (NAAT) for the detection of TB and RIF resistance.[WHO 2021] 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.[Chakravorty S et al., 2017, 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).[Zifodya JS et al., 2021, level III (Horne DJ)]

Recommendation 5

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

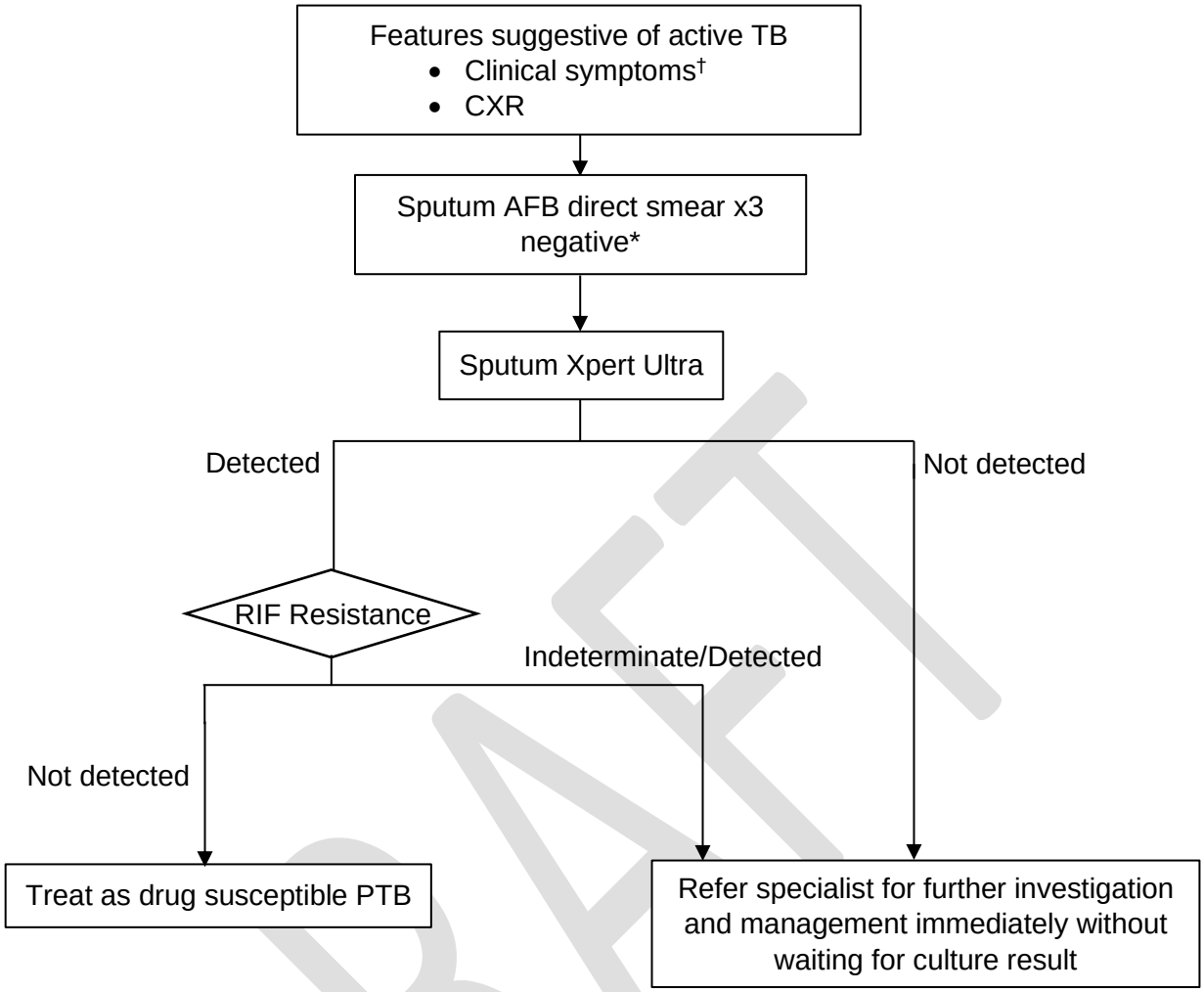
- **Tuberculosis Loop-mediated Isothermal Amplification Test**

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.[WHO, 2016b]

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.[Shete PB et al., 2019, 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.[WHO, 2021] Therefore, it is inferior to Xpert MTB/RIF for the diagnosis of smear negative pulmonary tuberculosis.

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



†Clinical symptom: current cough, fever, weight loss or night sweats
*Sputum sample should be sent for mycobateria culture and sensitivity 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

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.[TB & Leprosy Sector MoH, 2020] 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.

- **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.[Kohli M et al., 2021, 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)	96.9 (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 the table. This is due to the paucibacillary nature of the disease in the specimens.

Hence in EPTB, the gold standard for diagnosis is a composite reference test instead of mycobacterial culture. The composite reference standard might be based on the results of microbiological tests, culture or NAAT other than Xpert Ultra and Xpert MTB/ RIF, imaging studies; histology and clinical characteristics, and include at least one component test that is positive.

Recommendation 6

- In patients suspected to have extrapulmonary tuberculosis, the following specimens should be sent for Xpert Ultra as 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.[Makeshkumar V et al., 2014, level III]

- **Adenosine deaminase**

The measurement of adenosine deaminase (ADA) in pleural effusion is a useful diagnostic test for tuberculous pleural effusion. From the previous CPG edition, measurement of ADA level in pleura or cerebrospinal fluid may be considered as an adjunct in diagnosing pleural TB and tuberculous meningitis respectively.[MoH, 2012]

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.[Huan NC et al., 2020, level II-2]

A cohort study on the utility of ADA (clinical cut point of 30 U/L) vs Xpert Ultra when compared with composite reference standard in the diagnosis of pleural TB showed that:[Meldau R et al., 2019, 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 7

- 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 and TB involving the spinal cord, 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 computed tomography 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 computed tomography scan and MRI in patients with suspected CNS TB.[NICE, 2019]

Recommendation 8
- Computed tomography scan and/or magnetic resonance imaging should be use in the diagnosis in tuberculosis of 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.[ATS, 2016 (Nahid P et al.); WHO, 2010] 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.[Nene AM et al., 2019, level I]

A meta-analysis on different fluoroquinolones-based regimens in the treatment of TB meningitis showed fluroquinolones 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.[Rizvi I et al., 2018, level I]

Apart from that, there was no significant difference in either AE or death in the following comparison:[Rizvi I et al., 2018, 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).[NICE, 2019.]

Recommendation 9
- 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 isoniazid, rifampicin, pyrazinamide and ethambutol, 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.[WHO, 2017; MOH, 2012]

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.[Prasad K et al, 2016, level I]

In a cohort study of 146 patients with TB meningitis, early use of oral corticosteroids shortened the duration of hospitalisation. Early switch from IV to oral corticosteroids group had longer duration of hospitalisation compared with oral corticosteroids group (20.05±12.98 days vs 6.97±3.20 days, p<0.001). The early use of oral corticosteroids did not increase rate of readmission or mortality.[Paliwal VK et al., 2019, level II-2]

The recommended corticosteroid regimen for TB meningitis is shown below.

Table 6: Corticosteroid regimen for TB meningitis

Severity of disease	Regimen
Grade I disease	Week 1: IV/oral dexamethasone 0.3 mg/kg/day Week 2: 0.2 mg/kg/day Week 3: 0.1 mg/kg/day Week 4: a total of 3 mg/day, decreasing by 1 mg each week
Grade II and III disease	Week 1: IV/oral dexamethasone 0.4 mg/kg/day Week 2: 0.3 mg/kg/day Week 3: 0.2 mg/kg/day Week 4: 0.1 mg/kg/day, then decreasing by 1 mg each week

Adapted: Ministry of Health Malaysia. Management of Tuberculosis (3rd Edition). Putrajaya: MoH; 2012

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.[Ryan H et al., 2017, level I]

In an RCT assessing the role of add-on prednisolone in cervical lymph node TB, results showed that:[Bunkar ML et al., 2016, level I]

- at two months, significantly more patients with add-on prednisolone showed symptom relief compared with those without
- at two months, significantly higher complications in the form of abscess, sinus and/or appearance of new lymph nodes 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 relapse in the corticosteroids group.

In another Cochrane systematic review:

- 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.[Wiysonge CS et al., 2017, level I]

Recommendation 10

- Corticosteroids should be used in tuberculous meningitis and pericarditis.
  - Early use of oral corticosteroids is preferred in tuberculous meningitis when patients can tolerate orally.

- 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 from hematogenous or lymphatic spread. The pharmacological treatment of disseminated TB is dictated by 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). Adjunctive corticosteroids are added to the treatment. All cases with positive mycobacterial TB blood culture should be referred to the specialist for further management.

2.4. Recurrent Tuberculosis

TB recurs in a number of patients despite completion of treatment because of reactivation of TB (endogenous reactivation) or a new episode of infection (exogenous reinfection). In high transmission areas, reinfection is 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 both.[WHO, 2021] However, the specificity of Xpert Ultra for the diagnosis of active TB is reduced in patients with recurrent TB. In a meta-analysis of four good cohort studies of participants with previously treated TB, the accuracy of Xpert Ultra with pooled sensitivity and specificity of 84.2% (95% CI 72.5 to 91.7) and 88.2% (95% CI 70.5 to 96.6) was lower than participants of newly diagnosed with PTB with sensitivity of 90.9% (95% CI 84.7 to 95.3) and specificity of 94.9% (95% CI 91.3 to 97.2).[Zifodya JS et al., 2021, level III (Horne)] The reduction in specificity in this population may be due to the presence of dead tuberculous bacilli. Dead tuberculous bacilli may be detected in them for years.[Theron G et al., 2018, level II-2]

Other molecular tests like the Hain MTBDRplus, a WHO-recommended line probe assay for the detection of MDR TB, may also detect dead tuberculous bacilli.[WHO, 2021] Only mycobacterial culture is able to differentiate live from dead tuberculous bacilli. Therefore, both Xpert MTB/Rif (R) and Hain MTBDRplus should be combined with culture to confirm recurrent TB.

Liquid media for mycobacterial culture is the reference standard for bacteriological confirmation of TB.[MoH, 2016] BACTEC MGIT is the diagnostic platform used by MoH Malaysia.

Recommendation 11

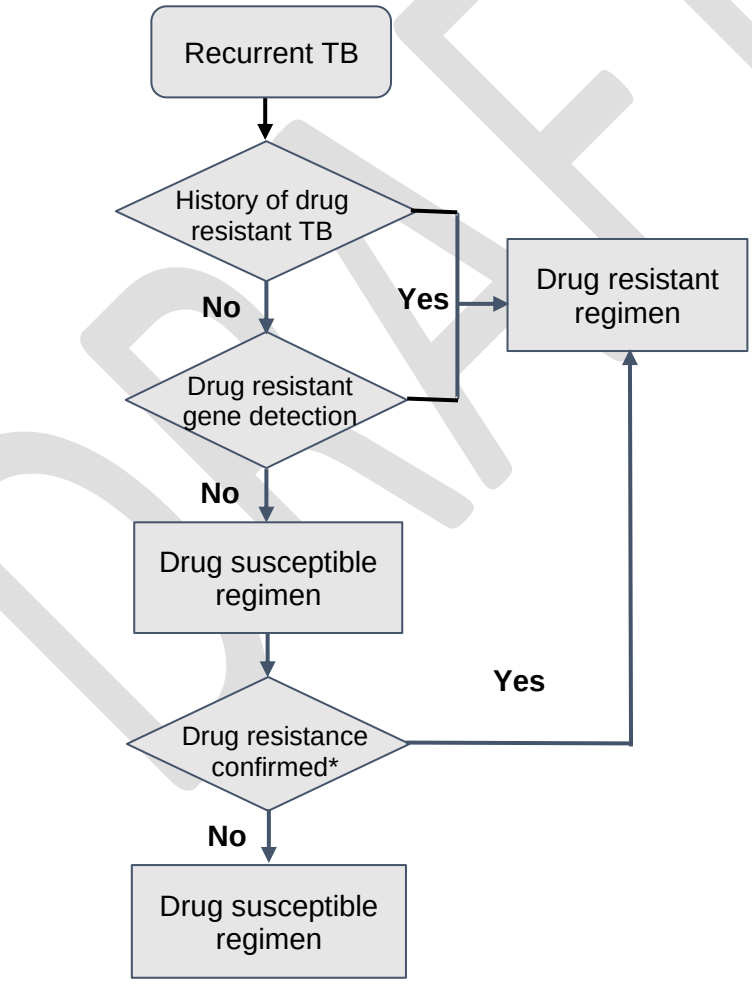
- Sputum should be sent for both Xpert Ultra and mycobacterial culture (BACTEC MGIT) for individuals suspected to have recurrent pulmonary tuberculosis.

b. Treatment

The treatment regimen for recurrent TB is determined by the presence of drug resistance. Hence, rapid drug molecular tests and mycobacterial culture (BACTEC MGIT) should be sent before starting treatment.

- International guidelines no longer recommend a standard retreatment regimen for TB.[NICE, 2019; WHO, 2017; ATS, 2016 (Nahid P et al.)]
- 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 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 **Treatment regimen for recurrent TB.**



*drug resistance confirmed on mycobacterial culture

Figure 2: 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.[WHO, 2010] Successful treatment of TB is paramount in ensuring best outcome and the risk of untreated TB to pregnant women and their foetuses should be clearly explained.[ATS, 2016 (Nahid P et al)]

For pregnant and lactating women, standard anti-TB regimen (2EHRZ/4HR) can safely be administered.[ATS, 2016 (Nahid P et al.); MoH, 2012; WHO, 2010] The CPG DG opines that pyridoxine 30 mg/day is recommended for all women taking INH who are either pregnant or breastfeeding.

RIF may cause yellow or orange coloured-milk, which is harmless.[LactMed, 2020] Breastfeeding should be continued in lactating mothers. However surgical mask should be used if the mother is infectious.[ATS, 2016 (Nahid P et al.); MoH, 2012] Drugs in breast milk should not be considered to serve as an effective treatment for TB or for LTBI in a nursing infant.[ATS, 2016 (Nahid P et al.); MoH, 2012]

Patients on oral contraceptive pills should use alternative contraception methods if they are on RIF until one month after stopping the anti-TB drug.[WHO, 2010; MoH 2012]

Recommendation 12

- Standard anti-tuberculosis (TB) regimen (2EHRZ/4HR*) may 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 contraceptives pills.

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

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, experts recommend close monitoring during TB treatment.[ATS, 2016 (Nahid P et al.)]

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is 2EHRZ/4HR.[WHO, 2010; ATS, 2016 (Nahid P et al.); MoH, 2012]

There is significant renal excretion of EMB and metabolites of PZA, and doses should therefore be adjusted.[ATS, 2016 (Nahid P et al.); MoH, 2012; WHO, 2010] Refer **Appendix 6** on **First-Line Anti-Tuberculosis Drug Dosage and Adverse Drug Reactions** for medication dosage.

A cross-sectional study looked at the safety and effectiveness of anti-TB treatment in 241 PTB patients with and without CKD. Those with CKD were grouped into mild, moderate and severe and their anti-TB dosage were adjusted based on renal function. Results showed no significant difference between the CKD and non-CKD in terms of:[Saito N et al., 2019, level III]

- frequency of in-hospital TB- related death
- sputum conversion rate at two months
- any adverse events

All four anti-TB drugs may be administered after hemodialysis to facilitate DOT as well as to avoid premature drug removal.[ATS, 2016 (Nahid P et al.); MoH, 2012]

Recommendation 13

- 2EHRZ/4HR* should be used in patients with tuberculosis and renal failure.
  - Pyrazinamide and ethambutol should be given three times per week in patients with creatinine clearance <30 ml/min or those receiving haemodialysis.

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

c. Tuberculosis with liver impairment

The management of TB in patients with chronic liver disease is challenging because of 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 people living with HIV (PLHIV).

The number of patients with HIV-TB coinfection 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 of HIV-TB coinfected patients from 2015 till 2020 (> 97.5%) were diagnosed with HIV prior to TB.

Smear negative PTB and EPTB are more common in PLHIV compared with HIV-negative individuals.[Sterling TR et al., 2010, 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.[MoH, 2012]

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 ART.[WHO, 2018a]

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 additional test 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 method for the diagnosis of TB which is currently unavailable in Malaysia. It is a rapid test that runs on urine hence it has advantages compared with conventional sputum tests which include:

i. specimen collection at any time of the day
ii. easier specimen collection
iii. detection of 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:[WHO, 2021]

- advanced disease
- serious illness
- CD4 count <200/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 a lower specificity [89.3% (95% CI 85.8 to 92.2) vs 95.6% (95% CI 93.0 to 97.4) for PTB diagnosis.[Bjerrum S et al., 2020, level II-2] Both LF-LAMs did not meet the optimal diagnostic accuracy standard of WHO for PTB.[Drain PK et al., 2019, 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).[Zifodya JS et al., 2021, level III (Horne)]

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.[Kerkhoff AD et al., 2020, level III]

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

Apart from that, 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.[Kerkhoff AD et al., 2020, 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:[WHO, 2019]

- 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

ART during TB treatment is significantly protective against mortality and results in earlier conversion of sputum and cultures to negative.[MoH, 2012] In TB-HIV coinfected patients, antiretroviral treatment (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 timing of ART in HIV-TB coinfected patients showed that early ART initiation when compared with later initiation was associated with:

- reduced all-cause mortality with IRR of 0.75 (95% CI 0.59 to 0.95)[Yan S et al., 2015, level I] and RR of 0.81 (95% CI 0.66 to 0.99)[Chelkeba L et. al., 2020, level I]
- fewer TB treatment failure with RR of 0.63 (95% CI 0.46 to 0.85)[Chelkeba L et. al., 2020, level I]

However early initiation of ART was associated with 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).[Chelkeba L et. al., 2020, level I]

In HIV-TB coinfection, it is recommended that following TB treatment, ART should be initiated within the first eight weeks of TB treatment. However, patients with CD4 cell count <50 cells/mm^3 should receive ART within the first two weeks of initiating TB treatment.[WHO, 2017]

Among PLHIV with TB meningitis, initiation of ART may be delayed until two months post-TB therapy as immediate ART is significantly associated with more severe ADRs compared with its initiation two months after the start of TB treatment. Caution is needed if early ART initiation is necessary.[MoH, 2012]

Recommendation 14

- In HIV-tuberculosis (TB) coinfection antiretroviral therapy (ART) should be initiated within eight weeks of anti-TB treatment.
  - for HIV-TB patients with known CD4 <50 cells/mm^3, ART should be initiated within the first two weeks of anti-TB treatment.
- In HIV with TB meningitis, initiation of ART may need to be delayed until two months post-TB treatment.

- **Anti-retroviral treatment regimen for TB-HIV co-infection**

Drug-drug interactions (DDI) and overlapping drug toxicities are important issues when treating PLHIV with anti-TB and ARV drugs.[MoH, 2017] For patients who are already on ARV, the choice of anti-TB should not interfere with the current ARV. For patients who are ARV naïve, the choice of anti-TB depends on ARV regimen that is planned to be started. Rifampicin interaction with ART is especially significant and thus requires special attention. To avoid DDI for patients who are already on ART, the following regimen in the table should be considered:

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 to discuss on anti-TB regimen. For those not suspected to have ARV drug resistance, standard anti-TB regimen can be initiated.

A prospective cohort study among HIV-TB patients on ART comparing RIF- and rifabutin (RFB)-based therapies, even though RMP group showed better improvement in the immune and virological response, both groups of patients had non-significant outcomes in the following:[Schmaltz CAS et al., 2019, level II-2]

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

Daily anti-TB regimen is recommended in TB-HIV co-infected patients as in other non-HIV-TB population.[CDC NIH 2020; BHIVA, 2018 (Bracchi M et al.); WHO, 2017; NICE, 2019; ATS, 2016 (Nahid P et al.)]

Recommendation 15

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

Further details on the interactions of antiretrovirals (ARV) with anti-TB are discussed under **Subchapter 4.2** on **Anti-tuberculosis Drug-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 TB-HIV coinfection 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%).[MoH, 2012]

EPTB is the most significant risk factor associated with IRIS than those without IRIS. Other risk factors include baseline haemoglobin <100 g/L (OR=2.2, 95% CI 1.1 to 4.6) and baseline CD4 <50 cells/µL (OR=4.1. 95% CI 1.8 to 9.5).[MoH, 2012]

Severity of IRIS can range from mild to life-threatening. Severe IRIS should be referred to 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.[MoH, 2012]

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

- **Co-trimoxazole prophylaxis**

WHO recommends that for all HIV-TB coinfected patients, co-trimoxazole preventive therapy be given as soon as possible and throughout TB treatment.[WHO, 2010] However, the ATS/CDC/IDSA recommends co-trimoxazole prophylaxis to be given only in HIV-TB coinfected patients with CD4 <200 cells/µL.[ATS, 2016]

In newly diagnosed HIV patients or those without baseline CD4 count, co-trimoxazole 960 mg daily should be initiated together with TB treatment.[MoH, 2012] Co-trimoxazole can be stopped once the CD4 >200 cells/ µL for two consecutive readings or CD4 100- 200 cells/µL and HIV viral load undetectable at least once according to the Malaysia HIV consensus guidelines.[MOH, 2017]

Recommendation 16

- Co-trimoxazole preventive therapy should be given during tuberculosis (TB) treatment in TB-HIV coinfection with unknown CD4 count or CD4 <200 cells/µL.

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.[WHO, 2020a] Diagnosis of children in TB is challenging due to the paucibacillary disseminated disease with wide range of clinical presentation mimicking common childhood illnesses. A positive TB contact history (usually adult) would be a strong indicator of TB in a symptomatic child. Risk factors for rapid disease progression are age <5 years old, malnutrition and HIV infection.

WHO recommends symptoms-based screening to exclude active TB based on the presence of any of the following conditions.[WHO, 2020b]

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, not eating well, 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 for intrathoracic TB in children is classified into the following:[Graham SM et al., 2015]

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

A good prospective cohort study using Xpert Ultra on 535 children demonstrated that induced sputum specimen was more sensitive than nasopharyngeal aspirate (NPA) in diagnosing intrathoracic TB. Sending two respiratory samples for Xpert Ultra improved the specificity and sensitivity of both IS and NPA. These are summarized in **Table 8**.[Zar HJ et al., 2019, 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

In children who are symptomatic with more severe TB in tertiary setting, gastric aspirate (GA) and bronchoalveolar lavage (BAL) have significantly better yield than NPA in both AFB smear and TB culture[Cakir E et al., 2018, 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 with only four confirmed TB:[Hanrahan CF et al., 2019, level III]

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

Recommendation 17

- 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

Refer to **Appendix 8** on **Procedure for Gastric Aspiration and Nasopharyngeal Aspiration in Children** for further information.

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

LF-LAM had low sensitivity and specificity for the diagnosis of intrathoracic TB in children as shown in the following evidence. 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 from 78.5% (95% CO 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 specificity between 74.4% (95% CI 58.9 to 85.4) and 80.5% (95% CI 68.3 to 89.4).[Nicol MP et al., 2020,level II-2, Nkereuwem E et al., 2021,level II-2] 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 bacteria contamination.

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

b. Treatment

- **Anti-tuberculosis regimens**

In children (<5 years old), higher dose of anti-TB drugs is required to achieve the effective bactericidal activity compared with older children and adults.[Thee S et al., 2012, level III] Anti-TB dose in children should be calculated in mg/kg and the total dose must not exceed the maximum dose allowed. Refer to **Table 9** on **Recommended Dose of Anti-TB Drugs in Children**.

Medication dose requires recalculation as the child gains weight particularly in neonates and young children in every two to four weeks.

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 not associated with increased risk of INH or PZA hepatotoxicity, or optic neuritis related to EMB.[Donald PR, 2011, level I; Donald PR et al., 2006, 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	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 the new flavoured dispersible child-friendly FDCs in treating children with TB. This new formulary contains anti-TB drugs dose proportion that is in-line with the revised anti-TB dose for children (refer to **Table 10**).[WHO, 2018b]

Table 10: Current WHO recommended formulation for children

Weight band	Numbers of tablets	
	Intensive phase: RHZ 75/50/150*	Continuation phase RH 75/50
4 - 7 kg	1	1
8 - 11 kg	2	2
12 - 15 kg	3	3
16 - 24 kg	4	4
>25 kg	Adult 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 this new anti-TB formulary include:[WHO, 2018b]

- 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 18

- Child-friendly fixed-dose formulation* should be used to treat tuberculosis in children.

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

The outcomes of TB patients treated 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 (range 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 region.[Goraya J et al., 2002, 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, without intervention, spontaneous rupture with chronic discharging sinus will occur. Healing will eventually take place by scarring.

Systematic review on five RCTs involving 237 children showed that fine needle aspiration can shorten the resolution of BCG abscess at 6 months (RR=0.13, 95% CI 0.03 to 0.55). There is no evidence of oral antibiotics (e.g. erythromycin) or oral anti-TB can prevent the progression of BCG abscess.[Cuello-Garcia CA et al., 2013, 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 transplacental spread of TB through umbilical vessels, aspirated or ingested 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 newborn is exposed to an infectious adult, usually mother but sometimes other household members.

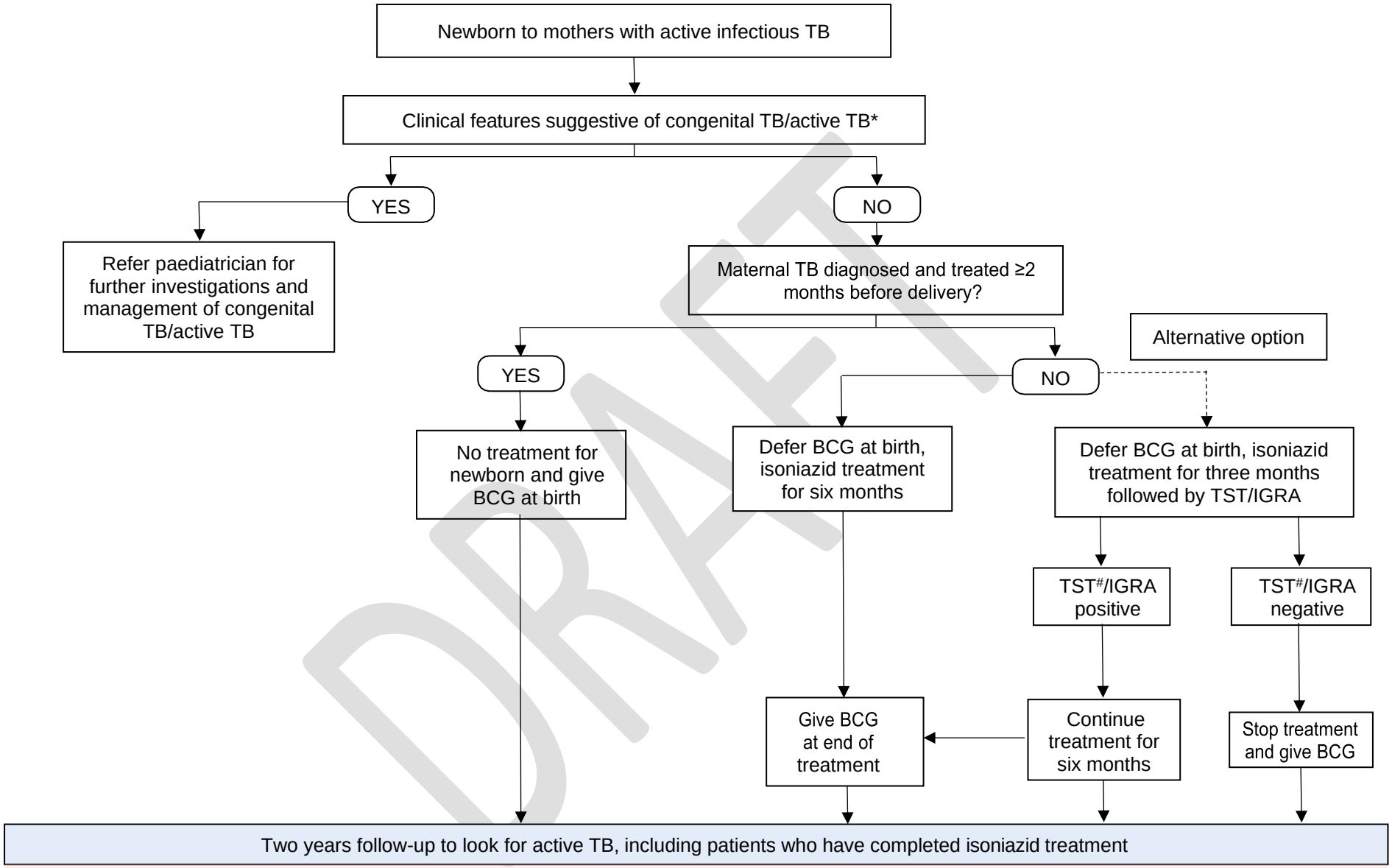
Both conditions are difficult to be distinguished and presentations are often non-specific. They tend to be disseminated and has high mortality. Symptoms are poor feeding, failure to thrive, fever, respiratory distress, hepatosplenomegaly, lymphadenopathy, abdomen distension with ascites or a “clinical sepsis” in disseminated TB. Identifying an infectious adult would be the key indicator of neonatal TB.

Investigations for both congenital and neonatal TB are similar as in older children and adults. It is important to note that congenital TB tends to be disseminated involving TB abdomen and meningitis. 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 histopathological examination.[MoH, 2012]

The management of newborns of mothers with TB depends on the mothers' TB infectious status at delivery. All newborns to mother with active TB need to be screened for TB. Mothers whose current sputum smear is positive or those receiving 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 the paediatrician with experience in treating TB.

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



*Refer text in **Subchapter 2.7** on **TB in Children** for diagnosis of active TB and congenital TB. #TST <5 mm is negative, TST ≥5 mm is positive

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. The practice of DOT for TB cases in Malaysia for year 2015 was 89.6%. The DOT supervisor was noted to be healthcare providers in 59.6% cases, family members 39.8% and, non-governmental organisations and community volunteers 1.2%.[MoH, 2018 (NSPTB)]

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).[Muller AM et al., 2018, 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.[WHO, 2020c] 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 the appropriate infrastructure. The advantages of using it are its potential observation of treatment adherence from a distance, reduce visit by healthcare providers and avoid travelling by patients. VOT is also more flexible to people's schedules. Patients should be educated on VOT and give consent for the procedure. A good and 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).[Story A et al., 2019, 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 patient 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. Apart from that, financial incentives used during anti-TB treatment may help patients adhere to and complete treatment. The incentives compared with no incentive decreased default rate by 26% (RR=0.74, 95% CI 0.61 to 0.90).[Muller AM et al., 2018, level I] Financial incentives may be in the form of travel or phone allowances for DOT/VOT.

Recommendation 19

- Directly observed treatment (DOT) should be done in the intensive phase of 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.[MoH, 2012] About a quarter of the world population (approximately 1.7 billion people) are estimated to have LTBI.[Houben RMG et al., 2016] In Malaysia, no published data is available on the prevalence of LTBI yet.

A person with LTBI has 5 - 10% risk of developing active TB during his/her lifetime, usually within the first five years after initial infection. 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.[WHO, 2015]

Under Pillar 1, Strategy 6 of the National Strategic Plan for TB Control (2016 - 2020), Malaysia aims to strengthen the programmatic management of LTBI.[MOH, 2018 (NSPTB)]

The general approach to the management of people with LTBI is illustrated in **Algorithm B** 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, as the testing and treatment of LTBI entails costs and/or risks.
WHO recommends the high-risk population that should be systematically tested and treated for LTBI are:[WHO, 2020b]

- household/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 and other associated occupational lung diseases

The testing and treatment of LTBI in other risk groups can be considered on an individual basis. Other risk groups that may be considered for LTBI testing and treatment by WHO are:

- healthcare workers
- immigrants for high TB burden countries
- prisoners
- illicit drug users

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

Testing and treatment for at-risk groups of LTBI may differ as discussed below.

- **Household or close contacts**

Household or close contacts are 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 started TB treatment.[DCD MOH, 2019] Contacts in close proximity for prolonged periods with an infected 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 was significantly associated with a larger bacillary load in the sputum of the index case patient and exposure to a high-aerosol TB case patient.[Jones-López EC et al., 2016, level II-2] However, the absolute proximity or the duration of exposure has not been well-established.[Menezes B et al., 2019, level I]

- **People living with HIV**

PLHIV are 18 times more likely to develop active TB disease than people without HIV. TB is also the leading cause of death among them.[WHO, 2020] 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 increases with progressive immunodeficiency.[CDC NIH, 2020] Even PLHIV on ART benefit from LTBI treatment.[WHO, 2020b] 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.[WHO, 2020b]

- **Other at-risk groups**

This group of people are at risk due to their immunocompromised health status or poor lung reserve. This includes patients having anti-TNF treatment, dialysis, organ or haematological transplant, silicosis or other occupational lung disease.

In the at-risk groups, active TB must be ruled out first before considering the diagnosis and treatment of LTBI. However, there is no gold standard test to diagnose LTBI. WHO recommends that either a TST or IGRA to be used to test for the infection.[WHO, 2020b]

- The at-risk groups that should be screened for LTBI should fulfil the following criteria to be diagnosed with LTBI:
  - **Absence of any clinical features suggestive of active TB** (cough, fever, night sweats, weight loss)
  - **Normal chest x-ray** or **static x-ray 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 for AFB smear and culture. In the presence of any unexplained abnormal findings, consider sending the chest x-ray for reporting
  - **A positive TST** or **IGRA test**

b. Tuberculin skin test

TST is performed via the Mantoux technique, which consists of intradermal injection of purified-protein derivative (PPD) on the inner surface 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.

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 guidelines as listed according to the categories in the **Table 11**.[MoH, 2012]

According to CDC and National Tuberculosis Controller Association (NTCA), the window period (duration between infection and skin test reactivity) is 8 - 10 weeks after exposure. 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.[ATS, 2000]

Table 11: TST cut-off value for different groups

Positive (TST) reaction	Types of individual
≥5 mm	• PLHIV • Organ transplant recipient • 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) 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.[WHO, 2020b]

Refer to **Appendix 9** on **Procedure for Tuberculin Skin Test**

c. 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 *Mycobacterium bovis,* BCG and most of the non-tuberculous mycobacteria.[Lewinsohn D et al., 2017 (ATS, 2017)] 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. They are also not affected by BCG vaccination status and thus useful for evaluation of LTBI in BCG-vaccinated individuals.[Zellweger JP et al., 2020, 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 be performed. Refer to **Appendix 10** 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.[Zhou G et al., 2020, level II-2]

- The pooled RR for disease progression in untreated individuals who were:
  - 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)

  IGRA has a significantly higher predictive ability than 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.[Lee S et al., 2019, 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 overall development of active TB was significantly more frequent in the IGRA positive vs IGRA negative group (p=0.001).

According to WHO, adult household contacts of bacteriologically confirmed PTB should be offered LTBI testing before treatment is started. The testing should not be a requirement for initiating TB preventive treatment for PLHIV, particularly in countries with a high TB incidence. This is because the benefits clearly outweigh the risks. These groups of patients who have a negative LTBI test should be assessed case by case for their individual risk of exposure to TB and the added advantage of receiving preventive treatment.[WHO, 2020b]

- LTBI testing is desirable but not required in HIV-positive population prior to initiation of LTBI treatment.

Recommendation 20

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

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

d. Treatment

LTBI treatment is designed to prevent the progression of asymptomatic TB infection to clinically active TB. Evidence has proven that treatment of LTBI can prevent 60 - 90% of cases from developing TB.[WHO, 2018a]

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 compliance and success of treatment, an effective, safe and short regimen is preferred for both adults and children.

e. HIV-negative adults

A local technology review showed the following LTBI treatment regimens were effective compared with placebo in preventing active TB:[Romli EZ et al., 2019, 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 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 with OR=0.35 (95% CI 0.19 to 0.61)

- RIF-PZA 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 good RCT, 4R was non-inferior to 9H in non-HIV adults with LTBI in preventing active TB. However, 4R had less adverse events of grades 3 to 5 within 146 days 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).[Menzies D et. al., 2018, level I]

The median rate of withdrawals from adverse events due to LTBI treatment regimens were as follows:[Romli EZ et al., 2019, 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.[Macaraig MM et al , 2018, level III]

f. HIV-positive adults

A large RCT on HIV-positive adults with LTBI comparing 1HP and 9H showed the following:[Swindells S et al., 2019, 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:[Hamada Y et al., 2018, 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:[Hamada Y et al., 2018, 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 latent TB treatment regimen with high treatment completion rate in adults with LTBI.

Recommendation 21

- 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 are contraindicated for INH-based regimens
- 6H or 9H may be used for patients who cannot tolerate or are contraindicated for rifamycin-based regimens

- In HIV-positive adults with LTBI, 1HP* may be considered for treatment.

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

*****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-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	Dosage
Isoniazid	Six months/ nine months	Daily	5 mg/kg, max 300 mg
Isoniazid + rifampicin	Three months	Daily	INH: 5 mg/kg, max 300 mg RIF: 10 mg/kg, max 600 mg
Rifapentine + isoniazid	Three months	Weekly	INH: 15 mg/kg, max 900 mg RPT: <50 kg; 750 mg (5 tablets) >50 kg: 900 mg (6 tablets; max dose)
Rifampicin	Four months	Daily	10 mg/kg, max 600 mg

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

Note: Pyridoxine 30 mg daily needs to be added if INH is prescribed.

g. Monitoring

Adherence to complete the full course of LTBI treatment is important to ensure the effectiveness of the treatment in preventing active TB. This can be achieved by health education and good support to the patients. They should be advised to contact their healthcare providers at any time if they have symptoms e.g. 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 its complication in patients receiving LTBI. The surveillance systems for treatment adherence and completion as well as resistance to TB drugs should be established for evaluation of treatment outcomes. The CPG DG suggests monitoring schedule for individuals on LTBI treatment as shown in **Table 13** below.

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

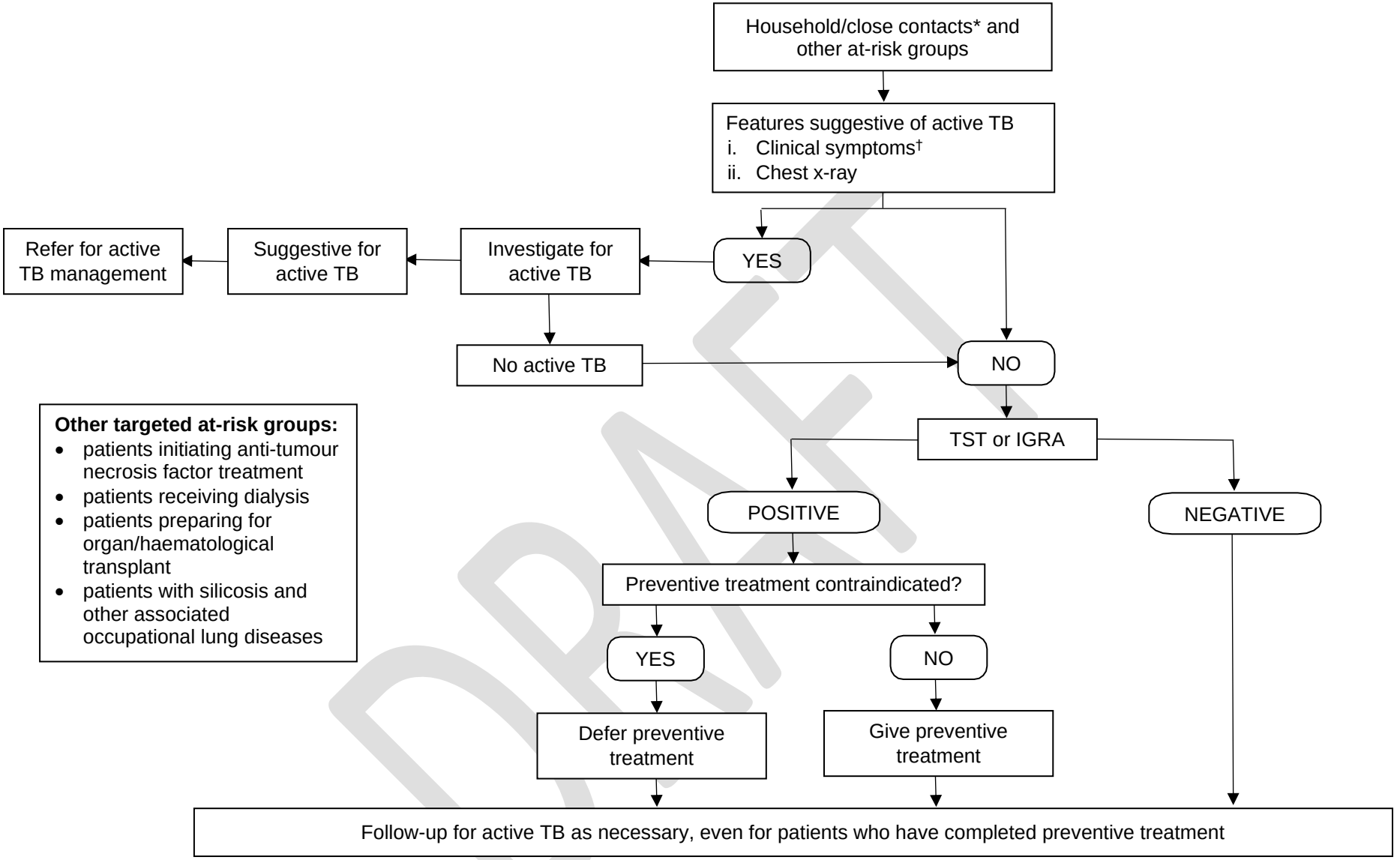
Time*	Investigation	Assessment
Day 1	FBC, RBS, RP, LFT HIV** CXR	Health education: • Adherence • Side effects • Symptoms of active TB
Week 2 - 4	LFT	
End of LTBI treatment	CXR	
Three months after end of treatment	-	Symptoms of active TB
Nine months after end of treatment	-	
18 months after end of treatment	CXR	

FBC=full blood count, RBS=random blood sugar, 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 who have completed treatment are advised to follow-up regularly for two years. Adults who developed active TB while on LTBI treatment or during follow-up should be referred to specialists 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 outcome reported. The LTBI treatment outcome proposed by this CPG DG is shown in **Appendix 11**.

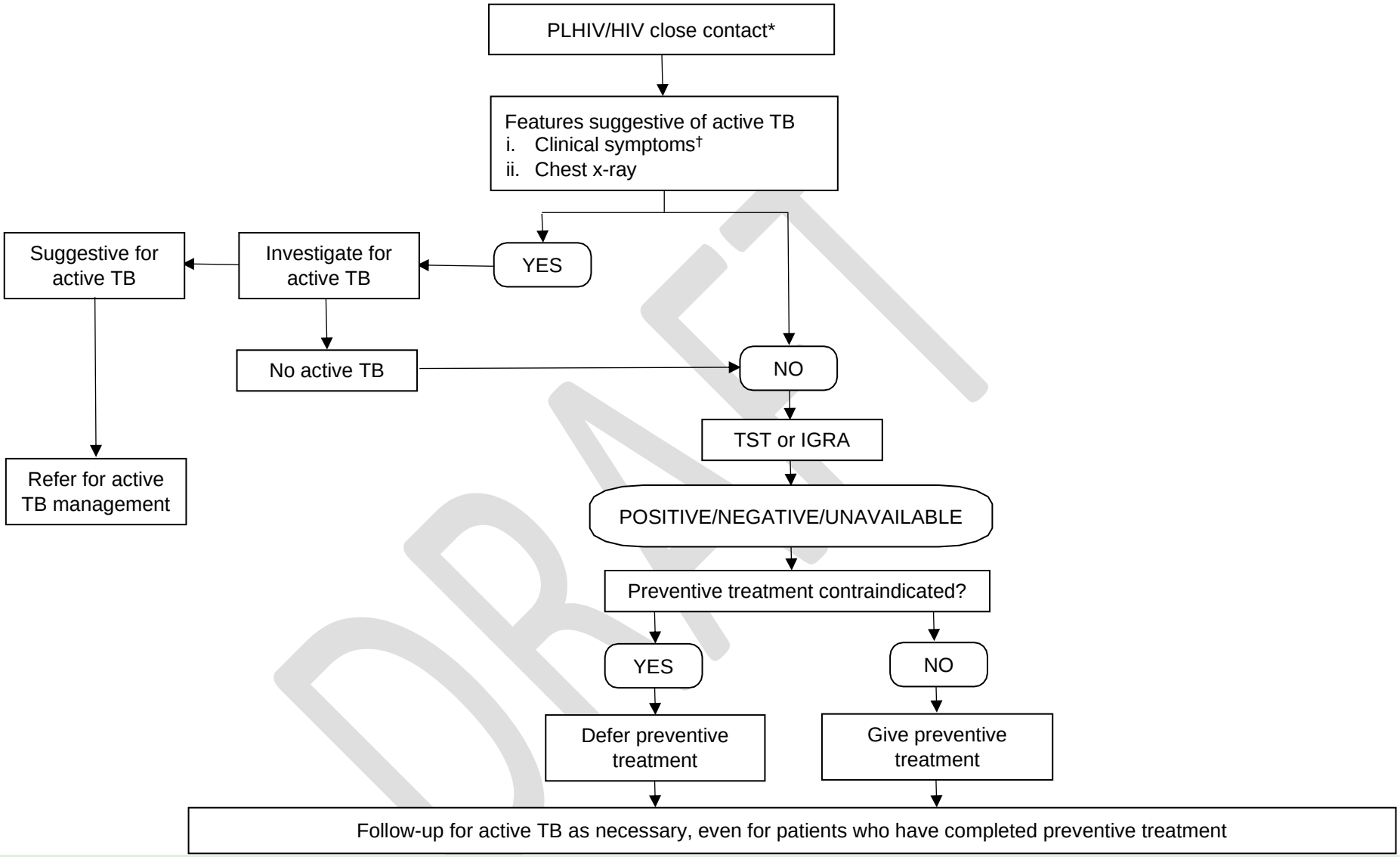
The management of LTBI in adults is shown in **Figure 4**.
The management of HIV-positive adults with LTBI is shown in **Figure 5**.



*Household or close contacts are individuals who live in the same household or are sharing the same air space with the 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 are sharing the same air space with the 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 TB 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.[Cruz AT et al., 2010, 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.[Martinez L et al., 2020, level II-2] Thus, early investigation and treatment is necessary to prevent active TB especially in children below 5 years and other specific groups who are at risk for LTBI and/or progression to TB disease.

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

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

a. LTBI tests

As in adults, 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 (or infection by) mycobacteria. A negative TST or IGRA result may not be reliable in infants younger than three months of age as the cell-mediated immune responsiveness may not be fully developed in young children.

- **Tuberculin skin test**

Interpretation of TST results in children is the same as for adults described earlier. Children may take 8 - 12 weeks to develop a positive TST result after last known exposure to TB disease.

- **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. Comparing to TST, IGRAs have a similar sensitivity but greater specificity for the diagnosis of TB infection. A positive TST could also be due to recent BCG vaccination and nontuberculous mycobacterial infection.

For diagnosis of LTBI in children ≥ 2 years, either IGRA or TST may be used;[WHO 2020b] IGRA is preferred if available. In a study in US involving 3,593 children (25% were <5 years old and 92% were born outside the US) with risk for LTBI or progression to TB disease screened with both TST and two IGRAs (Quantiferon Gold In-Tube test [QFT-GIT] and T-SPOT), the IGRAs 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] in comparison to the 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. Out of the 533 children with TST-positive and IGRA-negative results but not treated for LTBI, which included 54 children <2 years old, none developed disease. 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 United States.[Ahmed A et al., 2020, 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.[WHO, 2020b] However, a study in an US-based health system including 116 children <2 years (7 to 23 months) tested with QFT-GIT, none of the children who were TST positive but IGRA negative and went untreated developed TB disease.[Soler-Garcia

A et al., 2020, level III The American Academy of Paediatrics supports the use of IGRAs in children < 2 years as it is used by some experts even the practice is not yet widespread.AAP, 2018

A positive IGRA or TST result should be considered indicative of infection with *M. tuberculosis*. A negative IGRA or TST results cannot conclusively exclude a 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.Starke JR, 2020, level III

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

b. Excluding active TB

As in adult, all treatment for LTBI in children should be initiated only after active TB disease has been ruled out. WHO recommends symptoms-based screening to exclude active TB (refer **Subchapter 2.7** on **Tuberculosis in Children** for the symptoms-based screening and diagnosis of TB disease in children). Evaluation for TB disease must be pursued in all children with a positive TST or IGRA.

CXR are usually normal in children with LTBI but may show dense nodules with calcifications, calcified non-enlarged regional lymph nodes, or pleural thickening (scarring).Saiman La et al, 2004, level III If there are any unexplained CXR abnormalities or diagnostic uncertainties, cases should be referred to a centre with 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, addition of CXR increases the confidence of active TB has been excluded and lowers the concern that LTBI treatment is being administrated inappropriately (i.e., risk of wrongly treating an active TB disease with LTBI regime). For adults and adolescents living with HIV, WHO reiterated that the requirement of CXR as additional investigation should not pose a barrier to the provision of LTBI treatment. However, there were no clear statement on the role of additional CXR for infants and children living with HIV.WHO, 2020

- CXR should be done prior to LTBI treatment; however, if there is a difficulty in obtaining a CXR, LTBI treatment can be initiated in high-risk asymptomatic children. It needs to be done as soon as possible, ideally within 14 days of initiation of treatment.

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

WHO makes the following recommendations for the high-risk group of children to be screened for LTBI and given LTBI treatment after excluding active TB:WHO, 2020b

- Children <5 years (irrespective of HIV status) who are household contacts of people with bacteriological confirmed pulmonary TB should be given TB preventive treatment even LTBI testing is not available
- Children ≥5 years (irrespective of HIV status) who are household contacts of people with bacteriological confirmed pulmonary TB 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
- Infant 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 bacteriological confirmed PTB**

Any children contact of bacteriological confirmed PTB must be evaluated for active TB with a history, physical exam, chest radiograph, and TST or IGRA. Evaluation should be performed as soon as the contact is identified. If initial TST or IGRA is negative, it should be repeated 8 to 12 weeks following the last known exposure to TB.

- **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".[ATS, 2000, level III] It is warranted because the child's cellular immune response to TB may not have fully developed by the time of testing and because 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).[Starke JR et al., 2014, level III] If the initial TST or IGRA is negative, the child should be retested at 8 to 12 weeks. If the repeat test is negative, treatment may be discontinued at the discretion of the clinician. In any setting where LTBI test is not available, all children contacts <5 years should be offered LTBI treatment as recommended by WHO.[WHO, 2020b]

- **Children aged ≥5 years**

For immunocompetent child contacts ≥5 years of age with positive initial TST or IGRA and negative clinical evaluation, LTBI treatment may be given.[WHO, 2020b] However, if the initial LTBI testing is negative, decision regarding treatment may be deferred pending results of a second test, usually performed 8 to 12 weeks following the last date of contact with the index patient. This approach is warranted because testing for TB infection with TST or IGRA shortly following exposure may be negative, since immune reactivity to TB antigens following initial exposure to TB may take up to 10 weeks to develop. 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 beginning at 3 through to 12 months of age (for perinatal infected infant) or at the time HIV infection is diagnosed (in older children and adolescents)

For HIV-infected children aged ≥12 months in high TB transmission setting, treatment for LTBI should be offered regardless of CD4 cell count or if LTBI test is unavailable.[WHO, 2020b] 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.[Grant AD et al., 2005, 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.[WHO, 2020b]

If LTBI test is available and the result is negative, for HIV-infected children aged ≥12 months, decision on LTBI treatment after excluding active TB should be based on case-by-case assessments for the potential benefits and harm of LTBI.[WHO, 2020b]

For HIV infected infant <12 months old, the evidence of adult studies on treating HIV infected adults without history of contact cannot be applied. WHO recommends for infants <12 months of age, LTBI treatment should be offered only if there is history of contact with TB.[WHO, 2020b]

- **Children in other risk groups**

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

Recommendation 22

- 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 latent tuberculosis should be notified to the TB Control Programme for surveillance purposes.

d. LTBI treatment regimen

Similar to adults, CPG DG prefer an effective but shorter regimen for LTBI treatment in children to ensure adherence and success of the treatment.

Current regimen used to treat LTBI in children include:

a. RIF daily for four months (regimen abbreviation: 4R)
b. INH and rifapentine (RPT) weekly for three months (total in 12 doses) (administration via directly observed therapy preferred; regimen abbreviation: 3HP)
c. INH and RIF daily for three months (regimen abbreviation: 3R)
d. INH daily for six or nine months (regimen abbreviation: 6H/9H)

In a systematic review involving children below 15 years old with LTBI, 3- or 4-months daily RIF and INH (3HR/4HR) was safe and showed better completion rate than the 6 or 9 months INH (6H/9H) based on the following outcomes.[Assefa Y et al., 2018, level I]

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

Two recent good RCTs looked at alternative LTBI treatment regimen 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.[Diallo T et al., 2018, level I] Treatment completion with 4R showed an adjusted difference of 13.4 percentage points (95% CI 7.5 to 19.3).

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 AEs or treatment-attributed death.[Villarino ME et al., 2015, 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). Drug's toxicity was uncommon in either group and there were no instances of symptomatic hepatotoxicity.[Gaensbauer et al., 2018, level II-2]

The choice of regimen is based largely on the likelihood of adherence, the potential for adverse effects and preference (of the patient, provider, and/or public health program). The CPG DG recommends daily RIF for four months (for children of all ages except newborns 28 days and below) and weekly INH and RPT for three months (for children >2 years) as the preferred regimens, given a good safety profile and better completion rate. However, RPT is currently not available in Malaysia. Alternative regimes are 3HR and 6H if the preferred regime 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 regimens not compatible with rifamycin-based regimes should be treated with INH monotherapy.

For children <2 years of age on ART, treatment of LTBI with INH monotherapy is preferred as the potential for drug-drug interaction (DDI) with the shorter rifamycin-based regimens in individuals taking ART 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).[WHO, 2020b]

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, uremia, 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 23

- 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 and 6H.
- In HIV-infected children with LTBI, 6H is the preferred regimen for:
  - children <2 years of age
  - children ≥2 years on antiretroviral treatment not compatible with rifamycin-based regimen

3HR=three months daily isoniazid + rifampicin, 3HP=three months daily isoniazid+weekly rifapentine, 4R=four months daily rifampicin, 6H=six months daily isoniazid
*rifapentine is not yet available in Malaysia

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

Table 14: Recommended LTBI treatment regimens for children

Drugs	Duration	Interval	Dose
Isoniazid (6H)	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) 3. 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) 3. Maximum dose: 600 mg
Isoniazid + rifampicin (3HR)	3 months	Daily	Dose of INH and RIF same as above
Rifapentine + isoniazid (3HP)	3 months (12 doses)	Weekly	Isoniazid: 15 - 25 mg/kg, maximum 900 mg or 100 mg tablet according to weight: 10 - 15 kg: 3 tabs (300 mg) 16 - 23 kg: 5 tabs (500 mg) 24 - 30 kg: 6 tabs (600 mg) 31 - 34 kg: 7 tabs (700 mg) >34 kg: 7 tabs (700 mg) Rifapentine (150 mg tablet): 10 - 15 kg: 2 tabs (300 mg) 16 - 23 kg: 3 tabs (450 mg) 24 - 30 kg: 4 tabs (600 mg) 31 - 34 kg: 5 tabs (750 mg) >34 kg: 5 tabs (750 mg)

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

e. 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 weight if needed
- 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 age-gender appropriate growth chart is very important to ensue early detection of active TB cases.

Frequent dose adjustment for LTBI treatment will be needed for young infant 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.[WHO, 2018; AAP, 2004] Children with deranged LFT should be referred to specialist for initiation of LTBI treatment.

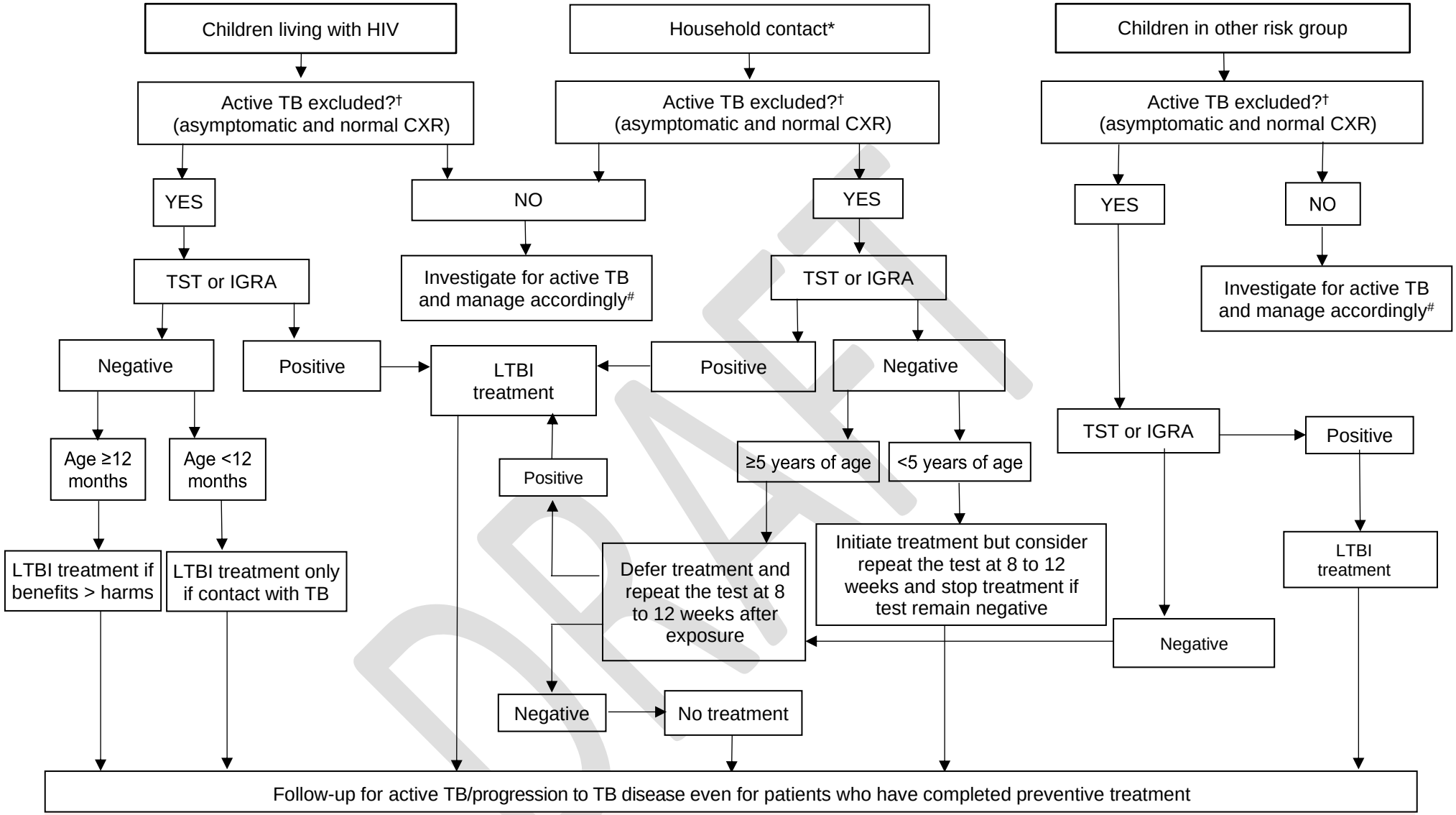
Routine LFT monitoring is not needed in children receiving LTBI treatment. However, laboratory evaluation is warranted for children who develop clinical symptoms of liver injury. Early signs of hepatitis include anorexia, nausea, vomiting and abdominal discomfort. Reduced activities and persistent fatigue/malaise/weakness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

Support and good counselling given to patients and families on importance of LTBI treatment will improve the acceptance and adherence. The children must be able to 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 side effect may affect the adherence and parents may default subsequent follow-up. Therefore, it is important to educate the patient and family about the potential side effects. 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 should be followed-up for two years with recommended interval as summarised in yellow box above regardless of LTBI treatment has been given or not. 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 reaction is suspected earlier. Neither is there any role of repeat TST or IGRA to assess the effectiveness of LTBI treatment.[AAP, 2018]

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

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 11**.



¥***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: Module 1: Prevention. Geneva: World Health Organization; 2020

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

4. SECTION III: ANTI-TUBERCULOSIS DRUG ADVERSE 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 National Pharmaceutical Regulatory Agency (NPRA) Pharmacovigilance, MoH indicates underreporting of these events, even for serious ADRs. Knowledge about anti-TB ADR rate is important to the 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.[ATS, 2016 (Nahid P et al.); Tostmann A et al., 2008, level III] For INH-induced neuropathy, risk factors include pregnancy, extremes of age, HIV infection, diabetes mellitus, alcoholism, malnutrition and chronic renal failure.[ATS, 2016 (Nahid P et al.)]

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. However, children are believed to experience less anti-TB ADR compared with adults.

Identifying the specific offending drug is challenging because anti-TB treatment uses combination of antibiotic therapy. In order to do so, tools e.g. the WHO-Uppsala Monitoring Centre causality assessment system are used.[WHO, 2013]

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 cytopenias, renal or liver impairment help to narrow the list of offending drugs. Additional investigations may be required as dictated by the clinical presentation.

There are many standards for the grading of ADRs. One such grading system is the Common Terminology Criteria for Adverse Events (CTCAE) grading of ADR. The general description of an ADR by CTCAE is summarised below.

CTCAE term				
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**	Life-threatening consequences; urgent intervention indicated	Death related to AE

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

Cutaneous ADRs are among the commonest 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. An example for the 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 (Available at: http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf)

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.[Duong TA et al., 2017, 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 drug-induced liver injury:

1. The American Thoracic Society criteria distinguishes between symptomatic and asymptomatic drug induced hepatitis:[ATS, 2006 (Saukkonen JJ et al.)]
   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.[DILI Expert Working Group 2011 (Aithal GP et al., 2011)]
   i. an ALT ≥5 times ULN
   ii. an ALP ≥2 times ULN
   iii. an ALT ≥3 times and total bilirubin 2 times 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.

In general, two methods for reintroducing anti-TB drugs may be used following an ADR:

i. Drug challenge

Drug challenge is the gold standard for diagnosing anti-TB ADR including drug hypersensitivity reaction.[Ariza A et al., 2020, level III] Drug challenge is used when multiple drugs may be responsible for the suspected ADR.

It is done with the least likely offending drug first or in the order of the drug's importance. In severe or serious ADR, drug challenge should be done in a graded manner when the patient has recovered.

Careful monitoring of the patient should be done during drug challenge while ADRs managed promptly and effectively. Stop drug challenge immediately when ADR appears.

Continue with drugs that were tolerated and perform drug challenge on new drugs once the patient recovers as shown in **Table 16**.

Table 16: A typical drug challenge schedule for severe or serious ADR in adults weighing >30 kg

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

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

It is not necessary to challenge with all anti-TB drugs. 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 ADR during drug challenge identifies the offending drug(s). However, sometimes more than one drug may cause the same reaction. It is prudent to continue drug challenge with other drugs in cutaneous drug reactions and DILI.

ii. Drug de-challenge

Drug de-challenge is done when one drug is suspected for causing an ADR and it is not safe to perform drug challenge. Examples include suspected RIF-induced-immune thrombocytopenia, -hemolytic anemia or -acute renal failure.[Aberer W et al., 2003, 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. Treatment of adverse drug reactions in active tuberculosis

The treatment 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[ATS, 2016 (Nahid P et al.)]
- in cases of mild to moderate ADR, addition of symptomatic treatment may be sufficient[WHO, 2010; ATS 2016]
- in cases of severe ADR, all anti-TB treatment should be interrupted unless the offending drug is known[ATS, 2016 (Nahid P et al.); NICE, 2019]

A bridging/interim regimen should be used in patients with severe TB who also experience a severe ADR until an alternative regimen could be given.[ATS, 2016 (Nahid P et al.); NICE, 2019] In practice, the regimen should contain at least three effective drugs in the intensive phase and two in the maintenance phase. An example of such regimen is the streptomycin-EMB-levofloxacin regimen used in EHRZ-associated drug induced liver injury.

Drug desensitisation may be attempted in cutaneous ADR except for SCARs (drug induced Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms and Acute Generalized Exanthematous Pustulosis). A retrospective review of 34 drug desensitisation procedures in HIV-positive adults with anti-TB ADR showed:[Siripassorn K et al., 2018, 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 small number of desensitisation procedures performed.

Recommendation 24

- In non-severe cutaneous adverse cutaneous reactions due to rifampicin or isoniazid, 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.[MoH, 2002] Two drug desensitisation techniques are used.

- In rapid desensitisation, the drug is given in escalating doses at hourly interval 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 reaction. Further

desensitisation for the day should be stopped. Same technique or principle of desensitisation can be applied on children with the help from 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.

i. 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 reactivation rate compared with other regimens.[Jindani A et al., 2004, Level I, Grace AG et al., 2019. Level I]

Other regimens used for the treatment of PTB include:

a. 2EHRZ/6HE[WHO, 2003]
b. 2HRZ/4HR[ATS, 2016 (Nahid P et al.)]
c. 6RZE[ATS, 2016 (Nahid P et al.)]
d. 2EHR/7HR[ATS, 2016 (Nahid P et al.)]

ii. New 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 relapsed rate compared with standard regimen (RR 3.56, 95% CI 2.37 to 5.37).[Grace AG et al., 2019, level I]

New anti-TB regimens that do not include RMP or INH are mainly in drug-resistant TB treatment. For patients who have absolute contraindication to INH or RIF, an INH- or RIF-resistant regimen may be used.[ATS, 2016 (Nahid P et al.)] These patients should be referred to specialists for management.

c. Treatment 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.[Peace C et al., 2018, level I]

The principles of management for ADR is 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-tuberculosis drug-drug interactions**

Anti-tuberculous rifamycins (RIF, RFB and RPT) are key drugs in (active and latent) tuberculosis 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 having the weakest enzyme inducing effect.[ATS, 2016 (Nahid P et al.)] Clinicians managing tuberculosis must be familiar with rifamycin drug interaction, particularly with new drugs. Refer to **Appendix 12** on **Clinically Significant Drug–drug 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.[ATS, 2016 (Nahid P et al.)] Refer to **Appendix 13** on **Clinically Significant Drug–drug Interactions Involving Isoniazid** for the description and management of INH drug interaction.

- **Anti-retroviral therapy and anti-tuberculosis drug-drug interaction**

It is important to emphasize on the potential DDI between ART and TB treatment following the initiation of TB treatment especially RIF.

Rifamycins play a key role in the success of TB treatment. People living with HIV-TB co-infection should receive rifamycin-containing treatment regimen despite potential drug interaction. RIF being a potent inducer of cytochrome P450 enzymes and the drug transporter P-gp, reduces bioavailability of a broad range of antiretroviral drugs especially protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and integrase inhibitors. RIF is a more potent inducer of the cytochrome P450 system than RPT, which in turn is more potent than RFB. No clinically significant interactions are expected between ARVs with INH, EMB or PZA.

a. Nucleoside/nucleotide reverse transcriptase inhibitors

There are no clinically significant interactions between NRTIs with either RIF or RFB[MoH, 2012] except tenofovir alafenamide due to insufficient evidence.

b. Non-nucleoside reverse transcriptase inhibitors

- **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 difference in mortality with RR of 1.08 (95% CI 0.99 to 1.18)[Mbuagbaw L et al.,2016, level I] and 0.70 (95% CI 0.44 to 1.13) respectively.[Jiang H et al., 2014, level I]

In the first meta-analysis, there was also no difference in the following outcomes:[Mbuagbaw L et al.,2016, level I]

- virological success (RR=1.08, 95% CI 0.99 to 1.18)
- progression to AIDS (RR=1.09, 95% CI 0.62 to 1.92)
- discontinuation rate (RR=0.92, 95% CI 0.59 to 1.42)

In the second meta-analysis, there was no difference in TB treatment outcomes (RR=1.01, 95% CI 0.96 to 1.06). However, EFV group was superior than NVP with:[Jiang H et al., 2014, 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 (RR=1.07, 95% CI 0.98 to 1.16)
- lower risk of ART discontinuation due to adverse events (RR=0.43, 95% CI 0.23 to 0.81)

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

Recommendation 25

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

c. Protease inhibitors (PIs)

RIF-based anti-TB regimen should not be used with PI-based ART.[MoH, 2012; WHO, 2010] RFB 150 mg once daily is the preferred rifamycin to be used in combination with PI-based ART.[WHO, 2010]

Recommendation 26

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

d. Integrase inhibitors

- **Raltegravir**

A recent large RCT on TB-HIV co-infected adults who were receiving RIF-based anti-TB treatment failed to show non-inferiority of standard dose raltegravir (RAL) 400 mg twice daily to EFV 600 mg once daily (between group difference of viral suppression was -5.2% which did not meet the predefined criterion for non-inferiority of -12%).[De Castro N, et al., 2021, level I]

The recommended dose of RAL when co-administered with RIF is 800 mg twice daily.[DoHHS, 2020 (AIDSinfo)]

- **Dolutegravir (DTG)**

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:[Kanters S et al., 2020, 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). Apart from that, neuropsychiatric AEs between them were comparable.[Kanters S et al., 2020, 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).[Dooley et al., 2020, level I]

In patients receiving integrase inhibitor-based ART, rifabutin-based anti-TB treatment may be used without adjusting INSTI dose.[DoHHS, 2020 (AIDSinfo)]

Recommendation 27

- Raltegravir may be used with rifampicin-based antituberculosis (anti-TB) regimen at 800 mg twice daily dosage.
- Dolutegravir 50 mg twice daily may be used with rifampicin-based anti-TB regimen.
- Patients on integrase inhibitor-based ART may use rifabutin-based anti-TB regimen without dose adjustment.

Refer to **Appendix 14** 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:
- wide dissemination of the CPG (soft- and hardcopies) to healthcare providers
- TB training activities held annually in all states
- Xpert Ultra is available in almost all states and some health clinics in Malaysia
- basic radiology services are available in all hospitals and some health clinics in Malaysia
- sputum microscopy services are available in most hospitals and health clinics in Malaysia

Existing barriers for application of the recommendations of the CPG are:
- current TB training programme for health care providers is still inadequate in frequency, breadth and depth on management of LTBI and TB in children
- lack of awareness and knowledge on LTBI among the healthcare providers and public leading to low acceptance to LTBI treatment
- healthcare facilities and human resources are lacking in remote or high TB burden areas for TB control and management
- rifapentine as the preferred option for LTBI treatment is not available in Malaysia

5.2. Potential Resource Implications

Several recommendations have been formulated for the management of active TB and LTBI in both adults and children. This has led to potential resource implications in terms of budget, healthcare infrastructures and human resources 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 ADA is currently available only in Sabah Public Health Laboratory. In order to diagnose TB early and prevent TB transmission, the diagnostic tests need to be expanded to more clinics.

In terms of diagnosis of LTBI, IGRA is more specific than TST. However, it is not widely available and can only be done by appointment, limited by the number of tests that can be done at the reference laboratories and the cost of the test itself. At present, IGRA is only done once in selected at-risk populations due to financial constraints.

The currently available FDC anti-TB drugs are not suited for children. The inclusion of the child-friendly FDC is critical to improve both the treatment effectiveness and adherence.

Syrup INH is not available for LTBI treatment in health clinics. It should be made available to improve treatment acceptance and adherence. Rifapentine (RPT) is one of the preferred short course regimens for LTBI due to its high treatment completion rate. However, it is not available in Malaysia.

Since 2020, the management of LTBI is being rolled out nationwide. Unfortunately, the surveillance system for management of LTBI is not fully optimised. Hence, a dedicated TB team for health clinics in high TB burden areas and the development of a web-based surveillance system for programmatic management of LTBI should be considered to facilitate the smooth running of the programme.

Online training module on active TB and LTBI treatment has not been developed. The availability of such module will rapidly increase the number of health care providers trained and improve the outreach of the training programme. This will enhance the health care providers knowledge and skills in TB management.

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

5.3. Clinical Audit Indicators

Several key performance indexes on TB management being monitored by MOH is in line with the CPG recommendations. Thus, the following are proposed as clinical audit indicators for the CPG:

TB treatment success (cured and completed) rate (Target 90%)	=	$\frac{\text{Number of successfully treated TB cases in a year}}{\text{Number of registered TB cases (all forms) in the same year}}$	x100%
TB mortality rate (Target ≤5 in 100,000 population)	=	$\frac{\text{Number of TB deaths in a year}}{\text{Estimated mid-year population in the same year}}$	x100,000
LTBI treatment coverage for each of the three priority groups*: (Target 90%)	=	$\frac{\text{Number of people in each priority groups enrolled on LTBI treatment in a year}}{\text{Number of people in each priority group eligible for LTBI treatment in a year}}$	x100%

*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 will be developed following the approval of the CPG by MoH which include launching of the CPG, Quick Reference and Training Module.

REFERENCES

1. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58(9):854-63.
2. Ahmed A, Feng PI, Gaensbauer JT, et al. Interferon-γ Release Assays in Children <15 Years of Age. Pediatrics. 2020;145(1).
3. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. Clinical pharmacology and therapeutics. 2011;89(6):806-15.
4. Albanna AS, Smith BM, Cowan D, et al. Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis. The European respiratory journal. 2013;42(3):721-32.
5. American Academy of Pediatrics Committee on Infectious Diseases. Red Book (2018) Report of the Committee on Infectious Diseases, 31st Edition. AAP; 2018.
6. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recommendations and reports: Morbidity and mortality weekly report Recommendations and reports. 2000;49(Rr-6):1-51.
7. Ariza A, Mayorga C, Bogas G, et al. Advances and novel developments in drug hypersensitivity diagnosis. Allergy. 2020;75(12):3112-23.
8. Assefa Y, Assefa Y, Woldeyohannes S, et al. 3-month daily rifampicin and isoniazid compared to 6- or 9-month isoniazid for treating latent tuberculosis infection in children and adolescents less than 15 years of age: an updated systematic review. The European respiratory journal. 2018;52(1).
9. Bjerrum S, Broger T, Székely R, et al. Diagnostic Accuracy of a Novel and Rapid Lipoarabinomannan Test for Diagnosing Tuberculosis Among People With Human Immunodeficiency Virus. Open forum infectious diseases. 2020;7(1):ofz530.
10. Bracchi M, van Halsema C, Post F, et al. British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2019. 2019;20(S6):s2-s83.
11. Braganza Menezes D, Menezes B, Dedicoat M. Contact tracing strategies in household and congregate environments to identify cases of tuberculosis in low- and moderate-incidence populations. The Cochrane database of systematic reviews. 2019;8(8):CD013077.
12. Broger T, Nicol MP, Sigal GB, et al. Diagnostic accuracy of 3 urine lipoarabinomannan tuberculosis assays in HIV-negative outpatients. The Journal of clinical investigation. 2020;130(11):5756-64.
13. Bunkar ML, Agnihotri SP, Gupta PR, et al. Add-on prednisolone in the management of cervical lymph node tuberculosis. The Indian journal of tuberculosis. 2016;63(2):96-9.
14. Çakır E, Özdemir A, Daşkaya H, et al. The value of nasopharyngeal aspirate, gastric aspirate and bronchoalveolar lavage fluid in the diagnosis of childhood tuberculosis. The Turkish journal of pediatrics. 2018;60(1):10-3.
15. Chakravorty S, Simmons AM, Rowneki M, et al. The New Xpert MTB/RIF Ultra: Improving Detection of Mycobacterium tuberculosis and Resistance to Rifampin in an Assay Suitable for Point-of-Care Testing. mBio. 2017;8(4).
16. Chelkeba L, Fekadu G, Tesfaye G, et al. Effects of time of initiation of antiretroviral therapy in the treatment of patients with HIV/TB co-infection: A systemic review and meta-analysis. Annals of medicine and surgery (2012). 2020;55:148-58.
17. Chen CC, Chiang CY, Pan SC, et al. Health system delay among patients with tuberculosis in Taiwan: 2003-2010. BMC Infect Dis. 2015;15:491.
18. Cruz AT, Starke JR. Pediatric tuberculosis. Pediatrics in review. 2010;31(1):13-25; quiz -6.
19. Cuello-García CA, Pérez-Gaxiola G, Jiménez Gutiérrez C. Treating BCG-induced disease in children. The Cochrane database of systematic reviews. 2013;2013(1):CD008300.
20. De Castro N, Marcy O, Chazallon C, et al. Standard dose raltegravir or efavirenz-based antiretroviral treatment for patients co-infected with HIV and tuberculosis (ANRS 12 300 Reflate TB 2): an open-label, non-inferiority, randomised, phase 3 trial. The Lancet Infectious diseases. 2021;21(6):813-22.
21. Diallo T, Adjobimey M, Ruslami R, et al. Safety and Side Effects of Rifampin versus Isoniazid in Children. The New England journal of medicine. 2018;379(5):454-63.
22. Donald PR, Maher D, Maritz JS, et al. Ethambutol dosage for the treatment of children: literature review and recommendations. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2006;10(12):1318-30.
23. Donald PR. Antituberculosis drug-induced hepatotoxicity in children. Pediatric reports. 2011;3(2):e16.

24. Dooley KE, Kaplan R, Mwelase N, et al. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020;70(4):549-56.
25. Drain PK, Gardiner J, Hannah H, Broger T, Dheda K, Fielding K, Walzl G, Kaforou M, Kranzer K, Joosten SA, Gilpin C. Guidance for studies evaluating the accuracy of biomarker-based nonsputum tests to diagnose tuberculosis. The Journal of infectious diseases. 2019 Oct 8;220(Supplement_3):S108-15.
26. Drugs and Lactation Database (LactMed) - Rifampin [Internet]. National Library of Medicine (US). Available at: http://www.ncbi.nlm.nih.gov/books/NBK501348/?report=reader)
27. Gaensbauer J, Aiona K, Haas M, et al. Better Completion of Pediatric Latent Tuberculosis Treatment Using 4 Months of Rifampin in a US-based Tuberculosis Clinic. The Pediatric infectious disease journal. 2018;37(3):224-8.
28. Gallardo CR, Rigau Comas D, Valderrama Rodríguez A, et al. Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis. The Cochrane database of systematic reviews. 2016;2016(5):CD009913.
29. Goraya JS, Virdi VS. Bacille Calmette-Guérin lymphadenitis. Postgraduate medical journal. 2002;78(920):327-9.
30. Grace AG, Mittal A, Jain S, et al. Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis. The Cochrane database of systematic reviews. 2019;12(12):CD012918.
31. Graham SM, Cuevas LE, Jean-Philippe P, et al. Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children: An Update. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61Suppl 3(Suppl 3):S179-87.
32. Grant AD, Charalambous S, Fielding KL, et al. Effect of routine isoniazid preventive therapy on tuberculosis incidence among HIV-infected men in South Africa: a novel randomized incremental recruitment study. Jama. 2005;293(22):2719-25.
33. Hamada Y, Ford N, Schenkel K, et al. Three-month weekly rifapentine plus isoniazid for tuberculosis preventive treatment: a systematic review. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2018;22(12):1422-8.
34. Hanrahan CF, Dansey H, Mutunga L, et al. Diagnostic strategies for childhood tuberculosis in the context of primary care in a high burden setting: the value of alternative sampling methods. Paediatrics and international child health. 2019;39(2):88-94.
35. Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS medicine. 2016;13(10):e1002152.
36. Huan N-C, Khor IS, Ramarmuty HY, et al. Optimising the utility of pleural fluid adenosine deaminase for the diagnosis of tuberculous pleural effusion. 2020;0(0):2010105820978998.
37. Jiang HY, Zhang MN, Chen HJ, et al. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a systematic review and meta-analysis. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases. 2014;25:130-5.
38. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet (London, England). 2004;364(9441):1244-51.
39. Johnston JC, Campbell JR, Menzies D. Effect of Intermittency on Treatment Outcomes in Pulmonary Tuberculosis: An Updated Systematic Review and Meta-analysis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2017;64(9):1211-20.
40. Jones-López EC, Acuña-Villaorduña C, Ssebidandi M, et al. Cough Aerosols of Mycobacterium tuberculosis in the Prediction of Incident Tuberculosis Disease in Household Contacts. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2016;63(1):10-20.
41. Kanters S, Vitoria M, Zoratti M, et al. Comparative efficacy, tolerability and safety of dolutegravir and efavirenz 400mg among antiretroviral therapies for first-line HIV treatment: A systematic literature review and network meta-analysis. EClinicalMedicine. 2020;28:100573.
42. Kerkhoff AD, Sossen B, Schutz C, et al. Diagnostic sensitivity of SILVAMP TB-LAM (FujiLAM) point-of-care urine assay for extra-pulmonary tuberculosis in people living with HIV. The European respiratory journal. 2020;55(2).

43. 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.
44. Lee S, Lee JE, Kang JS, et al. Long-term performance of the IGRA to predict and prevent active tuberculosis development in HIV-infected patients. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2019;23(4):422-7.
45. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2017;64(2):111-5.
46. Liew SM, Khoo EM, Ho BK, Lee YK, Mimi O, Fazlina MY, Asmah R, Lee WK, Harmy MY, Chinna K, Jiloris FD. Tuberculosis in Malaysia: predictors of treatment outcomes in a national registry. Int J Tuberc Lung Dis. 2015 Jul;19(7):764-71.
47. Macaraig MM, Jalees M, Lam C, et al. Improved treatment completion with shorter treatment regimens for latent tuberculous infection. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2018;22(11):1344-9.
48. Makeshkumar V, Madhavan R, Narayanan S. Polymerase chain reaction targeting insertion sequence for the diagnosis of extrapulmonary tuberculosis. The Indian journal of medical research. 2014;139(1):161-6.
49. Martinez L, Cords O, Horsburgh CR, et al. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. Lancet (London, England). 2020;395(10228):973-84.
50. Mbuagbaw L, Mursleen S, Irlam JH, et al. Efavirenz or nevirapine in three-drug combination therapy with two nucleoside or nucleotide-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naïve individuals. The Cochrane database of systematic reviews. 2016;12(12):CD004246.
51. Meldau R, Randall P, Pooran A, et al. Same-Day Tools, Including Xpert Ultra and IRISA-TB, for Rapid Diagnosis of Pleural Tuberculosis: a Prospective Observational Study. Journal of clinical microbiology. 2019;57(9).
52. Menzies D, Adjobimey M, Ruslami R, et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. The New England journal of medicine. 2018;379(5):440-53.
53. Ministry of Health, Malaysia. Management of Drug-Resistant Tuberculosis (1st Edition). Putrajaya: MoH; 2016.
54. Ministry of Health, Malaysia. Management of Tuberculosis (3rd Edition). Putrajaya: MoH; 2012.
55. Ministry of Health, Malaysia. Management of Tuberculosis (Second Edition). Kuala Lumpur: MoH; 2002.
56. Ministry of Health, Malaysia. National Strategic Plan for Tuberculosis Control (2016-2020). Putrajaya: Disease Control Division, MOH; 2018.
57. Ministry of Health, Malaysia. Manual Sistem Maklumat Tibi Kebangsaan (Semakan 2018). Putrajaya: Disease Control Division, MOH; 2019.
58. Ministry of Health, Malaysia. Malaysian Consensus Guidelines on Antiretroviral Therapy 2017. The Malaysian Society for HIV Medicine; 2017.
59. Müller AM, Osório CS, Silva DR, et al. Interventions to improve adherence to tuberculosis treatment: systematic review and meta-analysis. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2018;22(7):731-40.
60. 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.
61. National Institute of Health and Care Excellence. Tuberculosis (NG 33). London: NICE; 2019.
62. Nene AM, Patil S, Kathare AP, et al. Six versus 12 Months of Anti Tubercular Therapy in Patients With Biopsy Proven Spinal Tuberculosis: A Single Center, Open Labeled, Prospective Randomized Clinical Trial-A Pilot study. Spine. 2019;44(1):E1-e6.
63. Nguyen TBP, Nguyen TA, Luu BK, et al. A comparison of digital chest radiography and Xpert(®) MTB/RIF in active case finding for tuberculosis. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2020;24(9):934-40.

64. Nicol MP, Schumacher SG, Workman L, et al. Accuracy of a Novel Urine Test, Fujifilm SILVAMP Tuberculosis Lipoarabinomannan, for the Diagnosis of Pulmonary Tuberculosis in Children. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2021;72(9):e280-e8.
65. Nkereuwem E, Togun T, Gomez MP, et al. Comparing accuracy of lipoarabinomannan urine tests for diagnosis of pulmonary tuberculosis in children from four African countries: a cross-sectional study. The Lancet Infectious diseases. 2021;21(3):376-84.
66. Paliwal VK, Das A, Anand S, et al. Intravenous Steroid Days and Predictors of Early Oral Steroid Administration in Tuberculous Meningitis: A Retrospective Study. The American journal of tropical medicine and hygiene. 2019;101(5):1083-6.
67. 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 Americ; .2020. Available at: http://clinicalinfo.hiv.gov/sites/default/files/inline-files/adult_oi.pdf
68. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
69. Pease C, Hutton B, Yazdi F, et al. A systematic review of adverse events of rifapentine and isoniazid compared to other treatments for latent tuberculosis infection. Pharmacoepidemiology and drug safety. 2018;27(6):557-66.
70. Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. The Cochrane database of systematic reviews. 2016;4(4):CD002244.
71. Rizvi I, Malhotra HS, Garg RK, et al. Fluoroquinolones in the management of tuberculous meningitis: Systematic review and meta-analysis. The Journal of infection. 2018;77(4):261-75.
72. Romli EZ, Sabirin J. Programmatic Management of Latent Tuberculosis Infection. Putrajaya: Ministry of Health, Malaysia; 2019.
73. Ryan H, Yoo J, Darsini P. Corticosteroids for tuberculous pleurisy. The Cochrane database of systematic reviews. 2017;3(3):CD001876.
74. Saiman L, Colson P. Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents. Pediatrics. 2004;114:1175-201.
75. Saito N, Yoshii Y, Kaneko Y, et al. Impact of renal function-based anti-tuberculosis drug dosage adjustment on efficacy and safety outcomes in pulmonary tuberculosis complicated with chronic kidney disease. BMC infectious diseases. 2019;19(1):374.
76. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. American journal of respiratory and critical care medicine. 2006;174(8):935-52.
77. Schmaltz CAS, Demitto FO, Sant'Anna FM, et al. Tuberculosis-HIV treatment with rifampicin or rifabutin: are the outcomes different? Memorias do Instituto Oswaldo Cruz. 2019;114:e180420.
78. Shete PB, Farr K, Strnad L, et al. Diagnostic accuracy of TB-LAMP for pulmonary tuberculosis: a systematic review and meta-analysis. BMC infectious diseases. 2019;19(1):268.
79. Silva DR, Mello FCQ, Migliori GB. Shortened tuberculosis treatment regimens: what is new? Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia. 2020;46(2):e20200009.
80. Siripassorn K, Ruxrungtham K, Manosuthi W. Successful drug desensitization in patients with delayed-type allergic reactions to anti-tuberculosis drugs. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases. 2018;68:61-8.
81. Soler-Garcia A, Gamell A, Santiago B, et al. Diagnostic Accuracy of QuantiFERON-TB Gold Plus Assays in Children and Adolescents with Tuberculosis Disease. The Journal of pediatrics. 2020;223:212-5.e1.
82. Starke JR. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. Pediatrics. 2014;134(6):e1763-73.
83. Starke JR. Tuberculin Skin Test Versus the Interferon-γ Release Assays: Out With the Old, In With the New. Pediatrics. 2020;145(1).
84. Sterling TR, Pham PA, Chaisson RE. HIV infection-related tuberculosis: clinical manifestations and treatment. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2010;50 Suppl 3:S223-30.

85. Story A, Aldridge RW, Smith CM, et al. Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicentre, analyst-blinded, randomised, controlled superiority trial. Lancet (London, England). 2019;393(10177):1216-24.
86. Swindells S, Ramchandani R, Gupta A, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. The New England journal of medicine. 2019;380(11):1001-11.
87. Thee S, Seddon JA, Donald PR, et al. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. Antimicrobial agents and chemotherapy. 2011;55(12):5560-7.
88. Theron G, Venter R, Smith L, et al. False-Positive Xpert MTB/RIF Results in Retested Patients with Previous Tuberculosis: Frequency, Profile, and Prospective Clinical Outcomes. Journal of clinical microbiology. 2018;56(3).
89. Tostmann A, Boeree MJ, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. Journal of gastroenterology and hepatology. 2008;23(2):192-202.
90. Tuberculosis & Leprosy Sector, Disease Control Division. National Tuberculosis Prevention and Control Programme Achievement (2020). Putrajaya: MoH; 2020. (unpublished document)
91. Villarino ME, Scott NA, Weis SE, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA pediatrics. 2015;169(3):247-55.
92. Wiysonge CS, Ntsekhe M, Thabane L, et al. Interventions for treating tuberculous pericarditis. The Cochrane database of systematic reviews. 2017;9(9):CD000526.
93. World Health Organization. Laboratory services in tuberculosis control. Part II: Microscopy. Geneva: WHO; 1998.
94. World Health Organization. Chest radiography in tuberculosis detection. Summary of current WHO recommendations and guidance on programmatic approaches. Geneva: WHO; 2016
95. World Health Organization. Fixed-dose combinations for the treatment of TB in children. WHO; 2018. Available from: https://www.who.int/tb/FDC_Factsheet.pdf.
96. World Health Organization. Global Tuberculosis Report 2020. Geneva: WHO; 2020 (a).
97. World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: WHO; 2017.
98. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: WHO; 2018 (a).
99. World Health Organization. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV. Policy update (2019). Geneva: WHO; 2019
100. World Health Organization. Management of Tuberculosis Fourth Edition. Geneva: WHO; 2010.
101. World Health Organization. Systematic screening for active tuberculosis: Principles and recommendations Geneva: WHO; 2013.
102. World Health Organization. The End TB Strategy. Geneva: WHO; 2015.
103. World Health Organization. The Use of Loop-Mediated Isothermal Amplification (TB-LAMP) for the Diagnosis of Pulmonary Tuberculosis: Policy Guidance. The Use of Loop-Mediated Isothermal Amplification (TB-LAMP) for the Diagnosis of Pulmonary Tuberculosis: Policy Guidance. Geneva: World Health Organization; 2016
104. World Health Organization. The use of the WHO-UMC system for standardised case causality assessment. Geneva: WHO; 2013. Available at: http://www.who.int/publications/m/item/WHO-causality-assessment).
105. World Health Organization. Treatment Of Tuberculosis: Guidelines for National Programmes Third Edition. Geneva: WHO; 2003.
106. World Health Organization. WHO consolidated guidelines on tuberculosis: Module 3: diagnosis – rapid diagnostics for tuberculosis detection. Geneva: WHO; 2021.
107. World Health Organization. WHO consolidated guidelines on tuberculosis: Module 4: Treatment - Drug-resistant tuberculosis treatment. Geneva: WHO; 2020 (c).
108. World Health Organization. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment: Module 1: prevention. Geneva: WHO; 2020 (b).
109. Yan S, Chen L, Wu W, et al. Early versus Delayed Antiretroviral Therapy for HIV and Tuberculosis Co-Infected Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PloS one. 2015;10(5):e0127645.
110. Zar HJ, Workman LJ, Prins M, et al. Tuberculosis Diagnosis in Children Using Xpert Ultra on Different Respiratory Specimens. American journal of respiratory and critical care medicine. 2019;200(12):1531-8.

111. Zellweger JP, Sotgiu G, Corradi M, et al. The diagnosis of latent tuberculosis infection (LTBI): currently available tests, future developments, and perspectives to eliminate tuberculosis (TB). La Medicina del lavoro. 2020;111(3):170-83.
112. Zhou G, Luo Q, Luo S, et al. Interferon-γ release assays or tuberculin skin test for detection and management of latent tuberculosis infection: a systematic review and meta-analysis. The Lancet Infectious diseases. 2020;20(12):1457-69.
113. Zifodya JS, Kreniske JS, Schiller I, et al. Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis. Cochrane Database Syst Rev. 2021;2:CD009593.

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 pulmonary tuberculosis (PTB)?
- Xpert MTB/RIF
- Chest x-ray vs Xpert MTB/RIF in smear negative PTB
- Urine Lipoarabinomannan Assay
- Nasal pharyngeal aspirate
- TB LAMP

5.2 How accurate are the following diagnostic tools for the diagnosis of extra-pulmonary tuberculosis (EPTB)?
- Xpert MTB/RIF
- Urine Lipoarabinomannan Assay
- ADA vs Xpert MTB/RIF for pleural TB
- CNS Imaging

5.3 What is most accurate tuberculin skin test cut-off value for predicting progression from latent to active TB?

5.4 Is interferon gamma release assays (latest version) more accurate than tuberculin skin tests in predicting progression of latent to active TB?

Treatment

5.5 Are there alternative anti-tuberculosis (anti-TB) regimens safer and more effective than current regimen in:
- PTB
- EPTB (TB meningitis/TB LN/pleural TB/TB spine)
- Latent TB (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 antiretroviral therapy (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 self-administered treatment

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

5.13 What are the alternative safe and effective anti-TB regimens in adverse drug reaction to isoniazid and/or rifampicin?

Appendix 3

PROCEDURE FOR SPUTUM INDUCTION

1. Patients should rinse their mouth and gargle with water (to prevent specimen contamination).
2. Fill the nebuliser (preferably ultrasonic nebuliser) with 3% saline (e.g. 5 ml for children and 20 - 30 ml for adults).
3. Patients should sit upright, place the mouthpiece in their mouth, (apply nose clip) and turn nebuliser on.
4. Inhale and exhale through the mouthpiece only.
5. Gentle chest physiotherapy may be carried out during the procedure.
6. The procedure should be stopped when:
   - patient has produced 1 - 2 ml of sputum for each specimen collected
   - 15 minutes of nebulisation is reached
   - patient develop dyspnoea, chest tightness or wheeze
7. Transport the specimen (in a cool box) to the laboratory for processing as soon as possible (within 4 hours).
8. If it is likely to take >4 hours for the specimens to be transported, place them in the refrigerator (4 - 8 °C) and stored until transported.
9. The specimen should be labelled as induced-sputum sample.

The procedure should be done cautiously in patients with asthma and with poor lung function (FEV1<1 L) as sputum induction may lead to bronchospasm. Premedication with inhaled salbutamol is needed to prevent asthma exacerbation. It is recommended that adequate resuscitation facilities are available prior to the procedure.

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 MDR) • Xpert Ultra (when indicated) • Line Probe Assay (when indicated)
Tuberculous meningitis	• 1 - 5 ml CSF; • tuberculoma tissue biopsy	• Xpert Ultra • Mycobacterial culture • AFB smear (if Xpert Ultra not available) • ADA
Pleural TB	• 2 - 5 ml pleural fluid; • pleural tissue biopsy	• Mycobacterial culture • HPE • ADA
Lymph node TB	• Fine-needle aspiration of LN; • LN biopsy specimen; • excised LN	• Mycobacterial culture • Xpert Ultra • HPE
Bone or joint TB	• 1 - 2 ml of aspiration of joint fluid or periarticular abscesses; • periarticular tissue biopsy; • 3 - 5 ml of bone marrow aspirate (in MycoF blood culture bottle)	• Xpert Ultra (joint fluid or tissue only) • Mycobacterial culture • 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 • ADA
Peritoneal TB	• 1 - 2 ml ascitic fluid; • peritoneal tissue biopsy	• Xpert Ultra (biopsy only) • Mycobacterial culture • AFB smear • HPE • ADA
Disseminated (miliary) TB	• 5 ml of blood in plain tube (for PCR); • 5 ml of blood in MycoF blood culture bottle	• Mycobacterial culture • MTB PCR
Specimen storage and transport • For Xpert Ultra, specimens should be transported and stored at 2 - 8 °C prior to processing. The maximum time for storage and processing is seven days. Samples should be kept cool during transportation but not frozen. • For mycobacterial culture, specimen should be kept cool and must be sent as soon as possible. Failure to do so will result in specimen being contaminated with bacteria.		

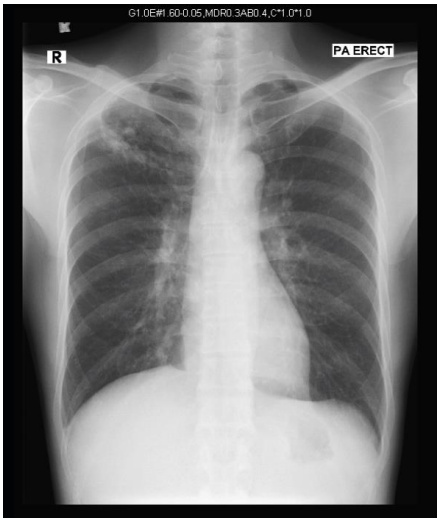
Further information can be obtained from MKAK website at: http://mkak.moh.gov.my/ms/

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.

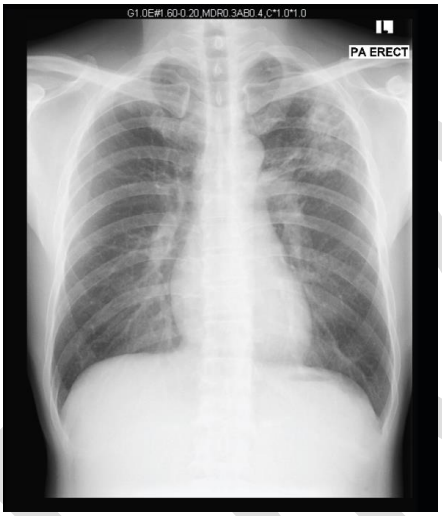
Appendix 5

GRADING OF PULMONARY TUBERCULOSIS SEVERITY BASED ON CHEST RADIOGRAPH IN ADULTS



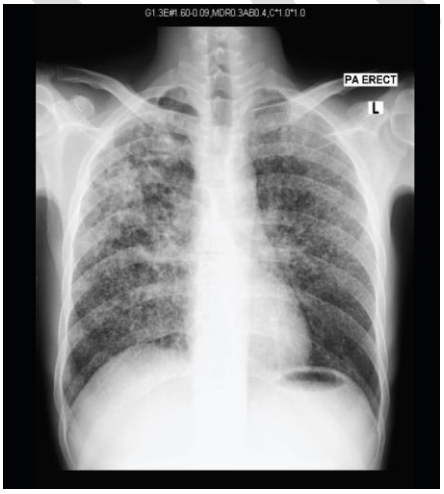
Minimal

- 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.

Appendix 6

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	300 mg OD	10 (7 - 15)	300	CrCl <10 ml/min/CAPD/HD/HDF/High Flux: Maximum 200 mg OD *No dose adjustment needed till CrCl <10 ml/min*	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, burning/numbness/ tingling sensation in hands or feet
Rifampicin	10 (8 - 12)	600	600 mg OD	15 (10 - 20)	600	CrCl <10 ml/min/CAPD/HD/HDF/High Flux: 50 - 100% of normal dose CAV/VVHD: Unknown dialysability Dose as in normal renal function *No dose adjustment needed till CrCl <10 ml/min*	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)	2000	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)	1000	CrCl <10 ml/min: 50 - 100% of normal dose CAPD: Not dialysed Dose as in CrCl < 10 ml/min	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, joint pain

						HD: 50 - 100% dialysed Dose as in CrCl <10 ml/min or 25 - 30 mg/kg post dialysis HDF/High Flux: Dialysed Dose as in CrCl <10 ml/min or 25 - 30 mg/kg post dialysis CAV/VVHD: Unknown dialysability Dose as in normal renal function	
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.							

References:

1. Ashley C & Dunleavy A, Editors. The Renal Drug Handbook: The Ultimate Prescribing Guide for Renal Practitioners 5th Edition. Boca Raton: CRC Press, Taylor & Francis Group; 2019.
2. Ministry of Health, Malaysia. Management of Tuberculosis (3rd Edition). Putrajaya: MoH; 2012.
3. 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.
4. Paediatric Formulary. UBQO Limited (Mobile Application Software)
5. Tomlin S & Kirk E, Editors. Guy's and St. Thomas', King's College and University Lewisham Hospitals Paediatric Formulary 9th Edition (Revised Dec 2012). Guy's & St Thomas' NHS Foundation Trust; 2012.

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

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 and a child with a low platelet count or bleeding tendency should not undergo the procedure.

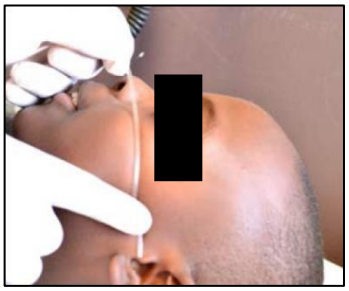
Gastric aspiration is generally not an aerosol-generating procedure, hence considered a low-risk procedure for TB transmission and can safely be performed at the child's bedside or in a routine procedure room.

1. Prepare the child and equipment as standard requirement for nasogastric tube insertion.
2. Attach a syringe to the nasogastric tube.
3. Aspirate gastric contents (2 - 5 ml) using the syringe attached to the nasogastric tube.
4. If no fluid is aspirated, insert 5 - 10 ml sterile water or normal saline and attempt to aspirate again.
5. Transfer gastric fluid 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 child by wrapping him/her in a piece of cloth.
3. Prepare 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 length of suction tube by placing end of the tube at external opening of the ear and extend it to the tip of the nose (**Picture 2**). Mark the length on the tube.
6. Instill two drops of sterile saline into each of the child's nostril.
7. Without applying suction, insert the tube through the nostril until the mark of the length measured (similar to performing 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 while aspirating
10. Collection should be >1 ml.

Picture 1: Mucus extractor



Picture 2: Measuring correct length of suction tube

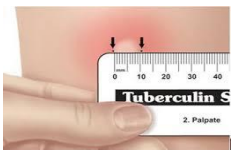
Adapted:

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 9

PROCEDURE FOR TUBERCULIN SKIN TEST

As before any test, the procedure needs to be explained to the patient, obtain verbal consent and check if the correct patient's information is labelled on the form. Below are the steps to perform the TST.

• Locate and clean the area for injection at the forearm 2 - 4 inches below the elbow joint. • Make sure the area is free from scars or any infection.	
• Check expiration date on the vial. • Use 1 cc syringe to draw 2 tuberculin units (TU) per 0.1 ml. • An injection is given at a 5° to 15° intradermally with the needle bevel can be seen below the skin • Immediately, a firm pale wheal will appear about 6 – 10 mm in diameter. If it does not, then repeat the test at least two inches away from the original site	
• Skin test should be read 48 - 72 hours after administration. If the patient does not return, a repeat test is required. • Fingertip can be used to find the margins of the induration (hard, dense, raised area) which should be measured. • Erythema surrounding the induration should not be measured. • Reading should be recorded in millimetres and not as positive or negative • If there is no induration, record as 0 mm • Interpretation and cut-off values for different populations is mentioned in **Subchapter 3.1** on **LTBI in Adults**.	 

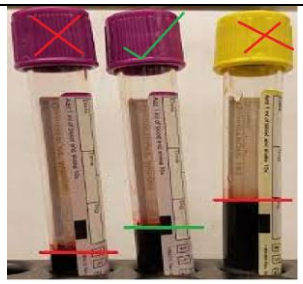
Adapted: Centre for Disease Control and Prevention. Mantoux Tuberculin Skin Testing Products. (Available at: http://www.cdc.gov/tb/education/mantoux/default.htm)

Appendix 10

QUANTIFERON SPECIMEN COLLECTION AND HANDLING

As before any test, the procedure needs to be explained to the patient, obtain verbal consent and check if the correct patient's information is labelled on the tubes and form. Below are the steps to perform the IGRA test.

<table>
<tr><td colspan="2">QuantiFERON®-TB Gold Plus (QFT®-Plus) is a unique approach to detection of TB infection. The test is performed by collection of 1 ml of whole blood into each of four QFT-Plus blood collection tubes.
• The gray cap tube (Nil) serves as the negative control and adjusts 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 2 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 >5ml of the patients' blood.
• Gently mix 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 1ml into each of the 4 QFT-Plus (to the center 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> 
4 QFT tubes</td><td>Blood collection
• Label QFT-Plus Blood Collection Tubes appropriately. Tubes should be at room temperature (17–25°C)
• Collect 1ml into each of the 4 QFT-Plus (to the center of the black mark on the side of the QFT-Plus tube label). 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.</td></tr>
</table>

	 Blood should be filled to center of black mark (indicated in green)  Invert the bottles 10 times to coat bottle like below to dissolve antigen on tube walls 	• New sample needs to be taken if blood level is outside the indicator mark. Tube handling • Immediately after filling the tubes, invert them ten (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 11

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.

Appendix 12

CLINICALLY SIGNIFICANT DRUG–DRUG INTERACTIONS INVOLVING RIFAMYCINS

Category of drugs	Type of drugs	Description
Anti-infectives	**Macrolide antibiotics** Azithromycin	Azithromycin has no significant interaction with rifamycins.
	Clarithromycin	Coadministration of clarithromycin and rifabutin results in significant bidirectional interactions that can increase rifabutin to toxic levels, hence increasing the risk of uveitis.
	Erythromycin	Erythromycin is a CYP3A4 substrate and clearance may increase when coadministered with rifamycins.
	Fluoroquinolones Ciprofloxacin	Monitor clinically as coadministration of rifamycins with ciprofloxacin may increase risk of rifamycin-induced lupus syndrome, possibly due to inhibition of rifamycin metabolism.
	Moxifloxacin	Monitor for reduced antimicrobial response and thus may require higher moxifloxacin dose.
	Doxycycline	May require use of a drug other than doxycycline.
	Azole antifungal agents Fluconazole, Itraconazole, Ketoconazole, Voriconazole	Itraconazole, ketoconazole and voriconazole concentrations may be subtherapeutic with any rifamycin. Fluconazole may need a higher dose when coadministered with rifamycins.
	Caspofungin	Monitor clinically and consider increasing caspofungin dose accordingly.
	Atovaquone	Consider alternative Pneumocystis jirovecii treatment or prophylaxis.
	Chloramphenicol	Consider alternative antibiotic.
Antimycobacterial/ antiprotozoal	Dapsone	Monitor clinically. Consider adjusting dapsone dose. Monitor for methemoglobinemia.
Antimalarials	Artemether, Lumefantrine	Avoid coadministration.
Hepatitis C direct-acting antivirals	Daclatasvir, Sofosbuvir, Glecaprevir/Pibrentasvir, Sofosbuvir/Ledipasvir, Sofosbuvir/Velpatasvir	Coadministration is contraindicated as it may decrease concentrations of these antivirals, resulting in decreased systemic exposure, loss of effectiveness and potential virological failure.

Immunosuppressive agents	Cyclosporine, Everolimus, Sirolimus, Tacrolimus	Avoid coadministration with rifampicin. If coadministered, higher immunosuppressive doses may be needed with frequent therapeutic drug monitoring (TDM) till a stable dose is achieved. Coadministration of cyclosporine or tacrolimus with rifabutin may need TDM to assist with dosing. Avoid coadministration of sirolimus or everolimus with rifamycins. Continue TDM even if rifamycins are stopped.
	Mycophenolic acid salts Mycophenolate mofetil, Mycophenolate sodium	Monitor effectiveness of mycophenolate and for possible adverse effects. Adjust mycophenolate dose if needed.
	Corticosteroids Beclomethasone, Betamethasone, Budesonide, Dexamethasone, Flucortolone, Fludrocortisone, Hydrocortisone, Methylprednisolone, Prednisolone, Triamcinolone	Monitor clinically and may require higher corticosteroids dose.
Hormone therapy	**Estrogens** Ethinyl estradiol, Estradiol, Estriol	Alternative/additional forms of contraception should be used during and for four weeks after rifamycin therapy.
	Progestogens Chlormadinone, Cyproterone, Desogestrel, Dienogest, Drospirenone, Dydrogesterone, Ethisterone, Etonogestrel, Gestodene, Hydroxyprogesterone, Levonorgestrel, Medroxyprogesterone, Megestrol, Norelgestromin, Norethisterone, Norgestrel, Progesterone	Avoid coadministration of progestogens-only oral contraceptives with rifamycins. If coadministered, alternative/additional forms of contraception should be used during and for four weeks after rifamycin therapy.
	Tamoxifen	May require alternate therapy or a regimen without rifamycins.
	Levothyroxine	Monitor of serum thyroid stimulating hormone and may require higher levothyroxine dose.

	Enzalutamide	Avoid coadministration.
Anticonvulsants	Lamotrigine, Phenytoin	Perform TDM and may require higher anticonvulsant dose.
	Carbamazepine	Use with caution. Perform TDM as coadministration of rifampicin, isoniazid and carbamazepine has been reported to cause both increase or decrease in carbamazepine levels.
Antidepressants	Mirtazapine	Monitor for decreased mirtazapine effect and thus may require higher mirtazapine dose.
Antipsychotics	Haloperidol, Quetiapine	Monitor clinically and may require higher antipsychotic dose.
	Risperidone	Monitor clinically and adjust risperidone dose as needed.
Barbiturates	Phenobarbitone	If coadministered with rifampicin, monitor for reduced response to both drugs.
Benzodiazepines	Diazepam, Triazolam, Zolpidem	Monitor clinically and may require higher psychotropic dose
Opioid agonists	Alfentanil, Codeine, Dihydrocodeine, Fentanyl, Morphine, Oxycodone, Pethidine, Remifentanil	If coadministered with rifampicin, monitor for reduced analgesic effects and increase opioid dose if necessary.
	Methadone	Coadministration with rifampicin and rifapentine may require higher methadone doses. Coadministration with rifabutin does not commonly cause methadone withdrawal.
Oral anticoagulants	Warfarin	Monitor prothrombin time and international normalised ratio (INR), may require higher warfarin dose. Adjust warfarin dose accordingly.
	Direct oral anticoagulants Apixaban, Dabigatran, Edoxaban, Rivaroxaban	Avoid coadministration of apixaban or rivaroxaban with rifamycins. Avoid coadministration of dabigatran or edoxaban with rifampicin. This may result in decreased anticoagulant effect.
Cardiovascular agents	**Calcium channel blockers** Verapamil, Diltiazem, Amlodipine, Felodipine, Lercanidipine, Nifedipine, Nimodipine	Monitor clinically and may require alternative cardiovascular drug.

	Beta-blockers Atenolol, Betaxolol, Bisoprolol, Carvedilol, Esmolol, Labetalol, Metoprolol, Nebivolol, Propranolol, Sotalol, Timolol	Monitor clinically and may require higher beta-blocker dose or alternative cardiovascular drug.
	Enalapril, Losartan	Monitor clinically and may require higher cardiovascular drug dose or alternative cardiovascular drug.
	Digoxin (especially in renal insufficiency)	Perform TDM, may require higher digoxin dose.
	Propafenone	Monitor clinically and may require alternative cardiovascular drug.
	Ranolazine	Avoid coadministration.
	Ticagrelor	Avoid coadministration.
	Ivabradine	Avoid coadministration.
Sulfonylurea hypoglycaemics	Glibenclamide, Gliclazide, Glimepiride, Glipizide, Tolbutamide	Monitor blood glucose and may require higher sulfonylurea dose or alternative hypoglycaemic.
Meglitinide hypoglycaemics	Repaglinide	Monitor blood glucose and may require higher meglitinide dose or alternative hypoglycaemic.
Antihyperlipidemic	Simvastatin, Fluvastatin	Monitor hypolipidemic effect and may require alternative antihyperlipidemic.
Methylxanthines	Aminophylline, Theophylline	Perform TDM and may require higher theophylline dose.
Tyrosine kinase inhibitors	Afatinib Ceritinib, Ibrutinib, Imatinib, Nilotinib, Nintedanib, Osimertinib	When coadministered with rifampicin, monitor for reduced effectiveness and consider higher afatinib dose. Original afatinib dose may be used 2 - 3 days after stopping rifampicin. Avoid coadministration.
Cyclin-dependent kinase inhibitors	Abemaciclib, Palbociclib, Ribociclib	Avoid coadministration.
Polyadenosine diphosphate ribose polymerase inhibitors	Olaparib	Avoid coadministration.

Mitogen-activated extracellular kinase inhibitors	Cobimetinib	Avoid coadministration.
Vascular endothelial growth factor receptor inhibitors	Axitinib	Coadministration is not recommended. If coadministered, adjust axitinib dose for optimal effectiveness.
Antineoplastic agents	Docetaxel, Paclitaxel	Monitor patient clinically and may require higher antineoplastic dose.

References:

1. Garrison K. The Drug-drug Interaction Potential of Antiviral Agents for the Treatment of Chronic Hepatitis C Infection. Drug Metabolism and Disposition. 2018; 46(8):1212-1225.
2. Härtter S, Koenen-Bergmann M, Sharma A, et al. Decrease in the oral bioavailability of dabigatran etexilate after co-medication with rifampicin. Br J Clin Pharmacol. 2012;74(3): 490-500.
3. Kvasnicka T, Malikova I, Zenahlikova Z, et al. Rivaroxaban - Metabolism, Pharmacologic Properties and Drug Interactions. Current Drug Metabolism. 2017;18:636-642.
4. Mendell J. The Effect of Rifampin on the Pharmacokinetics of Edoxaban in Healthy Adults. Clin Drug Investig. 2015;35:447-453.
5. MIMS Gateway - Drug Interactions Database (Available at: https://online1.mimsgateway.com.my/Malaysia)
6. 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.
7. Sparkes T, Lemonovich TL, AST Infectious Diseases Community of Practice. Interactions between anti-infective agents and immunosuppressants-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clinical transplantation. 2019;33(9):e13510.
8. University of Liverpool HEP Drug Interactions Interaction Checker (Available at: https://www.hep-druginteractions.org/checker)
9. Vakkalagadda B, Frost C, Byon W, et al. Effect of Rifampin on the Pharmacokinetics of Apixaban, an Oral Direct Inhibitor of Factor Xa. Am J Cardiovasc Drugs. 2016;16(2):119-27.
10. Vazquez S. Drug-drug Interactions in an Era of Multiple Anticoagulants: A Focus on Clinically Relevant Drug Interactions. Hematology Am Soc Hematol Educ Program. 2018; 2018(1): 339–347.

Appendix 13

CLINICALLY SIGNIFICANT DRUG–DRUG INTERACTIONS INVOLVING ISONIAZID

Category of drugs	Type of drugs	Description
Anti-infectives	**Azole antifungal agents** Ketoconazole	Monitor clinically.
Hepatitis C direct-acting antivirals	Daclatasvir, Sofosbuvir, Glecaprevir/Pibrentasvir, Sofosbuvir/Ledipasvir, Sofosbuvir/Velpatasvir	Coadministration has not been studied but concentration of daclatasvir may be increased due to inhibition of CYP3A by isoniazid. Generally, clinical significance is unknown. Monitor in chronic liver disease.
Rifamycins	Rifampicin, Rifabutin, Rifapentine	Monitor liver function as coadministration may lead to additive hepatotoxicity. Enzyme induction by rifampicin may increase levels of hepatotoxic metabolite of isoniazid. Use with caution especially among patients with impaired liver function, below two years old, elderly and malnourished.
Antiepileptics	Carbamazepine, Clomipramine, Lamotrigine, Phenobarbital, Phenytoin, Valproic acid	Perform TDM and adjust antiepileptic dose if needed. Monitor for antiepileptic toxicity. If carbamazepine is coadministered with isoniazid, monitor for hepatotoxicity as carbamazepine may increase levels of hepatotoxic metabolite of isoniazid.
Anti-parkinsonian drugs	Levodopa	Monitor clinically and consider higher levodopa dose as clinically appropriate.
Benzodiazepines	Triazolam, Diazepam	Monitor for increased effect of benzodiazepines.
Analgesics	Paracetamol	Consider limiting paracetamol to <4 gram daily when coadministered with isoniazid. Monitor hepatic function.
Muscle relaxants	Chlorzoxazone	Monitor for toxicity and adjust chlorzoxazone dose if needed.
Oral anticoagulants	Warfarin	Monitor INR and adjust warfarin dose accordingly when isoniazid is added or stopped.
Sulfonylurea hypoglycaemics	Glibenclamide, Gliclazide, Glimepiride, Glipizide, Tolbutamide	Monitor blood glucose level.
Methylxanthines	Aminophylline, Theophylline	Perform TDM and adjust aminophylline/theophylline dose as needed.
Corticosteroids	Prednisolone, Hydrocortisone	Monitor for reduced response to isoniazid. Based on mechanisms of action, prednisolone may decrease serum levels and clinical effects of isoniazid by increasing hepatic metabolism and renal clearance.

Immunomodulator	Thalidomide	Coadministration may result in additive neuropathy.
Anaesthetics (inhaled)	Desflurane, Halothane, Isoflurane, Sevoflurane	Based on mechanisms of action, isoniazid may increase metabolism of anaesthetics, causing increased release of nephrotoxic fluoride ions and resulting in nephrotoxicity.
Vinca alkaloids	Vincristine	Monitor clinically as isoniazid may increase the risk of vincristine neurotoxicity.

References:

1. Johannessen SI, Landmark CJ. Antiepileptic drug interactions - principles and clinical implications. Curr Neuropharmacol. 2010;8(3):254-267
2. MIMS Gateway - Drug Interactions Database (Available at: https://online1.mimsgateway.com.my/Malaysia)
3. University of Liverpool HEP Drug Interactions Interaction Checker (Available at: https://www.hep-druginteractions.org/checker)

Appendix 14

ANTIRETROVIRAL AND RIFAMYCINS DRUG-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 without dosage adjustment	May be combined without dosage adjustment	May be combined without dosage adjustment
Tenofovir alafenamide	Not recommended	Not recommended	Not recommended
Non-nucleoside reverse transcriptase inhibitors			
Efavirenz	May be combined; use EFV 600 mg once daily	Not recommended as EFV reduces the concentrations of coadministered rifabutin	May be combined without dosage adjustment
Nevirapine	Avoid coadministration. If no alternative, use NVP 200 mg twice daily with rifampicin (with no once-daily lead-in phase)	May be combined without dosage adjustment	Do not combine
Etravirine	Do not combine	If administered with etravirine and no protease inhibitor, rifabutin coadministration is acceptable.	Do not combine
Rilpivirine (RPV)	Do not combine	RFB: 300 mg once daily RPV: 50 mg once daily (limited data, use with caution)	Do not combine
Protease inhibitors			
Lopinavir/ritonavir (LPR/r)	Do not combine	RFB: 150 mg once daily LPR/r: 400 mg/100 mg twice daily	Do not combine
Atazanavir/ritonavir (ATZ/r)	Do not combine	RFB: 150 mg once daily ATZ/r: 300 mg/100 mg once daily	Do not combine
Darunavir/ritonavir (DRV/r)	Do not combine	RFB: 150 mg once daily DRV/r: 600 mg/100 mg twice daily	Do not combine
Integrase inhibitors			
Raltegravir	If coadministration with rifampicin is unavoidable, use RAL 800 mg twice daily	May be combined without dosage adjustment	May be combined without dosage adjustment

Dolutegravir	May be combined, use DTG 50 mg twice daily	May be combined without dosage adjustment	May be combined without dosage adjustment

References:

1. De Castro N, Marcy O, Chazallon C, et al. ANRS 12300 Reflate TB2 study group. Standard dose raltegravir or efavirenz-based antiretroviral treatment for patients co-infected with HIV and tuberculosis (ANRS 12 300 Reflate TB 2): an open-label, non-inferiority, randomised, phase 3 trial. Lancet Infect Dis. 2021;21(6):813-822.
2. Dooley KE, Kaplan R, Mwelase N, et al. International Study of Patients with HIV on Rifampicin ING study group. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clin Infect Dis. 2020;70(4):549-556.
3. Dooley KE, Savic R, Gupte A, et al. DOLPHIN Study Team. Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial. Lancet HIV. 2020;7(6):e401-e409.
4. Jiang HY, Zhang MN, Chen HJ, et al. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a systematic review and meta-analysis. International Journal of Infectious Diseases 2014; 25: 130-135.
5. Liverpool HIV Pharmacology Group *[database on the Internet]* Cheshire, United Kingdom: The University of Liverpool and Clubzap Ltd; 2021. HIV Drug Interaction Checker. (Available at: http://www.hiv-druginteractions.org)
6. Mbuagbaw L, Mursleen S, Irlam JH, et al. Efavirenz or nevirapine in three-drug combination therapy with two nucleoside or nucleotide-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naïve individuals. Cochrane Database Syst Rev. 2016;12(12):CD004246.
7. Podany AT, Bao Y, Swindells S, et al. AIDS Clinical Trials Group A5279 Study Team. Efavirenz Pharmacokinetics and Pharmacodynamics in HIV-Infected Persons Receiving Rifapentine and Isoniazid for Tuberculosis Prevention. Clin Infect Dis. 2015;61(8):1322-7.

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
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
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HIV	human immunodeficiency virus
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 lipoarabinomannan assay
LTBI	latent tuberculosis infection
max	maximum
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
TST	tuberculin skin test
U/L	unit per liter
ULN	upper limit of normal
VOT	video-observed treatment
WHO	World Health Organization

ACKNOWLEDGEMENT

The CPG DG members would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft
- Technical Advisory Committee of CPG for their valuable input and feedback
- Health Technology Assessment and Clinical Practice Guidelines Council for approving the CPG
- Dr Junainah Sabirin, Consultant Public Health Physician, on the development of the CPG
- Ms. Wong Wai Chee on retrieval of evidence
- National Pharmaceutical Regulatory Agency for their contribution in CPG development
- All those who have contributed directly or indirectly to the development of the CPG

DISCLOSURE STATEMENT

The panel members of both DG and RC had completed disclosure forms. None held shares in pharmaceutical firms or acts as consultants to such firms. Details are available upon request from the CPG Secretariat.

SOURCE OF FUNDING

The development of the CPG on Management of Tuberculosis (Fourth Edition) was supported financially in its entirety by the MoH Malaysia.