Singapore Tuberculosis Clinical Management Guidelines: A Modified Delphi Adaptation of International Guidelines for Drug-Susceptible TB Infection and Pulmonary Disease

Clinical Tuberculosis Guidelines Development Team

Clinical Guidelines

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Contents

1. Glossary

Term	Explanation
2HRZE/4HR	2-month intensive phase of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E), followed by 4-month continuation phase of H and R
2HRZ(E)/4HR	2-month intensive phase of HRZ with or without E followed by 4-month continuation phase of H and R
2HRZE/2HR	2-month intensive phase of HRZE followed by 2-month continuation phase of H and R
2HRZ(E)/2HR	2-month intensive phase of HRZ with or without E followed by 2-month continuation phase of H and R
2HRE/7HR	2-month intensive phase of HRE followed by 7-month continuation phase of H and R
2HPMZ/2HPM	8-week intensive phase daily H, rifapentine (P), moxifloxacin (M) and Z, followed by 9-week continuation phase daily H, P and M.
AFB	Acid-fast bacilli
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BW	Body weight
CAD-AI	Computer-aided detection-artificial intelligence
DOT	Directly observed treatment
IGRA	Interferon-gamma release assay
NAAT	Nucleic acid amplification test
NGS	Next-generation sequencing
PLHIV	People living with HIV
TST	Tuberculin skin test
VOT	Video-observed treatment

2. Executive Summary

1. What are the indications for screening for TB infection?

People living with human immunodeficiency virus (HIV), i.e. PLHIV, close contacts of persons with infectious TB disease and persons with clinical risk factors for TB should be screened for TB infection.

2. What are the indications for screening for TB disease?

PLHIV, close contacts of persons with infectious TB disease and persons with clinical risk factors for TB should be screened for TB disease.

3. What are the laboratory tests that should be performed to diagnose TB infection in adults?

- In adults, IGRA tests are preferred to the TST for diagnosis of TB infection.
- The TST can be an alternate diagnostic test, with a cut-off induration of 10 mm in general and 5 mm in at risk immunocompromised individuals.
- Parallel or sequential IGRA/TST testing is not recommended for immunocompromised individuals.

4. What are the laboratory tests that should be performed to diagnose TB infection in children?

- In children aged ≥5 years or children >2 years with prior BCG vaccination, commercially available IGRA tests are preferred to the TST for diagnosis of TB infection.
- In children aged 2-5 years without prior BCG vaccination, either TST or IGRA may be used for diagnosis of TB infection.
- In children aged 6 months to <2 years, the TST is recommended for diagnosis of TB infection.
- A TST cut-off induration of 10 mm is recommended (5 mm in at risk children who are immunocompromised).

5. What are the baseline tests to be performed before and after starting TB infection treatment?

- The possibility of TB disease must be excluded via a symptom screen and chest X-ray prior to initiating treatment for TB infection.
- Baseline AST and ALT testing can be performed prior to starting TB infection treatment, with subsequent AST and ALT testing on follow-up visits in individuals at high risk for hepatotoxicity from treatment or full liver function testing in those who have clinical features suggestive of liver dysfunction.

6. What are the preferred and alternate regimens for the treatment of TB infection in adults?

- The two preferred regimens for the treatment of TB infection in adults are rifampicin daily for 4 months (4R) or isoniazid daily for either 6 or 9 months (6H/9H).
- Alternative treatment regimens include isoniazid and rifampicin daily for 3 months (3HR) or isoniazid and rifapentine weekly for 3 months (3HP), should rifapentine become available in Singapore.
- For PLHIV, isoniazid and rifapentine daily for 1 month (1HP) may be another alternative regimen.
- Pyridoxine supplementation is recommended for all adults on an isoniazid-containing regimen.

7. What are the preferred and alternate regimens for the treatment of TB infection in children?

- The two preferred regimens for the treatment of TB infection in children are 4R or 6H/9H.
- Alternative treatment regimens include isoniazid and rifampicin daily for 3HR or weekly 3HP in children age ≥2 years, should rifapentine become available in Singapore.
- Pyridoxine supplementation is recommended for children at risk of peripheral neuropathy while on an isoniazid-containing regimen.

8. How should treatment be monitored?

TB infection treatment should be self-administered except in the case of the weekly 3HP regimen or in a situation where adherence to treatment is poor. In the latter cases, DOT or VOT will be preferred.

9. How should treatment interruptions be managed?

- For interruptions due to drug toxicity, the risk-benefit of continued treatment should be re-evaluated before resuming treatment.
- For interruptions due to hepatotoxicity, treatment drugs can be re-introduced once liver function of the affected individual has normalised.

10. How often should patients on TB infection treatment be followed up and for how long?

- Follow-up for patients on TB infection treatment can be at 4-6 week intervals, with longer intervals for adherent patients who are at low risk for drug adverse events.
- Follow-ups can be discontinued upon treatment completion.

11. How should post-treatment re-exposure to infectious TB be managed?

Re-treatment of individuals re-exposed to infectious TB can be considered.

12. What tests should be performed to diagnose TB disease?

- The workup for TB disease should include clinical history taking and examination, chest X-ray, and collection of samples for AFB smear microscopy, NAAT and mycobacterial culture.
- In children but not adults, the IGRA test or TST in the absence of prior BCG vaccination may be a supplementary test for diagnosing TB disease.

13. What are the types of clinical samples that should be sent?

- Sputum is the preferred clinical sample for the diagnosis of TB disease in adults and older children.
- In adults or children who are unable to properly expectorate, induced sputum is preferred, with early morning gastric aspirate considered an equivalent option in very young children or adults for whom sputum induction is unfeasible.
- Bronchoscopy with aspiration and lavage is an alternate option for sample collection in both adults and children.
- Nasopharyngeal aspiration is an alternate option for sample collection in children.

14. Excluding bronchoscopic sampling, what should be the minimum number of samples sent and when should the samples be collected?

- At least 2 samples should be sent for laboratory testing for TB disease, of which at least 1 sample should be an early morning sample.
- Same day collection of samples is preferred except in the case of gastric aspirate, for which alternate day collection of early morning samples is ideal.

15. Under what circumstances should CT thorax be considered for the diagnosis of pulmonary TB?

CT thorax may be considered as an additional imaging modality for the purposes of excluding another underlying diagnosis or for the evaluation of extrapulmonary TB disease with pulmonary involvement (i.e. pleural or pericardial disease).

16. What is the role of NGS as a clinical laboratory tool?

Whole genome sequencing (WGS) can be deployed in local clinical laboratories for genotypic prediction of TB drug resistance. It has demonstrable high sensitivity and specificity especially for first-line drugs, and the output can also be used for national TB surveillance.

17. What is the role of machine learning in the screening, diagnosis and follow-up of pulmonary TB?

- The panel recognises that a number of automated CAD-AI products have been certified by the Health Sciences Authority, and more are expected in the future. Some products have been deployed in other countries for chest X-ray screening for TB disease in various settings. While multiple studies have demonstrated comparable diagnostic performance (relative to a human radiologist) for the detection of chest X-ray changes associated with pulmonary TB, such findings will have to be validated within the local practice setting in Singapore. At present, deployment of CAD-AI products will require a human-in-the-loop, where a certified radiologist is still needed to provide a final read. In addition, due consideration must be given to the fact that current products have narrow capabilities, with potential to miss other non-specified abnormalities on a chest X-ray.
- The panel also recommended vigilance in this rapidly evolving field and timely updates of major developments.

18. What are the preferred and alternative regimens for the treatment of drug-susceptible pulmonary TB disease in adults?

- The preferred regimen for the treatment of drug-susceptible pulmonary TB disease in adults is 2HRZE/4HR.
- In persons age >70 years with low risk of drug resistance, pyrazinamide should be avoided, with 2HRE/7HR being the preferred regimen.
- An alternate regimen is 2HPMZ/2HPM – except in pregnant/breastfeeding women and PLHIV – should rifapentine become available in Singapore.
- For PLHIV with TB disease, care should be taken to avoid heightened risk of drug adverse effects due to interactions with antiretroviral therapy.
- Pyridoxine supplementation is recommended for all adults on an isoniazid-containing regimen.

19. What are the preferred and alternative regimens for the treatment of drug-susceptible pulmonary TB disease in children?

- The preferred regimen for the treatment of drug-susceptible pulmonary TB disease in children is 2HRZ(E)/4HR.
- In children with non-severe disease, a shortened 2HRZ(E)/2HR regimen may be considered after consultation with an experienced paediatric specialist.
- An alternate regimen of 2HPMZ/2HPM can be considered in children >12 years of age should rifapentine become available in Singapore.
- Pyridoxine supplementation is recommended for children at risk of peripheral neuropathy while on an isoniazid-containing regimen.

20. What are the other considerations for prolonging or shortening treatment for TB disease?

- In persons with TB disease who present with baseline cavitation and/or extensive disease on chest X-ray AND positive mycobacterial cultures after 2 months of treatment, the Panel strongly recommended that the treatment duration be extended to 9 months (2HRZE/7HR).
- Other considerations for extending treatment to 9 months (2HRZE/7HR) in persons with microbiologically-proven TB disease include the following:
    - Positive mycobacterial cultures after 2 months of treatment
    - Baseline cavitation and/or extensive disease on chest X-ray
    - Slow radiological improvement
    - PLHIV with CD_4 count <200 cells/mm^3 and not on anti-retroviral therapy
    - Poorly controlled diabetes mellitus throughout treatment course
- In persons with culture-negative but probable TB disease, treatment duration may be shortened to 4 months (2HRZE/2HR)

21. How should treatment of TB disease be monitored?

- In adults, observation of treatment is recommended for those with infectious TB disease, those who are at risk of adverse outcomes and/or those who are non-adherent to treatment.
- All children with TB disease should ideally undergo some form of observed treatment, including home supervision by an adult family member or caregiver.
- VOT is equivalent to DOT in terms of ensuring treatment adherence in those who are able to undergo VOT.

22. How should treatment interruptions be managed?

- The decision to continue or re-start TB treatment is based on the duration of the interruption, whether it occurred during the intensive (i.e. 2HRZE) or continuation (i.e. 4HR) phase and the bacteriological status prior to interruption.
- For interruptions due to hepatotoxicity, it is important to identify the culprit drug(s), with sequential re-introduction once liver enzymes return to <2 times the upper limit of normal.
- For interruptions due to other drug adverse events, continuation of TB treatment with symptom alleviation should generally be the norm for mild adverse events, but serious adverse events should result in the discontinuation of the offending drug(s).
- In severe or highly infectious persons with TB disease, initiation of an alternate treatment regimen is recommended while waiting for a serious drug adverse event to resolve.

23. How often should patients on TB disease treatment be followed up and for how long?

- Follow-up for patients on TB disease treatment can be at 2-4 week intervals during the intensive phase, and at longer 4-6 week intervals during the continuation phase.
- More frequent follow-ups are recommended for patients at high risk of adverse events or who have developed adverse events to treatment.
- Follow-ups can be discontinued upon treatment completion, except in patients at higher risk of poor outcomes, for whom follow-up until 1-2 years post-treatment can be considered.

24. What investigations should be performed prior to initiating and during treatment of TB disease?

- Before initiating TB treatment, if not already done elsewhere, work-up for TB disease should be performed as recommended above (Questions 12-17).
- Other baseline laboratory investigations in adults include – if not already done elsewhere – blood testing for HIV, AST/ALT, FBC, diabetes screening, and renal function.
- In children, similar baseline laboratory investigations can be considered except for diabetes screening which is unnecessary.
- Chest X-rays should be performed after completion of the intensive phase of treatment, and upon completion of TB treatment.
- Clinical samples should be collected for AFB smear microscopy and mycobacterial culture after completion of the intensive phase of treatment, and upon completion of TB treatment.
- In adults, visual assessments should be performed at initial and subsequent clinic visits if on an ethambutol-containing regimen.
- The patient should be weighed at all clinic visits.

25. Should there be post-treatment evaluation for post-TB lung disease?

Clinical assessment for post-TB lung disease, including a chest X-ray, can be performed at the end of treatment.

3. Introduction

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* complex. For decades, it was the leading cause of death worldwide from a single infectious disease before being displaced by COVID-19 during the pandemic years [1].

TB is endemic in Singapore, with over 2,000 cases of TB disease (formerly active TB) diagnosed each year. The prevalence of TB infection (formerly latent TB) in the Singapore resident population was recently estimated to be 12.7%, ranging from 2.4% in young adults (18-29 years) to 23.2% in the elderly (70-79 years) [2]. Critical to the elimination of TB are early diagnosis and treatment of TB disease as well as preventive treatment of those with TB infection who are at risk of progression to disease [1].

Singapore's clinical practice guidelines for the management of TB was first published in 2016 [3]. Over the past 7 years, there have been major new advances in the clinical management of TB, including but not limited to the use of computer-aided detection-artificial intelligence (CAD-AI) products for radiological screening for TB disease [4,5], next generation sequencing (NGS) for drug susceptibility testing of *M. tuberculosis* [6,7], new drug treatment regimens incorporating rifapentine for TB disease [8-11] and infection [8,12-18], and video-observed treatment (VOT) of TB disease in lieu of direct observation (DOT) [19,20].

4. Scope

The National TB Programme commissioned this update with the aim of providing healthcare professionals in Singapore with evidence-based and contextualised best practices for screening, diagnosis and treatment of both adults and children with drug-susceptible TB infection and pulmonary disease. These guidelines are not intended to replace the clinical judgment of the healthcare practitioner.

Recommendations for the clinical management of extrapulmonary TB disease and drug-resistant TB infection and disease are beyond the scope of these guidelines. All persons with rifampicin- or multidrug-resistant TB should be referred to the TB Control Unit (TBCU) at Tan Tock Seng Hospital for further management.

5. Methods

Guidelines development team

The Clinical Tuberculosis Guidelines Panel (Panel) was formed in August 2022 and was supported by the Public Health Translational Team (PHTT) from the Saw Swee Hock School of Public Health. Panel and PHTT members are listed in the Acknowledgements.

Selection of questions

The Panel agreed on the clinical questions for recommendations, based on prioritization of the key clinical decisions in managing drug-susceptible TB infection and disease.

Development strategy

Adaptation of guidelines in accordance with the ADAPTE framework was performed for the majority of this update [21]. The RIGHT-Ad@pt checklist [22] can be found at the link: http://www.right-statement.org/extensions/13.

The guidelines adaptation process is described in Appendix A. All major English language national and international TB management guidelines published between 1 January 2016 and 5 March 2023 are listed in Table 1. These were assessed with a modified AGREE II instrument [23], with assessment results provided in Appendix A. PHTT conducted an additional primary literature review using a targeted search approach for questions regarding recent advancements like CAD-AI, NGS, and VOT.

PHTT summarized guidelines and primary literature into reports for the Panel. Through a two-round modified Delphi process, consensus – meaning agreement or no objections from any Panel member – was reached on recommendations for each question. These recommendations are marked (*Adapted*), (*Adopted*) or (*De novo*) accordingly.

Draft guidelines were circulated to local stakeholder bodies for review, with relevant changes incorporated into the final version. These stakeholders include:

- Academy of Medicine Singapore:
    - Chapter of Family Medicine Physicians
    - College of Paediatrics & Child Health
    - College of Physicians:
        - Chapter of Infectious Diseases Physicians
        - Chapter of Respiratory Medicine Physicians
- Agency for Care Effectiveness, Ministry of Health (methodology review only)

Table 1. List of international guidelines reviewed and used in the preparation of the updated TB guidelines

Guidelines	Year published	Developing organizations	Region	Funder	Abbreviation [Reference]
ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update	2018	European Respiratory Society (ERS) and European Centre for Disease Prevention and Control (ECDC)	European Union	European Respiratory Society	ECDC-S [24]
Scientific Advice: Programmatic management of latent tuberculosis infection in the European Union	2018	European Respiratory Society and European Centre for Disease Prevention and Control	European Union	European Respiratory Society	ECDC-L [13]
Tuberculosis: NICE guideline	2019	National Institute for Health and Care Excellence (UK)	United Kingdom (UK)	UK government	NICE [25]
Guidelines for Tuberculosis Control in New Zealand, 2019	2019	Ministry of Health New Zealand	New Zealand	New Zealand government	NZ [14]
Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children	2017	American Thoracic Society, Infectious Diseases Society of America, Centers for Disease Control and Prevention (CDC)	United States	US CDC	CDC-2017 [26]
Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis	2016	American Thoracic Society, Infectious Diseases Society of America, Centers for Disease Control and Prevention (CDC)	United States	US CDC	CDC-2016 [27]
Screening for latent tuberculosis infection in adults: US Preventive Services Task Force Recommendation Statement	2016	US Preventive Services Task Force (USPSTF)	United States	US Department of Health	USPSTF [28]
Tuberculosis Screening, Testing and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis	2019	National Tuberculosis Controllers Association (NTCA), Centers for Disease Control and Prevention (CDC)	United States	US CDC	CDC-2019 [29]

Controllers Association and CDC, 2019					
Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Associations and CDC	2020	National Tuberculosis Controllers Association (NTCA), CDC	United States	US CDC	CDC-2020 [12]
WHO consolidated guidelines on tuberculosis. Modules 1-6	2020-2022	World Health Organization	Global	United States Agency for International Development and the Russian Federation	WHO [8]
Management of Tuberculosis (Fourth Edition) – Clinical Practice Guidelines	2021	Malaysian Health Technology Assessment Section, MOH Malaysia	Malaysia	MOH Malaysia	Malaysia [18]
Canadian Tuberculosis Standards	2022	Canadian Thoracic Society of the Canadian Lung Association (CTC) and Public Health Agency of Canada	Canada	CTC and Public Health Agency of Canada	Canada [17]
National Position Statement for the Management of Latent Tuberculosis Infection	2017	National Tuberculosis Advisory Committee	Australia	Australia	Australia-NTAC [15]
Tuberculosis – CDNA National Guidelines for Public Health Units	2022	Communicable Diseases Network Australia	Australia	Australia	Australia-CDNA [30]
Guidelines on targeted tuberculin testing and treatment of latent tuberculosis infection	2020	Department of Health of the Government of the Hong Kong SAR	Hong Kong SAR	Department of Health, Hong Kong SAR	Hong Kong [16]

6. Screening for TB

1. What are the indications for screening for TB infection?

Recommendation

- People living with human immunodeficiency virus (HIV), i.e. PLHIV, close contacts of persons with infectious TB disease and persons with clinical risk factors for TB should be screened for TB infection. (*Adapted*)

Remarks

Specific indications for screening for each at risk group are given in Table 2. The definition of close contacts as well as the protocol for identifying and screening them had previously been established by the National TB Programme (Contact Tracing Manual internal document). Recommendations for programmatic-level screening of other population groups (i.e. migrants from high TB burden countries, prisoners and healthcare workers, etc.) will not be further discussed here.

Multiple clinical and epidemiological factors increase the risk of TB disease progression and/or worse outcomes. However, the majority opinion of the Panel was that systematic TB screening for individuals with diabetes mellitus, tobacco/alcohol or other substance abuse, and the elderly in long-term care facilities might not be cost-effective in Singapore. Similarly, due to the heterogeneous nature of cancer, a single recommendation was deemed impractical.

Several guidelines highlighted prolonged moderate/high-dose corticosteroid use as a risk for TB reactivation [14,15,17,25,28]. However, the dose threshold and duration varied considerably. The Panel's majority consensus in the absence of clear evidence was a corticosteroid dose of >= 15 mg prednisolone equivalent for a duration of >8 weeks. Although other non-TNF biologics variably increase the risk of TB reactivation, these risks are lower and/or less well quantified compared to anti-TNF therapy.

2. What are the indications for screening for TB disease?

Recommendation

- PLHIV, close contacts of persons with infectious TB disease and persons with clinical risk factors for TB should be screened for TB disease. (*Adapted*)

Remarks

Details regarding the specific indications for screening for each population group are given in Table 2.

Table 2. Specific recommendations for screening for TB infection or disease

Population	Screening for infection	Screening for disease	Comments	Guidelines referenced
PLHIV	Universal screening on diagnosis of HIV	1. Universal screening on diagnosis of HIV 2. Workup from TB infection diagnosis[2]	HIV and TB co-infection rates are <3% of all HIV cases as of 2014 [31]	WHO, NICE, CDC-2017, USPSTF, Canada, ECDC-L, Australia-NTAC, New Zealand,

				Malaysia, Hong Kong
Close contacts	Yes. To follow National TB Programme protocol	Yes. To follow National TB Programme protocol	Nil	WHO, NICE, CDC-2017, Canada, ECDC-L, Australia-NTAC, New Zealand, Malaysia, Hong Kong
Other clinical risk factors: • Anti-TNF therapy • Steroids[1] • Organ transplant • Dialysis • Silicosis	Universal screening before initiation of treatment or on diagnosis of condition (silicosis)	1. Universal screening before initiation of treatment or on diagnosis of condition (silicosis) 2. Workup from TB infection diagnosis[2]	Nil	WHO, NICE, CDC-2017, USPSTF, Canada, ECDC-L, Australia-NTAC, New Zealand, Hong Kong

[1]Steroid dose >= 15 mg of prednisolone equivalent with duration >8 weeks
[2]If TB infection is diagnosed at any point after the initial TB screening event

7. Diagnosis of TB Infection

At present, there is no gold-standard test for the diagnosis of TB infection. Locally available tests include the TST and IGRAs that measure the adaptive immune response to *M. tuberculosis*. Both tests are less sensitive in immunocompromised persons and poorly predict likelihood of progression from TB infection to disease [35,36].

3. What are the laboratory tests that should be performed to diagnose TB infection in adults?

Recommendations

- In adults, IGRA tests are preferred to the TST for diagnosis of TB infection. (*Adopted*)
- The TST can be an alternate diagnostic test, with a cut-off induration of 10 mm in general and 5 mm in at risk immunocompromised individuals. (*Adopted*)
- Parallel or sequential IGRA/TST testing is not recommended for immunocompromised individuals. (*De novo*)

Remarks

Despite higher test costs, the Panel recommended IGRAs over the TST in view of their ease of testing and convenience for individuals.

In significantly immunocompromised adults (i.e. PLHIV with CD4 counts <200 cells/mm^3, anti-TNF therapy, organ or stem cell transplantation, high-dose steroids, etc.), the T-SPOT.TB test (Oxford Immunotec, UK) may be more sensitive than the QuantiFERON-TB Gold Plus (Qiagen, USA) QFT-Plus or the older QuantiFERON-TB Gold In-Tube (Qiagen, USA), albeit with wide confidence intervals in meta-analyses [35,36]. In view of the weak evidence, the Panel chose not to recommend

sequential or parallel IGRA/TST testing in immunocompromised populations despite such recommendations in several guidelines [12-15,17,25,26].

4. What are the laboratory tests that should be performed to diagnose TB infection in children?

Recommendations

- In children aged ≥5 years or children >2 years with prior BCG vaccination, commercially available IGRA tests are preferred to the TST for diagnosis of TB infection. (*Adapted*)
- In children aged 2-5 years without prior BCG vaccination, either TST or IGRA may be used for diagnosis of TB infection. (*Adopted*)
- In children aged 6 months to <2 years, the TST is recommended for diagnosis of TB infection. (*Adopted*)
- A TST cut-off induration of 10 mm is recommended (5 mm in at risk children who are immunocompromised). (*Adopted*)

Remarks

Several guidelines recommended TST only or preferentially over IGRA in children <5 years old [12-15,17,25,26]. Phlebotomy is challenging in young children, and their lower functional immune response increases the likelihood of indeterminate IGRA results [12-15,17,25,26,37]. WHO guidelines supported both tests but stated that a positive result should not be a prerequisite for TB infection treatment in close contacts and PLHIVs [8]. Both tests are not recommended in infants <6 months old due to very low test sensitivity.

8. Treatment of TB Infection

Prevention of TB disease by treatment of TB infection is a critical component of the WHO End TB Strategy [8]. The efficacy of current treatment regimens ranges from 60-90%, with a protective effect possibly lasting beyond a decade [38]. The decision to start TB infection treatment should be made jointly between the individual or his/her legal guardian and the physician, taking into consideration the benefits and risks of treatment as well as the person's preferences and values. In all special populations (i.e. PLHIV, pregnant women, children, etc), treatment should be initiated by or in close consultation with the relevant clinical specialists specific to these populations.

5. What are the baseline tests to be performed before and after starting TB infection treatment?

Recommendations

- The possibility of TB disease must be excluded via a symptom screen and chest X-ray prior to initiating treatment for TB infection. (*Adopted*)
- Baseline AST and ALT testing can be performed prior to starting TB infection treatment, with subsequent AST and ALT testing on follow-up visits in individuals at high risk for hepatotoxicity from treatment or full liver function testing in those who have clinical features suggestive of liver dysfunction. (*Adapted*)

Remarks

It is important to rule out TB disease before initiating treatment for TB infection via assessment for symptoms suggestive of disease and a chest X-ray [8,15-18,26], with sputum testing where indicated [16-18,26].

Several guidelines recommended baseline liver function testing for individuals at risk of hepatotoxicity [8,15,16,25], including those over the age of 35 years [8,15], with a history of liver

disease, harmful use of alcohol/other drugs, HIV infection [8,15,16,25], as well as pregnant and postpartum (<3 months) women [8,16]. Others recommended baseline testing for all individuals [14,17,18]. Risk-benefit assessments of treatment should be performed in individuals with abnormal liver function results [8].

6. What are the preferred and alternate regimens for the treatment of TB infection in adults?

Recommendations

- The two preferred regimens for the treatment of TB infection in adults are rifampicin daily for 4 months (4R) or isoniazid daily for either 6 or 9 months (6H/9H). (*Adopted*)
- Alternative treatment regimens include isoniazid and rifampicin daily for 3 months (3HR) or isoniazid and rifapentine weekly for 3 months (3HP), should rifapentine become available in Singapore. (*Adapted*)
- For PLHIV, isoniazid and rifapentine daily for 1 month (1HP) may be another alternative regimen. (*Adopted*)
- Pyridoxine supplementation is recommended for all adults on an isoniazid-containing regimen. (*Adapted*)

Remarks

The preferred and alternative treatment regimens are listed in Table 3. There is no clear benefit of administering 6H/9H as a thrice-weekly regimen except when prescribed as part of direct (or video-) observed treatment (DOT or VOT) [12,14,17].

WHO, ECDC-L and Malaysia guidelines favoured shorter regimens and those requiring less frequent administration by providers and patients, aiming to increase adherence and expedite completion [8,13,18]. This is particularly important for certain patient populations (i.e. homeless, prisoners or those due to start anti-TNF therapy).

For PLHIV, 6H/9H is preferred to avoid potential drug interactions between rifamycin-containing regimens and antiviral therapy [8,12,13,18,25]. The data for 1HP comes from a single randomized clinical trial in PLHIV living in a high TB prevalence region [40], and it is recommended as an alternative regimen for adult PLHIV in recent guidelines [8,12,18].

Rifapentine is not recommended in pregnant women at present due to limited data on its pharmacokinetics and safety during pregnancy [8,12,18]. While Canadian guidelines recommended avoiding isoniazid-containing regimens in pregnancy due to potential risk of maternal hepatoxicity [17], other guidelines had a different stance, citing insufficient evidence to warrant a separate recommendation [8].

Pyridoxine supplementation can reduce the risk of isoniazid-induced peripheral neuropathy. It is variously recommended for all persons [14,18], or only at-risk individuals [17,26,29] on an isoniazid-containing regimen. To simplify implementation, the Panel recommended pyridoxine supplementation for all adults on an isoniazid-containing regimen.

Table 3. Recommended treatment regimens for TB infection

Population	Preferred Regimen (dose)	Alternate Regimen	Comments
Adults	• 4R daily (10 mg/kg body weight (BW))	• 3HP weekly (isoniazid 15 mg/kg BW up to	• 3HP weekly is not recommended in

	• 6H/9H daily (5 mg/kg BW) with pyridoxine daily (10-25 mg)	900 mg; rifapentine up to 900 mg) with pyridoxine daily • 3HR with pyridoxine daily	pregnant/breastfeeding women
PLHIV	• 6H/9H daily (5 mg/kg BW) with pyridoxine daily (10-25 mg) • 4R daily (10 mg/kg BW)	• 3HP weekly with pyridoxine daily • 3HR with pyridoxine daily • 1HP daily (isoniazid 300 mg/day; rifapentine 600 mg/day)	• To be aware of potential drug interactions with antiretroviral therapy
Children	• 4R daily (<10 years: 15 mg/kg BW; ≥10 years: 10 mg/kg BW) • 6H/9H daily (<10 years: 10 mg/kg BW; ≥10 years: 5 mg/kg BW)	• 3HR daily • 3HP weekly (age ≥2 years only; weight-adjusted dosing [39])	• Isoniazid/rifapentine weekly dosing (2-14 years): ○ 10 to <16 kg = 300 mg/300 mg ○ 16 to <24 kg =500 mg/450 mg ○ 24 to <31 kg = 600 mg/600 mg ○ ≥31 kg = 700 mg/750 mg

7. What are the preferred and alternate regimens for the treatment of TB infection in children?

Recommendations

- The two preferred regimens for the treatment of TB infection in children are 4R or 6H/9H. (*Adopted*)
- Alternative treatment regimens include isoniazid and rifampicin daily for 3HR or weekly 3HP in children age ≥2 years, should rifapentine become available in Singapore. (*Adapted*)
- Pyridoxine supplementation is recommended for children at risk of peripheral neuropathy while on an isoniazid-containing regimen. (*Adopted*)

Remarks

3HP is currently recommended to children ≥2 years old due to the limited data on the efficacy and pharmacology of rifapentine in younger children.

8. How should treatment be monitored?

Recommendation

- TB infection treatment should be self-administered except in the case of the weekly 3HP regimen or in a situation where adherence to treatment is poor. In the latter cases, DOT or VOT will be preferred. (*Adapted*)

Remarks

Most guidelines endorsed self-administered treatment for TB infection, reserving observed treatment only for the 3HP regimen [12,17,18], or significant non-adherence [12-14]. Enforcing observed treatment for TB infection can pose a significant barrier for treatment [8,39].

9. How should treatment interruptions be managed?

Recommendation

- For interruptions due to drug toxicity, the risk-benefit of continued treatment should be re-evaluated before resuming treatment. (*Adopted*)
- For interruptions due to hepatotoxicity, treatment drugs can be re-introduced once liver function of the affected individual has normalised. (*Adopted*)

Remarks

The treating physician should carefully weigh the risk and costs of potential additional hepatic injury against the benefit of TB preventive treatment with the affected individual before continuing or re-initiating treatment.

The general recommendations for managing treatment interruptions during the treatment of TB infection according to duration of interruption and treatment regimen are adapted from the WHO guidelines Module 1 [8] and shown in Table 4 below. In all scenarios, it will be good to determine the reason for treatment interruption and to address them. The individual being treated (and the caregiver if relevant) should also be counselled on the importance of adherence, with a joint agreement on the best ways to improve adherence.

Table 4. Suggested actions for treatment interruptions during treatment of TB infection [8]

Regimen	**Duration of interruption**	**Next step**
3HR, 4R, 6H, 9H	<2 weeks	• Resume preventive treatment immediately upon return and add the number of days of missed doses to the total treatment duration
	≥2 weeks	• If treatment interruption occurs after more than 80% of doses expected in the regimen were taken, no action is required. Continue and complete the remaining treatment as per original plan. • If less than 80% of doses expected in the regimen are taken, and the treatment course can still be completed within the expected time for completion, i.e. treatment duration + 33% additional time, no action is required. Continue and complete the remaining treatment as per original plan. • If less than 80% of doses expected in the regimen are taken, and the treatment course cannot be completed within the expected time for completion, consider restarting the full course.
3HP	Weekly schedule of 1 dose missed	• If the missed dose is remembered within the next 2 days, the person can take the dose immediately. Continue the schedule as originally planned. • If the missed dose is remembered >2 days later, the person can take the missed dose immediately and change the schedule for weekly intake to the day the missed dose was taken until treatment completion. This will avoid 2 weekly doses being taken less than 4 days apart.
	>1 dose missed	• If between 1–3 weekly doses are missed, treatment can be continued until all 12 doses are taken, thus prolonging the treatment duration to a maximum of 16 weeks.

		• If, however, 4 or more weekly doses are missed, consider restarting the full course. • If adherence to a weekly routine is not possible, consider discontinuing 3HP and offering an alternative (daily) regimen.
1HP	≤1 week	• If more than 80% (23) of doses expected in the regimen are taken, no action is required. • If less than 80% (23) of doses are taken, resume treatment immediately upon return and add the missed doses to the total duration to complete the course within a maximum of 6 weeks.
	>1 week	• If more than 7 consecutive doses are missed, consider restarting the complete course of 1HP regimen. • If more than 7 doses are missed intermittently, resume preventive treatment immediately upon return and add the missed doses to the total treatment duration to complete the course within a maximum of 8 weeks. • If adherence to 1HP is not possible, consider discontinuing it and offering an alternative daily regimen or 3HP.

Interruptions due to drug hepatotoxicity

NICE [25], CDC-2016 [27], Malaysia [18] and New Zealand guidelines [14] address how treatment interruptions as a result of hepatotoxicity should be managed.

NICE guidelines provide specific instructions in terms of investigations, AST/ALT levels and the re-introduction of treatment drugs [25]. Treatment drugs can be introduced (sequentially in combination regimens over a period of no more than 10 days) when AST/ALT levels fall below twice the upper limit of normal, bilirubin levels return to the normal range, and clinical symptoms have resolved. If another reaction of similar/greater severity occurs with reintroduction of a particular drug, a regimen that does not contain the drug can be tried and the total regimen considered to be extended accordingly.

New Zealand [14] and Malaysian [18] guidelines provide comparatively less specific guidance. New Zealand guidelines state that treatment with a different drug can be considered with very close monitoring when LFTs have normalised while Malaysia guidelines state that drugs can be reintroduced when the liver function becomes normal and that physicians/paediatricians with experience managing TB should be consulted.

CDC guidelines address hepatotoxicity interruptions only in relation to PLHIV [52]. It does not provide specific instructions on AST/ALT levels and drug reintroduction but states the underlying principle that the ultimate decision on resumption of therapy with the same or different agents should be made after weighing the risk – in consultation with an expert in treatment TB in PLHIV – for additional hepatic injury against the benefit of preventing progression to TB disease [52].

Interruptions due to other drug adverse reactions

Canadian [17] and Malaysia [18] guidelines provide guidance on management of interruptions in relation to the extent of adverse events graded into levels of severity. Canadian guidelines grade adverse events into tiers based on their impact on instrumental activities of daily living (ADL). In general, Grade 1 and 2 adverse events (those not interfering with, or only modestly interfering with, instrumental ADLs) should result in greater monitoring but do not necessarily require stopping therapy. However, severe adverse events that interfere with normal daily activity, including the ability to go to work (Grade 3) or any life-threatening or disabling adverse event (Grade

4) should lead to a pause in treatment until recovery or permanent discontinuation. A change to an alternative regimen should be considered once the patient has recovered.

Malaysia guidelines recommend the Common Terminology Criteria for Adverse Events (CTCAE) to grade adverse drug reactions [53]. Symptomatic management and reassurance should be offered to all patients with ADR. For mild to moderate (Grade 1-2) reactions, TB infection treatment can be continued, while for severe (Grade 3-4) reactions, the treatment regimen should be withheld or switched [18].

No information on differences in the management of treatment interruptions in adults and children (≤ 16 years of age) was found in the reviewed guidelines.

10. How often should patients on TB infection treatment be followed up and for how long?

Recommendations

- Follow-up for patients on TB infection treatment can be at 4-6 week intervals, with longer intervals for adherent patients who are at low risk for drug adverse events. (*Adapted*)
- Follow-ups can be discontinued upon treatment completion. *(Adopted)*

Remarks

Most guidelines recommended monthly follow-up for treatment monitoring [8,12,14,16,17]. Canadian guidelines supported extending the interval between visits for adherent patients who are at low risk of drug toxicity.

11. How should post-treatment re-exposure to infectious TB be managed?

Recommendation

- Re-treatment of individuals re-exposed to infectious TB can be considered. (*Adopted*)

Remarks

Currently tests cannot determine if re-infection has occurred in an individual who had previously completed treatment for TB infection or disease. Canada guidelines conditionally recommend against re-treatment of re-exposed individuals unless they are at high risk of progression to TB disease [17]. However, WHO stated that prior treatment should not be a contraindication to TB preventive treatment in close contacts of infectious individuals [8]. As a precautionary measure, the Panel elected to adopt WHO's recommendation.

9. Diagnosis of TB Disease

The emergence of new technologies has prompted a consideration on their incorporation into TB diagnosis algorithms and guidelines.

12. What tests should be performed to diagnose TB disease?

Recommendations

- The workup for TB disease should include clinical history taking and examination, chest X-ray, and collection of samples for AFB smear microscopy, NAAT and mycobacterial culture. (*Adapted*)
- In children but not adults, the IGRA test or TST in the absence of prior BCG vaccination may be a supplementary test for diagnosing TB disease. (*Adapted*)

Remarks

WHO does not recommend AFB smear microscopy or mycobacterial culture in general for diagnosis of TB disease [8], partially due to resource constraints in low-middle income and high-burden TB countries. The Panel debated on the value of AFB smear microscopy given the widespread availability of NAAT locally. The consensus was to remain aligned with other major guidelines in recommending AFB smear microscopy at present [14,17,18,24-26,30], since these results still guide contact tracing operations.

Most guidelines support using either TST or IGRA as a supplementary diagnostic test in children, due to the challenges of obtaining clinical samples from young children as well as the paucibacillary nature of childhood pulmonary TB [8,14,17,18,24-26,30]. However, these tests are not recommended in adults due to their lower specificity and relative ease of obtaining clinical samples.

13. What are the types of clinical samples that should be sent?

Recommendations

- Sputum is the preferred clinical sample for the diagnosis of TB disease in adults and older children. (*Adopted*)
- In adults or children who are unable to properly expectorate, induced sputum is preferred, with early morning gastric aspirate considered an equivalent option in very young children or adults for whom sputum induction is unfeasible. (*Adopted*)
- Bronchoscopy with aspiration and lavage is an alternate option for sample collection in both adults and children. (*Adopted*)
- Nasopharyngeal aspiration is an alternate option for sample collection in children. (*Adopted*)

Remarks

Obtaining high quality sputum increases the yield of microbiological testing. NZ and Malaysia guidelines recommended induced sputum over expectorated sputum for the diagnosis of pulmonary TB disease [14,18], but the former is a secondary or equivalent option in other guidelines [8,17,24-26,30].

Nasopharyngeal aspirate – while relatively easy to perform – has considerably lower sensitivity for diagnosing TB disease (NAAT sensitivity of approximately 46% vs. 73% in gastric aspirate) in children [41]. It is recommended in three guidelines as an alternative when sputum or gastric aspirate collection is unfeasible [8,14,18].

Testing stool via NAAT is newly recommended by WHO for the diagnosis of pulmonary TB in children, with reasonable diagnostic sensitivity [8]. However, in view of the familiarity of obtaining induced sputum or gastric fluid samples at present coupled with additional laboratory processing steps for stool [17,41], the Panel elected not to recommend stool as an alternate sample type for TB diagnosis.

14. Excluding bronchoscopic sampling, what should be the minimum number of samples sent and when should the samples be collected?

Recommendations

- At least 2 samples should be sent for laboratory testing for TB disease, of which at least 1 sample should be an early morning sample. (*Adapted*)
- Same day collection of samples is preferred except in the case of gastric aspirate, for which alternate day collection of early morning samples is ideal. (*Adopted*)

Remarks

Most guidelines recommended a minimum of 3 samples [17,24-26,30], with most also preferring early morning collection [14,18,24-26]. Considering the marginal additional diagnostic yield for a third sample (2-3% on average) [24], the Panel elected to set the minimum at 2 samples, with at least 1 collected in the early morning. Fasted early morning samples are recommended for gastric aspirate collection as gastric emptying following food or water intake will significantly reduce diagnostic yield [41].

The pervasive issue of poor sample quality (especially in relation to smear microscopy) and intention to improve diagnostic yield were cited as rationale for the minimum number of 3 samples. Canadian guidelines add that multiple sample collection is particularly important for children as the yield of microbiological tests is low in the population [17]. New Zealand [14] and Malaysia [18] guidelines recommend a minimum of two samples. However, New Zealand recommends three samples for specimens for children, except for nasopharyngeal aspirate, where two samples are recommended [14]. These are summarized in Table 5 below.

Table 5. Sample collection recommendations according to international guidelines

Guideline	**Minimum number of samples**	**Collection time**	**Rationale and remarks**
WHO [8]	1	Spot or morning sample	One initial specimen with collection of additional ones as needed. For operational reasons, programmes may consider collecting two specimens upfront, with the first specimen promptly tested using NAAT, and the second for the additional testing.
CDC-2016 [27]	3	Morning (preferred)	Three specimens to improve sensitivity given the pervasive issue of poor sample quality. Sensitivity of first morning sputum specimen is greater than that of a single spot specimen.
Canada [17]	3	Collected on the same day, at least 1 hour apart (good evidence)	While it is conventional to collect three separate morning sputum specimens, it is well known that this scheme is inconvenient to patients, making dropouts during diagnosis common. Published research has demonstrated the feasibility of "frontloaded" diagnosis of TB using specimens collected on the same day and shown that the diagnostic yield is undiminished. For children, multiple sputum samples should be collected, as yield of sputum AFB smear microscopy and culture in children <10 years is low, and three samples have a higher yield than a single sample.

NICE [25]	3	Preferably including 1 early morning sample	The emphasis on early morning samples may be overemphasized, leading to delays in diagnosis when prompt diagnosis may be more important, especially for people with more severe disease. However, waiting to get a good optimal sample is appropriate for people who are relatively well.
New Zealand [14]	2 (for children: 3)	Ideally 3 specimens collected early in the morning on 3 separate days. Where not possible, collect 2 specimens on the same day, several hours apart For children: 3 early-morning specimens on consecutive days	N.A.
Malaysia [18]	2	When possible, at least one early morning specimen	Sputum collected in the early morning has the highest yield.
ECDC [15]	3 (with at least 2 for microscopic examination and 1 for nucleic acid amplification test)	At least one early morning specimen should be obtained, when possible EU/EEA countries may decide to collect three sputum samples on the same day (not necessarily on consecutive days)	Given that the collection of a third sputum sample has been shown to increase the diagnostic yield by 2–3%.
Australia-CDNA [30]	3	At least one early morning sample	N.A.

15. Under what circumstances should CT thorax be considered for the diagnosis of pulmonary TB?

Recommendation

- CT thorax may be considered as an additional imaging modality for the purposes of excluding another underlying diagnosis or for the evaluation of extrapulmonary TB disease with pulmonary involvement (i.e. pleural or pericardial disease). (*Adopted*)

Remarks

CT thorax was positioned across several guidelines as a non-routine and additional imaging modality to be considered for use for further diagnostic investigations [8,14,17,25].

16. What is the role of NGS as a clinical laboratory tool?

Recommendations

- Whole genome sequencing (WGS) can be deployed in local clinical laboratories for genotypic prediction of TB drug resistance. It has demonstrable high sensitivity and specificity especially for first-line drugs, and the output can also be used for national TB surveillance. (*Adapted*)

Remarks

NGS applications for TB currently include prediction of drug resistance via both WGS [6-8] and targeted NGS (tNGS) [8], and molecular epidemiological investigations of transmission via WGS. WGS is ideally performed on cultured *M. tuberculosis* isolates due to the need for high quality DNA, with techniques to enable direct sequencing from clinical samples still very much a work-in-progress. In Singapore, WGS is primarily used for public health surveillance. Routine WGS for drug susceptibility testing in clinical laboratories could eliminate the requirement for phenotypic testing in genotypic pan-sensitive *M. tuberculosis* isolates.

tNGS assays determine drug resistance via targeted panels that interrogate specific relevant regions of the genome, and can be used on DNA directly obtained from a clinical sample with a more rapid turnaround time. Commercially available tNGS assays have been developed, but none are available in Singapore at the time of writing. While tNGS shows good concordance with WGS in predicting drug resistance, it is currently limited to known resistance genotypic markers. WHO is currently developing a guideline on the use of tNGS for detecting drug resistance [42], and the Panel has no specific recommendation regarding tNGS at present.

17. What is the role of machine learning in the screening, diagnosis and follow-up of pulmonary TB?

Recommendations

- The panel recognises that a number of automated CAD-AI products have been certified by the Health Sciences Authority, and more are expected in the future. Some products have been deployed in other countries for chest X-ray screening for TB disease in various settings. While multiple studies have demonstrated comparable diagnostic performance (relative to a human radiologist) for the detection of chest X-ray changes associated with pulmonary TB, such findings will have to be validated within the local practice setting in Singapore. At present, deployment of CAD-AI products will require a human-in-the-loop, where a certified radiologist is still needed to provide a final read. In addition, due consideration must be given to the fact that current products have narrow capabilities, with potential to miss other non-specified abnormalities on a chest X-ray. (*De novo*)
- The panel also recommended vigilance in this rapidly evolving field and timely updates of major developments. (*De novo*)

Remarks

WHO guidelines recommended that CAD-AI products may be used in place of human readers for interpreting digital chest X-rays in screening and triaging individuals ≥ 15 years old for TB disease where TB screening is recommended [8]. Canada guidelines note that CAD-AI products may be valuable in closing diagnostic gaps in resource-limited and remote settings [17]. An online and regularly updated data repository of commercially available CAD-AI products for TB screening is maintained jointly by FIND and the Stop TB Partnership (https://www.ai4hlth.org/). Further details on CAD-AI products for TB disease screening are available in the Appendix B.

10. Treatment of TB Disease

Early diagnosis and completion of TB disease treatment are cornerstones of the global and local strategy for TB elimination [8]. However, adherence to treatment can be challenging because of its lengthy duration, pill burden and side effects [8,14,17,18,24,25,27,30]. Incomplete adherence increases the risk for drug resistance and relapse. In Singapore, treatment completion, relapse and case fatality rates are 65%, 6.1% and 0.4% respectively in 2020 [data, NTBP].

Although TB disease should be tackled at a programmatic level, a patient-centred approach focusing on increasing treatment literacy and enabling adherence is necessary. Comprehensive treatment support and tailored adherence monitoring interventions should be developed in collaboration with persons with TB disease [8]. A multi-disciplinary team involving physicians, nurse practitioners, public health personnel, social workers, and interpreters where necessary is the standard of care in Singapore. In all special populations (i.e. PLHIV, pregnant women, children, etc), treatment of TB disease should be initiated by or in close consultation with the relevant clinical specialists. Table 6 outlines the aspects and components of a TB disease treatment plan.

Table 6. Aspects and components of a TB disease treatment plan

Aspects	**Components**	**Guidelines referenced**
Principles	Patient-centered care with comprehensive and individualized treatment support	11,17,20,27,30,33
	Balancing patient rights/choices with public health and safety	11,20,27,28,30,33
Enablers, incentives and adherence interventions	Patient health education and counselling; improving treatment literacy	11,20,21,27,28,30,33
	Psychological, material (including food, financial and transport subsidies) and social support for patients	11,20,21,27,28,30,33
	Healthcare worker education and training	11,28
	Integration with patients' primary/specialty care where possible	11,20,27,28,30
	Observed treatment (DOT or VOT or family supervision for children)	11,17,20,21,27,28,30,33

18. What are the preferred and alternative regimens for the treatment of drug-susceptible pulmonary TB disease in adults?

Recommendations

- The preferred regimen for the treatment of drug-susceptible pulmonary TB disease in adults is 2HRZE/4HR. (*Adopted*)
- In persons age >70 years with low risk of drug resistance, pyrazinamide should be avoided, with 2HRE/7HR being the preferred regimen. (*Adapted*)
- An alternate regimen is 2HPMZ/2HPM – except in pregnant/breastfeeding women and PLHIV – should rifapentine become available in Singapore. (*Adopted*)
- For PLHIV with TB disease, care should be taken to avoid heightened risk of drug adverse effects due to interactions with antiretroviral therapy. (*Adopted*)
- Pyridoxine supplementation is recommended for all adults on an isoniazid-containing regimen. (*Adopted*)

Remarks

Treatment may be initiated based on strong clinical and radiological suspicion of TB disease, although clinical samples for microbiological diagnosis should be collected first if possible. Table 7 lists the preferred and alternative treatment regimens for TB disease where drug resistance is not expected. The first-line regimen of choice in all guidelines remains 2HRZE/4HR [8,14,17,18,24,25,27,30], which has a global treatment success rate exceeding 85% and low risk of adverse events [8].

Adverse events resulting in treatment interruption or discontinuation are more common among the elderly, particularly for pyrazinamide which accounted for >15% of such events [43]. A number of age thresholds (>65 to >80 years) were proposed in guidelines where use of pyrazinamide was cautioned [8,17,27], with the Panel setting it at >70 years based on existing local practice. Treatment duration should be extended to 9 months (2HRE/7HR) if pyrazinamide is excluded.

Following the completion of the TBTC Study 31 trial, where a shortened 2HPMZ/2HPM regimen was shown to be non-inferior to 2HRZE/4HR [9], WHO and CDC included 2HPMZ/2HPM as an alternate regimen in updated guidelines [8,10]. The Panel therefore also recommended this as an alternate treatment regimen, pending rifapentine availability in Singapore. The higher cost of the drug regimen will likely be offset by the shorter duration of treatment for both the individual and the national programme. However, insufficient data precluded the Panel from recommending this regimen for pregnant/breastfeeding women, PLHIV and children <12 years of age.

Table 7. Recommended treatment regimens for TB disease

Population	**Regimen & dose**	**Comments**

Adults, general	• 2HRZE/4HR with pyridoxine
	  ○ Isoniazid 5 mg/kg BW daily OR 10 mg/kg BW thrice-weekly
	  ○ Rifampicin 10 mg/kg BW daily or thrice-weekly
	  ○ Pyrazinamide 20-25 mg/kg BW daily or 30-40 mg/kg BW thrice-weekly
	  ○ Ethambutol 15-20 mg/kg BW daily or 25-40 mg/kg BW thrice-weekly
	  ○ Pyridoxine 10-25 mg daily or thrice-weekly
		• Daily dosing is preferred, particularly during the intensive phase [11]
		• Thrice-weekly dosing is more convenient for observed treatment (DOT or VOT)

	• 2HPMZ/2HPM with pyridoxine
	  ○ Isoniazid, pyrazinamide and pyridoxine doses as above
	  ○ Rifapentine 1200 mg daily
	  ○ Moxifloxacin 400 mg daily
		• Daily dosing only

Children	• 2HRZ(E)/4HR OR 2HRZ(E)/2HR
	  ○ Isoniazid 10-15 mg/kg BW daily (maximum 300 mg) or 20 mg/kg BW thrice-weekly (maximum 900 mg)
	  ○ Rifampicin 15-20 mg/kg BW daily (maximum 600 mg) or 20 mg/kg BW thrice-weekly (maximum 600 mg)
	  ○ Pyrazinamide 30-40 mg/kg daily (maximum 2 g)
	  ○ Ethambutol 15-25 mg/kg daily (maximum 1 g)
		• Daily dosing is preferred [11]

Regimens for PLHIV

The WHO guidelines is the only one with alternative and other recommended regimens (apart from 2HRZE/4HR) for PLHIV [8]. The guidelines state that the recommended and alternate regimens of 2HRZE/4HR, 2HPMZ/2HPM and 2HRZ(E)/2HR are applicable to PLHIV (including children and adolescents living with HIV - CALHIV). However, the following subgroup considerations should be taken into account:

- 2HPMZ/2HPM should not be used in PLHIV with CD4 count < 100 cells/µL, in view of insufficient data on this group for the regimen
- CALHIV on 2HRZ(E)/2HR need to be monitored closely, with extension of treatment to 6 months if there is insufficient progress, in view of limited evidence on this group for the regimen.

Extending treatment duration

Some of the guidelines (WHO, CDC-2016 and Canada) are inclined towards the same or longer TB disease treatment durations for PLHIV/certain PLHIV subgroups as compared to the general population [8,17,27]. WHO guidelines recommend that PLHIV with TB disease HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients (strong recommendation, high certainty of evidence), citing evidence of more likely treatment failure/relapse with intermittent versus daily dosing and higher risk of relapse with shorter versus longer rifampicin containing regimens [8]. Similarly, the guidelines recommend that the treatment duration for CALHIV with non-severe TB and on 2HRZ(E)/2HR be extended to 6 months if there is insufficient progress, in view of limited evidence on this regimen for this group [8].

CDC-2016 (conditional recommendation, very low certainty of evidence) and Canadian guidelines (poor evidence) recommend that the standard 6-month daily regimen be used for PLHIV receiving ART but that the continuation phase with INH and RIF be extended by an additional 3 months (total of 9 months of therapy) for PLHIV not receiving ART [27]. CDC-2016 guidelines cited evidence showing lower risk of recurrence when the continuation phase of treatment is extended in PLHIV populations predominantly not receiving ART [27].

Notwithstanding this, some guidelines also indicate caution with extending regimen duration for PLHIV indiscriminately without careful consideration. WHO guidelines point out that separate regimens for PLHIV can be challenging in operational terms and can create stigma. Other potential harms of extending treatment are acquired resistance to rifampicin, and a longer period during which ART options are limited. Canadian guidelines highlight that treatment duration need not be extended on the basis of HIV co-infection alone [17]. NICE guidelines also highlight that for PLHIV with TB disease and without central nervous system involvement, treatment should not be routinely extended beyond 6 months [25].

Daily versus intermittent treatment regimens

CDC-2016 [27] and Canadian guidelines [17], which allow for consideration of certain intermittent dosing frequencies, recommend daily over intermittent dosing for PLHIV in both the intense and continuation phases of treatment, citing evidence that twice- or thrice-weekly dosing during both phases have been associated with increased risk of treatment failure or relapse with resistance to rifamycin class, particularly in PLHIV. CDC-2016 guidelines recommend that daily dosing be given as DOT for PLHIV throughout the treatment [27]. Malaysia guidelines, which only recommend daily over intermittent dosing, further highlight that daily anti-TB regimens should be used throughout the treatment for PLHIV [18].

Initiation of antiretroviral therapy (ART)

Most guidelines recommend initiation of ART amidst TB treatment for ART-naïve patients [8,17,18,24,27]. They cite evidence indicating that earlier ART initiation resulted in reduced morbidity, mortality and incidence of additional HIV-defining illnesses, while balancing the risk of progressive HIV and TB disease with that of immune reconstitution inflammatory syndrome (IRIS). However, while WHO [8] and Canadian [17] guidelines recommend that ART be initiated as soon as possible (within 2 weeks of initiating TB treatment, regardless of CD4 cell count), CDC-2016 [27] and Malaysia [18] guidelines recommend that ART be initiated within 2 weeks of TB treatment for

patients with CD4 counts < 50 cells/mm3 and within 8 weeks (for Malaysia) or 8-12 weeks (for CDC) of TB treatment for patients with higher CD4 counts, noting also that early ART was associated with a higher risk of IRIS and IRIS-related death.

ECDC guidelines recommend that TB treatment should be started immediately and ART prescribed as soon as possible for PLHIV but do not indicate specific durations post TB treatment initiation for starting ART [24].

Almost all these guidelines highlight the specific exception of cases with central nervous system involvement/where signs and symptoms of meningitis are present, where ART initiation after start of TB treatment should be delayed, considering that immediate ART is significantly associated with more severe adverse events [8,17,18,27]. In this scenario, CDC and Canada guidelines indicate a delay of at least 2 weeks [17,27], but WHO guidelines recommend a delay of at least 4 weeks [8], while the Malaysian guidelines recommend a delay of 2 months [18].

Drug-drug interactions with ART

Several guidelines highlight that potential drug-drug interactions with co-administration of ART and rifamycins should be taken into consideration before initiating TB therapy [8,17,18,25,27]. While rifamycins are the only anti-TB agents to exert clinically important interactions with ART drugs and the breadth/magnitude of these interactions can be daunting, both CDC-2016 and Canadian guidelines emphasise the importance of using rifamycin-based treatment for PLHIV [17,27].

Rifamycins remain the most potent drug class for TB treatment and CDC guidelines state that the drug-drug interactions between rifamycins and ART drugs should be managed, not avoided [27]. Canadian guidelines strongly recommend a rifamycin (rifampin or rifabutin)-containing regimen for treatment of TB, despite the potential for drug-interactions with antiretroviral therapy [17].

CDC-2016 [27], Canadian [17] and Malaysia [18] guidelines, particularly CDC-2016, provide the most detailed recommendations on choice of drugs and dose adjustments for TB treatment with ART. The rest of the guidelines either address the issue broadly and/or refer to separate guidelines on PLHIV.

Several guidelines regard rifabutin as a reasonable substitute for rifampicin for PLHIV who must concurrently receive ART that have adverse drug interactions with rifamycins, as rifabutin is associated with weaker enzyme induction [17,18,27]. However, Canadian guidelines state that there is less published clinical experience with rifabutin in the treatment of PLHIV with TB, and rifampicin is usually preferred in this population [17].

It should be noted that rifabutin levels are contingent on the patient's adherence to the protease inhibitors, and that it is therefore important for patients to be compliant to ART as well when on TB treatment. Where ART adherence is in question, switching out of the protease inhibitor regimen should be considered so as not to risk subtherapeutic rifabutin levels.

CDC and Canadian guidelines note that the management of drug-drug interactions between ART and the rifamycins is an area of active research and recommendations change frequently [17,27]. It is therefore prudent to consult with an experienced pharmacist and a regularly updated clinical drug-interaction resource.

19. What are the preferred and alternative regimens for the treatment of drug-susceptible pulmonary TB disease in children?

Recommendations

- The preferred regimen for the treatment of drug-susceptible pulmonary TB disease in children is 2HRZ(E)/4HR. (*Adopted*)
- In children with non-severe disease, a shortened 2HRZ(E)/2HR regimen may be considered after consultation with an experienced paediatric specialist. (*Adapted*)
- An alternate regimen of 2HPMZ/2HPM can be considered in children >12 years of age should rifapentine become available in Singapore. (*Adapted*)
- Pyridoxine supplementation is recommended for children at risk of peripheral neuropathy while on an isoniazid-containing regimen. (*Adopted*)

Remarks

Where the population prevalence of drug-resistant TB is low, ethambutol may be omitted from the intensive phase of treatment for HIV-negative children [8].

The SHINE trial demonstrated non-inferiority of a 4-month regimen 2HRZ(E)/2HR to the standard 6-month regimen in children <16 years of age with non-severe (defined as respiratory tuberculosis confined to one lobe with no cavities, no signs of miliary tuberculosis, no complex pleural effusion, and no clinically significant airway obstruction or peripheral lymph-node tuberculosis) smear-negative TB [44]. The Panel supported consideration of this shortened regimen for non-severe TB in children in Singapore under the guidance of an experienced paediatric TB specialist, in line with WHO guidelines [8].

20. What are the other considerations for prolonging or shortening treatment for TB disease?

Recommendations

- In persons with TB disease who present with baseline cavitation and/or extensive disease on chest X-ray AND positive mycobacterial cultures after 2 months of treatment, the Panel strongly recommended that the treatment duration be extended to 9 months (2HRZE/7HR). (*Adopted*)
- Other considerations for extending treatment to 9 months (2HRZE/7HR) in persons with microbiologically-proven TB disease include the following: (*Adopted*)
    - Positive mycobacterial cultures after 2 months of treatment
    - Baseline cavitation and/or extensive disease on chest X-ray
    - Slow radiological improvement
    - PLHIV with CD_4 count <200 cells/mm^3 and not on anti-retroviral therapy
    - Poorly controlled diabetes mellitus throughout treatment course
- In persons with culture-negative but probable TB disease, treatment duration may be shortened to 4 months (2HRZE/2HR) (*Adopted*)

Remarks

CDC-16 and Canada guidelines recommended extending treatment to 9 months in individuals with baseline cavitation and/or extensive disease on chest X-ray who remain culture-positive after 2 months of treatment [17,27]. These patients are at the highest risk of relapse post-treatment (>10%) with the 2HRZE/4HR regimen [17,27,45]. Other factors associated with a higher risk of relapse are as listed above [17,27,45]. Although the Panel recommended considering treatment extension in the presence of these factors, current evidence does not suggest this results in lower relapse rates, and WHO guidelines do not recommend extending TB disease treatment beyond 6 months in such cases [8].

In persons with culture-negative TB, considerable evidence including from Singapore suggests that a shortened treatment duration is effective [27,46].

21. How should treatment of TB disease be monitored?

Recommendations

- In adults, observation of treatment is recommended for those with infectious TB disease, those who are at risk of adverse outcomes and/or those who are non-adherent to treatment. (*Adapted*)
- All children with TB disease should ideally undergo some form of observed treatment, including home supervision by an adult family member or caregiver. (*Adapted*)
- VOT is equivalent to DOT in terms of ensuring treatment adherence in those who are able to undergo VOT. (*Adapted*)

Remarks

DOT is a strategy to enhance TB disease treatment adherence and completion, and is a central tenet in TB control in Singapore [3]. While all international TB guidelines support DOT under varied situations; several also emphasize the importance of balancing individual rights with public health objectives [14,25,27,30]. In Singapore, nurse-led clinic and home DOT are practised alongside family supervision of TB treatment in young children. Despite concerns raised in guidelines including by WHO [8,27], Singapore's experience with family supervision in young children has demonstrated high treatment success rates.

In recent years, VOT has emerged as a cost-effective and patient autonomy-enabling alternative to DOT [19,20], endorsed by most guidelines [8,14,17,18,25]. However, it should be properly organized [8], with patient education [18] and in-person support within a proper monitoring and evaluation framework [17]. In general, the least restrictive effective interventions should be applied, with patients meaningfully involved in treatment-related decisions [30].

A detailed discussion of DOT and VOT along with other enablers for treatment adherence can be found in the Appendix C.

22. How should treatment interruptions be managed?

Recommendations

- The decision to continue or re-start TB treatment is based on the duration of the interruption, whether it occurred during the intensive (i.e. 2HRZE) or continuation (i.e. 4HR) phase and the bacteriological status prior to interruption (Table 8). (*Adapted*)
- For interruptions due to hepatotoxicity, it is important to identify the culprit drug(s), with sequential re-introduction once liver enzymes return to <2 times the upper limit of normal. (*Adopted*)
- For interruptions due to other drug adverse events, continuation of TB treatment with symptom alleviation should generally be the norm for mild adverse events, but serious adverse events should result in the discontinuation of the offending drug(s). (*Adopted*)
- In severe or highly infectious persons with TB disease, initiation of an alternate treatment regimen is recommended while waiting for a serious drug adverse event to resolve. (*Adopted*)

Remarks

Repeated and/or prolonged TB treatment interruptions lead to worse outcomes [47]. WHO, CDC-16 and NZ guidelines offer similar algorithms for clinical decisions regarding resuming or re-starting TB treatment after interruptions (Table 8).

Table 8. Management of treatment interruptions (adapted from WHO, CDC-16 and NZ guidelines) [11,17,30]

Timepoint of interruption	**Details of interruption**	**Recommendation**
Intensive phase	Lapse was <14 days in duration	Continue treatment to complete planned total number of doses[1]
	Lapse was ≥14 days in duration	Restart treatment
Continuation phase (6-month 2HRZE/4HR regimen)	Received ≥80% of doses and was sputum AFB microscopy negative initially	To determine if further treatment is necessary
	Received ≥80% of doses within 16 weeks and was sputum AFB microscopy positive initially	Continue treatment until all doses are completed
	Received <80% of doses and accumulated interruptions were <3 months in duration	Continue treatment until all doses are completed if all continuation phase doses can be completed within 6 months. But to restart treatment again from the intensive phase if treatment cannot be completed within this timeframe
	Received <80% of doses and accumulated interruptions were ≥3 months in duration	To restart treatment all over again from the intensive phase
Continuation phase (4-month 2HRZE/2HR regimen)	Completed ≥80% of doses within 8 weeks	To determine if further treatment is necessary
	Completed <80% of doses and accumulated interruptions were <1 month	Continue treatment until all doses are complete
	Completed <80% of doses and accumulated interruptions were ≥1 month	Restart treatment all over again from intensive phase

[1]If all intensive phase doses can completed within 3 months

In general, there is no evidence upon which to base detailed recommendations for managing interruptions, and recommendations are based on expert opinion/experience and will not cover all possible situations that may arise [8,27]. Common broad principles for deciding whether treatment should be continued or restarted include:

- The earlier the break in therapy and the longer its duration, the more serious the effect and the greater the need to restart treatment from the beginning.
- Continuous treatment is more important in the intensive phase of therapy when the bacillary population and chance of resistance acquisition is highest.
- The bacteriological status of the patient prior to and post-interruption are also important considerations. Interruptions are also more concerning in people with extensive disease (e.g. smear positive, cavitary/disseminated disease) and in people with advanced immune suppression (e.g. untreated HIV).

Interruptions due to hepatotoxicity

Drug-induced hepatitis is the most frequent serious adverse reaction to the first-line drugs. However, an asymptomatic increase in ALT concentration occurs in nearly 20% of patients treated with the standard 2RHEZ regimen, and therapy should not be altered because of modest asymptomatic elevations of ALT, but the frequency of clinical and laboratory monitoring should be increased. In most patients, asymptomatic ALT elevations resolve spontaneously [27].

WHO [8], CDC-2016 [27] and NICE [25] guidelines provide guidance on the management of treatment interruptions as a result of hepatotoxicity. All recommend that treatment be immediately withdrawn in cases where ALT/AST are ≥ 5 times higher than the upper limit of normal (with or without symptoms), or ≥ 3 times higher in the presence of symptoms or jaundice. Other causes of abnormal LFTs should be excluded before diagnosing drug-induced hepatotoxicity [25,27].

Responsible drugs should be identified, and a sequential reintroduction starting with the least hepatotoxic drug conducted once enzyme levels return to <2 times the upper limit of normal (Table 9). There is, however, limited evidence that sequential reintroduction of anti-TB drugs is associated with lower recurrence of drug-induced hepatotoxicity when compared to simultaneous reintroduction [25].

Table 9. Recommended timing and sequence for re-introduction of anti-TB drugs following development of hepatotoxicity

Guideline	When to re-introduce drugs	Timing/sequence of re-introduction
WHO [8]	When liver enzymes (ALT, AST) return to < 2 times the upper limit of normal	• Rifampicin to be restarted with ethambutol, with isoniazid re-introduced after 3-7 days, after checking ALT/AST. • If symptoms recur or aminotransferases increase again, the last drug added should be stopped and replaced with another.
CDC-2016 [27]	When ALT return to < 2 times the upper limit of normal. In patients with elevated baseline ALT from pre-existing liver disease, drugs can be restarted when ALT returns to near-baseline levels.	• Same as proposed by WHO (above) but based on ALT levels alone and with an approximate 1 week interval in between the reintroduction of drugs. • If rifampicin and isoniazid are tolerated and hepatitis was severe, pyrazinamide can be assumed to be responsible and should be discontinued.
NICE [25]	When ALT/AST return to < 2 times the upper limit of normal, bilirubin levels return to normal range, and hepatotoxic symptoms have resolved.	• Sequentially reintroduce each of the anti-TB drugs at full dose over a period of no more than 10 days, starting with ethambutol and either isoniazid (with pyridoxine) or rifampicin. • If another reaction of a similar/greater severity occurs because of reintroducing a particular drug, do not give that drug in future regimens and consider extending the total regimen accordingly.

Interruptions due to other drug adverse reactions

CDC-2016 guidelines provide guidance on how various types of non-hepatotoxic related adverse effects can be managed [27]. The more common adverse effects, evaluation of their severity and possible causes, and how they can be managed are listed in Table 10**Error! Reference source not**

found.. Children and adolescents experience adverse events caused by TB medicines much less frequently than adults.

Table 10. Common non-hepatotoxic adverse effects and their management (adapted from CDC-2016 guidelines [27])

Adverse reaction	Evaluation	Management
Gastrointestinal intolerance not associated with hepatotoxicity	Symptom evaluation and management	Can be treated with antacids, which have less impact on absorption or peak concentration of first-line drugs than administration with food.
Unexplained combination of nausea/vomiting/ abdominal pain	Should be evaluated with a physical examination and LFTs to assess for possible hepatotoxicity	• Same as proposed by WHO above but based on ALT levels alone and with an approximate 1 week interval in between the reintroduction of drugs. • If rifampicin and isoniazid are tolerated and hepatitis was severe, pyrazinamide can be assumed to be responsible and should be discontinued.
Rash that is mainly itchy without mucous membrane involvement or systemic signs such as fever	All anti-TB drugs can cause a rash, the severity of which determines management. Treatment is symptomatic for milder rash	Treatment is symptomatic with antihistamines, and all anti-TB medications can be continued.
Generalised erythematous rash	Fever and/or mucous membrane involvement suggests Stevens-Johnson syndrome, toxic epidermal necrosis, or drug reaction with eosinophilia and systemic symptoms syndrome or drug hypersensitivity syndrome	• Some experts manage severe systemic reactions in the inpatient setting, using an interval of several days between drug rechallenges and closely monitoring markers of hypersensitivity (such as rash, fever, transaminitis, eosinophilia, pruritus, etc). • When the rash has substantially improved, medications can be restarted individually at intervals of 2–3 days. If the rash recurs, the last drug added is stopped. If the first 3 drugs have been restarted without a rash, the fourth drug is dropped from the regimen unless the rash was mild and the drug essential. • Systemic corticosteroids may be used to treat severe systemic reactions (use of steroids to treat systemic reactions in cases of TB has not worsened outcomes).
Petechial rash	Suggests thrombocytopenia from a rifamycin (rifampicin or rifapentine) hypersensitivity	The rifamycin is permanently stopped if the platelet count is low. The platelet count is then closely monitored until definite improvement is noted.
Drug fever	Other causes of fever must be excluded. Patients with drug fever generally feel well	Stopping drugs usually resolves the fever within 24 hours. Once afebrile, the patient should restart drugs individually every 2–3

	despite body temperatures ≥ 39°C. Drug fever does not follow a specific pattern and eosinophilia need not be present	days, similar to the approach to drug rechallenge for rash (see above)
Optic neuritis	Onset is usually > 1 month after treatment initiation but can occur within days.	Ethambutol is promptly discontinued if visual abnormalities are found to avoid permanent deficits. If vision does not improve with cessation of ethambutol, isoniazid should be stopped as well as it is also a rare cause of optic neuritis.

In patients with severe adverse drug reactions where drug re-challenge is not recommended, TB disease treatment should be resumed with a regimen tailored corresponding to drug-resistant TB. As an example, an individual unable to tolerate rifampicin should be treated as if he/she had rifampicin-resistant TB disease.

Severe/highly infectious cases

In patients with severe or highly infectious TB, initiation of an alternate regimen is often required during the time an offending drug(s) is(are) held [25,27]. For a cutaneous reaction, a combination of at least 2 anti-TB drugs with low risk of cutaneous reactions (i.e. ethambutol and an aminoglycoside such as streptomycin) can be initiated with monitoring by a dermatologist for further reactions [25]. In hepatotoxicity-related interruptions, a combination of at least 2 anti-TB drugs of low hepatotoxicity (i.e. ethambutol, a fluoroquinolone such as levofloxacin or moxifloxacin and/or an aminoglycoside such as streptomycin) can be prescribed with close monitoring [25].

23. How often should patients on TB disease treatment be followed up and for how long?

Recommendations

- Follow-up for patients on TB disease treatment can be at 2-4 week intervals during the intensive phase, and at longer 4-6 week intervals during the continuation phase. (*Adapted*)
- More frequent follow-ups are recommended for patients at high risk of adverse events or who have developed adverse events to treatment. (*Adapted*)
- Follow-ups can be discontinued upon treatment completion, except in patients at higher risk of poor outcomes, for whom follow-up until 1-2 years post-treatment can be considered. (*Adopted*)

Remarks

The recommended follow-up schedule aligns with both local practice and international guidelines [8,14,17,18,24,27]. Post-treatment, Canada guidelines conditionally recommended that patients with a high risk for TB recurrence (extensive/disseminated disease, cavitation on chest X-ray with smear/culture positive disease, immunosuppression, a history of treatment interruptions or non-adherence, and/or an atypical treatment regimen) be followed up for 1-2 years [17]. WHO guidelines recommended post-treatment monitoring for potential relapse for shorter (<6 months) treatment regimens, including children and adolescents on 2HRZE/2HR [8].

24. What investigations should be performed prior to initiating and during treatment of TB disease?

Recommendations

- Before initiating TB treatment, if not already done elsewhere, work-up for TB disease should be performed as recommended above (Questions 13-18).

- Other baseline laboratory investigations in adults include – if not already done elsewhere – blood testing for HIV, AST/ALT, FBC, diabetes screening, and renal function. (*Adapted*)
- In children, similar baseline laboratory investigations can be considered except for diabetes screening which is unnecessary. (*Adapted*)
- Chest X-rays should be performed after completion of the intensive phase of treatment, and upon completion of TB treatment. (*Adopted*)
- Clinical samples should be collected for AFB smear microscopy and mycobacterial culture after completion of the intensive phase of treatment, and upon completion of TB treatment. (*Adopted*)
- In adults, visual assessments should be performed at initial and subsequent clinic visits if on an ethambutol-containing regimen. (*Adopted*)
- The patient should be weighed at all clinic visits. (*Adapted*)

Remarks

Clinical assessments coupled with weight measurements, chest X-ray and clinical sample (generally sputum) testing are important for evaluating treatment response and the risk of relapse/need for prolongation of treatment. The final clinical sample testing is recommended for confirming bacteriological cure [48].

Blood tests other than for liver function assessment need not be repeated if normal and if no drug adverse events manifest. AST and ALT should be repeated monthly or at each clinic visit in persons with a higher risk of hepatotoxicity.

Ocular toxicity from ethambutol is extremely rare in children, hence baseline and/or follow-up visual assessments are at the discretion of the treating specialist.

25. Should there be post-treatment evaluation for post-TB lung disease?

Recommendations

- Clinical assessment for post-TB lung disease, including a chest X-ray, can be performed at the end of treatment. (*Adapted*)

Remarks

Post-TB lung disease refers to an overlapping spectrum of diverse chronic respiratory conditions experienced after TB disease treatment [8,17,48]. They are under-recognised but contribute significantly to excess morbidity and mortality after post-TB treatment [49]. The Canada guidelines are the only ones that formally suggest assessing for post-TB lung disease. They advise that, within 6 months of finishing treatment, everyone should undergo lung function tests [17]. WHO guidelines recommended a chest X-ray at the end of treatment to manage post-treatment TB pulmonary sequelae [8]. Consensus-based standards for assessing, managing and rehabilitating post-TB lung disease have been developed by international experts [50].

11. Scheduled Review and Update

NTBP will convene a multidisciplinary team in 2026 to update these guidelines via a systematic review of available guidelines and evidence.

12. Appendices

Appendix A. Methodology

Given that many high quality guidelines on TB clinical management had been published since 2016 [8,12-18,24-30] (Table 1 of article), in particular from the World Health Organization [8], the Panel elected to adapt and contextualize recommendations from these guidelines as far as possible with regards to updating Singapore's TB clinical management guidelines. This would avoid duplication of efforts and minimize costs and resources while maintaining scientific rigour [22,51]. The ADAPTE process for adapting guidelines was selected as it was systematic and had also been used in multiple settings and for varied clinical conditions [21,23].

Formation of the guidelines development team

During the setup phase in June 2022, an organizing committee from the National TB Programme agreed on the guideline topic and developed the adaptation plan, identifying potential members for the multidisciplinary Clinical Tuberculosis Guidelines Panel (Panel) based on their clinical knowledge, methodological expertise and implementation expertise. Representation from all 3 healthcare clusters in Singapore was a key criterion. The Public Health Translational Team (PHTT) from the Saw Swee Hock School of Public Health was identified for its information retrieval and synthesis expertise.

The adaptation phase began with hybrid meetings for the Panel in August and September 2022. The process of guidelines development, list of clinical questions to be addressed and decision-making process for recommendations to the questions was agreed upon by the Panel during these meetings.

Guidelines and literature search

The PHTT then searched through PubMed, Google, country-specific government health ministry and relevant agency websites, and websites of key infectious diseases guidelines development organizations. They screened all English language national and international TB management guidelines published between 1 January 2016 and 5 March 2023. Areas of search were divided into 6 segments: TB infection screening, diagnosis, Treatment, as well as TB disease screening, diagnosis and treatment. Additional reviews of primary and secondary literature were conducted for questions related to video-observed treatment (VOT), post-TB lung disease, next generation sequencing (NGS), use of CT thorax in TB, and use of computer-aided detection-artificial intelligence (CAD-AI) products for TB screening, as there was insufficient content across the guidelines to address these questions.

Assessment of guidelines

Each identified guideline was evaluated by at least 2 members of the PHTT team with a modified AGREE II instrument, which assesses their quality across 6 domains (1. Scope and Purpose, 2. Stakeholder Involvement, 3. Rigour of Development, 4. Clarity of Presentation, 5. Applicability, 6. Editorial Independence), with "Rigour of Development" holding the largest weightage [23]. Guidelines were graded according to the domain items in the tool but on a 3-point scale ("yes", "no", "partial") instead of a Likert scale (1 to 7). A score is allocated to each guideline for each item in the tool where "yes" contributes a score of 1, "no" a score of 0, and "partial" a score of 0.5. Overall summary scores are then calculated for each guideline as a sum of its scores for all the individual items in the tool with the maximum score being 23. Guidelines are graded as "yes" for an item if the item is clearly reflected in the guideline, "no" if the item is entirely absent and "partial" if the item is present to some extent. We acknowledge that the line between "partial" and "yes" can be rather arbitrary and dependent on individual judgement. Guidelines with a summary score of 18 and above

(more than 75%) are considered guidelines of good quality, those with scores 11.5-17 (50-75%) are considered guidelines of moderate quality, and those with scores less than 11.5 are considered guidelines of poor quality. The scores are provided in Table A-1Table 1.

It is important to note that a low-scoring guideline does not necessarily mean that the recommendations are bad, but that quality indicators are either not met or cannot be assessed in case of absent documentation. Some guidelines also provide contextual insights on the relevance of recommendations for certain country/prevalence settings. Hence all guidelines evaluated and their AGREE II scores were circulated to the Panel for information and reference, and were still used for formulating the local guidelines.

Development of recommendations to questions

The PHTT compiled reports combining a summary of guidelines recommendations and primary literature which were circulated to the Panel. Two rounds of a modified Delphi process were implemented via hybrid meetings and email voting to achieve consensus – meaning agreement and/or no objections from any Panel member – on recommendations for each question in June and July 2023. During the meetings, the initial questions were discussed, and recommendations were made based on the PHTT compiled reports. Draft guidelines were then circulated to the Panel members for a final round of editing and comments.

The finalized draft was sent out to external professional (Academy of Medicine: Chapter of Family Medicine Physicians; College of Paediatrics & Child Health; College of Physicians: Chapter of Infectious Diseases Physicians, Chapter of Respiratory Physicians) and technical (Agency for Care Effectiveness – for a review of the methodology) stakeholders for review and comment, with relevant changes incorporated into the published guidelines.

Table A-1. Assessment of guidelines according to the modified AGREE II instrument [23]

Item	Guideline[1]														
	WHO [8]	CDC-2019 [29]	CDC-2017 [26]	CDC-2020 [12]	CDC-2016 [27]	USPSTF [28]	ECDC-L [13]	ECDC-S [24]	NZ [14]	Australia NTAC [15]	Australia CDNA [30]	HK [16]	Canada [17]	Malaysia [18]	NICE [25]
Domain 1: Scope and Purpose															
The overall objectives of the guideline are specifically described	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
The health questions covered by the guideline are specifically described	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes
The population to whom the guideline is meant to apply is specifically described	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Domain 2: Stakeholder involvement															
The guideline development group includes individuals from all relevant professional groups	Yes	Partial	Partial	Yes	Yes	Yes	Yes	Yes	Partial	No	Partial	No	Yes	Yes	Yes

The views and preferences of the target population have been sought	Yes	No	No	Yes	No	Yes	No	Yes	No	No	No	No	No	Partial	Yes
The target users of the guideline are clearly defined	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Domain 3: Rigour of development															
Systematic methods were used to search for evidence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes
The criteria for selecting the evidence are clearly described	No	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Partial	Yes	Yes
The strengths and limitation of the body of evidence are clearly described	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes
The methods for formulating the recommendations are clearly described	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes

The health benefits, side effects and risks have been considered in formulating the recommendations	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes
There is an explicit ink between the recommendations and supporting evidence	Yes	No	Yes	Yes	P	Yes	Yes	P	Partial	No	No	No	Yes	Yes	Yes
The guideline has been externally reviewed by experts prior to its publication	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
A procedure for updating the guideline is provided	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes	Yes	Yes
Domain 4: Clarity of presentation															
The recommendations are specific and unambiguous	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The different options for	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

management of the condition or health issue are clearly presented															
Key recommendations are easily identifiable	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Domain 5: Applicability															
The guideline describes facilitators and barriers to its application	Yes	No	Yes	No	Yes	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes
The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	No	No	No	Yes	Yes	Yes	Yes	Partial	No	Yes	No	Yes	No	Partial
The potential resource implications of applying the recommendations have been considered	Yes	No	Yes	Yes	Yes	Yes	Yes	P	Partial	No	No	No	Yes	Yes	Yes
The guideline presents monitoring	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

and/or auditing criteria															
Domain 6: Editorial independence															
The views of the funding body have not influenced the content of the guideline	Partial	No	No	No	Partial	Yes	Partial	P	No	No	No	No	Yes	Yes	Partial
Competing interests of guideline development group members have been recorded and addressed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes
Summary score	21	7.5	14.5	18	19	17	21.5	15.5	11	3	5.5	3	20	21.5	22

[1]WHO and Canada guidelines comprise multiple modules and chapters but are represented in a single column each for ease of inclusion in the table. The AGREE II scores were consistent across the different modules and chapters. Note that CDC and ECDC had more than one set of guidelines for different aspects of tuberculosis care and involving other different organizational co-sponsors. These are presented in separate columns as the modified AGREE II scores varied between them.

Appendix B. AI Products for TB Disease Screening

Computer-aided detection is being recommended for the first time as an alternative to human interpretation of digital CXR for screening and triage for TB disease. WHO recommends that CAD-AI products may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease among individuals ≥ 15 years old in populations in which TB screening is recommended (conditional recommendation, low certainty of evidence) [8]. Canadian guidelines mention that deep learning AI software for chest radiography detection of PTB have achieved sensitivity and specificity similar to human readers, exceeding thresholds set by WHO, and may be valuable in closing diagnostic gaps in resource-limited and remote settings [30]. Use of CAD-AI products in TB disease screening/diagnosis is not mentioned in other guidelines.

WHO guidelines note that the use of CXR for TB screening and triage is limited by the unavailability of trained personnel to interpret radiography images and substantial intra-and inter-reader variability in its accuracy, and that numerous CAD-AI software packages have been developed can potentially address these challenges [8].

The recommendation on use of CAD-AI products is in relation to its use for screening and triage purposes only, the former being to distinguish people with a higher probability of having TB disease from those with a low probability in a defined population group, while the latter differentiates among people presenting to a health facility those who should have further diagnostic evaluation for TB from those who should undergo further investigation for non-TB diagnoses. The two use cases will have to take into account different disease presentations in people, different TB prevalence in the populations and different ethical consequences, and will have to be evaluated separately. Sensitivity (>0.9) and specificity (>0.7) thresholds have been provided by WHO in its target product profile for CAD-AI products for TB screening [8].

A toolkit has been developed jointly by the WHO Global Tuberculosis Programme and the Special Programme for Research and Training in Tropical Diseases to provide a study protocol for conducting a CAD calibration study in a new setting. The study protocol provides the proposed research method, data collection and analysis, with sample size estimates, sampling options and data collection tools. An accompanying online tool provides analysis of the data collected from the CAD calibration study to estimate yield and cost at each CAD threshold score, including false-positive/negative results, sensitivity/specificity, NPV and PPV, proportions of prevalent cases diagnosed/missed and cost implications in terms of total costs and cost per true case detected. The user can then determine the preferred threshold score accordingly.

As with other screening tools, there is an inherent trade-off in the selection of the threshold score, with lower scores maximising the sensitivity of the tool to detect TB patients in the population being screened but incurring additional costs for diagnostic testing because of reduced specificity. Higher scores will reduce the volume and costs of diagnostic testing but will result in more missed cases. TB programmes will need to decide on a threshold score according to the needs/objectives of their programmes. The toolkit and accompanying online analysis tool is available at: https://tdr.who.int/activities/calibrating-computer-aided-detection-for-tb

The market of CAD-AI products for TB detection is constantly changing and expanding, with new versions of products and new companies coming online constantly. FIND and the Stop TB Partnership have jointly created an online data repository of the CAD products currently available on the market and their key characteristics as described above, based on results of surveys with developers. This provides a publicly accessible, regularly updated and living database to enable implementers to keep

abreast of the rapidly changing artificial intelligence landscape. The online repository can be found at https://www.ai4hlth.org/

Limitations and considerations on use of CAD-AI products

A drawback of using current CAD-AI interpretation in place of human readers is that it cannot detect other lung pathologies beyond TB. The capacity of CAD-AI technologies to simultaneously screen for multiple pulmonary or thoracic conditions can be attractive for programmes. However, no data on the performance of CAD-AI for differential diagnosis were yet available to be assessed by WHO's Guidelines Development Group at the time of development of the guidelines [8].

Resource-limited low- and middle-income countries may be more willing to accept the risk of missing incidentals (such as lung metastases, aortic aneurysm) when using an AI algorithm for TB screening, given the huge burden PTB poses in such settings. However, this is unlikely to be the case for high-income countries. In such better resourced settings, CAD-AI products can be used to triage/prioritise cases for early action with a human reader still completing a final check, rather than have a fully autonomous CAD-AI product with no complementing human reader.

There are also limitations to the generalisability of an AI algorithm when trained on a specific population. For example, training an AI algorithm in a population where the pre-test probability of TB is significantly higher than in Singapore will lead to degradation of performance of the algorithm (for TB detection) when deployed in Singapore. AI, however, can potentially accurately and efficiently filter out CXRs that are "normal" (by setting the algorithm to act at the correct point of the AUC curve) and may be helpful as a rule out rather than rule in capability when screening a population.

MOH Artificial Intelligence in Healthcare Guidelines (AIHGle)

AIHGle, developed by MOH, HSA and IHiS, and endorsed by Academy of Medicine Singapore, College of Family Physicians Singapore, Infocomm Media Development Authority, and PDPA Commission Singapore, was published in Oct 2021 [54]. It governs the development and implementation of "locked" Artificial Intelligence Medical Devices (AI-MDs). "Locked" AI-MDs are AI-MDs that do not automatically update their decision-making algorithms in response to new data.

AIHGle's governance of the development and implementation of "locked" AI-MDs operate along the three primary considerations that: (1) benefits are sufficient and should result in consistent, measurable improvements in the clinical outcomes of patients relative to baseline, (2) risks are mitigated with adoption of additional contingency measures in the event of failure, and (3) accountability is assured with documentation and legislation of the entire deployment process.

In brief, developers should work with subject matter experts to deliver the purported benefits, incorporate measures to mitigate risks (e.g. representativeness of training and testing datasets, robustness against external cybersecurity threats etc), and comply with legislation/obtain required approvals/establish necessary SLAs for the development/use of the devices. Post-development implementers should constantly evaluate the AI-MD to ensure its performance does not deteriorate over time, that built-in risk mitigation strategies are validated in real world settings, and that end users are provided contact channels to report malfunction/areas of concern.

The guidelines also briefly address considerations for novel innovations including "continuous-learning" AI-MDs and the use of "synthetic data".

Appendix C. Enablers for treatment adherence

DOT versus self-administered therapy (SAT)

All reviewed guidelines support the use of DOT for TB treatment, although the extent to which this is encouraged versus self- or other forms of supervision varies across the guidelines. CDC-2016 [27] and Malaysia guidelines [18] recommend use of DOT rather than SAT for routine treatment of patients with all forms of TB. CDC guidelines note that DOT has been widely used as the standard of practice in many TB programmes in the US and Europe, and has become the default programmatic approach to treating children with TB. While the guideline development group's systematic review did not find any significant differences between DOT and SAT when assessing several outcomes of interest, including mortality, treatment completion, and relapse, DOT was significantly associated with improved treatment success and increased sputum smear conversion during treatment, as compared to SAT. DOT can be advantageous for early recognition of adverse drug reactions/treatment irregularities and for the establishment of rapport between providers and patient [27]. Malaysia guidelines state that SAT may be offered to patients who cannot perform DOT [14].

Canadian, NICE, New Zealand and Australia-CDNA guidelines recommend the use of DOT for patients/situations at risk of adverse outcomes/non-adherence, and leave it to the discretion of providers to decide on use of DOT or self-administration with other forms of supervision for other cases/situations [14,17,25,30]. Canadian and Australian-CDNA guidelines point out that systematic reviews comparing DOT with SAT found no significant difference in terms of pooled outcomes of treatment success, including mortality, treatment completion and relapse, although DOT was associated with improved treatment success and increased sputum smear conversion during treatment, and SAT had lower rates of adherence and cure [17,30]. In addition, systematic reviews of observational studies have reported improved treatment outcomes with DOT in PLHIV and people with MDR-TB. At risk patients/situations (recommended for DOT) mentioned in these guidelines are listed in Box C-1.

Box C-1. Patients/situations recommended for DOT in reviewed guidelines

At risk patients/situations recommended for DOT in Canadian [24], NICE [15], New Zealand [14] and Australian-CDNA [30] guidelines include the following:

- PLHIV or other significant immunocompromising condition
- People with DR-TB/MDR-TB
- People with extensive disease and high infectiousness (eg. smear positive cavitary TB)
- People who are too ill to administer the treatment themselves
- People who have experienced/experiencing TB treatment failure/relapse
- People with substance use or mental health disorders
- People experiencing homelessness or unstable housing
- People currently in prison, or have been in the past 5 years
- Residence at a long-term care facility
- People with suspected or known non-adherence to TB therapy
- People who are in denial of the TB diagnosis
- Reasonable doubts about the ability of the parents/guardians to supervise treatment for children (for children)
- Children whose parents are members of the above groups
- Intermittent regimens*

* New Zealand guidelines do not recommend intermittent regimens but state that if they are ever used, they must be used with DOT.

New Zealand guidelines recommend a tiered approach to deciding on use of DOT and the level of supervision required, stating that SAT is possible where there are no risk factors and regular monitoring confirms good adherence. The guidelines report that between 2012 and 2015, 48% of TB cases in New Zealand had DOT during the intensive phase and 25& throughout the full course of treatment [14].

NICE guidelines point out the need to re-evaluate the need for DOT throughout the course of TB treatment whenever the person's (or in the case of children, parents') circumstances change [25]. While Canadian guidelines does not recommend DOT universally for all TB patients, they highlight, however, that all jurisdictions should have the capacity to provide daily, in-person, supportive care for people with TB disease. In the case of children/adolescents, where clinicians cannot provide this level of care, they should refer the patient to programmes with this capacity [17].

WHO recommendations support use of DOT or SAT with other forms of adherence interventions (e.g. psychological support, medication monitors etc), rather than the use of DOT alone or SAT alone, and with the emphasis on the use of such complementing interventions rather than DOT versus SAT [8]. The guidelines note that the overall evidence from a systematic review conducted on data from RCTs and observational studies was inconsistent in showing clear advantages of DOT alone over SAT and vice versa [8]. However, the evidence showed that patients who received DOT/SAT with combinations of adherence interventions had significantly improved treatment outcomes compared to those on DOT or SAT alone. The guidelines noted, however, that PLHIV patients benefit more from DOT than TB patients in general do and that SAT alone is not advisable for the sub-group [8]. WHO guidelines also uses the term 'treatment support' instead of the traditional term 'DOT', with a need to emphasize the need to support people in adhering to treatment.

Family supervision of treatment

Systematic reviews have suggested that DOT provided by family members is less consistently associated with higher success rates and have shown variable effects on study outcomes, including being associated with a lower rate of adherence [55,56]. The reviews suggested that this could be due to family members' limited understanding of/confidence in the efficacy of the treatment regimens (despite best educational efforts by healthcare staff) and tendency to discontinue treatment observation if it creates tension in the family, and therefore family-based supervision of treatment could only be potentially be effective within the conditions of close/effective complementing monitoring by health facility staff [55,56].

WHO guidelines state that DOT administered by trained lay providers or HCWs is recommended over DOT administered by family members or SAT [8], noting evidence of higher mortality rates, loss to follow-up and failure, and lower rates of successful treatment, cure and treatment adherence among patients who had DOT administered by family members versus healthcare workers, no significant differences among those with lay provider- versus HCW-administered DOT, and higher rates of treatment success and cure and a slightly lower rate of loss to follow-up among those with lay provider-administered DOT compared with SAT [8]. The guidelines note that while community- or home-based DOT has greater advantages over facility-based DOT, family members should not be the first or only option for administering DOT. Community- or home-based DOT by trained local lay persons or a combination of lay provider and HCW may be more feasible options. Given the complexity of family social dynamics, family members may not always be the best people to supervise treatment, and the suitability of such treatment adherence supervisors needs to be carefully analysed in each national or local context [8].

CDC-2016 guidelines state that parents should not supervise DOT for their children [27].

VOT

DOT is resource-intensive for health systems and inconvenient for patients. Several guidelines point out that virtual DOT through video-enabled devices, conducted through recorded videos or live streaming, has emerged as a cost-effective and patient autonomy-enabling way to deliver DOT, reducing visits/travelling by providers/patients and improving flexibility for patients. Canadian and Malaysian guidelines indicate that VOT has shown promise in a large RCT, where 70% of patients on VOT successfully completed ≥ 80% of a 2-month observation compared with only 31% of those on DOT [17,18].

WHO noted studies demonstrating the non-inferiority of VOT to in-person DOT [8], while CDC-2016 guidelines indicate earlier studies in low-incidence countries that have shown VOT using smartphones to be feasible, reporting high patient uptake, and being associated with similar adherence rates as in-person DOT [27]. Such evidence is reinforced by two recent systematic reviews/meta-analysis which noted significantly enhanced treatment completion with VOT compared to DOT in some studies, as well as improved medication adherence and bacteriological resolution [20,57].

Other than the Australia guidelines, which did not address VOT, all the guidelines recommend VOT as an alternative to clinic-based DOT [8,14,17,18,24,25,27]. NICE guidelines add that VOT has been useful particularly in those on longer regimens [25].

Several guidelines indicate accompanying conditions for VOT's use. WHO guidelines state that VOT can replace DOT under conditions where video communication technology is available and can be appropriately organised and operated by health care providers and patients [8]. Canadian guidelines highlight that VOT should be accompanied by in-person support and DOT when required, and operated within the framework of monitoring and evaluation, considering that it remains an area of active investigation [17]. Malaysian guidelines state that patients should be educated on VOT and give consent for the procedure [18].

Balancing patient rights and public health objectives

Several guidelines emphasise and elaborate on the importance of balancing the rights of the patient and public health objectives, of respectful treatment, and of patient involvement in development of the treatment plan [14,24,27,30]. Relevant enablers include operationalising patient choice and selection of treatment administration options, use of bilingual/medical interpreter services, and patient contracts.

CDC-2016 guidelines state that decisions regarding the use of DOT (e.g. whether it should be done in the office, clinic or patient's home etc) must be made in concert with the patient by appropriately trained personnel [27]. Australian guidelines highlight that the least restrictive public health interventions that are effective in achieving adherence should be applied, and patients should be involved in a meaningful way in making decisions concerning treatment supervision and overall care [17].

Treatment contracts

New Zealand guidelines provide detailed guidance on use of treatment contracts and legislation to support adherence [14]. Treatment contracts can be used at all levels of supervision when a patient's adherence is in doubt, and should be signed by the patient and countersigned by the public health nurse or medical officer of health. It can include:

- the time and place for delivering supplies of medication (or delivering DOT)
- the patient's agreement to contact the case worker if plans change

- the patient's intention to attend all appointments.

Legislation

New Zealand guidelines state that where adherence cannot be achieved through the use of directions, education, incentives and support and the patient poses a public health risk, the medical officer of health can issue an urgent public health order to detain the case or apply for a court order for treatment. A court order must be applied for and granted and the case has a right to appeal public health directions/court orders. Prosecution for breach of directions/orders should be a last resort [14].

Enablers and incentives

A diverse range of enablers and incentives, also known as adherence interventions, have been recommended/suggested across the guidelines for inclusion in the treatment plan, complementing DOT/Community-based DOT/VOT where these are used.

Enablers accorded a stronger basis of supporting evidence include patient health education, patient choice and selection of treatment administration options, material support (in forms of financial support, transport subsidies etc), psychological support, and staff education (e.g. educating the nurses/treatment supporters on administering DOT).

Systematic reviews of TB treatment monitoring methods have also noted instances of these interventions being effective as complementing interventions to DOT or as part of a combination of interventions in the treatment plan [56,58,59]. Effectiveness was seen as contributing to higher rates of treatment completion, treatment success, and cure, and reduced rates of mortality and loss to follow-up. Other enablers that have been noted to demonstrate effectiveness include patient reminder systems, integration with patient's primary/specialty care (resulting in convenience for the patient), and reinforcement [56,58,59].

The review studies also noted that effective treatment plans for longer-term regimens tended to be more complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, psychological therapy, and manual follow-up/supervision, effected in the form of multiple interventions/enablers [59]. Tailoring interventions to suit local or specific situations and contexts is also important.

Patient health education

This includes oral or written education on 'health literacy' via HCWs and can involve patients' social network/family work. It should be differentiated from psychological counselling. WHO guidelines' review of RCTs and observational studies and systematic reviews of TB treatment adherence monitoring note that patients who received such education had better rates of treatment success, treatment completion, cure and treatment adherence, and had lower rates of mortality and loss to follow-up [8].

Material support

Material support can be in the form of food, financial incentives, transport subsidies, living allowance, housing incentives, or financial bonuses after reaching treatment targets. WHO guidelines note higher rates of treatment success, completion and sputum conversion, and lower rates of treatment failure and loss to follow-up in patients who received material support compared with those who did not receive material support in studies reviewed [8]. While most of these studies were in low- and middle-income countries, the guidelines development group considered that material support will also be of significant value to TB patients in higher-income countries, especially those without a good social welfare system, since TB is a disease of poverty.

Food support was pointed out as an important incentive, protecting patients/their families from TB-associated costs and improving biological outcomes for patients [8].

Psychological support

Psychological support is varied and can include self-help groups, alcohol cessation counselling and TB clubs. WHO guidelines and systematic reviews of TB treatment adherence monitoring note from reviewed studies that patients with access to psychological support had higher rates of treatment completion, success, and cure, and lower rates of treatment failure, mortality, and loss to follow-up [8,56].

Staff education

This may include peer training, visual aids to help initiate conversations with patients, and other tools to aid in decision-making and as reminders. WHO guidelines state that staff education led to higher rates of treatment success and slightly lower rates of mortality and loss to follow-up from reviewed studies [8,58]. Better understanding of TB disease and treatment can also reduce any stigma HCWs may have towards patients.

Patient reminder systems

These include tracers such as SMS, telephone calls or automated telephone reminders, and medication monitors or computer systems used to aid HCWs in tracing patients. WHO guidelines and systematic reviews of TB treatment adherence monitoring note from reviewed studies that the use of such reminder systems was associated with higher rates of treatment success, cure, adherence, favourable outcomes, and 2-month sputum conversion, as well as lower rates of treatment failure, mortality, loss to follow-up and drug resistance acquisition [8,56,58]

WHO guidelines point out that the number of studies on digital health interventions (DHT) under this intervention category is limited [8]. A systematic review of DHT for improving TB medication adherence also noted that the interventions exhibited variable effects regarding effect direction and extent of improving adherence and clinical outcomes, and highlighted the importance of understanding and tailoring the DHT to the local context (including socio-economic, geographic, facility and behavioural factors) with personalised feedback [57].

Access to free treatment

Two guidelines (Canada and NICE) recommend that TB treatment should be provided free of charge [17,25]. Both guidelines state that people with TB disease should be provided all medications and services required to successfully complete TB therapy free of charge, regardless of their insurance coverage, eligibility for national coverage, or residency status.

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The list of members of the team and their contributions are displayed below in alphabetical order. Tay JY and Hsu LY wrote the first draft of these guidelines. All members of the Panel reviewed, edited and approved the guidelines.

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14. References

1. World Health Organization. Global Tuberculosis Report 2022. Available at: https://www.who.int/publications/i/item/9789240061729 [Last accessed 9 August 2023].
2. Yap P, Tan KHX, Lim WY, et al. Prevalence of and risk factors associated with latent tuberculosis in Singapore: a cross-sectional survey. Int J Infect Dis. 2018;72:55-62.
3. Wang YT, Chee CB, Hsu LY, et al. Ministry of Health clinical practice guidelines: prevention, diagnosis and management of tuberculosis. Singapore Med J. 2016;57:118-24.
4. World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases (TDR). Determining the local calibration of computer-assisted detection (CAD) thresholds and other parameters: A toolkit to support the effective use of CAD for TB screening. 2021. Available at: https://apps.who.int/iris/bitstream/handle/10665/345925/9789240028616-eng.pdf [Last accessed 12 August 2023].
5. The Stop TB Partnership. AI-powered computer-aided detection (CAD) software. Available at: https://www.stoptb.org/digital-health-technology-hub/ai-powered-computer-aided-detection-cad-software [Last accessed 12 August 2023].
6. CRyPTIC Consortium and the 100,000 Genomes Project, Allix-Béguec C, Arandjelovic I, et al. Prediction of susceptibility to first-line tuberculosis drugs by DNA sequencing. N Engl J Med. 2018;379:1403-1415.
7. World Health Organization. Catalogue of mutations in *Mycobacterium Tuberculosis* complex and their Association with drug resistance: supplementary document. 2021. Available at: https://apps.who.int/iris/handle/10665/341906 [Last accessed 11 August 2023].
8. World Health Organization. WHO consolidated guidelines on tuberculosis: Modules 1-6. 2020-2022. Available at: https://tbksp.org/en/guidance-books-solr [Last accessed 12 August 2023].
9. Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med. 2021;384:1705-18.
10. Carr W, Kurbatova E, Starks A, et al. Interim guidance: 4-month rifapentine-moxifloxacin regimen for the treatment of drug-susceptible pulmonary tuberculosis – United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71:285-9.
11. Pettit AC, Phillips PPJ, Kurbatova E, et al. Rifapentine with and without moxifloxacin for pulmonary tuberculosis in people with human immunodeficiency virus (S31/A5349). Clin Infect Dis. 2023;76:e580-9.
12. Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020;69:1-11.
13. European Centre for Disease Prevention and Control. Scientific Advice: Programmatic management of latent tuberculosis infection in the European Union. European Centre for Disease Prevention and Control. 2018. Available at: https://www.ecdc.europa.eu/en/publications-data/programmatic-management-latent-tuberculosis-infection-european-union [Last accessed 10 August 2023].
14. Ministry of Health, New Zealand. Guidelines for tuberculosis control in New Zealand, 2019. 2019. Available at: https://www.health.govt.nz/system/files/documents/publications/guidelines-tuberculosis-control-new-zealand-2019-august2019-final.pdf [Last accessed 10 August 2023].
15. Stock D, National Tuberculosis Advisory Committee. National position statement for the management of latent tuberculosis infection. Commun Dis Intell Q Rep. 2017;41:E204-8.
16. Tuberculosis & Chest Service, Department of Health of the Government of Hong Kong SAR. Guidelines on targeted tuberculin testing and treatment of latent tuberculosis infection. 2020. Available at: https://www.info.gov.hk/tb_chest/doc/2_LTBI_guide_TBCS_update%2019%20Dec%202020_Clean.pdf [Last accessed 10 August 2023].

17. Canadian Thoracic Society. Canadian Tuberculosis Standards 8th edition. Canadian J Respiratory, Crit Care, and Sleep Medicine. 2022;6 Suppl 1. Available at: https://www.tandfonline.com/toc/ucts20/6/sup1 [Last accessed 12 August 2023].
18. Ministry of Health Malaysia. Clinical practice guidelines: management of tuberculosis (4th edition). 2021. Available at: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG-_Management_of_Tuberculosis_(4th_Edition).pdf [Last accessed 10 August 2023].
19. 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. The Lancet. 2019;393:1216-1224.
20. Truong CB, Tanni KA, Qian J. Video-observed therapy versus directly observed therapy in patients with tuberculosis. Am J Prev Med. 2022;62:450-458.
21. ADAPTE. The ADAPTE process: resource toolkit for guideline adaptation. Version 2.0. 2010. Available at https://g-i-n.net/wp-content/uploads/2021/03/ADAPTE-Resource-toolkit-March-2010.pdf [Last accessed 11 August 2023].
22. Song Y, Alonso-Coello P, Ballesteros M, et al. A reporting tool for adapted guidelines in health care: the RIGHT-Ad@pt checklist. Ann Intern Med. 2022;175:710-9.
23. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182:E839-842.
24. Migliori GB, Sotgiu G, Rosales-Klintz S, et al. ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update. European Respiratory Journal. 2018;51:1702678.
25. National Institute for Health and Care Excellence. Tuberculosis: NICE guideline (NG33). 2019. Available at: https://www.nice.org.uk/guidance/ng33/resources/tuberculosis-pdf-1837390683589 [Last accessed 12 August 2023].
26. 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. Clin Infect Dis. 2017;64:111-5.
27. 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. Clin Infect Dis. 2016;63(7):e147-e195.
28. US Preventive Services Task Force. Screening for latent tuberculosis in adults: US Preventive Services Task Force recommendations statement. JAMA. 2016;316:962-9.
29. Sosa LE, Nijie GJ, Lobato MN, et al. Tuberculosis screening, testing, and treatment of U.S. health care personnel: recommendations from the National Tuberculosis Controllers Association and CDC, 2019. MMWR Morb Mortal Wkly Rep. 2019;68:439-43.
30. Australian Government Department of Health, Communicable Diseases Network Australia. Tuberculosis: CDNA national guidelines for public health. 2022. Available at: https://www.health.gov.au/sites/default/files/documents/2022/06/tuberculosis-cdna-national-guidelines-for-public-health-units.pdf [Last accessed 12 August 2023].
31. Nandar K, Ang L, Tey J, et al. Epidemiology of tuberculosis and HIV coinfections in Singapore, 2000–2014. HIV Medicine. 2018;19:59-64.
32. Chee CB, Teleman MD, Boudville IC, et al. Contact screening and latent TB infection treatment in Singapore correctional facilities. Int J Tuberc Lung Dis. 2005;9:1248-52
33. Centers for Disease Control and Prevention. At a glance: recommendations for correctional and detention settings. 2023. Available at: https://www.cdc.gov/correctionalhealth/rec-guide.html [Last accessed 1 September 2023]
34. Png ME, Yoong J, Ong CWM, et al. A screening strategy for latent tuberculosis in healthcare workers: cost-effectiveness and budget impact of universal versus targeted screening. Infect Control Hosp Epidemiol. 2019;40:341-9.

35. World Health Organization. Use of alternative interferon-gamma release assays for the diagnosis of TB infection: WHO policy statement. 2022. Available at: https://www.who.int/publications-detail-redirect/9789240042346 [Last accessed 13 August 2023].
36. Oh CE, Ortiz-Brizuela E, Bastos ML, Menzies D. Comparing the Diagnostic Performance of QuantiFERON-TB Gold Plus to Other Tests of Latent Tuberculosis Infection: A Systematic Review and Meta-analysis. Clin Infect Dis. 2021;73(5):e1116-e1125.
37. Zhou G, Luo Q, Luo S, et al. Indeterminate results of interferon gamma release assays in the screening of latent tuberculosis infection: a systematic review and meta-analysis. Front Immunol. 2023;14:1170579.
38. Getahun H, Matteelli A, Abubakar I, et al. Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J. 2015;46:1563-1576.
39. World Health Organization. WHO operational handbook on tuberculosis: module 1: prevention: tuberculosis preventive treatment. Chapter 5.1: recommended dosages of TPT medication. 2020. Available at: https://tbksp.org/en/node/1271 [Last accessed 13 August 2023].
40. Swindells S, Ramchandani R, Gupta A, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. N Engl J Med. 2019;380(11):1001-1011.
41. World Health Organization. WHO operational handbook on tuberculosis: module 5: management of tuberculosis in children and adolescents. 2022. Available at: https://tbksp.org/en/node/1730 [Last accessed 13 August 2023].
42. World Health Organization. Public notice: guideline development group meeting on targeted next-generation sequencing for detection of TB drug resistance. 2023. Available at: https://www.who.int/publications/m/item/public-notice--guideline-development-group-meeting-on-targeted-next-generation-sequencing-for-detection-of-tb-drug-resistance [Last accessed 14 August 2023].
43. Kwon BS, Kim Y, Lee SH, et al. The high incidence of severe adverse events due to pyrazinamide in elderly patients with tuberculosis. PLoS One. 2020;15:e0236109.
44. Turkova A, Wills GH, Wobudeya E, et al. Shorter treatment for nonsevere tuberculosis in African and Indian children. N Engl J Med. 2022;386:911-22.
45. Jo KW, Yoo JW, Hong Y, et al. Risk factors for 1-year relapse of pulmonary tuberculosis treated with a 6-month daily regimen. Respir Med. 2014;108:654-659.
46. Teo SK, Tan KK, Khoo TK. Four-month chemotherapy in the treatment of smear-negative pulmonary tuberculosis: results at 30 to 60 months. Ann Acad Med Singap. 2002;31:175-81.
47. Burman WJ, Cohn DL, Rietmeijer CA, et al. Noncompliance with directly observed therapy for tuberculosis: epidemiology and effect on the outcome of treatment. Chest 1997;111:1168–73.
48. Stadler JAM. Updated WHO definitions for tuberculosis outcomes: simplified, unified and future-proofed. Afr J Thorac Crit Care Med. 2022;28:10.7196/AJTCCM.2022.v28i2.224.
49. Allwood BW, Byrne A, Meghji J, et al. Post-tuberculosis lung disease: clinical review of an under-recognised global challenge. Respiration. 2021;100:751-63.
50. Migliori GB, Marx FM, Ambrosino N, et al. Clinical standards for the assessment, management and rehabilitation of post-TB lung disease. Int J Tuberc Lung Dis. 2021;25:797-813.
51. Fervers B, Burgers JS, Haugh MC, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. Int J Qual Health Care. 2006;18:167-76.
52. HIVgov and NIH's Office of AIDS Research. Mycobacterium tuberculosis Infection and Disease | NIH. Published February 17, 2022. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/mycobacterium-0 [Last accessed 2 September 2023]
53. U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). Version 5.0. Published 27 November 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf [Last accessed 2 September 2023].

54. Ministry of Health, Health Sciences Authority, Integrated Health Information Systems. MOH Artificial Intelligence in Healthcare Guidelines. October 2021. Available at: https://www.moh.gov.sg/licensing-and-regulation/artificial-intelligence-in-healthcare [Last accessed 2 September 2023].
55. Pradipta IS, Houtsma D, van Boven JFM, Alffenaar JWC, Hak E. Interventions to improve medication adherence in tuberculosis patients: a systematic review of randomized controlled studies. NPJ Prim Care Respir Med. 2020;30:21.
56. Alipanah N, Jarlsberg L, Miller C, et al. Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. PLoS Med. 2018;15:e1002595.
57. Ridho A, Alfian SD, van Boven JFM, et al. Digital health technologies to improve medication adherence and treatment outcomes in patients with tuberculosis: systematic review of randomized controlled trials. J Med Internet Res. 2022;24:e33062.
58. Suwankeeree W, Picheansathian W. Strategies to promote adherence to treatment by pulmonary tuberculosis patients: a systematic review. Int J Evid Based Healthc. 2014;12:3-16.
59. Müller AM, Osório CS, Silva DR, Sbruzzi G, de Tarso P, Dalcin R. Interventions to improve adherence to tuberculosis treatment: systematic review and meta-analysis. Int J Tuberc Lung Dis. 2018;22:731-74