

Singapore tuberculosis (TB) clinical management guidelines 2024: A modified Delphi adaptation of international guidelines for drug-susceptible TB infection and pulmonary disease

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ABSTRACT

Introduction: Tuberculosis (TB) remains endemic in Singapore. Singapore's clinical practice guidelines for the management of tuberculosis were first published in 2016. Since then, there have been major new advances in the clinical management of TB, ranging from diagnostics to new drugs and treatment regimens. The National TB Programme convened a multidisciplinary panel to update guidelines for the clinical management of drug-susceptible TB infection and disease in Singapore, contextualising current evidence for local practice.

Method: Following the ADAPTE framework, the panel systematically reviewed, scored and synthesised English-language national and international TB clinical guidelines published from 2016, adapting recommendations for a prioritised list of clinical decisions. For questions related to more recent advances, an additional primary literature review was conducted via a targeted search approach. A 2-round modified Delphi process was implemented to achieve

consensus for each recommendation, with a final round of edits after consultation with external stakeholders.

Results: Recommendations for 25 clinical questions spanning screening, diagnosis, selection of drug regimen, monitoring and follow-up of TB infection and disease were formulated. The availability of results from recent clinical trials led to the inclusion of shorter treatment regimens for TB infection and disease, as well as consensus positions on the role of newer technologies, such as computer-aided detection-artificial intelligence products for radiological screening of TB disease, next-generation sequencing for drug-susceptibility testing, and video observation of treatment.

Conclusion: The panel updated recommendations on the management of drug-susceptible TB infection and disease in Singapore.

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CLINICAL IMPACT

What is New

- This update to the 2016 Ministry of Health Clinical Practice Guidelines on the prevention, diagnosis and management of tuberculosis (TB) in Singapore incorporates new shortened regimens and recommendations on major new advances.
- Major new advances include the use of computer-aided detection-artificial intelligence products for radiological screening for TB disease, next-generation sequencing for drug susceptibility testing of *Mycobacterium tuberculosis*, and video-observed treatment of TB disease in lieu of direct observation.

Clinical implications

- These guidelines will largely be implemented by the National TB Programme team in Singapore.
- The primary aim is to standardise and improve the clinical management of TB infection and disease in Singapore, contributing to the global goal of TB elimination.

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 2000 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 directly observed treatment (DOT).^{19,20}

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 as well as 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.

METHOD

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.

Selection of questions

The Panel agreed on the clinical questions for recommendations, based on prioritisation 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 A copy of the RIGHT-Ad@pt checklist²² is provided in the Supplementary Materials Appendix S9.

The guidelines adaptation process is described in Supplementary Materials Appendix S1. All major national and international TB management guidelines published in the English language between 1 January 2016 and 5 March 2023 are listed in Table 1. These guidelines were assessed with a modified Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument,²³ with assessment results provided in Supplementary Materials Appendix S1. PHTT conducted an additional primary literature review using a targeted search approach for questions regarding recent advancements like CAD-AI, NGS and VOT.

PHTT summarised guidelines and primary literature into reports for the Panel. Through a

Table 1. List of international guidelines reviewed and used in the preparation of the 2024 TB guidelines.

Guidelines	Year published	Developing organisations	Region	Funder	Abbreviation ^{Ref}
European Union Standards for Tuberculosis Care - 2017 update	2018	European Respiratory Society 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)	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)	US	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	US	US Department of Health	USPSTF ²⁸
Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019	2019	National Tuberculosis Controllers Association, Centers for Disease Control and Prevention (CDC)	US	US CDC	CDC-2019 ²⁹
Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020	2020	National Tuberculosis Controllers Association, CDC	US	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
Clinical Practice Guidelines: Management of Tuberculosis (Fourth Edition)	2021	Malaysian Health Technology Assessment Section, MOH Malaysia	Malaysia	MOH Malaysia	Malaysia ¹⁸
Canadian Tuberculosis Standards	2022	Canadian Thoracic Society (CTS) of the Canadian Lung Association and Public Health Agency of Canada	Canada	CTS and Public Health Agency of Canada	Canada ¹⁷

Table 1. List of international guidelines reviewed and used in the preparation of the updated TB guidelines. (Cont'd)

Guidelines	Year published	Developing organisations	Region	Funder	Abbreviation ^{Ref}
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

^{Ref} Superscript numbers: refer to REFERENCES

2-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 Singapore 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 Disease Physicians
 - Chapter of Respiratory Physicians
- Agency for Care Effectiveness, Ministry of Health (methodology review only)

SCREENING FOR TB (QUESTIONS 1 AND 2)

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, one 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-anti-tumour necrosis factor (TNF) biologics variably increase the risk of TB reactivation, these risks are lower and/or less well quantified compared with 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 above in Section 1 and Table 2.

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

Population	Screening for TB infection	Screening for TB disease	Comments	Guidelines referenced ^a
PLHIV	Universal screening upon diagnosis of HIV	1. Universal screening upon diagnosis of HIV 2. Workup from TB infection diagnosis ^b	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 ^c • 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 ^b	Nil	WHO, NICE, CDC-2017, USPSTF, Canada, ECDC-L, Australia-NTAC, New Zealand, Hong Kong

HIV: human immunodeficiency virus; PLHIV: people living with HIV; TB: tuberculosis; TNF: tumour necrosis factor

^a Refer to Abbreviation of names of guidelines in Table 1.

^b If TB infection is diagnosed at any point after the initial TB screening event.

^c Steroid dose ≥ 15 mg of prednisolone equivalent with duration >8 weeks.

Superscript number: refer to REFERENCES

DIAGNOSIS OF TB INFECTION (QUESTIONS 3 AND 4)

At present, there is no gold-standard test for the diagnosis of TB infection. Available tests in Singapore include the tuberculin skin tests (TST) and interferon-gamma release assays (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.^{32,33}

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

Recommendations

- In adults, IGRAs are preferred to the TST for diagnosis of TB infection. (*Adopted*)
- The TST can be an alternative 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/mm³; individuals on anti-TNF therapy and/or high-dose steroids; recipients of organ or stem cell transplantation, etc.), the T-SPOT.TB test (Oxford Immunotec, UK) may be more sensitive than the QuantiFERON-TB Gold Plus (Qiagen, US) QFT-Plus or the older QuantiFERON-TB Gold In-Tube (Qiagen, US), albeit with wide confidence intervals in meta-analyses.^{32,33} 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 Bacillus Calmette-Guerin (BCG) vaccination, commercially available IGRAs 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.^{12-15,17,25,26,34} WHO guidelines supported both tests but stated that a positive result should not be a prerequisite for TB infection treatment for close contacts and PLHIVs.⁸ Both tests are not recommended in infants <6 months old due to very low test sensitivity.

TREATMENT OF TB INFECTION (QUESTIONS 5 TO 11)

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.³⁵ 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 individual'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 aspartate aminotransferase (AST) and alanine aminotransferase (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} those with a history of liver disease, harmful use of alcohol/other drugs and 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 alternative regimens for the treatment of TB infection in adults?

Recommendations

- The 2 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 DOT or video-observed treatment (VOT).^{12,14,17}

WHO, ECDC-L and Malaysia guidelines (Table 1) 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. the 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 randomised clinical trial in PLHIV living in a high TB prevalence region,³⁷ and it is recommended as an alternative regimen for adult PLHIV in recent guidelines (2020 to 2022).^{8,12,18}

Table 3. Recommended treatment regimens for TB infection.

Population	Preferred regimen (dose)	Alternative regimen	Comments
Adults	4R daily (10 mg/kg BW) 6H/9H daily (5 mg/kg BW) with pyridoxine daily (10–25 mg)	3HP weekly (isoniazid 15 mg/kg BW up to 900 mg; rifapentine up to 900 mg) with pyridoxine daily 3HR with pyridoxine daily	3HP weekly is not recommended in 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 dosing³⁹)	- 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

1HP: isoniazid and rifapentine daily for 1 month; 3HP: isoniazid and rifapentine weekly for 3 months; 3HR: isoniazid and rifampicin daily for 3 months; 4R: rifampicin daily for 4 months; 6H/9H: isoniazid daily for either 6 or 9 months; BW: body weight; PLHIV: people living with HIV
Superscript number: refer to REFERENCES

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 hepatotoxicity,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.

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

Recommendations

- The 2 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.^{8,36}

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. Further details on treatment interruptions are in Supplementary Materials Appendix S2.

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 recommended 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 for close contacts of infectious individuals.⁸ As a precautionary measure, the Panel elected to adopt WHO's recommendation.

DIAGNOSIS OF TB DISEASE (QUESTIONS 12 TO 17)

The emergence of new technologies has prompted a consideration for 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 acid-fast bacilli (AFB) smear microscopy, nucleic acid amplification test (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 the value of AFB smear microscopy given the widespread availability of NAAT in Singapore. 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 collected and sent to the laboratory for testing?**Recommendations**

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

- Nasopharyngeal aspiration is an alternative option for sample collection in children. (*Adopted*)

Remarks

Obtaining high-quality sputum increases the yield of microbiological testing. NZ and Malaysia guidelines (Table 1) 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% versus 73% in gastric aspirate) in children.³⁸ It is recommended in 3 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,^{17,38} the Panel elected not to recommend stool as an alternative 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 (i.e. day 1 and day 2) collection of early morning samples is ideal. (*Adopted*)

Remarks

The recommendations from international guidelines on this question are listed in Supplementary Materials Appendix S4. 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.³⁸

15. Under what circumstances should computed tomography (CT) scan of the 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 next-generation sequencing (NGS) as a clinical laboratory tool?

Recommendations

- Whole genome sequencing (WGS) can be deployed in clinical laboratories in Singapore 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 WGS⁶⁻⁸ 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 deoxyribonucleic acid (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,³⁹ 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, Singapore 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 the Stop TB Partnership and FIND (<https://www.ai4hlth.org/>). Further details on CAD-AI products for TB disease screening are available in the Supplementary Materials Appendix S5.

TREATMENT OF TB DISEASE (QUESTIONS 18 TO 25)

Early diagnosis and completion of TB disease treatment are cornerstones of 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 by the National Tuberculosis Programme).

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 multidisciplinary 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 4 outlines the aspects and components of a TB disease treatment plan.

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 2-month intensive phase of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E), followed by 4-month continuation phase of H and R (2HRZE/4HR). (*Adopted*)
- In persons aged >70 years with low risk of drug resistance, pyrazinamide should be avoided; the preferred regimen is a 2-month intensive phase of H, R and E followed by 7-month continuation phase of H and R (2HRE/7HR). (*Adapted*)
- An alternative regimen, should rifapentine become available in Singapore, is an 8-week intensive phase of daily H, rifapentine (P), moxifloxacin (M) and Z, followed by 9-week continuation phase of daily H, P and M (2HPMZ/2HPM)—except in pregnant/breastfeeding women and PLHIV. (*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*)

Table 4. Aspects and components of a TB disease treatment plan.

Aspects	Components	Guidelines referenced ^a
Principles	Patient-centered care with comprehensive and individualised treatment support	11,17,20,27,30
	Balancing patient rights/choices with public health and safety	11,20,27,28,30
Enablers, incentives and adherence interventions	Patient health education and counselling; improving treatment literacy	11,20,21,27,28,30
	Psychological, material (including food, financial and transport subsidies) and social support for patients	11,20,21,27,28,30
	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

DOT: directly observed treatment; VOT: video-observed treatment

^a Numbers: refer to REFERENCES

Table 5. Recommended treatment regimens for TB disease.

Population	Regimen and 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 phase¹¹ - 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 preferred¹¹

BW: body weight; DOT: directly observed treatment; VOT: video-observed treatment;

E: ethambutol; H: isoniazid; M: moxifloxacin; P: rifapentine; R: rifampicin; Z: pyrazinamide;

2HPMZ/2HPM: 8-week intensive phase of daily H, P, M and Z, followed by 9-week continuation phase of daily H, P and M;

2HRZ(E)/2HR: 2-month intensive phase of H, R and Z with or without E followed by 2-month continuation phase of H and R;

2HRZE/4HR: 2-month intensive phase of H, R, Z and E, followed by 4-month continuation phase of H and R;

2HRZ(E)/4HR: 2-month intensive phase of H, R and Z with or without E followed by 4-month continuation phase of H and R

Superscript numbers: refer to REFERENCES

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 5 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.⁴⁰ 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 practice in Singapore. Treatment duration should be extended to 9 months (2HRE/7HR) if pyrazinamide is excluded.

Following the completion of the Tuberculosis Trials Consortium (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 alternative regimen in updated guidelines.^{8,10} The Panel therefore also recommended this as an alternative 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.

Detailed recommendations for PLHIV with TB disease can be found in the Supplementary Materials Appendix S6.

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 alternative 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 shorter treatment for minimal TB in children (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 TB confined to 1 lobe with no cavities, no signs of miliary TB, no complex pleural effusion, and no clinically significant airway obstruction or peripheral lymph-node tuberculosis) smear-negative TB.⁴¹ 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 CD4 count <200 cells/mm³ 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-2016 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.^{17,27,42} Other factors associated with a higher risk of relapse are as listed in the immediate Recommendations above.^{17,27,42} 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.^{27,43}

21. How should the treatment of TB disease be monitored?

Recommendations

- In adults, observation of treatment is recommended for those with infectious TB disease, in particular 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 a central tenet in TB control in Singapore.³ While all international TB guidelines support DOT under varied situations,

several guidelines also emphasise 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 organised,⁸ with patient education¹⁸ and in-person support within a proper monitoring and evaluation framework.¹⁷ In general, the least restrictive and 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 Supplementary Materials Appendix S7.

Table 6. Management of treatment interruptions (adapted from WHO, NZ and CDC-2016 guidelines).^{8,14,27}

Timepoint of interruption	Details of interruption	Recommendation
Intensive phase	Lapse was <14 days in duration	Continue treatment to complete planned total number of doses ^a
	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

AFB: acid-fast bacilli; E: ethambutol; H: isoniazid; R: rifampicin; Z: pyrazinamide
2HRZE/2HR: 2-month intensive phase of H, R, Z and E followed by 2-month continuation phase of H and R;
2HRZE/4HR: 2-month intensive phase of H, R, Z and E, followed by 4-month continuation phase of H and R
^a If all intensive phase doses can be completed within 3 months.
Superscript numbers: refer to REFERENCES

22. How should treatment interruptions be managed?

Recommendations

- The decision to continue or restart 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 6). (*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. (*Adapted*)
- 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). (*Adapted*)
- In severe or highly infectious persons with TB disease, initiation of an alternative treatment regimen is recommended while waiting for a serious drug adverse event to resolve. (*Adapted*)

Remarks

Repeated and/or prolonged TB treatment interruptions lead to worse outcomes.⁴⁴ WHO, CDC-2016 and NZ guidelines offer similar algorithms for clinical decisions regarding resuming or restarting TB treatment after interruptions (Table 6). However, most recommendations are based on expert opinion and experience as there is no strong body of evidence available.^{8,27} A more comprehensive discussion of interruptions and how these might be addressed is provided in the Supplementary Materials Appendix S3.

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. (*Adapted*)

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 to 18). (*Adapted*)
- Other baseline laboratory investigations in adults include—if not already done elsewhere—blood testing for HIV, AST/ALT, full blood count, 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. (*Adapted*)
- 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. (*Adapted*)
- In adults, visual assessments should be performed at initial and subsequent clinic visits if on an ethambutol-containing regimen. (*Adapted*)
- 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 to confirm bacteriological cure.⁴⁵

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.^{8,17,46} They are under-recognised but contribute significantly to excess morbidity and mortality after post-TB treatment.⁴⁶ The Canada guidelines are the only ones that formally suggest assessing for post-TB lung disease. The guidelines 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.⁴⁷

IMPLEMENTATION CONSIDERATIONS

TB control in Singapore is overseen by the National TB Programme at the National Centre for Infectious Diseases, while the majority of persons with pulmonary TB disease are managed at the TB Control Unit, Tan Tock Seng Hospital. These guidelines will largely be implemented by the National TB Programme team, including their dissemination and education of TB care providers, with sourcing for rifapentine through the Global Drug Facility.

SCHEDULED REVIEW AND UPDATE

The National TB Programme will convene a multidisciplinary team in 2026 to update these guidelines via a systematic review of available guidelines and evidence.

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Supplementary Materials

- Appendix S1. Methodology
- Appendix S2. Managing treatment interruptions in TB infection
- Appendix S3. Managing treatment interruptions in TB disease
- Appendix S4. Recommendations for clinical sample collection
- Appendix S5. CAD-AI products for TB disease screening
- Appendix S6. Recommendations for PLHIV with TB disease
- Appendix S7. Enablers for treatment adherence
- Appendix S8. References for Supplementary Materials
- Appendix S9. RIGHT-Ad_{pt} checklist
- Appendix S10. Glossary
- Appendix S11. Members of the Clinical TB Guidelines Development Team

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