Clinical Tuberculosis Guidelines Development Team. Singapore tuberculosis (TB) clinical management guidelines 2024: A modified Delphi adaptation of international guidelines for drug-susceptible TB infection and pulmonary disease. Ann Acad Med Singap 2024;53:Online First.

Supplementary Materials

Appendices **Page**

Appendix S1. Methodology

Given that many high quality guidelines on TB clinical management had been published since 2016 [1-15] (Table 1 of article), in particular from the World Health Organization [1], 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 [16,17]. 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 [18,19].

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 [19]. 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 Supplementary Table S1 below.

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.

Table S1. Assessment of guidelines according to the modified AGREE II instrument. [19]

Item	**Guideline**[1]														
	WHO [1]	CDC-2019 [2]	CDC-2017 [3]	CDC-2020 [4]	CDC-2016 [5]	USPSTF [6]	ECDC-L [7]	ECDC-S [8]	NZ [9]	Australia NTAC [10]	Australia CDNA [11]	HK [12]	Canada [13]	Malaysia [14]	NICE [15]
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	P	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 management of the condition or health issue are clearly presented	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
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	Yes	No	No	No	Yes	Yes	Yes	Yes	Partial	No	Yes	No	Yes	No	Partial

the recommendations can be put into practice.															
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 and/or auditing criteria	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Domain 6: Editorial independence															
The views of the funding body have not influenced the content of the guideline	Partial	No	No	No	P	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.

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, Singapore: Chapter of Family Medicine Physicians; College of Paediatrics & Child Health; College of Physicians: Chapter of Infectious Disease 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.

Appendix S2. Managing treatment interruptions in TB infection

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 [1] and shown in Supplementary Table S2 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 S2. Suggested actions for treatment interruptions during treatment of TB infection. [1]

Regimen	**Duration of interruption**	**Next steps**
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 [15], CDC-2016 [5], Malaysia [14] and New Zealand guidelines [0] 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 [15]. 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 [9] and Malaysian [14] 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 [20]. 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 [20].

Interruptions due to other drug adverse reactions

Canadian [13] and Malaysia [14] 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 [21]. 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 [14].

No Information on differences In the management of treatment Interruptions In adults and children (⩽ 16 years of age) was found in the reviewed guidelines.

Appendix S3. Managing treatment interruptions in TB disease

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 [1,5]. 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).

<u>Interruptions due to hepatotoxicity</u>

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 [5].

WHO [1], CDC-2016 [5] and NICE [15] 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 [5,15].

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 (Supplementary Table S3). 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 [15].

Table S3. 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 [1]	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 [5]	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 [15]	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 [5]. The more common adverse effects, evaluation of their severity and possible causes, and how they can be managed are listed in Supplementary Table S4 below. Children and adolescents experience adverse events caused by TB medicines much less frequently than adults.

Table S4. Common non-hepatotoxic adverse effects and their management (adapted from CDC-2016 guidelines [5]).

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 despite body temperatures ≥ 39°C. Drug fever does not follow a specific pattern and eosinophilia need not be present	Stopping drugs usually resolves the fever within 24 hours. Once afebrile, the patient should restart drugs individually every 2–3 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 [5,15]. 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 [15]. 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 [15].

Appendix S4. Recommendations for clinical sample collection

Most guidelines (CDC-2016, Canada, NICE, ECDC-S and Australia-CDNA) recommend a minimum of three samples to be collected [5,8,11,13,15], with the pervasive issue of poor sample quality (especially in relation to smear microscopy) and intention to improve diagnostic yield cited as rationale for the number. Canadian guidelines add that multiple sample collection is particularly important for children as the yield of microbiological tests is low in the population [13]. New Zealand [9] and Malaysia [14] 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 [9]. These are summarized in Supplementary Table S5 below.

Table S5. Sample collection recommendations according to international guidelines.

Guideline	Minimum number of samples	Collection time	Rationale and remarks
WHO [1]	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 [5]	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 [13]	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 [15]	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 [9]	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 [14]	2	When possible, at least one early morning specimen	Sputum collected in the early morning has the highest yield.
ECDC [10]	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 [11]	3	At least one early morning sample	N.A.

Appendix S5. CAD-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) [1]. 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 [11]. 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 [1].

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 [1].

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 are 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 [1].

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 October 2021 [22]. 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 S6. Recommendations for PLHIV with TB disease

Regimens for PLHIV

The WHO guidelines are the only one with alternative and other recommended regimens (apart from 2HRZE/4HR) for PLHIV [1]. 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 [1,5,13]. 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 [1]. 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 [1].

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 [5]. 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 [5].

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 [13]. 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 [15].

Daily versus intermittent treatment regimens

CDC-2016 [5] and Canadian guidelines [13], 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 [5]. Malaysia guidelines, which only recommend daily over intermittent dosing, further highlight that daily anti-TB regimens should be used throughout the treatment for PLHIV [14].

Initiation of antiretroviral therapy (ART)

Most guidelines recommend initiation of ART amidst TB treatment for ART-naïve patients [1,5,8,13,14]. 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 [1] and Canadian [13] guidelines recommend that ART be initiated as soon as possible (within 2 weeks of initiating TB treatment, regardless of CD4 cell count), CDC-2016 [5] and Malaysia [14] 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 [8].

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 [1,5,13,14]. In this scenario, CDC

and Canada guidelines indicate a delay of at least 2 weeks [5,13], but WHO guidelines recommend a delay of at least 4 weeks [1], while the Malaysian guidelines recommend a delay of 2 months [14].

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 [1,5,13,14,15]. 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 [5,13].

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 [5]. Canadian guidelines strongly recommend a rifamycin (rifampin or rifabutin)-containing regimen for treatment of TB, despite the potential for drug-interactions with antiretroviral therapy [13].

CDC-2016 [5], Canadian [13] and Malaysia [14] 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 [5,13,14]. 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 [13].

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 [5,13]. It is therefore prudent to consult with an experienced pharmacist and a regularly updated clinical drug-interaction resource.

Appendix S7. 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 [5] and Malaysia guidelines [14] 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 [5]. Malaysia guidelines state that SAT may be offered to patients who cannot perform DOT [9].

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 [9,11,13,15]. 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 [11,13]. 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 S1.

Box S1. Patients/situations recommended for DOT in reviewed guidelines.

At risk patients/situations recommended for DOT in Canadian [8], NICE [10], New Zealand [9] and Australian-CDNA [11] 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 year
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 [9].

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 [15].

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 [13].

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 [1]. 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 [1]. 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 [1]. 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 [23,24]. 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 [23,24].

WHO guidelines state that DOT administered by trained lay providers or HCWs is recommended over DOT administered by family members or SAT [1], 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 [1]. 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 [1].

CDC-2016 guidelines state that parents should not supervise DOT for their children [5].

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 [13,14].

WHO noted studies demonstrating the non-inferiority of VOT to in-person DOT [1], 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 [5]. 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 [25,26].

Other than the Australia guidelines, which did not address VOT, all the guidelines recommend VOT as an alternative to clinic-based DOT [1,5,8,9,13-15]. NICE guidelines add that VOT has been useful particularly in those on longer regimens [15].

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 [1]. 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 [13]. Malaysian

guidelines state that patients should be educated on VOT and give consent for the procedure [14].

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 [5,8,9,11]. 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 [5]. 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 [13].

Treatment contracts

New Zealand guidelines provide detailed guidance on use of treatment contracts and legislation to support adherence [9]. 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 [9].

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 [24,27,28]. 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 [24,27,28].

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 [28]. 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 [1].

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 [1]. 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 [1].

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 [1,24].

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 [1,27]. 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 [1,24,27]

WHO guidelines point out that the number of studies on digital health interventions (DHT) under this intervention category is limited [1]. 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 [25].

Access to free treatment

Two guidelines (Canada and NICE) recommend that TB treatment should be provided free of charge [13,15]. 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.

Appendix S8. References for Supplementary Materials

1. 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].
2. Sosa LE, Njie 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.
3. 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.
4. 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.
5. 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.
6. US Preventive Services Task Force. Screening for latent tuberculosis in adults: US Preventive Services Task Force recommendations statement. JAMA. 2016;316:962-9.
7. 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].

8. European Centre for Disease Prevention and Control and European Respiratory Society. European Union Standards for Tuberculosis Care - 2017 update. https://www.ecdc.europa.eu/en/publications-data/european-union-standards-tuberculosis-care-2017-update. [Last accessed 18 February 2024].
9. 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].
10. 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.
11. 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].
12. 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].

13. 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].
14. 18. Malaysian Health Technology Assessment Section (MaHTAS). Medical Development Division, 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].
15. 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].
16. 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.
17. 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.
18. The ADAPTE Collaboration (2009). The ADAPTE process: resource toolkit for guideline adaptation. Version 2.0. Available at: https://g-i-n.net/wp-content/uploads/2021/03/ADAPTE-Resource-toolkit-March-2010.pdf [Last accessed 1 September 2023].
19. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182:E839-842.
20. 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]

21. 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].
22. 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].
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.

28. 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;22:731-740.

Appendix S9. RIGHT-Ad@pt checklist

The RIGHT-Ad@pt checklist

7 sections, 27 topics, and 34 items		Assessment	Page(s)	Note(s)
Basic information				
Title/subtitle				
1	Identify the report as an adaptation of practice guideline(s), that is include "guideline adaptation", "adapting", "adapted guideline/recommendation(s)", or similar terminology in the title/subtitle.	☒ Yes ☐ No ☐ Unclear		
2	Describe the topic/focus/scope of the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
Cover/first page				
3	Report the respective dates of publication and the literature search of the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
4	Describe the developer and country/region of the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
Executive summary/abstract				
5	Provide a summary of the recommendations contained in the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
Abbreviations and acronyms				
6	Define key terms and provide a list of abbreviations and acronyms (if applicable).	☒ Yes ☐ No ☐ Unclear		
Contact information of the guideline adaptation group				
7	Report the contact information of the developer of the adapted guideline.	☒ Yes ☐ No ☐ Unclear		
Scope				
Source guideline(s)				
8	Report the name and year of publication of the source guideline(s), provide the citation(s), and whether source authors were contacted.	☒ Yes ☐ No ☐ Unclear		
Brief description of the health problem(s)				
9	Provide the basic epidemiological information about the problem (including the associated burden), health systems relevant issues, and note any relevant differences compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear		
Aim(s) and specific objectives				
10	Describe the aim(s) of the adapted guideline and specific objectives, and note any relevant differences compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear		
Target population(s)				
11	Describe the target population(s) and subgroup(s) (if applicable) to which the recommendation(s) is addressed in the adapted guideline, and note any relevant differences compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear		
End-users and settings				
12	Describe the intended target users of the adapted guideline, and note any relevant differences compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear		

13	Describe the setting(s) for which the adapted guideline is intended, and note any relevant differences compared to the source guideline(s).	☐ Yes ☒ No ☐ Unclear
Rigor of development		
Guideline adaptation group		
14	List all contributors to the guideline adaptation process and describe their selection process and responsibilities.	☒ Yes ☐ No ☐ Unclear
Adaptation framework/methodology		
15	Report which framework or methodology was used in the guideline adaptation process.	☒ Yes ☐ No ☐ Unclear
Source guideline(s)		
16	Describe how the specific source guideline(s) was(were) selected.	☒ Yes ☐ No ☐ Unclear
Key questions		
17	State the key questions of the adapted guideline using a structured format, such as PICO (population, intervention, comparator, and outcome), or another format as appropriate.	☒ Yes ☐ No ☐ Unclear
18	Describe how the key questions were developed/modified, and/or prioritized.	☒ Yes ☐ No ☐ Unclear
Source recommendation(s)		
19	Describe how the recommendation(s) from the source guideline(s) was(were) assessed with respect to the evidence considered for the different criteria, the judgements and considerations made by the original panel.	☒ Yes ☐ No ☐ Unclear
Evidence synthesis		
20	Indicate whether the adapted recommendation(s) is/are based on existing evidence from the source guideline(s), and/or additional evidence.	☒ Yes ☐ No ☐ Unclear
21	If new research evidence was used, describe how it was identified and assessed.	☐ Yes ☐ No ☐ Unclear
Assessment of the certainty of the body of evidence and strength of recommendation		
22	Describe the approach used to assess the certainty/quality of the body/ies of evidence and the strength of recommendations in the adapted guideline and note any differences (if applicable) compared to the source guideline(s).	☒ Yes ☐ No ☐ Unclear
Decision-making processes		
23	Describe the processes used by the guideline adaptation group to make decisions, particularly the formulation of recommendations.	☒ Yes ☐ No ☐ Unclear
Recommendations		
Recommendations		
24	Report recommendations and indicate whether they were adapted, adopted, or *de novo*.	☒ Yes ☐ No ☐ Unclear
25	Indicate the direction and strength of the recommendations and the certainty/quality of the supporting evidence and note any differences compared to the source recommendations(s) (if applicable).	☐ Yes ☒ No ☐ Unclear

26	Present separate recommendations for important subgroups if the evidence suggests important differences in factors influencing recommendations and note any differences compared to the source recommendations(s) (If applicable).	☒ Yes ☐ No ☐ Unclear
Rationale/explanation for recommendations		
27	Describe the criteria/factors that were considered to formulate the recommendations or note any relevant differences compared to the source guideline(s) (if applicable).	☒ Yes ☐ No ☐ Unclear
External review and quality assurance		
External review		
28	Indicate whether the adapted guideline underwent an independent external review. If yes, describe the process.	☒ Yes ☐ No ☐ Unclear
Organizational approval		
29	Indicate whether the adapted guideline obtained organizational approval. If yes, describe the process.	☒ Yes ☐ No ☐ Unclear
Funding, declaration, and management of interest		
Funding source(s) and funder role(s)		
30	Report all sources of funding for the adapted guideline and source guideline(s), and the role of the funders.	☒ Yes ☐ No ☐ Unclear
Declaration and management of interests		
31	Report all conflicts of interest of the adapted and the source guideline(s) panels, and how they were evaluated and managed.	☒ Yes ☐ No ☐ Unclear
Other information		
Implementation		
32	Describe the potential barriers and strategies for implementing the recommendations (if applicable).	☒ Yes ☐ No ☐ Unclear
Update		
33	Briefly describe the strategy for updating the adapted guideline (if applicable).	☒ Yes ☐ No ☐ Unclear
Limitations and suggestions for further research		
34	Describe the challenges of the adaptation process, the limitations of the evidence, and provide suggestions for future research.	☒ Yes ☐ No ☐ Unclear

Appendix S10. 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 H, R and Z with or without E followed by 4-month continuation phase of H and R
2HRZE/2HR	2-month intensive phase of H, R, Z and E followed by 2-month continuation phase of H and R
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/7HR	2-month intensive phase of H, R, Z and E followed by 7-month continuation phase of H and R
2HRE/7HR	2-month intensive phase of H, R and E followed by 7-month continuation phase of H and R
2HPMZ/2HPM	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.
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

Appendix S11. Members of the Clinical TB Guidelines Development Team

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.

Name	Institution	Specialty/role	Contribution
Clinical Tuberculosis Guidelines Panel			
ANG Lay Teng, Michelle	National Centre for Infectious Diseases	Bioinformatics Senior Scientific officer	Review of evidence, discussion of recommendations
CHAN Si Min	1. National University Hospital 2. Yong Loo Lin School of Medicine	Paediatrics (Infectious Diseases)	Review of evidence, discussion of recommendations
CHENG Tim-Ee, Lionel	Singapore General Hospital	Radiology	Review of evidence, discussion of recommendations
CHEONG Hau Yiang	Changi General Hospital	Infectious diseases (Adult)	Review of evidence, discussion of recommendations
CHEW Ka Lip	National University Hospital	Clinical microbiology	Review of evidence, discussion of recommendations

CHLEBICKI, Piotr Maciej	Singapore General Hospital	Infectious diseases (Adult)	Review of evidence, discussion of recommendations
HSU Li Yang	1. Saw Swee Hock School of Public Health 2. Yong Loo Lin School of Medicine	Infectious diseases (Adult)	Review of evidence, discussion of recommendations, Panel chair
KAW Jon Leng, Gregory	Tan Tock Seng Hospital	Radiology	Review of evidence, discussion of recommendations
KEE Chin Leong, Adrian	1. National University Hospital 2. Yong Loo Lin School of Medicine	Respiratory medicine (Adult)	Review of evidence, discussion of recommendations
NG Chung Wai, Mark	SingHealth Polyclinics	Family Medicine	Review of evidence, discussion of recommendations
ONG Twee Hee, Rick	Saw Swee Hock School of Public Health	Bioinformatics	Review of evidence, discussion of recommendations

ONG Wei Min, Catherine	1. National University Hospital 2. Yong Loo Lin School of Medicine	Infectious diseases (Adult)	Review of evidence, discussion of recommendations
QUAH Lishan, Jessica	Changi General Hospital	Respiratory medicine (Adult)	Review of evidence, discussion of recommendations
SELVAMANI D/O Balasubramaniam	National University Polyclinics	Family Medicine	Review of evidence, discussion of recommendations
SNG Li Hwei	Singapore General Hospital	Microbiology	Review of evidence, discussion of recommendations
TAN Bee Xian, Jamie	Singapore General Hospital	Microbiology	Review of evidence, discussion of recommendations
TAN Cher Heng	Tan Tock Seng Hospital	Radiology	Review of evidence, discussion of recommendations
TAY Jun Yang	National Centre for Infectious Diseases	Infectious diseases (Adult)	Review of evidence, discussion of recommendations

Teo Li San, Lynette	1. National University Hospital 2. Yong Loo Lin School of Medicine	Radiology	Review of evidence, discussion of recommendations
THOON Koh Cheng	KK Hospital	Paediatrics (Infectious Diseases)	Review of evidence, discussion of recommendations
YAN Zherong, Gabriel	National University Hospital	Microbiology; Infectious diseases (Adult)	Review of evidence, discussion of recommendations
Public Health Translational Team			
CHEN I-Pei, Jacinta	Saw Swee Hock School of Public Health	Senior manager	Systematic review of guidelines and primary literature, evidence synthesis
Hud Bin Mohammed Helmi	Saw Swee Hock School of Public Health	Student on internship	Systematic review of guidelines and primary literature, evidence synthesis
KHOO, Benjamin Bing Jie	Saw Swee Hock School of Public Health	Student on internship	Systematic review of guidelines and primary literature, evidence synthesis
LEE Yi Xin, Dawn	Saw Swee Hock School of Public Health	Student on internship	Systematic review of guidelines and primary literature, evidence synthesis

NG Xian Yi, Bob	Saw Swee Hock School of Public Health	Research assistant	Systematic review of guidelines and primary literature, evidence synthesis
Park Jia Ying	Saw Swee Hock School of Public Health	Research assistant	Systematic review of guidelines and primary literature, evidence synthesis
TAN Ying Ting, Belinda	Saw Swee Hock School of Public Health	Student on internship	Systematic review of guidelines and primary literature, evidence synthesis
YANG Qian	Saw Swee Hock School of Public Health	Senior manager	Systematic review of guidelines and primary literature, evidence synthesis