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Index-TB Guidelines: Guidelines on extrapulmonary tuberculosis for India

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Extrapulmonary tuberculosis (EPTB) is frequently a diagnostic and therapeutic challenge. It is a common opportunistic infection in people living with HIV/AIDS and other immunocompromised states such as diabetes mellitus and malnutrition. There is a paucity of data from clinical trials in EPTB and most of the information regarding diagnosis and management is extrapolated from pulmonary TB. Further, there are no formal national or international guidelines on EPTB. To address these concerns, Indian EPTB guidelines were developed under the auspices of Central TB Division and Directorate of Health Services, Ministry of Health and Family Welfare, Government of India. The objective was to provide guidance on uniform, evidence-informed practices for suspecting, diagnosing and managing EPTB at all levels of healthcare delivery. The guidelines describe agreed principles relevant to 10 key areas of EPTB which are complementary to the existing country standards of TB care and technical operational guidelines for pulmonary TB. These guidelines provide recommendations on three priority areas for EPTB: (*i*) use of Xpert MTB/RIF in diagnosis, (*ii*) use of adjunct corticosteroids in treatment, and (*iii*) duration of treatment. The guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, which were evidence based, and due consideration was given to various healthcare settings across India. Further, for those forms of EPTB in which evidence regarding best practice was lacking, clinical practice points were developed by consensus

on accumulated knowledge and experience of specialists who participated in the working groups. This would also reflect the needs of healthcare providers and develop a platform for future research.

Key words Diagnosis - extrapulmonary tuberculosis - GRADE guidelines - treatment duration

Introduction

Extrapulmonary tuberculosis (EPTB) describes the various conditions caused by *Mycobacterium tuberculosis* infection of organs or tissues outside the lungs. There are many forms of EPTB, affecting every organ system in the body. Some forms, such as TB meningitis and TB pericarditis, are life-threatening, while others such as pleural TB and spinal TB can cause significant ill-health and lasting disability. The burden of EPTB is high ranging from 15-20 per cent of all TB cases in HIV-negative patients, while in HIV-positive people, it accounts for 40-50 per cent of new TB cases[1]. The estimated incidence of TB in India was 2.1 million cases in 2013, 16 per cent of which were new EPTB cases, equating to 336,000 people with EPTB[2].

Most of the resources for research, diagnosis and treatment are aimed at pulmonary TB as this form is

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Table I. The key questions addressed in the guidelines

Question	Should GeneXpert MTB/ RIF be used in diagnosis?	Should corticosteroids be used routinely?	How long should ATT be given in the treatment of
Specific EPTB considered	Lymph node TB; TB meningitis; pleural TB?	TB pericarditis; TB meningitis; pleural TB?	Lymph node TB; abdominal TB; TB meningitis?

Definitions - GeneXpert MTB/RIF, GeneXpert MTB/RIF is an automated cartridge-based nucleic acid amplification test that can identify MTB DNA and resistance to RIF. ATT, antituberculosis treatment; TB, tuberculosis; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin; EPTB, extrapulmonary TB

Table II. Principles of extrapulmonary tuberculosis care

Principle 1	Patients first
	The provider should adopt a patient-centred approach to manage EPTB, to promote well-being and adherence to treatment and to relieve suffering. Patients have the right to be fully informed about their care at every stage, to be able to make decisions about their treatment and to be treated with dignity and respect
Principle 2	Promoting early diagnosis
	Providers should be informed of the clinical features and risk factors for various forms of EPTB and carry out prompt clinical evaluation and appropriate diagnostic investigation
Principle 3	Access to a tissue-based diagnosis
	Where facilities exist, all patients suspected of having EPTB should have appropriate samples taken for microbiological and/or histological testing unless diagnostic sampling is deemed to risk undue harm
Principle 4	Avoiding unnecessary invasive and costly tests
	Providers should consider the impact of diagnostic tests on patient management before referring patients for costly or invasive tests or repeating these tests
Principle 5	Access to HIV testing
	As EPTB is particularly associated with HIV, integrated counselling and testing should be made available to all patients suspected of having EPTB
Principle 6	Identifying patients with concurrent active pulmonary TB
	All patients suspected of EPTB should have clinical assessment for pulmonary TB in line with RNTCP guidance for investigating suspected pulmonary tuberculosis
Principle 7	Ensuring effective treatment
	All patients should receive an appropriate treatment regimen
Principle 8	Addressing drug resistance
	All patients with a diagnosis of EPTB should be risk-assessed for drug resistance prior to starting treatment, and drug susceptibility testing should be available for all patients at risk of drug-resistant tuberculosis
Principle 9	Promoting adherence
	Providers should monitor adherence and address factors leading to interruption or discontinuation of treatment. Services should promote retention of patients in care
Principle 10	Record keeping and public health promotion
	A reliable, well-maintained record of all diagnostic tests, treatments given, treatment monitoring, outcomes and adverse events should be kept for each patient, and data should be collected at national programme level for the purposes of healthcare system planning and development

EPTB, extra-pulmonary TB; TB, tuberculosis; RNTCP, Revised National TB Control Programme

most common and also most important with regard to TB control and public health. However, EPTB in all its forms has a significant impact on people suffering from the disease, their families, economy and health system. Diagnosis can be difficult, and delay can cause harm, but most people with EPTB can be cured if they have access to diagnosis and treatment with anti-TB drugs in time.

The main objective of these guidelines is to provide guidance on up-to-date, uniform, evidence-informed practices for suspecting, diagnosing and managing various forms of EPTB at all levels of healthcare delivery. These are aimed at clinicians and health workers at every level of care, in the public and private sectors, as well as healthcare providers, TB programme managers and policymakers. These can contribute to the Revised National TB Control Programme (RNTCP) towards improving the detection, care and outcomes in EPTB, further to help the Programme with initiation of treatment, adherence and completion while minimizing drug toxicity and overtreatment and to practices that minimize the development of drug resistance.

In 2014, the leadership of the Central TB Division and Directorate General of Health Services of the Ministry of Health and Family Welfare, Government of India, recognized the need to develop evidence-informed guidelines for EPTB to sit alongside the guidelines for pulmonary TB from the RNTCP that were already in use. The guidelines development process was initiated by the Department of Medicine at the All India Institute of Medical Sciences (AIIMS), New Delhi, which is the World Health Organization (WHO)-Collaborating Centre for Training and Research in TB and also the Centre of Excellence for EPTB. A group of expert clinicians representing different specialties was recruited from various institutions across India, who formed 10 technical advisory committees representing different organ systems affected by EPTB. A methodology support team was also constituted formed of representatives from Cochrane South Asia (Vellore, India) and Cochrane Infectious Diseases Group (Liverpool School of Tropical Medicine, UK). The guidelines process was overseen and administered throughout by the core committee.

At the first guidelines meeting in March 2015, the technical advisory subcommittees (TACs) presented scoping reviews prepared for each form of EPTB to the core committee and methodology support team. This raised many potential points of equipoise that could be subject to formal evidence-informed guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process. From this process, the core committee identified priority topics cutting across several organ systems in EPTB for guideline development. These were the areas where systematic review of the evidence was feasible given the available study data and time and resource constraints, where there were current important dilemmas in what to recommend and where decisions could improve patient care and patient outcomes or had important resource implications. The committee viewed this guidelines process as an essential step in embedding evidence-based processes and part of a long-term vision for the country. There was also an appreciation that while the nature of the disease and the topics appeared clinical, all the decisions had potentially profound public health expenditure and management

Box 1. Steps in synthesizing the evidence used for the main guidelines

1. Identify the question (or objective) of the review
2. Identify the outcomes that are most important - to patients, to clinicians, to policymakers
3. Write a protocol setting out the inclusion criteria for the review - what studies will help to answer the question?
4. Two researchers then carry out steps 5 and 6 independently, to limit bias in the review process
5. Perform a structured search of the literature and screen the results using the inclusion criteria set out in the protocol - only include studies that can address the review question
6. Perform data extraction from each study using a pre-defined tool - find the data in the included studies that answer the question and describe each of the studies and their populations
7. Perform a risk of bias assessment of each study using a pre-defined tool - how reliable are the data from each study?
8. Resolve any discrepancies between the two researchers' data collection by discussion
9. Perform data synthesis that is appropriate - this could include performing a meta-analysis across studies, or simply describing the findings, depending on the level of heterogeneity between the studies and the types of studies included in the review
10. Summarize the findings in a Table and apply the GRADE criteria to assess the level of certainty and the applicability of the effects estimates

implications, as well as public health impacts in terms of improved outcomes.

The methodology support team, along with the members of TACs, prepared the evidence summaries for review by the guidelines panel between March and July 2015. As part of this process, existing systematic reviews were updated, and where no review was available, new systematic reviews were developed and carried out.

We limited our systematic reviews to areas where substantive evidence was available or there was an urgent priority for evidence-based clinical policy. Hence, the key questions covered in the evidence review were prepared (Table I).

The Core Committee recognized the need to revisit many of the topic areas identified in the scoping process for systematic evidence review to inform the next iteration of these guidelines.

Box 2. Summary of recommendations by INDEX-TB guidelines panel

Recommendations: Diagnosis of EPTB using the Xpert MTB/RIF test

Lymph node TB

(*i*) Xpert MTB/RIF should be used as an additional test to conventional smear microscopy, culture and cytology in FNAC specimens.
(*ii*) Strong recommendation, low-quality evidence for sensitivity estimate, high-quality evidence for specificity estimate.

TB meningitis

(*i*) Xpert may be used as an adjunctive test for TBM. A negative Xpert result on a CSF specimen does not rule out TBM. The decision to give ATT should be based on clinical features and CSF profile.
(*ii*) The conditional recommendation, low-quality evidence for sensitivity estimate, high-quality evidence for specificity estimate.

Pleural TB

(*i*) Xpert MTB/RIF should not be used to diagnose pleural TB.
(*ii*) Strong recommendation, low-quality evidence for sensitivity estimate, high-quality evidence for specificity estimate.

Recommendations: Adjunctive steroids in the treatment of EPTB

TB Meningitis

(*i*) Steroids are recommended for TB meningitis in HIV-negative people.
(*ii*) Duration of steroid treatment should be for at least four weeks with tapering as appropriate.
(*iii*) Strong recommendation, high-quality evidence.
(*iv*) Steroids may be used for TB meningitis in HIV-positive people, where other life-threatening opportunistic infections are absent.
(*v*) The conditional recommendation, very low-quality evidence.

TB Pericarditis

(*i*) Steroids are recommended for HIV-negative patients with TB pericarditis with pericardial effusion.
(*ii*) Conditional, low-quality evidence.
(*iii*) Steroids are recommended for HIV-positive patients with TB pericarditis with pericardial effusion.
(*iv*) Conditional, low-quality evidence.

Recommendations: Duration of treatment for EPTB

Lymph node TB

(*i*) Six-month ATT standard first-line regimen is recommended for peripheral lymph node TB.
(*ii*) Strong recommendation, low-quality evidence.

Abdominal TB

(*i*) Six-month ATT standard first-line regimen is recommended for abdominal TB.
(*ii*) Strong recommendation, very low-quality evidence.

TB meningitis

(*i*) TB meningitis should be treated with standard first-line ATT for at least nine months.
(*ii*) Conditional recommendation, very low-quality evidence.

FNAC, fine-needle aspiration cytology; ATT, antituberculosis treatment; TB, tuberculosis; CSF, cerebrospinal fluid; EPTB, extrapulmonary TB; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin

Table IIIA. Role of Xpert MTB/RIF in diagnosing lymph node tuberculosis

Recommendation	Xpert MTB/RIF should be used as an additional test to conventional smear microscopy, culture, and cytology in FNAC specimens
Strength of recommendation	Strong
Evidence	(*i*) Pooled sensitivity against culture 83.1 per cent (95% CI 71.4%-90.7%) (13 studies, 955 specimens with 362 culture-positive, low-quality evidence) (*ii*) Pooled specificity against culture 93.6 per cent (95% CI 87.9%-96.8%) (13 studies, 955 specimens with 362 culture-positive, high-quality evidence)[14] (*iii*) In a population of 1000 patients with presumptive LNTB where 200 truly have the disease, if treatment was determined only by GeneXpert: a) 166 (142-182) would be correctly treated for TB (low-quality evidence) b) 34 (58-18) with TB would be missed (low-quality evidence) c) 48 (96-24) without TB would be treated (high-quality evidence)
Advantages of using the test	(*i*) Quicker diagnosis (*ii*) May lead to fewer patients being treated with ATT when they do not have LNTB (no direct evidence available) (*iii*) Reduced stigma from reduction in overtreatment (*iv*) May identify rifampicin resistance (evidence not formally reviewed)
Disadvantages of using the test	(*i*) Patients with false negative Xpert results may have ATT withheld or stopped inappropriately (*ii*) False negatives may go onto develop disseminated disease (*iii*) False positives exposed to ATT unnecessarily (*iv*) May falsely diagnose rifampicin resistance - harm to patient from side effects of second-line drugs and high cost (*v*) Cost implications of managing missed cases (repeat diagnostic sampling, repeat hospital/ clinic visits) (*vi*) Stigma for patients given a false positive diagnosis (*vii*) Litigation for misdiagnosis
Explanatory notes	The guidelines group considered the evidence for the diagnostic accuracy of Xpert MTB/RIF in lymph node specimens obtained by fine needle aspiration and biopsy. In making the recommendation, the group considered the context of a district-level healthcare centre, acknowledging that the current basis for diagnosis of LNTB under the RNTCP is cytological examination and smear microscopy for acid-fast bacilli of fine needle aspirate from an affected lymph node (FNAC). The group considered whether there was sufficient evidence to recommend that Xpert MTB/RIF replace FNAC as the principle diagnostic test and concluded that this would be inappropriate given the fact that one in five patients is missed by Xpert MTB/RIF. The group agreed that Xpert MTB/RIF can be useful in confirming a diagnosis in patients suspected of LNTB when considered alongside the results of FNAC, noting that a negative Xpert MTB/RIF test does not rule out LNTB. Diagnostic investigations should be carried out in the context of care quality that can assure patient safety, in line with the guidelines' principles 3 and 4. Xpert MTB/RIF is of use where clinicians have appropriate expertise in carrying out diagnostic sampling from lymph nodes safely and accurately and where there is access to Xpert MTB/RIF testing in a laboratory with adequate quality assurance.

ATT, antituberculosis treatment; TB, tuberculosis; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin; FNAC, fine-needle aspiration cytology; LNTB, lymph node tuberculosis; CI, confidence interval

Details of the methods used in the preparation of each review are laid out in chapter 2 of the main guidelines document[3-5]. The general principles of systematic review followed those set out in the Cochrane Handbook[6] (Box 1). Evidence summaries were produced by members of the TAC and the methodology support team and presented to the guidelines panel at the second meeting in July 2015. The guidelines panel considered the evidence in accordance with the GRADE criteria and decided on recommendations by consensus.

The guidelines process adhered to the GRADE criteria[7] to produce a set of recommendations that were explicitly linked to the evidence they were based on, with consideration given to the various healthcare settings across India. The use of GRADE was in line with the WHO Handbook for Guideline Development[8].

Table IIIB. Role of Xpert MTB/RIF in diagnosing tuberculous meningitis

Recommendation	Xpert may be used as an adjunctive test for TBM. A negative Xpert result does not rule out TBM. Decision to give ATT should be based on clinical features and CSF profile
The strength of recommendation	Conditional
Evidence	(*i*) Pooled sensitivity against culture 80.5 per cent (95% CI 59.0-92.2%) (13 studies, 839 specimens with 159 culture-positive, low-quality evidence) (*ii*) Pooled specificity against culture 97.8 per cent (95% CI 95.2-99.0%) (13 studies, 839 specimens with 159 culture-positive, high-quality evidence)[14] (*iii*) In a population of 1000 patients with presumptive TB meningitis where 100 truly have the disease, if treatment was determined only by Xpert MTB/RIF result: a) 81 (59-92) would be correctly treated for TB (low-quality evidence) b) 19 (41-8) with TB would be missed (low-quality evidence) c) 18 (45-9) without TB would be treated (high-quality evidence)
Advantages of using the test	(*i*) If Xpert is positive, it is highly likely to be TBM - this could increase access to a reliable diagnosis (*ii*) Quick result (*iii*) Already widely available
Disadvantages of using the test	(*i*) High number of false negatives - significant concern that this could lead to missed or delayed diagnosis although direct evidence of the impact of Xpert MTB/RIF test results on patient outcomes in TBM is lacking (*ii*) Delayed diagnosis leads to worse outcomes (death) (*iii*) Additional costs
Explanatory notes	The group noted that the stakes were high in the diagnosis of TB meningitis due to the high mortality associated with this disease, particularly when the diagnosis was delayed. Although the sensitivity of smear microscopy of CSF specimens is extremely low and Xpert MTB/RIF has a higher sensitivity than this test, the fact that one in five patients with TB meningitis is missed by Xpert MTB/RIF raised concerns that patients could be harmed by delayed treatment if clinicians relied on a negative result. The guidelines panel concluded that as Xpert MTB/RIF is not sufficiently sensitive for TB meningitis, the decision to give or withhold ATT should not be based on a negative Xpert result alone. A positive Xpert MTB/RIF result may be reassuring due to the high specificity of the test, but it should only be used as an adjunct to other diagnostic methods. A concentration step in the processing of CSF before using Xpert MTB/RIF appears to increase the sensitivity of the test. In a subgroup analysis, a concentration step involving centrifugation and resuspension of the sample appeared to enhance the sensitivity of Xpert [84.2% (95% CI 78.3-90.1%) versus 51.3% (95% CI 35.5-67.1%) for unconcentrated samples; specificity 98.0% (95% CI 96.7-99.2%) versus 94.6% (95% CI 90.9-98.2%) for unconcentrated samples].

ATT, antituberculosis treatment; TB, tuberculosis; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin; CI, confidence interval; CSF, cerebrospinal fluid; TBM, tuberculous meningitis

The GRADE criteria require that:

(*i*) Quality of evidence, as well as the effect estimate, is clearly defined.

(*ii*) Risk of bias of the relevant studies, directness of evidence, consistency of results, precision and other sources of bias in the available evidence are considered and reported for each important outcome.

(*iii*) Evidence summaries are used as the basis for judgments about the quality of the evidence and the strength of recommendations.

(*iv*) The balance of desirable and undesirable consequences, quality of evidence, values and preferences should be considered and reported when deciding on the strength of a recommendation.

(*v*) The strength of recommendations should be clearly reported and defined.

After the guidelines panel made the recommendations, the writing committee put together the guidelines document. Part of this process included the collation of expert opinion-based advice for clinicians on aspects of EPTB diagnosis and treatment not covered by the evidence-informed recommendations in a compendium of clinical practice points. These were based on the expert opinion of senior clinicians in medicine and surgery from across India and provided a basis for further refinement in evidence-informed guidelines development in future. This section of the

guidelines seeks to address all aspects of diagnosis and treatment of EPTB and should be used as a reference.

Principles of extrapulmonary tuberculosis (EPTB) care

In line with the International Standards of TB Care[9], the guidelines group as a whole agreed on a set of principles about what every EPTB patient in India needs as a basic standard of care. These principles relate to a basic standard of care that all providers should seek to achieve, a complementary set to the Standards for TB Care in India[9] and the recently developed technical operational guidelines for pulmonary TB in 2016[10]. The principles are detailed in Table II.

Summary of recommendations

Box 2 provides the evidence-based recommendations made by the INDEX-TB guidelines panel. Tables III-V contain summaries of the evidence-to-decision process. The evidence summaries considered by the panel are available on the ICMR website[11].

Evidence to decision

Xpert MTB/RIF for EPTB

Xpert MTB/RIF is a commercially available diagnostic test for *M. tuberculosis* complex (MTB), which uses polymerase chain reaction (PCR) to test specimens for genetic material specific to MTB, and simultaneously detects a gene which confers resistance to rifampicin, *rpoB*[12]. It is manufactured by Cepheid, Sunnyvale, California, USA. Unlike other commercial PCR-based tests, it is a fully automated test using the GeneXpert® platform. The specimen is loaded into a cartridge, and all the steps in the assay are fully

Table IIIC. Role of Xpert MTB/RIF in diagnosing pleural tuberculosis

Recommendation	Xpert MTB/RIF should not be used to diagnose pleural TB
Strength of recommendation	Strong
Evidence	(*i*) Pooled sensitivity against culture 46.4% (95% CI 26.3-67.8%) (14 studies, 841 specimens with 92 culture-positive, low-quality evidence) (*ii*) Pooled specificity against culture 99.1% (95% CI 95.2-99.8%) (14 studies, 841 specimens with 92 culture-positive, high-quality evidence) (*Source*: Ref 14) (*iii*) In a population of 1000 patients with presumptive pleural TB where 200 truly have the disease, if treatment was determined only by Xpert MTB/RIF results: a) 92 (52-136) would be correctly treated for TB (low-quality evidence) b) 108 (148-64) with TB would be missed (low-quality evidence) c) 8 (40-0) without TB would be treated (high-quality evidence)
Committee's view on advantages of using the test	(*i*) If Xpert is positive, it is highly likely to be pleural TB - this could increase access to a reliable diagnosis although direct evidence of the impact of Xpert MTB/RIF test results on patient outcomes in pleural TB is lacking (*ii*) May help in avoiding invasive procedures such as pleural biopsy (closed and thoracoscopic) (*iii*) Quick result (*iv*) Already widely available
Committee's view on disadvantages of using the test	(*i*) High number of false negatives - significant concern that this could lead to missed or delayed diagnosis although direct evidence of the impact of Xpert MTB/RIF test results on patient outcomes in pleural TB is lacking (*ii*) Delayed diagnosis leads to worse outcomes (pleural thickening, impaired lung function, active pulmonary TB) (*iii*) Additional costs
Explanatory notes	Although the pooled estimate of specificity was high, the sensitivity of Xpert MTB/RIF in pleural fluid specimens was very low, with more than half of all pleural TB patients being missed by this test. The guidelines panel felt that although a positive Xpert result might help if the diagnosis was unclear, there were concerns regarding possible harm to patients associated with reliance on this test, whether the result was positive or negative. Anecdotally, some group members described patients they had treated who had positive Xpert results and were started on ATT but also had malignancy, diagnosis of which was delayed as the positive Xpert test had led to a diagnosis of pleural TB.

ATT, antituberculosis treatment; TB, tuberculosis; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin; CI, confidence interval

Table IVA. Role of corticosteroids in treating tuberculosis meningitis in HIV-negative people

Recommendation	Steroids are recommended for TB meningitis in HIV-negative people. Duration of steroid treatment should be for at least four weeks with tapering as appropriate
Strength of recommendation	Strong
Evidence	(*i*) Corticosteroids reduce death from TB meningitis from 41/100 people to 31 (27-36) per 100 people (9 studies, 1318 participants, high-quality evidence). These studies were conducted in a variety of settings, and only one included HIV-positive people (n=98) (*ii*) Disabling neurological deficit is not common in survivors, and steroids may have little or no effect on this outcome (RR 0.92, 95% CI 0.71-1.20%; eight trials, 1295 participants, low-quality evidence)
Committee's view on advantages of using steroids	Reduced mortality from TBM
Committee's view on disadvantages of using steroids	(*i*) Adverse effects of steroids such as gastrointestinal bleeding, bacterial infection, high blood pressure and high blood sugar (*ii*) Increased numbers of survivors with severe disability although the evidence from the review does not support this
Explanatory notes	
The group reviewed the results of the systematic review. The main findings of the review are stated above. The panel considered the evidence relevant and applicable to the Indian context, noting that three of the eight studies included were carried out in India, with three others carried out in Southeast Asia. The group noted that the effects may be greater for patients with British MRC stage I and II, which indicate mild and moderate severity in TBM, but the recommendation should stand for all TBM patients[16]. MRC staging is explained in the Clinical Practice Points, Section 2-CNS TB[3]. Duration of corticosteroids was discussed. The group agreed that there was no clear evidence for any one regimen of steroids and debated what the best option would be. The expert group agreed that steroids should be given for at least four weeks and then tapered. Some patients may need longer treatment with steroids, up to six or eight weeks, and decision to extend the course of steroids should be made on the basis of disease severity and presence of complications of TBM.	

MRC, Medical Research Council; CNS, central nervous system; TB, tuberculosis; TBM, tuberculous meningitis; CI, confidence interval; RR, relative risk

automated and contained within the unit. One of the reagents is powerfully tuberculocidal, making the used test cartridges safe to handle outside of a specialist laboratory environment. This allows the test to be brought closer to the clinical setting.

Xpert MTB/RIF was originally designed to test sputum samples from patients with active pulmonary TB and had been shown to have high accuracy for diagnosing TB in these patients[13]. Several investigators have tested the diagnostic test accuracy of Xpert MTB/RIF in non-respiratory specimens for the diagnosis of various forms of EPTB and have shown that accuracy varies considerably with specimen type and bacillary load. For this evidence summary, a systematic review carried out by Denkinger *et al*[14] was used. In this review, diagnostic test accuracy studies using Xpert MTB/RIF and culture for the diagnosis of *M. tuberculosis* infection in three forms of EPTB were summarized, with pooled estimates of sensitivity and specificity[14]. As there was little data on sensitivity and specificity of Xpert MTB/RIF for the diagnosis of rifampicin resistance, this was not addressed in this review and hence has not been addressed within these recommendations. To ensure that the guidelines group was able to make recommendations based on the most up-to-date information, a summary of studies published since this review was undertaken in 2013 was also presented to the guidelines group.

The decision-making process for each of the recommendations on Xpert MTB/RIF is summarized in Tables IIIA-C. The evidence summaries and decision tables used by the guidelines panel are available in the complete guidelines document[3].

Corticosteroids in EPTB

The guidelines panel considered evidence from the updated Cochrane review on corticosteroids for managing tuberculous meningitis (TBM)[15]. The evidence considered for various decisions on the use of corticosteroids is provided in Tables IVA-E.

The guideline group considered the evidence separately for HIV-negative and HIV-positive individuals because HIV co-infection is associated with particular complications of TBM disease and particular adverse events associated with steroid use.

Table IVB. Role of corticosteroids in treating tuberculous meningitis in HIV-positive people

Recommendation	Steroids may be used for TB meningitis in HIV-positive people, where other life-threatening opportunistic infections are absent
Strength of recommendation	Conditional
Evidence	(*i*) Corticosteroids reduce death from TB meningitis from 41/100 people to 31 (27-36)/100 people (9 studies, 1318 participants, high-quality evidence) (*ii*) Eight out of the nine studies either excluded HIV-positive people or did not report HIV status. One study included 98 HIV-positive people of 545 participants[17]. A subgroup analysis showed that corticosteroids had no effect on mortality in this group (RR 0.90, 95% CI 0.67-1.20%), although this result should be interpreted with caution as the authors did not stratify the randomization by HIV status, and the number of HIV-positive participants is small (*iii*) The very small numbers of events reported in this single study for the outcome disabling neurological deficit mean that we do not know what the effect of corticosteroids is in HIV-positive people for this outcome
Committee's view on advantages of using steroids	Reduced mortality from TBM
Committee's view on disadvantages of using steroids	(*i*) Adverse effects of steroids such as gastrointestinal bleeding, bacterial infection, high blood pressure and high blood sugar (*ii*) Increased numbers of survivors with severe disability (*iii*) Increased morbidity and mortality from opportunistic infections and HIV-associated cancers (*iv*) Increased adverse drug reactions and interactions with ARVs
Explanatory notes	The group was concerned about the lack of evidence for the use of steroids in people with HIV and TBM. There are circumstances where steroids are clearly indicated, for example, in cases of raised intracranial pressure/mass effect from a tuberculoma. Steroids are associated with increased risk of serious, life-threatening opportunistic infections in patients with advanced HIV disease. The criteria to be taken into account are stage of TBM disease, evidence of raised intracranial pressure or mass effect, CD4 cell count, and presence or absence of other opportunistic infections. Giving long courses of steroids in patients with HIV may be undesirable, especially in patients with advanced HIV disease. Specialist advice in managing such cases is warranted. Important opportunistic infections to rule out include cryptococcal meningitis and cerebral toxoplasmosis. There is evidence that steroids are associated with increased adverse events and disability in patients with HIV-associated cryptococcal meningitis[18].

TB, tuberculosis; TBM, tuberculous meningitis; CI, confidence interval; RR, relative risk; ARVs, antiretrovirals

The guidelines group reviewed evidence summarized from the updated Cochrane review[15].

Interventions for treating tuberculous pericarditis[20]

The group considered the evidence for HIV-positive people with TB pericarditis separately, principally because there was a concern about corticosteroids leading to increased risk of HIV-associated adverse events.

Corticosteroids in treating pleural TB

Pleural TB is one of the most common forms of EPTB. Characterized by pleural effusion, it usually resolves without treatment of any kind, but untreated patients may experience longer duration of the acute symptoms and risk recurrence of active TB at a later point in time[21]. Pleural TB can be complicated by massive effusion leading to respiratory compromise in the short term and pleural thickening, fibrosis and pleural adhesions causing impaired respiratory function in the medium to long term.

Pleural TB is thought to be caused by a delayed-type (type IV) hypersensitivity reaction, following mycobacterial infection of the pleura[22]. This explains the tendency towards resolution of the effusion and associated symptoms with or without treatment of the TB infection. There appears to be a spectrum of disease in pleural TB in terms of the extent of the underlying lung infection, which could be important in terms of patient outcomes and the potential for corticosteroids to be effective. The extent of underlying lung infection seems to be an important determinant of outcome[23].

This review was conducted because there was uncertainty about the efficacy of corticosteroids in reducing the short-term and long-term effects on the acute symptoms of pleural TB and the long-term sequelae. Steroids are associated with several adverse effects, especially in people with HIV, and administering them in the absence of evidence of efficacy may be exposing patients to unnecessary risk.

Table IVC. Role of corticosteroids in treating tuberculous pericarditis in HIV-negative people

Recommendation	Steroids are recommended for HIV-negative patients with TB pericarditis with pericardial effusion
Strength of recommendation	Conditional
Evidence	(*i*) The review included six studies, all from Sub-Saharan Africa (*ii*) The majority of the participants in these trials were HIV positive; these estimates are based on disaggregated data for HIV-negative participants where possible (*iii*) Corticosteroids may have no effect on all-cause mortality (RR 0.85, 95% CI 0.64-1.11%, 810 participants, 3 studies, low-quality evidence) but probably reduce death from pericarditis (RR 0.55, 95% CI 0.31-0.98%, 810 participants, 3 studies, moderate-quality evidence) (*iv*) Corticosteroids may have no effect on progression to constrictive pericarditis (RR 0.62, 95% CI 0.35-1.1%, 431 participants, 1 study, low-quality evidence) (*v*) The guideline group further downgraded the quality of the evidence by one for indirectness as all the studies took place in Sub-Saharan Africa and because the HIV status of some participants was uncertain (*iv*) Most of the data came from one large trial in mainly HIV-positive patients. Steroids were associated with more people developing cancer, mainly HIV-related cancers. The authors noted that some of these patients also received immunotherapy with *M. indicus pranii*.
Committee's view on advantages of using steroids	(*i*) Increased survival although the results of the systematic review do not support this (*ii*) Reduced incidence of constrictive pericarditis (*iii*) Reduced need for pericardiectomy although the review did not find clear evidence of this (*iv*) Reduction of ATT-associated adverse effects although the results of the systematic review do not support this
Committee's view on disadvantages of using steroids	(*i*) Adverse effects of steroids such as gastrointestinal bleeding, bacterial infection, high blood pressure and high blood sugar (*ii*) Increased numbers of survivors with severe disability due to constrictive pericarditis
Explanatory notes	The group noted that the effects estimates in the review suggest that steroids have little or no effect on all-cause mortality but probably reduce mortality from TB pericarditis. The largest study (which had one-third HIV-negative participants) showed a reduction in the number of participants with constrictive pericarditis at the end of treatment in the analysis of all patients. The GRADE tables are based on data disaggregated into people that are HIV positive and HIV negative. Both these analyses give point estimates that show reduced risk of constrictive pericarditis with steroids, although the disaggregation means that in the smaller group of patients who are HIV negative, this is not significant. The group felt that risk of constrictive pericarditis and associated morbidity was the most important outcome, and this was the basis of the recommendation. The recommendation, therefore, only relates to steroid use in patients who present with pericardial effusion caused by TB pericarditis; the group did not recommend steroids for patients presenting with constrictive TB pericarditis.

M. indicus, *Mycobacterium indicus*; ATT, antituberculosis treatment; TB, tuberculosis; CI, confidence interval; RR, relative risk

Duration of treatment in EPTB

Duration of treatment in peripheral lymph node tuberculosis (LNTB)

Lymph node tuberculosis can present with the involvement of peripheral, mediastinal and/or abdominal lymph nodes as well as enlarged lymph nodes perceivable clinically or visualized on chest X-ray, abdominal ultrasound scan or computed tomography, and clinical features sometimes include weight loss, fever and night sweats. The problem of persistently enlarged lymph nodes at the end of treatment has vexed clinicians and some practitioners extend treatment duration in such patients, fearing relapse of active TB disease in this group. The evidence for the decisions are provided in Tables VA-C.

Duration of treatment in abdominal TB

Abdominal TB can present with isolated involvement of any of the following sites: peritoneal, intestinal, upper gastrointestinal (oesophageal, gastroduodenal), hepatobiliary, pancreatic and perianal. The clinical features as well as diagnostic modalities depend on the site of involvement. Internationally, most guidelines recommend treating all types of abdominal TB with the same regimen as for pulmonary TB – a two-month intensive phase with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) followed by a four-month continuation phase with isoniazid and rifampicin. However, the evidence base for this practice is extrapolated from the studies of pulmonary

Table IVD. Role of corticosteroids in treating tuberculous pericarditis in HIV-positive people

Recommendation	Steroids are recommended for HIV-positive patients with TB pericarditis with pericardial effusion
Strength of recommendation	Conditional
Evidence	(*i*) The review included four studies all from sub-Saharan Africa (*ii*) The majority of the participants in these trials were HIV positive; these estimates are based on disaggregated data for HIV-positive participants where possible (*iii*) Corticosteroids may have no effect on all-cause mortality (RR 1.14, 95% CI 0.88-1.49%, 997 participants, 2 studies, low-quality evidence), or on death from pericarditis (RR 1.33, 95% CI 0.68-2.62%, 939 participants, 1 study, low-quality evidence) (*iv*) Corticosteroids probably reduce progression to constrictive pericarditis (RR 0.51, 95% CI 0.28-0.94%, 997 participants, 2 studies, moderate quality evidence) (*v*) Corticosteroids may have no effect on HIV-associated opportunistic infections over two years follow-up (RR 1.12, 95% CI 0.82-1.53%, 939 participants, 1 study, low-quality evidence). These may increase the risk of HIV-associated cancer over two years follow up, but the information was from one trial and participants also received *M. indicus pranii* which might have confounded the result[19]
Committee's view on potential advantages of using steroids	(*i*) Increased survival although the results of the systematic review do not support this (*ii*) Reduced incidence of constrictive pericarditis (*iii*) Reduced need for pericardiectomy although the review did not find clear evidence of this (*iv*) Reduction of ATT-associated adverse effects although the review did not find clear evidence of this
Committee's view on potential disadvantages of using steroids	(*i*) Adverse effects of steroids such as gastrointestinal bleeding, bacterial infection, high blood pressure and high blood sugar (*ii*) Increased adverse events associated with HIV such as opportunistic infections and cancer (*iii*) Increased numbers of survivors with severe disability
Explanatory notes	As for HIV-negative people, the group considered the outcome of greatest clinical significance to be risk of constrictive pericardial disease following TB pericarditis. Again, the group recognized that there was a lack of evidence of effect on mortality. The evidence for steroids increasing the risk of HIV-associated cancers was also considered. The group felt that this may be of less concern in India as the epidemiology of HIV-associated diseases is different compared with Africa, notably prevalence of Kaposi's sarcoma is low. The group concluded that the priority was to reduce rates of constrictive pericardial disease as this is associated with long-term morbidity and the need for invasive surgery (pericardiectomy) for patients, and high cost and resource use for the healthcare system. Therefore, they made a conditional recommendation to use steroids in HIV-positive people with TB pericarditis with pericardial effusion. Steroids may be even more risky in patients with advanced HIV disease with low CD4 cell counts and may increase the risk of opportunistic infections and HIV-associated cancers. This risk needs to be balanced with the risk of constrictive pericarditis in HIV-positive people with TB pericarditis.

M. indicus, *Mycobacterium indicus*; ATT, antituberculosis treatment; TB, tuberculosis; CI, confidence interval; RR, relative risk

TB cases, and direct evidence for the optimum duration of treatment in abdominal TB has been lacking.

Shorter duration of treatment may increase compliance, leading to reduced numbers of relapses as well as the emergence of drug resistance strains. Furthermore, shorter regimens decrease the risk of anti-tubercular drug toxicity. Whether six-month regimen achieves successful treatment rates as good as with nine-month regimen without significantly increasing the number of relapses is the key concern for accepting a shorter antitubercular treatment (ATT) regimen. The present review aims to evaluate the effects of treatment with the six-month regimen as compared to the nine-month regimen for abdominal TB.

Duration of treatment in tuberculous meningitis

TBM constitutes a medical emergency, and it is essential to start ATT as soon as it is suspected to reduce rapidly progressing, life-threatening outcomes. In contrast to pulmonary TB, there is a lack of standardized international recommendations for treating TBM. This is partly due to the limited existing evidence regarding the optimal choice and dose of antitubercular drugs, as well as the most appropriate duration of treatment for this form of EPTB.

Two main arguments have led to the perception that longer treatment (than for pulmonary TB) is needed for TBM to bring about microbiological cure and prevent relapse. The first one is that the blood–brain barrier

Table IVE. Role of corticosteroids in pleural tuberculosis

Recommendation	Steroids are not routinely recommended in pleural TB
Strength of recommendation	Conditional
Evidence	(*i*) The review included four studies all from Sub-Saharan Africa (*ii*) The majority of the participants in these trials were HIV positive (*iii*) Corticosteroids may reduce pleural effusions at four weeks (RR 0.76, 95% CI 0.62-0.94%, 394 participants, 3 studies, low-quality evidence), but we do not know whether corticosteroids have an effect on resolution of pleural effusion at eight weeks (RR 0.72, 95% CI 0.46-1.12%, 399 participants, 4 studies, very low-quality evidence) (*iv*) Corticosteroids may reduce pleural thickening at the end of follow up (RR 0.69, 95% CI 0.51-0.94%, 309 participants, 4 studies, low-quality evidence) (*v*) Corticosteroids may increase the risk of adverse events (RR 2.80, 95% CI 1.12-6.98%, 586 participants, 6 studies, low-quality evidence) (*vi*) This review found insufficient data to estimate the effect of corticosteroids on respiratory function (*vii*) The reviewers deemed it inappropriate in this case to attempt to generate separate estimates for HIV-positive and HIV-negative people due to a lack of disaggregated data
Committee's view on potential advantages of using steroids	(*i*) Faster recovery (*ii*) Reduced chest X-ray changes at the end of treatment (*iii*) Return to baseline lung function (*iv*) Reduced long-term pulmonary disability
Committee's view on potential disadvantages of using steroids	(*i*) Adverse effects of steroids such as gastrointestinal bleeding, bacterial infection, high blood pressure and high blood sugar (*ii*) The risk of adverse events, such as HIV-related cancer, due to further immunosuppression in HIV-positive people
Explanatory notes	Pleural TB is not associated with high mortality; therefore, the group felt that the most important outcome to consider was respiratory function. The review found insufficient data addressing this outcome, and the group felt that the outcomes reported in the review were not appropriate proxy measures for this outcome. The group noted that chest X-ray appearance at the end of treatment may be important to some patients for social or financial reasons, but otherwise, pleural thickening causing chest X-ray changes was not a clinically relevant outcome. Given a lack of evidence of effect on respiratory function and the risks associated with steroid use, the group made a conditional recommendation against the use of steroids for pleural TB.

TB, tuberculosis; CI, confidence interval; RR, relative risk

hinders the penetration of antitubercular drugs to reach adequate drug concentration in the infected site. The second one concerns relapse rates. When assessing pulmonary TB regimens, relapse rates of 5 per cent are generally considered acceptable[24]. However, relapse of TBM is fearsome as it is a life-threatening condition and can lead to severe neurodisability. Thus, whether any risk of relapse is tolerable for TBM is to be considered when establishing TBM regimens. However, longer ATTs reduce compliance and increase drug toxicity and costs[25].

The standard first-line regimen for drug-sensitive TBM, according to the WHO guidelines[26], is a two-month intensive phase with isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin followed by a 10-month continuation phase with isoniazid and rifampicin (2HRZE or S/10HR). Several different regimens are used in the current practice, with variations regarding doses, selection of the fourth drug and duration of treatment from six to more than 24 months. There are variations in practice regarding the number of drugs used in both the intensive and continuation phases. As an example, the South African regimen consists of a six-month intensive course with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) with no continuation phase. A study reviewing the duration of treatment for TBM by comparing case series of both adults and children showed similar completion and relapse rates between six-month treatment regimens including at least isoniazid, rifampicin and pyrazinamide and longer treatment[25].

Given the potentially devastating outcomes of relapse on one hand, and the disadvantages of long therapy on the other hand, we performed a systematic review of literature in an attempt to establish the most appropriate duration of treatment for TBM.

Table VA. Duration of antituberculosis treatment for lymph node tuberculosis

Recommendation	Six months ATT standard first-line regimen (2RHZE/4RHE) is recommended for peripheral lymph node TB
Strength of recommendation	Strong
Evidence	(*i*) The review included two randomized controlled trials, one from multiple secondary care hospitals in the United Kingdom and another from a single tertiary care hospital in Hong Kong, China. Participants were adults and adolescents with newly diagnosed peripheral and mediastinal LNTB, and HIV status was not reported in either study (*ii*) There may be no difference between six-month and nine-month ATT regimens in terms of relapse rates (RR 0.89, 95% CI 0.37-2.16%, 253 participants, 2 studies, low-quality evidence). There is probably no difference between six-month and nine-month ATT regimens in terms of successful treatment at the end of follow up (21-55 months) (RR 1.11, 95% CI 0.97-1.26%, 312 participants, 2 studies, moderate-quality evidence) (*iii*) A review of five prospective cohort studies (706 participants) where patients with residual lymphadenopathy at the end of ATT were followed up demonstrated that relapse in this subgroup of patients was uncommon - six cases of relapse were reported across all studies
Committee's view on advantages of six months treatment	(*i*) Cure rates and relapse rates are similar in the data collected for six months and nine months (low-quality evidence) (*ii*) Patients more likely to complete shorter regimens (*iii*) Less exposure to adverse effects of ATT
Committee's view on disadvantages of six months treatment	Theoretically risk of relapse higher with shorter regimens, but existing evidence is unclear
Explanatory notes	
The guidelines group considered evidence from randomized controlled trials comparing six months with nine months ATT in terms of outcomes such as relapse after completion of ATT, treatment completion and default. The group noted that the rates of relapse in the six months and nine-month groups were similarly very low although there were concerns that the pooled data were still not sufficiently powered to detect a difference in this uncommon event. The group noted that all the evidence pertained to peripheral LNTB and that other factors needed to be taken into consideration for patients with mediastinal or abdominal LNTB or disseminated TB. No recommendation was made regarding treatment duration in these patients. A subgroup of patients, dubbed partial responders, have persisting small volume lymphadenopathy (<1 cm) at the end of treatment. The group agreed that the available evidence suggests that a few partial responders appear to relapse and that these patients generally do not require extension of ATT and can be managed by observation only. Further evidence is required to make firm recommendations for this particular group. While this recommendation applied to adults and children with LNTB, the group noted that the evidence only relates to adults and adolescents, and hence, providers treating children should bear in mind that this recommendation is based on indirect evidence for children.	

TB, tuberculosis; CI, confidence interval; RR, relative risk; ATT, antituberculosis treatment; LNTB, lymph node tuberculosis

Research priorities and future update of the guidelines

The scoping process that informed the choice of priority topics for these guidelines also highlighted many other areas of uncertainty and variation in practice which could benefit from further research. The main guidelines document contains a list of topics identified by the guidelines panel as priority areas for further research[3]. In addition, the process highlighted the need for standardized case definitions and outcome definitions in all forms of EPTB.

The core committee and Government of India recognized that these guidelines represented the start of a process of developing evidence-informed EPTB guidelines in India and this would be further developed over time. There was a commitment to updating aspects of these guidelines in the next three to six years, by which time these topics would be revisited and additional priority topics considered.

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Table VB. Duration of antituberculosis treatment for abdominal tuberculosis

Recommendation	Six-month ATT standard first-line regimen is recommended for abdominal TB
Strength of recommendation	Strong
Evidence	The review included three randomized controlled trials, two from India and one from South Korea, with 328 participants. One trial included both gastrointestinal TB and peritoneal TB patients, and the other two included gastrointestinal TB patients only. None of the studies included children or HIV-positive people. We do not know whether there is a difference in relapse rates between patients treated for six months and those treated for nine months (RD 0.01, 95% CI−0.01-0.04%, 328 participants, 3 studies, very low-quality evidence)
Committee's view on advantages of six months treatment	(*i*) Patients more likely to complete shorter regimens (*ii*) Less exposure to adverse effects of ATT
Committee's view on disadvantages of six months treatment	Theoretically risk of relapse higher with shorter regimens, but existing evidence does not support this
Explanatory notes	
The guidelines group reviewed the evidence and felt that for new patients with abdominal TB and with low risk of drug resistance, six months ATT followed by a period of observation was appropriate. The group recognized the paucity of data to answer this question but noted particularly that there were very few relapses in both arms across all studies. The group noted that the available evidence came from patients with gastrointestinal and peritoneal TB patients, and was concerned that other forms of abdominal TB, while comparatively rare, may require different management. The group agreed that some patients may require extension of ATT and the need for this should be assessed by the treating clinician, with particular regard to the patient's total ATT dosing. The gastroenterologists in the group pointed out that some patients have lasting sequelae which may cause symptoms mimicking relapse of abdominal TB or failed treatment. It is important to differentiate these patients, who have peritoneal adhesions or luminal strictures, from patients with active TB disease. Continued ATT in these patients is not required and could be harmful.	

TB, tuberculosis; CI, confidence interval; ATT, antituberculosis treatment; RD, risk difference

Table VC. Duration of antituberculosis treatment for tubercular meningitis

Recommendation	TB meningitis should be treated with standard first-line ATT for at least nine months
Strength of recommendation	Conditional
Evidence	The review included six observational (cohort) studies, with two reporting a comparison between short (six- to nine-month regimens) and long (12 months or more) regimens. The studies were from a variety of settings: Turkey, Ecuador, Papua New Guinea, South Africa and two from Thailand. None reported the HIV status of the participants who were a mix of adults and children. As the data were from a highly heterogeneous set of observational studies, a meta-analysis was not performed. The data were presented to the group in a Table demonstrating the absolute numbers of relapsed cases, defaulters, all-cause deaths and deaths after six-month treatment across all studies. The evidence was graded as very low quality.
Committee's view on advantages of shorter treatment	(*i*) Patients are more likely to complete shorter regimens (*ii*) Less exposure to adverse effects of ATT (*iii*) Low numbers of relapses (*iv*) Good cure rates
Committee's view on disadvantages of shorter treatment	(*i*) Longer ATT regimens are associated with poor compliance (*ii*) Longer regimens expose patients to increased risk of adverse effects of ATT (*iii*) Concern that shorter regimens may increase the risk of relapse, leading to death or disability
Explanatory notes	
The group recognized that there was very low-quality evidence for the use of six to nine months versus 12 months or longer ATT in TB meningitis. There is considerable variation in existing guidelines, with the WHO currently recommending 12 months and the RNTCP recommending nine months for adults and 12 months for children. There is also considerable variation in the current clinical practice, with some clinicians reporting that they are happy to treat for nine months while others are treating for 12 or 18 months as a minimum. The neurologists in the group were particularly concerned about this question, highlighting that this is an area of clinical equipoise. The paediatricians present were also concerned as TBM disproportionately affects children and is an important cause of childhood mortality and disability. The key factors dictating mortality in TB meningitis may be early treatment and the use of corticosteroids, and the role of treatment duration remains unclear. Extension of ATT may sometimes be indicated, and this should be assessed by the treating clinician on a case-by-case basis. There was disagreement about the optimum duration of treatment, with some group members arguing that 12 months should be the minimum duration recommended; however, the final recommendation was the consensus view of the group. All group members recognized that there was a need for high-quality, large-scale randomized trials to answer this question.	

TB, tuberculosis; ATT, antituberculosis treatment; RNTCP, Revised National TB Control Programme; WHO, World Health Organization

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