

# Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

## Treatment of Pulmonary Tuberculosis: What Every GP Should Know

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### Abstract

*Nearly 50% of patients with TB in India are treated in the private sector. GPs therefore share the responsibility of TB control in India, and play a major role in preventing the spread of the disease by curing patients and arresting transmission. Every GP will need to consider TB as a differential diagnosis in persons with cough lasting two weeks or more, or with abnormal findings on chest radiography. In such patients, TB must first be microbiologically confirmed, either using sputum smear microscopy, Xpert MTB/RIF (i.e., GeneXpert), or liquid cultures. Once TB is confirmed, the next step is to begin the correct anti-tuberculosis therapy (ATT) regimen, as recommended by Standards for TB Care in India (STCI) and the International Standards for TB Care (ISTC). All patients who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen for a total of 6 months. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of isoniazid and rifampicin given for 4 months (ethambutol can also be added to the continuation phase in areas with high levels of isoniazid resistance). Treatment can be given daily or as thrice-weekly intermittent dosing. Adherence to the full course of ATT is very important to ensure high cure rates and to prevent the emergence of drug-resistance. If patients have any risk factors for drug-resistance, or do not respond to standard ATT, they must be investigated for MDR-TB using drug-susceptibility tests (DST) like GeneXpert, line probe assays, and liquid cultures. MDR-TB requires long-term and specialized treatment. So, patients should be referred to chest specialists, either in the private sector, or in the public sector where free MDR treatment is available.*

Key words: tuberculosis; treatment; drug regimen; adherence

### INTRODUCTION

Previous articles in this series have covered various aspects of TB, including laboratory and radiological diagnosis.<sup>1,4</sup> Given the high incidence of TB in India, every GP in India must have a high index of suspicion for the disease in all patients with cough for more than two weeks, and in all patients with chest x-ray abnormalities.

If TB is suspected, it is important to order sputum tests that can microbiologically confirm TB.<sup>1</sup> Sputum TB tests that are widely used include smear microscopy, cultures, and molecular tests such as GeneXpert. These tests are all endorsed by the World Health Organization (WHO) and available at more affordable prices in the private sector, via the IPAQT initiative ([www.ipaqt.org](http://www.ipaqt.org)), which includes over 75 accredited private labs across India.<sup>4,5</sup>

It is important to note that pulmonary TB cannot be reliably detected by any blood test. Therefore, sputum is the most important sample to collect.<sup>2</sup> Chest x-rays are often very helpful, but they are not specific for TB, and must be followed by microbiological tests.<sup>3</sup>

**Once TB is diagnosed, there are several key steps to ensure that patients have good outcomes:**

- Assessment for multidrug-resistant TB (MDR-TB) risk factors

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- Selection of correct first-line drug regimen, duration and dosage
- Ensuring treatment adherence
- Monitoring treatment success
- Management of adverse events
- Notification of TB cases
- Referral of patients with suspected MDR-TB

## The effective treatment of tuberculosis has three aims:

• *The rapid reduction of bacillary load to ensure clinical improvement and to arrest transmission.* This is achieved through the use of potent bactericidal drugs such as isoniazid and rifampicin.

• *The prevention of the emergence of drug resistant strains.* The emergence of such strains is dependent on bacillary load and spontaneous mutations occurring in multiplying bacilli within the lungs. The concurrent use of multiple anti-tuberculous drugs is aimed at suppressing the growth of such mutants, and is an important component of an adequate regimen for treatment.

• *Prevention of relapse.* This is achieved through prolonged treatment, especially with a regimen that includes rifampicin, and monitoring of adherence to ensure elimination of any residual, persistent organisms, which are known to responsible for relapse.

## STANDARDS FOR TB CARE

Two important standards for TB care were released in March 2014: the 3rd edition of the International Standards for TB Care (ISTC)<sup>6</sup>, and the 1st edition of Standards for TB Care in India (STCI).<sup>7</sup> These standards establish the best practices for TB diagnosis, treatment and follow-up, and must be followed by all practitioners. Important recommendations from these standards are provided below.

## ASSESSMENT FOR MDR-TB RISK FACTORS

Before TB treatment is start-

ed, practitioners must assess the patient for MDR-TB risk. According to the ISTC, 'an assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance (if known), should be undertaken for all patients. Drug susceptibility testing should be performed at the start of therapy for all patients at a risk of drug resistance. Patients who remain sputum smear-positive at completion of 3 months of treatment, patients in whom treatment has failed, and patients who have been lost to follow-up, or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely an Xpert MTB/RIF (GeneXpert) test should be the initial diagnostic test. If rifampicin resistance is detected, liquid culture and testing for susceptibility to isoniazid, fluoroquinolones and second-line injectable drugs should be performed promptly.<sup>6</sup>

## SELECTION OF CORRECT FIRST-LINE DRUG REGIMEN

In India, several studies have shown widespread use of incorrect and irrational TB drug prescriptions, especially in the private sector.<sup>8-10</sup> Incorrect prescriptions can lead to emergence of drug-resistance and result in poor patient outcomes.<sup>11,12</sup> This underscores the importance of clinician education and adherence to standards.

According to the ISTC, 'all patients who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen using quality assured drugs. The **initial phase** should consist of two months of isoniazid, rifampicin,

pyrazinamide and ethambutol. The **continuation phase** should consist of isoniazid and rifampicin given for 4 months. The doses of antituberculosis drugs used should conform to WHO recommendations. Fixed dose combination drugs may provide a more convenient form of drug administration.<sup>6</sup>

The STCI recommends that the continuation phase should consist of three drugs (isoniazid, rifampicin and ethambutol) given for at least four months.<sup>7</sup> This is because of the high levels of isoniazid resistance in India.

Evidence suggests that both daily and thrice-weekly intermittent drug regimens are acceptable for first-line TB therapy, provided mechanisms are put in place to ensure adherence. Intermittent drug therapy makes it easier to implement directly observed therapy (DOT), while daily treatment provides a great margin of safety. Dosages of drugs must be based on body weight and acceptable ranges are shown in **Table 1** (based on ISTC).<sup>6</sup>

Where possible, according to STCI and ISTC, fixed dose drug combinations (FDC) should be used because they reduce the number of pills taken daily, increase patient convenience and reduce the potential for medication errors.<sup>6,7</sup>

With respect to duration of therapy, 6 months is the standard for first-line therapy. The STCI recommends that the duration of the continuation phase can be extended by 3 – 6 months in special situations like bone and joint TB, spinal TB, and central nervous system involvement.<sup>7</sup>

## ENSURING TREATMENT ADHERENCE

Since drug-sensitive TB requires at least 6 months of continuous therapy, ensuring adherence is a big challenge. Providing support for, and making every effort to ensure

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**Table 1 – Doses of first-line antituberculosis drugs in adults and children**

| Drug                | Recommended dose in mg/kg body weight (range) |              |                            |             |                               |
|---------------------|---|--------------|----------------------------|-------------|-------------------------------|
|                     | Daily regimen                                 |              | Three times weekly regimen |             |                               |
| <b>Isoniazid</b>    | <b>Dose</b>                                   | <b>Range</b> |                            | <b>Dose</b> | <b>Range</b>                  |
| Children            | 10  | (7-15),      | maximum 300 mg/day         |             |                               |
| Adults              | 5   | (4-6),       | maximum 300 mg/day         | 10          | (8-12), maximum 900 mg/dose   |
| <b>Rifampicin</b>   |   |              |                            |             |                               |
| Children            | 15  | (10-20),     | maximum 600 mg/day         |             |                               |
| Adults              | 10  | (8-12),      | maximum 600 mg/day         | 10          | (8-12), maximum 600 mg/dose   |
| <b>Pyrazinamide</b> |   |              |                            |             |                               |
| Children            | 35  | (30-40),     | maximum 2000 mg/day        |             |                               |
| Adults              | 25  | (20-30),     | maximum 2000 mg/day        | 35          | (30-40), maximum 3000 mg/dose |
| <b>Ethambutol</b>   |   |              |                            |             |                               |
| Children            | 20  | (15-25),     | maximum 1000 mg/day        | 30          | (25-35), maximum 2400 mg/dose |
| Adults              | 15  | (15-20),     | maximum 1600 mg/day        |             |                               |

Source: ISTC, 3rd edition (reference 6)

adherence should be considered to be part of the prescription for the treatment of TB. It is important to develop an approach that is tailored to each patient and one that involves an agreement between the GP and the patient.

Every TB patient should receive counseling at the start of TB treatment. They should be informed that they have a curable disease called TB, and that completion of the entire 6 month course is critically important to prevent poor outcomes.

Patients should also be informed about likely adverse drug events, and they should get a clear plan on when to come back for follow-up visits. Mobile phone reminders may help with improving adherence and follow-up visits. Patients also need to be advised about diet, return to work, smoking and alcohol cessation, and may need to be screened for comorbid conditions like diabetes and HIV.

Doctors can also work with local community-based and non-governmental organizations, and enlist community health workers as 'treatment supporters' to supervise and support the patient with treatment

completion. To ensure treatment adherence, it is also important that doctors maintain some written record on what treatment was started, when, dosages, adverse reactions, results of follow-up lab tests, etc.

## MONITORING TREATMENT SUCCESS

Weight of the patient should ideally be monitored on a monthly basis, and drug dosages adjusted to reflect the change in weight. The STCI recommendation states that 'response to therapy in patients with pulmonary tuberculosis, new as well as retreatment cases, should be monitored by follow-up sputum microscopy (one specimen) at the time of completion of the intensive phase of treatment and at the end of treatment.'<sup>7</sup>

## MANAGEMENT OF ADVERSE EVENTS

Drug-induced hepatitis is the most common major adverse reaction associated with ATT. Severe nausea, jaundice or confusion should make the physician suspect the possibility of hepatitis. Advancing age and pre-existing liver disease

are known risk factors, and special monitoring and care needs to be exercised in these groups of patients. All TB drugs should be stopped when hepatitis is suspected. The monitoring of the drug-induced hepatitis, and re-introduction of drugs is beyond the scope of this article and can be found elsewhere.<sup>13</sup>

Any reported visual impairment should warrant the stopping of ethambutol. Severe skin rashes may have to be treated by stopping all drugs and re-introducing them one at a time under observation, to identify the offending agent. Common minor side effects include nausea and anorexia, and can be minimized by taking the medications with small meals or just before bedtime. Joint pains caused by pyrazinamide can be treated with non-steroidal anti-inflammatory drugs, and pyridoxine supplements may be used to alleviate the mild tingling and numbness in the hands and feet that may be caused by isoniazid.

## NOTIFICATION OF TB CASES

As per Government of India order and STCI recommendations,

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## CLINICAL HIGHLIGHTS

- ❑ GPs should follow the recommendations of the recently published Standards for TB Care in India (STCI) and the International Standards for TB Care (ISTC), and ensure that quality of TB care is aligned with best practices. All TB cases must be notified to local governmental authorities.
- ❑ Treatment of drug-sensitive TB involves the use of 4 drugs, and lasts 6 months. Rifampicin, Isoniazid, Pyranzinamide and Ethambutol are prescribed for the initial two-month **intensive phase**, and Rifampicin and Isoniazid are continued for 4 more months in the **continuation phase** after the intensive phase
- ❑ Prescribing the drugs in the correct dosage is important for efficacy and the prevention of the emergence of drug resistant strains. The dosage is decided based on the weight of the patient.
- ❑ Every possible avenue should be explored to ensure adherence to treatment. These include identifying barriers to adherence, and the use of directly observed treatment (DOT), either physician administered, or with the help of facilitators, family or community support.
- ❑ Monitoring the response to treatment is an important component of care. All patients on ATT should be monitored by follow-up sputum microscopy at the time of completion of the intensive phase of treatment and at the end of treatment
- ❑ Minor adverse reactions to TB medications include nausea, gastric intolerance, neuropathy, and joint pains that can be managed symptomatically and do not warrant stoppage of medications. Major adverse reactions include hepatitis, severe skin reactions, optic neuropathy and renal failure. Symptoms and signs suggesting a major reaction should be treated by stoppage of drugs, close monitoring and careful re-introduction in accordance with published guidelines.
- ❑ Having a close contact with drug-resistant TB, having a relapse of TB after being declared cured, or being re-treated for TB after having defaulted on treatment in the past are risk factors for drug-resistant TB. Such patients, and those who fail treatment (have a positive sputum smear at 5 months) should be investigated for drug-resistant TB with culture and drug susceptibility testing of sputum.
- ❑ Since MDR-TB requires long-term and specialized management, patients should be referred to chest specialists.

'all health establishments must report all TB cases and their treatment outcomes to public health authorities (District Nodal Officer for Notification).<sup>7</sup> By notifying all TB cases to the local health authorities, private practitioners can seek help from the RNTCP to help follow-up patients who default.

## REFERRAL OF PATIENTS WITH SUSPECTED MDR-TB

All patients with risk factors for drug-resistance (e.g., patients with a history of previous TB treatment), must be investigated for MDR-TB using drug-susceptibility testing. Since MDR-TB requires long-term and specialized manage-

ment, patients should be referred to chest specialists, either in the private sector, or in the public sector where free treatment is available under the programmatic management of drug-resistant TB.

In conclusion, GPs have a critical role to play in the control of TB at a community level, especially in India, where a majority of TB patients seek care in the private sector. Ensuring the best standards of TB treatment comprises the prescription of the right drugs in the right regimens, monitoring patients for signs of response to treatment and signs of adverse reactions to medications, and supporting the patient in maintaining adherence to treatment. ■

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# CIS CME—Questions

Treatment of Pulmonary Tuberculosis:  
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## Questions

- 1** Which of the following is the correct drug regimen for a newly diagnosed patient with pulmonary tuberculosis?
  - a. 2 months of Streptomycin, Rifampicin, Isoniazid, Pyrazinamide and Ethambutol followed by 4 months of Rifampicin and Isoniazid
  - b. 8 months of Rifampicin, Isoniazid and Ethambutol
  - c. 2 months of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol followed by 4 months of Rifampicin and Isoniazid
  - d. 6 months of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol
- 2** Which of the following tests should be used to monitor the success of treatment for a patient with pulmonary tuberculosis?
  - a. Chest radiograph
  - b. Sputum smear examination
  - c. TB IgG, IgM antibodies
  - d. TB Gold test (interferon-gamma release assay)
- 3** When should one suspect the possibility of drug-resistant TB?
  - a. When the patient has been treated for TB in the past
  - b. When the patient is in close contact with a patient who has drug-resistant TB
  - c. When the patient has defaulted from treatment before the present illness
  - d. All of the above
- 4** Which of the following statements is true about intermittent treatment?
  - a. It is superior to daily treatment
  - b. It can be given twice a week
  - c. It should be prescribed only when treatment is supervised
  - d. When prescribed, it must include an injectable drug
- 5** Which of the following is false regarding adverse reactions to TB drugs?
  - a. Jaundice is a common adverse effect and is self-limiting
  - b. Nausea is a common adverse effect, is usually self-limiting and can be treated with symptomatic management
  - c. Joint pains are an adverse reaction to pyrazinamide and usually respond well to non-steroidal anti-inflammatory drugs
  - d. The elderly and those with pre-existing liver disease are more susceptible to drug induced hepatitis

*(See answers on the next page)*

# CIS CME—Answers

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*Questions on the previous page*

## Answers

- 1 The correct answer is (c).** Injectable drugs are not part of the regimen for newly diagnosed pulmonary tuberculosis. The standard regimen for the treatment of TB lasts 6 months, with 4 drugs (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) prescribed in the first two months (intensive phase), and Rifampicin and Isoniazid continued for another 4 months (continuation phase). In India, because of high levels of INH resistance, the Standards for TB Care in India recommends the addition of ethambutol to the continuation phase.
- 2 The correct answer is (b).** Sputum smear examination is recommended at the end of the intensive phase of treatment and at the end of treatment. Investigations for drug resistant TB need to be performed if the smear continues to be positive at 3 months. Treatment is considered to have failed if the smear at end of treatment is positive. Improvements in chest radiographs, while reassuring in the clinical context, are not specific enough to be used to monitor disease. TB IgG and IgM are serological tests that have been banned and have no role in the management of TB. IGRA (e.g., TB Gold) is a test to diagnose latent TB, and has no role in the diagnosis or monitoring of active disease.
- 3 The correct answer is (d).** Relapse, retreatment and having a close contact with drug-resistant TB are important risk factors for drug-resistant TB, and questions pertaining to these risk factors are very important in the initial assessment of patients with TB.
- 4 The correct answer is (c).** While intermittent treatment is an accepted modality of treatment, it is recommended only when compliance is ensured through direct supervision, and given for a minimum of three times a week. Twice-weekly regimens are not acceptable. Injectable drugs are not part of a standard intermittent treatment regimen for newly diagnosed pulmonary TB.
- 5 The correct answer is (a).** Jaundice is a sign of hepatitis and warrants stoppage of all TB medications, and investigations for drug-induced hepatitis. It is more common in the elderly and in patients with pre-existing liver disease.