Revised National Tuberculosis Control Programme

Daily Regimen in Treatment of Drug Sensitive Tuberculosis

Technical & Operational Guidelines

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Central TB Division
Directorate General of Health Services
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Dr. Jagdish Prasad
M.S. M.Ch., FIACS
Director General of Health Services

सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
स्वास्थ्य सेवा महानिदेशालय
निर्माण भवन, नई दिल्ली-110 108

GOVERNMENT OF INDIA
MINISTRY OF HEALTH & FAMILY WELFARE
DIRECTORATE GENERAL OF HEALTH SERVICES
NIRMAN BHAWAN, NEW DELHI-110 108
Tel : 23061063, 23061438 (O), 23061924 (F)
E-mail : dghs@nic.in

दिनांक/Dated.....

PREFACE

The Revised National Tuberculosis Control Programme (RNTCP), which was launched in 1997, based on World Health Organization recommended Directly Observed Treatment Short-Course (DOTS) strategy, employing thrice weekly regimen for treatment of drug sensitive Tuberculosis (TB), is being successfully implemented in the country. Since inception, the programme has met Global benchmarks for case detection and treatment outcome.

RNTCP had adopted the intermittent short-course chemotherapy regimen for treatment of drug sensitive TB until now, which was an effective and operationally feasible way of TB treatment under programmatic settings. However, there are a significant proportion of TB patients outside the programme who are managed by other sectors (Private, NGOs, Corporates, etc.) and are being treated on daily regimen. Under the 12th Five Year Plan (2012-17), the RNTCP has envisioned 'Universal Access to Quality TB Diagnosis and Treatment', which envisages engagement of all care providers. To achieve the same, Standards for TB Care in India (STCI) have also been laid down. The STCI states that 'patients should be given daily regimen under direct observation'. In order to bring parity in management of TB patients across all sectors, and also to address the growing threat of emergence of Drug Resistant TB due to non-standard treatment practices across various sectors, it has been a felt need of the programme to consider moving to daily regimen. Moreover, the National Expert Committee to Examine Type of Drug Regimen for Drug Sensitive TB has also recommended RNTCP to move towards daily regimen for drug sensitive TB.

Accordingly, it has been decided to introduce daily regimen for treatment of drug sensitive TB under the Revised National Tuberculosis Control Programme.

As a first step, technical and operational guidelines have been developed by Central TB Division (CTD), Directorate General of Health Services, MoHFW to facilitate this transition. These guidelines will be used for training of various cadres of Staff at the National, State, District and Sub-District levels, and will be an important tool to facilitate smooth and seamless transition to daily regimen for drug sensitive TB under RNTCP.

I am very hopeful that this Guideline will be instrumental in updating users on various components of this important step being taken by the Revised National Tuberculosis Control Programme. I wish the CTD endeavour all success.

Jprasad

(Dr. Jagdish Prasad)

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1. BACKGROUND

The Revised National Tuberculosis Control Programme (RNTCP) was launched in India in 1997 based on World Health Organization endorsed Directly Observed Treatment Short-Course (DOTS) strategy, employing the thrice weekly treatment regimen.

The Standards for TB Care in India, 2014, which were jointly laid down by Ministry of Health & Family Welfare, Government of India and World Health Organization, in consultation with experts, based on available evidences and WHO Treatment of TB Guidelines (2010), state that 'all patients should be given daily regimen. The initial phase should consist of two months of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E). The continuation phase should consist of three drugs, Isoniazid (H), Rifampicin (R) and Ethambutol (E) given for at least four months'.

The National Technical Working Group (NTWG) on TB/HIV (2013) has recommended use of daily regimen using Fixed Dose Combination (FDC) first line TB treatment for PLHIV patients.

Considering the above, the National Expert Committee to examine type of drug regimen for drug sensitive TB has recommended RNTCP to move towards introducing daily regimen for drug sensitive Tuberculosis in India.

2. TREATMENT OF TUBERCULOSIS

The principle of treatment for tuberculosis (other than confirmed Drug Resistant forms of TB) henceforth will be to administer daily fixed dose combinations of first – line anti-tuberculosis drugs in appropriate weight bands.

Fixed dose combination drugs for TB under daily regimen are packaged to cover 4 weeks of treatment, i.e. 28 days, and would be dispensed on a daily basis. Thus, the effective number of doses that the patient would be receiving in a month would be 28.

2.1. For a new TB case, the treatment will be of 6 months (24weeks). The intensive phase (IP) will consist of 8 weeks of Isoniazid, Rifampicin, Pyrazinamide & Ethambutol in daily Fixed Dose Combinations in four weight bands. There will be no need for extension of IP. Only Pyrazinamide will be stopped in the Continuation Phase (CP) while the rest of the three drugs will be continued for another 16 weeks as daily dosages. The CP can be extended by 12 to 24 weeks in certain forms of TB like CNS TB, Skeletal TB and Disseminated TB, based on clinical decision of the treating physician.

2.2. For previously treated case of TB, the treatment will be of 8 months (32 weeks). The intensive phase will consist of Injection Streptomycin, INH, Rifampicin, Pyrazinamide & Ethambutol in daily dosages as per weight bands. Injection Streptomycin will be stopped after 8 weeks and the remaining four drugs will be continued for another 4 weeks. There will be no need for extension of IP. At the start of CP, Pyrazinamide will be stopped while the rest of the drugs- Rifampicin, INH & Ethambutol will be continued for another 20 weeks as daily dosages in the CP. The CP can be extended by three to six

months in certain forms of TB like CNS TB, Skeletal TB, and Disseminated TB, based on clinical decision of the treating physician.

2.3. As recommended by National Expert Committee on Diagnosis and Treatment of TB under RNTCP and the Drug Specification Committee, the following daily short-course treatment regimen and dosages are being adopted:

Table 1 : RNTCP Daily Treatment Regimen

Type of TB Case	**Treatment regimen in IP**	**Treatment regimen CP**
New	2HRZE	4HRE
Previously treated	2HRZES + 1HRZE	5HRE

H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin

Prefix to the drugs stands for number of months

Treatment under the daily regimen would be administered as per following drug dosages in 4 weight bands for Adults :

Table 2: Daily Dosage Schedule for Adults

Weight category	**Number of tablets to be consumed**		**Inj. Streptomycin***
	Intensive phase	Continuation phase	
	H R Z E	**H R E**	
	75/150/400/275 mg per tab	75/150/275 mg per tab	gm
25-39 kg	2	2	0.5 gm
40-54 kg	3	3	0.75 gm
55-69 kg	4	4	1 gm
≥70	5	5	1 gm

***** *Inj. Streptomycin (15 mg/kg (12–18 mg/kg) daily, maximum daily dose 1000 mg). Patients aged over 50 years may not be able to tolerate more than 750 mg daily. Similarly, patients weighing less than 50 kg may not tolerate doses above 500-750 mg daily.*

Adults weighing less than 25 kg will be given loose drugs as per body weight.

It may be noted that the pill load for TB patients across various weight bands will be as mentioned in table 2 (for example, a patient in the weight band range of 25-39 kg needs to consume only 2 tablets whereas another patient in 55-69 kg range would need 4 tablets)

Table 3: Dose of essential first line anti-TB Drugs under daily regimen (Adult)

Name of Drug	Daily Dose (mg/kg body wt.)
Isoniazid	5 mg/kg (4–6 mg/kg) daily
Rifampicin	10 mg/kg (8–12 mg/kg) daily
Pyrazinamide	25 mg/kg (20–30 mg/kg) daily
Streptomycin	15 mg/kg (12–18 mg/kg) daily
Ethambutol	15 mg/kg (15–20 mg/kg) daily

As the drugs under daily regimen are packaged to cover 4 weeks of treatment, i.e. 28 days, and would be dispensed on a daily basis, the effective number of doses that the patient would be receiving in a month would be 28, hence the total no. of doses would be as follows:

Table 4: Doses in RNTCP Daily Regimen

Type of TB Case	Doses in IP	Doses in CP
New	56 doses (8 weeks x 7 days/week) or 28*2	112 doses(16 weeks x 7 days/week) or 28*4
Previously treated	84 doses (12 weeks x 7 days/week) or 28*3	140 doses(20 weeks x 7 days/week) or 28*5

For the time being, pediatric patients would continue to be treated with the currently available drugs/ regimen till the time the required pediatric formulations are available with the programme.

As practiced for intermittent regimen, RNTCP has retained the concept of 'One Patient-One Box' for daily regimen also. The daily regimen patient-wise box consists of blister packs of Schedule 9 (for Intensive Phase) and Schedule 10 (for Continuation Phase) packed in separate laminated pouches in a single millboard/ grey board box; the number of blister packs in each pouch will be as per the weight band.

3. OPERATIONAL GUIDELINE FOR TREATMENT INITIATION

Treatment should be initiated by a trained medical officer (MO). Efforts should also be made to look for co-morbidities like diabetes, liver disease, renal disease, neurological disorders, substance abuse, especially tobacco (in any form) & alcoholism. The patient should be assured

that s/he will be supported during the entire course of treatment by the MO and peripheral health care workers.

The TB patient should be counselled about the disease, its mode of spread and the treatment (dosage schedule, duration, common side-effects, etc.) and should be encouraged to involve family members for treatment support. Counselling should be offered on methods to prevent transmission of disease (cough etiquettes, proper disposal of sputum) and to get all close contacts (especially household contacts) screened at the earliest.

The MO needs to initiate a treatment card (in duplicate when required) for each patient at the time of initiation of treatment. Each patient must be given a TB Identity Card. Patient-wise box as per weight band is to be made available at the treatment centre.

The product-code-wise details of PWBs are given below:

Table 5: Product Code-wise details of PWBs

Product Code	Product Description	No. of strips in IP	No. of strips in CP	Unit
PC-1D-1	Daily regimen treatment Box for New Cases for weight Band (25-39kg)	4	8	PWB
PC-1D-II	Daily regimen treatment Box for New Cases for weight Band (40-54kg)	6	12	PWB
PC-1D-III	Daily regimen treatment Box for New Cases for weight Band (55-69kg)	8	16	PWB
PC-1D-IV	Daily regimen treatment Box for New Cases for weight Band (≥70 Kg)	10	20	PWB
PC-2D-1	Daily regimen treatment Box for Re-Treatment Cases for weight Band (25-39kg)	6	10	PWB
PC-2D-II	Daily regimen treatment Box for Re-Treatment Cases for weight Band (40-54kg)	9	15	PWB
PC-2D-III	Daily regimen treatment Box for Re-Treatment Cases for weight Band (55-69kg)	12	20	PWB
PC-2D-IV	Daily regimen treatment Box for Re-Treatment Cases for weight Band (≥70 Kg)	15	25	PWB
PC-5D-I	Inj Streptomycin 500 mg Vial	56 doses	-	Vials/Kit
PC-5D-II	Inj Streptomycin 750 mg Vial	56 doses	-	Vials/Kit
PC-5D-III	Inj Streptomycin 1gm Vial	56 doses	-	Vials/Kit

The concerned health worker should register the treatment card in Nikshay immediately after initiation of treatment by the Medical Officer and note the Nikshay ID in the treatment card. Till paper- based registration of cases in TU level treatment register continues, STS should note the Nikshay ID in the TB register.

4. TREATMENT SUPPORT

Adherence to regular and complete treatment is one of the important factors for relapse free cure from TB. To assess and foster adherence, a patient-centred approach to administration of

drug treatment should be adopted. It should be based on the patient's needs and mutual respect between patient and the provider. A good treatment support plan should be developed at the time of initiation of treatment.

All efforts should be made to monitor adherence to treatment. An extensive network of treatment supporters already exists within the programme. The principle of direct observation is to be applied logically and judiciously. In situations where an institutional or community DOT provider is not accessible, a family member or other suitable person may act as a treatment supporter. While all efforts must be put in to find a treatment supporter close to the patient's residence and acceptable to the patient, treatment should not be denied to any patient who is unable to undergo treatment from a DOT provider for any valid reason. In addition, other measures to promote treatment adherence among patients may be explored as per local needs. ICT modalities like frequent calls, SMS reminders, IVRS etc. may also be deployed to promote adherence.

Treatment support program is not restricted to observation of treatment alone. Nutritional and financial support, ancillary drugs, co-morbidity management, etc. are some other requirements. To avail these, patient has to be linked to appropriate social support schemes like Rasthriya Swasthya Bima Yojana (RSBY), State-supported schemes for financial support for TB patients, Corporate Social Responsibiliy (CSR) initiatives, counselling services, etc. Capacity building and engaging with local community based organizations, self-help groups, patient support groups, Panchayati Raj Institutions (PRI) should be explored and effectively utilized to promote treatment adherence.

5. FOLLOW-UP OF TREATMENT

Patients should be closely monitored for treatment progress and disease response. There are two components of follow up:

5.1. Clinical follow-up : Patients will be clinically followed-up on a monthly basis at the nearest health facility. Additionally, the medical officer should also conduct the review when he visits the house of the patient. Improvement in symptoms, weight gain etc. may indicate good prognosis. Symptoms and signs of adverse reactions to drugs should be specifically looked for. Appropriate management of co-morbid conditions is essential for getting a better prognosis to TB treatment.

5.2. Laboratory investigations : Necessary laboratory investigations need to be done to assess prognosis of the disease or to manage co-morbidities or adverse reaction. In case of pulmonary tuberculosis, sputum smear microscopy should be done at the end of IP and end of treatment. A negative sputum smear microscopy result at the end of IP may indicate good prognosis. However, in the presence of clinical deterioration, the medical officer needs to thoroughly review the patient, both clinically and with investigations including culture & DST or repeat sputum examination. Response to treatment in extra-pulmonary TB may be best assessed clinically. Help of radiological and other relevant investigations may be taken.

Results of sputum smear examination and weight should be updated in Nikshay by the concerned health worker.

6. Prevention and management of adverse drug reactions

Most TB patients complete their treatment without any significant adverse drug effects. Most of the adverse effects can be prevented by proper counselling of patients, and their impact minimized through early identification and management.

A serious event or reaction is any untoward medical occurrence that, at any time during treatment, which:

- Resulted in death
- Drug induced hepatitis
- Required in-patient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/ incapacity
- Resulted in termination of drugs due to ADR

The patient treatment cards should be modified for recording any adverse events and their management. All adverse drug reactions reported by patients or observed are to be recorded in the treatment card and captured in the NIKSHAY-ADR reporting system and existing Pharmacovigilance practices.

7. Treatment outcomes

The treatment outcomes will be recorded and reported as per existing RNTCP guidelines.

8. Recording and Reporting

The recording and reporting mechanism would be as per RNTCP guidelines.

9. Supply chain management of drugs

The stocking norms will remain the same as mentioned under existing RNTCP guidelines.

Loose drugs will be required as a provision in the event wherein patients may not tolerate FDCs in the daily treatment regimen. The reconstitution of unconsumed drug boxes should be done using daily regimen drug boxes only.

For in-patient care, drugs will be separately issued by the program.

10. Drug quality assurance

Existing drug quality assurance mechanisms will continue to apply for drugs under daily regimen.

11. Cut-off for initiation of daily regimen and Transfer in / Transfer out mechanism

A cut-off date will be decided to roll-out daily regimen. Prior to this date, all patients already put on intermittent treatment regimen in the State would continue on the same regimen.

For the patients who need a transfer out to another District/State where daily regimen is not being implemented, PWB/drugs will be sent to the particular State through RNTCP mechanism.

Communication to all concerned at State/District and Central TB Division will be done. Similarly, for transfer-in cases, the existing PWB will be transferred to recipient district with information to DTO/STO/CTD.

12. Advocacy, communication and Partnerships

An integrated Advocacy, Communication and Community Engagement strategy for all relevant stakeholders needs to be used to enable smooth and seamless transition, implementation and adoption of the daily regimen protocol.

The involvement of partners and partnerships would have a key role to play in the transition to daily regimen. Partners providing services through partnership options should be involved for community engagement and for treatment adherence support.

13. Training

Training on the transition from intermittent to daily regimen is a major component that would require efforts and commitment at all levels. Nationwide cascade of training will follow for each cadre. ICT tools such as training videos and interactive training sessions should be used during implementation. National Institutes at Central level and STDCs at State level will be responsible for coordinating these trainings.

14. Supervision & Monitoring

Continuous monitoring and supervision by Central and State teams will be essential. A standardized check list will be used at all levels by the supervising officers/consultants.

15. Helpdesk

The existing Nikshay helpdesk will be utilized during the transition period to address queries related to daily regimen.