Report of the meeting of the Expert Committee on DOTS-Plus
11th & 12th April, 2005. New Delhi

Background

By March 2005, the RNTCP covered a population of over 1 billion (90%) with plans to achieve nation-wide coverage during 2005. The thrust of the RNTCP has earlier been on establishing a good quality DOTS programme to address factors leading to drug resistance and thus prevent the possible emergence of MDR-TB. By achieving 86% success rate and 72%case detection rate in the year 2004, the RNTCP has established itself as a sound strategy to provide access to good quality TB services.

Recent studies conducted by TRC and NTI, have found MDR-TB levels of less than 1% to 3.4% in new cases and about 12% in re-treatment cases. The issue of the treatment of those pulmonary tuberculosis patients who remain smear-positive following a fully supervised Category II re-treatment regimen, has previously not been well addressed by the RNTCP. Although these cases represent a small minority of the overall caseload of tuberculosis patients, still it is a serious concern for the programme managers, both from an epidemiological and human rights viewpoint.

Hence, the RNTCP envisages to provide treatment services for MDR-TB patients in the second phase of the project. Recognizing the complexity and the requirement for high levels of resources, DOTS-Plus will be introduced as pilot projects in a few highly specialized centres. A two-day meeting of experts was held in Delhi to specifically guide the RNTCP in developing a strategy for treatment of MDR-TB cases. List of participants is given in Annex A. Following are the recommendations that emerged from the meeting.

Group - 1: *Definitions (MDRTB Suspect, Case), Intake criteria, diagnostic algorithm, Pre-treatment evaluations including laboratory issues, follow up schedule and related investigations by laboratory, infection control measures*

Definitions to be used at DOTS Plus pilot site

- MDR-TB Suspect: A Category II patient who is smear positive at the end of the fifth month of treatment or later
- MDR-TB Case: An MDR-TB suspect who is sputum culture positive and has resistance to isoniazid and rifampicin, with or without resistance to other anti-tubercular drugs (DST result from an RNTCP accredited laboratory).
- Criteria for sending specimens: When a case of TB who is on Cat II remains smear positive at the end of fifth month or later, samples will be sent for culture and susceptibility testing to an accredited laboratory

Intake criteria

- First fifty 'Failures of Cat II' under RNTCP with documented evidence of MDR-TB from an RNTCP accredited laboratory
- Priority will be given to patients residing in local or identified district / zone / area of the respective DOTS-Plus site.
- A commitment from the patient before starting treatment to adhere with treatment

Exclusion criteria

- Less than 15 years of age
- Pregnancy and lactation
- Psychiatric illness*
- Epilepsy*
- Alcoholism*

- Inability or unwillingness to complete the DOTS Plus treatment
- Known intolerance to a DOTS Plus drug
- Renal and hepatic dysfunction
- Terminal illness?
- Permanent residence outside the DOTS Plus area

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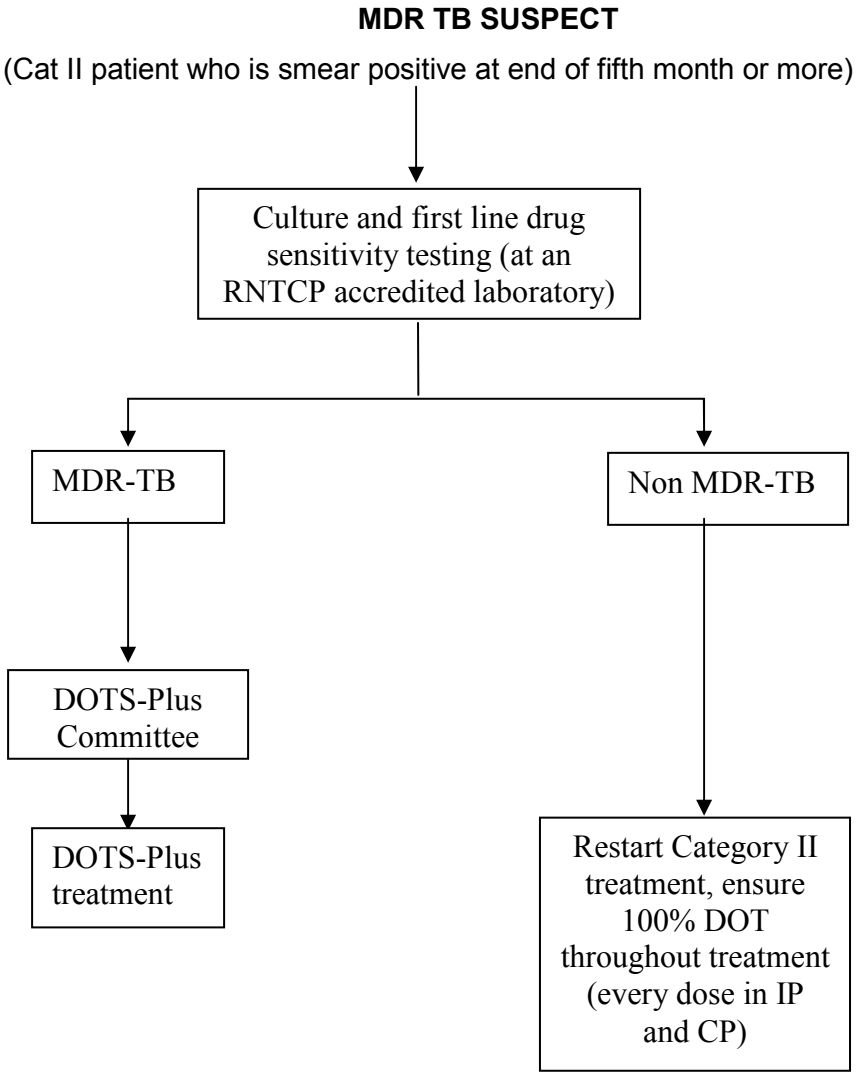
* These criteria would be reviewed after gaining experience

Diagnostic algorithm



Pre-treatment Evaluation

- Initial physician evaluation
- Culture and drug susceptibility testing:
    a. Two specimens (overnight) at each test time
    b. CPC transportation if delay in transportation will exceed 72 hours
    c. Conventional solid egg based media (LJ) for primary culture
    d. Indirect DST for SHRE using economic variant of proportion method on LJ media
- Chest radiograph
- Laboratory analysis (includes liver function tests, creatinine, blood urea nitrogen, complete blood count, ß-HCG for women, electrolytes, TSH)
- Home visit
- Socioeconomic interview
- Family planning counseling (work with RCH, if pregnancy occurs during treatment - terminate pregnancy or stop treatment)
- Contact screening as per standard RNTCP guidelines

Follow up schedule -during treatment

Schedule for sputum smear microscopy, culture and sensitivity follow up examinations

	IP monthly follow up examinations				**Extension of IP (1-3 months)**			**CP Quarterly follow up examination in months**						
	1st FU	2nd FU	3rd FU	4th FU				1 qtr		II qtr	III qtr	IV qtr	V qtr	VI qtr
No IP extension →	3	4	5	6	-	-	-	7	9	12	15	18	21	24
IP extension 1 month →	3	4	5	6	7	-	-	8	10	13	16	19	22	25
IP extension 2 months →	3	4	5	6	7	8	-	9	11	14	17	20	23	26
IP extension 3 months →	3	4	5	6	7	8	9	10	12	15	18	21	24	27

***** The number in each cell indicates the month of follow up examination

** CP will have follow up sputum examination on 7 occasions irrespective of the duration of treatment. The first quarter in the CP will have two examinations and the rest 5 will be in the subsequent quarters till the end of treatment

- Two specimens for AFB at the end of 3, 4, 5, 6, 7, 9, 12, 15, 18, 21, 24 months
- Two specimens for culture at the end of 3, 4, 5, 6, 7, 9, 12, 15, 18, 21, 24 months
- Culture specimen to NRL for Second line drug DST for positive cultures at IRL at crucial months (initial sites only depending on potential workload)
- Monthly weight
- Chest radiograph every six months
- Physician evaluation including adverse drug reaction monitoring every month for six months, then every three months for two years
- Creatinine and electrolytes monthly for 3 months, then every 3 months during injectable phase

Group - 2: *Hospitalization, Treatment regimens, DOT provision, Outcome definitions, treatment of adverse reactions*

Hospitalization

- Initially, all patients should be admitted to the designated specialized institution for at least 2 to 4 weeks during which necessary investigations will be undertaken, MDR-TB treatment initiated, drug tolerance monitored, intensive counseling and health education given to patient, linkages in the field developed and contact assessment undertaken
- Subsequent hospitalization may be required for management of ADR, complications and to assess need for surgical intervention, social reasons etc

Treatment

- Standardized treatment regimen was chosen over individualized treatment regimen for operational reasons.
- **The Intensive Phase (IP)** will consist of five drugs: 1. Kanamycin (Km), 2. Ofloxacin (Ofx), 3.Ethionamide (Eto), 4. Pyrazinamide (Z) and 5.Ethambutol (E). Where resistance to Ethambutol is present, it will be replaced by PAS or Cycloserine (Cs) in this order of preference.
- All drugs in IP would be given daily for 6 days a week; every dose in DOTS Plus should be supervised. Where drugs are to be taken twice a day, the second (evening) dose will be given under direct observation of a DOT provider identified close to the patients home
- The intensive phase should be given for a minimum duration of 6 months, extended up to 9 months if necessary. IP regimen would be given till at least three consecutive negative smears AND last available culture is negative. If the smear and/or culture results are not available, IP will be extended till such result is obtained; up to a maximum of 9 months
- In rare cases where the patient remains sputum positive by culture at 9 months and patient is tolerating injectable drugs, injectable will continue till sputum conversion.
- Decision to stop IP and start CP will be ratified by the hospital's DOTS Plus Committee
- **Continuation Phase (CP)** will consist of three drugs: 1. Ofloxacin (Ofx), 2. Ethionamide (Eto), and 3. Ethambutol (E). As in IP, where resistance to Ethambutol is present, it will be replaced by PAS or Cycloserine (Cs) in this order of preference
- These would be given daily for 6 days a week; every dose in DOTS Plus should be supervised. Where drugs are to be taken twice a day, the second (evening) dose will be given under direct observation of a DOT provider identified close to the patients home
- The CP drugs should be given for at least 18 months after culture conversion
- Intolerance to any drug in CP: offending drug may be replaced by PAS or Cycloserine

Thus the regimen recommended for use in DOTS Plus site is: 6-9 months of daily Km Ofx Eto E Z during the IP and Ofx Eto,E for at least 18 months after culture conversion.

Dosages

Observed average body weight of the MDR-TB patient in India is 40 kgs. So drugs are proposed to be made available for two weight bands:

Drugs	< 40 kg body wt.	≥ 40 kg body wt.
Kanamycin	500 mg	750 mg
Ofloxacin	600 mg	800 mg
Ethionamide	500 mg	750 mg
Ethambutol	800 mg	1200 mg
Pyrazinamide	1500 mg	1750 mg

PAS	10 gm	12 gm
Cycloserine	500 mg	750 mg

Outcome Definitions

- Cure: Patient has completed treatment and is culture negative for the last 12 months of treatment. A single intervening positive culture (isolated positives) should be ignored provided it is followed by 3 consecutive negative cultures.
- Treatment completed. A patient who has completed entire treatment but due to lack of bacteriological results does not fulfill the definitions of cure
- Default: A patient who interrupted treatment for two or more consecutive months
- Death: A patient who died from any cause during treatment
- Failure: A patient with more than one positive culture in the last 12 months of treatment with a minimum of five cultures performed in last 12 months. A patient will also be considered treatment failure if one of the last three cultures during treatment is positive or if he/she is persistently culture positive and decision has been taken to terminate treatment early by the DOTS plus committee.
- Adverse reactions: A patient who could not continue STR due to severe adverse drug reactions as decided by the DOTS plus committee
- Transfer out: A patient has been transferred to another MDR-TB unit and whose outcome will be reported by the receiving unit
- Still on treatment: A patient who is still on treatment at the time of the cohort reporting

Adverse drug reactions (ADRs)

- The protocol used by TRC, Chennai for management of adverse drug reactions would be used in the pilot sites.
- Training on management of ADR should be incorporated at all levels
- RNTCP to provide ancillary drugs for the treatment of ADRs
- Decision to change or stop treatment can only be made by the hospital DOTS Plus Committee

Group - 3: *Information systems - recording and reporting, Linkages with field and mechanisms for follow up of discharged patients, Drugs - procurement, packaging, distribution system*

Recording

- Laboratory request forms for culture and drug sensitivity test which will also act as referral form to the IRL.
- DST Laboratory Register at the IRL
- Patient details record (case sheet) at hospital
- Patient Identity Card
- Patient treatment book which will consist of a treatment card, adverse reaction monitoring chart and bacteriology chart
- Referral form to respective DTO for ambulatory treatment
- MDR-TB Register maintained at State hospital

Patient flow (linkages with field and records)

- Fill sputum culture and sensitivity form for Cat II failure
- Send sputum/patient to IRL with culture form and treatment card of first line drugs
- MDR diagnosis at IRL communicated to DTO by email, telephone and post/courier
- DST Laboratory register at IRL
- DTO/MOTC facilitate in address verification of patient
- Patient sent to designated State MDR Hospital for admission

- Hospital fills up patient details record, patient Identity card and treatment book. Treatment book consists of Rx card, adverse reaction monitoring chart, bacteriology chart
- Local DOT provider and family treatment supporter identified and trained by MO
- Discharge after one month with 1 week drug supply to patient. DTO would be informed a week prior to discharge of the patients from the MDR Hospital.
- Where possible, DTO would be requested to coordinate in transfer of remaining IP drugs, copy of treatment book and referral form through the MO-TC and STS. Where it is not physically possible, the same would be sent by courier/ messenger.
- DTO to send back portion of referral form to State hospital as feedback on receipt of patient and drugs
- Sputum samples for culture as and when required to be sent to IRL by courier (patient could also go if possible)
- DTO to send copies of treatment book to State hospital at the end of every quarter
- State hospital to maintain MDR TB register
- State hospital to supply CP drugs to DTO 6-monthly (first supply before IP is over)

Reporting
- Case finding report (quarterly, annually)
- Conversion report (quarterly and annually; after 13 to 15 months later, just like RT report of DOTS). For example, patients initiated on treatment in Q1 2005, will be reported in the Q1 2006 report
- Treatment outcome report (quarterly and annually; after 31 to 33 months later, i.e. after 10 quarters). For example patients initiated on treatment in Q1 2005 will be reported in Q3 2007
- MDR-TB register to be computerized in the form of a line-list at State hospital/IRL level and networked
- Separate quarterly drugs and lab supplies report from State

Drug procurement
- Second line drugs will be procured at national level annually with 6-monthly trenches
- Two mechanisms for procurement of second line drugs is available for consideration of the RNTCP: International Competitive Bidding (ICB) and Green Light Committee (GLC)
- The advantages of procurement by ICB is that it is a known system for the country, quality assured drugs can be bought at low cost. The long lead time is a disadvantage.
- On the other hand, GLC mechanism has a shorter lead time, quality of drugs is assured by international standards. The disadvantage is a higher cost of drugs, tax to be paid, need to obtain Port clearance for drugs sourced from outside country, and the mechanism of transfer of funds to GLC
- Recommended submission of application to GLC which could make the procurement through WHO to avoid taxation

Drug packaging
- Recommended packaging of drugs into multi-drug single day blisters
- State hospital to further package drugs into 6-month IP and 6-month CP packs
- Additional loose drugs need to be considered

Drug distribution system
- Manufacturer to send drugs directly to State hospitals
- RNTCP to provide funds and guidelines for drug stores at hospital
- State hospital releases drugs to DTO
- Quarterly reporting of drug stocks to CTD

Other related issues

- State DOTS Plus Committee, responsible for overall implementation of the DOTS plus project would be formed in all DOTS Plus sites and will comprise of the following members:
    - State TB Officer
    - Head of the hospital where patient is to be managed
    - STDC Director/Officer in charge of IRL
    - District TB Officer of the DOTS Plus site
    - Microbiologist of IRL
    - Additional members as decided by the State
- State DOTS Plus committee will submit a plan for the DOTS Plus project which is approved by the State Government (Secretary, Health) and CTD.
- Hospital DOTS Plus Committee would be formed at the hospital managing the MDR-TB patients. This committee would comprise of Senior physician of the hospital, microbiologist of the laboratory where smears and C/S is being performed, and the District TB Officer of the district in which the DOTS Plus site is situated. They will review particulars of the patients before treatment is initiated, coordinate in smooth referral of patients on discharge and take decisions to change/stop treatment, should the need arise.
- Provisions would be required for purchasing ancillary drugs, storage of second line drugs at the DOTS Plus site, for transportation of specimens for testing to IRL, support for travel of patient and an attendant to IRL/State hospital and increased honorarium for DOT providers of MDR-TB patients
- Laboratory issues to be looked into for DOTS Plus site
    - Standard operating procedure for IRL including IQC measures
    - IRL proficiency testing for culture and DST by NRL.
    - If DST for pyrazinamide is to be conducted at IRL– to be explored (For the time being this task will be entrusted with NRL since it is difficult to establish DST for Pyrazinamide which requires to be set up in LJ medium under acidic condition.)
    - Parallel research for rapid testing - swab method for rapid culture, direct DST for HR & PNB test- to be explored at IRL
    - Linkage with respective NRL for second line DST (capacity building at NRL – 1 culture specimens at time 0 to NRL for Second line drug sensitivity testing)
    - Guidelines for packaging and transportation of sputum for culture
- Management of MDR-TB in special situations would need further review and consultation. This includes MDR-TB with pregnancy, MDR-TB with HIV infection, MDR-TB in Extra pulmonary site and Paediatric patients, MDRTB in patients with renal/hepatic failure. Preventive therapy to pediatric and adult contacts of MDR-TB patients also needs further discussion
- Capacity to be built at NRL for susceptibility of second line drugs
- Infection control –guidelines need to be developed which is appropriate in context. However, wards could be planned with natural ventilation and health care workers rotated to decrease exposure
- Application to GLC for procurement of second line drugs - to put up as an agenda in next CCM meeting

Annex A. List of participants

1. Dr. V. K. Arora, Addl. Secretary and Director, LRS Institute
2. Dr. L. S. Chauhan, DDG (TB), Central TB Division

Group1.
1. Dr. Mohammed Aziz, WHO, Geneva.
2. Dr. S. K. Sharma, AIIMS, New Delhi.
3. Dr V K Dhingra, New Delhi TB Centre.
4. Dr. V. H. Balasangameshwara, NTI, Bangalore.
5. Dr. C. N. Paramasivan, TB Research Centre, Chennai.
6. Dr. Fraser Wares, WHO, India.
7. Ms. Abigail Wright, WHO, Geneva.
8. Dr. Maninder Kaur, Central TB Division, Delhi
9. Dr. Ranjani Ramachandran, TRC, Chennai.
10. Dr. V. P. Myneedu, LRS Institute, New Delhi.

Group 2
1. Dr. Rohit Sarin, LRS Institute, New Delhi.
2. Dr. Roopak Singla, LRS Institute, New Delhi.
3. Dr. N. K. Jain, SMS Medical College, Jaipur
4. Dr. R.N. Solanki, BJ Medical College, Gujarat.
5. Dr. Rajeshwari Ramachandran, TB Research Centre, Chennai.
6. Dr. M. S. Jawahar, TB Research Centre, Chennai.
7. Dr. Ernesto Jaramillo, WHO, Geneva
8. Dr. P. P. Mandal, Central TB Division, Delhi
9. Dr. Yamuna Mundade, Central TB Division, Delhi.
10. Dr. Jamie Tonsing, Central TB Division, Delhi.

Group 3
1. Dr. Prahlad Kumar, Director, NTI, Bangalore.
2. Dr. K. R. John, CMC, Vellore
3. Dr. S. Sahu, WHO, India.
4. Dr. S. S. Lal, WHO, India
5. Dr. Sophiya Vijay, NTI, Bangalore.
6. Dr. V. S. Salhotra, Central TB Division, Delhi
7. Dr. Pritish Vaidyanathan, NTI, Bangalore.
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