Minutes of the fourth DOTS-Plus committee meeting held on 17th and 18th January at LRS institute of TB and Chest Diseases

The meeting was held at LRS Institute of TB and Chest Diseases on 17th and 18th January, 2008. The list of participants is at **Annex-I.**

DDG (TB) welcomed all the participants and updated them on the progress made in DOTS-Plus programme over the past one year. DDG informed the group that the states of Gujarat and Maharashtra had initiated DOTS-Plus services from March 2007 following a national level training. The first patients have been put on treatment in the two states in August 2007 and till date a total of 75 patients have been started on Cat IV. As the IRLs of these two states are still under the process of accreditation the respective NRLs (TRC for Gujarat and NTI for Maharashtra) have been entrusted with the culture and DST activities in the interim. It is planned to commence the DOTS-Plus activities in another 7 states in 2008 and in all the remaining states across the country by 2010. DDG highlighted that the key challenge in the scaling up of DOTS-Plus services across the country was establishment of an accredited laboratory by the respective states. He further mentioned that the programme is seriously viewing the emerging threat of XDR-TB and steps are being taken to address the issue. The prevalence of XDR-TB is being estimated amongst the MDR-TB isolates identified in DRS surveys undertaken in Gujarat and Maharashtra. A meeting of experts was called in September 2007 at TRC to discuss the problem, prevention, management and control of MDR and XDR-TB outside of the programme setting. The outcome of the meeting was the development of a consensus statement. The consensus statement has been communicated to the states for wider dissemination to all health care providers guiding them on management of MDR-TB and the rational use of anti TB drugs. The statement is also available on the programme website. DDG informed the members that the programme was collaborating with FIND for demonstration of the rapid culture methods and newer diagnostics (e.g. molecular techniques) at identified sites in the country. DDG also stressed on the need to develop guidelines on control of airborne infection in hospital settings and urged the group to give their valuable inputs in this regards. He concluded with thanks to LRS for holding the meeting and requested Dr Behera, Director LRS to chair the meeting for the next two days.

This was followed by a presentation from Gujarat and Maharashtra updating the members on the progress of implementation of DOTS-Plus in the two states. The following issues were discussed after the above presentations.

- **Monthly testing of serum creatinine during the intensive phase (IP):**

  The utility of testing serum creatinine monthly during IP was questioned as the experience of LRS and TRC indicates that almost all the MDR-TB patients receiving Kanamycin had normal creatinine levels at the end of IP. However the group felt that it would be prudent to continue with the current guidelines at present and revisit the issue after analyzing the serum creatinine results in the cohort of the first 100 Category IV patients enrolled in Gujarat and Maharashtra.

- **Substitution of follow up cultures with smears:**

  In view of the preliminary evidence generated by TRC on the concordance between culture and smear results, the substitution of follow up cultures with smears was discussed by the members. It was informed by Dr Fraser that co-relation of culture and smear results was being established through a global analysis of data from the initial global DOTS-Plus pilot sites. It was therefore agreed that the decision to replace follow up cultures with smears may be deferred till the results of the aforesaid study were available. In the meantime, TRC, LRS, Gujarat and Maharashtra were requested to collate and analyse the smear and culture data available on their own MDR-TB cohorts.

- **Ratio of weight wise category of patients initiated on treatment:**

  To accurately forecast the drug requirements it was decided that all the sites should analyze and provide CTD the data on the ratio of ≤ 45 Kg and > 45 Kg patients at the time of initiation on treatment and data on proportion of patients who crossed the ≤ 45 Kg weight band during treatment.

- **Updating of treatment cards:**

  It was stressed that adequate efforts should be made by the DTOs with the assistance of STS to update, timely and accurately, the treatment cards maintained at the DOTS-Plus site, DTC and the PHI/DOT Provider level.

- **It was emphasized that states should ensure that the initiation of DOTS-Plus activities should not in any way compromise or hamper the core DOTS services (i.e. Cat I, II and III services). All Cat-II patients should be effectively monitored and sustained efforts to improve their treatment outcomes must be ensured.**

- **Liquid Culture methods:**

  The issue of undertaking rapid liquid culture to avoid delay in diagnosis and treatment initiation the programme was discussed by the Committee. It was informed by TRC and LRS that liquid culture had several intrinsic technical and operational challenges and is recommended only for labs that have an established track record in performing culture and DST on solid media. Additionally it requires to be housed in a WHO BSL-3 facility. It was informed that in collaboration with FIND, RNTCP is undertaking a demonstration project for liquid culture at LRS and the IRLs of Ahmedabad and Hyderabad which will provide more information on the suitability of the rapid culture methods in the programmatic field setting.

The group discussed the following issues pertinent to the progress of DOTS-Plus in Maharashtra. The group noted that the number of MDR-TB patients initiated on treatment in the state was far lower than anticipated. The deliberations and decisions taken in this regards are reflected below:

- Considering the fact that that the IRL had demonstrated proficiency in DST for R and H at the time, the 62 MDR cases identified during the period of proficiency testing should be traced within the next 15 days and if found eligible, as per the criteria laid out in the guidelines (e.g be form within the catchment area for Cat IV services, not been placed on SLDs, etc), be initiated on treatment at the earliest.
- The group discussed the crisis caused by the recent sudden transfer of the key staff of IRL and abolishing of the LT and nurses posts. It was informed that CTD had taken up the matter with the Health Secretary and DHS. The STO and STDC Director were asked to follow up the matter and ensure that the human resource requirements are met within the next 2-3 months. The state must ensure that once in place, trained laboratory staff at the IRL must remain in post for at least 3 years to ensure stability and proficiency of the laboratory.
- It was noted that the IRL as yet does not have a cold room or power backup. The state officials were asked to expedite the same and were informed that the finances for the cold room and uninterrupted power supply should be met from the state funds.
- Concern was raised in relation to the stock of Cat IV drugs in the state, some of which was at the risk of expiry. This includes kanamycin, cycloserine and pyridoxine. It was decided that the state should calculate the drug requirement for the next 6 months and take necessary steps to transfer the surplus "at risk of expiry" drugs to Gujarat and/or LRS within the next one month.

The members discussed the role of the NRLs in the accreditation of IRLs which was crucial for the early diagnosis and treatment of the MDR-TB cases. The Committee recommended that

- NRLs should henceforth adopt a more proactive approach and take complete responsibility for accreditation of the IRL assigned to them.
- The NRLs should appraise the concerned higher authorities (Principal Secretary, DHS etc.) on the findings and recommendations made by the team during the pre-accreditation visits to the IRLs. In this regards, the NRLs should intimate the respective concerned authorities well in advance about their forthcoming visit to the IRL.

Some queries were raised regarding the required number of cultures and DST to have been performed by the IRL prior to and for submission for proficiency testing. It was informed by Dr Ranjini from TRC that for proficiency testing the IRLs should have undertaken at least 100 cultures and DST from different categories of patients to provide the whole spectrum of resistance pattern (including H mono, R mono , two, three, four drug and MDR). From these 100 isolates, the NRL will randomly select 10 for re-testing. It was also informed that the panel testing will be initiated by the NRL who will send a send a panel of 20 strains to the IRL. The panel will consist of pansensitive, monoresistant, MDR and poly resistant strains). The IRL should sub-culture these 20 strains and then set up DST and report to NRL the results of DST. This exercise will be done twice a year for the first two years. It was decided that this information should be communicated to all IRLs and also be reflected in the RNTCP accreditation document.

This was followed by presentations and discussions on the agenda items as below:

- **Drugs and Logistics**

  The presentations highlighted the drugs and logistic systems for Cat IV drugs in Gujarat and Maharashtra. A modified system was proposed to the Committee **(Annex II)**, which will be integrated with the existing drug and logistic system under RNTCP. A quarterly reporting format for the Cat IV drugs, which will be incorporated in the quarterly PMR, was also presented **(Annex-III)**. The members made the following observations.

  - The group agreed on the proposed drug and logistic system.
  - The members suggested that the proposed Cat IV drug reporting format should be revised to include information on PWBs for different weight bands ($\leq$ 45 Kg and > 45 Kg) separately.
  - CTD should take up with the respective states to provide additional space at the SDS, DDS and TU DS for storing Cat IV drugs.
  - The efforts of Gujarat in developing a 3 monthly Cat IV PWB, from the loose Cat IV drugs, were appreciated. The State was requested to provide inputs for training the SDS staff of other states for preparation of Cat-IV PWBs.
  - Drugs during the CP will be supplied in 3-monthly boxes.

- **Initial compulsory hospitalization of up to one month of MDR-TB patients:**

  Dr Fraser made a presentation highlighting the refusal of diagnosed MDR-TB patients for admission to the DOTS-Plus site for treatment initiation as recommended in the DOTS-Plus guidelines. Considering the significant number of MDR patients in Gujarat who had refused Cat IV treatment on account of compulsory initial hospitalization, it was decided that if appropriate, patients can be discharged 1 week post-treatment initiation. All attempts should be made for initial hospitalization of the patients. This should allow for pre-treatment assessment and initiation of Cat IV treatment. However treatment must not be denied if patient refuses hospitalization. For such cases, alternative arrangements should be made locally for initial investigation and initiation of Cat IV Treatment on a fully ambulatory basis. The group unanimously rejected the suggestion of providing financial incentive to patients for the period of hospitalization.

- **Recording and reporting formats:**

  No changes were suggested to the existing recording and reporting formats. The committee accepted the proposal to have a web based MIS for DOTS Plus recording and reporting. The committee recommended that in the interim, till the software for the web based MIS is available, the states should utilize the electronic formats developed by CTD for transmission of data. To facilitate this it was proposed that, if required, the DOTS-Plus sites should be provided with a computer and internet connection.

- **Certification for MTP in pregnant MDR-TB Patients:**

  It was brought to the notice of the Committee that the State DOTS-Plus site Committee was advising MTP for the diagnosed MDR-TB patients who were pregnant so that they could be initiated on treatment. However, the Obstetricians were demanding a justification certificate from the treating physicians in this regards. The members recommended that the DOTS-Plus site committee could certify that the "patient is suffering from MDR-TB which is detrimental to the health of the patient and the fetus and that the treatment for MDR-TB, which is essential for saving the life of the patient, is potentially teratogenic. Therefore if the patient is willing then the pregnancy may be terminated". However, as per legal requirement, the relevant records of the patient should be maintained for at least 5 years.

- **Steps to reduce deaths amongst MDR-TB patients prior to treatment initiation:**

  It was recommended by the Committee that an audit of all deaths amongst MDR-TB patients prior to initiation of treatment should be done by the respective DTO as per the format to be developed by CTD. Analysis of modifiable factors should be undertaken and all efforts should be made to decrease operational delays in diagnosis and initiation of treatment. Some more suggestions made in this regard were:

  - Establishment and accreditation of IRLs to be expedited as per the CTD plan
  - Identification and monitoring of Cat II patients who are positive at 3 months so as to avoid delay in sending their sputum sample for culture and DST if they remain positive at 4^{th} month.
  - Provision of CPC containing McCartney bottles at DMCs where Cat II patients who are positive at 3 months are identified to prevent delay in transportation of the sputum samples for culture and DST

- **Reimbursement of travel cost to patients:**

  The members deliberated on this issue and recommended that the actual cost of travel, undertaken by public transport, incurred towards scheduled and emergency visits to DOTS-Plus site and DTC should be reimbursed to ensure better adherence to treatment.

- **Results of Second line DST from Gujarat :**

  TRC presented the results of the second line DST done on the MDR-TB isolates identified during the DRS survey conducted in Gujarat **(Annex IV)**. XDR-TB was detected in 4% of the MDR-TB cases found amongst the smear positive re-treatment cases enrolled in the Gujarat DRS survey. However, XDR-TB was not found in any new case. Concerns were raised about high levels of ofloxacin and ethionamide resistance. The level of ofloxacin resistance is perhaps one of the highest documented anywhere in the world and is therefore a serious issue. Regarding ethionamide, it is a known fact that in-vitro resistance does not

correlate well with in-vivo resistance and that Eto resistance can be linked with cross-resistance to H. It was suggested that TRC should continue the work with Borstel lab to genotype resistant strains to further understand and explore the effect of possible cross resistance of Eto with H.

The Committee opined that all MDR-TB cases registered at DOTS-Plus sites should continue to have DST for second line drugs performed at the time of identification as an MDR-TB case. The results of the SLD DST will be co-related with treatment outcomes, when available, of these patients.

The committee also recommended that flouroquinolones must not be used as a first line anti-TB treatment drug and should be used with caution in other respiratory infections, preferably only after excluding TB. To prevent the irrational use of SLDs, CTD should widely disseminate the consensus statement on the management of MDR-TB outside the RNTCP setting via the medical college task forces and professional medical associations.

- **Capacity building of NRLs for conducting Second line DST:**

  The Committee opined that the capacity to undertake DST for kanamycin, capreomycin and ofloxacin needs to be built at all the NRLs. DST for Eto is not needed at this time at all the NRLS, but it should be continued at TRC. It was also recommended that since JALMA and LRS were already doing SLD DST, they should exchange resistant strains with TRC for re-checking. It was informed that 2 LTs from NTI had been trained recently in SLD DST at TRC. Also LRS should coordinate with TRC for training the newly recruited microbiologist in this regards.

- **Involvement of private culture and DST facilities:**

  In view of the challenges faced by RNTCP in establishing the network of culture and DST labs in public sector facilities and also to provide wider access to RNTCP diagnostic services for the large number of MDR-TB cases in the country it was proposed to involve well equipped and quality assured culture and DST labs existing in the private sector through a new RNTCP scheme.

  The Committee welcomed and approved the proposal with the following comments:

  - It was stressed that the accreditation of such private labs must be as per the existing RNTCP guidelines for accreditation of culture and DST laboratories in medical colleges.
  - As the existing RNTCP system for accreditation is only for solid media, a mechanism for accreditation of labs who use liquid media needs to be developed. If required, RNTCP can arrange for panel testing of such labs by an out of country WHO SNRL laboratory.
  - CTD should finalise the proposed scheme for contracting for culture and DST services from private culture and DST labs at the earliest.

- **Airborne infection control :**

Dr Puneet made a presentation on the airborne infection control measures at the DOTS-Plus indoor facility, followed by an update on NTF recommendation for formation of an Infection Control expert group at the national level. The Committee recommended:

- To form a working group (as recommended by NTF) to draft national guidelines for infection control.
- Each DOTS-Plus site needs to draft an airborne infection control plan.
- Infection control measures in health facilities in the Indian setting needs to be realistic, focusing mainly on simple administrative measures and cough hygiene, without creating undue fear in the minds of health workers and fellow patients.

This was followed by an update on the progress in planning of the initiation of DOTS-Plus services by Andhra Pradesh, Delhi, Haryana, Kerala, Rajasthan, Tamil Nadu and West Bengal. The Committee made the following observations and recommendations:

- **AP**: AP has shown good progress and the intake of MDR-TB suspects was expected to start in April 2008. It was informed that the process of procurement of Cat IV drugs through GLC was underway and would be supplied to the state in April/May 2008.
- **Haryana:** It was informed that the process of procurement of Cat IV drugs through GLC was underway and would be supplied to the state in April/May 2008. Since the state IRL is not expected to be accredited by this time, it was suggested that LRS may do the culture and DST for the identified MDR-TB suspects for the interim period. Intake of MDR-TB suspect is expected to start in March/April 2008.
- **Rajasthan:** The Cat IV drugs would be supplied to the state in May/June 2008. It was decided that NTI will undertake the culture and DST for the MDR-TB suspects identified till the IRL is accredited. Intake of MDR-TB suspects is expected to start in May 2008.
- **Delhi:** Intake of MDR-TB suspects is expected from April 2008. It was recommended that the catchment area for the Delhi DOTS-Plus site should not include the area which falls under the existing LRS DOTS-Plus services for identification of MDR-TB suspects. However, the MDR-TB patients being treated at LRS under the existing DOTS-Plus site would be included in the Delhi Cat IV cohorts for reporting purposes, but not for the supply of drugs at this time.
- **Kerala:** Intake of MDR-TB suspects to begin in Aug/Sept 2008. All districts of Kerala are to planned to be included in DOTS-Plus site catchment area.
- **Tamil Nadu:** Intake of MDR-TB suspects to commence towards the end of 2008. It was decided that TRC would undertake the culture and DST of MDR-TB suspects till the state IRL was accredited. The Committee recommended that the catchment area for the MDR-TB suspects of the state DOTS-Plus site should not

include that of the existing TRC DOTS-Plus study area. The issue of parallel MDR-TB management at ITM and Tambaram was discussed, and it was suggested that the STO should sensitize these institutes on the consensus statement for management of MDR-TB.

- **WB:** Intake of MDR-TB suspects to commence in Oct 2008. It was recommended that NTI will provide culture and DST facility as a back-up plan to expedite this timeline. It was recommended that the State should include only contiguous districts neighboring Kolkata, which is the DOTS-Plus site, for identification of MDR-TB suspects.
- **DOTS Plus training:** The tentative dates for the national level DOTS Plus training of the above mentioned states will be as follows:
    - Andhra Pradesh and Haryana: 25th to 29th February, 2008
    - Delhi and Rajasthan: March 2008
    - Kerala: June 2008
    - West Bengal: July 2008
    - Tamil Nadu: August 2008
- Some of the other recommendations made by the committee were:
    - State level DOTS-Plus Committees should have representation from higher level State Govt. authorities (e.g. Principal Secretary, DHS, etc.) to ensure administrative commitment.
    - In the remaining 4 states (Chattisgarh, Jharkhand, Orissa and Uttarakhand) where IRL equipment has been supplied, CTD needs to follow-up aggressively on progress to date with the respective state. In addition, the plans and progress for the remaining states need to be expedited by CTD.
    - States should ensure that the trained laboratory staff (Microbiologist, LTs etc.) should not be transferred from the culture and DST laboratory.

This was followed by a presentation from Gujarat on the Eli-Lilly initiative on involvement of NGOs in the DOTS-Plus activities in Ahmedabad. The Committee opined that considering the long duration of treatment for MDR-TB patients, ensuring adherence to treatment will be a challenge for the programme and hence NGOs should be involved to provide patient support.

The Committee emphasized that CTD, NRLs , STOs and IRLs should prepare their respective action plans with timelines and implement the recommendations made in the meeting. It was decided that CTD would review the progress fortnightly and the next meeting would be held in June 2008. The meeting ended with thanks to all the participants for their valuable inputs.

List of Participants

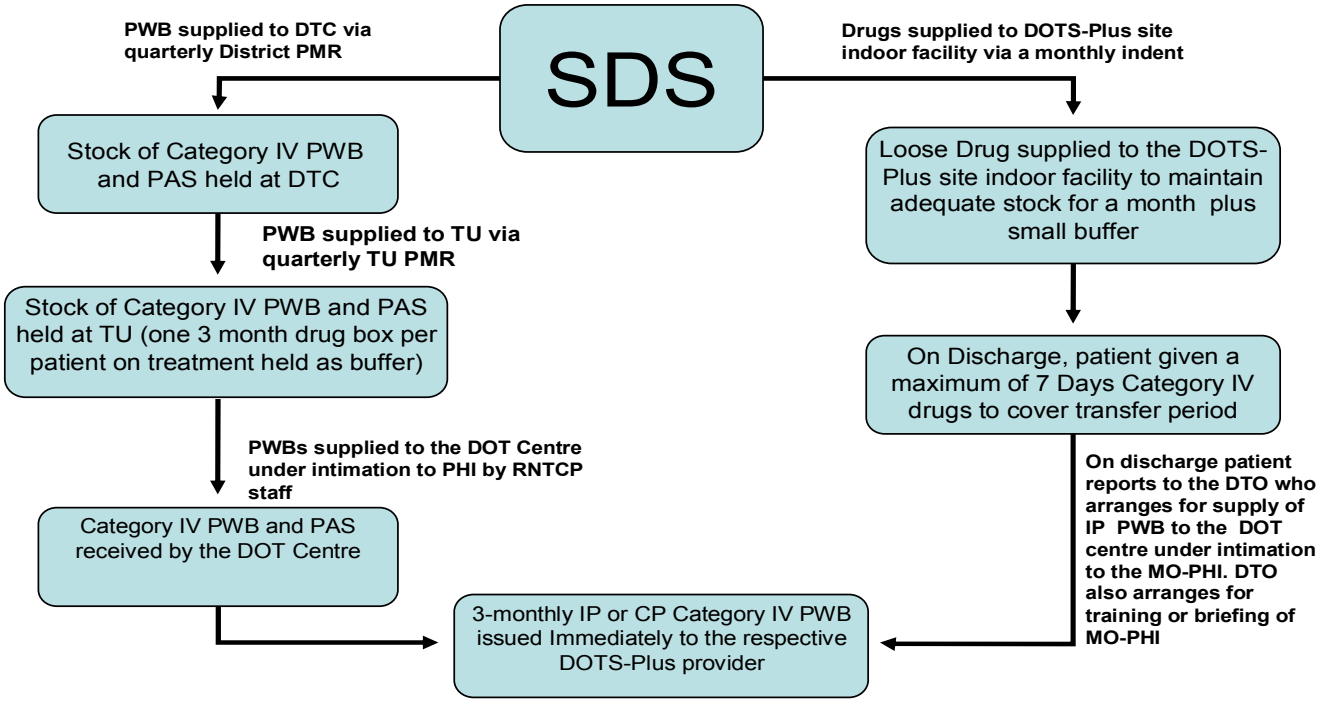
Annex-I

1. Dr L S Chauhan, DDG(TB)
2. Dr P R Narayanan, Director, TRC Chennai
3. Dr D Behera, Director, LRSI New Delhi
4. Dr P Kumar, Director, NTI Bangalore
5. Dr Rohit Sarin, AMS, LRSI New Delhi
6. Dr P Saxena, CMO, CTD
7. Dr S K Chaturvedi, CMO, CTD
8. Dr Devesh Gupta, CMO, CTD
9. Prof Jai Kishan, Chairman, Zonal Task force (North)
10. Prof R N Solanki, Chairman, Zonal Task force (West)
11. Dr A S Singh, Chairman, Zonal Task force (East)
12. Prof K Venu , Chairman, Zonal Task force (South)
13. Dr Rajeshwari Ramachandran, TRC Chennai
14. Dr P Vishalakshi, Microbiologist, LRSI, New Delhi
15. Dr Ranjini Ramachandran, Microbiologist, TRC Chennai
16. Dr Preetish Vaidyanathan, NTI Bangalore
17. Dr Kajal Banik, Focal person, IMA
18. Dr Dheeraj Gupta, PGIMER Chandigarh
19. Dr Rupak Singla, LRSI, New Delhi
20. Dr S N Gaur, President, NCCP
21. Dr Santha Devi, Independent TB Expert
22. Dr Fraser Wares, WHO-India
23. Dr S Sahu, WHO-India
24. Dr Puneet Dewan, WHO-SEARO
25. Dr Sai Babu, STO AP
26. Dr Vijay Garg, STO Haryana
27. Dr Kar, STO, West Bengal
28. Dr K N Gupta, STO Rajsthan
29. Dr E Subburam, STO Tamil Nadu
30. Dr A Gajbhiye, STDC Director, Maharashtra

31. Dr Bhalodia , STDC Director, Gujarat
32. Dr A V V Sathyanarayana, STDC Director, AP
33. Dr V K Dhingra, STDC Director, Delhi
34. Dr Duttachoudhary, STDC Director, West Bengal
35. Dr Mallik Parmar, WHO Consultant
36. Dr Kalpesh Rahevar, WHO Consultant
37. Dr Ambarish Dutta, WHO Consultant
38. Dr Santosha, WHO Consultant
39. Dr Shankar Matta, WHO Consultant
40. Dr Geetha Joesph, WHO Consultant
41. Dr Sreenivas, WHO Consultant
42. Dr Shivani Chandra, WHO Consultant
43. Dr Sanjay Sinha, WHO Consultant
44. Dr Sheena George, WHO Consultant - CTD
45. Dr Geetanjali Sharma, WHO Consultant - CTD
46. Dr Srinath, WHO Consultant - CTD
47. Dr Reuben, WHO Consultant - CTD
48. Dr Neeraj Raizada, WHO Consultant - CTD
49. Dr Sarabjit Chadha, WHO Consultant - CTD

Annex II

Flow of drugs



Annex III

Proposed Format for Quarterly Report

	Cat-IV Regimen - DTC /TU Level							
I	**Patient Wise Boxes**							
S.No.	**Item**	**UOM**	**Stock on first day of the Qtr**	**Stock received during the Qtr**	**Reconstituted Boxes**	**Consumption during the Qtr**	**Stock on last day of the Qtr (c+d+e) –f**	**Quantity Requested for DTC/TU (f x SN) – g**
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
1	IP (≤ 45 Kg Body Weight Patient	PWB						
2	IP (< 45 Kg Body Weight Patient	PWB						
3	CP (≤ 45 Kg Body Weight Patient	PWB						
4	CP (< 45 Kg Body Weight Patient	PWB						
5	PAS containing drugs for 1 mnth in 3 small boxes	Carton of 3 boxes						

II	**Loose Drugs**		**RNTCP CATEGORY IV REGIMEN: 6 (9) Km Ofx Eto Cs Z E / 18 Ofx Eto Cs E**					
S.No.	**Item**	**UOM**	**Stock on first day of the Qtr**	**Stock received during the Qtr from boxes to be reconstituted**	**Stock used for reconstitution during the Qtr**	**Stock on last day of the Qtr (c+d) –e**	**DOE (If more than 1 DOE is available in stock, pls mention all DOEs along with the quantities) Stock**	**DOE**
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
1	KANAMYCIN (Km) - 500 mg	Vials						
2	KANAMYCIN (Km) - 750 mg	Vials						
3	OFLOXACIN (Ofx) - 200 mg	Caps						
4	OFLOXACIN (Ofx) - 400 mg	Caps						
5	CYCLOSERINE (Cs) -250 mg	Tabs						
6	ETHIONAMIDE (Eto) - 250 mg	Tabs						
7	PYRAZINAMIDE (Z) - 500 mg	Tabs						
8	PYRAZINAMIDE (Z) - 750 mg	Tabs						
9	ETHAMBUTOL(E) - 200 mg	Tabs						
10	ETHAMBUTOL(E) - 800 mg	Tabs						
11	PYRIDOXIN - 100 mg	Tabs						

*** SN= Stocking Norm**

Annex IV

Second Line DST for Gujarat DRS - Final Results Jan 2008

	New (1571)	Prev Rx (1047)	Total (2618)
Total No of MDR Strains	37	182	219
Test Not Possible	0	3	3
DST Results available	37	179	216
Sens to All II line Drugs (K Eth Of)	18	101	119
Any Resistance			
Kanamycin (K)	0	7 (3.9%)	7 (3.2%)
Ethionamide (TH)	15 (41%)	45 (25%)	60 (28%)
Ofloxacin (Oflo)	7 (19%)	45 (25%)	52 (24%)
MonoResistance			
Kana	0	0	0
Ethion	12 (32%)	30 (17%)	42 (19%)
Oflox	4 (11%)	26 (15%)	30 (14%)
Any Two Drug Resistance			
K + Oflo	0	4 (2.0%)	4 (1.9%)
K + TH	0	0	0
Oflo + TH	3	12 (6.7%)	15 (7.0%)
Any Three Drug Resistance			
K + Oflo + TH	0	3 (1.7%)	3 (1.4%)
XDR TB (Resist to K & Of)	**0**	**7 (4.0%)**	**7 (3.5%)**