Final Minutes of the sixth DOTS-Plus committee meeting held on 10th and 11th July 2009 at LRS Institute, New Delhi

The meeting was held at LRSI, New Delhi on 10th and 11th July, 2009. The list of participants is at Annex-I.

Day 1

Dr L S Chauhan, DDG (TB) welcomed all the participants and informed about the encouraging progress in scaling up of MDR TB activities in the last one year. DDG-TB also informed the participants about India's participation in the 'Ministerial meeting of high MDR/XDR countries' at Beijing in April 2009. During this meeting India along with the other countries with a high burden of MDR/XDR TB have committed to accelerate efforts to prevent M/XDR-TB through effective TB care and control, and to scale-up the diagnosis and treatment of M/XDR-TB. This will be done by developing and implementing strategic M/XDR-TB policies and plans that respect human rights, as part of national TB control plans, in line with the Millennium Development Goals , the Global Plan to Stop TB, 2006-2015, and overall health system strengthening efforts. Dr Chauhan on behalf of the Committee requested Prof S K Sharma and Dr Behera to Chair the meeting.

This was followed by presentation by Dr LS Chauhan on the RNTCP plan (2009-14) to address the problem of MDR-TB in the country. The members were informed about the revised vision of the programme for implementing and scaling up MDR TB services . This included introducing these services in all the states across the country 2010. By 2012 these services will be offered to all smear positive retreatment cases and new cases who have failed treatment and by 2015 these services will be made available to all smear positive cases registered under the programme. The programme intended to treat at least 30000 MDR cases annually by 2013. The members were also informed about the RNTCP comprehensive laboratory scale up plan under which a network of 43 quality assured laboratories will be established which will be capable of undertaking rapid tests like LPA (Line Probe Assay) and liquid culture besides the conventional solid culture. These labs, supported by identified existing laboratories in the public and private sector, will be able to perform at least 220000 cultures and DSTs essential for diagnosing and following up 30000 MDR patients annually. The members were also briefed about the funding sources for the scale up of the MDR TB services.

The presentation was followed by a discussion in which the following points were highlighted.

- In response to the query by Dr Sharma on the number of private sector labs involved with the programme, DDG informed that presently the programme had accredited two private sector labs (CMC, Vellore and BPRC, Hyderabad) for culture and DST, however there are several private labs, including Hinduja (Mumbai), SRL Ranbaxy (Mumbai and Gurgaon), Quest (Gurgaon), which are under the accreditation process. The members emphasised that private sector labs providing culture and DST for TB could be accredited by the programme to ensure quality and validity of the test results. It was also suggested that the programme should publicize the names of the accredited private sector labs and disseminate information on the accreditation process. Dr Behera suggested that clinicians should accept C & DST results only from accredited labs which will force them to get accreditation from RNTCP. DDG informed that the programme was encouraging reputed private labs, including those performing liquid culture, to apply for accreditation keeping in view that post accreditation these labs should support the programme in providing diagnostic and follow up services. Further the programme is taking steps, including the constitution of a laboratory task force, to augment the accreditation capacity of the NRLs which is presently limited.

- Dr Sharma pointed out on the wide use of non-specific tests like IGRA and ELISA for diagnosis of TB. It was suggested that the programme should take steps to discourage the use of such tests for diagnosing TB till further evidence proves their efficacy. DDG informed that the programme did not recommend the use of these tests for diagnosing TB and these tests were used mainly by the private practitioners. Dr Wares further informed that during the IMPACT meeting, held in April 2009, this issue was discussed by the professional medical associations and it was decided that the Indian Association of Medical Microbiologists (IAMM) would issue guidance on the utility of all the different available diagnostic tools for TB for the benefit of the clinicians.

- Dr Sharma suggested that the programme should consider supporting the establishment of negative pressure in-patient facilities at tertiary care centres for treatment of MDR TB patients. In response, Dr Behera cited the experience of LRS in establishing the negative pressure ward in the institute which has clearly shown that such facilities are not only extremely expensive and time consuming to set up but are also difficult to maintain. The Committee was of the opinion instead of establishing negative pressure in-patient facilities, existing environmental measures – such as excellent ventilation – should be sufficient to reduce the risk of transmission of MDR TB to healthcare providers in DOTS-plus sites.

- In response to a query by Dr Sharma on the status of DST for Ethambutol and Pyrazinamide it was informed that the programme was presently performing DST for Rifampicin, INH, Streptomycin and Ethambutol. However for the purpose of accreditation proficiency for Rifampicin and INH only was being considered. It was also informed that DST for Pyrazinamide isdifficult to perform on solid media and l the results are unreliable and of limited clinical relevance. .

- It was suggested that the programme should consider accrediting private labs for second line DST. In this regards it was informed that the presently there would be small number of patients requiring second line DST which could be managed by the NRLs which have been strengthened to undertake these tests. Further as per the plan the programme will soon introduce LPA for diagnosis of MDR TB. This would also open the possibility of using this test for second line DST (especially Kanamycin and fluoroquinolones) which is presently being standardized by the manufacturers.

Following the discussion, Dr Singla made a presentation on the recommendations of the DOTS Plus sub-committee which had been constituted after the last DOTS Plus Committee meeting. The Sub-committee met on two occasions, the detailed minutes of which are attached as Annex II and Annex III. The key recommendations of the Sub-Committee and the observations and decision of the DOTS Plus Committee (in italics) are as below:

1. **Guidelines for the programmatic management of XDR-TB patients**

    - Patients on Category IV treatment whose 4th month culture result (available after 6 months of treatment) was positive, should be "suspected of treatment failure". It should be ensured that the 6th month follow-up culture of these patients should be done in time and if found positive, the culture isolate is to be sent by the respective IRL to the NRL for second line DST. In addition, any Category IV patient who has culture converted but is found to have 2 consecutive positive cultures subsequently, would also be "suspected of treatment failure". In such cases, the culture isolate of the second positive culture would be sent by the respective IRL to the NRL for second line DST.

      The Committee accepted the recommendation that SLD DST should be performed for: (1) patients on category IV treatment whose 6thmonth follow-up culture is positive; and (2) any category IV patient who has culture converted but is found to have 2 consecutive positive cultures subsequently, and are to be considered as "XDR-TB suspects". It was informed that as per the available data from Gujarat, more than 10% of the MDR cases, who became culture negative, converted between 4 and 6 months of treatment. It was therefore pragmatic to identify "XDR suspects" on the basis of 6th month culture result. This would also avoid additional burden on the NRLs. The Committee also emphasised on timely performance of follow up cultures, particularly among those patients with positive 4 month follow-up cultures. It was further informed that to ensure early detection of "XDR suspects" the programme was considering to perform critical follow up cultures (e.g. 4th and 6th month) by liquid culture method, where such capacity was available.

    - NRL would perform second line DST in case of an XDR-TB suspect on at least Kanamycin, Capreomycin and Ofloxacin.

      Dr Sharma suggested that besides ofloxacin DST should also be performed on levofloxacin as studies have shown that levofloxacin might be effective in some cases of ofloxacin resistance. Dr Ranjini clarified that in vitro resistance to ofloxacin indicates resistance to many other fluoroquinolones including levofloxacin though in vivo results may differ. Hence performing DST for levofloxacin along with ofloxacin would not be of any additional benefit. The Committee accepted the recommendation.

- Patients diagnosed as XDR-TB on second line DST should be given an outcome of "Switched to Category V" and they should be further managed with a standardized treatment regimen (Category V) under the programme. With the development of an RNTCP Category V treatment regimen, consideration should be taken of discontinuing the use of the "Treatment stopped due to other reasons" outcome. CTD needs to discuss this further and come to a final decision on the matter.

  It was suggested that the Cat IV patients found to be XDR should be given an outcome of 'Failure'. However as these patients do not qualify as failures technically it was decided that they may be given an outcome of "Switched to Category V" as recommended. The Committee accepted the recommendation.

- Category V treatment would be initiated by DOTS-Plus site committee after concurrence of CTD. The Committee also recommended that all XDR-TB patients who are considered for Category V regimen, will be screened by the DOTS-Plus committee and if found suitable will be referred to a thoracic surgeon for consideration of surgery to improve the treatment outcomes. Identification must be done for the site (tertiary centres) with such surgical facilities.

  The Committee accepted the recommendation. Dr Jawahar suggested that the option of surgery should also be considered for all Cat IV patients also for improving their treatment outcomes.CTD should identify and compile a list of thoracic surgeons and institutes willing and able to offer such surgery.

- *T*he Sub-Committee after reviewing the treatment regimens and their outcomes reported in recent studies on management of XDR-TB; the recommendations of the WHO guidelines (2008); the efficacy, adverse effects and cost of the individual drugs, recommended that the Category V treatment regimen would consist of 7 drugs, with 2 reserve/substitute drugs. The dosage of the drugs would vary as per the weight of the patient (≤ 45Kg or > 45Kg). All drugs would be given on a daily basis. Injections of Capreomycin will be given 6 days/week. The details of the drugs and daily dosages is as per the table below:

Drugs	**Dosage/day**	
	≤45 Kgs	**>45 Kgs**
Capreomycin (Cm)	750 mg	1000 mg
PAS	10 gm	12 gm
Moxifloxacin (Mfx)	400mg	400 mg
High dose INH (High dose-H)	600 mg	900 mg
Clofazimine (Cfz)	200 mg	200 mg
Linezolid (Lzd)	600 mg	600 mg
Amoxyclav (Amx/Clv)*	1000/250 mg BD	1000/250 mg BD
Pyridoxine	100mg	100mg
Reserve/Substitute drugs		
Clarithromycin (Clr)	500 mg BD	500 mg BD
Thiacetazone (Thz)†¥	150 mg	150 mg

*The amoxycillin content should be 1000mg and clavulinic acid 250 mg in the selected combination

†Subject to availability

¥ Not be used in HIV + patients

Dr Rajeswari expressed concern over the use of Linezolid with high dose INH as both the drugs were known to cause peripheral neuropathy. Dr Sharma suggested the use of Azithromycin in place of Clarithromycin. However, in view of the insufficient data available on the use of Azithromycin as an anti-TB drug it was decided to use Clarithromycin in Cat V until more evidence on use of Azithromycin was available. Since the Amoxy-Clav combination containing 1000mg amoxicillin and 250 mg clavulinic acid is not available in India, it was decided to replace it with the available combination containing amoxicillin 875mg and clavulinic acid 125mg which is also recommended by WHO guidelines for the programmatic management of drug-resistant tuberculosis (Emergency Update 2008).

The Committee accepted the recommendations with the above mentioned changes. The Committee further recommended that CTD should work out a suitable mechanism for the procurement and logistics for the Cat V drugs.

- It was decided that the reserve/substitute drugs would be used in the following conditions:
  - In case the patient was on PAS in Category IV, PAS will be replaced with one of the reserve drugs in the Category V regimen.
  - If the patient is unable to tolerate one or more of the drugs

The Committee recommended that in addition to the use of reserve drugs for the above mentioned conditions, they will also be used if the patient is found to be resistant to Capreomycin.

- The Category V regimen would be of 24-30 months duration, with 6-12 months Intensive Phase (IP) and 18 months Continuation Phase (CP). The Intensive Phase will consist of Cm, PAS, Mfx, High dose-H, Cfz, Lzd, Amx/Clv while the Continuation phase will consist of PAS, Mfx, High dose-H, Cfz, Lzd, Amx/Clv. The change from IP to CP will be done only after achievement of culture conversion i.e. 2 consecutive negative cultures taken at least one month apart. In case of delay in culture conversion, the IP can be extended from 6 months up to a maximum of 12 months. In case of extension, the DOTS-Plus site Committee, which will be responsible for initiating and monitoring the Category V regimen, can decide on administering Capreomycin injection intermittently (3 times/week) for the months 7 to 12.

The Committee accepted the recommendation.

- Patients would be admitted at the DOTS-Plus site preferably for at least one month for pre-treatment evaluation and Cat V treatment initiation. The admission period will be reviewed from time to time based on the feed back received from the DOTS-Plus site committees. The patient will be discharged thereafter to continue ambulatory treatment under direct observation.

The Committee accepted the recommendation

- XDR-TB patients will undergo the following tests as a part of the pre-treatment evaluation prior to initiating Category V treatment:
  - Complete Blood Count with platelets
  - Thyroid Function Tests (TFT)
  - Liver Function Tests (LFT)
  - Kidney Function Tests (KFT)
  - S. Electrolytes
  - Blood Sugar
  - Pregnancy test
  - All patients would be offered HIV testing after pre-test counseling
  - Chest X Ray
  - Surgical evaluation

The Committee accepted the recommendation with the suggestion that a thorough clinical examination should be done during the pre-treatment evaluation. Further it was also recommended

that only TSH levels should be tested as they are sufficient to assess the thyroid function of the patient.

- Follow up schedule: The follow up schedule will be as follows:
  - Culture will be done monthly during IP starting after 3 months of Category V treatment. i.e. 3, 4, 5, and 6, and quarterly during CP i.e. 9, 12, 15, 18, 21 and 24
  - In case of extension of IP due to delay in culture conversion, the follow up schedule will be modified accordingly.
  - Other tests
    - CBC - weekly in first month, then monthly to rule out bone marrow suppression, anemia as a side effect of Linezolid
    - KFT, Sr. Electrolyte – monthly during the period that Inj Capreomycin is being administered
    - LFT - monthly in IP and 3 monthly during CP
    - CXR - 6 monthly,
    - TFT & other tests as and when clinically indicated

  The Committee accepted the recommendation with the suggestion the number and time of visits by the Cat V patient to the DOTS Plus site for follow up should be detailed in the guidelines.

- The treatment outcome definitions for Category V will be similar to the ones existing for Category IV. The Central TB Division will further develop the treatment outcomes. The records and reports for Category V will developed by the Central TB Division.

  The Committee accepted the recommendation

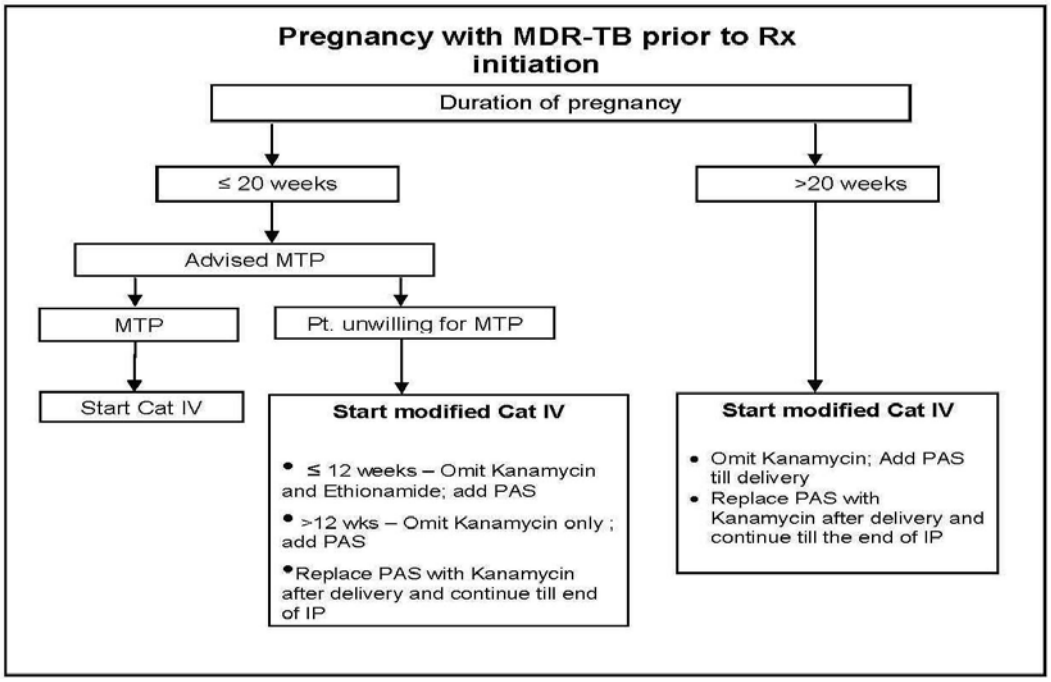
2. Mangement of pregnant patients under DOTS-Plus

Recommendations of the Sub-Committee along with the observations of the DOTS-Plus Committee (in italics) are as below:

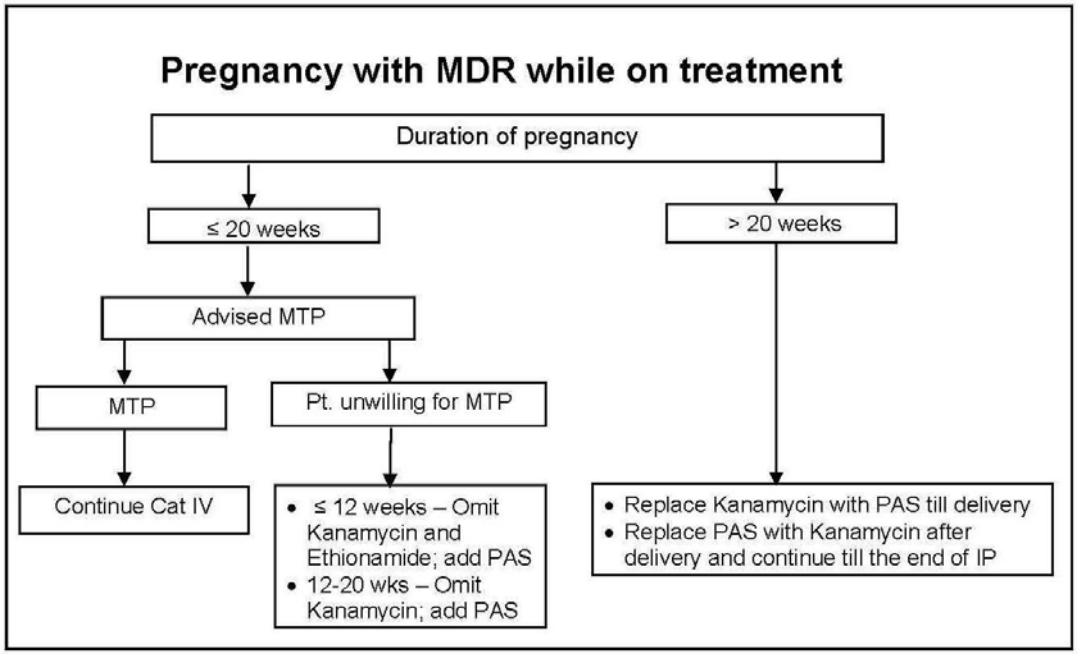
- All female MDR suspects and MDR patients of childbearing age should be counseled intensively in relation to the use of for contraceptive methods, and it should be ensured that all females of childbearing age diagnosed as MDR should undergo pregnancy testing before starting Cat IV regimen.

  The Committee accepted the recommendation while emphasising on the need for intensive and regular counselling of all female MDR suspects and patients in the child bearing age group which should be recorded in the Cat IV treatment card (Cat II in case of MDR suspects).

- For MDR patients who are pregnant prior to initiation of Cat IV treatment, the sub-committee recommended that all such patients (up to 20 weeks pregnancy) should be counseled and advised MTP. For patients who are unwilling for MTP or have a pregnancy of >20 weeks, they should be started on a modified Cat IV regimen as outlined in the flow chart below.



- For MDR patients who become pregnant while on treatment, it was recommended that such patients should be advised to undergo MTP if the duration of pregnancy is up to 20 weeks. For patients who are not willing for MTP or if the duration of pregnancy is >20 weeks, the Cat IV regimen is modified as per the flow chart below.



Dr Sharma expressed his concern over the use of PAS in pregnancy as it was known to cause neonatal goitre. It was informed that the Sub-Committee, which had Dr J B Sharma (Assoc. Prof. of Gynaecology, AIIMS) as one of the members, had recommended the use of PAS after thorough review of the available literature. The Committee accepted both the above recommendations, with a suggestion to verify the safety of PAS in pregnancy.

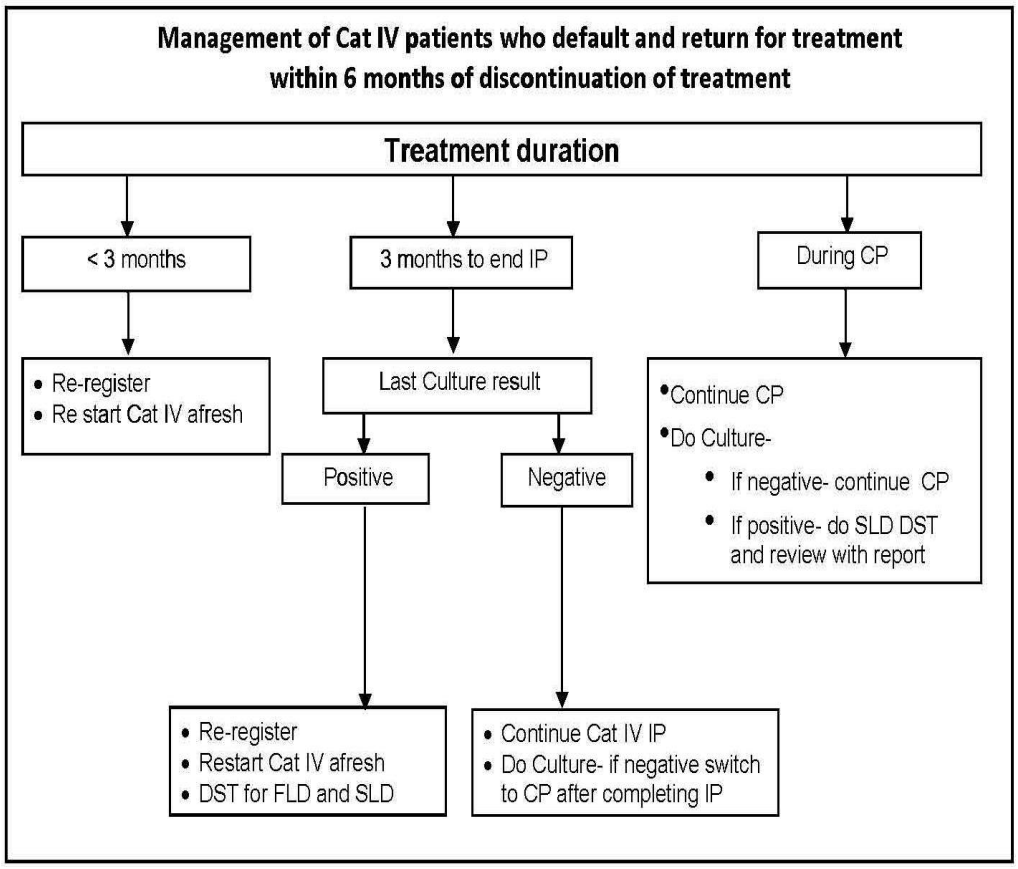
3. Management of patients who default for more than two months under DOTS-Plus and report back to the programme again.

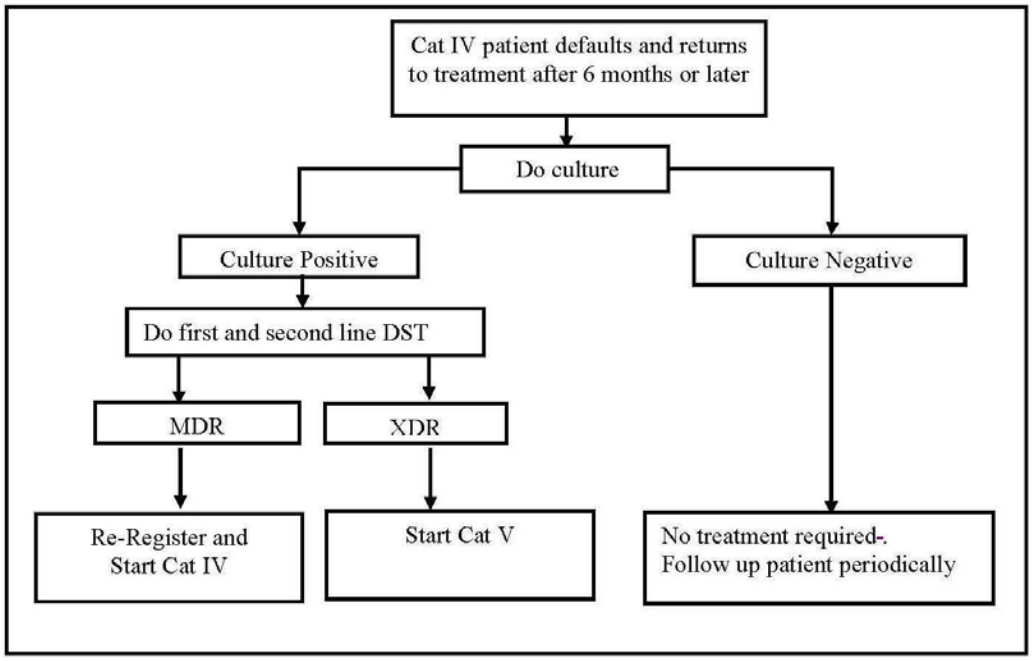
- All efforts should be made to ensure that Cat IV patients do not interrupt treatment or default. Appropriate action should be taken to promptly retrieve patients who fail to come for DOT.

  The Committee emphasised on preventing default through regular and effective counselling of all Cat IV patients and intensive and timely efforts for retrieval of those who interrupt treatment.

- The Sub-Committee recommended that further action for patients who return to treatment after having defaulted would be done on the basis of duration of discontinuation of treatment, as follows:
  - less than 6 months; or
  - 6 months or more.

  The recommendations for the two groups are given in the flow charts below:





The Committee accepted the recommendation that once a patient has defaulted, he/she should be given an outcome of default for that cohort. However some members were of the view that all such patients if returning to treatment, irrespective of the duration of default, should be re-registered for treatment and decision to continue treatment or start treatment afresh can be taken on the basis of the duration of treatment taken prior to default. However there was a concern regarding re-registration of all defaulted patients who return to treatment as this would lead to an increase in the number of MDR cases due to double registration. It was also suggested that these patients may be re-registered under the earlier number suffixed by 'A'. The Committee finally decided that CTD should deliberate and resolve this issue.

One of the other issues discussed was regarding the treatment to be provided to defaulted patients, returning back to treatment 6 months or later, while awaiting the results of DST for first and second line drugs. It was decided that these patients should be treated symptomatically during the interim period.

4. Management of drug resistant patients other than MDR e.g. Mono and poly non-MDR TB

- All cases of Rifampicin mono-resistance will be treated with a Category IV regimen. CTD to discuss this further and finalise the operational issues related to this decision.
- The Sub-Committee was of the view that there was presently insufficient data to conclude that mono- and poly-drug resistant cases respond poorly to Category II treatment. Hence it was decided that additional data should be collected from the Gujarat DRS (completed in 2006), Andhra Pradesh DRS (ongoing), LRS and the DOTS-Plus sites on the response of such cases to Category II treatment.
- The Sub-Committee also recommended undertaking a randomized controlled trial to compare Category II treatment with a modified Category IV regimen for mono- and poly- drug resistant cases.

All the recommendations of the Sub-Committee were unanimously accepted by the DOTS-Plus Committee.

5. Replacement of Ofloxacin by Levofloxacin in the RNTCP Cat IV regimen

The Sub-Committee was of the view that there was sufficient evidence to show that levofloxacin, the levo-isomer of ofloxacin, was more effective than ofloxacin. The WHO guidelines for the programmatic management of drug-resistant tuberculosis (Emergency Update 2008), also states that levofloxacin is more effective than ofloxacin whilst having similar adverse effect profile and that levofloxacin *may* have some efficacy in vivo against a small subset of ofloxacin resistant strains. The guidelines therefore recommend that levofloxacin is presently the fluoroquinolone of choice for treatment of MDR-TB. In terms of costs levofloxacin was comparable, if not slightly cheaper than ofloxacin. Further patients presently on the RNTCP Category IV regimen with ofloxacin could be safely switched over to levofloxacin. The recommended dose of

levofloxacin is 500mg for patients ≤45 Kgs and 750 mg for patients >45 Kgs. There would also be an additional benefit in terms of reduction in the number of pills for MDR-TB patients weighing less than 45 Kg, as the patient will have to take only 1 tablet of levofloxacin 500mg against 2 tablets of ofloxacin (one 400mg + one 200 mg). In view of the additional benefits of levofloxacin, the Sub-Committee strongly recommended that ofloxacin should be replaced with levofloxacin in the Category IV regimen.

Dr Santha expressed concern over the inclusion of levofloxacin in the Cat IV regimen, as it was a comparatively newer drug and there was insufficient data on its safety profile when used for long durations. It was informed that levofloxacin was actually the active component of Ofloxacin and there were sufficient evidence on its efficacy and safety. It was also suggested by some members that Moxifloxacin should be used in place of Ofloxacin as apart of Cat IV regimen. Dr Puneet made a presentation on this issue, wherein it was highlighted that there is inadequate evidence to support the contention that Moxifloxacin would be more efficacious in Cat IV relative to Levofloxacin/Ofloxacin. Given the high prevalence of Ofloxacin resistance observed in India and the very limited in-vitro evidence that some proportion of Ofloxacin resistant isolates may be susceptible to Moxifloxacin, it is possible that Moxifloxacin may be a part of future improved regimens. It was felt that additional evidence was required on prevalence of Ofloxacin resistance in the Cat IV population; extent of Ofloxacin - Moxifloxacin cross resistance in Indian isolates and clinical trials to assess the effectiveness of MFX containing regimens in OFX sensitive and OFX resistant MDR TB.

The Committee accepted the recommendation of replacing ofloxacin with levofloxacin in the Cat IV regimen, whilst recommending that additional evidence is needed prior to any consideration of the use of Moxifloxacin in the Cat IV regimen.

This was followed by a presentation by Dr Wares on the culture conversion rates of the initial cohort of Cat IV patients initiated on treatment primarily in Gujarat with a few cases from Maharashtra. It was informed that the diagnostic DST, including DST for fluoroquinolones, of this cohort of patients had been performed at TRC. The data had been analyzed to study the effect of fluoroquinolone resistance on culture conversion amongst these patients. The key findings of the rapid desk review were:

- Very high levels (>50%) of initial fluoroquinolone resistance observed in initial cohort of Cat IV patients in Gujarat
- Interim results at 12 months amongst fluoroquinolone sensitive cases show 40% with unfavourable status (Cul +ve / Dead / Defaulted) as compared to 62% amongst fluoroquinolone resistant cases.
- Interim results at 6 months in Maharashtra also shows ≈35-40% unfavourable status
- DRS data (2005-06) from Gujarat shows 25% fluoroquinolone resistance in previously treated TB patients at entry to Cat II treatment
- Almost 24% FQ resistance seen in the first cohort of MDR-TB cases detected in Kerala

It was observed that, although preliminary, emerging data indicated that fluoroquinolone resistance appears to be very common and associated with poorer culture conversion and interim outcome results. The following limitations were recognized.

- Analyses performed on a very limited numbers of patients in Gujarat (N=105 for 6 month culture conversion; N=77 for 12 month culture conversion) all of whom were “failures of Category II treatment” and also often were “chronic” cases. The results seen may not be extrapolated to Cat I, II and III failures.
- Second Line DST and follow up cultures data was unavailable for some patients.
- Data on amplification of resistance while on treatment was not available for majority of patients
- Other potential risk factors such as age, extent of disease, adherence to treatment, co-morbidities, and prior exposure to other anti-TB drugs could have a bearing on culture conversion and vital status, but were not included in the analyses.

A number of recommendations were made.

The Committee whilst expressing concern over the poor interim outcome results observed amongst the initial cohort of Cat IV cases in Gujarat, felt that there was presently insufficient data to conclude that fluoroquinolone resistance

was as high amongst all types of MDR suspects, or to assess the effectiveness of the present Cat IV regimen in patients with fluoroquinolone resistance. The Committee recommended that:

- *There was an urgent need to generate more data on the prevalence of fluoroquinolone resistance amongst all types of MDR suspects (Cat I, II and III failures). It was observed that although it had been previously decided to perform SL DST on all Cat IV cases detected in Gujarat and Maharashtra, this was not being routinely done. The Committee recommended that it should be ensured that Gujarat and Maharashtra routinely send the diagnostic culture isolates of all MDR-TB cases already diagnosed to TRC and NTI respectively for second line DST.*
- *In addition, it was decided that TRC and NTI will henceforth perform second line DST (at least for Ofloxacin and Kanamycin) on the diagnostic and '0' month (pre-treatment) culture isolates of all MDR-TB cases from Gujarat and Kerala (TRC), and AP and West Bengal (NTI), for a period of at least one year. CTD needs to take the necessary steps to operationalise this recommendation.*
- *CTD and Gujarat team to undertake field review to document and analyse the potential confounders in patients in Gujarat in the initial cohorts to better understand risk factors for poor interim outcome.*
- *It should be ensured that second line DST should be performed on all Cat IV patients who are "suspected to be failing Cat IV treatment".*
- *A comprehensive, integrated electronic information system linking the labs, the DOTS-Plus sites and districts to improve information transmission and allow for better analyses of available data, should be developed and implemented on a priority basis.*
- *CTD and NRLs should consider undertaking rapid surveys for fluoroquinolones in NSP cases, and include SL DST in DRS surveys for Cat II patients on entry to treatment.*

Following the discussion, Dr Solanki made a presentation justifying the inclusion of contacts of MDR TB patients under Cat IV services as MDR suspects. The data from Gujarat shows that the total number of close contacts of 136 confirmed MDR TB cases who were screened, were 823. Amongst these, 42 were found to be chest symptommatics and 8 were found to be smear positive PTB cases. Therefore inclusion of contacts of MDR cases who have been found to have smear positive PTB cases will increase the workload marginally.

The Committee recommended that all efforts should be made to screen the close contacts of MDR TB cases as per the RNTCP guidelines, and those found to be smear positive PTB cases will be included as MDR suspects and offered culture and DST. Till the availability of the C & DST results, these patients will be initiated on Cat I or II based on the previous treatment history.

This was followed by a presentation and discussion on the revision of the existing exclusion criteria. It was informed that in the last DOTS-Plus Committee meeting, it was decided to withdraw pregnancy and existing severe mental illness as exclusion criteria. Presently there are two exclusion criteria:

- Age < 15 years
- Having had over 1 month of treatment with any second line anti-TB drugs

It was informed that the exclusion criteria had been included initially mainly to restrict the number of patients to be enrolled, with an understanding that the excluded groups would be included in the ambit of the programme when more experience had been gained in implementation of MDR TB services and services were more widely available. The data available from the nine states which are currently implementing DOTS-Plus, shows that a very small number have been excluded based on the above 2 criteria (90 from amongst around 4,000 suspects). Further, from an ethical point of view RNTCP is now obliged to provide the Cat IV services to all MDR suspects irrespective of age and history of second line drugs.

In view of the inclusion of the MDR suspects who are <15 years of age and also for the benefit of low weight adults, it was proposed to add another weight band to the existing two which would be 16-25 Kgs.

The Committee endorsed the recommendation of withdrawing the remaining two exclusion criteria and the addition of another weight band for patients between 16-25 Kgs. The Committee suggested that the doses for the paediatric age group be finalized in consultation with the paediatricians.

Day 2

The proceedings of the second day began with an update by individual states on the progress of implementation of DOTS- Plus services.

Gujarat

- Dr R N Solanki presented the progress update of DOTS- Plus in Gujarat on behalf of the STO. The key highlights of the presentation were:
    - Till the end of 2Q09, a total of 877 MDR suspects had been subjected to C&DST with 290 diagnosed as MDR TB. Out of these, 200 had been initiated on Cat IV treatment.
    - DOTS Plus services were presently available in 10 districts (AMC, Gandhinagar, Sabarkantha, Mehsana, Anand, Nadiad, Ahmedabad(R), Banaskantha, Patan and Surendranagar).
    - As per the expansion plan, the State would initiate DOTS-Plus services in:
        - 7 more districts in August 2009
        - 6 more districts in Jan 2010
        - 7 more districts in June 2010, thus covering the entire state.
    - Besides the IRL in Ahmedabad, the State planned to have 2 more accredited laboratories to support the DOTS-Plus activities. This includes a private laboratory in Surat (Micro-Care) which has applied for accreditation and would be enrolled under the NGO Culture and DST scheme on successful accreditation. The other laboratory is proposed to be established at the Jamnagar Medical College.
    - The State had identified 3 more DOTS-Plus sites in addition to the existing one at BJMC, Ahmedabad. These are proposed to be at GMC Vadodara, GMC Surat and GMC Jamnagar.
    - The key constraint faced by the State was lack of adequate manpower at the DOTS-Plus site and districts.

The Committee commended the State for being one of the first states to initiate DOTS-Plus services. The Committee while appreciating the expansion plan cautioned the State that the quality of basic DOTS services should not be compromised while scaling up of DOTS-Plus services. Instead the DOTS-Plus activities should strengthen the basic DOTS services. With regards to the issue of an adequate manpower, DDG informed that the programme is in the process of making provision for additional staff at DOTS-Plus site and district for effective implementation and supervision of DOTS-Plus services.

It was informed that NGOs were supporting treatment adherence through counselling under a project funded by Eli-Lilly. The Committee recommended that such NGO support was essential for ensuring treatment completion and suggested that if the pilot project is found to be successful and feasible, it should be replicated in other states also. In response to the information that a particular NGO was providing incentives, in the form of food rations, to MDR patients in Ahmedabad, the Committee opined that such practices should not be encouraged and instead the patients should be linked to the social welfare schemes for necessary support.

Kerala

- This was followed by a presentation by Dr Kumari H Prema, STO Kerala.
    - Till the end of 2Q09, a total of samples from 674 MDR suspects have been sent for C&DST. Out of 173 results available, 92 are MDR out of which 70 have been initiated on treatment.
    - The whole state is covered under DOTS-Plus. There are presently two DOTS-Plus sites - one at TB Sanatorium Trivandrum and the other at Calicut medical college.
    - One of the innovations highlighted in the presentation was that the pre-treatment evaluation was being done at district level, following which the patient was referred to the DOTS-Plus site. This reduced the duration of stay at the DOTS-Plus site.
    - The State has managed additional support from NRHM for one Medical Officer and one TBHV for both DOTS-Plus sites.

- The key constraints faced by the State are:
  - Management of Non MDR poly resistant cases
  - Retaining trained contractual staff at the IRL
  - Preparation of CPC bottle

The Committee appreciated the progress and the innovations made by Kerala in the implementation of DOTS-Plus services. The additional support from NRHM was recognised as an example of effective coordination between RNTCP and NRHM. It was pointed out that as per the guidelines, the CPC bottles should be prepared at the DTC, any further decentralisation is presently not recommended.

Rajasthan

- This was followed by a presentation by Dr K N Gupta, STO Rajasthan
  - Rajasthan initiated DOTS-Plus services in 7 districts from May 2009. At the end of 2Q09, samples from 399 MDR suspects have been sent for C&DST (117 to NTI and 282 to IRL at Ajmer). Out of the 32 confirmed MDR cases, 16 have been put on Cat IV treatment. The DOTS-Plus site is at SMS, Jaipur.
  - The IRL has been accredited in March 2009 and the lab at SMS Jaipur is under accreditation process. The State has planned to augment its laboratory capacity by establishing accredited labs at Medical Colleges Udaipur and Jodhpur and involving Desert Medical Research Centre at Jodhpur.
  - The State had plans to scale up DOTS-Plus services to another 8 districts in October 2009, with another DOTS-Plus site at Medical College, Jodhpur.

The following issues were raised by the STO during the presentation.

- Clarification was sought regarding the inclusion of patients, who had relapsed after having taken Cat II in the past, as MDR suspects.

  The Committee opined that as per the present policy, such patients should be initiated on Cat II and if found to be smear positive after 4 months of treatment or later should be taken as MDR suspects.

- It was informed that the Inj Kanamycin 750 mg (for patients >45 Kgs) and Ethambutol 200 mg, which were required for Cat IV patients weighing >45Kgs, had not been supplied centrally. Also Pyridoxine, to be procured by the State as directed by CTD, was not available as per the technical specifications provided.

  DDG clarified that Inj Kanamycin 750 mg could not be procured centrally as there were no bids for the same. It was clarified as there would be only a small number of Cat IV patients weighing >45 Kgs, two vials of Inj Kanamycin 500 mg may be used for such patients. In case Pyridoxine was not available as per the technical specifications provided by CTD, a decision in this regards can be taken by the State Health Society under information to CTD.

- It was suggested that the State may be allowed to give honorarium to all Cat IV DOT providers including health workers in view of similar provision by other health programmes.

  It was clarified that as per the programme policy, only non-salaried DOT providers were eligible for honorarium, hence the above suggestion was not acceptable. The State was asked to intensify efforts in involving private practitioners as Cat IV DOT providers.

- Dr Gupta informed that in certain situations, especially when the laboratory equipment at the district hospital/DOTS-Plus site breaks down, the pre-treatment evaluation has to be done from private laboratories to avoid delay in initiation of treatment. It was requested that this expenditure towards investigations and also those for ancillary drugs required for management of adverse reactions may be allowed to be met from the miscellaneous head of RNTCP funds.

  DDG informed that the programme was providing free treatment, diagnostic and follow up services to all Cat IV patients. It was therefore expected that the State Government should at least provide

investigations and ancillary drugs free of cost to these patients. In special situations, as cited above, these costs may be met from NRHM funds.

- Clarification was sought on whether patients, who are outside the programme and have been diagnosed as MDR from RNTCP accredited laboratories (especially NRLs), can be initiated on Cat IV treatment.
  It was clarified that such patients can be initiated on Cat IV treatment, only if they fulfil the necessary eligibility criteria as per the programme guidelines. The Committee also recommended that NRLs should not undertake C&DST for patients from states which have an accredited RNTCP laboratory. Such patients should be referred back to the programme in the respective states for necessary investigations and treatment.

- Clarification was sought regarding reimbursement of travel costs to the district TB centre for patients (and one attendant) who are not willing for referral to the DOTS-Plus site and are investigated and initiated on treatment at the DTC.

  It was informed that presently the reimbursement is restricted to travel costs for visiting the DOTS-Plus site. However this will soon be extended to scheduled and emergency visits to the DTC also. The proposal is presently under approval.

- *In response to a query regarding the provision of Counsellors at the DOTS-Plus site, it was clarified that presently there was no such provision under RNTCP. The Committee opined that the DOTS-Plus sites, being tertiary care centres, would be having Counsellors whose services can be sought for Cat IV patients who will be few in number. Also under the newly introduced 'Adherence Scheme', NGOs can be enrolled for providing counselling services to Cat IV patients.*

- Dr Gupta informed that the suppliers of the IRL equipment, despite having signed the Annual Maintenance Contract (AMC), were demanding Rs 50,000/- for visiting the IRL for maintenance/repair of the equipment.

  DDG clarified that the supplier had signed the AMC with the State and was bound to honour the terms and conditions of the same. Any violation of the contract by the supplier should be dealt severely and appropriate legal action should be initiated by the State in this regards.

- STO also sought CTD's support on the following:
  - Rajasthan had recruited additional manpower for DOTS-Plus activities (1 Medical Officer, 2 lab attendants and 3 lab technicians) for a period of one year and purchased computers and accessories with NRHM support. It was requested that RNTCP should make a provision for supporting the additional manpower and maintenance of the equipment purchased once NRHM support was over.
  - There was a requirement of additional equipment for the IRL at Ajmer, including an additional compressor for cold-room and funds for AMC of cold-room and incubator.

  DDG informed that there is a proposal for provision of additional manpower for DOTS-Plus activities (1 Medical Officer and 1 Statistical assistant at the DOTS-Plus site, and 1 DOTS-Plus and TB-HIV supervisor for each district) which is expected to be approved shortly. Also a provision was being made for providing computers with internet connection to all DOTS-Plus sites.

  For the additional equipment for the IRL, the State was asked to include them in the State PIP.

Haryana

- This was followed by presentation by Dr Rakesh Sehl , STO Haryana.

  - At the end of 2Q09, the total of number suspects examined is 219. Total MDR diagnosed is 23, out of which 17 have been placed on Cat IV treatment.

- Presently 7 districts (Rohtak, Bhiwani, Jhajjar, Jind, Panipat, Karnal, and Sonepat) are covered under DOTS- Plus.
- The IRL is under accreditation and the samples are being sent to LRS for C&DST for the interim. The process of recruitment of contractual Microbiologist has been initiated.
- The State plans to expand DOTS-Plus services to another 10 districts in March 2010 and cover the entire State by September 2010.

DDG welcomed the new STO and assured him of all necessary support. The State was advised to expedite the process of recruitment of the contractual Microbiologist and take necessary steps for accreditation of the IRL which has been delayed considerably. It was informed that a GLC and GLI mission will be visiting Haryana in last week of July to assess the status of the DOTS-Plus services in the State. The State was asked to make the necessary preparations and rectify the shortcomings for the forthcoming mission.

Tamil Nadu

- This was followed by a presentation by Dr Ranjana on behalf of STO Tamil Nadu
  - At the end of 2Q09, the total of number suspects examined is 101. Total MDR diagnosed is 24 ,out of 6 have been placed on Cat IV treatment.
  - Presently 4 districts (Kancheepuram, Villupuram, Cuddalore and Thiruvenmalai) are covered under DOTS- Plus.
  - There are 2 accredited laboratories in the State IRL and CMC, Vellore. The signing of MoU with CMC is underway.
  - The State plans to expand to another 5 districts shortly. The National level training for these districts has been undertaken, and the state and district level trainings are underway.

The Committee observed that the recruitment of MDR suspects for C & DST and MDR cases for Cat IV treatment has been very slow and asked the state to intensify the efforts in this regards. One of the reasons for the poor recruitment is the existence of a parallel system of MDR TB treatment at GHTM Tambaram and ITM, Chennai. The Committee recommended that the State should take necessary steps to immediately discontinue this parallel system for residents of districts where DOTS-plus services are available, and integrate these institutes under DOTS-Plus. Dr Wares pointed out that TRC was also recruiting MDR patients from Chennai for research study. These patients are being treated as per programme guidelines and should be included and reported in the cohort of patients under treatment.

West Bengal

- This was followed by a presentation by Dr Dutta Choudhary STO, West Bengal.
  - At the end of 2Q09, the total of number suspects examined is 118. Total MDR diagnosed is 37, out of which 20 have been placed on Cat IV treatment.
  - Presently only Kolkata is covered under DOTS-Plus.
  - The IRL has successfully completed the proficiency testing and will be accredited shortly. Presently the samples are being sent to NTI for C&DST.
  - The State plans to expand DOTS-Plus services to another 5 districts by the end of 2009.
  - Some of the constraints highlighted were:
    - Sub-optimum level of participation of the private medical college adjacent to the DOTS-Plus site.
    - There are no facilities at the DOTS-Plus site for undertaking essential investigations for pre-treatment evaluation
    - The MDR suspect identification and sending the samples to IRL for forward transmission to NRL has been a time consuming process.
    - Tendency of some specialists to prescribe second line drugs e.g quinolones as an adjunct to first line anti TB drugs.
    - Manpower shortage faced by the DOTS-Plus site for maintenance of records and updating of Cat IV treatment cards.

The Committee recommended that the State should intensify efforts to enhance the recruitment of MDR suspects. It was observed that the selection of the DOTS-Plus site has not been optimal as facilities for undertaking basic investigations were not available. The Committee recommended that the selection of the DOTS-Plus site should be based on the certain criteria which include:

- *Availability of necessary facilities for admitting and undertaking pre-treatment evaluation of the MDR patients and management of adverse reactions and complications associated with treatment of MDR TB.*
- *Availability of staff which has some prior experience of treating MDR TB.*

It was observed that 2 MDR patients had not been put on Cat IV treatment as they had been declared cured under Cat II. It was clarified that all cases diagnosed as MDR should be initiated on Cat IV treatment irrespective of their outcome under Cat II.

It was informed that the state would receiving 100 courses of second line drugs and needs to expedite the expansion plan. The National level DOTS-Plus training for the expansion districts has been planned in August/September 2009.

Delhi

- This was followed by a presentation by Dr Vashist, STO- Delhi.
    - At the end of 2Q09, the total of number suspects examined is 833. Total MDR diagnosed is 185, out of which 118 have been placed on Cat IV treatment.
    - The whole state has been covered under DOTS-Plus from Jan 09. There are 4 DOTS-Plus sites - Lok Nayak Hospital Chest Clinic; Rajan Babu TB Hospital; Dept of Medicine, AIIMS; and LRS Institute.
    - The State presently has 2 accredited laboratories LRS Institute and the New Delhi TB Centre. The laboratory at AIIMS is under accreditation. There are another 5 labs in the State which can be involved.
    - It was informed that the State was also undertaking a project on providing home care services to MDR patients which was being supported by Eli-lilly.
    - The key constraints faced by the programme are:
        - Migration leading to treatment interruption and default
        - MDR suspects from NCR region which are actually not covered under DOTS-Plus
        - Need for additional staff
        - Uninterrupted drug supply and short shelf life of second line drugs

The Committee discussed the plan for having seven accredited labs in Delhi. In view of the fact that the accreditation and the ongoing quality assurance was a resource intensive process, it was suggested that the State should review and rationalise the number of laboratories based on the expected workload. It was also suggested that some of these laboratories once accredited can be linked for provision of services to other States.

In response to a query by Dr Dewan, STO Delhi informed that areas for each of the DOTS-Plus sites were well demarcated and that, for residents of Delhi, there was no parallel system of treating MDR outside RNTCP at the identified DOTS-Plus sites.

The Committee commended the State on the rapid expansion but expressed concern that the implementation of DOTS-Plus services should not affect the basic DOTS. Further the Committee suggested that a training of all the DTOs, who have not yet been trained at the National level, should be conducted on priority at LRS Institute.

Andhra Pradesh

- This was followed by a presentation by Dr Shailaja on behalf of STO, Andhra Pradesh .
    - At the end of 2Q09, the total of number suspects examined is 344. Total MDR diagnosed is 102, out of which 67 have been placed on Cat IV treatment.

- Presently 8 districts (Hyderabad, Rangareddy, Medak, Nalgonda, East Godavari, West Godavari, Krishna and Guntur) are covered under DOTS-Plus. There are 2 DOTS-Plus sites - AP Chest Hospital at Hyderabad and Guntur Medical College.
- The State presently has 2 accredited laboratories - IRL and BPRC laboratories at Hyderabad.
- The State plans to expand to another 3 districts in October 2009 and cover the entire state by April 2010.
- The key constraints faced by the programme are:
  - Timely submission of follow up culture by districts
  - At the DOTS-Plus site, inadequate Infection control measures and availability of IEC material
  - At District level/sub-district level
    - Ensuring treatment adherence
    - Additional human resource
    - Supervision of DOTS-Plus patients
    - Counselling and motivation of patients at all levels

Maharashtra

- This was followed by a presentation by Dr Katti, Deputy STO Maharashtra
  - At the end of 2Q09, the total of number suspects examined is 759. Total MDR diagnosed is 210, out of which 115 have been placed on Cat IV treatment.
  - Presently 13 districts (Nagpur Corp, Nagpur Rural, Wardha, Bhandara, Gondia, Gadchiroli, Chandrapur, Akola, Amravati, Amravati Corp, Buldana, Washim, Yavatmal) are covered under DOTS-Plus. DOTS-Plus services will be initiated in Mumbai shortly. The State has a well conceived plan to scale up to the entire state in a phased manner by 2011-12.
  - There are presently 2 DOTS-Plus sites - BJMC, Nagpur and Medical College, Akola (presently under renovation).
  - The State presently has one accredited laboratory - IRL, Nagpur. Two laboratories are under the accreditation process - Hinduja Hospital and GMC & JJ Hospital, both in Mumbai.
  - On the recommendation of the NRL and CTD, the IRL has taken several measures to reduce the high contamination rate. These include:
    - Ensuring preparation of fresh CPC solution and use within one month.
    - Instructions issued to all concerned to send the sample on the same day of collection thus reducing the time gap between sputum collection and sputum processing.
    - Restricted entry to the laboratory
    - The floors of the media preparation room and culture processing room are mopped with 5% phenol daily.
    - The DST work is shifted to the bio-safety cabinet where culture processing is done.

The Committee appreciated Andhra Pradesh and Maharashtra on their progress and plan for scale up of DOTS-Plus services. It was recommended that the States should ensure that the timelines as reflected in the expansion plan are adhered to.

The States were asked to monitor and ensure timely reporting of the Cat IV drug stocks at the district level (including the stock at TU level) every quarter as per the format provided by CTD.

Dr Mundade (FIND, India) made a presentation on the status and future of diagnostic tools for TB. This was followed by presentation by Dr Raizada (FIND, India) on the results of the validation phase of the molecular Line Probe Assay (LPA) study as a part of the RNTCP-FIND collaborative projects in India.

The highlights of the presentation were:

- The LPA was successfully established in 2 RNTCP IRLs and 1 medical college, and labs demonstrated proficiency with a standard protocol.
- LPA was highly accurate in the detection of rifampicin resistance from direct sputum specimens. H resistance was detected with lower sensitivity, hence those results would have to be interpreted with caution.

        - Sensitivity and specificity for rifampicin detection, after reconciling the results with NRL re-testing of specimens with discordant results, was 96% and 99%, respectively.
        - Sensitivity and specificity for detection of isoniazid, after reconciling results with NRL re-testing of specimens with discordant results, was 72% and 98%, respectively.
    - The demonstration study would use the LPA

The committee agreed that the results of evaluation phase were as per the previous scientific reports from India and elsewhere. It is recommended that the study may proceed further with the demonstration phase to answer the challenges of using the LPA for patient diagnosis under the programmatic conditions. In demonstration sites at Andhra Pradesh, Gujarat and Maharashtra, patients detected as having rifampicin resistance by LPA would be immediately offered Category IV treatment. The committee agreed with the presented plans for management of patients with discordant LPA and LJ DST results, but expressed concern that the supply of Cat IV drugs needs to be adequate to manage all patients eligible for Cat IV treatment at the study sites.

This was followed by a discussion on the constitution of a writing group for the revising of the DOTS-Plus training modules for the Medical and Paramedical staff. The following members volunteered for the same:

1. Dr Santha Devi
2. Dr Rajeswari Ramachandran
3. Dr Sarin
4. Dr Singla
5. Dr Venu
6. NTI-1
7. Representatives from CTD and WHO
8. STDC Ahmedabad-2
9. STDC Hyderabad-2

NTI offered to coordinate the activity. It was decided that as a first step, the DOTS-Plus guidelines will be updated, incorporating the decisions taken in the present DOTS-Plus Committee meeting. The updated guidelines will be circulated to all the members following which a meeting of the group will be held tentatively in the last week of August 2009 to discuss the further plan of action.

DDG informed the members that henceforth prior to the actual implementation of DOTS-Plus activities the respective State, Culture and DST lab, State Drug Store and districts will be critically appraised by a Central level team. In this regards, CTD has developed a DOTS-Plus appraisal format which will be circulated to all members of the DOTS-Plus Committee for their comments.

The meeting ended with a vote of thanks to all the members.

List of Participants

Annex-I

1. Dr S K Sharma, AIIMS, New Delhi
2. Dr D Behera, Director, LRSI, New Delhi
3. Dr L S Chauhan, DDG(TB)
4. Dr P Kumar, Director, NTI Bangalore
5. Dr Rohit Sarin, LRSI New Delhi
6. Dr Rupak Singla, LRSI, New Delhi
7. Dr Nevin Wilson, UNION SEA
8. Dr Devesh Gupta, CMO, CTD
9. Dr R N Solanki, Chairman, Zonal Task force (West)
10. Dr K Venu , Chairman, Zonal Task force (South)
11. Dr Rajendra Prasad, KGMU, Lucknow
12. Dr Shaheed Jawahar, TRC, Chennai
13. Dr S N Gaur, VPCI, New Delhi
14. Dr Santha Devi
15. Dr Rajeshwari Ramachandran, WHO
16. Dr Fraser Wares, WHO-India
17. Dr S Sahu, WHO-India
18. Dr Puneet Dewan, WHO-SEARO
19. Dr Ranjini Ramachandran, WHO SEARO
20. Dr Yamuna Mundade, FIND
21. Dr Neeraj Raizada, FIND
22. Dr M M Puri, LRSI
23. Dr Neeta Singla, LRSI
24. Dr Vishalakshi, LRSI
25. Dr Anand, NTI
26. Dr Srinath, UNION OR Fellow, CTD
27. Dr Ajay Thirumala, WHO Consultant, CTD
28. Dr Sarabjit Chadha, WHO Consultant, CTD

Additional participants on day 2:

1. Dr Ranjana, MO-STC, Tamil Nadu
2. Dr Prema Kumari, STO, Kerala
3. Dr Shailaja, Epidemiologist, STDC, Andhra Pradesh
4. Dr Katti,
5. Deputy STO, Maharashtra
6. Dr Vashist, STO Delhi
7. Dr Rakesh Sehl, STO Haryana
8. Dr K N Gupta, STO, Rajasthan
9. Dr Duttachoudhary, STO, West Bengal