To avail these, Healthcare providers should endeavor to derive synergies between various social welfare support systems like RSBY, TB pension schemes, national rural employment guarantee scheme,corporate social responsibility (CSR) initiatives, counselling centres etc.to mitigate out of pocket expenses such as transport and wage loss incurred by people affected by TB.

All individuals with active TB should receive (i) an assessment of their nutritional status and (ii) appropriate counselling based on their nutritional status at diagnosis and throughout their treatment. (iii)If malnutrition is identified, it should be managed according to WHO recommendations. Linkages for extra nutritional support for TB patients or of his/her contacts on IPT may be explored with existing Govt. schemes like public distribution system (PDS) or Food security act.

Under the programme, compensation is provided for transport costs incurred by DR TB patient for sending specimen for follow upor for travel to DR-TB centre. In addition, TB patients in tribal and difficult areas get Rs. 750.Treatment supporters are also provided incentive to ensure completion of treatment as below:

Category I	Rs. 1000 per patient
Category II	Rs. 1500 per patient
Category IV / V	Rs. 5000 per patient

The compensation may be given to TB HIV patients for visits to ART centers. For enablers or incentives refer to **Annexure 8**. If required, linkages with various social support systems to be explored and ensured, for additional treatment support. Capacity building and engaging with local community based organizations, self-help groups, patient support groups, PRI could prove to be effective intervention to promote treatment adherence.

All patients, should have free or affordable quality assured diagnostic and treatment services, which should be provided at locations and times so as to minimize workday or school disruptions and maximize access.

Box: Choices for ICT based Treatment adherence support

Mobile based "Pill-in-Hand" adherence monitoring tool In this mechanism, each time a patient takes a dose of medication, a hidden number appears which is printed on the strip behind the drug. The patient need to send a missed call to a particular contact number with the digits appeared on drug package. This will be documented at a centralized ICT unit. And thus, an electronic treatment record of each patient will be maintained to monitor the treatment adherence.

Because the sequence of hidden numbers cannot be predicted by patients, but are known by the system for each month of medication prescribed, the system offers high confidence that patients who respond correctly have indeed dispensed their medication.

S/he can also be providing the option of where in the patients treatment would be remotely followed up with help of Interactive Voice Response (**IVR**), **SMS** reminders.

Specially designed **electronic pill boxes** or strips with GSM connection and pressure sensor can be used to monitor the pill consumption by tracking the weight of the remaining pills.

The treatment provider can use the **Patient Compliance toolkit;** a mobile app for patients to report treatment compliance using video, audio or text message.

Automated pill loading system, which will load the dosage as per the pre-programmed settings. Medication dispenser: a color-coded reminder system built in the dispenser that will hold drugs.

Treating doctors can be provided with **innovatively designed cards** to educate them on correct TB prescription methods. Doctors will then give these cards to TB patients, instructing them to SMS the server/ customer care centre (CCC) the unique code on the card which will register them on the network and also SMS the unique codes printed on their TB drugs as they take them. The CCC will then deliver phone interventions like reminders to take medicines, financial incentives, follow up calls, and TB health tips via SMS and phone balance recharge, mobile APP for scheduled dose reminders and alerts.

A Short Messaging service **(SMS) gateway** to be made available by which the patient can report day to day events like pill consumption, minor side effects or his need for help through simple and shortcut SMS templates. The gateway can allow incoming services in pre-recorded or Interactive Voice Response (IVR) mode to inform patients about their test results, as follow up reminders and as periodic counselling messages.

Follow up of Treatment

Patients should be closely monitored for treatment progress and disease response. There are two components of follow up: (1) Clinical follow up and (2) Laboratory follow up

1. **Clinical follow up** should be done at least monthly. Patient may visit the clinical facility for reviews or the medical officer may conduct the review when he visits the house of the patient. Improvement on chest symptoms, increase in weight etc. may indicate good prognosis. Control of co-morbid conditions like HIV and diabetes by appropriate treatment is essential for getting a better prognosis to TB treatment. Symptoms and signs of adverse reactions to drugs should be specifically asked. Detailed description of symptoms and signs of adverse reaction to anti-TB drugs and pharmacovigilance program is described in relevant section.

2. **Laboratory investigations** may be those to assess the prognosis of the disease or to manage co-morbidities or adverse reaction. In case of pulmonary tuberculosis, sputum smear microscopy should be done at the end of IP and end of treatment. A negative sputum smear microscopy result at the end of IP may indicate good prognosis. However, in the presence of clinical deterioration, the medical officer may consider repeating sputum smear microscopy even during CP. This will provide the patient an early opportunity to undergo drug susceptibility testing if s/he is found to be sputum smear positive. At completion of treatment, a sputum smear and/or culture should be done for every patient. This is very important because, culture is a more sensitive and specific test compared with smear microscopy to detect the presence of M.tb in biological specimens.

   Chest x-ray may be a good tool to assess the progress and it is to be offered to drug sensitive pulmonary TB patients whenever required and available. For drug resistant TB patients, it is to be carried out at end of IP, at end of treatment and whenever required.

   Response to treatment in extrapulmonary TB may be best assessed clinically. Help of radiological and other relevant investigations may be taken.

   Response to treatment in children: In children in their early ages are unable to produce sputum, the response totreatment among them may be assessed clinically. The help of radiological andother relevant investigations may also be taken.

Long term follow up: After completion of treatment, the patients should be followed up at the end of 6, 12, 18& 24 months. In presence of any clinical symptoms and/or cough, sputum microscopy and/or culture should be considered. This is important in detecting recurrence of TB at the earliest.

In case of DR-TB patients, the DTO will ensure that an updated copy of the treatment card is sent to the designated DR-TB Centre, preferably electronically, every month for updating the DR-TB Register. Clinical follow-up should be done monthly. For collection of the follow-up samples for culture, the patient will need to go to their respective sputum collection centre, where the DTO will arrange for the samples to be collected and transported to the respective RNTCP-certified Culture and DST laboratory. The patient will need to go to the DR-TB Centre for the decision to end treatment, for managing severe adverse drug reactions, and for any change of regimen or dosage. All referrals from the DTC to the DR-TB Centre or vice versa should be made on Referral for Treatment Form. The receiving health facility should communicate the receipt of patient to the referring centre through an e mail.

Type of Case	Follow up schedule	Extension of treatment	Action on follow up positive	Long term follow up
Drug sensitive Pulmonary TB (New & Previously treated TB)	**Microbiological**: One specimen at the time of completion of the intensive phase of treatment, and at the end of treatment. **Weight:** Monthly **Chest X-Ray: if required** **Physician evaluation** : whenever required	Extension of IP is not required	If the sputum smear is positive in follow-up at any time during treatment, DST should be done as per presumptive DR-TB case	After completion of treatment the patients should be followed up with clinical and/or sputum examination at the end of 6, 12, 18 and 24 months.
Multi Drug resistant Pulmonary TB *(with or without additional drug resistance)*	**Microbiological:** One sputum specimen will be collected and examined by culture at least 30 days apart from the 3rd to 7th month of treatment (i.e. at the end of the months 3, 4, 5, 6 and 7) and at 3-monthly intervals from the 9th month onwards till the completion of treatment (i.e. at the end of the months 9, 12, 15, 18, 21 and 24). If any culture during CP or end of treatment is positive then it should be followed by monthly culture for 3 months. **Weight:** Monthly **Chest X-Ray** at end of IP, end of treatment and whenever clinically Indicated **Physician evaluation** including adverse drug reaction monitoring every month for six months, then every three months for two years **S. Creatinine** monthly for first 3 months,	In MDR TB cases IP can be extended for maximum three months (maximum duration of IP – 9 months). In all MDR TB with additional drug resistant cases (including XDR TB) patients, IP can be extended for maximum 6 months (maximum duration of IP – 12 months)*.	On follow up if sputum culture is found to be positive at 6 months or later, repeat DST for second-line drugs to decide on further course of action. DST to other additional second line drugs may also be done if laboratory facilities are available to guide treatment.	

	then every 3 months during the injectable phase **Thyroid Function Test** during pre-treatment evaluation and whenever indicated **For additional drug resistance** :- ECG: once a month in IP whenever Moxifloxacin is used **Complete Blood Count with Platelets Count:** weekly in first month, then monthly to rule out bone marrow suppression and anaemia as a side effect of Linezolid **Kidney Function Test**- monthly creatinine and addition of monthly serum electrolytes to the monthly creatinine during the period that Inj. Capreomycin is being administered **Liver Function Tests**: monthly in IP and 3 monthly during CP **Chest X-Ray:** every 6 months in XDR-TB patients			
Mono- / Poly-Drug resistant Pulmonary TB	**Microbiological**: One sputum specimen is collected and examined with smear and culture at 2nd and 3rd months & then culture examination at 3-monthly intervals till completion of the treatment. **Weight:** Monthly **Chest X-Ray: if required** **Physician evaluation** : whenever required	IP can be extended for maximum three months (maximum duration of IP – 6 months).	If the sputum /culture is positive in follow-up at any time during treatment, DST should be done as per presumptive DR-TB case	After completion of treatment the patients should be followed up with clinical and/or sputum examination at

				the end of 6, 12, 18 and 24 months.
Extra Pulmonary TB	In patients with extra-pulmonary tuberculosis the treatment response is best assessed clinically. The help of radiological and other relevant investigations may also be taken as above.	-Extension of IP or and/or CP in DS EPTB may be required in consultation with the specialist concerned. -Extension of IP DR-TB EPTB may be required in consultation with the specialist concerned. - Refer to guidelines for EPTB duration of treatment.		
Pediatric TB	In children, who are unable to produce sputum, the response to treatment may be assessed clinically. The help of radiological and other relevant investigations may also be taken.	Same as above		

***Extension of IP in DR-TB patients**

MDR TB patients

IP should be given for at least six months. After 6 months of treatment, the patient will be reviewed and the treatment changed to CP if the 4th or 5th month culture result in solid or liquid culture is negative respectively. If the 4th or 5th month culture result remains positive, the treatment is extended by 1 month. Extension of IP beyond 1 month will be decided on the results of sputum culture of 5th or 6th and 6th or 7th months. If the result of the 4th month culture is still awaited after 6 months of treatment, the IP is extended until the result is available, with further treatment being decided according to the culture result. The IP can be extended up to a maximum of 3 months after which the patient will be initiated on the CP irrespective of the culture result. The recommended duration for CP is 18 months.

***Schedule for sputum culture examinations for MDR-TB**

IP extension	Intensive phase				Extension of IP (1-3 months)			Continuation phase					
No	3	4	5	6	-	-	-	9	12	15	18	21	24
1 month	3	4	5	6	7			10	13	16	19	22	25
2 months	3	4	5	6	7	8		11	14	17	20	23	26
3 months	3	4	5	6	7	8	9	12	15	18	21	24	27

** For MDR TB with additional drug resistance (including XDR TB) patients and XDR-TB IP extension can be upto 1-6 months.*

MDR TB with additional drug resistance (including XDR TB) patients

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 DR -TR Centre Committee, which will be responsible for initiating and monitoring the regimen for XDR TB, can decide on administering second line injectable intermittently (3 times/week) for the months 7 to 12.In case of extension of IP, the follow up culture months will shift by every month of extension of IP

Mono/poly DR TB patients

IP should be given for at least 3 months. After 3 months of treatment, the patient will be reviewed. If after the 3rd month smear result remains positive, the sputum sample is sent for genotypic DST to Rifampicin by CBNAAT or LPA and Liquid/solid culture & DST to see for resistance amplification. Shifting of IP to CP will be based on result of culture. The IP can be extended up to a maximum of 3 months after which the patient will be initiated on the CP irrespective of the culture result. The recommended duration for CP is 9 months.

At any time during treatment, if and when the results of additional DST are available, the patient must be referred to the DR TB center for complete clinical review by the committee and possible treatment modification.

Contact investigation

- All close contacts, especially household contacts should be screened for TB.
- In case of paediatric TB patients, **reverse contact tracing** for search of any active TB case in the household of the child must be undertaken.
- Particular attention should be paid to contacts with the highest susceptibility to TB infection

The highest priority contacts for active screening are:

- Persons with symptoms suggestive of tuberculosis
- Children aged < six years
- Contacts with known or suspected immune-compromised patient, particularly HIV infection
- Contacts with Diabetes Mellitus
- Contacts with other higher risks including pregnancy smokers and alcoholics etc.
- Contacts of patients with DR-TB.

All close contacts of DR-TB cases should be identified through contact tracing and evaluated for active TB disease as per RNTCP guidelines. If the contact is found to be suffering from pulmonary TB disease irrespective of the smear results, he/she will be identified as an "Presumptive MDR-TB". The patient will be initiated on regimen for new or previously treated case based on their history of previous anti-TB treatment. Simultaneously two sputum samples will be transported for culture and DST to a RNTCP-certified C&DST laboratory.

Isoniazid Preventive Therapy

Children are more susceptible to TB infection, more likely to develop active TB disease soon after infection, and more likely to develop severe forms of disseminated TB. Children < 6 years of age, who are close contacts of a TB patient, should be evaluated for active TB by a medical officer/paediatrician. After excluding active TB he/she should be given INH preventive therapy irrespective of their BCG or nutritional status. The dose of INH for preventive therapy is 10 mg/kg body weight administered daily for a minimum period of six months. The INH tablets should be collected on monthly basis. The contacts should be closely monitored for TB symptoms.
In addition to above, INH preventive therapy should be considered in following situation:-

- For all HIV infected children who either had a known exposure to an infectious TB case or are Tuberculin skin test (TST) positive (>=5mm induration) but have no active TB disease.
- All TST positive children who are receiving immunosuppressive therapy (*e.g.* Children with nephrotic syndrome, acute leukemia, *etc.*).
- A child born to mother who was diagnosed to have TB in pregnancy should receive prophylaxis for 6 months, provided congenital TB has been ruled out. BCG vaccination can be given at birth even if INH preventive therapy is planned.

Close contacts of index cases with proven DR-TB should be monitored closely for signs and symptoms of active TB as isoniazid may not be prophylactic in these
cases. Although alternative prophylaxis treatments have been suggested, there is no consensus regarding the choice of the drug(s) and the duration of treatment. Prompt treatment of MDR-TB is the most effective way of preventing the spread of infection to others. The following measures should be taken to prevent spread of DR-TB infection:

1. Early diagnosis and appropriate treatment of MDR-TB cases;
2. Screening of contacts as per RNTCP guidelines

Further research into effective and non-toxic chemoprophylaxis in areas of high MDR-TB prevalence is required.

Death Audit

The Medical Officer should conduct an in-depth audit of all the deaths occurring amongst the TB patients irrespective of initiation of treatment. Similarly, DTO should conduct death review of all MDR-TB patients died. This would be beneficial inunderstanding the causes leading to the deaths and guide the programme in taking appropriateaction to prevent them.

Prevention and management of adverse drug reactions

Most TB patients on first line drugs complete their treatment without any significant adverse drug effects. However, a few patients do experience adverse effects and some of the drug induced side effects can be prevented. Moreover, many second line drugs are associated with more side effects during long duration of treatment. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly. All Health personnel should monitor patients about adverse drug effects and inform patients to report to health system in case of any of the side effects. Health-care workers need to be informed and trained about the methodology and channels for reporting ADRs.

Adverse effects of Anti TB drugs

Anti-TB treatment with first-line drugs is generally safe and well tolerated. Side effects to anti-TB drugs are common. Trivial side effects may lead to reduced compliance with treatment. These adverse effects must be recognized early, to reduce associated morbidity and mortality. Following table shows the side effects-of essential first line anti TB drugs :-

Drug	Main effects	Rare effects
Isoniazid	Peripheral neuropathy Skin rash Hepatitis Sleepiness and lethargy	Convulsions Psychosis Arthralgia Anaemia
Rifampicin	Gastrointestinal: abdominal pain, nausea, vomiting Hepatitis Generalised cutaneous reactions Thrombocytopenic purpura	Osteomalacia Pseudomemberanous colitis Pseudoadrenal crisis Acute renal failure Haemolytic anaemia
Pyrazinamide	Arthralgia Hepatitis Gastrointestinal	Cutaneous reactions Sideroblastic anaemia
Ethambutol	Retrobulbar neuritis	Generalised cutaneous reactions Arthralgia Peripheral neuropathy Heapatitis (very rare)

Following table shows the side effects-of second line anti TB drugs :-

Drugs	Side effects
Injectables– *Kanamycin / Capreomycin*	• Ototoxicity • Nephrotoxicity • Vertigo • Electrolyte imbalance
Quinolones– *Ofloxacin, Levofloxicin, Moxifloxacin*	• Gastro Intestinal symptoms: diarrhoea, vomiting, and abdominal pain • Central nervous system (CNS): dizziness and convulsions • Phototoxicity and photosensitivity • Tendinopathy and tendinitis • Skin rash • Cardiotoxicity – QT prolongation • Arthralgia
Ethionamide	• Gastro-intestinal: epigastric discomfort, anorexia, nausea, metallic taste, vomiting, • excessive salivation, and sulfurous belching • Psychiatric: hallucination and depression • Hepatitis • Hypothyroidism and goitre with prolonged administration • Gynaecomastia, menstrual disturbances, impotence, acne, headache, and peripheral • neuropathy
Cycloserine	• CNS: dizziness, slurred speech, convulsions, headache, tremor, and insomnia • Psychiatric: confusion, depression, altered behaviour, and suicidal tendency • Hypersensitivity reaction
PAS	• Gastro-intestinal: anorexia, nausea, vomiting, and abdominal discomfort • Skin rash • Hepatic dysfunction • Hypokalemia • Hypothyroidism and goitre with prolonged administration

Management of ADRs

What to do if symptoms of adverse effects occur

If symptoms of adverse effects occur the following should be done:

- the dose of drugs should be checked
- all other causes of symptoms should be excluded
- the seriousness of the adverse effects should be estimated

- the adverse effects should be registered
- the drugs may need to be stopped and should eventually be reintroduced gradually when symptoms disappear
- development of drug resistance should be avoided.

A symptom-based approach to the management of the most common adverse effects is adopted. These side effects are classified as major or minor. In general, a patient who develops minor adverse effects should continue the TB treatment and be given symptomatic treatment. If a patient develops a major side-effect, the responsible drug or the entire regimen may need to be stopped and the patient should be urgently referred to a clinician or health care facility for further assessment and treatment. Patients with major adverse reactions should be managed in a hospital. States need to identify such facilities with sufficient infection control measures and expertise. In DR-TB patients, the DR-TB committee needs to be involved in the management and modification of the regimen if required.
Management of ADRs by medical practitioners and health workerare detailed in Annexure 9 & 10

Pharmacovigilance in TB control programme

Pharmacovigilance is defined by the World Health Organization (WHO) as the *"science and activities relating to the detection, assessment, understanding and prevention of adverse e ects or any other drug-related problem".*
It is a fundamental activity to inform the management of patient safety measures in health care. Pharmacovigilance is a *public health surveillance activity*. There are 3 methods for reporting on pharmacovigilance activities

- Spontaneous reporting- Spontaneous (or voluntary) reporting means that no active measures are taken to look for adverse effects other than the encouragement of health professionals and others to report safety concerns. Reporting is entirely dependent on the initiative and motivation of the potential reporters. This is the most common form of pharmacovigilance, sometimes termed passive reporting

- Targeted reporting- It focuses on capturing ADRs in a well-defined group of patients on treatment. Health professionals in charge of the patients are sensitized to report specific safety concerns.

- Active surveillance- It is a pro-active efforts made to elicit adverse events. Events detected by asking patients directly, screening patient records, laboratory & clinical tests. It is best done prospectively

Causality assessment- "Estimating the probability of a relationship between exposure to a medicine and the occurrence of an adverse reaction".For assessing the causality the causality assessment committee.Establishing causality is a process which begins by examining the relationship between the medicine and the event. Two basic questions need to be addressed separately:

- Is there a convincing relationship between the drug and the event?
- Did the drug actually cause the event?

The relationship of a single case-report can be established, but it may not be possible to establish a firm opinion on causality until a collection of such reports is assessed or new knowledge is gained. Causality for individual reports, even those with a close relationship, can seldom be established beyond doubt and our assessments are based on probability. A causality assessment should be seen as provisional and subject to change in the light of further information on the case, or new knowledge coming from other sources. For details "a practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis" by WHO may be referred.

Under the Pharmacovigilance Programme of India (PvPI) set up by the Ministry of Health and Family Welfare (MoHFW), Govt. of India in July 2010 routine reporting and monitoring of ADRs will be continued. Simultaneously, the pharmacovigilance activity will be implemented in phase-wise manner.

Priority is given to establishing pharmacovigilance at DR-TB centres for drug resistant Cases. The DR-TB centres would be linked with ADR monitoring centres established under PvPI in medical colleges to initiate reporting of ADR in systematic manner. With introduction of daily anti-TB treatment regimen priority will be given to establish pharmacovigilance at ART centres for TB-HIV patients. It will be further expanded in districts / health institutions along with expansion of daily regimen to other TB patients. The standardized suspected ADR reporting form (Annexure 11) and needs to be filled by the treating doctor.

Treatment in special situations

TB in Pregnant and Lactating women

Before initiating treatment for tuberculosis, women of childbearing age should be asked about current or planned pregnancy and counseled appropriately. A successful treatment of TB is important for successful outcome of pregnancy. With the exception of streptomycin, the first line anti-TB drugs are safe for use in pregnancy. Streptomycin is ototoxic to the fetus and should not be used during pregnancy.

A breastfeeding woman should receive a full course of TB treatment. Correct chemotherapy is the best way to prevent transmission of TB to baby. Breast feeding has to be continued. After ruling out active TB, the baby should be given 6 months of isoniazid preventive therapy, followed by BCG vaccination. Breast feeding should not be discouraged. The mother should be advised about cough hygiene measures such as covering the nose and mouth while coughing, sneezing or any act which can produce sputum droplets.Mothers receiving INH and their breastfed infants should be supplemented with vitamin B6 (pyridoxine), recommended dose of Pyridoxine in infants is 5 mg/day.

DR-TB in pregnancy

Teratogenicity has been demonstrated with only some of the drugs used to treat MDR-TB. Women of child bearing age identified as presumptive MDR TB case should be advised to use a reliable and appropriate contraceptive method till the results of culture and DST are available. And if a woman is diagnosed with DR-TB and receiving second line treatment, she should be intensively counselled to use birth control measures because of the potential risk to both mother and foetus. All women of childbearing age should be tested for pregnancy as part of the pre-treatment evaluation and whilst on treatment if there is a history of amenorrhea of any duration. MDR-TB patients found to be pregnant prior to treatment initiation or whilst on treatment are evaluated in consultation with a Gynaecologist/Obstetrician taking into consideration the following factors:

- Risks and benefits of MDR-TB treatment
- Severity of the MDR-TB
- Gestational age
- Potential risk to the foetus

Further management of MDR-TB patients who are pregnant prior to initiation of treatment or whilst on treatment are based on the duration of pregnancy.

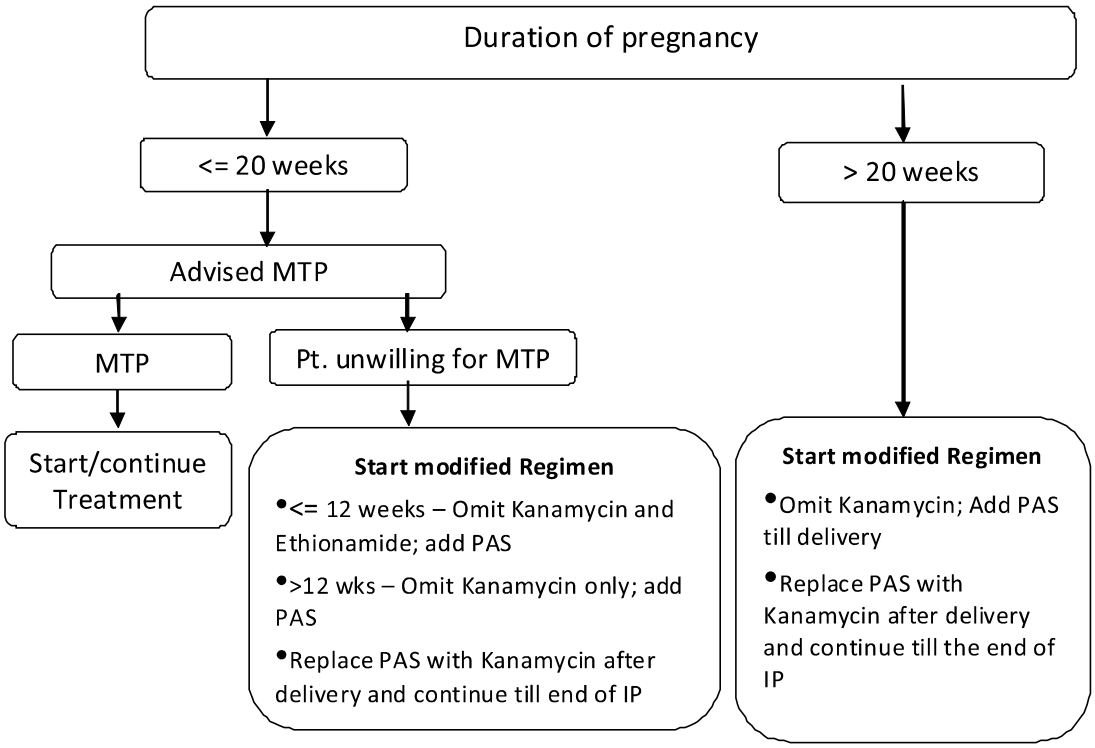
- If the duration of pregnancy is <20 weeks, the patient should be advised to opt for a Medical Termination of Pregnancy (MTP) in view of the potential severe risk to both the mother and foetus. If the patient is willing, she should be referred to a Gynaecologist/Obstetrician for MTP following which treatment can be initiated (if the patient has not started treatment) or continued (if the patient is already on treatment) by the DR-TB Centre Committee.

- For patients who are unwilling for MTP or have pregnancy of >20 weeks (making them ineligible for MTP), the risk to the mother and foetus needs to be explained clearly and a modified Regimen for MDR TB should be started as detailed below:

  – For patients in the first trimester (⩽ 12 weeks), Kanamycin and Ethionamide are omitted from the regimen and PAS is added.
  – For patients who have completed the first trimester (>12 weeks), Kanamycin is replaced with PAS. Post-partum, PAS may be replaced with Kanamycin and continued until the end of the Intensive Phase.

Pregnant MDR-TB patients need to be monitored carefully both in relation to the treatment and the progress of the pregnancy. This approach should lead to good results, since the patient should be smear-negative at the time of parturition, and mother and infant do not need to be separated. Breast-feeding should be encouraged as long as the patient is sputum negative.

The management of MDR-TB patients with pregnancy is summarised in the flow chart:



TB and Contraceptive pills usage

As Rifampicin is a potent inducer of hepatic enzymes, the protective efficacy of oral contraceptive pills may be decreased. Oral contraceptives might have decreased efficacy due to vomiting and drug interactions with second line anti-TB drugs. Hence, women suffering from TB and using contraceptive pills should be advised to use some alternative anti-contraception method. Use of barrier methods (Condoms/diaphragms), IUDs (CuT) or depot-medroxyprogesterone (Depo-provera) are recommended based on
individual preference and eligibility.

Management of TB in patients with liver disorders

Patients with hepatitis virus carriage, a past history of acute hepatitis, current excessive alcohol consumption can receive the usual TB regimens provided that there is no clinical evidence of chronic liver disease. However, hepatotoxic reactions to anti-TB drugs may be more common among these patients and should therefore be anticipated. In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment. If the liver disorder is severe, lesser hepatotoxic drugs have to be used. Expert consultation is advisable in treating patients with advanced or unstable liver disease. Clinical monitoring (and liver function tests, if possible) of all patients with pre-existing liver disease should be performed during treatment. If the serum alanine aminotransferase level is more than 3 times normal before the initiation of treatment, the following regimens should be considered:

- ***Containing two hepatotoxic drugs:***
  9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented);
  2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 7 months of isoniazid and rifampicin;
  6–9 months of rifampicin, pyrazinamide and ethambutol.
- ***Containing one hepatotoxic drug:***
  2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol
- ***Containing no hepatotoxic drugs:***
  18–24 months of streptomycin, ethambutol and a fluoroquinolone.

DR-TB in patients with pre-existing liver disease

Pyrazinamide, PAS and Ethionamide are potentially hepatotoxic drugs. Hepatitis occurs rarely with the fluoroquinolones. The potential for hepatotoxicity is increased in elderly, alcoholics and in patients with pre-existing liver disease. In general, most of second line drugs can be safely used in presence of mild hepatic impairment, as they are relatively less hepatotoxic than the first-line drugs. However, pyrazinamide and ethionamide should be avoided in such patients. Once a patient on second line drugs develops hepatitis, other aetiologies should also be excluded such as viral hepatitis, alcoholic hepatitis, drug induced hepatitis by non-TB drugs etc. The further management should be on the same guidelines as in non- MDR-TB patients. MDR patients having deranged liver function test (LFT) during pre-treatment evaluation should be strictly monitored through monthly LFTs while on treatment. However routine LFT is not recommended in all cases.

TB patient with renal failure and severe renal insufficiency

Patients suffering from Chronic Kidney Diseases (CKD) are at an increased risk of developing Tuberculosis. Active TB should be excluded in patients with CKD by appropriate investigations in patients who have an abnormal chest x-ray or a history of prior pulmonary or extrapulmonary TB that has been either inadequately or not previously treated. Chemoprophylaxis in standard doses should be given. TB should be considered in all patients with unexplained systemic or system-specific symptoms as extrapulmonary TB is common, particularly in patients on dialysis, with peritoneal TB being common in patients on chronic ambulatory peritoneal dialysis.

Any patient with active TB, either pulmonary or extrapulmonary, should receive standard chemotherapy agents, albeit with dose interval modifications where appropriate. Isoniazid and rifampicin are eliminated by biliary excretion, so no change in dosing is necessary. There is significant renal excretion of ethambutol and metabolites of pyrazinamide, and doses should therefore be adjusted. For patients with stages 4 and 5 chronic renal disease and on hemodialysis, dosing intervals should be increased to three times weekly for ethambutol, pyrazinamide and the aminoglycosides.

Treatment can be given immediately after haemodialysis to avoid premature drug removal. With this strategy there is a possible risk of raised drug levels of ethambutol and pyrazinamide between dialysis sessions. Alternatively, treatment can be given 4 to 6 hours before dialysis, increasing the possibility of premature drug removal but reducing possible ethambutol or pyrazinamide toxicity. Three times per week administration of these two drugs at the following doses is recommended: pyrazinamide (25 mg/kg), and ethambutol (15 mg/kg). These doses are the ones used in daily regimens. While receiving isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine in order to prevent peripheral neuropathy. Because of an increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. If streptomycin must be used, the dosage is 15 mg/kg, two or three times per week, to a maximum of 1 gram per dose, and serum levels of the drug should be monitored. In post renal transplant cases, Rifampicin in particular can interact with immunosuppressive regimens, increasing the chance of graft rejection, and doses of mycophenolate mofetil, tacrolimus and cyclosporine may need adjustment. Corticosteroid doses should be doubled in patients receiving rifampicin.

DR-TB in patients with renal impairment

Renal insufficiency due to longstanding TB disease itself, previous use of aminoglycosides or concurrent renal disease is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal impairment. Consideration needs to be taken that MDR-TB patients require aminoglycosides for 6 months or more. In patients with mild renal impairment, the dose of aminoglycosides may be reduced. In the presence of severe renal failure, the aminoglycoside therapy should be discontinued and replaced with other potent non-nephrotoxic antituberculosis drugs. Other drugs, which also might require dose or interval adjustment in presence of mild to moderate renal impairment, are: Ethambutol, Quinolones, Cycloserine and PAS. In the presence of severe renal impairment many other drugs may also require adjustments (refer table as below).

Adjustment of anti-TB drugs in renal insufficiency[a]

Drug	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Ethambutol	15-25 mg/kg per dose three times per week (not daily)
Rifabutin	Normal dose can be used, if possible monitor drug concentrations to avoid toxicity.
Rifapentine	No adjustment necessary
Streptomycin	12-15 mg/kg per dose two or three times per week (not daily)
Capreomycin	12-15 mg/kg per dose two or three times per week (not daily)
Kanamycin	12-15 mg/kg per dose two or three times per week (not daily)
Amikacin	12-15 mg/kg per dose two or three times per week (not daily)
Ofloxacin	600-800 mg per dose three times per week (not daily)
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Cycloserine	250 mg once daily, or 500 mg / dose three times per week
Terizidone	Recommendations not available
Prothinamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylicacid	4 g/dose, twice daily maximum dose
Bedaquiline	No dosage adjustments required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/clavulanate	For creatinine clearance 10-30 ml/min dose 1000 mg as amoxicillin component twice daily; For creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily
Imipenem / cilastin	For creatinine clearance 20-40 ml/min dose 500 mg every 8 hours; For creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20-40 ml/min dose 750 mg every 12 hours; For creatinine clearance <20 ml/min dose 500 mg every 12 hours
High dose isoniazid	Recommendations not available

[a] source: Companion Handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis 2014.
Estimated creatinine clearance calculations:
Men: Ideal Body Weight (kg) x (140-age) / 72 x serum creatinine (mg/dl)
Women: 0 85 x Ideal Body Weight (kg) x (140-age) / 72 x serum creatinine (mg/dl)

TB in patients with seizure disorders

The use of isoniazid and rifampicin may interfere with many of the anti-seizure medications. Drug interactions should be checked before their use.High dose isoniazid also carries a high risk of seizure and should be avoided in patients with active seizure disorders.

The prophylactic use of oral pyridoxine (vitamin B6) can be used in patients with seizure disorders to protect against the neurological adverse effects of isoniazid or cycloserine. The suggested prophylactic dose for at risk patients on isoniazid is 10 to 25 mg/day and for patients on cycloserine is 25 mg of pyridoxine for every 250 mg of cycloserine daily. The optimal prophylactic dose of pyridoxine for children has not been established, nonetheless 1–2 mg/kg/day has been recommended in some reports with a usual range of 10–50 mg/day for paediatric patients at risk for neurological sequel.

DR-TB in patients with seizure disorders

Some patients requiring treatment for DR-TB will have a past or present medical history of a seizure disorder. The first step in evaluating such patients is to determine whether the seizure disorder is under control and whether the patient is taking anti-seizure medication to control the disorder. If the seizures are not under control, initiation or adjustment of anti-seizure medications will be needed prior to the start of DR-TB therapy. In addition, if other underlying conditions or causes for seizures exist, they should be corrected.

Among second line drugs, Cycloserine, Ethionamide and fluoroquinolones have been associated with seizures, and hence should be used carefully amongst MDR-TB patients with history of seizures. Pyridoxine should be given with Cycloserine to prevent seizures. Cycloserine should however be avoided in patients with active seizure disorders that are not well controlled with medication. In cases where no other drug is appropriate, Cycloserine can be given and the anti-seizure medication adjusted as needed to control the seizure disorder. The risk and benefits of using Cycloserine should be discussed with the patient and the decision on whether to use Cycloserine are made together with the patient.

Antiepileptic drugs may have drug interactions with Cycloserine and fluoroquinolones. Hence close monitoring of serum levels of anti-epileptic drugs should be done. One should remember that TB itself might involve central nervous system and may cause seizures. However when seizures are present for the first time during anti-TB therapy, they are likely to be the result of an adverse effect of one of the anti-TB drugs.

DR-TB in patients with psychosis

For DR-TB patients with a concurrent psychiatric illness, it is advisable to have an evaluation carried out by a psychiatrist before the start of treatment for DR-TB. The initial evaluation documents any pre-existing psychiatric condition and establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any identified psychiatric illness at the start or during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with DR-TB, often connected with the chronicity and socioeconomic stress factors related to the disease. If a health care worker with psychiatric training is not available, the treating healthcare provider should document any psychiatric conditions the patient may have at the initial evaluation.

Treatment with psychiatric medication, individual counselling, and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or adverse psychiatric effect due to medication. Group therapy has been very successful in providing a supportive environment for DR-TB patients and may be helpful for patients with or without psychiatric conditions (adequate measures to prevent infection risk should be in place for the group therapy). Fluoroquinolones and Ethionomide have been associated with psychosis. Pyridoxine prophylaxis may minimize risk of neurologic and psychiatric adverse reactions.

Cycloserine may cause severe psychosis and depression leading to suicidal tendencies. However the use of Cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects of Cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug often outweigh the potential higher risk of adverse effects. Close monitoring is recommended if Cycloserine is used in patients with psychiatric disorders.

If patient on Cycloserine therapy develops psychosis, anti-psychotic treatment should be started and Cycloserine therapy should be temporarily suspended. Once symptoms resolve and patient is stabilized Cycloserine therapy may be resumed. Such patients may require anti-psychotic treatment till anti-TB treatment is completed. When any patient on MDR-TB treatment develops psychosis, other aetiologies such as psycho- social stresses, depression, hypothyroidism, illicit drug and alcohol use, should also be looked for.

All healthcare workers treating drug-resistant TB should closely work with a psychiatrist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation, and any situation involving the patient's being a danger to him/her self or others. Mechanisms to deal with psychiatric emergencies (often inpatient psychiatric hospital admissions) should be available on twenty-four hours basis. Proper infection control measures must be taken for the smear-positive patient who requires any hospitalization.

Extra pulmonary TB

The burden of EPTB ranges from 15-20% of all TB cases in HIV-negative patients while among PLHIV, it accounts for 40-50% of new TB cases. With advent of diagnostics cases of drug-resistant EPTB are likely to be identified more in the country.

All EPTB patients should be tested for HIV. All patients suspected of EPTB should have clinical assessment for active PTB. All patients should receive an appropriate treatment regimen, and the provider should monitor adherence and address factors leading to interruption/discontinuation of treatment. All patients with a diagnosis of EPTB should be risk-assessed for drug resistance prior to starting treatment, and drug susceptibility testing should be available for all patients at risk of drug-resistant tuberculosis.

Extra pulmonary TB should be treated with the same regimens as pulmonary TB. The duration of continuation phase may be extended by 3 to 6 months in special situations like TB meningitis, Bone & Joint TB, Spinal TB with neurological involvement and neuro- tuberculosis. Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis. In tuberculous meningitis, ethambutol should be replaced with streptomycin.

Although sometimes required for diagnosis, surgery plays little role in the treatment of extra pulmonary TB. It is reserved for management of late complications of disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis and neurological involvement from Pott's disease (spinal TB). For large, fluctuant lymph nodes that appear to be about to drain spontaneously, aspiration or incision and drainage appear beneficial. For further details on management of EPTB, refer to Index-TB guidelines on management of EPTB.

Treatment regimen and schedule for EP MDR-TB cases will remain the same as for pulmonary MDR-TB. EP MDR-TB patients will undergo all those pre -treatment investigations as done for pulmonary MDR-TB patients. In addition, ultrasound of abdomen of the patient will also be done, if necessary, to rule out involvement of other organs and abdominal nodes. Unlike microbiological follow up examination schedule in pulmonary DR-TB, culture from the affected EPTB site can bedone only till the specimen is available. The follow up is mainly based on clinical parameters.

Clinical Monitoring and follow up of DR-TB patients:

1. Weight Gain
2. Decrease or increase in symptoms (e.g. healing of ulcer / scrofuloderma)
3. Increase or Regression in size of nodes (possibility of Immune Reconstitution Inflammatory Syndrome (IRIS) should be considered and differentiated from disease progression)
4. Appearance of new nodes
5. If chest symptomatic, monthly sputum for AFB and chest X- ray (to rule out pulmonary involvement)
6. Other Extra-pulmonary sites should be monitored (USG abdomen if necessary)
7. Serum Creatinine – monthly for the first three months of treatment and then quarterly till the patient receives Kanamycin and further when clinically indicated
8. Liver function test – as clinically indicated
9. USG -abdomen – if necessary
10. Monitoring for drug adverse reactions

Treatment outcome will depend on availability of culture reports of specimens taken from affected site, treatment completion and clinical improvement of the patient.

Hospitalization

The usual mode of TB treatment is domiciliary, but in patients with pneumothorax or large accumulations of pleural fluid leading to breathlessness; massive haemoptysis etc. the patients might need hospitalization. These patients can be managed in general hospitals preferably in wards where adequate air borne infection control measures are taken to prevent the spread.

Role of surgery in management of MDR-TB

In DR-TB patients with localized disease, surgery, as an adjunct to chemotherapy, can improve outcomes provided skilled thoracic surgeons and excellent post-operative care are available. When unilateral resectable disease is present, surgery should be considered for the following cases:

- Absence of clinical or microbiological response to chemotherapy despite six to nine months of treatment with effective anti-tuberculosis drugs;
- High risk of failure or relapse due to high degree of resistance or extensive parenchymal involvement;
- Morbid complications of parenchymal disease e.g. haemoptysis, bronchiectasis, bronchopleural fistula, or empyema;
- Recurrence of positive culture status during course of treatment; and
- Relapse after completion of anti-tuberculosis treatment.

If surgical option is under consideration at least six to nine months of chemotherapy is recommended prior to surgery.

Latent Tuberculosis Infection (LTBI)

Latent tuberculosis infection (LTBI) is the presence of Mycobacterium tuberculosis in the body without signs and symptoms, or radiographic or bacteriologic evidence of tuberculosis (TB) disease. Studies have demonstrated that Isoniazid (INH) taken for at least 6 months in persons with LTBI reduced subsequent TB incidence by 25 to 92 per cent, the differences in effectiveness largely explained by differences in treatment completion. Recently WHO has published detailed guidelines for management of LTBI. (WHO Guidelines on the management of latent tuberculosis infection) There was consensus of the WHO Panel on the equivalence of 6-month INH, 9-month INH, and 3-months once a week Rifapentine plus high dose INH as treatment for LTBI.

India, with one-fourth of the global burden of TB, has 40 per cent of the population infected with M.Tb. Treating 40 per cent of the population for LTBI based on Tuberculin Skin Test (TST) positivity or Interferon Gamma Release Assay is neither rational nor practicable, thus emphasizing the need for a focussed approach. In clinical situations, the most obvious group for LTBI treatment would include high-risk patients such as those receiving long term corticosteroids, immunosuppressants, HIV-infected and juvenile contacts of sputum-positive index cases.

Treatment of Nontuberculous Mycobacterial (NTM) Lung Diseases

Under programme conditions sometimes the report of culture examination shows presence of Nontuberculous Mycobacteria (NTM). NTM represent a broad array of organisms that have been isolated from soil and water, and exposure to these reservoirs is thought to be the source of human infection. A review of several studies observed that in India 1-4% of laboratory isolates among presumptive TB cases or presumptive MDR-TB cases are NTMs. In TB-HIV co-infected cases the probability of NTM may be increased. The clinician (DTO/MOPHI/DR-TB Committee etc.) should not ignore such reports. A careful clinical correlation is required in such cases as some of these patients may be wrongly put on MDR/XDR-TB regimen as these patients may be found to be resistant to all commonly used first line and second line anti-TB drugs. One should not diagnose NTM based on single culture report. In presence of NTM the commonly used molecular tests, such as LPA or CBNAAT will be negative, which should prompt the clinician to think of NTM. Such cases should be referred to DR-TB committee for further management through general health services.The American Thoracic Society (ATS) Guidelines (An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases) may be referred for the management of patients suffering from NTM infection.

Treatment outcomes

The treatment outcome definitions make a clear distinction between three types of patient groups ("cohorts"):

1. Patients treated for drug-susceptible TB;
2. Patients treated for RR-/MDR-TB/XDR-TB
3. Patients treated for mono-/poly- DR-TB

The groups are mutually exclusive. Any patient found to have DR-TB and placed on second-line treatment is removed from the rifampicin-susceptible TB treatment cohort. DR-TB patients who were not started on a Mono/Poly/MDR-TB regimen are assigned an outcome from those for rifampicin-susceptible TB. This means that the basic TB register and the Second-line TB treatment register need to be coordinated to ensure proper accounting of treatment outcomes.

Treatment outcomes for drug-susceptible TB patients

Cured: Microbiologically confirmed TB patients at the beginning of treatment who was smear or culture negative at the end of the complete treatment

Treatment completed: A TB patient who completed treatment without evidence of failure or clinical deterioration BUT with no record to show that the smear or culture results of biological specimen in the last month of treatment was negative, either because test was not done or because result is unavailable.

Treatment Success: TB patients either cured or treatment completed are accounted in treatment success

Failure: A TB patient whose biological specimen is positive by smear or culture at end of treatment.

Failure to Respond A case of paediatric TB who fails to have microbiological conversion to negative status or fails to respond clinically / or deteriorates after 12 weeks of compliant intensive phase shall be deemed to have failed response provided alternative diagnoses/ reasons for non-response have been ruled out.

Lost to follow up: A TB patient whose treatment was interrupted for 1 consecutive month or more

Not Evaluated - A TB Patient for whom no treatment outcome is assigned. This includes former "transfer-out"

Treatment Regimen Changed - A TB patient who is on first line regimen and has been diagnosed as having DRTB and switched to drug resistant TB regimen prior to being declared as failed

Died: A patient who has died during the course of anti-TB treatment

Outcomes for RR-/MDR-TB and /or XDR-TB patients

Cure: Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase

Treatment completed: Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase

Treatment success: The sum of cured and treatment completed.

Treatment failed : Treatment terminated or need for permanent regimen change of at least two or more anti-TB drugs in CP because of:

- Lack of microbiological conversion by the end of the intensive phase or
- Microbiological reversion in the continuation phase after conversion to negative or
- Evidence of additional acquired resistance to fluoroquinolones or second line injectable drugs or
- Adverse drug reactions (ADR)

Conversion and reversion

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining *Treatment failed*, reversion is considered only when it occurs in the continuation phase.

Died: A patient who dies for any reason during the course of treatment

Loss to follow up: A patient whose treatment was interrupted for one consecutive month or more

Not Evaluated - A patient for whom no treatment outcome is assigned.

Treatment Regimen Changed - A TB patient need for permanent regimen change of at least one or more anti-TB drugs prior to being declared as failed

Outcomes for mono-/ poly-drug resistant TB patients

Cure: A microbiologically confirmed TB at the beginning of treatment who was culture-negative in the last month of treatment and on at least one previous occasion

Treatment completed: A patient who has completed treatment according to guidelines but does not meet the definition for cure or treatment failure due to lack of microbiological results.

Failure: Treatment terminated or need for permanent regimen change of at least two or more anti-TB drugs in CP because of:

- Evidence of additional acquired resistance to rifampicin, fluoroquinolone or second line injectable during treatment
- Severe ADR
- Culture positive during CP or at end of treatment

Died: A patient who dies for any reason during the course of M/XDR-TB treatment

Loss to follow up: A patient whose treatment was interrupted for one month or more for any reasons.

Not Evaluated - A DR-TB Patient for whom no treatment outcome is assigned, this includes former "transfer-out".

Treatment outcome is defined by reviewing her/his Tuberculosis Treatment Card. The treatment outcome and the date the patient stopped treatment is written in the appropriate column in the Tuberculosis treatment card. The date on which the patient stopped treatment is the date of the last dose of drugs taken. Details of Treatment outcome should be updated in NIKSHAY.

The MO of the PHI should record the treatment outcome in the treatment card and sign it. The treatment card of the patients whose outcome has been declared should be handed over to the STS during his routine monthly visits. Every patient started on treatment has to be given one and only one treatment outcome.