Revised National TB Control Programme

Instructions for administering Purified Protein Derivative (PPD):

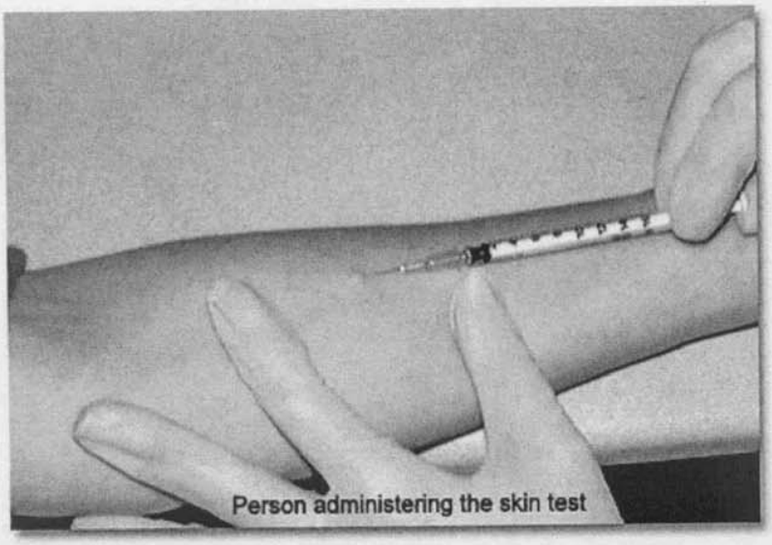
Supplies needed:

- Vial of tuberculin – 1tuberculin units (TU) purified protein derivative (PPD) 1.5 ml solution
- Single-dose disposable tuberculin syringe
- 2x2 gauze pads or cotton balls
- Alcohol swabs
- Puncture-resistant sharp disposal container
- Mantoux Tuberculin Skin Test Record Form
- Appointment cards
- Gloves

Preparation before administration:

- Purified protein derivative (PPD) solution must be kept refrigerated at 2-8°C (DO NOT FREEZE)
- To avoid fluctuations in temperature, do not store on the refrigerator door
- Read the vial label to ensure that the correct solution and tuberculin unit (TU) strength have been selected
- Check the expiration date and the date that the vial was opened. The vial should be discarded if it has been open for more than 30 days or the expiration date has passed. The vaccine vials comes in a pack of ten in a box which also has the vaccine vial monitor (VVM) indicator. All the vials should be taken from a single box, the vaccine vials should not be taken if the VVM on the box has changed its color or if it has crossed the expiry date.
- Select a well-lighted area for administering the test. Have all the equipment and supplies on hand
- Introduce yourself to the patient
- Verify that the correct patient receives the test
- Ask the patient if he/she has any allergies
- Review the patient's tuberculin skin test history. Inquire about documentation of previous tuberculin skin test results
- Provide patient education to answer questions, address fears, and ease anxieties. Discuss the purpose of the test, testing procedure, and the time frame for returning to have the test read. If the patient cannot return 48-72 hours after the test to have the indurations measured and evaluated, do not administer the test. Instead, schedule another time that is more convenient for the patient

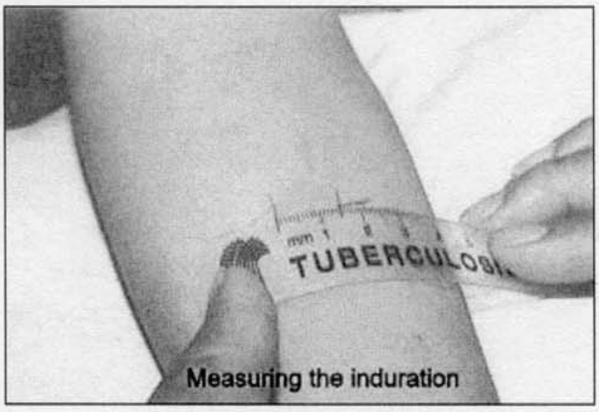
Administration of Skin Test: (Syringes must be filled immediately prior to administration)



Person administering the skin test

- Wash your hands with soap and water
- On a firm, well-lighted surface, expose the patient's arm and slightly flex at the elbow. The injection should be replaced on the palm-side-up surface of the forearm, about 2 to 4 inches below the elbow. Avoid areas of skin with veins, sores, rashes, scars, or excess hair
- Wear the gloves
- Clean the injection site with an alcohol swab, using circular motion beginning in the center and working your way outward. Allow the site to dry completely before injection
- Wipe the top of the vial with a new alcohol swab and allow it to dry thoroughly
- Fasten the needle tightly on the syringe by holding the cap and twisting it onto the tip of the syringe. Remove the needle cap and make sure that the needle bevel is facing up
- Hold vial between your thumb and fingers and insert the needle through the stopper. Inject air into the empty space, not the solution, in the vial
- Invert the vial. With the tip of the needle below the fluid level in the vial, draw out slightly more than 0.1 ml of solution
- Remove the needle from the vial. Hold the syringe in an upright position and gently tap the syringe to break up any air bubbles
- Expel all air from the syringe and excess solution from the needle, leaving exactly 0.1 ml of tuberculin solution in the syringe
- Stretch the skin taut over the injection site to provide a surface that is easy for the needle to penetrate. This can be accomplished by stretching the skin between the thumb and index finger or grasping the patient's forearm and gently pulling the skin from under the arm
- Hold the syringe between your thumb and index finger with the needle bevel facing up and the syringe parallel to the forearm

- With the needle against the patient's skin, insert the needle slowly at a 5 to 15 degree angle, just below the surface of the skin (you should be able to see the bevel of the needle just below the skin surface)
- Release the stretched skin and hold the syringe in place. Slowly inject the tuberculin solution, forming a 6 to 10 mm wheal (pale, raised area with distinct edges; has orange peel appearance and does not disappear immediately)
- If no wheal forms or if it is less than 6 mm in diameter, repeat the test approximately 2 inches from the original site or on the opposite arm
- Remove the needle without massaging or pressing the area and immediately discard the used syringe in the sharps container
- If minor bleeding occurs, use a 2x2 gauze pad or cotton ball to dab the injection site
- Do not cover the site with an adhesive bandage as it could cause irritation
- Wash your hands
- Record the following information on the record-keeping form: the date, time, location of injection site, name of manufacturer, lot number, and expiration date of PPD solution, name of person administering the skin test
- Inform the patient that mild itching, swelling, or irritation is normal and usually goes away within 1 week
- Explain how to care for the injection site: avoid scratching the site, keep the site clean and dry, and avoid creams, lotions, or adhesive bandages
- Inform the patient that it is important to return within 48 to 72 hours to have the test result read
- Give the patient a written appointment to return for the skin test reading



Measuring the induration

Annexure 7

Setting- specific screening strategy

Urban Slums

Urban slum dwellers are at higher risk of developing TB due to overcrowding, poor basic health services infrastructure and their health seeking behaviour. Health is not a priority for them and risk of TB transmission is high in slums. Urban slum-dwellers require focussed efforts and support from the tuberculosis programme.

Intensified case finding efforts in these areas can include:-

- House to house, periodic symptom screening of all the mapped urban slums to actively screen for presumptive TB cases.
- Liaising with NUHM, NPSP and other departments delivering health care services in urban slums for mapping and line listing of providers
- Utilization of Urban slum schemes as in the revised NGO-PP partnership guidelines.

Household and Close Contacts of TB

Household contact:- *A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case.*

Close contact:- *A person who is not in the household but shared an enclosed space, such as a* ***social gathering****,* ***workplace*** *or facility, for extended periods in a day with the index case.*

-Since the transmission can happen from the index case to the contact any time (before the diagnosis of TB or during the treatment) all contacts must be evaluated. In case of Pulmonary Tuberculosis, it is recommended that contact screening is conducted for household and close contacts

It is important to screen household and close contacts for TB as they are more prone to get infected with TB. Some of them may be asymptomatic and others may ignore these symptoms. Chest X-ray screening should be done for all the contacts. Symptom screening should be done whenever X-ray facility is not available.

- The index case should be interviewed as soon as possible after diagnosis (generally within 1 week) to elicit the names of household and close contacts. Data from the contact investigation should be collected in a standardized format and should routinely be evaluated. (Information to be recorded in the treatment card)
- Reverse contact tracing should be done for all paediatric TB patients.

Health Care Workers

Health care workers are at greater risk of getting TB infection and also at a higher risk of getting active disease. The National Airborne Infection Control guidelines advocate Health Care worker Surveillance as a component of the Hospital / Health facility Infection Control Plans.

- Pre placement screening and routine annual screening with Chest radiography of all the health care workers is strongly recommended.
- If Health care worker surveillance is an existing policy in the health institution, facility or department then chest X-ray screening may be added on to the protocol.
- Healthcare workers presenting with symptoms of TB should be evaluated.

Malnourished Children

Malnutrition is a strong risk factor for progression from TB infection to disease among children. As per the TB management guidelines in the paediatric population issued by RNTCP, all malnourished children are eligible for TB screening and diagnostic evaluation.

- Active screening for TB symptoms with chest X-ray as the screening tool (or symptom screening if X- ray is not available) should be undertaken among children with malnourishment that attend any health facility .
- Engage and collaborate with Nutritional Rehabilitation Centres for routine screening of TB in malnourished children attending these centres.
- Regular symptomatic screening of malnourished children attending the Anganwadi centres.

Antenatal Clinics/MCH clinics

Antenatal clinic attendee rates are very high in the country as the RCH programme receives high priority and is a leading public health programme in the country. Screening pregnant women for TB in MCH clinics provides an exceptional opportunity to identify and reach women in need of TB case diagnosis as a majority of women access health care during pregnancy at least once. Strengthening linkages between maternal health and TB management can contribute to the reduction of maternal and newborn mortality too.

- TB Symptoms screening must be undertaken for all mothers attending the antenatal clinics at every visit and those who are symptom screen positive must be immediately linked to the nearest laboratory for early TB diagnosis and decision on TB treatment initiation.

Prison inmates

Predisposing factors such as overcrowding, long-term close contact with inmates and lack of easy access to adequate health services may lead to high rates of TB transmission in prisons. Duration of stay of inmates in the prison is unpredictable and turnover is also high, resulting in undiagnosed or delayed diagnosis of TB.

The intensified case finding activity should include:

- Symptom screening at **Entry;** when prisoners enter the prisons.
- **Periodic mass screening** with chest X-ray. If chest x-ray is not available then symptom screening should be done.

Patients with Co morbidities

Patients with chronic illness like malignancy, on dialysis, on immune-suppressants, long term steroids have higher risk of tuberculosis - Symptom screening for TB should be done on all patient visits to the health facilities for follow up examinations

Patients with past history of TB

Chances of TB relapse or recurrence is higher in people with a past history of TB. Efforts to actively screen for TB symptoms in this group could be a high case yielding activity. The programme now advocates that all TB cases after successful completion of treatment need to be followed up for a period of one year after with follow up examinations at 6^{th}, 12^{th},$18^{th}$and 24^{th}month.

- Active symptom screening by health staff may be undertaken by visiting the homes of those patients at prescribed intervals
- House to house visits may be undertaken of all patients notified and treated by private sector to screen for TB symptoms at prescribed intervals.

Occupational high risk group

Several occupations increase risk for tuberculosis. It is known that thousands of workers and local residents are exposed to hazardous silica levels during stone crushing operations and suffer from silicosis, lung cancer, and other lung diseases. Other occupations include coal and other mining works, tobacco (bidi rolling) and carpet weaving. Vulnerable and socially marginalised groups including tribal communities, children and migrant population are often working in these industries that do not have access to routine health services. Active case finding efforts in these groups will help to identify those suffering from TB early.

- Screening should be done by X-ray and in case X-ray is not available then symptom screening should be done by holding periodic health camps.

Congregate Settings

People in settings like transit camps, night shelter, old age home, orphanages and de addiction centres may have ill ventilated and unsanitary environment and hence, at higher risk of developing tuberculosis.

- In all such congregated settings Symptom screening should be done by holding periodic health camps.

Hard to Reach Areas

People living in difficult, hard to reach and inaccessible areas like certain Tribes or indigenous population delay seeking health care for their symptoms. They are also dependent on local informal providers and traditional healers as their first points of contact for health care, which can lead to delay in diagnosis. Periodic active screening programmes must be planned and implemented to detect TB cases early in this population

- Symptomatic screening may be done by holding periodic health camps or even by house to house survey

- Mobile medical units equipped with microscopes and digital X-ray machines available under NHM can be used.
- Sputum collection centres must be planned and established in strategic locations with the help of local NGOs

Missed cases in health system

Opportunity should not be missed to diagnose TB among people who approach health facility for any other illness. Systems should be strengthened and actively monitored so as to ensure all presumptive TB cases are identified timely and are referred for diagnostic evaluation

- Establish sputum collection centres in all the primary health centres which do not have DMC
- Enhancing the skills of MOs by providing special training package on interpretation of X-ray.
- Wherever X-ray &histo-pathological/FNAC services are not available then outsourcing these services should be done.

Annexure 8

Enhanced enables and incentives under programme are given below:

Item	Existing norm	Proposed by MoHFW and approved by MSG
Existing Incentives		
Revision of incentives to Community DOT provider providing treatment support to Category I TB patients	250/- for completed course of treatment	Rs1000/- for the completed course of treatment
Revision of incentives to Community DOT provider providing treatment support to Category II TB patients	250/- for completed course of treatment	Rs1500/- for the completed course of treatment
Revision of incentives to Community DOT provider providing treatment support to Drug Resistant TB patients	Rs.2500/- for completed course of treatment (Rs.1000/- at the end of IP and Rs 1500/- at the end of CP)	Rs.5000/- for completed course of treatment. (Rs.2000/- at the end of IP and Rs 3000/- at the end of CP)
Incentives to patient in tribal and difficult areas	Rs.250/patient and one attendant	Rs 750/patient and one attendant
Incentive to volunteers for sputum sample transport in tribal and difficult areas	Rs.200/month/volunteer. If less than one visit per week then Rs 100/ month	Rs.25 per sample transported to the DMC
Travel cost to MDR TB patient/suspect to DRTB centre (outside district)	Actual travel cost using any public transport	Up to Rs 1000/visit/patient restricted to actuals by a public transport
Travel cost to MDR TB patient/suspect to DRTB centre (within district)	Actual travel cost using any public transport	Up to Rs 400/visit/patient restricted to actuals by a public transport
New Incentives		
Transportation cost for co-infected TB -HIV patient travel	NIL	Up to Rs.500/patient for only the first visit restricted to actuals by a public transport
Incentive related to Injection prick	NIL	Rs.25/injection prick

Annexure 9

Ready Reckoner for General Practitioners

Important general instructions:

1. Ensure that patient completes full course of anti-TB therapy
2. Side effects of anti-TB drugs can be an important cause of patient stopping medication, especially with second line drugs.
3. Prevention and early detection of side effects are needed
4. Alcohol, smoking and use of illicit drugs increase side effects
5. Relevant history, clinical examination and lab tests are important to evaluate risk factors and diagnosis of side effects at an early stage
6. For contraception, ask patient to seek advice from family health center as oral contraceptives are less effective with some anti-TB drugs
7. Educate, counsel and reassure patients for self-limiting side effects
8. For side effects and serious side effects, take immediate action and refer patient to specialist / tertiary center; as suggested below
9. Report serious side effects to PvPI center (Procedure for reporting: Call your nearby PvPI center and provide complete information about side effects. Contact details of the nearest PvPI center are: Name of the Centre - _____; Contact no: _____; National toll free number: **1800 180 3024**)
10. Advice nutritious diet to TB patients
11. Advice patients about respiratory hygiene and provide information on preventing spread of TB (using facemask, tissue paper and cover face)

ADRs with anti-TB drugs, their prevention and management:

ADRs	Diagnosis	Suspect Drug(s)	Differential Diagnosis / Other causes	Prevention	Management
Nausea and Vomiting	Clinical, based on complaints by patient	All oral anti-TB drugs	Hepatitis	Take anti- TB medication with banana	Symptomatic management. Exclude hepatitis / hepatoxicity
Rash, urticaria	Clinical	All anti-TB drugs	Steven Johnson syndrome, Anaphylactic reaction, Exfoliative dermatitis, Herpes infection	Seek past history of allergy before starting treatment and as applicable.	If rash involves <10% body surface area (BSA) and is not associated with mucous membrane involvement, treat with anti-histaminics. Stop suspect anti-TB drug and refer patient to specialist if indicated. Desensitization can be attempted. If it fails, substitute the suspect drug with alternate drug
Diarrhea	Clinical	All oral anti-TBdrugs	Bacterial dysentery Amoebic dysentery, Malabsorption syndrome, Pseudomembranous colitis	Use of clean and potable water for drinking, washing hands before eating and drinking any thing	AdviceOral Rehydration Solution (ORS)200 ml, after each loose stool. Check for infective causes.
Liver enzymes- SGOT/ SGPT increased (up to 2xULN)	Increase of liver enzymes after starting anti-TB drugs	Frequent & Severe: PZA INH RIF Rare: EMB Ethionamide FQs PAS Cycloserine	Viral hepatitis – rule out by negative serological tests for A, B, C and E. Alcoholic hepatitis - AST:ALT > 2:1 with history of alcohol intake Amoebic liver abscess – Ultrasound / CT to detect cystic lesions / abscess	Up to 2xULN is not serious. DIH reported in 8-30% of patients. Cannot be prevented. Avoid simultaneous administration of other hepatotoxic drugs. It can worsen to severe hepatitis, which can be prevented by monitoring	Usually drugs are not withdrawn. Check for other potential hepatotoxic agents e.g. alcohol

			Mass in ultrasound/CT→ Liver biopsy to rule out Hepatoma	of LFT in high risk patients every 15 days & taking appropriate action if liver enzymes increase.	
Hepatitis (Severe)	ALT/ AST >3×ULN with symptoms of Nausea, vomiting, anorexia, jaundice, dark colored urine OR ALT/ AST >5×ULN without symptoms	Frequent & Severe: PZA INH RIF Rare: Ethionamide PAS Cycloserine Clarithromycin Clofazimine Imipenem-cilastatin	Investigate as above to rule out: Viral hepatitis Alcoholic hepatitis - Amoebic liver abscess Hepatoma	Early detection of raised liver enzymes to prevent worsening & reduce associated morbidity & mortality	Management includes withdrawal of potential causative drugs & supportive treatment. Later, when enzyme levels return to normal, then gradually reintroduce the drugs. (Refer to flowcharts)
Exfoliative and allergic dermatitis	Clinical based on symptoms- Pruritus, widespread erythema and epidermal sloughing	Frequent: FQs Rare: RIF PAS Cycloserine linezolid Amoxicillin-clavulanate clarithromycin Clofazimine	Asteatotic Eczema Contact Dermatitis, Drug-Induced Bullous Disorders Drug-Induced Photosensitivity Nummular Dermatitis Perioral Dermatitis Phytophotodermatitis	Early detection and management can prevent worsening	Topical hydrocortisone or oral antihistamines may be helpful to control pruritus. Anti-TBmedications should not be discontinued unless an equally effective drug is available for substitution. Refer to specialist if indicated.
Stevens-Johnson and Toxic epidermal necrosis	Clinical based on total body surface area (BSA)involvement of more than 10% and/ or mucous membrane	Rare: INH RIF EMB FQs Amoxicillin-clavulanateclari	Staphylococcal scalded skin syndrome Irradiation – History of radiation Trauma - History Progressive systemic sclerosis (scleroderma) –	Early detection and management can prevent worsening	Immediate drug withdrawal and referral to specialistis recommended. Reintroduction is not recommended. Supportive therapy like antihistamines, anti-inflammatory agents may be helpful in the meantime.

	involvement	thromycin imipenem-cilastatin	ANCA antibodies		
Psychosis (Severe)	Symptoms of Hallucinations, paranoia, suicidal or abnormal thoughts or actions	Frequent & Severe: Cycloserine Frequent: INH Rare: RIF, FQs Clarithromycin Clofazimine Imipenem-cilastatin	Post-traumatic Stress Disorder, Delusional disorder, Schizophrenia, Schizophreniform Disorder	Careful monitoring. Psychiatric counseling at the start of treatment in patients at risk of psychiatric disorders.	Refer to specialist for further evaluation.Consider suspectdrug withdrawal. Refer to specialist.
Peripheral neuropathy	Clinical symptoms of Burning and paresthesia in extremities. Electromyography (nerve conduction studies)for confirmation	Frequent: INH Rare: EMB FQs PAS Ethionamide Cycloserine Linezolid (Severe)	Neuropathy due to high dose of pyridoxine Diabetic neuropathy Peripheral demyelinating disease	Supplementing the anti-TBdrugs with Pyridoxine 5-10 mg orally once a day if patient is on INH, Pyridoxine 50 mg per day with Linezolid and with every 250 mg Cycloserine.	Check for Pyridoxine compliance. Give paracetamol / NSAIDsto alleviate pain. Drug withdrawal is not indicated. Start Pyridoxine 100 mg per day. If no response, increase dose of Pyridoxine to 200 mg. Refer to specialist if no response or if patient is taking Linezolid.
Ototoxicity/ Hearing loss/ Deafness	Symptoms-Tinnitus, vertigo, Loss of balance and equilibrium. Audiometry for confirmation	Frequent & Severe: AGs Rare: Linezolid clarithromycin imipenem-cilastatin	Ear wax, otitis media, Traumatic hearing loss, Meniere's disease Acoustic neuroma	Monitoring of early symptoms can prevent permanent ear damage	Consider withdrawal of the suspect drug. Refer to specialist for further evaluation
Optic neuritis	Vision loss, Peri-ocular pain, Dyschromatopsia(disorder of color vision). Based on	Frequent & Severe: EMB Rare: PAS	Brain Tumor, Giant cell arteritis, Retinal detachment, Multiple sclerosis, Closed-angle glaucoma,	Regular ophthalmologic examination	Consider withdrawal of the suspect drug. Refer to specialist for further evaluation

	symptoms and ophthalmic examination for confirmation	Ethionamide Clofazimine Linezolid (severe)	Cataract, Macular degeneration, Diabetic retinopathy		
Immune Nephrotoxicity	Serum creatinine >2×baseline. Presence of Auto-antibodies in the blood is confirmatory	RIF, especially when restarted after stopping for few weeks	Urinary tract infection, Post streptococcal glomerulonephritis, Minimal change disease, Rapidly progressing glomerulonephritis	Patients should be counseled not to stop and restart rifampicin randomly,on their own	Consider drug withdrawal and refer tospecialist.
Flu Syndrome	By symptoms-Chills, malaise, dry cough, shortness of breath, loss of appetite, body aches and nausea	Frequent: RIF(specially with intermittent regimen)	Viral infections: Influenza, Dengue Fever: Dengue NS1 antigen test positive	Patients on daily regimen have reported lower frequency and less severe flu as compared to the patients on intermittent regimen	Oral antihistaminic and paracetamol, according to the symptoms
Arthralgia / arthritis	Joint pain, swelling involving one or more joints, High uric acid levels. Demonstration of tophi crystals in joint is confirmatory of Gout	Frequent & Severe: PZA Rare: EMB INH	Osteo-arthritis Rheumatoid arthritis	Early diagnosis and management can prevent progression and can improve quality of life	Therapy with paracetamol / NSAIDs can be used for pain relief as needed / Colchicine can be given in gout.
Thrombocytopenia	Blood platelet count <50000 mg/dl indicates thrombocytopenia, Drug induced thrombocytopenia is diagnosed by excluding other causes of	Frequent & Severe: RIF FQs Rare: INH EMB PZA AGs	Dengue hemorrhagic fever – Dengue NS1 antigen test positive Malaria – Peripheral blood smear, malaria antigen test Liver Cirrhosis – Liver biopsy Thrombotic Thrombocytopenic Purpura	Patients should be advised not to skip the doses of anti-TB drugs as the incidence of drug-induced thrombocytopenia has been reported to be higher when the drug is not taken continuously	Manage with platelet transfusion and consider withdrawal of suspect drug. It is important to remember that anti-TBdrugs can cause thrombocytopenia.

	thrombocytopenia	PAS Ethionamide Cycloserine Amoxicillin-clavulanate Clarithromycin Imipenem-cilastatin Linezolid	– Blood picture showing thrombocytopenia and hemolytic anemia with clinical symptoms Acute Leukemia – Bone marrow examination	As such thrombocytopenia cannot be prevented.Regular monitoring of platelet levels can facilitate early detection & thus, reduce the associated morbidity & mortality	
Leucopenia	Leucocyte count less than 2000/mm^3 Neutropenia: Absolute neutrophil count less than 1000/mm^3 Routine blood counts	<u>Rare:</u> INH EMB RIF FQs AGs Ethionamide Linezolid Amoxicillin-ClavulanateClarithromycin Imipenem-cilastatin	Typhoid, malaria, dengue, Rickettsial infections, HIV, thyroid disorders, aplastic anemia, rheumatoid arthritis, vitamin B12 or folate deficiency, mineral deficiencies of copper and zinc etc. Bone marrow diseases: Myelodysplastic syndrome, leukemia, Autoimmune disorders: SLE Bone marrow damage or suppression Drugs like: Clozapine, Valproate, Lamotrigine, Interferons, and Bupropion.	Monitoring of the complete blood count as indicated, will help in early identification. Avoid simultaneous administration of other drugs that can cause leucopenia.	If the total leucocyte count is <2000/ mm^3 or absolute neutrophil count < 1000/mm^3. **Refer the patient to specialist as this is serious.**
Nephrotoxicity	Serum creatinine more the twice the baseline with symptoms of Oliguria, Appetite loss, General ill feeling and fatigue	<u>Frequent & Severe:</u> **AGs** <u>Rare:</u> Linezolid	Chronic renal failure, Alcoholic ketoacidosis, Diabetic ketoacidosis, Metabolic acidosis, Urinary tract infection	Dose adjustment in patients with pre-existing renal disease, monitoring of renal function as indicated	Dose adjustment in patients with pre-existing renal disease. In cases of lack of response consider drug withdrawal and refer to specialist.

Hyperglycemia	Fasting blood sugar more than 160 mg/dl with polydypsia, polyphagia, polyuria.	Rare: RIF INH FQs Moxifloxacin Clofazimine	Hyperglycemia: Uncontrolled diabetes mellitus, Impaired glucose tolerance	Regular Blood sugar monitoring in high risk patients can help in early detection.	Individualized diet, exercise, patient educationand glucose-lowering therapies.
Hypoglycemia	Blood sugar less than 55 mg/dl with weakness, palpitation, loss of consciousness, seizures.	Rare: INH Ethionamide Clarithromycin	Hypoglycemia: Prolonged starvation, Pheochromocytoma, Cushing's syndrome	Regular Blood sugar monitoring in high risk patients for early detection	In case of severe hypoglycemia, withhold all hypoglycemic medications. Glucose to be given orally or I.V. as appropriate.
Hypothyroidism	TSH level >10 mIU/L with tiredness, increased sensitivity to cold, weight gain, constipation, depression, lethargy	Rare: PAS Ethionamide Cycloserine	Hypothyroid Goitre - TSH levels high Myxoedema - Hashimotos thyroiditis – Anti-thyroid antibodies Riedels thyroiditis - Antibodies	Early diagnosis, followed by prompt treatment can help to preventworsening.	All patients with TSH >10 mIU/L, whether symptomatic or not, should be started on Levothyroxine
Pseudomembranous colitis	Watery diarrhoeawith or without blood, associated with stomach cramps and highfever,stool examination	Frequent & Severe: Amoxicillin-clavulanate ClarithromycinI mipenem-cilastatin Linezolid Rare: RIF FQs	Viral diarrhea Bacterial diarrhea, Amoebic dysentery Malabsorption syndrome – Chronic condition accompanied with weight loss	Judicious use of antibiotics, use of probiotics	Vancomycin and metronidazole are effective. Refer to specialist. Consider withdrawal of the suspect drug.

Gynaecomastia	Clinical symptoms and biopsy	Rare: INH RIF Ethionamide	Lipomas, dermoid cysts, sebaceous cysts, ductal ectasia, hematomas, and fat necrosis FNAC will provide the clear diagnosis	Resolves after stopping anti-TB drugs	Reassure patient and in severe cases, withdraw suspect drug.
Pellagra-like syndrome	Based on clinical symptoms of Dementia, Dermatitis and Diarrhea	Rare: INH Ethionamide	Chronic alcoholism – Malnutrition Amino acid imbalance - Hypoalbuminemia	Supplementation with nicotinamide and pyridoxine	Check for compliance. Increase the dose of nicotinamide and pyridoxine if required.
QT prolongation Torsade de pointes Arrhythmia	QTc≥ 501 ms on at least two separate ECGs and or arrhythmia on ECG	Rare: FQs Moxifloxacin Clofazamine Linezolid Clarithromycin	Hypokalemia, Metabolic acidosis, Atrial fibrillation, atrial flutter, ventricular arrhythmia, Paroxysmal supraventricular tachycardia	ECG of patient on FQs as and when indicated	Refer to specialist for management

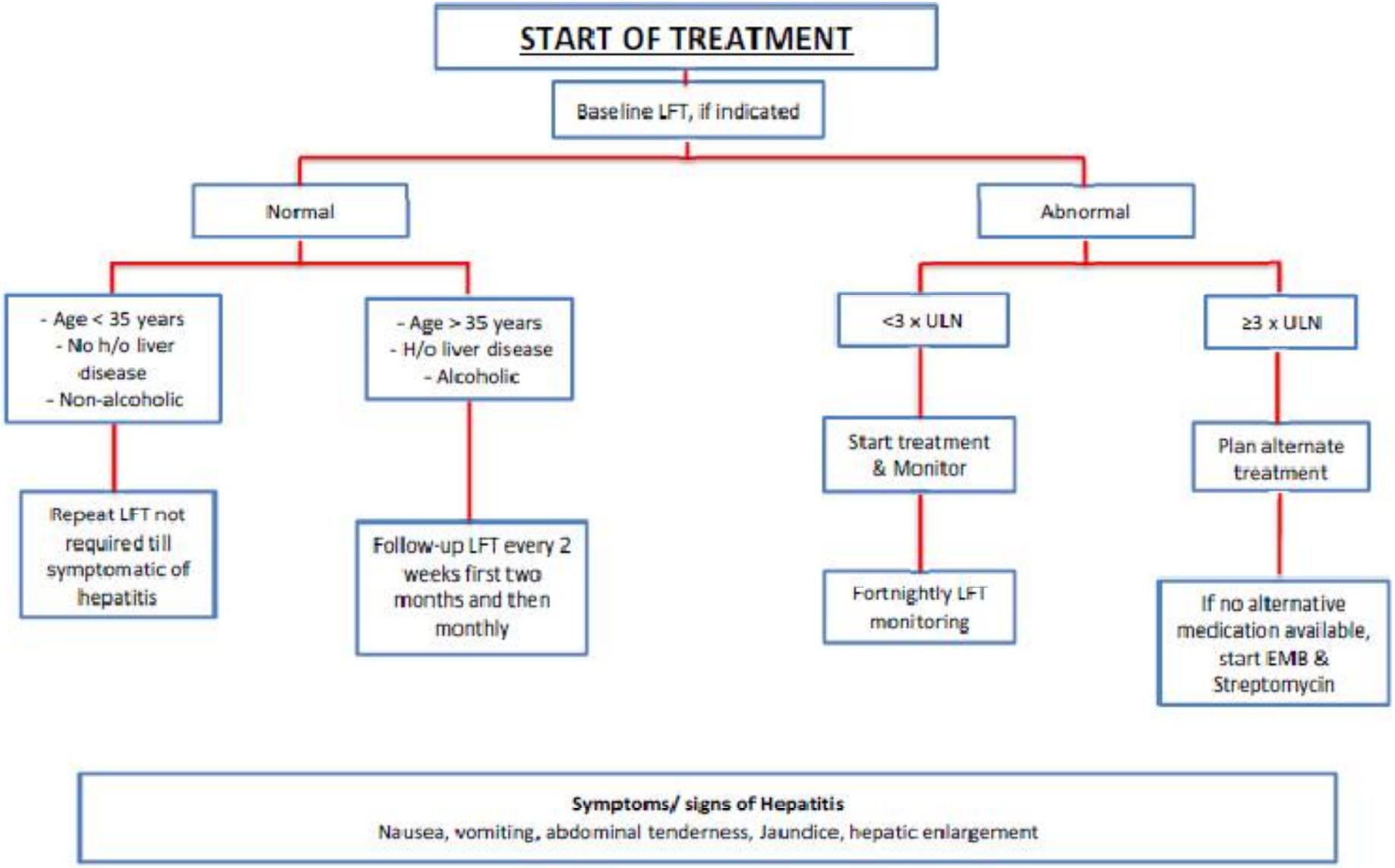
Pancreatitis, Peptic ulcer, Depression, Encephalopathy, Pneumonitis, Myopathy, Rhabdomyolysis, Congestive cardiac failure, Pericarditis have also been reported **rarely**with anti-TBdrugs.Peripheral neuropathy, anemia, thrombocytopenia, leucopenia and optic neuritis with Linezolid (2nd line drugs) can be sever and need immediate referral to specialist.
Frequent: Seen in 1-10% patients
Rare: Seen in less than 1% patients

Laboratory tests for TB patients:

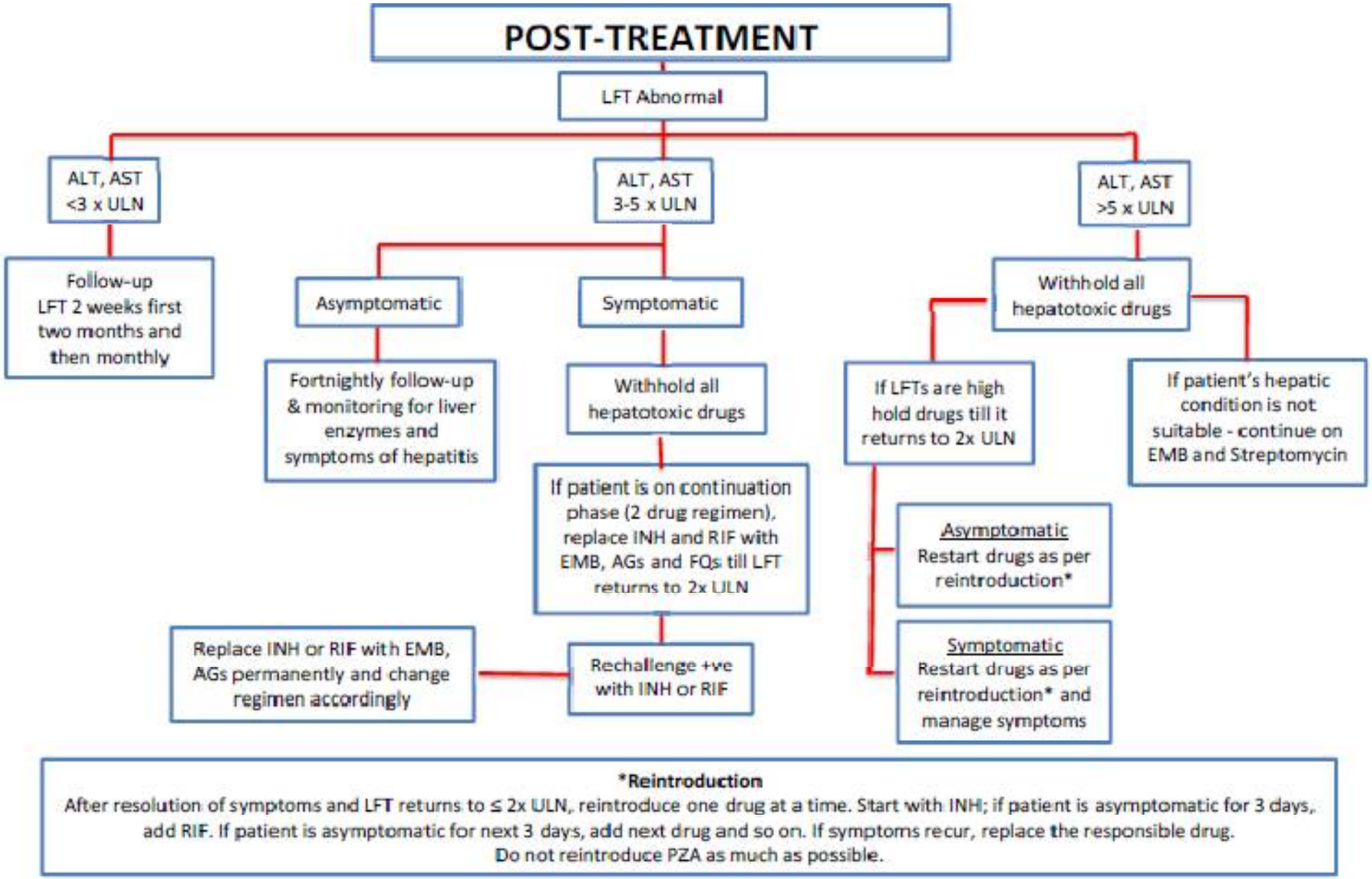
Time points	Laboratory tests
Baseline (Before initiating treatment if indicated)	1. LFT (ALT, AST, Serum bilirubin) 2. RFT (Serum creatinine, Blood Urea, Urine routine and microscopy) 3. Complete blood count, peripheral smear and Hb 4. Blood glucose: Fasting and post-prandial (Random in non-diabetics) 5. Total serum proteins, Albumin and Globulin 6. Serum uric acid 7. Serum electrolytes 8. Thyroid function tests (T3, T4 and TSH) 9. Ophthalmologic examination 10. Psychiatric consultation (before starting Cycloserine) 11. In females: Urine pregnancy test and USG of abdomen and pelvis
After 1.5 months	Ophthalmologic examination (for patients taking Ethambutol), if indicated
After 2 months of treatment as indicated	Tests 3 to 8 mentioned at the baseline will be repeated. Ophthalmologic examination: If EMB is stopped at or before 2 months, not required. If EMB is continued and ophthalmologic examination was not performed at 1.5 months, then it should be done.

Tests to be performed at 2 months will be repeated at 4 and 6 months if and as and when indicated.

Algorithm for the Management of Hepatitis: Flowchart 1:



Algorithm for the Management of Hepatitis: Flowchart 2



Warning symptoms for some serious adverse reactions:

Warning Symptoms	For Medical officer / General practitioner (GP): When to refer the patient
• Rash • Skin lesions on oral cavity, nose	If mucous membranes are involved OR rash is more than 1/10th of body surface area without mucous membrane involvement OR associated with fever and generalized swelling (edema); **refer to specialist / tertiary care center immediately.**
Pain in eye/s, Blurring of vision and Disturbance in color vision	Indicates **Eye toxicity.** **Refer the patient to specialist for evaluation.**
Loss of hearing / Diminished hearing, Ringing in the ears, Dizziness and Loss of balance	Indicates **Ear toxicity**. **Refer the patient to specialist** for evaluation.
Puffiness of face, Swelling over feet and Oliguria, Anuria	Indicates **Kidney toxicity**. Treat the symptoms and**refer the patient to specialist for evaluation.**
Hallucinations, Seeing abnormal things and Suicidal or abnormal thoughts or actions	Indicates **Psychiatric disturbances.** **Refer the patient to specialist** for evaluation.

Absolute contraindications of anti-TBdrugs:(Benefit – Risk) have to be carefully assessed.

Drug	Absolute contraindications	Reason
Rifampicin	With Saquinavir and Ritonavir	Potential for hepatotoxicity is increased. Rifampicin is CYP3A4 inducer and can decrease Saquinavir level and effect
Ethambutol	Optic neuritis	Ethambutol can cause optic neuritis
Pyrazinamide	Acute porphyria Gouty arthritis Hepatic diseases	Pyrazinamide can precipitate acute porphyria Can inhibit excretion of urates Can cause drug induced hepatitis
Neomycin Kanamycin, Tobramycin, Amikacin, Capreomycin, Streptomycin	Concurrent use of two aminoglycosides With potent diuretics e.g. Furosemide Soon after use of anesthetics and muscle relaxants	Can potentiate nephrotoxicity Can potentiate ototoxicity Can result in respiratory paralysis
Levofloxacin, Ofloxacin, Moxifloxacin	History of tendon disorders	Associated with risk of tendinitis and tendon rupture
Ethionamide	Severe hepatic impairment	Risk of worsening
Cycloserine	Epilepsy, Psychiatric illness-Depression, Severe anxiety, Psychosis Severe renal insufficiency	Can precipitate seizures Can lead to severe psychosis and depression Can lead to Cycloserine toxicity
Clarithromycin	With Pimozide, Astemizole With Lovastatin or Simvastatin Hypokalemia and in patients with prolonged QT interval	Risk of QT prolongation Can cause rhabdomyolysis Risk of further QT prolongation
Imipenem	With Valproic acid and Probenecid	Decrease in valproic acid concentration and Increase in plasma levels of imipenem
Linezolid	With Monoamine oxidases A or B inhibitors (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) within two weeks	Risk of MAO inhibition leading to serotonin syndrome

Algorithm for reintroduction of anti-TB drugs - To be done by experts only:

Adverse drug reaction	Advice on reintroduction
Hepatotoxicity	• Reintroductionafter liver enzyme returns to ≤ 2 X ULN
Ocular toxicity	• Main suspect drug is EMB • Reintroduction of Ethambutol is not recommended
Immune mediated Nephritis	• Main suspect drug is RIF • Reintroduction with RIF is not recommended
Non serious cutaneous ADRs -no mucous membrane involvement or less than 10 % of BSA.	• After withholding all drugs reintroduce one drug at a time
Serious Cutaneous adverse drug reactions - mucous membrane involvement or more than 10 % of BSA.	• Reintroduction is not recommended (applies for all anti-TBdrugs).
Immune thrombocytopenia	• Main suspect drug is RIF • Reintroduction with RIF is not recommended
Gynecomastia	• Symptoms takes long time to resolve (4-12 month) hence usually reintroduction is not required.
Aplastic Anemia	• Main suspect drug is INH • Reintroduction with INH is not recommended
Nephrotoxicity	• Main suspect drugs are AGs. • AGs can be reintroduced at low doses after the renal function returns to normal.
Ototoxicity	• Main suspect drugs are AGs. • Reintroduction of AGs is not recommended.
Cardiac arrhythmias including Torsede pointes (TdP)	• Main suspect drugs are FQs. • Reintroduction with FQs is not recommended.
Diarrhea	• Reintroduction is recommended with one drug at a time every fourth day, once diarrhea is resolved
Seizures	• Main suspect drugs are FQs. • Reintroduction with FQs is not recommended.
Psychosis	• Main suspect drugs iscycloserine. • Reintroduction with cycloserine can be done at low dose but if symptoms recur than completely discontinue the drug.

Stepwise increase in the dosage for Reintroduction

1. Reintroduction of anti-TB drugs:

Drug	Day 1	Day 2	Day 3
Isoniazid	50 mg	Full dose	Full dose
Rifampicin	75 mg	300 mg	Full dose
Pyrazinamide	250 mg	1000 mg	Full dose
Ethionamide / Prothionamide	125 mg	250 mg	Full dose
Fluoroquinolones	50 mg	200 – 250 mg	Full dose
Cyclosporine	125 mg	250 mg	Full dose
Ethambutol	100 mg	500 mg	Full dose
PAS	1 g	4 g	Full dose
Capreomycin	125 mg	500 mg	Full dose
Kanamycin	125 mg	500 mg	Full dose
Amikacin	125 mg	500 mg	Full dose

If the test dose of any drug causes a reaction, discontinue this drug, unless it is deemed essential to the regimen. If that is the case, desensitization can be considered.

2. Reintroduction of the drugs should be in hospitalized patients.

3. In patients with severe rash,dose increment should be slower than stated above.

4. For key drugs, Isoniazid, Rifampicin, Ethambutol, detailed desensitization protocol with very small dose and method of dosage preparation is available on the website (http://www.who.int/topics/tuberculosis/en/)

Commonly used ancillary medicines:

Management of adverse reaction often requires use of ancillary medicines to reduce or lessen side effects. Below is list of indications and commonly used medicines for management of adverse reactions.

Indication	Drugs
Nausea, vomiting, Stomach upset	Domeperidone, metoclopramide, prochlorperazine, promethazine, ondansetron
Heartburn, indigestion and acidity	H2-blockers (ranitidine etc.), proton pump inhibitors (omeprazole, pantoprazole etc) Antacid syrups and the antacids if prescribed should be takenat least 2 hours apart from anti-TB drugs
Oral candidiasis	Fluconazole, clotrimazole lozenges, nystatin suspension
Diarrhoea	ORS sachets
Prophylaxis of neurological complications of cycloserine and isoniazid	Pyridoxine (vitamin B6)
Musculoskeletal pain, Arthralgia, headaches	Give paracetamol / ibuprofen / aspirin/ diclofenac. If caused by fluoroquinolones, refer tospecialist immediately. Tendonitis can progress to tendon rupture.
Cutaneous reactions, itching	Hydrocortisone cream, calamine lotion
Systemic hypersensitivity Reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate) Systemic corticosteroids (prednisone, prednisolone, Dexamethasone) are reserved only for very severe reactions
Bronchospasm	Inhaled beta-agonists (salbutamol, albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium and magnesium replacement therapy (oral formulations)
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants

	(amitriptyline)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Any hypnotic
Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal Effects), Buromazine, thioridazine
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Peripheral neuropathy	Amitriptyline, gabapentin
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, Promethazine

Ready Reckoner for Health Worker

Annexure 10

Important general instructions:

Common side effects of anti-TB drugs and their management

1. Ensure that patient completes full course of anti-TB therapy
2. Side effects of anti-TB drugs are important cause of patient stopping medication
3. Prevention and early detection of side effects are needed
4. Alcohol, smoking and use of illicit drugs increaseside effects
5. Relevant history, clinical examination and lab tests are important to evaluate risk factors and diagnosis of side effects at an early stage
6. For contraception, ask patientto seek advice from family health center as oral contraceptives are less effective with some anti-TB drugs
7. Educate, counsel and reassure patients for self-limiting side effects
8. Side effects and serious side effects requiring immediate action ⟶ **refer patients to Medical officer**
9. Report serious side effects to PvPI center (Procedure for reporting: Call your nearby PvPI center and provide complete information about side effect. Contact details of the nearest PvPIcenter are: Name of the Centre **-** _____;Contact no: _____;

   National toll free number:**1800 180 3024**)
10. Advice nutritious diet to TB patients
11. Advice patients about respiratory hygiene and provide information on preventing spread of TB (use facemask, tissue paper and cover face)

Ready Reckoner for Health Worker

Table 1: Some common and rare side effects of anti-TB drugs are as follows:

Common (Seen in 1-10% patients)	Rare (Seen in less than 1% patients)
Nausea, Vomiting, Gastritis, Hepatitis, Hypersensitivity reactions, Cutaneous reactions	Flu like syndrome, Peripheral neuropathy, Ocular toxicity, Dysglycemia, Gynaecomastia, Hypothyroidism, Joint related side effects, Tendinopathy and tendinitis, Myelo-suppression, Anaemia, Thrombocytopenia, Psychosis, Seizures, Prolongation of QT interval

Table 2: Symptoms, causative drugs and action to be taken by Health worker:

Symptoms	Which drugs cause	Action by Health Workers
Upper abdominal pain - Frequent	All oral anti-TB drugs	Indicates **gastritis.** Advise patients to increase fluid intake. Patients should not take antacids / acid lowering agents together with first line anti-TB drugs as it reduces the absorption of drugs. **Refer to Medical Officer**
Nausea, vomiting	All oral anti-TB drugs	Reassure patient. Advice patient to take drugs embedded in a banana. Give drugs with less water and over a longer period of time (e.g. 20 minutes). However, later in the day, patients should take sufficient water. **If above measures fail, refer to Medical Officer.**
Nausea, vomiting with yellowness of skin and dark colour urine	Mainly by Pyrazinamide, Rifampicin and Isoniazid	Indicates**Liver toxicity** **Refer to Medical officer urgently**
Loose motions frequency >4 times, liquid stools	Mainly by PAS, Ethionamide, Isoniazid, Rifampicin, Ofloxacin, Levofloxacin,	Counsel patients on food and personal hygiene. Advice 200 ml Oral rehydration solution (ORS) after every loose

	Moxifloxacin	stool to maintain hydration. **Refer to Medical officer**
Loose motions associated with dryness of skin and mouth, decreased urination, tiredness and sunken eyes	Same as above	Indicates**Dehydration(Serious)** **Refer to Medical officer urgently**
Itching / Rashes	Mainly by Ethambutol, Rifampicin, Streptomycin	Reassure patient **If rash persists, refer to Medical Officer**
Itching / Rashes involving very large body area or present in mouth, nose associated with swelling and fever	Mainly by Ethambutol, Rifampicin, Streptomycin	Indicates systemic involvement (**Serious**) **Refer to Medical officer urgently**
Tingling /burning /numbnessin hands and feet	Mainly Isoniazid, Cycloserine	Check that patient is taking Pyridoxine. **Refer to Medical officer.**
Pain in Joints	Mainly Pyrazinamide	Paracetamol can be given if only 1-2 joints are involved. Reassure patient that it is a self-limiting condition. If > 2 joints are involved or pain is not relieved, **refer to Medical officer.**
Impaired vision: Pain, Blurring of vision, Disturbance in color vision	Mainly Ethambutol	Indicates**Eye toxicity**. **Refer to Medical officer urgently**
Flu-like syndrome: Chills, dry cough, shortness of breath, loss of appetite, body ache, malaise	Mainly Rifampicin	Reassure patient. If not controlled, refer patient to **Medical Officer** for evaluation.
Swelling of face or legs, less or no urine	Amikacin, Kanamycin, Capreomycin, Streptomyin	Indicates**Kidney toxicity**. **Refer to Medical officer urgently**

Ready Reckoner for Health Worker

Seeing abnormal things, change of thoughts, suicidal thoughts	Mainly Cycloserine	Indicates **Psychiatric disturbances.** **Refer to Medical officer urgently**
Tiredness, lethargy, headache, giddiness, pale look, palpitations	Mainly Linezolid, Isoniazid, Rifampicin, Pyrazinamide, Ofloxacin, Levofloxacin, Moxifloxacin	Indicates**Anemia.** Patients can be advised rest in DOTS center post-dosing to avoid giddiness. Advice patients on nutrition Refer **to Medical Officer** for evaluation.
Ringing in ears, Loss of hearing, dizziness and loss of balance leading to recurrent fall	Mainly Streptomycin, Amikacin, Kanamycin, Capreomycin	Indicates**Ear toxicity.** **Refer to Medical officer urgently**
Slowness of activities, swelling of face, swelling in neck, disproportionate weight gain	Mainly PAS and Ethionamide	Indicates **Thyroid involvement.** **Refer to Medical officer urgently**
Pain and swelling in muscles and Tendons, difficulty in movement	Ofloxacin, Levofloxacin and Moxifloxacin	Indicates **Tendonitis** **Refer to Medical officer urgently**
Seizure: Convulsion	Isoniazid, Cycloserine, Ofloxacin, Levofloxacin, Moxifloxacin	**Refer to Medical officer urgently**
Orange and reddish color of urine sweat, phlegm (sputum), saliva or tears may be noticed. As this is quite common with rifampicin and reassure patients.		

Annexure 11

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

CDSCO
Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
FDA Bhavan, ITO, Kotla Road, New Delhi
www.cdsco.nic.in

(AMC/ NCC Use only
AMC Report No.
Worldwide Unique no.

A. Patient Information

1.Patient Initials _____	2.Age at time of Event or date of birth ----------	3. Sex ☐M ☐ F 4. Weight ____Kgs

12. Relevant tests / laboratory data with dates

B .Suspected Adverse Reaction

5. Date of reaction stated (dd/mm/yyyy)
6. Date of recovery (dd/mm/yyyy)
7. Describe reaction or problem

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the action
- ☐ Death (dd/mm/yyy)____
- ☐ Life threatening
- ☐ Hospitalization-initial or prolonged
- ☐ Disability
- ☐ Congenitial anomaly
- ☐ Required intervention to prevent permanent impairment / damage
- ☐ Other (specify)

15. Outcomes
- ☐ Fatal
- ☐ Continuing
- ☐ Recovering
- ☐ Recovered
- ☐ Unknown
- ☐ Other (specify)____

C.Suspected medication(s)

S.No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if known give duration)		Reason for use of prescribed for
								Date started	Date stopped	
i.										
ii.										
iii.										
iv.										

Sl.No As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. Reporter (see confidentiality section in first page)

16. Name and Professional Address :_____
_____
Pin code : _____ E-mail _____
Tel. No. (with STD code): _____
Occupation _____Signature _____

17. Causality Assessment

18. Date of this report (dd/mm/yyyy)

ADVICE ABOUT REPORTING

- **Report adverse experiences with medications**
- **Report serious adverse reactions. A reaction is serious when the patient outcome is:**

  - death
  - life-threatening (real risk of dying)
  - hospitalization (initial or prolonged)
  - disability (significant, persistent or permanent
  - congenital anomaly
  - required intervention to prevent permanent impairment or damage

- **Report even if:**

  - You're not certain the product caused adverse reaction
  - you don't have all the details, however, point nos. **1, 5, 7, 8, 11, 15, 16 & 18** (see reverse) are essentially required.

- **Who can report:**

  - Any health care professional (Doctors including Dentists, Nurses and Pharmacists)

- **Where to report:**

  - Please return the completed form to the nearest ***Adverse drug reaction Monitoring Centre (AMC)*** or to ***National Coordinating Centre***
  - A list of nationwide AMCs is available at: http://cdsco.nic.in/pharmacovigilance.htm

- **What happens to the submitted information:**

  - Information provided in this form is handled in strict confidence. The causality assessment is carried out at Adverse Drug Reaction Monitoring Centres (AMCs) by using WHO-UMC scale. The analyzed forms are forwarded to the National Coordinating Centre through the ADR database. Finally the data is analyzed and forwarded to the Global Pharmacovigilance Database managed by WHO Uppsala Monitoring Center in Sweden.

  - The reports are periodically reviewed by the National Coordinating Centre (PvPI). The information generated on the basis of these reports helps in continuous assessment of the benefit-risk ratio of medicines.

  - The information is submitted to the Steering

interventions that may be required.

Reaction Reporting Form

For VOLUNTARY reporting
of suspected adverse drug reactions by
health care professionals

Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India
FDA Bhawan, ITO Kotla Road, New Delhi – 110002
www.cdsco.nic.in

Pharmacovigilance Programme of India for Assuring Drug Safety

(PvPI)

***National Coordinating Centre*,**
Indian Pharmacopoeia Commission
Ministry of Health & Family Welfare,
Govt. of India
Sector-23, Raj Nagar, Ghaziabad-201 002.Tel.:0120-2783400, 2783401, 2783392, FAX: 0120-2783311
E.mail: ipclab@vsnl.net

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not ex-
and will not disclose the reporter's identity in response to a request from the public. **Submission of a report does not constitute**

caused or contributed to the reaction.