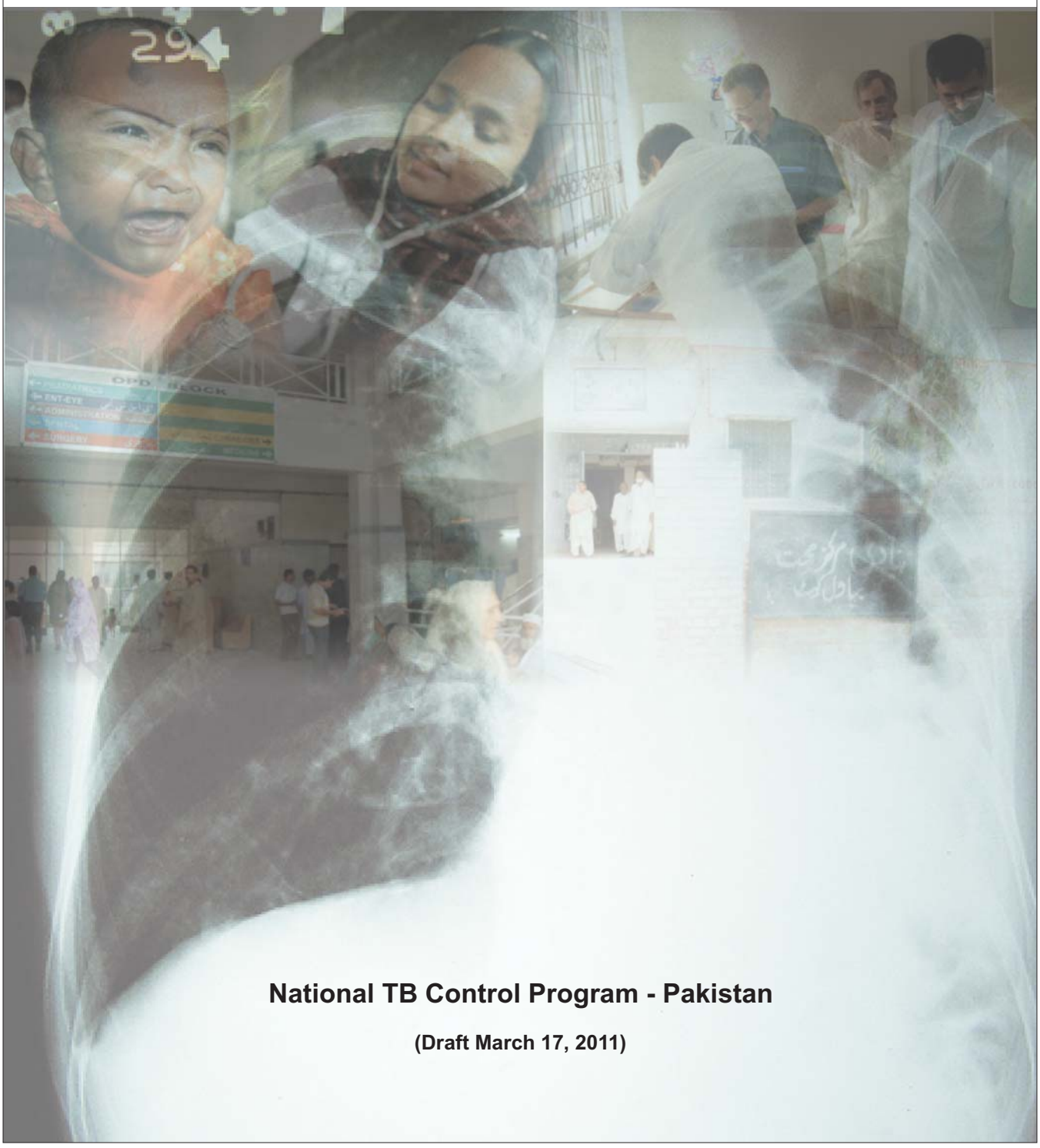
MDR-TB
CASE MANAGEMENT

CONSULTATION DESK GUIDE



National TB Control Program - Pakistan

(Draft March 17, 2011)

SECTION I

DIAGNOSE & TREAT MDR-TB CASES

ASSESS & DIAGNOSE A CASE OF MDR-TB

Identify and refer MDR-TB suspects (at the peripheral clinic)

Assess your patient's MDR-TB risk through record review and interview.

- **Failure** of re-treatment regimens (CAT-II)
- **Failure** of new case treatment regimens (CAT-I)
- **Failure** of other treatment regimens used in private sector
- **Contacts** – smear-positive contact of known MDR-TB case
- **Institution** with outbreak or high prevalence or risk of MDR-TB
- **Residence** in areas with high MDR-TB prevalence
- **Other** e.g. smear positive with history of using anti-tuberculosis drugs of poor or unknown quality

Educate the MDR-TB suspect

Refer to a treating hospital (with referral form & record)

Assess and diagnose MDR-TB patients (at the treating hospital)

Educate the MDR-TB suspect

Register the MDR-TB suspect

Send sputum samples for smear, culture and DST (R/H)

Interpret DST results and **inform** patient about MDR-TB diagnosis

Admit the MDR-TB patient

Conduct a baseline clinical assessment - history, physical examination, and baseline investigations (use NTP baseline clinical assessment form).

Initiate treatment (see next page for details)

DECIDE CLINICAL MANAGEMENT OF A MDR-TB CASE

Admit the patient to hospital to carry out baseline clinical assessment, to observe initial response to drugs (i.e. allergies, side effects etc.), and to arrange for decentralized care.

Decentralized care is preferred when the patient has no serious medical condition such as respiratory distress, significant hemoptysis, renal or liver failure etc. and arrangements for decentralized care have been made.

Step 1: **Register** the patient.

Step 2: **Review** the clinical and laboratory findings and decide if there is a special situation to be considered for treating the patient such as pregnancy, renal insufficiency (see pages 4 - 5).

Step 3: **Prescribe** the standard MDR-TB regimen, and send sample for DST for the selected drugs.

	Standard Regimen	**First alternative**	**Second alternative**
G-1	Pyrazinamide		
G-2	Kanamycin	Capreomycin	Streptomycin or Amikacin
G-3	Levofloxacin	Moxifloxacin	Ofloxacin
G-4	Ethionamide Cycloserine or/and PAS	Protionamide	
G-5		Clofazimine Amoxicillin/clavulanate	

Note:

- If your patient (or source case) is known to be resistant to one of the standard 2nd line drugs, use an alternate drug from the same group, and reinforce the regimen by adding a fifth 2nd line drug to the regimen.
- If first choice drug is not suitable or available use an alternative drug from the same group.
- If special situation, see page 4 - 5 for the prescription of drugs.
- If required, add two G-5 drugs to reinforce 2nd line standard regimen.

Step 4: **Prescribe** the right dosage of selected drugs

Note: Daily dose for adults and children

Drug	**Daily recommended dose (in mg) by body weight**			
	< 33 kg	**33-50 kg**	**51-60 kg**	**> 70 kg**
Kanamycin# (1 g vial)	15 – 20 mg /kg / day	500 – 750	1000	1000
Levofloxacin (250, 500mg)	7.5 – 10 mg/kg/day (Adult 750)	750	750	750
Cycloserine# (250 mg)	10 - 15 mg/kg/day	500	750	1000
Ethionamide (250 mg)	15 – 20 mg/kg/ day	500	750	1000
PAS (4g sachets, Jacobus PASER)	150 mg/kg/day	8 grams	8 grams	8 grams
Vitamin B-6	3 – 4 mg/kg/day	100 – 150	150	200
Amikacin (1 g vial)	15 – 20 mg / kg/ day	500–750	1000	1000
Capreomycin# (1 g vial)	15 – 20 mg/kg/day	500 – 750	1000	1000
Ofloxacin (200, 300, 400 mg)	15 –20 mg/kg/day (Adult 800)	800	800	800 – 1000
Moxifloxacin (400 mg)	7.5 – 10 mg/kg/day (Adult 400)	400	400	400
Clofazimine (50, 100 mg)	3 – 5 mg/kg/day	200 – 300	200 – 300	200 – 300
Pyrazinamide (500mg)	30-40 mg/kg/day	1000 – 1750	1750 – 2000	2000 –2500

 # Child daily dose upper limit is 30mg/kg for Kanamycin & Capreomycin, and 20 mg/kg for Cycloserine.

- Generally give as **once daily**; but may be twice daily if side effects.
- Exceptions which are given as a **twice daily** dose (split the above daily dose) are cycloserine, Ethionamide, PAS, and Ofloxacin.
- **Start** Ethionamide, Cycloserine and PAS on a lower dose and increase over a two-week period.

Step 5: **Educate** the patient about their drugs – see section II, CDG p34

MDR-TB TREATMENT IN SPECIAL SITUATIONS

Pregnancy

- Treat with 2nd line drugs, despite the small risk to the fetus.
- Delay treatment until the 2nd trimester, unless life-threatening.
- Give four oral 2nd line drugs of known efficacy.
- Add an injectable after child birth. Give Capreomycin, if required during pregnancy.
- Avoid Ethionamide.

Contraception (if not pregnant)

- Strongly advise, provide, or guide her access to contraception.
- Injectable contraceptives e.g. Depo-Provera and barrier methods are preferable to oral pills.
- If your patient prefers contraceptive pills, then advise them to take them at a different time from their TB medication.
- If they vomit within 2 hours of taking the contraceptive pill, add barrier method for one month (after no vomiting).

Mother with MDR-TB

- Use formula milk where possible instead of breast feeding, with infant care by other family members (until mother become smear-negative).
- Limit the infant's contact with smear-positive mother to the outdoors or well-ventilated places, or
- Use a "N-95 respirator" or surgical mask (if possible).

Child with MDR-TB

- No drugs are absolutely contra-indicated in children.
- If DST results for the source case are known, then adjust the regimen accordingly.
- Dose at the higher end of the recommend range in mg/kg/day (see tables - CDG page 3 and 49) unless a particular reason otherwise.
- Adjust the drug doses, as child gains weight during treatment.

Diabetes

- Ensure effective control of diabetes - liaise with physician
- No oral hypoglycemic is contra-indicated, but may need increased dose.
- Ethionamide/Protionamide may disturb sugar control.
- Monitor creatinine and potassium levels more frequently.

MDR-TB TREATMENT IN SPECIAL SITUATIONS

Renal insufficiency

- Renal insufficiency is not uncommon in long standing TB cases.
- Estimate creatinine clearance:

$$\text{Creatinine Clearance} = \frac{((140 - \text{age}) \text{ (ideal body weight in kg}^{\#} \text{ for men) (x 0.85 for women)}}{(72) \text{ (serum creatinine in mg/dl)}}$$

Ideal weight = 50kg + 2.3 kg per inch over 5 ft

- Adjust the dose and/or the interval between doses based on the creatinine clearance
- If severe renal insufficiency (creatinine clearance < 30 ml/min): check the creatinine clearance weekly, and readjust medications accordingly:

Medication adjustment in severe renal insufficiency

Drug	**Change in Frequency**	**Recommended**	
		Per Dose	**Frequency**
Kanamycin	Yes	12 – 15 mg/kg	Three times/ week*
Levofloxacin	Yes	750 – 1000 mg	Three times/ week
Cycloserine	Yes	250 mg	Once daily
Ethionamide	No	250 – 500 mg	Once daily
PAS	No	4 gm	Twice daily
Amikacin	Yes	12 – 15 mg/kg	Three times/ week*
Capreomycin	Yes	12 – 15 mg/kg	Three times/ week*
Ofloxacin	Yes	600 – 800 mg	Three times/ week
Moxifloxacin	No	400 mg	Once daily
Pyrazinamide	Yes	25 – 35 mg/kg	Three times/ week
Streptomycin	Yes	12 – 15 mg/kg	Three times/ week*

* Injectable dosing frequency may need to be reduced to twice per week, if needed.

Liver disorders

- No drug is contra-indicated except Pyrazinamide.
- In acute concurrent hepatitis (unrelated to TB), defer treatment or treat with four non-hepatotoxic drugs.
- In chronic liver disease, use usual drugs but monitor liver enzymes.
- Stop if significant liver inflammation.

Seizure disorders:

- H/o seizures: check for anti-seizure medication and control.
- If not well controlled, initiate or adjust anti-seizure medication, and avoid cycloserine (if possible) or give cycloserine only after adjusting anti-seizure medication.

Psychiatric ill-health and Addiction

- Identify and address psychiatric illness throughout the treatment.
- Treat illness with medication, counseling, and group therapy.
- Cycloserine, despite known psychiatric side-effects, should be used in these patients if necessary, but monitor closely.
- Offer treatment for addiction, if substance dependence is found.

Administering Adjuvant therapies

The additional therapies required for other medical conditions or complications have been discussed elsewhere in the desk guide.

Steroids:

- Steroids are known not to increase mortality in MDR cases.
- Steroids alleviate symptoms in severe respiratory insufficiency, exacerbations of COPD, laryngeal TB, and central nervous system involvement.
- Dose Prednisolone 1mg/kg, gradually decrease to 10mg per week

Surgery:

- In resectable disease, surgery plus chemotherapy improves results if a good surgeon and post-operative care is available.
- Surgery may be considered for the following MDR-TB cases:
  - Persistent or severe hemoptysis
  - Patients with higher level of resistance
  - Localized cavities or destroyed lung tissue, and has remained culture positive despite 3 – 6 months of treatment (or were culture negative).
- Surgery should occur early after smear conversion. If not possible, then after at least three months of chemotherapy.
- Give medication both prior to and after surgery. Every patient should get treatment for 18 – 24 months of consecutive negative culture, and no less than 6 months after the surgery.

FOLLOW-UP AT HOSPITAL – INVESTIGATIONS

Monthly visits to the MDR Center are required. At each visit:

- **Investigations** – smears, culture and other tests
- **Clinical assessment** – treatment progress, adherence, side effects
- **Review** and manage MDR-TB treatment
- **Evaluate** and manage nutritional status
- **Manage** treatment non-response, suspension and interruptions
- **Monitor** and manage other known medical conditions

Core Investigations:

- Routine tests in MDR-TB and frequency, other tests as needed.

Test	Whom?	Frequency?	Comments
Smears	All patients	Monthly throughout	EQA important
Cultures	All patients	Monthly, then every 2 months in continuation.	EQA important
X-ray (chest)	All patients	Six monthly	-
Blood tests	Age < 50 yrs	Six monthly	Monthly Hgb. & ESR. Clinician may suggest more BTs, if required.
	Age > 50 yr	Three monthly	
Creatinine and potassium	Age < 50 yrs	Monthly	When on injectable. Then every 2nd month.
	Renal insufficient, or age > 50 yr, or diabetes.	Weekly for first month, and then monthly	If increased, check weekly until stabilized. More detail – CDG p25
Liver enzyme	Hepatitis risk	1 – 3 monthly	Every month - if HIV^+
TSH	All patients	At nine months	Baseline - if age > 50 6 monthly - if Eto/ Pto
Audio/ visual exam	All patients	Detailed - at start then as needed Basic – audio & visual - monthly	Audiometry – every 2 month when injectable. ↑ visual check - if diabetes

- Record the smear and culture results in MDR-TB01, and all laboratory results in the "follow-up clinical assessment" form.

FOLLOW-UP AT HOSPITAL – CLINICAL ASSESSMENT

Clinical Assessment:

The clinical assessment is carried out and recorded in the "follow-up clinical assessment" form.

Ask, look, and document if changes in:

- TB symptoms: cough? hemoptysis?, breathless?, night sweats?, weight loss?
- Vital signs: temperature, pulse, respiration, blood pressure,
- General physical exam: general well-being, body systems/parts.
- Other complaints/ conditions – indicating side effect (see page 9) or an arising medical condition (not previously known)

Assess Adherence

Talk to the patient (and his accompanying person)

- Ascertain the regularity and dose of drugs taken (card review, patient interview, and count empty blisters/ injection vials)
- Encourage if found adherent, and guide if any deviation noted.
- Remind how important it is to take all medications, every day, as prescribed

Interpret the Investigations and Clinical Assessment:

#	Laboratory Results		Clinical condition	Remarks
	Smear	Culture		
1	Positive	Positive	Not applicable	Infectious
2	Positive	Negative	Improving	Ni viable bacilli
			No change	Possible false negative culture (EQA), repeat smear/culture
3	Negative	Positive	Not applicable	Still infectious, less bacterial load
4	Negative	Negative	Not applicable	Non-infectious

FOLLOW-UP AT HOSPITAL – IDENTIFY SIDE EFFECTS

Symptoms/signs indicating side effects: (see CDG pages: 16 - 29)

- *Allergic reaction* – rash, fever, hepatitis.
- *Depression* – appetite sleep disturbance, loss of interest, lack of energy, inability to concentrate, feeling of hopelessness
- *Electrolyte imbalance* – **if** moderate then fatigue, cramps, mood changes, weakness; **if** severe then tetany, paralysis, arrhythmias.
- *GIT intolerance* – nausea, loose stools, abdominal bloating, gastritis, gastric ulcers.
- *Headaches* – migraines or cluster headaches
- *Hepatitis* – nausea, diminished appetite, jaundice, scleral icterus, tea colored urine, pale stools.
- *Hypothyroidism* – fatigue, cold intolerance, dry skin, constipation, enlarged thyroid & delayed deep tendon reflex
- *Musculoskeletal effects* – arthralgias, arthritis, myalgias
- *Nephrotoxicity* – raised serum creatinine, oliguria or anuria, volume overload signs, uremic symptoms.
- *Ototoxicity* - hearing loss, tinnitus, nystagmus, ataxia, unsteadiness.
- *Peripheral neuropathy* – sensory disturbances, difficulty walking, weakness, decreased deep tendon reflex.
- *Psychosis* – visual or auditory hallucinations, delusions, paranoia, bizarre behavior.
- *Seizures* – aura, loss of consciousness, involuntary movement or flaccidity, bowel or bladder incontinence, confusion.

FOLLOW-UP – REVIEW TREATMENT & MANAGE NUTRITION

Adjust MDR-TB **drugs** in response to the treatment review including DST results and side effects (CDG pages 16 - 29)

- o split the dose into twice daily if minor intolerance/ side effects
- o change the dose (reduce - if renal insufficiency or weight loss)
- o stop one or more drugs, and reinitiate when stabilized, or substitute if side effects are difficult/not possible to manage.
- o substitute the standard regimen drug with an alternate drug from same group (also consider adding 5th drug), if DST shows resistance (P-2).

Stop the **injectable** (i.e. graduate), if the following three criteria are met:

- o completed treatment for at least six months, and
- o culture is negative on two consecutive follow-ups (30 days apart), and
- o taken 4 months of intensive phase treatment after the 1st conversion.

Prescribe **ancillary** drugs and other measures, including referral to a psychiatrist or other specialist, to manage the side effects

Manage Nutrition

Continued weight loss or failure to gain weight during therapy is considered an urgent management issue.

Check for diminished food intake, intolerance to food items, and other symptoms such as insomnia and fatigue or nausea and vomiting.

- o If early satiety
  - advice to take frequent meals (i.e. 6 – 8 times / day)
- o If intolerance to food items e.g. milk products, fatty foods.
  - advice to avoid triggering foods.
- o If accompanying symptoms of insomnia, fatigue, loss of interest, loss of concentration, psychomotor retardation
  - rule out or manage depression
- o If accompanying nausea, vomiting, diarrhea, jaundice, fatigue, weakness
  - rule out hepatitis and manage symptoms.
- o If none of above mentioned reasons or accompanying conditions
  - encourage high-protein, high-calorie diet; provide food support (if possible); monitor food intake and weight gain
- o If no response to above interventions/ measures
  - consider appetite stimulant (e.g. medroxyprogesterone) and also tube feeds in life-threatening situations.

FOLLOW-UP – MANAGE TREATMENT NON-RESPONSE

Assess the patient with treatment non-response:

- Assess the patient clinically – including review of: regimen, adherence, and clinical indicators (such as weight gain)
- Exclude other illnesses leading to – decreased drug absorption or immune suppression
- Exclude lab. contamination – repeat smear and culture (twice)

Take measures to manage the treatment non-response:

- <u>If clinical non-progress or deterioration (with positive culture)</u>
  - Repeat the comprehensive DST
  - Modify the regimen for interim period (i.e. till repeat DST results):
    - Maximize the doses of all drugs
    - Change injectable (i.e. an alternate with known efficacy)
    - Add two other 2nd line drugs (if possible)
    - Consider adjuvant surgery – if recommended/available
  - Adjust the modified regimen after 2 – 3 months (if required and feasible), in light of DST results and clinical response
  - Continue the modified (+/- further adjusted) regimen for 3 – 6 months after culture is found negative.
  - Extend the treatment duration for 18 months from the date of negative-culture

- <u>If good clinical response (but positive culture)</u>
  - If confident about clinical response - do not modify the treatment regimen
  - If less confident about clinical response – modify the regimen, and then consider resuming the prior regimen if repeat culture is reported negative.

FOLLOW-UP AT HOSPITAL – TREATMENT SUSPENSION

Identify the cases for treatment suspension:

- If measures to manage the treatment non-response are found not effective within 3 – 4 months, then consider failure and treatment suspension.
- There is no simple definition for failures. However the signs that indicate treatment suspension (due to no-response/ failure) are:
  - persistent positive smear or culture past 8th treatment month
  - extensive and bilateral lung disease with no option for surgery
  - high-grade resistance with no option to add two more drugs
  - overall clinical deterioration e.g. weight loss, respiratory insufficiency

Clinical team decides to suspend the MDR-TB treatment, if

- Drugs have been taken as prescribed, and there is no possibility of adding medicines or performing surgery.
- The situation and the decision to suspend treatment and start supportive care are explained to the patient and family members.
- The supportive measures may include:
  - **Pain control** – codeine with acetaminophen for moderate pain, and stronger analgesics if pain is severe.
  - **Respiratory insufficiency** – administer oxygen (2 – 4 L/min via nasal tube or if > 5L/min then use mask), and morphine (if available)
  - **Nutritional support** – as for MDR-TB patients.
  - Regular **visit** with medical staff (preferably at district health facility)
  - **Ancillary** medicines – continued as required.
  - **Infection control** - both at home settings and institutions.
  - **Hospice or nursing home care** – only where adequate infection control arrangements are in place to avoid risk to other inhabitants and carers.

FOLLOW-UP – MANAGE TREATMENT INTERRUPTION

If interruption is more than 2 weeks but less than 2 months

On the same day

Assess		Act	
Clinical	**Laboratory**	**Regimen**	**Other**
Assess for deterioration, and record. Review the adherence/ supervision	Sputum for culture Also DST, if patient is **S$^+$** on retrieval.	Continue on same regimen	Educate on adherence Consider changes in supervision arrangements
Note: DST is done when either smear or culture is found positive.			

On the subsequent day

Situation (If)	Action	Comments
Culture negative	Continue the same regimen	Count the previous drug intake in treatment duration
Culture positive	Continue same regimen Also sputum for DST, (if not sent earlier because of patient being **S$^-$** on retrieval)	**Later:** Clinical panel review DST and decide adjust/ change of regimen

If interruption is more than 2 months

- Declare default, and reassess as new MDR-TB suspect
- If re-diagnosed as MDR-TB, then decide to start again the treatment right away or wait for new DST results

(Note: If treatment restarted – new registration and arrangements)

FOLLOW-UP AT HOSPITAL – MANAGE OTHER CONDITIONS

Monitor and manage other medical conditions

The other known medical conditions are monitored and managed, and notes are recorded in the "follow-up clinical assessment" form.

Diabetes:

- o Monitor:
  - Blood sugar 2 – 4 times per week if sugar control stable, if not stable then more frequently.
  - HbA1c every 3 months if treatment changes or if HbA1c > 7, then every 6 months if HbA1C < 7.
  - BP every month, and retinal changes every year.
- o Manage:
  - If creatinine rising - check clearance, adjust dosage, and monitor weekly until stabilized.
  - Adjust the dosage/ scheduling of diabetes drugs (if required)
  - Consider ACE-inhibitors, if albuminuria > 300mg/ 24 hours

Renal Disease:

- o Check creatinine (weekly or more frequently), and adjust drugs.
- o Check albuminuria – if > 300mg/24 hour – consider ACE-inhibitor

Liver Disease:

- o Monitor liver enzymes – stop the responsible drug if enzymes rise > 5 times of normal value, or > 3 times normal value but with symptoms
- o Monitor concurrent hepatitis (unrelated to drugs), clinically judge:
  - Defer the MDR-TB treatment until acute hepatitis is resolved
  - Continue MDR-TB treatment with four non-hepatotoxic drugs

Seizures:

- o Monitor the intake of anti-seizure medication and control
- o Adjust anti-seizure medication, if required for seizure control.

Substance Use:

- o Monitor substance consumption, facilitate access to quit services
- o If repeated interruptions due to addiction – suspend MDR-TB treatment until successful treatment of addiction

DECLARE TREATMENT OUTCOMES

Cured	A culture-positive# patient who has: o Completed at least the minimal recommended **length** of treatment (i.e. 18 months) after the first culture was found negative. o Had at least **five** consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment **Note**: If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.
Treatment Completed	A culture-positive# patient who has: o Completed at least the minimal recommended **length** of treatment (i.e. 18 months) after the first culture was found negative. **But** o Had less than five consecutive cultures examined from samples collected at least 30 days apart in the final 12 months of treatment **Note**: These also include patients who are extra-pulmonary or had negative cultures at the start of treatment.
Failed	A culture-positive# patient who has: o Had two or more of the five cultures recorded positive in the final 12 months of treatment **OR** o Had one of the final three cultures recorded positive **OR** o Had clinical decision made to terminate treatment early because of poor response or adverse events **Note**: Failures on clinical grounds can be indicated separately to do sub-analysis.
Died	o Known to have died of any reason during the course of MDR-TB treatment
Defaulted	o Has interrupted treatment for 2 consecutive months or more for any reason.
Transfer-red Out	o Has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.

A positive culture requires greater than 10 colonies on solid media. If less than 10 colonies are detected in one culture, a second culture should be done. If both cultures show any number of colonies, the culture should be interpreted as positive.

MANAGE POSSIBLE SIDE EFFECTS – ALLERGIC REACTIONS

Assess:

- Anaphylaxis (within minutes of administering the offending drug):
  - *signs of airway obstruction* such as sensation of lump in throat, wheezing, stridor, swollen tongue;
  - *other symptoms*: shock, pruritis and urticaria, cramps
- Severe reaction (within days or weeks of administering drug):
  - rash, fever, hepatitis, Stevens Johnson syndrome.

Manage:

- If anaphylaxis or severe reactions:
  - Hospitalize and provide basic life support i.e. maintain airways, breathing and circulation
  - Treat with epinephrine, corticosteroids, anti-histamines
  - Suspend all anti-TB drugs, and determine the offending drug, if possible.
- In moderate reactions: (but not anaphylaxis)
  - When patient improved, reinstate anti-TB as "challenge".
  - One drug reinstated in small increasing dose to reach recommended dose in 4 days, then another drug added in the same way, then next.

Drug	Sequence	Day 1 (mg)	Day 2 (mg)	Day 3 (mg)	Day 4
Injectables	1st	125	250	500	15–20 mg/kg
Levo/Oxfloxacin	2nd	125	250	500	750 mg
Ethionamide/ Prothionamide	3rd	62.5	125	250	15 mg/kg
Cycloserine	4th	62.5	125	250	15 mg/kg
PAS	5th	Am:100 pm:200	am:500 pm:1000	am:2000 pm:2000	150 mg/kg

Note: Use the above table only where the reaction is moderate (i.e. not severe).

- In severe reactions, smaller doses should be used over a longer period of time as "challenge".

MANAGE SIDE EFFECTS – PERIPHERAL NEUROPATHY

TB drug causes:	Injectables, Cycloserine and Ethionamide.
Other causes:	Vitamin deficiencies, diabetes, hypothyroidism, alcoholism, and other drugs (e.g. for cancer)

Assess:

Sensory disturbance: numbness of feet, tingling and/or burning sensation in lower extremities, leg pain

Motor disturbance: leg weakness when walking, decreased deep tendon reflex.

Laboratory: Nerve conduction studies, where feasible

Manage:

Rule out other causes, if found treat accordingly.

Treat as neuropathy related with MDR-TB drugs

- **First step**:
  - Confirm patient is taking the proper dose of pyridoxine
  - Replace drugs most likely responsible, but only if acceptable alternate drug is available.
  - Initiate low-dose Amitriptyline 25 mg OD, may go up to 75 mg OD
- If no improvement, then **second step:**
  - Decrease dose of responsible drug (within therapeutic limits), then resume normal dose once pain is controlled
  - Consider analgesics such as Ibuprofen, Paracetamol and/or NSAID
- If no improvement, then **third step**:
  - Consider neurology consultation
  - Gabapentin (start 300mg OD, increase to 300 – 600 mg TID)
  - Consider anticonvulsant Carbamazepine (start 200mg BID, increase to 600 mg BID)

MANAGE SIDE EFFECTS – GASTROINTESTINAL INTOLERANCE

TB drug causes: PAS, Ethionamide, Protionamide, Pyrazinamide.
Other causes: Infective diarrheas, hepatitis related nausea/vomiting, and gastritis related with tobacco or other medications

Assess:

Mild symptoms: nausea, loose stool (> 3 - 4 /day), abdominal bloating

Moderate symptoms: vomiting, gastritis (with epigastric burning, sour taste), gastric ulcer (with severe pain)

Severe signs: hematemesis or melena

Late symptoms: fat malabsorption, lactose intolerance

Manage gastritis and gastric ulcers:

Best is to take preventive measures – take drugs with or after food, avoid coffee and cigarettes, start low-dose Ethionamide and then increase in 1 – 2 weeks.

Severe signs (hematemesis or melena), consult specialist.

Mild or moderate symptoms: rule out or manage other causes, **if** no other cause found then

- Administer gastric-acid suppressants such as H2-blockers (e.g. cimetidine or ranitidine) or proton-pump inhibitors (e.g. Omeprazole), and reassure the patient
- If no improvement, then:

  Administer antacids on as needed or standing basis (3 hours before or after TB drugs) e.g. Calcium carbonate for elders & pregnant or Aluminum hydroxide or Magnesium hydroxide. Also reassure.
- If no improvement, then:

  Consider dose reduction or temporary discontinuation of Ethionamide or PAS
- If no improvement, then:

  Refer for GI consultation.

MANAGE SIDE EFFECTS – GASTROINTESTINAL INTOLERANCE

Manage Diarrhea (i.e. > 3 – 4 loose stools/ day):

Check if stools are:

- loose or watery?
- blood or mucous in stools?
- accompanied with fever?

Manage if:

- loose stools, encourage intake of liquids, also check electrolytes if significant volume loss
- watery stools

  with **no** fever and blood or mucous:

  - Rehydrate with liquids, and oral rehydration solution (ORS), also check and replace electrolytes as needed
  - If no improvement, then: Administer anti-diarrheals e.g. Aluminium hydroxide (3 hours after TB drugs), or Loperamide 2 mg after each episode (up to 10mg/ day).

  with fever or blood or mucous:

  - Rule out infections (e.g. amoebic, bacillary) and parasite infestations. Examine stools for parasites or culture for infections, and blood count.
  - Treat according to results. Rehydrate and if no improvement treat (as above), and avoid anti-motility agents.

MANAGE SIDE EFFECTS – GASTROINTESTINAL INTOLERANCE

Nausea and Vomiting

Most patients get nausea and vomiting, but don't stop treatment.

Ask about vomiting; frequency, amount, color-blood, thirst, weakness

Look for signs of dehydration? dry mouth, sunken eyes, low blood pressure, weakness or collapse, and blood or jaundice

Manage:

Severe sign (i.e. blood/ "coffee ground" vomit?) – refer or arrange emergency care in hospital.

Jaundice signs – rule out or manage hepatitis (CDG P-24)

Dehydration signs - rehydrate with e.g. 1 - 2 L of normal saline over 6 hours, and consider admission if dehydration persists.

- If no improvement, then:
  - rehydrate with IV normal saline, check electrolytes
  - give ethionamide or clofazimine as three separate doses
  - give medications at night, with a short acting benzodiazepine
- If no improvement, then:
  - Give anti-emetics 30 minutes prior to TB drugs e.g. Proclorperazine, Diphenhydramine, Phenergan or Metoclopramide (monitor for dystonia etc.)
  - Consider reduced dose of Ethionamide and/or PAS.
- If no improvement, then: refer for GI consultation.

MANAGE SIDE EFFECTS – ELECTROLYTE ABNORMAILTIES

TB drug causes: Injectables, more with capreomycin.
Other causes: vomiting and diarrhea.

Ask about fatigue, myalgias, cramps, paresthesias, lower extremity weakness, mood change or confusion.

Look for signs of severe hypokalemia i.e. tetany, paralysis, cardiac arrhythmias. (Note: can be present without symptoms or signs).

Check if low serum potassium (< 3.5 mg/dL) or magnesium (<1.5 mg/dL) or calcium (<8.5 mg/dL)

Manage: Replace **potassium (and magnesium),** oral or IV (see below)

Table: Replacement of potassium

Potassium level mg/dL)	**Quantity KCl**	**When to do next control** (sooner if vomiting or diarrhea)
3.7 or more	None	Monthly
3.4 – 3.6	40 meq oral	Monthly
3.0 – 3.3	60 meq oral	Two weeks
2.7 – 2.9	80 meq oral	One week
2.4 – 2.6	80 – 120meq oral	1 – 6 days
2.0 – 2.3	60 meq IV and 80 meq oral	Every 6 – 24 hours
< 2.0	60 meq IV and 100 meq oral	Every 6 hour with IV replacement. Consider holding injectable until > 2.4

Table: Replacement of magnesium

Magnesium level (meq//L)	**Quantity of Magnesium** (Total daily dose)	**When to do next control**
1.5 or more	None	Monthly
1.1 – 1.4	1000 – 1200 mg	Monthly
0.8 – 1.0	2000 mg (consider IM)	Two weeks
< 0.8	3000 – 6000 mg (IV or IM)	One week

MANAGE SIDE EFFECTS – ELECTROLYTE ABNORMALITIES

Potassium (and magnesium) - continued

- Treat for associated conditions such as vomiting and diarrhea
- Administer empiric magnesium repletion, or check Mg and act (see table CDG P-21).
- Discontinue any arrhythmia inducing drugs (e.g. digoxin, amytriptyline)
- If no improvement, then: increase "K" and "Mg" repletion, and also administer Amiloride 5 – 10 mg OD, or spironolactone 25 mg OD
- If severe and no improvement, then: consider admission and holding or changing the injectables.

Also Manage: Replace **calcium,** oral or IV (see table below)

Table: Replacement of calcium

Tot. Calcium level - mg/dL (adjusted for low albumin)*	**Quantity of Calcium** (Total daily dose)	**When to do next control**
8.5 or more mg/dL	None	-
7.5 – 8.4 mg/dL	500 mg TID	Monthly
7.0 – 7.4	1000 mg TID	1 – 2 weeks
<7.0	Consider IV, and taper to 1000 mg TID	One week

If **symptomatic** – manage the hypocalcaemia on emergency basis:

- Give IV infusion of 2 gm of calcium gluconate (180 mg elemental calcium or 20ml of 10% calcium gluconate) over 10 minutes, then 6 gm calcium gluconate in 500 ml DSW over 4 - 6 hours.
- Taper the IV infusion, with oral 1-2 gm of elemental calcium - TID
- Also treat associated conditions, administer empiric magnesium repletion, and discontinue any arrhythmia inducing drugs
- If severe and no improvement, then: consider admission and holding or changing the injectables.

If **long-term** therapy

- Give oral 0.5 – 1.0 gm - TID

* Adjusted calcium for hypoalbuminemia = 0.8 (4.0 – measured albumin) + reported calcium

MANAGE POSSIBLE SIDE EFFECTS – FEVER

TB drug causes:	All drugs. TB treatment failure
Other causes:	Infections of chest, meninges, abdomen, urinary tract, gastrointestinal tract, abscess injection site.

Fever (> 38 C) look for and treat the cause as for other patients, but also consider TB treatment failure. (In HIV settings see TB/HIV Clinical Manual).

Ask about site and nature of symptoms, do a systems review.

Look for the chest signs, meningitis, acute abdomen, UTI, abscess, gastro-enteritis.

Manage: Diagnose and treat as usual (plus some MDR TB related issues)

Increased cough, difficult breathing, discolored sputum, red throat?

- If so, check if weight loss, low appetite, night sweats? If present do AFB and culture? - rule out TB treatment failure (see CDG P 11-12)

Headache, photophobia, rigid neck or lethargy?

- If so, rule out or manage meningitis

Severe abdominal pain (worse on movement), can't eat or vomiting

- If so, rule out or manage appendicitis, pelvic inflammatory disease, cholescystitis, pancreatitis, enteritis.

Urinary frequency, urgency or dysuria?

- If so, do urinalysis and rule out or manage UTI (likely bacterial, less likely fungal cystitis – if yes, treat with fluconazole)

Pain, swelling, warmth (e.g. at injection site)?

- If so, decide if is abscess?, infected hematoma? or phlebitis (if on IV therapy), and treat accordingly (aspirate, or incise and drain, if abscess then treat with anti-staphylococcal therapy)

Diarrhea with blood or mucus?

- If so, rule out or manage bacillary or amoebic dysentery. Also examine feces for ova and parasites. (viral – ORS, bacterial – ORS and antibiotic, parasitic – metronidazole for 5 – 7 days)

Rash? (But with no other localizing signs).

- If yes, consider drug fever, and discontinue suspected drugs

No localizing symptoms or signs?

- Do sputum, blood, urine cultures, chest X-ray, HIV test, other investigation as required. Consider infectious disease consultation.

MANAGE POSSIBLE SIDE EFFECTS – HEPATITIS

TB drug causes:	Ethionamide, PAS, Pyrazinamide, Flouroquinolones (floxacins).
Other causes:	virus infections (A – E, herpes, rubella), other drugs (sulpha drugs, anti-epileptic, erythromycin), and alcohol use.

Ask about nausea, vomiting, loss of appetite, dark urine, and pale stools.

Look for jaundice of sclera.

Check liver function tests (serum bilirubin and transaminases)

Manage:

Acute hepatitis – Bilirubin >1.5, SGOT (AST) and/or SGPT (ALT) > 3 - 5 times normal value (i.e. > 3 if symptoms, and > 5 if asymptomatic)

- o Suspend all TB drugs until clinical and laboratory improvement
- o Rule out or manage other causes of acute hepatitis:
  - Virus infections – Hep. A – E, herpes, rubella.
  - Other drugs e.g. sulpha drugs, paracetamol, anti-epileptic, erythromycin
  - Other causes e.g. alcohol, autoimmune disease
- o Treat symptoms, as needed, and consider admission if severe.
- o Follow for clinical improvement and normalization of liver function tests (LFTs), then consider to re-initiate anti-TB medication.

Stabilize liver functions - clinical and laboratory normalization

- o reinitiate anti-TB drugs, one-by-one, with monitoring of LFTs
- o replace, if possible, the likely causative drug or hepatotoxic drugs with an alternate drug(s)
- o Follow serum liver tests every 1 – 2 months thereafter.

MANAGE POSSIBLE SIDE EFFECTS – NEPHROTOXICITY

TB drug causes:	Injectables.
Other causes:	sepsis, other medications (NSAID, ACEi, sulpha drugs, diuretics)

Ask about malaise, nausea, drowsiness or reduced urine (< 0.5ml/kg/hour or <30 ml/hour)

Look for edema or shortness of breath, and confusion

Monitor creatinine, urea and electrolytes, at start, regularly and if symptoms

Manage:

Acute renal failure - creatinine or urea raised compared to baseline?, and/or cellular casts or blood in urine

- Suspend nephrotoxic drugs (i.e. injectables) until clinical and electrolyte improvement
- Check electrolytes including K, Mg and HCO3 (and consider Ca and phosphorus), correct if abnormal and manage fluids (CDG p 21 – 22)
- Rule out or manage other causes of acute renal failure:
  - medical e.g. diabetes, dehydration, congestive heart failure, urinary obstruction, UTI, large prostate?
  - other drugs e.g. NSAIDs, ACEi, sulpha drugs, diuretics?
- Treat symptoms, fluid and electrolyte disturbances, as needed.
- Follow for clinical improvement and normalization of creatinine and urea, then consider to re-initiate injectables.

Stabilized renal functions - clinical and laboratory normalization (CDG p 5)

- change aminoglycoside to capreomycin (if not taking already), or
- reduce dose of injectables or replace it with an oral anti-TB drugs
- adjust all drug doses according to creatinine clearance (CDG p 5)
- Follow serum urea and creatinine every 2 – 4 weeks (CDG p 7).

MANAGE POSSIBLE SIDE EFFECTS – HEADACHES

TB drug causes:	All drugs (especially Cycloserine)
Other causes:	migraine, meningitis, psychosocial stressors

Headaches are often a side effect of anti-tuberculosis treatment. However, it is important to rule out other causes.

Manage:

Headaches accompanied by fever, neck rigidity, photophobia, confusion, somnolence.

- If so, rule out meningitis and take to hospital.

Headaches, with prior history of discrete episodes of pulsating headaches, with nausea, vomiting, and vision changes. Each episode lasting few hours, relieved by darkness and sleep.

- If so, manage migraine with analgesics, low-dose beta-blockers, sumatriptan, and supportive measures.

Headaches where meningitis and migraine have been ruled out

- If so, manage the therapy related headaches as follows:
  - administer anti-inflammatory drugs as needed (e.g. acetaminophen, ibuprofen, aspirin)
  - if no response to one drug, then try different one
  - address psychosocial stressors (if found and is feasible)
  - encourage adequate fluid intake
  - confirm proper dose of pyridoxine
  - avoid NSAID agents if hemoptysis or sever gastritis
- If no improvement, then:
  - administer Amitriptyline 50 – 150 mg at night
  - consider mild opioid-containing analgesic (e.g. acetaminophen with codeine)
- If no improvement and severe symptoms, then consider:
  - reduce cycloserine dose (if included in the regimen)
  - consult neurologist

MANAGE POSSIBLE SIDE EFFECTS – CLINICAL DEPRESSION

TB drug causes:	Cycloserine, Ethionamide.
Other causes:	psychosocial stressors, hypothyroidism, drug dependence

Clinical depression is a group of symptoms, lasting more than two weeks, that interferes with normal social and physiological functioning.

Ask about appetite and sleep disturbances, difficulty to concentrate, lack of interest in previously enjoyed activities, lack of energy.

Look for depressed mood; slowing of thought, speech and movement; feeling of helplessness or guilt; and suicidal ideation.

Manage:

Patient presents with > 2 weeks of depression symptoms/ signs

- If so, rule out or manage suicidal or homicidal ideation (hospitalization, close surveillance and psychiatric consultation).

Delusions, hallucination, incoherent thought or speech, inappropriate behavior

- If so, rule out or manage psychosis (see CDG P-28)

Hypothyroidism signs i.e. weakness, cold intolerance, dry skin, hair loss, heavy menstruation, weight gain, myxedema, elevated TSH.

- If so, rule out or manage hypothyroidism (see CDG P-30)

Symptoms of depression present, but possibility of suicidal ideation, psychosis and hypothyroidism are ruled out:

- Is so, rule out or manage the side effects of drugs (cycloserine and others) by making changes in dose or regimen, according to the severity of symptoms.
- Also provide counseling to patient and family, ensure emotional support from family, and organize group therapy (where possible)

Symptoms of depression persist after above therapy

- If so, consider psychiatric consultation
- Initiate anti-depression therapy e.g. Amytrptyline, Nortriptyline.
- Use tricyclic anti-depressants with caution, if convulsions history.
- Consider anti-psychotics and/or benzodiazepines, if symptoms.

MANAGE POSSIBLE SIDE EFFECTS – PSYCHOSIS

TB drug causes:	Cycloserine, Flouroquinolones (-floxacins), Ethionamide.
Other causes:	psychosocial stressors, hypothyroidism, drug Dependence, depression, and other drugs

Psychosis is a group of symptoms that indicate disintegration of personality or a loss of contact with reality.

Ask about visual or auditory hallucinations, delusions.

Look for unintelligible thought or speech, bizarre behavior, and suicidal ideation.

Manage:

Patient presents one or more symptoms/ signs of psychosis

- If so, rule out or manage suicidal or homicidal ideation (consultation, hospitalization, close surveillance, and also hold cycloserine)

Symptoms of psychosis present, but possibility of suicidal ideation ruled out

- If so, rule out or manage other causes of psychosis e.g. psychosocial stressors, hypothyroidism, drug dependence, depression, and other drugs (antidepressants, benzodiazepines)

If other causes of psychosis are ruled out

- If so, rule out or manage TB drugs related psychosis:
  - Hold cycloserine, evaluate psychosocial stressors, and confirm proper dose of pyridoxine
  - Administer
    - Risperidone oral 0.5 – 2.0 mg BID or
    - Haloperidol 1 – 5 mg oral or IM or IV, and repeat hourly or as needed

Symptoms of psychosis persist after above therapy

- If so, continue to hold cycloserine, and replace it with an alternate TB drug (if possible). Also consider benzodiazepines (caution if elderly or inadequate respiration), and psychiatric consultation.

Symptoms of psychosis resolved

- If so, reinitiate cycloserine at low dose (if essential to regimen) and then discontinue anti-psychotic therapy after several weeks.

Symptoms of psychosis recur

- If so, continue Risperidone (0.5 – 3 mg oral) until completion of DOTS-Plus treatment, and co-administer Biperiden 2 mg oral BID

MANAGE POSSIBLE SIDE EFFECTS – SEIZURES

TB drug causes: Cycloserine, Fluoroquinolones (-floxacins).

Other causes: infections (CNS), other drugs (tricyclics), electrolyte imbalance, hypoglycemia, hypoxia, uremia, hepatic failure

Ask about sensory disturbances e.g. audio or visual hallucinations.

Look for loss of consciousness, involuntary movement or flaccidity of a body part, bowel or bladder incontinence, sensory disturbances e.g. numbness, dizziness.

Check for blood chemistry (glucose, LFTs, creatinine, electrolytes, urea), and head (CT or MRI) if required to exclude other causes.

Manage:

Patient presents with one or more symptoms and signs of seizure

- If so, rule out or manage other likely causes for seizures e.g. meningitis, encephalitis, cerebro-vascular accidents, space occupying lesion, glucose, electrolytes, renal or hepatic failure.

Patient is unconscious:

- Is so, protect patient's head and body from possible injury and tongue from possible biting, and observe till patient stops seizing.

Patient remains unconscious i.e. continue to seize.

- If so, hospitalize and administer emergency care:
  - suspend cycloserine and consider suspend flouroquinolones
  - protect airway and provide oxygen
  - phenytoin 20mg/kg IV (not in DW) and diazepam 5–1 0 mg IV (caution in patients with depressed respiratory function)

Patient stop seizing (after above measures)

- If so, anti-epileptic therapy for the remainder of DOTS-Plus
  - phenytoin 3 – 5 mg/kg/day
  - carbamazepine 600 – 1200 mg/day
  - phenobarbitol 60 – 120 mg/day
  - valproic acid 750 – 1250 mg/day

Patient is stabilized with anti-epileptic therapy

- reinitiate the cycloserine and flouroquinolones in low dose.

MANAGE POSSIBLE SIDE EFFECTS – HYPOTHYROIDISM

TB drug causes:	ethionamide, prothionamide, PAS.
Other causes:	iodine deficiency, drugs (lithium), radio-iodine treatment in past, pregnancy related dysfunction.

Ask about fatigue, loss of appetite, weight gain, constipation, cold intolerance, hair loss.

Look for dry skin, coarse hair, occasional depression and psychosis, enlarged thyroid, delayed deep tendon reflexes.

Check for TSH (> 10mU/L)

Manage:

Patient presents with symptoms and signs of hypothyroidism, and TSH > 10mU/L.

- If so, treat with levo-thyroxine for the whole DOTS-Plus
  - administer therapeutic daily dose (adult: 100 – 200mcg, but for patients above 60 years start with 50 – 100mcg per day)
  - repeat TSH (if available) every month, and adjust the thyroxine dose (in 12.5 – 25mcg increments) until correct dose is found.
  - check TSH every four months, once found stable.

Patient on levo-thyroxine completes the DOTS-Plus treatment

- If so, continue thyroxine for 2 – 3 months after completion:
  - where TSH available: repeat TSH and decide the discontinuation of levo-thyroxine accordingly
  - where TSH is not available: discontinue levo-thyroxine after 2- 3 months and follow symptoms.

MANAGE POSSIBLE SITUATIONS – HEMOPTYSIS

Hemoptysis is the expectoration of blood originating from the larynx, trachea, bronchi or lungs. Hemoptysis may present as anything from a blood-streaked sputum to a large quantity of blood.

Rule out or manage:

- Blood from nose (epistaxis), and not mouth.
- Blood from GIT (vomiting), and not respiratory tract or lungs

Assess, if blood is not from nose and GIT:

- Amount of blood expectorated (in one episode and in 48 hours)
- X-rays chest
- Hematocrit, and type and cross-match of blood.
- AFB and culture, if accompanied with fever and productive cough

Manage:

Hemoptysis minor or moderate (blood < 150 ml, or < 500 ml in 24 hrs)

- Prescribe bed rest, and monitor patient closely.
- Administer codeine cough suppressant (15 – 60mg, six hourly)
- Initiate antibiotics, if evidence of respiratory infection.
- Avoid NSAIDs and Aspirin.

Hemoptysis massive (i.e. blood > 150 ml, or > 500 ml in 24 hrs)

- Hospitalize, maintain IV line, and administer IV fluid (1 - 2 liters normal saline within the first hour, and then maintain fluids)
- Lay patient in dependent position, check vital signs frequently
- Administer oxygen (if needed), and vitamin K (if coagulopathy)

Hematocrit < 30%

- Transfuse with matched blood, and monitor hematocrit closely.

Recurrent episode of hemoptysis, without improvement:

- Consider bronchoscopy, and may also evaluate for surgical resection.

MANAGE POSSIBLE SITUATION – RESPIRATORY INSUFFICIENCY

Difficult breathing and/or respiratory rate > 30 per minute.

Ask about breathing difficulty, tight chest, abrupt onset, previous trauma or immobilized state, headache, cough, hemoptysis.

Look for respiratory rate, wheezing, confused or agitated, cyanosis, fever, hemoptysis.

Check for:

- Chest X-ray, complete blood count (& differential), AFB & culture
- If available, then pulse oximetry & arterial blood gas

Manage: Diagnose and treat as usual (plus some MDR TB related issues)

Wheezing, prolonged expiration, tight chest

- If so, rule out or manage bronchospasm by:
  - administer bronchodilator inhalation and treat infection
  - administer oral or intravenous steroids
  - consider long-term use of inhaled bronchodilators & steroids or nebulized bronchodilators
  - admit if using neck muscles to breath or difficult to speak.

Sharp pain, sudden onset, previous trauma

- If so, rule out or manage pneumothorax (i.e. administer <2L/min oxygen and take to hospital for chest tube placement or surgery)

Chest pain, tachycardia, fever (+/-), positive ECG and chest X-rays

- If so, rule out or manage pulmonary embolus (administer <2L/min oxygen, anticoagulant if not contraindicated, and take to hospital)

Fever, productive cough, infiltrate on chest X-ray, bronchospasm (+/-)

- If so, rule out or manage pneumonia (i.e. antibiotic & oxygen if need)

Increased cough, difficult breathing, fever, weight loss, low appetite, night sweats

- If so, check AFB/ culture to rule out or manage TB failure

Hypoxemic (i.e. confused, agitated, cyanosed) or hypercapnic (i.e. headache, sedated)

- If so, administer <2L/min oxygen and take to hospital

If none above then consider allergic reaction, panic attack, gastro-esophageal reflux.

MANAGE MDR-TB IN KNOWN HIV^{+} CASES

This desk guide is generally sufficient, in a low prevalence HIV country such as Pakistan (i.e. HIV prevalence is less than 1% in the antenatal women, but higher in particular risk-behavior groups).

Clinicians caring for TB-HIV patients, e.g. in the ART and/or VCT centers, need to have TB-HIV clinical guidelines, e.g. from national programs, WHO publications or website.

If TB patient is a known HIV^{+} case:

- The threshold for doing **DST** may be lowered in those TB patients with known HIV (preferable: DST all patients ill with TB-HIV)
- Start anti-retroviral treatment (**ART**) promptly in MDR TB patients, according to initial **CD4**, monitor the trend in CD4.
- Consider immune reconstitution syndrome where symptoms occur, relating to HIV related infections including TB, during the initial week of ART.
- Administer standard MDR-TB regimen as well as social support, unless there is a known reason for variation in the prescription.
- Suspect and treat HIV-related other infections.
- Consider the **ART** drug **side effects** and **interactions** with MDR TB drugs and manage.
- Management of conditions, such as diarrhea or headache, may be related to the MDR TB and/or HIV related infections or the ART drugs (see other guidelines for management of coinfections).

If TB patient is NOT a known HIV^{+} case:

- Consider counsel and **test** for HIV (where feasible) in TB patients with known risk behaviors e.g. injectable drug users, prisoners, STI patients and sex workers and men who have sex with men.

SECTION - II

INFORM ABOUT MDR-TB DISEASE & ITS TREATMENT

Demonstrate a caring, respectful and friendly attitude. Speak clearly and simply. Encourage patient to ask questions.

Towards the end of each interaction, ask checking questions (to ensure that the patient remembers important messages and knows what to do next). Reinforce earlier messages, giving information as needed.

Education Table 1: MDR-TB Suspect – referral for diagnosis

Ask the patient:	Then give relevant messages on:
What do you think why your disease has not responded to the treatment you have taken?	- You are suspected to have tuberculosis that is resistant to common TB drugs (i.e. These TB germs are not killed by common drugs). - This type of TB is called MDR-TB. - MDR-TB treatment needs another set of "high potency" medicines to be taken for 18-24 months.
What you may do now to get your disease diagnosed and treated.	- More advanced sputum tests are required for diagnosing your disease. - This testing facility is available only at few big hospitals. The nearest such hospital is __(name the hospital)_____ - These hospitals offer the testing (and also treatment, if required) **free-of-charge**. However, you have to visit the hospital to get these free-of-charge services. - You may need to stay there for few days (if hospital is far from home) or visit the hospital for 2/3 times (if day-trip to the hospital is feasible).
Why is this important for him/her to visit the hospital	- This is a deadly disease, and if not treated, a person is very likely to die within a couple of years. - The patient (if not treated) is likely to transmit the same deadly form of disease to his/her family members/friends. - The earlier the treatment starts the better, so as to be cured and avoid passing on the disease to others
How would you access these services at the hospital (where patient is being sent)	- Identify the hospital department and the room for patient to report - Inform about hospital outpatient routine i.e. work days and timings - Instruct to take along the: o Referral Form (etc.) o Morning sputum sample o Other TB records (TB01, TB02 etc.)
Do you have any question(s) to ask?	- Listen to patient questions/ concerns and carefully respond. - Discuss and agree with the patient a plan for his/her visit to the hospital.

Education Table 2: MDR-TB Suspect – about the diagnosis process

Questions	Then give relevant messages on:
Why do you think you have been referred here today? What do you think may have caused your illness?	<u>Possible diagnosis of MDR-TB</u> You have been referred to the hospital because you are suspected to have TB that is resistant to common TB drugs. This suspicion is because your disease/ symptoms have not responded to the treatment that you have already taken (and/or you have had close contact with someone who has MDR-TB). It is possible that the drugs you are taking or took before did not kill the TB germs. This type of TB (called MDR-TB) can be cured if "high potency" drugs are taken daily for 18-24 months.
How do we know if you have MDR-TB?	<u>Diagnostic tests to be done (smear, culture, DST)</u> Just like the diagnosis for common TB, we will ask you to provide sputum samples. The sputum sample will be sent for a couple of tests to see if you have TB germs in your lungs? and if they respond to common drugs? • A test called "culture" would determine if there are live TB germs in your sputum. • Then another test called drug susceptibility test (DST) would determine if your TB germs can be killed by common drugs or would need the "high potency" drugs. The hospital, with the support of National TB Control Program, has arranged free-testing facilities for MDR-TB suspects.
When will you receive results of the test?	<u>Timelines for receiving results (from day of sputum collection)</u> ▪ Smear results - 1 to 2 days after sputum collection. ▪ Culture results - 6 – 8 weeks after sputum collection ▪ DST test results will be ready: o 3-4 months after sputum collection (regular test) o 5-6 days after sputum collection (if rapid testing) **If DST result shows you have MDR-TB we will inform you.**
How will you be informed about test results?	<u>Record patient contact details for communicating the test results</u> Explain patient that we are going to record his/her contact details in a register (MDR-TB Suspect Register). • The patient is requested to give the exact name, detailed address and contact numbers (telephone and mobile), so that he/she can be informed, about test results and further treatment required, through making a phone call and/or writing a letter.

What is treatment like for MDR-TB?	<u>Supervised treatment for at least 18 – 24 months</u>
	• If diagnosed to have MDR-TB, you will need at least 18 months of continuous treatment with second-line drugs - 6 days per week.
	  • You may initially need some time in hospital to complete the assessment and see that the drugs are well tolerated.
	  • Then you can receive the daily treatment (free of cost) from an identified health center, close to your place of residence.
	  • Each month you visit the hospital for free-checkup, drug delivery and social support (arranged through the National TB Control Program).

How can you avoid spreading TB or MDR-TB?	<u>How to stop transmission of TB at home</u>
	To prevent the spread of TB to others in the family and community:
	  • Cover your mouth and nose when coughing or sneezing.
	  • Open windows and doors to allow fresh air to flow through the home. An electric fan directing the air to the outside will help.
	  • Avoid meeting new people inside your home; meeting outside is recommended while you are smear and culture positive
	  • Avoid sleeping with someone in the same room, if possible.
	There is no need to eat a special diet or to sterilize dishes or household items.

Do you know what you should do for treatment?	• In situations with regular DST (i.e. results within 3 - 4 months): Patients continue treatment with first line drugs (either CAT-I or CAT-II). Explain that the patient should take the prescribed drugs regularly until the results of the DST are available which should be in 3-4 months. Treatment will be monitored closely with check up sputum tests . • In situations with rapid DST (i.e. results within a week): Patients continue their current treatment, and asked to report back within a week, so that treatment (MDR-TB or otherwise) can be started in light of DST results.

Education Table 3: MDR-TB Diagnosis and Next Key Steps

Ask the patient:	Then give relevant messages on:
What do you think about your disease?	▪ Your tuberculosis is found to be resistant to common TB drugs. ▪ You need to take "high potency" medicine for about 24 months ▪ Medicines, provided free-of-charge, are taken daily under the supervision of a health worker.
How MDR-TB care is made patient friendly?	▪ Only initial few days of hospitalization, then ▪ Monthly follow-up visit to the hospital ▪ Daily treatment is arranged at a DOTS clinic more accessible for the patient ▪ Social support package to enable patient successfully complete the treatment.
What are the next key steps?	<u>What to expect; what to do next</u> ▪ Patient admission to the hospital for initial few days/ months for: o Comprehensive baseline clinical and laboratory assessment o Patient education about disease, its treatment, and spread-prevention. o Initiation of the prescribed drugs - to readily identify and manage side effects, if any. o Selection of a suitable DOTS clinic (through patient dialogue with the treatment coordinator - hospital staff) for decentralized care delivery. o Explanation and enrolment in the social support scheme, if patient agrees. ▪ Treatment Coordinator visit to patient place to: o Enable clinic staff, get patient registered with MDR-TB clinic, o Assess patient social circumstances, o Screen and refer household contacts, and o Inform the district
What the rights of MDR-TB patients and their corresponding responsibilities?	▪ <u>Patient right includes access to:</u> o Free-of-charge diagnosis and treatment o Information and confidentiality ▪ <u>Patient responsibility mainly includes</u>: o Adhere to the treatment protocols o Take measures to prevent transmission of MDR-TB

Education Table 4: MDR-TB Treatment Initiation

Ask the patient questions such as:	**Then give relevant messages on:**
What do you understand about your disease i.e. multi-drug resistant tuberculosis?	<u>MDR-TB</u> The drug-resistant TB germ is more difficult to treat than the ordinary TB germ. Even so, most forms of drug-resistant TB can be cured if treated early and all of the medicines are taken regularly during the required duration of treatment.
How do you think TB and MDR-TB are different? How do you think they are the same?	<u>The difference between TB and MDR-TB</u> ▪ The germ causing TB and MDR-TB is the same, but MDR-TB germ is more difficult to kill. ▪ MDR-TB is not curable with the medicines that we use to treat ordinary TB, **so** we have to use other medicines, called second-line anti-TB drugs. ▪ Treatment of MDR-TB with second line drugs is: o much longer - usually 18-24 months, or more. o cause more side effects o requires much more resources o last option left for treating TB i.e. if not successful then no further treatment available. ▪ It is more difficult to treat, and we all have to put in a greater effort in order to succeed ▪ If it is not treated correctly, would lead to resistance to more drugs. The disease can become incurable and you could die. **MDR-TB patients can be cured by always taking your prescribed medicines**
Why do you think you have MDR-TB?	<u>Why the patient has MDR-TB</u> ▪ The germ became resistant during previous treatment(s) (i.e. acquired), Mainly because medicines were: o incorrect or of poor quality, or o taken for less than required period or with interruptions. ▪ You may have caught MDR-TB germ from another person with MDR-TB (primary).
How do you think that drug-resistant TB spreads?	<u>Transmission of drug-resistant TB</u> ▪ MDR-TB, just like ordinary TB, spreads when a person with TB coughs or sneezes, and sprays TB germs into the air that are inhaled by others who then become infected. ▪ It is easy to pass on the germs to household members

	especially when an untreated infectious MDR-TB patient lives in crowded conditions with others. Anyone can be infected with MDR-TB. However, not everyone who is infected with TB will become sick. The household members can still have infection, even if no disease symptoms.
What are the details of patient's treatment regimen?	<u>What is treatment like for MDR-TB?</u> ▪ At least 18 - 24 months of continuous treatment with four or more second-line drugs. ▪ The drugs are taken 6 days per week i.e. every day except Sunday. One injection and three or more type of tablets and capsules are taken on daily basis. ▪ The number of each type of tablets or capsules to be taken daily depends on your body weight. ▪ The drugs used to treat MDR-TB are very expensive but will be provided for free (through the National TB Control Program). ▪ These drugs can cause more side effects than the ordinary TB drugs. ▪ An initial period of hospitalization is required to complete the assessment and see that the prescribed drugs are well tolerated. ▪ You can receive the daily treatment (free of cost) from an identified health center, close to your place of residence. ▪ Each month you will visit the hospital for free-checkup, drug delivery and social support (arranged through the National TB Control Program).
Why is there a need for supervised treatment?	▪ If all the prescribed drugs are not taken regularly in the recommended quantity, your MDR-TB will not get cured, and you will continue to spread MDR-TB to your family and friends. It is dangerous to stop or interrupt treatment, because then the disease may become incurable. ▪ MDR-TB treatment is expensive, long and may be the last option for you to get cured. Every measure must be taken to ensure treatment compliance leading to success. ▪ A designated health worker at the selected DOTS-Plus Clinic (near your place of residence) will ensure that you take every day the correct drugs regularly for the required time (i.e. under his supervision). By seeing you regularly, the doctor at the facility will also note whether you are improving or have problems like side effects.

How can you avoid spreading MDR-TB?	<u>Preventing the spread of multi-drug resistant TB</u> Initially while your sputum is still positive, you need to limit your contact with other people. However, when you become negative, you may be able to go back to your usual activities. The essential preventive measures include: ▪ Take all your treatment every day so that you become non-infectious which is the first step towards being cured. ▪ Cover your mouth and nose with a cloth or tissue when coughing or sneezing. ▪ Open windows and doors to allow fresh air to flow through the home. An electric fan to blow the air outside the house will help. ▪ Do not spit anywhere. If you need to, spit directly into a can or tissue paper (then, safe disposal of contaminated materials). ▪ Avoid meeting new people inside your home; meeting outside is recommended while you are smear and culture positive ▪ If possible, do not share your bedroom with other people until your doctor says you are no longer infectious. ▪ There is no need to eat a special diet or to separate eating utensils or household items.
What are the supportive services that are available during (and after) treatment to help the patient cope with their illness and treatment?	<u>Supportive services</u> Inform patients about the following existing services or support available to assist his/her coping: ▪ A monthly food basket scheme for MDR-TB patients ▪ Support to facilitate patient's monthly travel to the hospital ▪ Counseling and group therapies for MDR-TB patients ▪ Designated facility, near patient residence, for daily care
How can we know that none of your family members has so far been infected with MDR-TB?	▪ Interviewing all household members for TB symptoms (especially cough). ▪ All under five year old and all others with cough are examined for TB and MDR-TB by: o Physical examination o Sputum examination o Chest x-rays (possibly) o Skin testing (called PPD) for children ▪ The examination is done at the designated health facility in your home district. There are no charges, if government hospitals and/or rural health center are used for the examination services.

Education Table 5: MDR-TB Drugs

Drug	Important Information
Kanamycin Capreomycin Amikacin Streptomycin	• The injection is given for 6 months at least and is a very important drug. • Rotation of injection sites is advised to avoid local discomfort. It is also advised to place warm compress in the area. • If there is bleeding after injection which does not happen often, apply pressure on the injection site. • Inform your doctor immediately if you experience any of the following symptoms: o swelling, pain and redness on the injection area, o ringing in the ears, deafness, dizziness, vertigo o skin rash, problem in urination, and muscle weakness
Levofloxacin Ofloxacin Moxifloxacin Gatifloxacin?	• Common side effects include difficulty sleeping, abdominal pain, decreased appetite, headache and dizziness. • Special precaution: Avoid taking drugs or food containing milk, aluminum, magnesium or zinc within 2-3 hours of ingestion. • Drink a lot of water and limit exposure to sunlight by using umbrella, sunglasses and wearing long-sleeves. • Common side effects include: o vomiting, abdominal pain, diarrhea, o hypersalivation and metallic taste to the mouth. o dizziness, sensitivity to light.
Ethionamide Protionamide	• Eating sweets may help decrease the unpleasant taste. • You may experience light sensitivity. Limit exposure to sunlight. If this could not be avoided, using sunglasses and umbrella may help • If you experience dizziness, do not drive a vehicle or operate machinery that needs alertness and attention
Cycloserine	• Inform doctor immediately if you experience the following symptoms: o dizziness, decrease in mental and speech ability, confusion, nervousness o hearing voices others cannot hear, sleeping difficulty, depression. o headache, chills, numbness of feet and hands, • Avoid driving vehicle/operating machinery that needs alertness/ attention

PAS	• To increase absorption of PAS granules: o Mix with an acidic juice such as orange, pineapple or mango juice. o Do **not** mix with water, soft drinks or iced tea. • Common side effects include vomiting, abdominal pain and diarrhea. • If symptoms persist, consult your doctor immediately. • If you feel thirsty drink more fluids, and if you are found to have signs of dehydration, you will need oral re-hydration or your doctor may administer fluids intravenously. • It is normal to see empty granules in your feces.

Education Table 6: Decentralized Delivery of MDR-TB Care

Ask the patient questions such as:	**Then give relevant messages:**
Do you know the requirements for daily drug intake?	Requirements for daily drug intake: • A designated public or private sector clinic (local) with: o especially trained doctor, health worker and facility to manage second line drugs. o links with the treating hospital. o an easy access to your place of residence, so that you can visit the clinic on daily basis.
Do you know how this can be managed close to your place of residence?	How decentralized delivery of care is managed: • A designated government or private clinic will be identified in consultation with you. • The clinic staff will be provided (from hospital) one month medicine for the next month of your treatment. • You will have to visit the clinic on daily basis (six days a week), so that the: o The health worker can administer (and record) the recommended daily dose of an injection and tablets/ capsules, and help you addressing problems related with regular drug-intake. o The doctor can check you on weekly basis (and also in-between if needed). This is to see if you are making progress and to make sure side effects, if any, are identified and managed in-time. • In case you do not attend the clinic, the clinic staff will contact you or family (either on telephone or home visit) to make sure that you do not miss the daily dose. • Every month, the clinic staff will remind you and facilitate your follow-up visit to the treating hospital.
How would you remain linked to the treating hospital?	You will visit the hospital for monthly follow-up of MDR-TB treatment During the monthly follow-up visit you will get: • Clinical assessment - of the progress and side effects, if any. • Laboratory investigations - to make sure treatment is working and if any change in management is required. • Prescription and supply of medicine for the next month (medicine is handed over to clinic staff where you choose to get your daily drugs). • Counseling or any other expert consultation, if required. • Social support – food basket & travel support – for yourself.

Would you allow me to arrange decentralized care for you?	• This is neither required nor feasible for the hospital to keep you hospitalized for the whole treatment duration (i.e. 18 – 24 months) • This is more important for you to live normal life in your home area and get quality care close to your place of residence. • You are not required to pay any fee for the drugs and services. Ask if he/she has any questions regarding MDR-TB care (at these clinics?)
Let us select a clinic more suitable for you to attend?	• Inform the patient selection of suitable clinic: o Share the list and map of existing public and private clinics in patient's area of residence o Identify one or more clinic found near patient's place of residence o Discuss the travel logistics between the patient's residence and the clinic o Let patient choose more accessible and acceptable clinic for his/her care
Call the staff at the selected clinic to inform and confirm the MDR-TB care for the patient.	• Hospital staff will call the staff at selected clinic. The call is to: o inform clinic about the MDR-TB patient and o confirm clinic's commitment to deliver MDR-TB care to the patient. • When the selection of the clinic is finalized, in light of patient choice and clinic staff response, the selected DOTS clinic is recorded on CAT-IV Treatment Card. • Then, the Treatment Coordinator plan and arrange (i.e. date and time) for a joint meeting of patient, clinic staff and Treatment Coordinator.

Note: Guidelines to conduct joint meeting & patient home visit included in the training of treatment coordinators

Education Table 7: Stopping MDR-TB Treatment

Ask the patient questions such as:	**Then give relevant messages:**
How do you feel about finishing treatment? (for patients whose outcome is cured or treatment completed)	▪ Congratulations! You have just finished a long and difficult treatment. I am very proud of the commitment and dedication you have shown over the last two years. You no longer have to take any medications. ▪ However, it is possible that the disease will reappear. If you develop any TB symptoms such as cough, back or chest pain, blood in the phlegm, or unexplained fever or weight loss, let us know immediately so we can conduct the proper tests to see what the problem is. ▪ If any of your close contacts have TB symptoms, bring them in and let the staff know that you at one point had MDR-TB so they know the person is a contact of a former MDR-TB patient
Discuss the reason for stopping treatment (treatment failures)	▪ You have been through so many difficulties with your medicines. Unfortunately, they seem not to be helping you. It is time that you take a break from your treatment. ▪ You will continue to get supportive therapy as required. ▪ It is best that you avoid crowded enclosed areas and sleeping with others in the same room if it is possible. Cover your mouth and nose when you cough or sneeze. Open the windows in your room to allow air to flow out. If possible use an electric fan to direct the air outside.
How will you keep your body healthy?	▪ Leading a healthy lifestyle is good at all times but after a long treatment such as the one for MDR-TB exercising, eating healthy food, not smoking or drinking and getting enough rest will help you recover, combat other illnesses and reduce the risk of relapse of TB. ▪ People with weak defenses get sick from TB more often than healthy people. Now that you are cured, try to maintain a healthy lifestyle. A healthy lifestyle includes regular exercise, a balanced diet, not smoking, drinking, or using drugs and getting enough sleep.

SECTION-III

ADMINISTERING SECOND LINE DRUGS

Drug Administration Table 1: Administering Drugs under Supervision

How to administer drugs under supervision

1. Greet the patient in a cordial manner, addressing the patient by his or her name. Ask briefly if the patient had any problems since the last visit.
2. Take out the corresponding MDR-TB Treatment Card for the patient.
3. Open the patient's packet of medication. Check the daily dose against the MDR-TB Treatment Card for accuracy before administering it to the patient.
4. Put the **tablets** into the patient's medicine cup and provide water to assist in swallowing. Watch the patient swallow the tablets. If it is difficult to swallow them one after the other, the patient may pause briefly. The drugs should be taken in one sitting.
    a. If PAS[#] granules are used, ensure that cool temperature is maintained. Take PAS granules and mix in a glass of acidic liquid i.e. **lemon water** or fruit juice such as orange, apple, or pineapple. Granules will not dissolve, so make sure patient ingests the granules in the mixture.
    b. Fluoroquinolones should not be taken within two to three hours of a meal containing milk or any product with calcium, magnesium, aluminum and iron. So advise the patient not to consume these products (e.g. yogurt, antacids and nutritional supplements) during two hours before and after taking the fluoroquinolone.
5. If the patient becomes nauseated when taking the pills, suggest taking the drugs with food or drink.
6. The **injection** dose is prepared after administering the oral drugs. The correct dose is checked, from the DR-TB 01 Treatment Card, before preparing the injection dose (i.e. patient may require 1gm, 750mg or 500mg). Always use a sterile needle and syringe for intramuscular administration of the injection dose (Note: The reconstituted injection dose must be used within 24 hours and kept refrigerated).
7. Verify that the patient is okay and reconfirm the next day's appointment. (See the recording of supervised dose below).

(# If PAS sachet appears bloated or if granules appear discolored – don't administer this to the patient. Also note that water, tea and other non-acidic juices are not appropriate for PAS)

Drug Administration Table 2: Missed doses and possible solutions

Reason dose missed	Possible solutions
Patient feel better	▪ Explain that although the patient may feel better now, if the drugs are not taken for the prescribed time, the disease will return and may have become more resistant and difficult to treat. ▪ Explain that the patient may die if MDR-TB treatment is stopped.
Patient is experiencing a drug reaction	▪ Give appropriate advice or remedies for the drug reaction, like ancillary drugs for free. Make a referral to a specialist if necessary (see NTP case management deskguide for MDR-TB)
Going to DOTS-Plus Clinic is inconvenient	▪ Find a DOTS-Plus Clinic that is more convenient and accessible for the patient. ▪ Treatment supporter for helping patient to attend.
Patient has poor relationship with the health worker	▪ Try to identify the cause of the problem and speak with the health worker as well as the patient about possible solutions. ▪ Ensure patient is being treated with respect.
Patient dislikes coming because of long queue	▪ Make arrangements in the clinic so that MDR-TB patients are attended rapidly
Boss at work keeps the patient late	▪ Offer to talk with the boss and explain the importance of the treatment; although this is not always possible as some MDR-TB patients don't want their bosses to know about their illness.
Patient feels alone or depressed or lacks support	▪ Refer the patient to patient support groups, group therapy sessions or one-on-one counseling ▪ Talk to the patient's family, if available, to try to gain support ▪ Identify a co-patient who is able to encourage this patient to continue treatment
Patient can not leave children at home	▪ Suggest that a family member or neighbor watches the children when the patient comes to treatment ▪ Remind family members that the patient must continue treatment to protect their health, particularly the health of the children ▪ If possible, identify an MDR-TB treatment partner closer to the patient's home, in accord with the patient

Drug Administration Table 3: MDR-TB Drugs for Pregnant Women

Drug	Safety Class*	Comments
First line drugs		
Isoniazid	C	Experience in gravid patients suggests safety. Use pyridoxine during pregnancy.
Rifampicin	C	Experience in gravid patients suggests safety.
Ethambutal	B	Experience in gravid patients suggests safety.
Pyrazinamide	C	Use with caution when essential. Most references suggest it is safe to use.
Streptomycin	D	Avoid use when possible. Documented ototoxicity in developing fetus. Carefully consider the risks and benefits.
Second line drugs		
Fluoroquinolones	C	Use with caution when essential. No teratogenic effects in humans when used for shorter durations (2 – 4 weeks). Limited long-term experience in gravid patients, but given bactericidal activity, benefits may over weigh risks.
Kanamycin/ Amikacin	D	Avoid use when possible. Documented toxicity to developing fetal ear. Carefully consider the risks and benefits.
Capreomycin	C	Avoid when possible. Generally injectables are avoided in the gravid patients. However, in life threatening situations when an injectable is needed, capreomycin could be considered.
Ethionamide	C	Avoid use when possible. Teratogenic effects observed in animal studies. Significantly worsen the pregnancy-associated nausea.
Cycloserine	C	No significant experience in gravid patients. Animal studies have not documented toxicity.
PAS	C	Use with caution when essential. Not considered teratogenic.
Clofazimine	C	Use with caution when essential. Drug appears to be safe during pregnancy when used at lower doses for leprosy, but experience is limited.
Clarithromycin	C	Avoid use when possible. May be teratogenic.
Rifabutin	B	Experience in gravid patients suggests safety.
Amoxicillin/ clavulanate	B	Experience in gravid patients suggests safety.

Drug safety classification (as used in table above for pregnant women).

Safety Class	Evidence
A	Safety established using human studies
B	Presumed safety based on animal studies
C	Uncertain safety, no human studies and animal studies show an adverse effect
D	Unsafe, evidence of risk that may be justifiable under certain clinical circumstances

Drug Administration Table 4: Pediatric dosing of second-line drugs

Drug	Daily dose (mg/kg)	Frequency	Maximum daily
Kanamycin	15 – 30 (20)	Once daily	1 g
Levofloxacin	7.5 – 10	Once daily	750 mg
Ethionamide	15 – 20	Twice daily	1 g
Cycloserine	10 – 20 (15)	Once or twice daily	1 g
p-aminosalicylic acid	150	Twice or thrice daily	12 g
Amikacin	15 – 22.5 (20)	Once daily	1 g
Capreomycin	15 – 30	Once daily	1 g
Streptomycin	20 – 40	Once daily	1 g
Ofloxacin	15 – 20	Twice daily	800 mg
Moxifloxacin	7.5 – 10	Once daily	400 mg
Protionamide	15 – 20	Twice daily	1 g

Drug Administration Table 5: MDR-TB Drugs Cross-resistance

Drug 1	Drug 2	Qualitative description of cross-resistance
Kanamycin	Streptomycin	Low
Kanamycin	Amikacin	High
Kanamycin	Capreomycin	Some cross-resistance exists. Highly kanamycin R strains can be R to capreomycin yet low-dose kanamycin R strains retain susceptibility to capreomycin.
Capreomycin	Streptomycin	Low
Ethionamide	Isoniazid	Cross-resistance has been reported among strains with low-dose H resistance.
Levofloxacin	Ciprofloxacin	Variable in vitro cross-resistance. Further in-vivo clinical studies are required.
Rifabutin	Rifampicin	High

Source: PIH Guide to Medical Management of MDR-TB

Drug Administration Table 6: Commonly Used Ancillary Medicines

Indications	Drugs
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.) Avoid antacids because they can decrease absorption of fluoroquinolones
Oral candidiasis (non-AIDS patients)	Fluconazole, clotrimazole lozenges
Diarrhea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Dimenhydrinate

Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal effects)
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis cycloserine neurologic complications	Pyridoxine (vitamin B6)
Peripheral neuropathy	Amitriptyline
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium and magnesium replacement

ADAPT MDR TB MANAGEMENT (Including for HIV)

Adaptation of this desk guide is required for all countries, for example including the national MDR regimens/drugs.

Countries with a generalized epidemic of HIV (i.e. more than 1% HIV positive antenatal women), and/ or significant % of TB patients with HIV then all sections of the desk guide will need to be reviewed and revised by an expert group.

Use the resource documents (used in developing this guide), which can be downloaded from WHO and PIH freely.

Resources:
In general www.who.int/health topics

Revision of MDR case management guidelines:

- WHO. Guidelines for the programmatic management of DR TB, 2008. http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html
- Partners in Health. The PIH Guide to Medical Management of MDR Tuberculosis. PIH 2003. http://www.pih.org/inforesources/MDRTB/PIH_Guide_book_final.pdf
- The DOTS Plus Handbook, PIH http://www.pih.org/inforesources/tb_manual/full_text.pdf

Clinicians with TB-HIV patients (plus the PIH Guide above):

- WHO. TB/HIV A Clinical Manual, WHO/HTM/TB, http://whqlibdoc.who.int/publications/2004/9241546344.pdf
- WHO. IMAI. Tuberculosis care and TB-HIV co-management http://www.who.int/hiv/pub/imai/TB_HIVModule23.05.07.pdf

This guide, as a decision-aid, does not cover all possible situations and/or solutions related with the management of MDR TB. The clinical judgment of the doctor remains the basis for final decision-making, and this aid should only be taken as a supplement and not a substitute of the clinical acumen. This desk guide has been developed for low HIV settings, from more detailed guidelines, and in particular:

- WHO: Guidelines for the programmatic management of drug resistant tuberculosis (Emergency update) 2008, and
- WHO: Management of drug-resistant tuberculosis - Training for health facility staff (Generic Training Modules – Draft: 2009)
- Partners in Health: The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis. PIH 2003.

Developed by:

- National TB Control Programme Pakistan.
- Association for Social Development Pakistan
- Nuffield Center for International Health and Development, University of Leeds, UK.

Supported by:

- Communicable Disease Research Programme (COMDIS, DFID-UK)

Nuffield ASD NTP