CHAPTER 7

Drug-sensitive and drug-resistant tuberculosis

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Tuberculosis

Tuberculosis is the most common cause of morbidity and mortality in people living with HIV. It is caused by the organism *Mycobacterium tuberculosis* (MTB), which is transmitted through the air via infectious respiratory droplets that originate from a person with active pulmonary disease, most commonly as a result of coughing.

It is important to distinguish between infection with MTB and active disease due to MTB. Upon inhalation of MTB, a person with a healthy immune system will ‘control’ it, such that in most cases the MTB remains latent, with only a 10% lifetime risk that it will ever develop into active TB disease. However, those with weakened immune systems, such as young children and people living with HIV (PLHIV), are less able to control the MTB and have an approximate 10% risk per year that the Mycobacterium will begin to replicate uncontrollably, leading to active TB disease and the development of symptoms.

• When TB disease involves the lungs (i.e. pulmonary TB or PTB), a person will have coughing and certain other ‘constitutional’ symptoms, e.g. loss of appetite, loss of weight, fever and night sweats.

• TB disease can also spread and cause active disease outside the lungs in almost any organ in the body – called extrapulmonary TB (EPTB). The symptoms and signs of EPTB will depend on exactly which organ is involved (e.g. headache if TB meningitis, effusion if joint involvement, etc.).

Types of active TB disease

It is helpful to think of active TB disease according to the following:

• smear-positive pulmonary TB, the most infectious form

• smear-negative pulmonary TB, which is more difficult to diagnose, often leading to a dangerous delay in initiation of treatment

• extrapulmonary TB (EPTB), which is also difficult to diagnose, and requires good and thorough clinical assessment.

Each of the above 3 types of TB disease can be caused by either drug-sensitive or drug-resistant (DR-TB) strains. DR-TB requires a longer duration of treatment.

If drug-sensitive TB treatment is given to someone with DR-TB, it is likely to make the drug resistance worse.
TB and HIV together = ‘double trouble’.

The clinical presentation and diagnostic approach are different when someone with active TB is co-infected with HIV. This is because active TB disease presents differently in the presence of a weakened immune system.

Pulmonary TB is more difficult to diagnose using smear microscopy:

- Since immune systems are weaker in PLHIV, there is less cavity formation in the lungs in response to active TB disease.
- As a result, HIV-positive people tend to cough up fewer TB germs, not enough to be seen on microscopic examination, so their smear microscopy results are often reported as ‘negative’, despite the presence of active TB.

Therefore, never tell PLHIV, who have symptoms of TB but ‘negative’ smear results, that they do not have TB. They may have active TB, but need other tests to prove it.

TB disease is more often located outside of the lungs in HIV-positive people i.e. extra-pulmonary TB (EPTB).

For the above reasons, a clinician will have to frequently order additional investigations in order to prove the diagnosis of active TB. Fortunately, there are a number of newer diagnostic tests that can assist with this. Since PLHIV are at risk of rapid clinical deterioration due to active TB, clinicians need to avoid excessive delays in diagnosis.

Five ‘I’s to reduce the burden of TB in PLHIV

A number of different strategies can be employed to reduce the burden of TB in PLHIV in your setting:

1. **intensified case-finding (ICF)** through TB symptom screening at each visit of a PLHIV to a health facility, plus screening strategies within the community
2. **isoniazid preventive therapy (IPT)** to prevent development of active TB disease
3. **TB infection control (IC)** measures to reduce the risk of transmission to others
4. **integration** of TB and HIV services in high-burden settings to improve outcomes
5. **earlier initiation** of ART, i.e. at higher CD4 counts, to help prevent development of active TB disease

The 2nd, 3rd, and 5th ‘I’s directly prevent the occurrence of new cases of active TB, while the 1st and 4th ones indirectly do so.
TB and HIV services should be integrated in settings where both diseases are common.

Approximately 10% of people living with HIV develop active TB every year, while up to 70% of those receiving treatment for TB are HIV-positive in high HIV burden settings (whether they know it or not).

Integration of HIV and TB services helps to reduce overall morbidity and mortality, both by reducing diagnostic delay of TB in HIV patients, and by encouraging TB patients to know their HIV status, which in turn allows for earlier care and treatment of other HIV-related conditions. In addition, integration allows for more efficient use of human resources for health, as it prevents some duplication of work that currently exists in parallel TB and HIV programmes.

Some of the objectives of TB/HIV integration include:

• Screening for TB symptoms in all children and adults living with HIV at every visit to a health facility (including at HIV testing sites, antenatal clinics, etc.), followed by rapid evaluation for active TB disease in all those who are coughing or who have at least one other TB symptom.
• All people receiving TB treatment know their HIV status.
• All HIV-positive people with pulmonary or extrapulmonary TB (drug-sensitive or drug-resistant TB) being initiated on ART.

Clinical presentation of pulmonary TB

Typical presentation

The presentation of active TB disease affecting the lungs generally differs between those in the early stages of HIV infection and those in the late stages. A contact history with a known TB case is a strong indicator of underlying TB in the presence of symptoms. Symptoms of pulmonary TB (PTB) in those having mild immunodeficiency (i.e. higher CD4 counts) are similar to those experienced by HIV-negative patients:

• chronic cough (≥2–3 weeks), not fully responding to antibiotics
• loss of appetite
• recent unintentional weight loss (≥1.5 kg within 4 weeks)
• drenching night sweats
• fever ≥2 weeks
• general weakness and tiredness
• chest pain – the position of which (left or right) could indicate the presence of a pneumonitis or pleural effusion
• sometimes haemoptysis (blood in the sputum when coughing).
**Atypical presentation**

With more advanced immunodeficiency (i.e. lower CD4 counts), an HIV-positive person with PTB is likely to present with different symptoms:

- general malaise and weakness (deterioration has been severe if the patient is having difficulty with activities of daily living i.e. washing themselves, making food)
- looks ‘really sick’
- significant weight loss (>10% of previous body weight)
- less coughing, which tends to be dry (i.e. no cough)
- shortness of breath
- anemia
- often associated with disseminated TB (i.e. miliary TB) and/or extrapulmonary TB (meaning involvement of any organ outside of the lungs).

**Clinical presentation of extrapulmonary TB**

The clinical presentation of extrapulmonary TB (EPTB) will depend on the organ system in which the active TB disease is present. Since pulmonary TB can occur simultaneously with EPTB, sputum specimens should be sent for TB investigations if possible (if dry cough, perform sputum induction).

**Table 7.1 Clinical presentation of EPTB**

(Table continued on next page.)

<table>
<thead>
<tr>
<th>Site</th>
<th>Symptoms</th>
<th>Investigations</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meninges (covering the brain and spinal cord)</td>
<td>Headache/confusion and fever, leading to vomiting, stiff neck and loss of consciousness.</td>
<td>Lumbar puncture and investigation of CSF (protein, glucose, cell count, AFB, TB culture, GeneXpert – plus India ink, CrAg/CLAT, VDRL).</td>
<td>TB meningitis is common in children, in whom symptoms tend to be non-specific (e.g. drowsiness, irritability).</td>
</tr>
</tbody>
</table>
| Lymph nodes (see Appendix 14) | One or more enlarged (e.g. >2 cm), painless nodes in the neck, axillae, or inguinal areas. | • Needle aspiration if node is fluctuant (= easy)  
• Fine needle aspirate cytology (FNAC) if not fluctuant (= not so easy)  
• See Appendix 4 in 2014 MSF TB Guide. | TB-related lymphadenopathy can also occur inside the chest or abdominal cavities. |
<table>
<thead>
<tr>
<th>Site</th>
<th>Symptoms</th>
<th>Investigations</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardium (i.e. TB pericarditis)</td>
<td>Chest pain and symptoms related to heart failure (shortness of breath, peripheral oedema, and sometimes abdominal swelling).</td>
<td>Chest x-ray. Echocardiogram.</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion (often one-sided)</td>
<td>Chest pain (often unilateral) and shortness of breath.</td>
<td>Chest x-ray. Pleural tap for: • straw-coloured fluid suggests TB vs pus (empyema) • TB investigations • ADA • albumin.</td>
<td>• AFB often not found in pleural fluid in TB-related pleural effusion. • In a high TB burden setting, a clinical diagnosis of TB can be made upon finding of a one-sided pleural effusion in a PLHIV and having TB symptoms. • A high ADA with lymphocytosis in pleural fluid is indicative of TB. • NB: The differential diagnosis of a bilateral pleural effusion is wider.</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Non-specific symptoms (e.g. alteration in bowel habit) that can include pain and distension due to ascitic fluid.</td>
<td>Abdominal ultrasound. Ascitic tap for: • TB investigations • ADA • albumin.</td>
<td>A ‘doughy’ abdomen is sometimes described on palpation as being suggestive of abdominal TB.</td>
</tr>
<tr>
<td>Spine (also known as Pott’s disease)</td>
<td>Localised pain, followed by deformation.</td>
<td></td>
<td>Destruction of the spine may lead to neurological symptoms and signs.</td>
</tr>
<tr>
<td>Joint</td>
<td>Swelling, but not so much pain, usually involving a hip, knee or elbow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miliary TB (also known as disseminated TB)</td>
<td>Constitutional symptoms (fever, weight loss) which can lead to serious morbidity if it goes undiagnosed.</td>
<td>Choroidal tubercles on fundoscopic exam. Determine TB LAM of urine (if CD4 &lt;100). Miliary pattern on chest x-ray.</td>
<td>Also known as disseminated TB, caused by haematological spread of bacilli throughout the body.</td>
</tr>
</tbody>
</table>

Note that active TB disease can involve almost any organ in the body: kidneys, adrenal glands, thyroid, breast, genitals, skin, etc.
Clinical danger signs

Clinical danger signs requiring urgent hospital referral include:

- severe respiratory distress (e.g. from pulmonary TB with/without bacterial superinfection)
- severe wheezing; not responding to bronchodilators (consider severe airway compression)
- headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (consider TB meningitis)
- big liver and spleen (consider disseminated TB)
- breathlessness and peripheral oedema (consider pericardial effusion or ‘fluid around the heart’)
- distended abdomen with ascites (consider abdominal TB)
- acute angulation of the spine (consider TB of the spine).

Screening for TB in PLHIV

Intensified case finding (ICF) for TB can help increase the chances of early detection; TB symptom screening should be performed routinely in PLHIV, in health facilities and within the community. Screening for TB is easy, and can be performed in less than 30 seconds by any trained health care worker.

- **Caregivers of children** should be asked about current cough, fever, poor weight gain and contact history with a TB case.
- **Adults and adolescents** should be asked about the presence of four symptoms: current cough, fever, weight loss and night sweats.

All children and adults found to have one or more TB symptoms during the screening process need to be **evaluated for TB** using a setting-specific TB diagnostic algorithm (see pages 97 and 98).

Those infected with HIV but not reporting one or more symptoms are unlikely to have active TB disease and should be considered for isoniazid preventive therapy or IPT (see page 110 for more on IPT).18

Important exceptions are those being ‘worked up’ to start ART; in this group, ‘subclinical TB’ is common, which implies the need for routine TB investigations even in the absence of TB symptoms.19

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Evaluating for active TB disease in PLHIV

A TB diagnostic algorithm specific to your setting should already exist (if not, get together with your colleagues and create one.). Such algorithms help to standardise the diagnosis of TB using clinical examination and locally available investigations, with or without a course of antibiotics, and are especially helpful in diagnosing smear-negative PTB without unnecessary delay. For examples of TB diagnostic algorithm, see Algorithms 7.1 (smear microscopy as first test) and 7.2 (GeneXpert as first test) on pages 97 and 98.

1. Always perform a good physical examination in an adult or child whom you suspect has active TB.

2. Send two sputum samples for testing with GeneXpert (preferred) and/or smear microscopy. Make sure the patient provides sputum from the lungs, and not saliva from the mouth. Although early morning sputum has traditionally been requested, there is now sufficient evidence that a same-day diagnostic approach (i.e. ‘spot–spot’) is equivalent in terms of diagnostic accuracy. Thus, efforts should be made, whenever possible, to diagnose TB on the same day of presentation.20

3. If concomitant bacterial infection is suspected, prescribe an antibiotic while waiting for the sputum test results (amoxicillin in a typical adult dosage of 500 mg, 3 times daily or, if allergic to penicillin, erythromycin 500 mg, 4 times daily).

4. If GeneXpert detects MTB or if acid-fast bacilli (AFB) are seen on smear microscopy, start TB treatment.

5. It is important to note that if GeneXpert does not detect MTB and if AFB are not seen under a microscope, the person may still have active TB disease. If TB symptoms persist (despite the antibiotic), other investigations are necessary. These investigations will depend on the person's symptoms/signs and on which ones are available in your setting.

Investigations

1. Chest x-ray – note that CXR presentations of TB in PLHIV ‘are now well characterised and should no longer be considered atypical for TB in HIV prevalent settings’.21 These include:
   - miliary or diffuse shadowing
   - large heart (especially if symmetrical and rounded)
   - pleural effusion
   - enlarged lymph nodes inside the chest.

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If the chest x-ray and clinical picture are consistent with active TB, then the patient should be started on TB medication without delay, and the response to TB treatment monitored.

See Appendix 17B for a 'tick sheet' that can assist non-radiologists in the interpretation of paediatric chest x-rays through systematic review and recording, particularly with respect to findings suggestive of active TB disease.

2. Repeat GeneXpert (if available).

3. Other molecular test or TB culture (if available).

4. Determine TB LAM is a newer lateral flow assay (i.e. ‘dipstick’) test of the urine that can identify disseminated TB antigen. However, this test should be reserved for those with low CD4 counts, since its sensitivity is poor at higher CD4 counts.

5. If one or more large and/or chronically infected lymph nodes (LN) are present in the neck, axillae or groin, which have not responded to a course of antibiotics, TB-related lymphadenopathy is very likely.
   - If the LN is fluctuant, needle aspiration is a relatively straightforward procedure to obtain a specimen for testing.
   - If the LN is not fluctuant, fine needle aspiration cytology (FNAC) should be performed.
     - If a pleural effusion is present, perform thoracentesis ('pleural tap') in order to look at the pleural fluid and exclude empyema.
     - Ultrasound is useful to detect abnormalities suggestive of abdominal TB (enlarged para-aortic nodes, ascites, splenic hypodensities) or TB pericarditis (pericardial effusion).

6. If the number of investigations is limited in your setting such that they do not allow you to prove a diagnosis of TB, but the person continues to have TB symptoms and is clinically deteriorating, it is acceptable to initiate empiric TB treatment. However, it is important to continue trying to confirm the diagnosis of TB and to monitor closely the response to therapy.

7. If the person is at risk of DR-TB, a specimen must be sent for drug sensitivity testing (DST). If GeneXpert is not available in your setting, then you should arrange for TB culture + DST. Note however that a culture/DST result could take up to two months.

8. Don’t forget to start all TB patients on cotrimoxazole prophylaxis and initiate ART in order to prevent other opportunistic infections (OIs), plus pyridoxine (vitamin B6) to reduce the risk of peripheral neuropathy.
Xpert MTB/RIF (also known as ‘GeneXpert’)

GeneXpert is a new molecular diagnostic tool that can detect the DNA of MTB in sputum (and certain extrapulmonary specimens) within two hours. It has a number of advantages compared to smear microscopy:

• It has a higher sensitivity than smear microscopy and will often detect TB in smear-negative samples: In controlled clinical validation trials, one GeneXpert test was able to detect MTB in 72.5% of ‘smear-negative, culture-positive’ cases. In demonstration studies, the overall sensitivity of a single GeneXpert test in culture-proven cases of TB was 91%; in comparison the sensitivity of a single direct smear microscopy was 60%. Since GeneXpert is not 100% sensitive, clinicians must be aware that it may be necessary to repeat GeneXpert testing if TB is still suspected and there has been a negative result.

• Access to GeneXpert testing is likely to reduce the need for CXR in your setting.

• GeneXpert is fully automated and does not require a high-level laboratory.

• It can also detect rifampicin resistance in less than two hours, which is a much quicker turn-around-time compared to culture and drug sensitivity testing (DST), which can take up to eight weeks.
Algorithm 7.1 Smear-negative algorithm for management of HIV-positive patients suspected of having TB (pulmonary presentation with or without enlarged lymph nodes)

Note: This algorithm to be used in settings where GeneXpert is not available for diagnosis.

Pulmonary presentation =
cough > 14 days and/or CXR infiltrate with or without night sweats, recent weight loss, or deteriorating level of function.

Sputum smear x 2.
Needle aspiration if lymph node > 2 cm (send for TB smear +/- culture and cytology).
Amoxicillin 500 mg TDS x 7 days (or erythromycin if allergic to penicillin).

If large pleural effusion is present, perform pleural tap to look for straw-coloured fluid and exclude empyema. Send sample for protein, ADA, cell count and TB smear +/- culture (if possible).

Consider PCP if RR >30, cyanosed, and ‘ground glass’ bilateral infiltrate on chest x-ray – especially if not on CPT.

Symptoms and signs resolved, weight stable and smears negative.

Smear(s) positive or granulomas on needle aspiration of lymph node.

No sputum produced (dry cough) or smears negative and patient remains symptomatic.

• Chest X-ray.
• Additional sputum for smear and culture ( +/- blood for CRP).

Start TB treatment if clinical picture and Chest X-ray are consistent with active TB.

Monitoring on TB treatment: symptoms, weight, temperature, Karnofsky score, repeat CRP (after 2 weeks) and Hb (after 1 month).

TB treatment Complete regimen 1 or 2.

Favourable response.
Poor response at 8 weeks (or earlier if deteriorating).

Refer for further TB and other investigations (or to hospital if sick and needs admission).
Algorithm 7.2 TB diagnostic algorithm in settings where GeneXpert is available for use as the initial diagnostic test

* Suspect = cough >2 weeks, or fever >3 weeks, or weight loss >5% or chest pains or TB contact in the household.

- **PTB Suspect**
  - Offer HIV testing and counselling.
  - Provide 2 quality sputum specimens (does not need to be early morning).
  - Give course of antibiotic (e.g. amoxicillin) if concomitant bacterial infection suspected.

- **Positive result with no RIF resistance**
  - Ensure TB IC measures in place.
  - Start treatment for drug-sensitive TB.

- **Positive result with RIF resistance**
  - Ensure TB IC measures in place.
  - Consider repeating GeneXpert (for rapid confirmation of RIF resistance).
  - Refer for possible MDR-TB treatment.

**DANGER SIGNS:**
Resp. rate > 30/min and fever > 39° and/or pulse > 120/min and/or unable to walk or perform activities of daily living (dressing, etc.).

Refer for hospitalisation. (If not possible, consider empiric TB therapy.)

**Negative result:**
- Clinical reassessment for other causes.
- If atypical bacterial infection suspected, give a course of antibiotics (erythromycin/azithromycin).
- CXR.

**Positive result with no RIF resistance:**
- CXR suggestive of TB.

**PTB still suspected, CXR not suggestive:**
- Clinical reassessment for other causes.
- If atypical bacterial infection suspected, give a course of antibiotics (erythromycin/azithromycin).
- CXR.

**Repeat GeneXpert from one additional quality sputum.**

**Negative result:**
- Clinical reassessment and rule out other causes.
- Other investigations as necessary.

**Positive result with no RIF resistance:**
- Ensure TB IC measures in place.
- Start treatment for drug-sensitive TB.

**Positive result with RIF resistance:**
- Follow right side of this algorithm.

Send two additional sputum specimens for culture and first and second-line DST.
Clinical staging of TB patients co-infected with HIV

In HIV-positive patients, a diagnosis of pulmonary TB (PTB) means that the adult or child is in clinical stage 3 of HIV infection (see Appendix 1). Children with extrapulmonary TB (EPTB) are all considered to be in clinical stage 4, except for those with lymph node TB, who remain in clinical stage 3. All adults with EPTB are considered by the World Health Organisation (WHO) to be in clinical stage 4.

Note that patients having a pleural effusion together with PTB should be classified as clinical stage 4; this is because a pleural effusion, although inside the chest cavity, remains outside of the lungs. Using the same logic, those people with TB pericarditis or TB lymphadenopathy are also classified as being in clinical stage 4.

Children and adults with a miliary pattern on chest x-ray have disseminated TB, which being a type of EPTB, means that they are all in clinical stage 4.

TB management

TB treatment regimens

Drug-sensitive TB can be cured relatively inexpensively, using a combination of 4 or more anti-TB drugs.

- **New TB cases** are patients who have never been treated for TB before (or have taken anti-TB drugs for <1 month). They are prescribed a Category I TB treatment regimen for a total of 6 months, consisting of a 2-month intensive phase with four drugs: rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) followed by a 4-month continuation phase with rifampicin and isoniazid (RH). Sputum smear monitoring should be performed at 2 months, 5 months, and at end-of-treatment for all PTB cases (and EPTB cases with pulmonary involvement).

- **Retreatment cases** are patients who have received one month or more of anti-TB drugs in the past. They have traditionally been prescribed a Category II treatment regimen for a total of 8 months, consisting of 2 months of RHZE plus streptomycin injections, 1 month of RHZE, and 5 months of RHE. Sputum smear monitoring should be performed at 3 months, 5 months and at end-of-treatment for all PTB cases (and EPTB cases with pulmonary involvement).

- **Dosages** for all of the first-line anti-TB drugs mentioned above are based on the child’s or adult’s weight. See Table 7.2 for a summary of the dosages for these individual drugs.
**Fixed-dose combinations (FDCs) are commonly available in 4-in-1, 3-in-1, and 2-in-1 combinations; these reduce pill burden and can improve adherence. If not available in your national TB guidelines, tables showing the daily dose of anti-TB drugs using FDCs can be found in Appendix 8 of the 2014 MSF TB Guide.**

### Table 7.2 Dosages of first-line anti-TB drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid (H)</strong></td>
<td>Child &lt;30 kg: 10 mg/kg once daily (maximum 300 mg daily).</td>
<td>Maximum dose 300 mg daily. Do not give to those with severe liver disease.</td>
</tr>
<tr>
<td></td>
<td>Adults and children &gt;30 kg: 5 mg/kg once daily.</td>
<td></td>
</tr>
<tr>
<td><strong>Rifampicin (R)</strong></td>
<td>15 mg/kg once daily.</td>
<td>Should be taken on an empty stomach. Maximum dose 600 mg daily. May cause orange-red discoloration of body fluids.</td>
</tr>
<tr>
<td><strong>Pyrazinamide (Z)</strong></td>
<td>35 mg/kg once daily.</td>
<td>Maximum dose 2000 mg daily. In those with renal impairment, give 25 mg/kg/dose, 3 times per week.</td>
</tr>
<tr>
<td></td>
<td>25 mg/kg once daily.</td>
<td></td>
</tr>
<tr>
<td><strong>Ethambutol (E)</strong></td>
<td>20 mg/kg once daily.</td>
<td>Maximum dose 1200 mg daily. In those with renal impairment, give 15–25 mg/kg/dose, 3 times per week.</td>
</tr>
<tr>
<td></td>
<td>15 mg/kg once daily.</td>
<td></td>
</tr>
</tbody>
</table>
Notes on treatment of drug-sensitive TB

1. Settings with access to GeneXpert (or other rapid DST) should be phasing out the use of Category II treatment regimens: a person with a prior history of TB treatment who is diagnosed as having active TB, using GeneXpert, can, in many cases, take Category I TB treatment, as long as GeneXpert does not detect rifampicin (R) resistance (and as long as mono-resistance to isoniazid is not suspected).

2. GeneXpert is currently only recommended for diagnosis of TB. Those diagnosed with active TB, using GeneXpert, still need to have ‘response to therapy’ monitored using smear microscopy.

3. Rifampicin interacts with a number of other medications. Be particularly careful if the patient is taking:
   - warfarin (higher dose needed)
   - contraceptives (decreased efficacy)
   - fluconazole (decreased levels)
   - certain ARVs (decreased levels of nevirapine and most protease inhibitors).

An excellent, evidence-based resource to help clinicians to recognise and avoid drug-drug interactions is maintained by the University of Liverpool and available for free at the following web address: www.hiv-druginteractions.org/

4. For all patients receiving isoniazid (abbreviated as INH or just ‘H’) in a TB treatment regimen, give pyridoxine (vitamin B₆) to help prevent peripheral neuropathy:
   - adults and children >5 years: 10 mg OD
   - children <5 years: 5–10 mg OD.

Monitoring the response to TB therapy

All those on TB treatment need to be monitored for a response to therapy.

- The basis for monitoring is a good clinical examination.
- Those improving on treatment for PTB will show improvement of symptoms: less coughing, night sweats, and improved appetite.
- There will be an improvement in the person’s general condition, including an increased ability to perform activities of daily living.
- More objectively, there should be weight gain (another important reason to check the weight at every visit).
Follow-up sputum specimens are collected routinely during treatment and at the end of treatment in order to check for the presence of AFB using smear microscopy.

If a person on TB treatment is not clinically improving, especially if the TB diagnosis was made empirically, a thorough reassessment and new investigations are necessary. The differential diagnosis includes:

- drug-resistant TB (DR-TB)
- bacterial pneumonia
- bronchiectasis with bacterial superinfection
- lung abscess or empyema
- PCP
- disseminated fungal infections (e.g. cryptococcosis)
- Nocardia
- Non-tuberculous mycobacteria (NTM)
- Kaposi’s sarcoma (KS)
- Other cancers, including bronchial carcinoma and lymphoma
- Congestive heart failure.

Don’t forget that immune reconstitution inflammatory syndrome (IRIS) can cause temporary worsening of TB symptoms several weeks after initiation of ART.

Poor adherence, malabsorption, TB paradoxical reactions and drug-related adverse events could also contribute to a lack of clinical improvement.

For more details on monitoring response to TB therapy with sputum testing, including management according to smear results, see your national TB programme guidelines or Section 9.4 in the 2014 MSF TB Guide.

### Possible adverse events due to first-line TB drugs

Each of the drugs used to treat drug-sensitive TB may result in adverse events (i.e. side effects). Whether they be minor side effects (e.g. nausea) or major ones (e.g. hepatitis), all side effects need to be diagnosed and managed early, so as not to negatively affect adherence.

The international standard for those on drug-sensitive TB treatment is to clinically monitor for such side effects, not with routine laboratory testing. However, in those at high risk for specific adverse events, it is prudent to monitor with suitable laboratory investigations (e.g. ALT regularly in a person with a pre-existing liver problem).

Some of the more common possible side effects due to first-line anti-TB drugs and their general management are outlined in the table below. Note that sometimes it will not be possible to know for certain which drug is responsible for a specific side effect. Also, make sure to rule out other causes for the symptoms (e.g. a new infection), instead of automatically blaming it on a TB drug.
### Table 7.3 Possible side effects due to first-line anti-TB drugs and their general management

<table>
<thead>
<tr>
<th>Possible side effect</th>
<th>Drugs likely responsible</th>
<th>Suggested management (See also Appendix 22)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>All</td>
<td>Ensure hydration. Give anti-emetic 30 minutes prior to TB treatment.</td>
<td>Nausea and vomiting generally subside over time. Always rule out other causes.</td>
</tr>
<tr>
<td>Peripheral neuropathy (PN)</td>
<td>H, E</td>
<td>Pyridoxine.</td>
<td>Pyridoxine should routinely be given to all those being initiated on TB treatment in an effort to prevent PN. If possible, avoid concomitant use of d4T. (See page 176 in Chapter 10 Neurological conditions.)</td>
</tr>
<tr>
<td>Orange urine</td>
<td>R</td>
<td>None.</td>
<td>It is important to warn the person at the time of initiation to expect this.</td>
</tr>
<tr>
<td>Rash</td>
<td>S, E, Z, R, H (in order of likelihood, from most to least)</td>
<td>Stop TB therapy if any concern of a generalised hypersensitivity reaction (e.g. mucous membrane involvement), and re-introduce drugs in a stepwise fashion, starting with the least likely drug. (See the 2014 MSF TB Guide for more details.)</td>
<td>In addition to mucosal involvement, monitor closely for general signs (fever, headache, vomiting, etc.), as these may represent a generalised hypersensitivity reaction, which can result in mortality (especially if the culprit drug is not discontinued).</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>S</td>
<td>Replace/discontinue likely offending drug.</td>
<td>Reduce dosages of all renally excreted drugs according to CrCl.</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>E</td>
<td>Replace/discontinue Ethambutol.</td>
<td>Early diagnosis depends on screening with the Ishihara test at each visit (see Appendix 21B).</td>
</tr>
</tbody>
</table>
| Hepatitis            | Z (most likely), H, R, E | Stop TB therapy if hepatitis is moderate or severe, and re-introduce drugs individually while monitoring liver function closely, with least likely drug introduced first. (See the 2014 MSF TB Guide for more details.) | In those who are severely ill with TB, such that stopping therapy would be too risky, some clinicians continue TB therapy with anti-TB drugs known to be less toxic (e.g. streptomycin or amikacin 15 mg/kg daily, moxifloxacin 400 mg daily or levofloxacin 750 mg daily, and ethambutol 800–1200 mg daily) until resolution of the hepatitis (normal bili/ALT <100) allows for the reintroduction of other drugs from the initial regimen. It helps to grade the level of hepatotoxicity as follows:  
  – mild: ALT <5 times normal (no jaundice)  
  – moderate: jaundice or ALT 5–10 times normal  
  – severe: jaundice or ALT >10 times normal  
**Example of re-challenge regimen:**  
Day 1: Start rifampicin (normal doses).  
Day 8: Add isoniazid (normal doses).  
Day 15: Add pyrazinamide (normal doses) – clinician's discretion.  
Rechallenge should not be attempted if the hepatitis resulted in hepatic failure. Consult an expert for further management. |
1. If an adult or child already on ARVs is diagnosed with TB, the ARV regimen may need to be modified according to Table 7.4.

2. If TB infection is present before the person has been initiated on ART, the following notes apply:
   - All HIV-infected adults and children with active TB disease are eligible for ART.
   - Start TB treatment first.
   - For the choice of ARVs in the ART regimen, refer to Appendices 9A to 9D and Table 7.4.
   - Those at high risk of mortality should be initiated on ART within two weeks if possible. See Table 7.5 for the optimal timing of ART initiation if the person is already on TB treatment.
   - If the person is clinically stable and has a higher CD4 count, some clinicians prefer to delay ART until just after the intensive phase of drug-sensitive TB treatment (i.e. 2 months) unless other serious HIV-related conditions are present (e.g. KS). This reduces the pill burden, the risk of additive drug side effects and the risk of IRIS.²³

### Table 7.4 Changes to ARV regimen if TB treatment needed

<table>
<thead>
<tr>
<th>Current regimen includes</th>
<th>Change drug to</th>
<th>Patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NVP</strong></td>
<td>EFV</td>
<td>Non-pregnant adults. Pregnant women in the 2nd or 3rd trimester</td>
</tr>
<tr>
<td></td>
<td>Different options:</td>
<td>Children &lt;3 years or &lt;10 kg.</td>
</tr>
<tr>
<td></td>
<td>• Use a triple NRTI regimen (e.g. ABC + 3TC + AZT), returning to the other regimen once TB treatment has been completed.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• LPV/r super-boosted with additional ritonavir.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Use NVP up to dose of 200 mg/m².</td>
<td></td>
</tr>
<tr>
<td>**LPV/r ******</td>
<td>Double dose of LPV/r*.</td>
<td>Adults.</td>
</tr>
<tr>
<td></td>
<td>LPV/r boosted with additional ritonavir.</td>
<td>Children.</td>
</tr>
<tr>
<td><strong>Atazanavir/ritonavir (ATV/r)</strong>****</td>
<td>Temporarily change to LPV/r (as above).</td>
<td>All, since ATV/r cannot be used with rifampicin.</td>
</tr>
<tr>
<td><strong>d4T</strong></td>
<td>Consider change to TDF** to reduce the risk of peripheral neuropathy, unless patient requires an anti-TB injectable (e.g. Am/Km, Cm, S).</td>
<td>Adults and older children*** (provided CrCl &gt;50 ml/min and VL if available is undetectable).</td>
</tr>
</tbody>
</table>

**Notes:**

* Continue double dose LPV/r (or additional ritonavir) for two weeks after stopping the rifampicin-containing TB regimen.

** Do not substitute one drug (e.g. d4T to TDF) if patient is suspected of failing ART.

*** According to the WHO, ‘TDF seems to be efficacious in children and adolescents aged 2 years to <18 years at the current US FDA-approved doses. The benefits of using TDF in children need to be balanced against the potential risk of toxicity’. But the current lack of paediatric formulations limits the use of TDF to older children weighing >35 kg.

**** Since it causes less enzyme induction compared to Rifampicin, Rifabutin can be used together with protease inhibitors such as LPV/r and ATV/r. If available, change Rifampicin to Rifabutin. (For more information on the use of Rifabutin, see Chapter 12 and Appendix 9 in the 2014 MSF TB guide.)
Table 7.5 Timing of ART initiation in an adult already on treatment for TB

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Timing of ART initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TB cases with CD4 count &lt;50 cells/µl (except TB meningitis)</td>
<td>Within 2 weeks if possible.</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>Between 4–6 weeks (NB: Risk of intracranial IRIS).</td>
</tr>
</tbody>
</table>
| Pregnant women                                                                    | • Within 2 weeks if CD4 <50 cells/µl.  
                                         | • If clinically stable, try to wait until the end of the 1st trimester, then initiate with EFV).  
                                         | • Otherwise within 8 weeks. |
| Young children (especially <1 year of age)                                         | Within 2 weeks if possible. |
| All TB cases with CD4 count >50 cells/µl                                            | Between 2-8 weeks*. |
| All DR-TB cases                                                                    | Within 2 weeks if possible. |

* If the person is clinically stable and has a higher CD4 count, some clinicians prefer to delay ART until just after the intensive phase of drug-sensitive TB treatment (i.e. 2 months) unless other serious HIV-related conditions are present (e.g. KS). This reduces the pill burden, the risk of additive drug side effects, and the risk of IRIS.

(See Appendix 19 for an approach to patients who deteriorate on TB treatment.)

**TB in children**

- All HIV-infected children with active TB disease are eligible for ART.
- Begin ART as soon as TB drugs are tolerated (preferably within two weeks), irrespective of clinical stage, in case of MDR/XDR-TB, very low CD4 percentage (i.e. <5–10%), and/or <1 year of age.
- If TB treatment and ARVs are being taken at the same time, changes may be necessary to the ART regimen (see Table 7.4 above).
- Monitor for drug interactions.
- Monitor for side effects, especially hepatitis.
- Since the patient will be taking a large number of tablets, ensure adequate counselling is done in order to maintain adherence.
Clinical presentation of TB in children

- Common presenting symptoms of TB disease in children include:
  - persistent cough >14 days
  - fever >38°C for over 1 week (after excluding other causes of fever)
  - weight loss or failure to gain weight (don't forget to look at the ‘Road to Health’ card)
  - unusual fatigue (e.g. not able to play as usual).
- Extrapulmonary presentations of TB (EPTB) are common in children. Symptoms will depend on the part of the body involved:
  - A visible mass in the neck, not responding to a course of antibiotics and without a visible local cause probably represents lymph node TB in a high TB burden setting.
  - Other common presentations of EPTB in younger children include meningitis and miliary/disseminated disease.
  - Osteoarticular TB disease is more common in older children.
  - See Table 7.1 above for other presentations of EPTB.

Active screening

- Active screening for TB disease in HIV-infected children is essential at each and every visit.
- Ask the child’s caregiver about poor weight gain, fever or current cough – if none of these are present, then the child is unlikely to have active TB, and can be considered for IPT (see later in this section).  
- Always ask about contact with an adult with active TB disease (see Algorithm 7.3 below).

Diagnosis

Diagnosis of TB in children is difficult, especially in the HIV-positive child. Other pulmonary conditions may present with symptoms similar to TB (bacterial pneumonia, fungal pneumonia, LIP, etc.). If the child is able to produce sputum, it is often paucibacillary (i.e. containing few TB germs), so sputum smears are often reported as ‘negative’.

Thus, we need to use many pieces of information to make the diagnosis of TB in a child: contact history and clinical presentation are most important. Other investigations may also help: a child over five years old is generally old enough to

try to produce sputum, whereas in the younger child, induced sputum (preferred) or gastric aspirate will have to be considered. Depending on local resources, CXR, TB skin testing and needle aspiration of large, fluctuant lymph nodes should be performed.

- **Induced sputum or gastric aspiration** can increase the yield of sputum production (see below) in facilities where there are trained staff to perform these.

- A raised, thickened area >5 mm in diameter following a **TB skin test (TST)** in an HIV-positive child is considered a positive result. It tells us that the child has inhaled TB at some point in the past; however, it does not necessarily mean that the child currently has active TB disease. A TST result is just another clue that can help us to make a diagnosis of active TB. **Remember, though, that a negative test does not exclude active TB.**

- **CXRs are even more difficult to interpret in HIV-infected children, and can be normal in up to one third of those with active TB.** The eye of an experienced clinician is often needed to make a diagnosis and TB should not be diagnosed from the CXR alone. The most common feature on x-ray is hilar lymphadenopathy. Other features may also be present, including alveolar consolidation, cavitation or miliary pattern.

- A miliary pattern in a child who does not look sick most likely means the child has lymphoid interstitial pneumonia (LIP), not disseminated TB.

- Needle aspiration of fluctuant lymph nodes ≥ 1 cm is relatively straightforward, so should be performed without hesitation, and aspirated material sent in a sputum container for microscopy, molecular testing (e.g. GeneXpert) and/or culture. Fine-needle aspiration of non-fluctuant lymph nodes is more difficult. See Appendix 4 in the 2014 MSF **TB Guide** for details on fine needle aspirate cytology (FNAC).

The following can help to improve the yield of TB tests on sputum in children:

- Induced sputum collection: First give a bronchodilator (e.g. salbutamol), followed by nebulisation with hypertonic saline solution. An older child will then usually be able to expectorate sputum; if not, suctioning of the pharynx will be necessary to obtain a specimen for testing, as in younger children. (Check www.samumsf.org for sputum induction videos.)

- Gastric washings or gastric aspirates are commonly performed procedures, but require a child to be fasting overnight.

- Send specimens for microscopy, molecular testing (e.g. GeneXpert) and/or culture.
Remember to keep a high index of suspicion for TB in a child. In other words, if you think the child might have TB, be sure to investigate further.

If an HIV-positive child has persistent TB symptoms after a course of antibiotics, even if there is no known history of contact and/or the TB skin test is negative, strongly consider a diagnosis of TB.

If CXRs are not available, and the child has chronic symptoms and a known TB contact, strongly consider initiating empiric TB treatment (sputum collection should be attempted whenever possible).

The presence of certain findings on clinical examination in children with TB symptoms in a high TB prevalence area is enough to warrant immediate initiation of TB treatment:

- non-painful lymphadenopathy with fistula
- angle deformity of the spine.

### Management

- Management of TB is the same as for HIV-negative children.
- Children with certain types of EPTB (e.g., TB meningitis and of the joint) are often given a prolonged duration of treatment (e.g., up to 12 months).
- Ethambutol is now considered safe for children of any age, including little risk of ocular toxicity, provided that it is correctly dosed at 20 mg/kg/day.
- Thus, 4 drugs (including ethambutol) should be used in the intensive phase of treatment.
- Streptomycin should be avoided in children, due to the risk of irreversible auditory nerve damage.
- Inpatient management should be considered for children that are seriously ill.
- Nutritional support is very important, especially if the child is malnourished.
- The child needs CTX prophylaxis and enrolment for ART (see Table 7.5 on page 106 for timing of ART initiation).
- Pyridoxine to help prevent peripheral neuropathy: give 5–10 mg daily for those <5 years, and 10 mg daily for those >5 years.
If the child’s symptoms worsen despite TB therapy, questions to ask include:

- Are the TB drug dosages correct for the child’s weight?
- Is the child being given the medication appropriately?
- If the child is severely malnourished, is this being managed appropriately?
- Is there a reason to suspect drug-resistant TB (e.g. index case is known to have DR-TB, is a relapse case, or is also not responding to therapy)?
- Has the child developed IRIS (if on ARVs)?
- Is there another reason for the child’s illness, other than or in addition to TB?

Perform a thorough clinical assessment and investigate.

Prevention of TB infection and disease

TB prevention should be a focus of every HIV/TB program. A series of TB infection control (IC) measures help to prevent transmission of MTB to others, while isoniazid preventive therapy (IPT) can be used to prevent the development of active TB disease in individual adults and children living with HIV.

Isoniazid preventive therapy (IPT)

In adults

IPT involves prescribing a single TB medication, isoniazid (INH), for six months or more, in order to prevent development of active TB disease for up to two years. For details on eligibility and the duration/dose of INH, refer to your national TB guidelines or the 2014 MSF TB Guide.

Before using INH, one must be certain that the person does not have active TB; or else the situation will be made worse, as giving INH monotherapy to a person with active TB would promote resistance of the TB organism against INH.

The following criteria exclude a patient from consideration for IPT:

- Symptoms and/or signs of TB, i.e. patients who are currently ill with new or worsening cough, with or without sputum production, haemoptysis, night sweats, fever or measured weight loss of more than 5%.
- The person is unlikely to adhere to IPT.
- The risks outweigh the potential benefits (e.g. the presence of jaundice or active hepatitis).
- The strain of TB is unlikely to be sensitive to isoniazid.
In children

IPT should be offered to the following children:

1. Contacts of PTB cases:
   - all HIV-positive (and HIV-exposed) children <15 years
   - all HIV-negative children under 5 years of age
   - newborns of smear-positive mothers.
2. HIV-positive children between 1–15 years, regardless of contact history.
3. HIV-positive children <15 years, post-TB treatment (i.e. as secondary prophylaxis).

Note: Unlike adults, TB skin testing (TST) does not have a role in determining which child will benefit from IPT. TST can, however, be used to evaluate a child for active TB disease.

- Children on INH prophylaxis should receive pyridoxine to avoid PN
  - >5 years, 10 mg OD
  - <5 years, 5–10 mg OD.
- The dose of INH for preventive therapy in children is 10 mg/kg/day for 6 months (see Table 7.6 below).
- For details on the duration and dose of INH in children, refer to your national TB guidelines or Chapter 16 in the 2014 MSF TB Guide.

Table 7.6 Dosage recommendations for IPT in children

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Daily isoniazid (INH) 100 mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–3.4</td>
<td>¼ tablet</td>
</tr>
<tr>
<td>3.5–6.9</td>
<td>½ tablet</td>
</tr>
<tr>
<td>7–9.9</td>
<td>1 tablet</td>
</tr>
<tr>
<td>10–14.9</td>
<td>1 and ¼ tablet</td>
</tr>
<tr>
<td>15–19.9</td>
<td>1 and ½ tablet</td>
</tr>
<tr>
<td>20–24.9</td>
<td>2 tablets</td>
</tr>
<tr>
<td>25–29.9</td>
<td>2 and ½ tablets</td>
</tr>
<tr>
<td>≥30</td>
<td>3 tablets</td>
</tr>
</tbody>
</table>

Of note, health care workers in high TB-burden settings are a group of adults in whom WHO strongly recommends the use INH preventive therapy.
TB infection control

TB infection control (IC) refers to a set of measures/controls that can reduce the transmission of TB.

1. **Administrative controls.** These are the most important and include:
   - Prompt identification of infectious TB cases (e.g. cough triage and ‘fast track’ for coughing patients).
   - Physical separation of patients known or suspected of having TB (e.g. a person with pulmonary TB should sleep in a separate room while infectious).
   - Coughing patients to wear surgical masks.
   - Patients to be instructed about cough hygiene.
   - Infection control policy and functioning infection control committee to be in place.
   - Infection control risk assessment to be undertaken in all health care facilities.

2. **Environmental controls:**
   - Maximise natural ventilation.
   - Avoid being downwind from an infectious patient.
   - Maximise the amount of natural light in a room.
   - NB: In resource-limited settings, mechanical ventilation and UV lamps are not the priority.

3. **Personal respiratory protection:**
   - At-risk staff to wear N95 respirator masks.

The most effective way to prevent TB transmission is through early diagnosis and treatment of active TB disease. TB patients quickly become non-infectious once started on an effective treatment regimen.
Algorithm 7.3 Management of an HIV-infected child contact of a known case of active TB

Documented TB exposure in an HIV-infected child
Close contact with any TB patient, where close contact is defined as any household contact or contact outside the household that is of sufficient duration to pose a high risk of infection.

No current symptoms or signs.

- Evaluate for TB using one or more of the following: molecular testing (e.g. GeneXpert), smear microscopy, and/or CXR (depending on availability).
- If no evidence of TB, follow up after 1–2 weeks.
- If symptoms persist, refer if symptoms suggestive of TB.
- Preventive INH 10 mg/kg/ day for 6 months (see Table 7.6 on page 111).

Symptoms or signs present.

- TB diagnosed.
  - Treat for TB. Enter into TB register.
  - Follow up after 1–2 weeks.

- No evidence of TB.
  - Child is well.
  - Symptoms persist.
  - Re-evaluate for active TB.
  - Observe for symptoms.
  - Refer if symptoms suggestive of TB.
Drug-resistant tuberculosis (DR-TB)

Drug-resistant TB (DR-TB) is an increasingly recognised threat. Worldwide, 3.7% of new cases and 20% of previously treated cases are estimated to be due to TB strains that are multidrug-resistant. However, it is important to note that the rate of DR-TB varies considerably by region, and that the vast majority of DR-TB cases currently go undiagnosed (and therefore untreated).

If someone on TB treatment in your setting has been adherent to their treatment but is not improving, one of the first diagnoses to think of and to rule out is DR-TB. Known contacts of patients with DR-TB who present with TB symptoms should also be investigated for DR-TB, particularly if HIV positive or <5 years.

Classification of DR-TB

DR-TB can be classified into four categories:

1. **Mono-resistant**: Resistance to one of the first-line anti-TB drugs: ethambutol (E), rifampicin* (R), isoniazid (H), pyrazinamide (Z).
2. **Polydrug-resistant (PDR)**: Resistance to two or more of the first-line drugs, but not R and H together (see MDR below).
3. **Multidrug-resistant (MDR)**: Resistance to at least R and H.**
4. **Extensively drug-resistant (XDR)**: Resistance to R, H and one or more of the anti-TB injectable drugs (capreomycin, kanamycin, amikacin) and any of the fluoroquinolones (e.g. ofloxacin).

Notes:

* Note that rifampicin mono-resistance is treated similarly to a case of MDR-TB.
** The term ‘pre-XDR’ is informally used to refer to MDR-TB strains that have additional resistance to either an injectable or a fluoroquinolone (i.e. halfway between MDR and XDR-TB).

Clinical presentation

What are the symptoms of DR-TB?

The symptoms of DR-TB are the same as those of drug-sensitive TB (DS-TB) – see page 90.

DR-TB patients may present with cough, weight loss, fatigue, night sweats, chest pain and/or more atypical symptoms if they are HIV positive with advanced immunodeficiency.


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Who gets DR-TB?

Transmission of DR-TB is the same as drug-sensitive TB – i.e. airborne. Anyone can get DR-TB but certain people are more at risk, including:

- a person who has been in close contact with someone with DR-TB (especially if living in the same household)
- health care workers, including laboratory workers and auxiliary staff (e.g. hospital cleaners)
- those in congregate settings: miners, prisoners and prison guards
- those with a history of TB drug use: relapse after treatment; return after default; treatment failure (greatest risk); history of using poor or unknown quality of drugs; history of illness or other medications that interfere with TB drug absorption
- those with weakened immune systems (since at increased risk for all forms of TB).

How is DR-TB diagnosed?

(See Table 7.7 on page 116.)

Although DR-TB can be suspected clinically, the actual diagnosis of DR-TB has to be made in a laboratory. When a person is suspected to have DR-TB, one or more specimens is sent for smear microscopy, molecular testing and/or culture and drug sensitivity testing (DST).

Which people need to have one or more specimens sent for DST (i.e. active case finding for DR-TB)?

- all re-treatment TB cases
- patients on TB treatment who remain sputum smear positive after 3 months
- symptomatic close contacts of confirmed DR-TB cases
- symptomatic individuals from known high-risk groups:
  - health care workers
  - other employees of health care facilities (e.g. cleaners)
  - laboratory workers
  - those in congregate settings (e.g. prisoners, miners).

Remember: Rifampicin resistance detected by GeneXpert needs to be confirmed by DST, since GeneXpert can sometimes give a ‘false positive’ RIF result and it is important to know about resistance to additional drugs.
### Table 7.7 Testing for DR-TB

<table>
<thead>
<tr>
<th>Test</th>
<th>Role</th>
<th>Time to result</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Xpert MTB/RIF (i.e. GeneXpert)</strong></td>
<td>Can detect rifampicin (RIF) resistant strains of MTB.</td>
<td>&lt;2 hours</td>
<td>Rifampicin resistance detected by GeneXpert needs to be confirmed by DST (especially true for low prevalence settings) since GeneXpert can sometimes give a ‘false positive’ result.</td>
</tr>
<tr>
<td><strong>Line Probe Assay (LPA), also known as ‘Hain test’</strong></td>
<td>Used to detect H and R resistant strains in smear- and culture-positive specimens (but not smear-negative ones).</td>
<td>&lt;2 hours</td>
<td>Not yet validated for DST of second-line drugs.</td>
</tr>
<tr>
<td><strong>Culture/DST, also known as phenotypic DST</strong></td>
<td>Can be used to detect resistance to first-line drugs (H, R, Z, E, S).</td>
<td>2–3 weeks if liquid culture (e.g. MGIT).</td>
<td>DST results to H, R, FQs and injectables tend to be reliable and reproducible. DST of other drugs is much less reliable. There is cross-resistance between the injectables amikacin (Am) and kanamycin (Km), and also capreomycin (Cm) but less so.</td>
</tr>
<tr>
<td></td>
<td>Can be used to detect resistance to second-line drugs (injectables, FQs, etc.).</td>
<td>&gt;1 month if solid culture (L-J).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Even longer, since second-line DST is usually performed sequential to first-line DST.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smear microscopy</strong></td>
<td>Determines level of infectiousness in those with PTB:</td>
<td></td>
<td>Note that EPTB patients are not infectious (unless they have co-existing PTB).</td>
</tr>
<tr>
<td></td>
<td>• Smear-positive PTB patients are more infectious.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Smear-negative PTB patients are less infectious.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Assessing a DR-TB patient

**History:**
It is important to get detailed information about:

- the TB treatment history (for each episode of TB) and to understand if there were adherence issues in the past
- a history of exposure to a known case of DR-TB
- any conditions that can weaken the immune system (HIV infection, diabetes mellitus, renal disease, malignancies or chronic malabsorption syndrome)
- the psychosocial context of the patient.

**Physical exam should be comprehensive:**
- weight and body mass index.

**Baseline investigations:**
- repeat smear, culture and DST prior to starting DR-TB treatment
- HIV screening (if not already done) and CD4 count if found to be HIV-positive
- chest x-ray
- pregnancy test (if of child-bearing age)
- audiometry (baseline, within 3–7 days if possible, and monthly during the intensive phase of treatment)
- potassium
- serum creatinine and calculate creatinine clearance (CrCl)
- full blood count, or at least haemoglobin (Hb)
- liver blood test – ALT
- Thyroid-stimulating hormone – TSH
- fasting blood glucose (FBG)
- urinalysis
- colour vision test if on ethambutol or linezolid (using Ishihara test in Appendix 21B)
- Electrocardiogram (ECG) in settings where clofazamine and newer TB drugs (bedaquiline, delamanid) being used.

**Infection control**
Infection control in the home of the patient will need a detailed initial assessment, in order to reduce the risk of transmission to others in the household during the period of infectivity.

All close contacts need to be screened for TB symptoms. All contacts <5 years should be assessed by a clinician and assessed regularly for a total of two years. See page 93 for more information on contact tracing.
Individualised counselling should be provided by a trained DR-TB counsellor, using a standard model for information giving and education of patient and family.

Management of DR-TB

Standardised regimens are usually recommended in the guidelines of national TB programmes (NTP). For example, the standardised regimen for multidrug-resistant TB (MDR-TB) mentioned in the 2011 South African guidelines includes an intensive phase of kanamycin/amikacin, moxifloxacin, ethionamide, terizidone, and pyrazinamide (taken at least six times per week) followed by a continuation phase that includes the latter four oral drugs.

For strains having advanced resistance, e.g. extensively drug-resistant (XDR) TB, the treatment regimen will likely have to be individualised, based on the results of DST and treatment history.

The principles of DR-TB treatment can be summarised as in Table 7.8. Those with mono- and poly-drug-resistant TB (apart from mono-resistance to RIF, which is treated similarly to MDR-TB) are often treated for lesser durations, e.g. 9–12 months. See Chapter 11 in the 2014 MSF TB Guide for further details.
### Table 7.8 Principles of DR-TB treatment

(See Appendix 20 for drug dosages.)

<table>
<thead>
<tr>
<th></th>
<th>Aim to have at least four second-line anti-TB drugs likely to be effective in a DR-TB regimen.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Start by choosing an injectable drug (from Group 2) based on the DST result and treatment history.</td>
</tr>
<tr>
<td></td>
<td>• kanamycin</td>
</tr>
<tr>
<td></td>
<td>• amikacin</td>
</tr>
<tr>
<td></td>
<td>• capreomycin</td>
</tr>
<tr>
<td>3</td>
<td>Then add a fluoroquinolone (FQ, Group 3), ideally a later generation one:</td>
</tr>
<tr>
<td></td>
<td>• moxifloxacin</td>
</tr>
<tr>
<td></td>
<td>• levofloxacin</td>
</tr>
<tr>
<td>4</td>
<td>Add at least two bacteriostatic drugs from Group 4:</td>
</tr>
<tr>
<td></td>
<td>• ethionamide (or prothionamide)</td>
</tr>
<tr>
<td></td>
<td>• cycloserine</td>
</tr>
<tr>
<td></td>
<td>• para-aminosalicylic acid (PAS)</td>
</tr>
<tr>
<td></td>
<td>Choice is based on treatment history and side effect profile.</td>
</tr>
<tr>
<td></td>
<td>Note that all three of these drugs may have to be included in order to have four second-line</td>
</tr>
<tr>
<td></td>
<td>drugs likely to be effective.</td>
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<tr>
<td>5</td>
<td>If the regimen does not yet contain four second-line drugs likely to be effective, add Group 5</td>
</tr>
<tr>
<td></td>
<td>drugs:</td>
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<tr>
<td></td>
<td>• bedaquiline (if available)</td>
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<tr>
<td></td>
<td>• linezolid</td>
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<tr>
<td></td>
<td>• clofazimine</td>
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<tr>
<td></td>
<td>• amoxicillin/clavulanic acid</td>
</tr>
<tr>
<td></td>
<td>• high-dose isoniazid (in certain circumstances)</td>
</tr>
<tr>
<td>6</td>
<td>Add Group 1 drugs as follows:</td>
</tr>
<tr>
<td></td>
<td>• Pyrazinamide (Z) is added routinely, unless resistance has been documented or there is</td>
</tr>
<tr>
<td></td>
<td>intolerance.</td>
</tr>
<tr>
<td></td>
<td>• Ethambutol (E) is not routinely added, unless it is likely to be effective.</td>
</tr>
<tr>
<td>7</td>
<td>The duration of the intensive phase of DR-TB treatment (i.e. the phase containing the injectable)</td>
</tr>
<tr>
<td></td>
<td>is guided by culture results: until at least four months after the TB culture becomes negative, or</td>
</tr>
<tr>
<td></td>
<td>at least eight months, whichever is longer.</td>
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<tr>
<td>8</td>
<td>The total treatment duration is also guided by culture results: at least 18 months after the</td>
</tr>
<tr>
<td></td>
<td>culture becomes negative. The duration may need to be further extended in chronic cases</td>
</tr>
<tr>
<td></td>
<td>having extensive pulmonary damage.</td>
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<tr>
<td>9</td>
<td>A combination of sputum smear microscopy and culture should be used to monitor response to</td>
</tr>
<tr>
<td></td>
<td>therapy, together with clinical assessment.</td>
</tr>
<tr>
<td>10</td>
<td>All HIV-infected DR-TB patients should receive ART, irrespective of CD4 count, and as early as</td>
</tr>
<tr>
<td></td>
<td>possible following initiation of anti-TB therapy.</td>
</tr>
</tbody>
</table>

Source: Modified from Figure 10.1 in the 2014 MSF *TB Guide*. 
Model of care for DR-TB treatment

Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalisation. Treatment should be directly observed (i.e. DOT); if the person lives far from the health facility, then a community-based ‘treatment supporter’ can be trained to provide such support close to the person’s home.

Adherence and psychosocial support are very important in a DR-TB programme, as are the provision of ‘enablers’ (e.g. food and transport) to ensure that a person with MDR-TB can successfully complete the entire course of treatment.

If the patient is clinically unstable or if there are significant psychosocial difficulties, admission to a health facility may be required initially (or later if the patient suffers from a serious adverse event).

TB infection control measures should be employed in the home (or health facility) during the initial period of infectiousness, in order to reduce the risk of transmission to others.

The basic principles of MDR-TB treatment include:

- The treatment regimen should include a minimum of four drugs that are likely to be effective, preferably five to six.
- Whenever possible, include first-line anti-TB drugs that are likely to be effective.
- Do not rely on drugs to which resistance is suspected but cannot be confirmed due to unreliable DST. For example, if a patient was taking Z and failed a Category I or II regimen (i.e. smear and culture positive) the strain of MTB is likely to be resistant to Z. These drugs may be included if tolerated, but cannot be relied upon as effective.
- Extrapulmonary DR-TB is treated using the same strategies (and duration) as pulmonary DR-TB.

HIV and DR-TB

The risk of mortality is higher in a DR-TB patient co-infected with HIV; thus it is important to make the diagnosis early and start DR-TB treatment early. All HIV-positive DR-TB patients are eligible for ART, regardless of CD4 count.

If a patient with DR-TB is co-infected with HIV, then the ARV tenofovir (TDF) is best avoided during the intensive phase of treatment, due to the additional risk of nephrotoxicity from both TDF and the second-line injectable drug (i.e. amikacin/kanamycin, capreomycin).

Patient support

Support of DR-TB patients is of paramount importance and should be offered throughout treatment.

A DR-TB patient can have difficulty adhering to the prolonged treatment regimen for a number of reasons, including:

- psychological distress
- social problems
- knowledge and beliefs regarding the purpose of treatment
- separation from family/friends
- adverse events (due to medication or other reasons)
- inconsistent immediate effect
- lack of trust in the provider.

Strategies to support patients with these numerous difficulties are many, but a basic package of support should include:

- DR-TB patients should receive sufficient information and education about their disease and its treatment to enable them to have some responsibility for their own outcome. It is very important that patients understand that if they do not adhere to their treatment, they risk amplifying the resistance of their strain of DR-TB, such that it may become less treatable, and the strain can be passed on to their families.

- Psychological support – individually and/or in groups.

- Intense medical support to treat side effects of drugs, addictions, other medical conditions, psychiatric disease and other pre-existing conditions or results of treatment.

- Social support, including ‘enablers’ such as social grants, food, accommodation, and transport, plus other needs of the patients and their families. It is important that these resources are accessible in the community.

- Some flexibility in treatment delivery to enable patients to stay adherent.

Early identification of DR-TB treatment interruption

If a person interrupts DR-TB treatment, he or she should be traced immediately and the reasons for interruption explored. Every effort should be made to help the patient resume treatment and prevent a similar occurrence in the future.

Each DR-TB programme needs to have a good monitoring system in place to identify treatment interruption promptly (i.e. within 1–2 days). DR-TB patients that miss clinic visits should receive a phone call and/or home visit in order to determine the reason(s) for this.
Monitoring someone on DR-TB treatment

Drug-related adverse events are more common with the use of second-line anti-TB drugs. Patients on treatment for DR-TB need to be monitored carefully to identify any such adverse events early and assess response to therapy. Such close monitoring is crucial to improve the chance of a successful outcome.

Adverse events: Second-line anti-TB drugs are associated with a number of different adverse events, from minor to life threatening. It is the responsibility of the health care worker to be aware of all potential adverse events of these drugs and monitor their patients appropriately. (See Appendix 21A for a monitoring schedule for MDR-TB patients.)

Response to therapy: If a person is responding well to DR-TB treatment, then smear and culture results should ‘convert’ from positive to negative within the first few months. Conversion is officially defined as two consecutive negative culture results collected at least one month apart.

It is also important to monitor patients for the further development (known as ‘amplification’) of drug resistance, hence the need for a repeat DST if culture remains positive after four months of treatment or becomes positive again after conversion.

Monitoring programme:

- At the start of DR-TB treatment, the patient should be assessed daily (by the person directly observing therapy) for any side effects to medication.
- A clinician should see the patient at least weekly during the first month and more often if any problems develop. Once stable, the clinician can see the patient every two weeks in the first three months, followed by monthly visits.
  - Check the patient’s weight at each clinic visit.
  - In between monthly visits to the clinician, other DR-TB team members will see the patient and should signal any concerns.
- Thyroid stimulating hormone (TSH) every six months (every three months if HIV positive) to screen for hypothyroidism if on ethionamide (Eto) and/or para-aminosalicylic acid (PAS).
- Check creatinine and calculate creatinine clearance monthly while on an injectable.
- Potassium is very important to monitor monthly while an injectable anti-TB drug is being given:
  - Check magnesium if hypokalemia (= low potassium) has been detected.
- Audiometry monthly to screen for hearing loss during the injectable phase. If audiometry is not available, patients must at the very least be actively asked at each visit if they are experiencing any problems with hearing.
- Screen for optic neuropathy monthly using the Ishihara test in anyone on linezolid or ethambutol. See Appendix 21B.
• Check haemoglobin monthly in those on linezolid or other drugs that can cause anaemia.

• ALT should be checked every 1–3 months in patients receiving pyrazinamide and those at risk of hepatitis (and as necessary in anyone having symptoms of hepatitis).

• Electrocardiogram (ECG) monitoring will be necessary if drugs are being used, especially in combination, which can prolong the QT interval: clofazimine, moxifloxacin, and the newer TB drugs (bedaquiline, delamanid).

• **Smear and culture** monthly.

• Repeat DST if:
  • culture remains positive at four months
  • patient is clinically deteriorating
  • culture becomes positive again after conversion.

• Chest x-ray can be rechecked after 6 months of treatment.

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**Adverse events are more frequent** in patients taking second-line anti-TB drugs and potentially more severe than in patients taking first-line anti-TB drugs. Early recognition and aggressive management of all adverse events is essential, whether they are minor or major (life-threatening), to avoid treatment default.

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**Continuation phase monitoring**

• Examination by clinician monthly unless there is a medical necessity to see the patient more often. Other DR-TB team members see the patient in between and signal any concerns to the clinician.

• Patient’s weight should be checked monthly.

• ALT, FBC, creatinine if clinically indicated.

• TSH levels every six months in patients on PAS and/or ethionamide.

• Repeat Ishihara test monthly if on ethambutol or linezolid.

• Smear and culture done monthly.

• DST if:
  • patient is deteriorating clinically
  • culture remains positive or culture becomes positive again after conversion.
Adverse events related to drugs used in DR-TB regimens

Side effects occur more commonly with second-line anti-TB drugs, compared to first-line anti-TB drugs. Patients (and their treatment supporters) need to be informed of symptoms of these side effects and when to notify the health care provider.

Timely and aggressive management of all adverse events is essential, whether they are minor (non-life-threatening) or major (life-threatening). (See Appendix 22 and page 118, Management of DR-TB).

Contact tracing related to DR-TB

All household contacts and others having a long duration of exposure, especially if in the same indoor space, are at risk of having inhaled the DR-TB strain and developing active disease (the latter especially if having a weakened immune system).

Asymptomatic adult contacts

WHO does not recommend routine use of second-line drugs for chemoprophylaxis in cases where patients have had contact with DR-TB. Asymptomatic adult contacts should be advised that they have been exposed to a drug-resistant (DR) strain of TB, advised of the symptoms of TB and, if they develop any of these symptoms, advised that they must go to their clinic and report that they have been in contact with DR-TB. By doing this, they will be investigated for active DR-TB disease with smear microscopy, culture and DST.

Symptomatic adult contacts

Symptomatic contacts should be evaluated for DR-TB, with GeneXpert (result within days) and/or traditional culture and DST (result within weeks).

Paediatric contacts

All child contacts of DR-TB cases should be evaluated for active TB disease by a clinician. This includes:

- Thorough review of symptoms: Symptoms of TB in children can be non-specific, e.g. chronic cough or wheeze, failure to thrive and recurrent fevers.
- Clinical examination to look for:
  - any change in weight
  - signs of TB on examination e.g. enlarged lymph node(s), respiratory signs, pleural effusion, ascites, etc.
- The following investigations should be considered, even if no symptoms or obvious signs of TB, especially in contacts <5 years of age and HIV-infected children of any age:
  - TB skin testing (TST)
  - chest x-ray (AP and lateral)
• culture and DST: If the child is young and/or cannot expectorate, sputum induction or gastric aspiration should be performed.

All MDR and XDR-TB patients co-infected with HIV should be initiated on ARVs after two weeks, regardless of CD4 count.