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HIV and TB in Practice for nurses: Drug-resistant TB

By Lesley Odendal

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In this edition

This edition covers drug-resistant tuberculosis (TB). It summarises the key recommendations on the diagnosis and treatment of drug-resistant TB for nurses, and highlights examples of best practice in the management and care of people with drug-resistant TB.

What is drug-resistant TB (DR-TB)?

Drug-resistant TB (DR-TB) is TB that has become resistant to the main anti-tuberculosis medication. There are four types of drug-resistant TB:

1 Monoresistant TB: TB that is resistant to only one anti-tuberculosis drug
2 Polyresistant TB: Resistant to more than one anti-tuberculosis drug, but not the combination of isoniazid (INH) and rifampicin (RIF).
3 Multidrug-resistant (MDR) TB: Resistant to at least isoniazid (INH) and rifampicin (RIF), the two most effective anti-tuberculosis drugs.
4 Extensively drug-resistant (XDR): Resistant to at least INH and RIF (MDR-TB), plus any fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin).

What are the causes of drug-resistant TB?

Drug-resistant TB can be caused in two ways.

Acquired or secondary resistance

Acquired resistance is due to poor management or non-adherence to treatment in people who have previously been treated for TB. When doses of TB medication are missed or the wrong dose is prescribed, TB bacilli can become resistant to the medication.

Often people with drug-resistant TB are blamed for not taking their TB treatment and 'causing their own drug resistance'. There are many reasons why a person may not have adhered to their TB treatment (see table below).

Primary resistance

Primary TB drug resistance is due to person-to-person transmission from somebody who already has drug-resistant TB. Drug-resistant TB is spread from person to person through the air, in the same way that drug-susceptible TB is transmitted.

Drug-resistant TB can be spread when a person with active drug-resistant TB disease talks, coughs, sneezes or sings. The drug-resistant TB particles are released into the air through droplets of saliva or respiratory fluid, which when inhaled, infect another person.

A person with primary drug resistance is infected with the same strain of drug-resistant TB bacilli as the person who is spreading the disease. For example, if a person who has MDR-TB coughs and infects someone else then the new infection will be with MDR-TB strains. Likewise an infectious person who expectorates bacilli with XDR-TB can infect others with XDR-TB.

Patient factors leading to non-adherence	Health system & prescribing factors leading to non-adherence and drug resistance
• Lack of resources to get to and from the clinic for Directly Observed Treatment (DOT). • Intolerance or toxicity to the anti-TB drugs. • Misunderstanding about the importance of taking all the TB drugs at the prescribed dose and time. • Disbelief in the efficacy or necessity of the treatment, especially once the patient begins to feel better. • Substance abuse leading to missed treatments. • Cultural issues, where the patient does not believe the medication works.	• Interrupted drug supply due to drug stock-outs. • The provider may not prescribe an adequate TB regimen. • Poor quality formulation may provide sub-therapeutic levels of the drug which may lead to the development of resistance. • There may be a dispensing or administration error regarding the correct dose. • The patient may not be prescribed a large enough dose to be effective. • The patient may have been incorrectly diagnosed as having latent TB infection (LTBI), rather than active TB, and treated with isoniazid monotherapy. • The TB patient may be taking therapy for another disease. That therapy may coincidentally contain a single drug active against TB (such as, rifabutin in an HIV patient for Mycobacterium avium complex [MAC] prophylaxis or repeated courses of a fluoroquinolone for community-acquired pneumonia). • The TB medicines may interact with other drugs being taken by the patient.

Diagnosing drug-resistant TB

Drug-resistant TB can only be diagnosed by a laboratory test. Early diagnosis and treatment of TB is critical for good patient treatment outcomes. This is particularly true for people living with HIV. There are two main ways of diagnosing drug-resistant TB.

1. **Culture and phenotypic tests**

The laboratory grows TB on a medium and does sensitivity tests on the TB germ, called drug-sensitivity testing (DST). Smear microscopy will diagnose TB, but will not tell if that TB strain is sensitive or resistant to TB drugs.

Conventional culture and drug-sensitivity testing based on solid media can take between six and eight weeks to produce a result. Liquid culture systems reduce the delays in obtaining DST results to around 10 days. Many countries do not have access or have limited access to this kind of testing.

2. **New molecular tests**

There are new molecular tests that are able to detect TB drug-resistance within two hours. The Xpert MTB/RIF is a new test for tuberculosis which can detect if a person has TB and whether the strain is resistant to rifampicin, one of the most important

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first-line TB drugs. It does not require a microscope, but is a kind of automated test to look for the DNA specific to the TB bacterium. If there are TB bacteria in the sample, the machine will detect their DNA and automatically multiply it. This technique is called PCR (polymerase chain reaction), and allows the machine to also look at the structure of the genes. This is important to detect if a TB bacterium has developed resistance to drugs.

The Line-probe assay (HAIN strip test) is able to detect rifampicin and isoniazid resistance by testing either in isolates or clinical specimens. The results can usually be available within 48 hours.

Where available, new molecular tests prevent delay in the diagnosis of drug-resistant TB.

Speedy diagnosis is essential

People who have drug-resistant TB may initially respond to first-line TB treatment, but many will not improve or will relapse after an initial improvement. This is a sign that the first-line TB treatment is not working and that their TB may be resistant to the first-line TB drugs. It is very important to test the sputum from such patients with one of the laboratory tests mentioned above.

It is very important to diagnose drug-resistant TB as soon as possible. If a TB patient with drug-resistant TB is prescribed the regular TB medication, the patient will be taking medication which will not work. This means that such patients will remain infectious and can pass drug-resistant TB to others.

Identifying drug resistance in a patient with TB as early as possible is critical in order to treat the patient with the most appropriate anti-TB drug regimen, minimise the risk of transmission, minimise potential drug side-effects, provide the best chance of cure, prevent further drug resistance and to offer appropriate care to contacts.

Case-finding strategies of drug-resistant TB may vary depending on the laboratory capacity to diagnose drug-resistant TB. In some settings, all TB patients are tested with culture and DST. However, in most settings, only patients with an increased risk of DR-TB or who are suspected of having DR-TB are tested.

Indicators that someone may be at risk of having drug-resistant TB include:

- A previous episode of TB treatment.
- Exposure to an individual with infectious drug-resistant TB, including in facilities where drug resistance has occurred such as correctional institutions, homeless shelters, or other congregate settings.
- Developing TB or TB signs and symptoms and being a close contact of someone who has confirmed drug-resistant TB.
- Lack of conversion of sputum smear or cultures to negative while taking anti-TB medication.
- Worsening of TB symptoms or radiography findings while on TB treatment.
- Lack of adherence to prescribed TB medication.
- History of an inappropriate treatment regimen, including the administration of single-drug therapy, too few effective drugs or inadequate drug doses.

There are important questions relating to a person's history of TB which you must ask a potential drug-resistant TB patient in order to assess their risk for drug-resistant TB. Ask him/her:

- Have you been told you had TB before (or ask for haemoptysis [coughing blood], long-standing cough, night sweats and other suggestive symptoms)?
- Have you been treated for TB?
- Have you received injections for a lung problem?
- Have you been prescribed a combination of drugs for 6 months or more ?

If your patient answers yes to any questions which indicate s/he may have been previously treated for TB, the following questions should be asked:

- In which country were you treated? (This will help assess which regimen the person was on or the likelihood of being primarily infected with a DR-TB strain, such as in countries of the former Soviet Union in eastern Europe.)
- What drugs did you receive?
- How many different drugs? How many pills each day? What size and colours were the pills/capsules?
- How long were you on treatment?
- When did you start?
- When did you stop? Why did you stop (completed treatment, adverse reaction)?
- Did you take medications daily? Did you take every pill?
- Were you ever without medication? Did you miss medication sometimes? How often?
- Did healthcare workers observe you taking your medications?
- Did you feel better?
- Did you ever have a sputum examined? What was the result?
- If positive, did your subsequent sputa test negative?
- Did your doctor ever tell you: That you had to be treated for TB longer? That you had a return of TB? That you had drug resistance?
- Did your TB symptoms return after finishing treatment?

TB infection control and contact tracing

It is important to implement TB infection control measures throughout your facilities, because even if your facility is not treating any DR-TB cases, there may be many undiagnosed cases of DR-TB.

DR-TB is transmitted in the same way as drug-susceptible TB. The infection control methods for DR-TB are the same as those of all TB (see *TB Infection Control* Nurses Bulletin). However, given the seriousness of DR-TB, it is recommended that facilities and programmes treating DR-TB make every effort to implement TB infection control measures including administrative, environmental and personal controls.

All close contacts of DR-TB patients (such as household members, co-workers, fellow students) should be identified through contact tracing and evaluated for active TB. If the contact has symptoms of active TB disease, it is important for culture and DST to be performed to see if the person also has DR-TB.

If DST is not available, or while DST results are awaited, a regimen based either on the resistance pattern of the index case or on the most common resistance pattern in the community should be started.

If the contact person does not have active TB disease, it is important to explain to the person that they should immediately be

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screened for DR-TB if they have any symptoms of TB, such as cough, weight loss, fever, and night sweat. A letter should be given to the person explaining that they are a close contact of someone who has DR-TB which they can give to a health professional if they ever experience symptoms of TB. This will prompt the investigation of DR-TB in the close contact.

Treatment of drug-resistant TB

In order for people with drug-resistant TB to be cured, they need to be given TB drugs which they are not resistant to. Treatment regimens for drug-resistant TB will be different from country to country or programme to programme depending on the resources available. There are three ways of designing a TB drug regimen for drug-resistant TB.

Standardised treatment

Drug-resistance surveillance data from representative patient populations are used to design a treatment regimen that is most likely to cure people with drug-resistant TB in the area. This is done especially in countries and programmes where individual drug-sensitivity testing (DST) is not available due to a lack of funds or capacity in the laboratories.

Empirical treatment

Empirical treatment is when each regimen is designed for the person with drug-resistant TB based on their previous history of anti-TB treatment. In this case, people will be given a second-line regimen which does not include the anti-TB treatment which they have been exposed to previously and may have developed resistance to. The drug-resistance surveillance data of the population which the patient comes from are also considered.

In cases where an empirical regimen is used, it is usually adjusted when drug-resistance testing results on the individual patient become available.

Individualised treatment

In individualised treatment the patient's drug-resistant TB regimen is designed based on their previous history of anti-TB treatment and individual drug-sensitivity results.

The recommended time for treatment of drug-resistant TB is guided by culture conversion. In the treatment of patients with MDR-TB, an intensive phase of 8 months is suggested for most patients. In patients not previously treated for MDR-TB, a total treatment duration of 20 months is suggested for most. The duration of intensive and continuation phases of treatment may be modified according to the patient's response to therapy. In the treatment of patients with MDR-TB, four second-line anti-TB drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, are included in the intensive phase. Regimens need to include at least pyrazinamide, a later-generation fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine (or terizidone) or PAS (p-aminosalicylic acid) if cycloserine cannot be used.

Building a treatment regimen for MDR-TB

- Step 1: Begin with any first-line TB drug regimen that has certain, or almost certain, efficacy. If a first-line drug has a high likelihood of resistance, do not use it. Use a first-line oral agent drug which is available, namely ethambutol or pyrazinamide.
- Step 2: Add an injectable agent (kanamycin, amikacin or capreomycin) based on DST and treatment history. Streptomycin should not be used, even if DST suggests susceptibility, because of high rates of resistance with DR-TB strains and higher incidence of ototoxicity (damage to the ear and hearing loss).
- Step 3: Add a fluoroquinolone (levofloxacin, moxifloxacin or ofloxacin) based on DST and treatment history.
- Step 4: Add second-line oral bacteriostatic agent drugs (cycloserine or terizidone, ethionamide or prothionamide, or PAS) until there are at least four second-line drugs likely to be effective. This choice should be based on treatment history, adverse effect profile, availability and cost.

Consider adding Group 5 drugs (clofazimine, linezolid, amoxicillin, clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazid or clarithromycin) if there are not four second-line drugs that are likely to be effective from steps one to four. The anti-TB activity of many of these drugs is unclear. If drugs are needed from this group, it is recommended to add at least two, as anti-TB DST is not reliable for the drugs in this group.

Treatment for XDR-TB

- Step 1: Use any of the first-line anti-TB drugs that may be effective (ethambutol or pyrazinamide).
- Step 2: Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents, it is recommended to use one the patient has never used before.
- Step 3: Use a later-generation fluoroquinolone such as moxifloxacin.
- Step 4: Use both ethionamide (or prothionamide) and cycloserine (or terizidone) if they have not been used extensively in a previous regimen or any that are likely to be effective.
- Step 5: Use two or more drugs from Group 5 (clofazimine, linezolid, amoxicillin, clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazid or clarithromycin).
- Step 6: Consider high-dose isoniazid treatment if low-level resistance to this agent is documented.

For pregnant women

Pregnant women can and should be treated for drug-resistant TB. Treatment for drug-resistant TB should be started in the second trimester, or sooner if the condition of the woman is severe. Avoid injectable agents. For the most part, aminoglycosides should not be used in the regimens of pregnant women and can be particularly toxic to the developing foetal ear. Capreomycin may carry the same risk of ototoxicity, but is the drug of choice if an injectable agent cannot be avoided. Ethionamide should be avoided as it can increase the risk of nausea and vomiting associated with pregnancy.

Treatment of MDR-TB in people living with HIV

Antiretroviral therapy (ART) use during treatment with second-line TB drugs improves cure rates and decreases risk of death among MDR-TB patients living with HIV. ART should be started as early as possible, regardless of CD4 counts, in all MDR-TB patients living with HIV. Second-line anti-tuberculosis treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment. This is especially important in those HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells cells/mm^3), who should receive ART immediately within the first two weeks of initiating TB treatment.

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Although the use of ART in combination with second-line anti-tuberculosis drugs can increase the pill burden for the people in your care, potentially resulting in lower rates of adherence, there is limited evidence of increased risk of adverse events among people receiving the combined treatment compared with people who do not receive ART. It may be necessary to consider overlapping adverse events or toxicities when deciding particular combinations of ARV and second-line TB drugs.

MDR-TB patients living with HIV should receive a comprehensive package of HIV care, including prevention, diagnosis, treatment and care interventions. Cotrimoxazole preventive therapy (CPT) should be provided as part of a comprehensive package of HIV care. In addition, regular monitoring of treatment response, care for opportunistic infections, provision of safe water, sanitation and hygiene, nutritional and psychosocial support should be provided. Client-centred and integrated TB and HIV services should be provided for MDR-TB patients living with HIV at the same place and time as much as possible. Retention of patients in HIV care and ART should be ensured for all patients after completion of TB treatment.

Adherence support

Being adherent to DR-TB medication is challenging, as the side-effects are unpleasant and treatment lasts two years or more. It is important that people with DR-TB are given support to assist them in adhering to their medication. Educating a person about DR-TB and the importance of adhering to their medication daily is an important way of ensuring adherence. It is also recommended that DR-TB medication is taken through directly observed treatment (DOT), where the patient is observed taking their treatment daily, although coming to the clinic daily may be a burden to adherence.

Community-based care and support, such as the use of community health workers (CHW) to assist in supporting patients to adhere to their treatment and to provide emotional support is recommended. In reality, a combination of interventions appropriate for the specific circumstances of the patient is necessary to support adherence. Patients diagnosed with DR-TB who are homeless, prisoners or people who inject drugs, often experience additional barriers to accessing health services and adhering to treatment. In some settings, peer support has been used with encouraging results.

There needs to be a strong system of monitoring in place for a patient to be traced and followed-up if they miss treatment, and which allows the patient to be followed throughout treatment. The use of mobile phones to send text reminders and to reach patients missing doses has been used in different settings.

This usually involves a DOT worker visiting the patient's home on the same day as the missed treatment to find out why the patient has missed their treatment and to encourage the patient to go back onto treatment as soon as possible. It is important that the patient is addressed in a sympathetic, friendly and non-judgemental manner and that every effort is made to address reasons for the patient missing treatment doses.

Models of care

Community-based care

Community-based treatment involves allowing patients to take treatment at home or being given their treatment daily in their communities. In the early phase after diagnosis of DR-TB, patients may need to be hospitalised especially if they are very sick, if they need to undertake tests, if they have no help at home or no one can administer injectable drugs to them.

In some programmes all treatment is given outside hospitals. Given the high number of patients and the fact that transmission of DR-TB in hospitals is a risk, community-based care is recommended.

Clinic-based treatment

In some DR-TB treatment projects, patients travel to a clinic each day to receive DOT.

In order to ensure good adherence in this system, there should be no barriers to travel or the patient should live near the treatment facility. If this is not the case, the patient should be given support to ensure they can travel to the clinic daily.

The patient should be smear-negative if travelling on public transportation or waiting in common waiting rooms.

Hospitalisation

Hospitals should provide acceptable living conditions, sufficient activities so that patients avoid boredom, adequate food, a heating system in cool areas, fans or cooling systems in hot climates and proper TB infection control measures.

The World Health Organization recommends that patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalisation.

Drug-resistant TB and healthcare workers

Many healthcare workers become very anxious when they are told that their facilities or programmes will be treating patients with DR-TB because they fear contracting DR-TB. This is understandable given the seriousness of DR-TB. However, it is important to remember that DR-TB is everywhere and that people with undiagnosed DR-TB have been visiting your facility. This is why infection control is so important. It is better to find and treat DR-TB than not to. When people with DR-TB are not diagnosed or not provided with treatment, they are more likely to spread DR-TB in your community or in your facility.

Additional resources

1. *Drug-resistant Tuberculosis: A survival guide for clinicians. 2nd Edition*. Curry International TB Center, 2011. http://www.currytbcenter.ucsf.edu/drtb/docs/MDRTB_book_2011.pdf

2. World Health Organization. *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis: 2011* update. 2011. http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf.

3. World Health Organization. *Management of MDR-TB: A field guide*. 2009. http://whqlibdoc.who.int/publications/2009/9789241547765_eng.pdf

4. Arentz M et al. *Use of Anti-Retroviral Therapy in Tuberculosis Patients on Second-Line Anti-TB Regimens: A Systematic Review*. PLoS ONE 7(11): e47370, 2012. doi:10.1371/journal.pone.0047370

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