



Tuberculosis—an overview

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Abstract: Tuberculosis (TB) remains one of the deadliest infectious diseases responsible for millions of deaths annually across the world. In this paper we present a general overview of TB including the pathogenesis, diagnosis, and treatment guidelines. In preparation of this write up, we searched PubMed for relevant articles on TB. Additionally, we searched the websites of international institutions like the World Health Organisation (WHO) and the US Centres for Disease control and Prevention (CDC) for related reports and clinical guidelines. This paper has been written with the intention to offer general education to health professionals, policy makers, patients and the public.

Keywords: Tuberculosis (TB); drug-resistance; pathogenesis; drug therapy; infectious diseases

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Background

Tuberculosis (TB) remains one of the major global health threats leading to morbidity and mortality (1,2). One in three persons across the world representing 2–3 billion individuals are known to be infected with *Mycobacterium Tuberculosis* (*M. Tuberculosis*) of which 5–15% are likely to develop active TB disease during their lifetime (3). In 2014, an estimated 9.6 million people fell ill due to TB, around 1.5 million people died from the disease including 1.1 million HIV-negative persons and 400,000 HIV patients (3). While TB is present in every country majority of TB sufferers live in low income and middle income countries especially in regions such as Sub-Saharan Africa and South East Asia (2). Over the past decade, significant progress has been made towards TB control with most of the TB targets set as part of the Millennium Development Goals (MDGs) having been achieved (3). TB mortality for instance has declined by 47% since 1990, with nearly all of that happening in the era of the MDGs. In all, effective diagnosis and treatment of TB has been estimated to have saved over 40 million lives between 2000 and 2014 (3).

While these achievements are remarkable, there are calls for intensified efforts to eradicate the disease. In 2014, the World Health Assembly (WHA) adopted the End TB strategy with targets linked to the newly adopted Sustainable Development Goals (SDGs) (4). The End TB strategy serves as the key guide for countries to reduce TB deaths by 90% by 2030 as well as achieve an 80% reduction in TB incidence rate compared with 2015 (4). TB still pose as a huge threat to economic development as over 90% of TB-related deaths occur among adults in the most productive age groups. Emerging issues such as Multi-drug and extensively drug resistant TB is seen as a major challenge in effective control of the disease in many regions. Treatment outcomes for drug resistant TB are still poor and inadequate reporting remains a growing challenge. Of the 480,000 cases of multidrug-resistant TB (MDR-TB) estimated to have occurred in 2014, only about 25% were detected and reported (3). Moreover, just around 30% of the over 7,000 MDR-TB patients from 13 countries were successfully treated in 2007 (3). The evidence base around TB and its management is rapidly

changing. In this paper, we provide a general overview of TB by highlighting the pathogenesis, diagnosis, and treatment guidelines. In preparation of this material, we searched PubMed for relevant articles on TB. Additionally, we searched the websites of major institutions like the World Health Organisation (WHO) and the US Centres for Disease Control and Prevention (CDC) for related guidelines and reports. This paper has been written with the intention to offer general education to health professionals, policy makers, patients and the public.

Pathogenesis of TB

TB is an airborne bacterial infection caused by *M. Tuberculosis* which affects any part of the body and most commonly the lungs (5). *M. Tuberculosis* is exposed to the air as droplet nuclei from coughing, sneezing, shouting or singing of individuals with pulmonary or laryngeal TB. Transmission occurs through inhalation of these droplet nuclei which passes through the mouth or nasal cavities, the upper respiratory tract, bronchi and finally reaches the alveoli of the lungs (6). Once the *M. Tuberculosis* or the tubercle bacilli reaches the alveoli, they are ingested by alveolar macrophages resulting in the destruction or inhibition of a greater proportion of the inhaled tubercle bacilli (7). The small unaffected proportion multiplies within the macrophages and is released upon death of the macrophages. Live released tubercle bacilli spread via the bloodstream or lymphatic channels to any part of the body tissues or organs in addition to highly susceptible areas of TB infection such as the lungs, larynx, lymph nodes, spine, bone or kidneys (8). In about 2 to 8 weeks (9), an immune response is triggered which allows white blood cells to encapsulate or destroy majority of the tubercle bacilli. The encapsulation by the white blood cells results in a barrier around the tubercle bacilli forming a granuloma (7). Once inside the barrier shell, the tubercle bacilli is said to be under control and thus establishing a state of latent tuberculosis infection (LTBI). Persons at this stage show no symptoms of TB, are unable to spread the infection and as such not considered as TB cases (10). On the other hand, if the immune system fails to keep the tubercle bacilli under control, rapid multiplication of the bacilli ensues which leads to a progression from LTBI to a case of TB. The time for progression to TB may be soon after LTBI or longer occurring after many years. A TB case is highly infectious and can spread the bacilli to other people (11).

Diagnosis of TB

There are five key components of a complete evaluation of TB disease. These are: (I) medical history taking; (II) physical examination; (III) test for *M. Tuberculosis* infection; (IV) chest radiograph and (V) bacteriologic examination of clinical specimens (12). The overall diagnosis commences with medical history taking to investigate the suspected patient's presenting symptoms. In the case of Pulmonary TB, this usually manifest as combination of one or more of the following symptoms; coughs (often lasting longer than 3 weeks with or without sputum production), coughing up blood, chest pain, loss of appetite, unexpected weight loss, night sweats, fever and fatigue (12,13). In the case of extra pulmonary TB (i.e., TB developing outside the lungs), presenting symptoms will often be dictated by the part of the body affected, although, some symptoms such as loss of appetite, night sweat and fever may be more general (14). For TB meningitis for instance, patients may present with headache or confusion (12), whereas patients experiencing TB of the spine may present with severe back pain (15,16). Other issues investigated in the initial assessment of a patient include demographic factors, previous exposure to TB including treatment adherence and any underlining disease. This is then followed by physical examination which evaluates the individual's total condition and informs diagnostic methods. Nonetheless, the physical examination is not intended to confirm or rule out TB.

Testing for *M. Tuberculosis* is achieved either through skin or blood tests. The skin test is known as Mantoux tuberculin test which is initiated by injecting a standard dose of tuberculin fluid into the skin of the lower portion of the arm (17). The results depend on the diameter in millimetres of a skin reaction characterised by an induration (a palpable raised hardened area free from erythema) after 48 to 72 hours of testing. A diameter of 0 to 4 mm represents a negative skin test. 5 to 9 mm is a doubtful result while 10 mm or more is positive for LTBI or TB (18). The CDC (19), further classifies the interpretation of the positive results based on the individual's risk of progression from LTBI to TB. Therefore, for example, in immunocompromised individuals or persons who have undergone organ implants, an induration of 5 mm or more is considered positive.

The blood tests are also known as Interferon-Gamma Release Array (IGRA) which measures the extent to which the immune system reacts to the tubercle bacilli. The United States Food and Drug Administration (FDA) (17),

has approved the use of two IGRAs; QuantiFERON-TB Gold In-Tube test (QFT-GIT) and T-SPOT® TB test (T-Spot). A positive response from IGRA test infers the presence of tubercle bacilli. Conversely, a negative response implies the absence of TB infection (17). However, a 2011 policy statement from the World Health Organization (WHO) expressed concern towards low and middle income countries' use of IGRA as economically unwise compared with skin test and does not recommend its use in these countries (20). Since skin and blood tests are unable to distinguish between LTBI and TB disease, further tests such as chest radiography, computerized tomography (CT) scan and bacteriologic examination of clinical specimens are required (12).

Furthermore, drug susceptibility testing (DST) is performed on the isolated tubercle bacilli specimen to test for resistance to any of the first-line anti-tuberculosis drugs. Resistance to isoniazid and rifampicin in the first line drugs is diagnosed as multidrug resistant TB (MDR-TB) (21). DST involving second-line drugs are conducted under special cases such as previous TB treatment, contact with patient diagnosed of drug resistant TB, confirmed resistance to first-line anti-TB drugs or positive cultures following more than 3 months of treatment (12). Following second-line drug susceptibility test, diagnosis can be made for extensively drug resistant TB (XDR-TB) if in addition to isoniazid and rifampicin resistance, the TB isolate shows additional resistance to at least one of the three injectable second line drugs (i.e., amikacin, kanamycin or capreomycin) and any of the fluoroquinolones (21).

Risk factors for drug resistant TB

From a microbiological point of view, MDR-TB and XDR-TB are caused by genetic mutation of the *M. Tuberculosis* which renders anti-TB agents ineffective against the mutant tubercle bacilli (22). However, Caminero (23) proposes two categories of risk factors for drug resistant tuberculosis. The first category, he describes as 'those facilitating the selection of resistance in the community' and the second as 'specific conditions that appear to increase some patient's vulnerability to resistance' (23). The following section will discuss the risk factors under these two categories.

Factors facilitating the selection of resistance in the community

The major contributing factor to the development of

drug resistant TB in communities is poor National Tuberculosis Programmes (NTP). This may be as a result of lack of funding to facilitate training of staff and implementation of administrative controls towards patient management. Another contributing factor may be lack of DOTS (Directly Observed Therapy Short Course) strategy implementation or its efficiency where they are implemented which may result in inadequate or lack of treatment monitoring (23). Also, the NTP offers guidelines for national implementation which may vary in its implementation from country to country resulting in non-standardised treatments which subsequently increases risk of drug resistance (24). Inadequacy in drug supply characterised by frequent drug shortages, substandard quality of available drugs or inappropriate regimen or dosage can also contribute to increasing risk of resistant tuberculosis. In a survey on isoniazid supply conducted by the United States' National Tuberculosis Controllers Association (NTCA) in January, 2013, conclusions on patient care interferences were made about 79% of health facilities reported procurement difficulties of isoniazid within the month of December, 2012 alone (25). On the other hand, 15% reported discontinued supply of isoniazid within the same month. This consequently led to 69% of the health facilities switching suppliers of isoniazid while 68% delayed treatment of LTBI and 88% switching to alternative regimen. Such inconsistencies increase chances of drug resistant TB as well as transmission. Patients can also contribute to increasing the risk of drug resistant tuberculosis. This is made possible when patients receiving treatment do not adhere to treatment regimen as a result of lack of money to afford treatment, social stigmatisation or treatment complication by incidence of adverse events (24).

Specific conditions which increase some patients' vulnerability to resistance

Caminero (23) further categorises the risks of acquiring drug-resistant TB into three sets of vulnerable groups. The first group are patients who based on bacteriological results are classified as being at high risk of drug-resistant TB. These patients belong to the Category II TB treatment failures involving 2 months of isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin, followed by 1 month of isoniazid, rifampicin, pyrazinamide and ethambutol and a 5-month continuous phase of isoniazid, rifampicin and ethambutol. Other high risk patients for drug-resistant TB are those classified under Category

I and II who have failed on two occasions, rifampicin containing regimen (24,26) and also areas which do not have access to DST laboratories. In a review conducted by Faustini *et al.* (27) in Europe, the most significant risk factor for drug-resistant TB was unsuccessful previous treatment. Similar observation was made in an Iranian study whereby 95.7% of MDR-TB cases were attributed to previously failed treatment (28). The second group of patients are those who are at high risk of drug-resistant TB based on close contact with drug-resistant TB patients or patients classified as Category I TB regimen failure. Close contacts with MDR-TB cases have been reported to have a different resistant strain from the index case (24,29). Due to this high risk of acquiring MDR-TB, suspected close contacts with MDR-TB cases are initiated similar TB regimen to the index case in the absence of DST results and consequently modified when DST results are available. For patients with Category I treatment failure, the risk of MDR-TB is variable from among countries. Under this condition, some countries record low MDR-TB rate such as Malawi (30) and Benin (31) while others have recorded rates above 80% such as in Vietnam (32) and Peru where a study reported MDR-TB in three quarters of patients with drug susceptibility results (33). Hence conduct of surveillance in this treatment failure category is a good guide in ascertaining the risk and rate of MDR-TB occurrence in a particular country. The third group of patients are those at moderate risk of acquiring drug resistant TB. One environment of such risk is the incidence of TB treatment failure in the private facility. TB treatment given in the private sector usually falls short of proper supervision and may increase chance of isoniazid and rifampicin resistance if they are included in treatment (34,35). Another group of patients at moderate risk of acquiring MDR-TB are those who remain smear positive at the second or third month of treatment initiation (33). Again, patients who relapse after treatment completion and those who return following default fall under this third group of patients (31,32). In addition, persons in facilities where MDR-TB outbreak or high prevalence rate is reported stand a chance of acquiring the resistant bacteria. Institutions at risk include prisons, sheltered homes, hospitals, clinics and laboratories where infection outbreaks are known to be highly reported (36,37). Furthermore, certain co-morbidities which interfere with drug absorption or induce profuse diarrhoea such as in HIV-positive patients result in sub-maximal serum drug concentrations and a potential risk to drug resistance (38). Also, persons residing in countries with high prevalence

rate of MDR-TB are equally at risk of acquiring resistant strains. Immigration can also put other countries of low or no incidence of MDR-TB at risk of recording drug-resistant cases. In Europe, immigration has been reported as one of the leading contributing factor to the rising prevalence of MDR-TB (39). The European review by Faustini *et al.* in their stratified analysis found a higher rate of MDR-TB among foreign born patients compared with nationals though a much significant association was observed with previous treatment failure (27). Another Iranian study also reported immigration and refugee status as being a significant risk factor for MDR-TB (28) transmission between the Afghan and Iranian ethnicities when Afghan complicated MDR-TB cases are referred from Afghanistan to Iran.

Prevention of drug-resistant tuberculosis

One of the major efforts of WHO and its partners is to ensure preventive measures toward halting the increasing prevalence of drug-resistant TB (40). Within different countries, there is the need for primary research to determine factors contributing to treatment default (40). This will be essential to inform the implementation of strategies into NTPs geared towards addressing the social determinants which contribute to patient default.

Another way of preventing drug resistant TB is to improve adherence of patients to treatment. This can be achieved by developing patient care plans aimed at separated treatment options (i.e., inpatient, outpatient or community-based treatment) as well as reducing pill burden in TB regimen strategy. A clustered randomised controlled trial conducted by Thiam *et al.* (41) in Senegal to evaluate new strategic recommendation on improving patient adherence to TB treatment resulted in 88% treatment success in the intervention group compared with 76% in the control group. In addition, patient default rate was reduced to 5.5% in the intervention group as opposed to 16.8% in the control group. Some of the interventions investigated were allocating more time to counselling and communication between healthcare providers and TB patients, decentralising treatment outlets to stations nearer to patients, choice of DOT supporter by patient and strengthening supervision activities.

A third preventive measure is addressing the efficiency of health financing towards TB control. This has been the main target of WHO and Global Fund to support countries financially with national TB programmes towards the control of TB. In 2012 alone, the Global Fund accounted for 82%

of the total international funding toward TB (42). Yet there are calls for more sustainable funding to support global TB control goals (43). In light of this concern, different regions of the world have embarked on strategies to increase funding for TB control. The African Union for instance at its meeting held July, 2013, signed a commitment to support the Global Fund in achieving its US\$15 billion replenishment fund towards combating HIV/AIDS, TB and Malaria. One call of action towards this African Union commitment was the encouragement of member states to adhere to the contribution 0.7% gross domestic product towards the Global Fund (44).

Furthermore, MDR-TB and XDR-TB can be prevented by strengthening the full capacity of primary health care involvement in TB care, control and prevention. One such effort is being undertaken in ten regions in Ukraine supported by the USAID. The focus of the project is targeted at primary health care level to provide best TB services by introducing modern laboratory diagnostics, improving access to TB/HIV co-infection interventions and programmes to effectively manage MDR-TB and XDR-TB (45). Another TB prevention project was also carried out by USAID in Belarus after a survey conducted in 2011 reported an alarming increase in MDR-TB cases. The project targeted at developing guidelines for TB care and prevention in primary healthcare facilities (46).

Finally, managing contacts of MDR-TB and XDR-TB patients can be considered. Contacts of MDR-TB and XDR-TB patients ought to be evaluated as quickly as possible to reduce risk of transmission (47). However, preventive therapy for MDR-TB and XDR-TB contacts should be based on individual risk assessment as studies supporting this intervention is very limited (48). IGRA may be administered to contacts who have recently received BCG vaccine. Contacts that are immunocompromised may be treated with MDR-LTBI prophylaxis regimen which usually involves at least two anti-tubercular drugs which the resistant strain is susceptible (47).

Guidelines for TB management

As part of global TB strategies, evidence-based guidelines have been developed to support NTPs (24,49,50). These guidelines provide guidance on issues such as TB case definitions, administration of standard and individualised treatment regimens, drug treatment monitoring, supervision and patient support. The subsequent section will discuss some of these relevant aspects of TB management often

communicated in various guidelines.

Case definitions

This is the first step in TB management which ensures patient registration and the administration of the appropriate standard regimen (49). It follows diagnosis based on clinical examination and laboratory tests which confirms the presence of *M. Tuberculosis*. For sputum smear or culture confirmed TB cases, HIV and MDR-TB status are assessed. Also, a case may be defined as a result of treatment outcomes such as relapsed, defaulted or failed (49).

Standard and individualised treatment regimen

The aims of TB regimen include ensuring cure, preventing resistance and improving quality of life of the patient (49). The standard treatment regimen is tailored at a defined group of TB patients such as new TB cases, previously treated cases, drug resistant patients and special cases.

New case

According to the WHO guideline (49), for new cases, a 6-month standard regimen which involves 2 months intensive phase treatment with isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) is recommended. For tuberculosis meningitis, ethambutol is replaced with streptomycin. This is followed by a 4-month continuous phase treatment involving isoniazid and rifampicin. The guideline further indicates, that in environments with high levels of isoniazid resistance and susceptibility testing of isoniazid is absent or results are delayed prior to commencement of the continuous phase, ethambutol is added to isoniazid and rifampicin (49).

Previously treated patients

With regards to previously treated patients, all patients are recommended to have DST as part of efforts towards early identification of MDR-TB (51). The results of the DST determine the individualised treatment regimen for each patient. Sputum from these patients is taken as specimen for culture and DST before or at the beginning of treatment for susceptibility tests on at least isoniazid and rifampicin (52). The initiation of DST prior to treatment depends on its availability in a country. DST may be available as rapid molecular testing which gives results within 1–2 days or conventional type which delivers results within weeks (liquid medium) or months (solid

Table 1 Classes of TB drugs (49,50)

Group	Drugs
First line drugs	Pyrazinamide
	Ethambutol
	Rifabutin
Second line drugs	Group A: fluoroquinolones
	Levofloxacin
	Moxifloxacin
	Gatifloxacin
	Group B: second-line injectable agents
	Amikacin
	Capreomycin
	Kanamycin
	Streptomycin
	Group C: other core second-line agents
	Ethionamide
	Prothionamide
	Cycloserine
	Terizidone
	Linezolid
	Clofazimine
	Group D: add-on agents (not part of the core MDR-TB regimen)
	D1 (pyrazinamide, ethambutol, high-dose isoniazid)
	D2 (bedaquiline delamanid)
	D3 (p-aminosalicylic acid imipenem-cilastatin meropenem amoxicillin-clavulanate, thioacetazone)

medium) (52,53). Thus countries whose laboratories are equipped with the rapid molecular test rely on the DST results before commencing treatment in previously treated patients. However in settings lacking rapid molecular tests and conventional DST is available, empirical regimens based on available drug resistance surveillance is started while awaiting DST results (49). This is initiated in order to render the patient less infectious to minimise the risk of transmission to contacts. The empirical treatment is usually based on the available drug resistant surveillance which usually depicts a high likelihood of MDR-TB for patients

with failed treatment and a low or medium chance of MDR-TB for patients returning after default or relapse (49). For patients who have failed treatment or those classified as high risk for MDR-TB, empirical treatment for MDR-TB is initiated and subsequently adjusted once DST is available. On the other hand, patients who have relapsed from treatment, defaulted or previously treated patients in countries with low or medium surveillance results for MDR-TB are retreated with first line drugs while awaiting DST results and regimen modified according to DST results when available (49). Retreatment regimen with first line drugs involves two months intensive phase with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. This is continued with one month of isoniazid, rifampicin, pyrazinamide and ethambutol. Additional five months treatment with isoniazid, rifampicin and ethambutol is continued after the one month. On the other hand, in countries where DST is not routinely available, patients are started on the MDR-TB empirical treatment as described above as a temporary measure (49). Following that, the NTP manager is recommended to make arrangements to have DST performed in other countries where DST is available. While this is initiated, the ultimate goal required of the NTP manager is to facilitate the establishment of an in-country DST laboratory. Countries requiring financial support in setting up the DST laboratory, financial assistance may be obtained from international organisations such as the Global Fund to fight AIDS, Tuberculosis and Malaria (49,54).

Drug-resistant (MDR-TB and XDR-TB) patients

These groups of patients are detected based on DST results and once results are available, treatment is tailored accordingly. As a guideline by WHO (49), four principles underline the design of MDR-TB treatment regimen. Firstly, the regimen should contain medicines with proven efficacy. Secondly, drugs of possible cross-resistance should be avoided. For example, cross-resistance is known to occur between rifampicin/rifabutin and amikacin/kanamycin (55). Thirdly, unsafe drugs are excluded. Drugs are classified as unsafe if the quality is unknown or results in severe allergic reactions such as deafness, renal failure and psychosis. Finally, drug selection is made from the five groupings of anti-tubercular drugs in a hierarchical manner. This leads to the choice of anti-tubercular drugs for drug-resistant patients. Anti-tubercular drugs for drug-resistant TB regimen have recently been regrouped by the WHO to optimise treatment success (*Table 1*) (50). Under the

new WHO recommendations, treatment regimen for drug resistant TB should include first line drug; pyrazinamide (except when there is reliable DST results for resistance to pyrazinamide) and four core second-line drugs to achieve a minimum of five effective drugs (50). The second line drugs are selected one each from Group A and Group B plus a minimum of two drugs from Group C. Additional drugs may be added from Groups D2 and D3 to make achieve a minimum of five drugs if previous selections to not meet the minimum number of five effective drugs. Additionally, high dose of isoniazid and/or ethambutol may be included to further strengthen the regimen. The duration of regimen may either be short term or long term. Short term treatment lasting between 9–12 months is recommended for drug resistant TB patients who have not been previously treated with second-line drugs or have not shown resistance to fluoroquinolones or the second-line injectables. On the contrary, longer regimen involving 18 months or more is recommended for MDRTB and XDRTB patients (50).

HIV and TB co-infections

The treatment of HIV and TB co-infection is hugely dependent on the joint effort between HIV/AIDS and TB programmes (56). Prior to treatment, HIV and TB counselling and testing are recommended for all contacts with the case (57). TB patients living with HIV and have not yet started the anti-retroviral therapy (ART) are initially given TB treatment which is followed by preventive therapy with co-trimoxazole and finally ART. Although co-trimoxazole has unclear activity pertaining to this condition, it is accepted based on clinical experience to prevent malaria and *Pneumocystis jirovecii* and also treat other bacterial infections present in HIV and TB co-infected patients (49). The ART is initiated as soon as possible following TB treatment initiation and usually within the first eight weeks of initiating the TB treatment irrespective of CD4 counts (58). However in HIV patients with significantly low CD4 count (<50 cells/mm³) without tuberculous meningitis, ART is initiated within two weeks. Conversely, for a patient who is already on ART and has been diagnosed TB, TB treatment should be initiated immediately with particular concerns of modifying treatment to cope with drug interactions and overlapping toxic effects (49).

Extra-pulmonary TB patients

Extra-pulmonary TB (EPTB) can affect any part of the body and particularly the lymph, pleura, bone and joints,

pericardia and the meninges (49). For patients in whom EPTB is suspected, HIV testing is recommended. This is because incidence rate of EPTB in HIV-positive patients remains high (59). The treatment regimen of EPTB is similar to that of pulmonary TB with the difference lying between the treatment duration for the intensive phase. For the management of EPTB of the bones and joints, intensive phase treatment is extended to 9 months while that of the meninges is extended to between 9–12 months (60). As mentioned earlier, for EPTB of the meninges, ethambutol is replaced with streptomycin. Additionally, for EPTB of the meninges and pericardia, adjuvant corticosteroid treatment is recommended except in suspected drug resistant cases (60). Surgery seldom plays a role in the management of EPTB except in few instances where it is required for diagnosis. It is usually required in very advanced stages of EPTB involving complications such as hydrocephalus, obstructive uropathy, constrictive pericarditis and TB of the spine (49). Drainage and incision have also been useful in EPTB resulting in large lymph nodes (60).

TB in special cases

Special cases of pregnancy and breast feeding, liver disease and renal failure are discussed in this section. Women of child bearing age are inquired of plans of pregnancy before TB regimen is initiated. TB treatment in a pregnant TB patient is a contributing factor to the success of the pregnancy. With the exception of streptomycin which causes ototoxicity in the growing foetus, all the first line drugs are safe to use in pregnancy (49). For breastfeeding mothers, it is advised that the baby continues breastfeeding and not separated from mother while the mother is administered full course of TB regimen. Upon ruling out active TB in baby, isoniazid preventive therapy of 6 months is given to the baby which is followed by Bacillus Calmette-Guérin (BCG) vaccination (61). In most instances, supplementation with pyridoxine is recommended when isoniazid is administered to both pregnant and breastfeeding mothers to prevent peripheral neuropathy (49,62). For patients with pre-existing liver disease, TB treatment regimen is guided by limiting the inclusion of hepatotoxic anti-tubercular drugs (63). With this in view, three TB regimen options have been recommended by WHO (49). The first option involves reducing the hepatotoxic drugs in the standard regimen from three to two. The first available choice under this option is 9 months of isoniazid and rifampicin. Ethambutol is added when DST results are unfavourable to isoniazid. A second choice involves 2 months treatment with isoniazid,

Table 2 Definitions of TB treatment outcomes (excludes patients treated for rifampicin-resistant or multidrug-resistant TB) (66)

Outcome measure	Definition
Cure	A patient with positive sputum smear and culture results at the start of treatment and becomes sputum smear and culture negative within the last month of treatment in addition to at least one previous occasion
Treatment completed	A patient who has completed treatment with no evidence of failure but there is no confirm that sputum smear or culture results in the last month of treatment and on at least one previous occasion was negative either because tests were not done or that results are not available
Treatment failed	A patient who remains sputum smear or culture positive 5 months or later into the treatment duration
Died	A patient who dies before commencing or during treatment from any possible cause
Lost to follow up	A patient whose treatment has been interrupted for two continuous months or more or who did not start treatment
Not evaluated	Any patient with no treatment outcome assigned including for instance cases transferred to other treatment units
Treatment success	A patient who has both completed treatment and is cured

rifampicin, streptomycin and ethambutol which is followed by 6 months continuous phase of isoniazid and rifampicin. The third choice also involves 6–9 months rifampicin, pyrazinamide and ethambutol. The second option is the use of one hepatotoxic drug with treatment regimen of 2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol. The third option is the total exclusion of hepatotoxic drugs involving 18–24 months of streptomycin, ethambutol and fluoroquinolone (49). Key monitoring parameter in pre-existing liver disease is the liver function tests throughout the duration of treatment (64). In special cases of renal failure or severe renal insufficiency, the recommended TB regimen is 2 months treatment with isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin coupled with dose adjustment based on the excretion pathway of the drug (49). Thus dose adjustment is not required for isoniazid and rifampicin as they undergo biliary excretion. However, dose adjustment is required for the renally excreted anti-tubercular drugs such as ethambutol and the metabolites of pyrazinamide. The dose is adjusted to three times a week per kilogram body weight (pyrazinamide; 25 mg/kg and ethambutol; 15 mg/kg) (60). Due to high risk of nephrotoxicity and ototoxicity, streptomycin is avoided in cases of renal failure and severe renal insufficiency. Nonetheless, if the use of streptomycin is inevitable, a recommended dose of 15 mg/kg to a maximum of 1 gram is administered at a dosing frequency

of 2–3 times a week (49).

Drug treatment monitoring, patient supervision and support

Monitoring treatment regimen is focused on tracking record of treatment response and taking appropriate actions, managing interruption of treatment, cohort evaluation of treatment outcomes and the detection and management of drug induced adverse reactions (49). Record of treatment response is achieved by performing sputum smear microscopy and culture at regular intervals and the regimen adjusted to suit the appropriate susceptibility pattern (58). Additionally, monthly measurement of patient's weight is recommended to inform weight depended dose adjustments (65). Treatment interruptions by defaulting patients or HIV co-infection are recorded and patients returning after default are tested again for drug susceptibility (49). Cohort evaluation of treatment outcomes (*Table 2*) helps in accessing the treatment success of a particular choice of regimen as well as the efficacy of the drugs involved. Adverse reactions are closely monitored by health personnel through observations and record of signs and symptoms (67). Patients are also briefed on likely symptoms of drug induced adverse effects to encourage reporting of their incidence. Cure is achieved for TB treatment as a result of a collective effort of the patient and TB programme staff. As such, patient supervision and

support through Directly Observed Treatment Short course (DOTS). Under DOTS, the TB programme staffs observe the intake of every dose on the treatment regimen ensuring the patient takes the right drug with the correct doses and at the appropriate intervals (68). DOTS also enhance communication between patient and staff which opens opportunities for further TB education, early identification of non-adherence and adverse reactions (49,68,69).

Conclusions

Tuberculosis remains one of the most deadly infectious diseases and has claimed millions of lives for many years. While significant progress has been made towards controlling the global burden of TB over the past decade, more efforts are still needed. Emerging issues such as multi drug-resistance threatens to revert the progress made regarding TB care and control. The knowledge base for TB remains a rapidly expanding area and global guidelines are continually being refined for instance to incorporate new anti-tubercular drugs to tackle issues of resistance. Health professionals, policy makers, patients and the general public need to keep up-to-date with current trends in TB management and control. This will be essential for efficient adoption of global guidelines to country-level situation, particularly taking into consideration issues such as disease burden, health system structures and available resources.

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Footnote

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