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Review Article

CLASSIFYING NEW ANTI-TUBERCULOSIS DRUGS AND MANAGEMENT OF ITS ADR AS PER WHO: A SHORT REVIEW

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ABSTRACT

The classification of new anti-tuberculosis (TB) drugs from World Health Organization (WHO) is important as it helps to aware and know current Newly introduced anti-TB Drugs for clinician and health workers to build an appropriate anti-TB regimen for drug susceptible (DS), multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases that do not fulfill the criteria for the shorter MDR-TB regimen. The World Health Organization (WHO) has recently approved a revision of the classification of new anti-TB drugs based on current evidence on each drug. In the previous WHO guidelines, the choice of drugs was based on efficacy and toxicity in a step-down manner, from group 1 first-line drugs and groups 2–5 second-line drugs, to group 5 drugs with potentially limited efficacy or limited clinical evidence. In the revised WHO classification, exclusively aimed at managing drug-resistant cases, medicines are again listed in hierarchical order from group A to group D. Treatment of drug susceptible tuberculosis (DS-TB) requires regimens containing first line drugs (FLDs') whereas drug resistant tuberculosis (DR-TB) are treated with regimens comprising combination of both second line drugs (SLDs') and few FLDs'. Adverse drug reactions (ADRs') to these anti-tubercular drugs are quite common as they are being used for longer duration. The occurrence of ADRs' may be influenced by multiple factors and may range from mild gastrointestinal disturbances to serious hepatotoxicity, ototoxicity, nephrotoxicity peripheral neuropathy, cutaneous ADRs', etc. Most of ADRs' are minor and can be managed without discontinuation of treatment. Some ADRs' can be major or severe causing life-threatening experience leading to either modification or discontinuation of regimen and even mortality if not recognized and treated promptly.

Key words: Anti-TB drugs, MDR/XDR-TB, Fluoroquinolones, Adverse drug reactions, Drug resistant, First line drugs, Second line drugs

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacteria Mycobacterium tuberculosis. Tuberculosis (TB) has been present in the human population since antiquity - fragments of the spinal column from Egyptian mummies from 2400 BCE show definite signs of tuberculosis [4].Tuberculosis (TB) is a disease caused by germs that are spread from person to person through the air. TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys, or the spine. Most infections show no symptoms, in which case it is known as latent tuberculosis. Around 10% of latent infections progress to active disease which, if left untreated, kill about half of those affected. Typical symptoms of active TB are chronic cough with blood containing mucus, fever, night sweats, and weight loss. Infection of other organs can cause a wide range of symptoms [5]. In 1834, Dr. Johann Schonlein named the disease tuberculosis. However, it was not until March 24, 1882, that Dr. Robert Koch discovered Mycobacterium tuberculosis, which is the bacterium that causes TB. [6]

Introduction of M tuberculosis into the lungs leads to infection of the respiratory system, medically termed as "Pulmonary Tuberculosis" wich is most common type of TB. But the bacterium can also affect other parts of your body besides the lungs, causing "extrapulmonary tuberculosis" (or TB outside of the lung). However, the organisms can spread to other organs, such as the lymphatics, pleura, bones/joints, or meninges, and cause extrapulmonary tuberculosis. [7]

At the beginning of the 19th century, there was a scientific debate about the exact etiology of tuberculosis. Many theories existed that time, describing the disease as an infectious disease, a hereditary disease, or a type of cancer. In 1882 a German physician and microbiologist, Robert Koch, successfully identified, isolated, and cultured the tubercle bacillus in animal serum. Afterward, he produced animal models of tuberculosis by inoculating the bacillus. In 1882, his groundbreaking work was published in the Society of Physiology in Berlin. In 1905, Koch won the Nobel Prize for Medicine and Physiology. During this time, TB killed one out of every seven people living in the United States and Europe. Dr. Koch's discovery was the most important step taken toward the control and elimination of this deadly disease. [8]

A century later, March 24 was designated World TB Day: a day to educate the public about the impact of TB around the world.

The World Health Organization (WHO) has previously updated the classification of new anti-tuberculosis (TB) drugs in 2011 and 2016 respectively, based on a meta-analysis and expert panel recommendations. [1] During the period between the publication of the first WHO anti-TB drug classification and the revised version, an independent proposal for a new classification was made available in the literature. [2] Evidence for further reclassification is lacking and will only be forthcoming with data from new randomized controlled trials (RCTs) aimed at developing better (more effective and tolerated) regimens. However, even though a new classification is not required, discussion on possible future steps has begun, [2] with particular focus on some of the existing second-line anti-TB drugs. [2]

The classification of anti-TB drugs is important as it helps the clinician to build an appropriate anti-TB regimen for multi drug resistant (MDR) and extensively drug-resistant (XDR) TB cases that do not fulfil the criteria for the shorter MDR-TB regimen. [9,10]

The management of MDR-TB patients has been considered to be complicated and challenging because of prolonged duration of 24-27months of treatment and high toxicity profile of SLDs'. The prevalence of ADRs' observed in various studies conducted worldwide ranged from 69% to 96%. [11,12]

Patients may experience a variety of ADRs' when managed with these anti-tubercular drugs. Treatment with these drugs can also be associated with adverse event which is defined as any untoward medical occurrence but not necessarily have a causal relationship. ADRs' to these agents are common and cause significant morbidity and even sometimes mortality if not detected early. [13,14] Most of ADRs' are minor and can be managed without discontinuation of treatment. Some can be serious or major causing life-threatening experience leading to either shorter or prolonged hospitalization, significant disability, congenital anomaly or even mortality if unrecognized and untreated promptly. Timing, the pattern of illness, the results of investigations, and re-challenge will help attribute causality to a suspected ADR. [15] Various factors such as the dose and time of day at which the medication is administered, patient age, nutritional status, the presence of pre-existing diseases or dysfunctions like impaired liver function, impaired kidney function, human immunodeficiency virus (HIV) co-infection, and alcoholism may be related to ADRs' to anti tubercular drugs. [16]

Classification:

For the better approach to eradicate Tuberculosis (TB) from all world The World Health Organization (WHO) has been given their recent updated guidelines for better treatment as well as the problems creates during its can easily solved by health workers in very efficient manner. The World Health Organization (WHO) has previously updated the classification of new anti-tuberculosis (TB) drugs in 2011 and 2016 respectively, based on a meta-analysis and expert panel recommendations. During the period between the publication of the first WHO anti-TB drug classification in 2011 and the revised version, an independent proposal for a new classification was made by WHO in 2016.

In the previous WHO guidelines (2011), the choice of drugs was based on efficacy and toxicity in a step-down manner, from group 1 to group 5 (Table 1). Group 1 included first-line drugs and groups 2–5 included second-line drugs. Group 5 included the drugs with (at the time) potentially limited efficacy or limited clinical evidence. [3,10]

According to the new WHO drug classification (2016), patients with rifampicin-resistant or MDR-TB require a regimen with at least five effective TB medicines during the intensive phase: pyrazinamide and four core second-line TB drugs (see Table 1), one each from group A and group B, and at least two from group C. If the minimum number of effective TB medicines cannot be composed, an agent from group D2 and other agents from D3 should be added to bring the total to five.[9]

(1) WHO 2011 TB drugs classification	(2) WHO 2016 TB drugs classification
Group 1 : First-line oral anti-TB drugs • **Isoniazid** • **Rifampicin** • **Ethambutol** • **Pyrazinamide**	**Group A : Fluoroquinolones** • **Levofloxacin** • **Moxifloxacin** • **Gatifloxacin**
Group 2 : Injectable anti-TB drugs (injectable or parenteral agents) • **Streptomycin** • **Kanamycin** • **Amikacin Capreomycin**	**Group B : Second-line injectable agents Amikacin** • **Capreomycin** • **Kanamycin** • **(Streptomycin)**
Group 3 : Fluoroquinolones • **Levofloxacin** • **Moxifloxacin** • **Gatifloxacin** • **Ofloxacin**	**Group C : Other core second-line agents** • **Ethionamide/ Prothionamide** • **Cycloserine/ terizidone** • **Linezolid** • **Clofazimine**
Group 4 : Oral bacteriostatic second-line anti-TB drugs • **Ethionamide/ prothionamide** • **Cycloserine/terizidone** • **p-Aminosalicylic acid**	**Group D : Add-on agents (not core MDR-TB regimen components)** • **D1 : Pyrazinamide, Ethambutol, High-dose isoniazid** • **D2 : Bedaquiline, Delamanid** • **D3 : p-Aminosalicylic acid, Imipenem–cilastatin, Meropenem, Amoxicillin–clavulanate, (Thioacetazone)**
Group 5 : Anti-TB drugs with limited data on efficacy and long-term safety in the treatment of drug-resistant TB (MDR-TB) • **Linezolid Delamanid** • **Bedaduiline Clofazimine** • **Amoxicillin-clavulanate Imipenem-cilastatin** • **Meropenem High-dose isoniazid** • **Thioacetazone Clarithromycin**	

2.1. Group 1:

In accordance with drug susceptibility testing (DST), all active group 1 drugs (Table 1) should be included in the regimen, taking into consideration that isoniazid, rifampicin/rifabutin, and pyrazinamide are core drugs and ethambutol is a companion drug. Streptomycin is no longer used routinely. High-dose isoniazid can be added to an MDR/XDR-TB regimen when the katG mutation is not detected by line probe assay, but should not be counted as one of the four active drugs.(although recent evidence suggests the mutation confers intermediate resistance only). Pyrazinamide should always be used, as DST is unreliable; however, it should not be counted as one of the four active drugs.1-3-10 Rifabutin should be considered if sensitivity is proven and a favorable mutation profile exists. More specifically, if rifampicin resistance is detected with rifabutin susceptibility, rifabutin should be added to the regimen, but not counted as one of the four active drugs. As the new WHO classification is aimed at managing drug resistant cases and not all cases, as in the previous classification, group 1 drugs lose priority. In the new WHO classification they belong, in fact, to group D1. [17]

2.2. Group 2:

The ex-group 2 included the injectable SLDs (having bactericidal (but not sterilizing) activity and a safety profile worse than fluoroquinolones (cumulative toxicity leading to deafness or kidney problems). They have been included in group B, which immediately follows fluoroquinolones (2) (Figure 1). The possibility to use streptomycin in exceptional cases to treat MDR-TB (especially in selected XDR-TB cases not using previously this drug and with drug susceptibility testing showing susceptibility) might deserve further discussion. [9, 10, 18]

2.3. Group A:

According to the new WHO classification,1 group A now includes fluoroquinolones and group B includes injectable second line drugs. Fluoroquinolones (particularly the later generation fluoroquinolones such as high-dose levofloxacin, gatifloxacin, or moxifloxacin) are core drugs, demonstrating bactericidal and sterilizing activity and a good safety profile.[9, 3, 18, 19] their use predicts a favorable outcome in the treatment of MDR-TB.[19],[20] They are the best agents for the treatment of MDR-TB.

2.3. Group B:

The second-line injectable drugs have only bactericidal and no sterilizing activity. As their safety profile is clearly worse than that of fluoroquinolones, they remain a step below them on the ranking.[9, 10, 18] Furthermore, the second group in the drug hierarchy (group B) may in future include three core oral medicines, linezolid, bedaquiline, and delamanid (and eventually sutezolid, tedizolid, and pretomanid), if these drugs prove to be more effective and better tolerated than the injectables. This has been proposed in a recent article as group 3 (similar to the current group B, because in this article group 1 is composed of first-line drugs).[9] Moreover, having an oral group B could mean that it may soon be possible to have an injectable-free regimen to treat MDR-TB patients; this will mean potentially less toxicity, less monitoring, and fewer hospital stays and visits, and possibly better adherence.

2.4. Group C:

Linezolid, clofazimine, ethionamide /prothionamide, and cycloserine / terizidone are included in group C. Linezolid is a core oral drug with bactericidal and sterilizing action. [24] there is ample evidence of its efficacy, including RCTs and meta-analyses.[21, 22] The drug is generic and active, its documented toxicity being the primary barrier to continued use. However, this can be mitigated with lower doses and therapeutic drug monitoring.[22, 23] Linezolid has the efficacy needed to be part of a future hypothetical all-oral group B. With effectiveness in mind, the second drug in this group could be ethionamide/prothionamide, which has moderate bactericidal activity but with an appreciable toxicity profile. [25] the third agent could be clofazimine, as this has possible sterilizing activity and good tolerance. The last one could be cycloserine, the worst of the four, with practically no bactericidal or sterilizing activity and with a poor toxicity profile.

2.5. Group D:

Group D1 includes pyrazinamide, ethambutol, and high-dose isoniazid. Group D2 includes bedaquiline and delamanid. These may have the efficacy needed to be part of a future hypothetical alloral group B, given that evidence on their safety is growing, although it is still incomplete. Data regarding their safe combination and whole treatment duration over the recommended 6 months are gradually emerging. Recent case reports show the safe and effective use of bedaquiline up to 18 months and the concomitant use of both group D2 drugs. Bedaquiline has all of the characteristics of a core drug, targeting both actively replicating and dormant bacilli. [26, 27, 28] RCTs provide some evidence on efficacy and safety. [29, 30] while additional experience derived from observational studies and compassionate use programs completes the current picture.[26, 31, 33] Concerns regarding the safety of bedaquiline arose from the unexplained higher number of deaths in the bedaquiline group in a licensing study.

The most common adverse reaction associated with bedaquiline is a QTc interval increase on electrocardiogram. [29, 30] An RCT with long-term follow-up to 120 weeks reported that bedaquiline was well tolerated and led to good outcomes. [31] The reporting of adverse events is crucial for recommendations on bedaquiline use.[34]therefore monitoring, active pharmacovigilance, and proper management of adverse reactions are foremost among the five criteria in place for the use of this agent. Finally, a possible issue is cross-resistance with clofazimine. [35]

2.6. Linezolid:

Linezolid is a core oral drug. Increasing evidence on its efficacy is accumulating, including meta-analyses and two RCTs, in addition to observational studies. Unfortunately, the current cost and the documented toxicity have been a barrier to its wider use. [36, 37] However, the cost of a generic, quality-assured compound is decreasing and a recent report suggests that tolerability can be increased lowering the initial dose or adjusting it during treatment [e.g., using therapeutic drug monitoring (TDM)]. [38, 39]

2.7. Delamanid and bedaquiline:

Delamanid can also be considered a core drug because of its bactericidal and sterilizing activity; it does not show cross resistance with other anti-TB drugs. Some RCTs and observational studies have addressed its efficacy, [40] and there are also some positive experiences from its compassionate use. WHO recommendations on delamanid use [41] include the same five implementation criteria as in the case of bedaquiline. [34] As mentioned above, a significant limitation of bedaquiline and delamanid use is that, so far, they can be utilized only for the first 6 months of treatment. When treating XDR-TB patients, these drugs are added to an optimized background regimen that often includes weak and poorly tolerated medications (from the limited options remaining), with severe side effects mandating interruption of either the whole treatment or of the offending compound. When this happens, the regimen becomes even weaker and, once bedaquiline or delamanid is completed after 6 months, the regimen is prone to fail. The possibility of maintaining bedaquiline and/or delamanid for the entire duration of treatment will be an important step forward, as well as their use in patients with MDR-TB patterns of resistance beyond XDR-TB [10], or the so-called pre-XDR-TB (e.g., TB sustained by strains resistant to either fluoroquinolones or second line injectables). [19, 26,27]

Management of adverse drug reactions:

Management of ADRs' associated with anti-tubercular drugs is considered to be an essential component in order to achieve adequate adherence leading to favorable outcome. DRTB patients with SLDs' requires special care as these drugs are more toxic. Principles of pharmacovigilance have been adopted by national TB control programmes all over the world. Pharmacovigilance is defined by the WHO as the “science and activities relating to the detection, assessment and prevention of ADRs or any other drug-related problem”. [42]

The objective is to improve patient care by assessing both risk and benefit received from the drug. Routine surveillance of ADRs' according to a framed protocol is an integral part of national programmes which should be performed by symptom based reporting followed by laboratory investigations at baseline and as when clinically indicated. Occult ADRs' should be detected timely by laboratory investigations in order to prevent unrecognized serious effects. Monitoring should be frequent and more intense particularly in high risk groups such as elderly, HIV or hepatitis coinfection, alcoholism, drug addiction, anemia, any preexisting illnesses, diabetes mellitus, hypoalbuminemia, malnutrition, chronic kidney disease, chronic liver disease, disseminated involvement, family history of frequent ADRs' or atopy/allergy and use of ancillary medications, antiretroviral therapy or medications for treating opportunistic infections with high probability of drug interactions. A grading system has been devised to assess severity of all types of ADRs' in order to maintain accuracy and consistency in surveillance. [43] This system includes five grades

Grade 1: Mild symptoms requiring only observation and no intervention;
Grade 2: Moderate symptoms requiring medical intervention such as ancillary drugs;
Grade 3: Severe symptoms with inability to carry social or functional activities requiring medical intervention or even hospitalization;
Grade 4: Life-threatening symptoms with inability to perform basic health care requiring medical intervention or hospitalization in order to prevent permanent impairment, disability or death and
Grade 5: Mortality associated with ADR(s). Concept of active TB drug-safety monitoring and management (aDSM) has been introduced by WHO to provide active surveillance for detection of major or severe ADRs' associated with novel DR-TB regimens and newer drugs by systematic clinical and laboratory assessment.[44] Drugs have to be re-introduced in DR-TB regimens in sequence according to WHO revised grouping in case

there is documented resistance or intolerance. Symptoms based approach to management of minor and major ADRs' to FLDs' are tabulated in Tables 2 and 3.

Table 2: Symptoms based approach to the management of minor ADRs' to first line anti-tubercular drugs not requiring stoppage of treatment.

Symptoms	Drug	Management
Abdominal pain, nausea Burning of the Feet	- Related to rifampicin - Related to isoniazid - Peripheral neuropathy	- Reassure the patients - Continue isoniazid, and give pyridoxine 50e100 mg daily - Large dose of pyridoxine, may - interfere the action of isoniazid
Drowsiness Gastrointestinal Upset	- Related to isoniazid - Any oral medications	- Reassure the patients - Reassure patients - Give drugs with less water - Give drugs over longer period of time (e.g. 20 minutes) - Give drugs with small amount of food
Joint pains	- Related to pyrazinamide	- If these measure fails, provide anti-emetic - Continue pyrazinamide - Use aspirin or nonsteroidal anti-inflammatory drugs
Red urine Women on rifampicin	- Related to rifampicin - **Rifampicin may reduce the effectiveness of oral** contraceptive pills	- Use intermittent directly observed treatment if possible - Reassure the patients - Alternative method of contraception should be provided

Table 3: Symptoms based approach to major ADRs' to first line anti-tubercular drugs requiring stoppage of treatment.

Symptoms	Drug	Management
Loss of hearing	- Related to streptomycin	- Otoscopy to rule out wax - Pure tone audiometry to be performed
Dizziness	- If true vertigo and nystagmus, related to streptomycin	- Stop streptomycin if no other explanation - Stop streptomycin - If just dizziness with no nystagmus, try dose
Generalized reactions including shock and purpura Jaundice/Hepatitis	- May be due to rifampicin, pyrazinamide and/or streptomycin, thiacetazone - May be due to drug induced hepatitis (Pyrazinamide/Rifampicin/Isoniazid) - Either liver enzymes more than 5 times of upper limit of normal or more than 3 times of upper limit of normal with symptoms of hepatitis or jaundice (bili- rubin >3 mg/dl)	- reduction for one week - If there is no improvement stop streptomycin - Stop all medications - Use different combination of drugs - Stop all anti-tubercular drugs until jaundice resolves and liver enzyme revert to baseline levels or < 2 times of upper limit of normal - Rule out other causes/pre-disposing factors - Re-introduce same regimen either, gradually or all at once - If hepatitis has been life-threatening and was not of viral origin it is safer to use regimen like streptomycin, ethambutol and fluoroquinolones and cycloserine if required
Moderate to severe skin rash Visual impairment Vomiting/confusion	- Related to all first line anti-tubercular drugs - Related to ethambutol - Suspect drug induced hepatitis	- Rifampicin should be re-introduced followed by isoniazid in increasing dosages under regular LFT monitoring - Pyrazinami- Continue isoniazid, and give pyridoxine 50 e100 mg daily.

	- **Large dose of pyridoxine, may interfere the action of iso- niazidde should not be necessarily re-introduced and regimen should be continued for atleast 9 months.** - **Stop all anti-tubercular drugs** - **Re-introduce drug one by one once the rash has subsided** - **Visual examination/ophthalmologist opinion** - **Stop ethambutol** - **Urgent liver function test** - **If liver enzyme test unavailable, stop all drugs and observe**

ADR management is crucial to improve treatment compliance of DR-TB patients. Majority of the side effects and ADR management is possible with a simple intervention, which can be easily executed even at peripheral level. Following drugs can be used for common side effects or ADR reported by patients. [45]

Table 4: Drugs used in management of adverse event

ADRs	Suggested drugs to manage the ADR
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate, domperidone
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.,), Proton pump inhibitors (omeprazole, lansoprazole, etc.,) Avoid antacids because they can decrease absorption of fluoroquinolone eg. alumnium hydroxide
Oral candidiasis (non-AIDS patient)	Fluconazole, clotrimazole lozenges, Nystatin suspension, itroconazole liquid
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Any hypnotic
Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal Effects), Buromazine, thioridazine
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B6)

Peripheral neuropathy	Amitriptyline
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, Promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine, diclofenac
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity Reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.,), inhaled corticosteroids (beclomethasone, etc.,), oral steroids(prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium, magnesium and calcium replacement therapy (oral and intravenous formulations)

The N/DDR-TBC Committee would be consulted to take decisions regarding reduction/termination of any drug. If any drug is withheld/ terminated due to ADR, it would be replaced with an appropriate substitute drug as per DR-TBC committee. Before starting treatment, the patient should be instructed in detail about potential adverse effects that could be produced by the prescribed drug regimen and if and when they occur, to notify a healthcare provider. Proper management of adverse effects begins with pretreatment patient education. Depending on the severity of ADRs, following actions may be indicated:[45]

- if adverse effect is mild and not serious, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option;
- Most adverse effects of a number of second-line drugs are dose-dependent. Reducing the dosage of the offending drug or terminating it is another method of managing adverse effects; and
- Psychosocial support is an important component of the management of adverse effects. This may be provided through patient education and motivation by treatment supporter, patient support groups like patients association/organization or through group discussions while in the hospital.

Conclusions:

The WHO has recently provided an important and useful evidence-based new classification of anti-TB drugs, which is the present roadmap allowing clinicians to correctly design safer and more effective MDR- and XDR-TB treatment regimens. As more evidence becomes available, further changes are likely to occur, particularly with the new drugs and some of the previous group 5 drugs. It is hoped that ongoing RCTs will soon provide the necessary information to further improve the clinical and programmatic approach to the management of MDR- and XDR-TB cases.

The treatment of TB can cause a variety of ADRs'. ADRs' of varying severity are common during treatment of DS-TB and DR-TB. Most ADRs' can be successfully managed on an outpatient basis through a community-based treatment program, even in a resource-limited setting. Concerns about severe ADRs' in the management of DR-TB patients are justified, however, they should not cause delays in the urgently needed rapid scale-up of SLDs'. ADRs' can be detected by clinical evidence in resource-limited settings. DR TB can be cured successfully with appropriate combination of drugs if ADRs' associated with them can be managed aggressively and timely. Newer and less toxic drugs are needed to treat DR-TB patients over large scale. Accurate diagnoses and knowledge of the pharmacological properties of the drugs involved will allow professionals to tailor their approach to each individual case in near future.

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