Pharmacotherapy for multidrug resistant tuberculosis

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ABSTRACT

The current global concern in the treatment of tuberculosis (TB) is the emergence of resistance to the two most potent drugs namely, isoniazid and rifampicin. Emergence of multidrug resistance tuberculosis (MDR-TB) is now a health problem faced by most of the developing countries as well as developed countries across the globe. MDR-TB is a man-made disease that is caused by improper treatment, inadequate drug supplies, and poor patient supervision. HIV infection and AIDS have been implicated as important cause for this. The review of a published literature suggests that the most powerful predictor of treatment of MDR-TB is a history of treatment of TB. Although the treatment is efficacious, there are also a number of adverse effects caused by drugs used in the treatment of MDR-TB.

Key words: Cycloserine, ethionamide, kanamycin, multidrug resistance tuberculosis, para-aminosalicylic acid

INTRODUCTION

Multidrug resistance tuberculosis (MDR-TB) is defined as resistance to isoniazid and rifampicin, with or without resistance to other anti-TB drugs.[1] The prevalence of MDR-TB is 1–3% in new cases and around 12% in retreatment cases.[2,3] MDR-TB differs from drug-resistant tuberculosis (TB), which is a case of TB resistant to one or more anti-TB drugs. Initiation of drug therapy in patients with MDR-TB requires an assessment of history of treatment as well as meticulous laboratory parameters to characterize the susceptibility of the specific strain. Irregular, incomplete, and inadequate treatment is the commonest means of acquiring drug resistant organisms. Poor compliance is also an important factor of acquisition of drug resistance. Anti-TB drugs are classified in Table 1. [1]

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Biological and molecular basis of resistance

Tubercular bacilli have spontaneous, predictable rates of chromosomally born mutations that confer resistance to antimicrobial agents. These mutations are unlinked; hence, resistance is usually not associated to an unrelated drug. That the mutations are not under linked is the cardinal

Table 1: Classification of anti-tuberculosis drugs

Groups	Drugs
Group 1: First-line oral anti-tuberculosis agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2: Injectable anti-tuberculosis agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Vincomycin (Vi)
Group 3: Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin, (Lfx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)
Group 4: Oral second-line anti-tuberculosis agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizidone (Trd); Para-aminosalicylic acid (PAS); Thioacetazone (Th)
Group 5: Agents with unclear role in treatment of drug-resistant tuberculosis	Clofazimine (Cfz), Linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); Thioacetazone (Thz); Imipenem/ cilastatin (Ipm/Cln); High dose isoniazid (high dose H); Clarithromycin (Clr)

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principle underlying chemotherapy of TB. This means that if mutations causing resistance to isoniazid occur in about 1 in 10^8 replication of bacteria, the probability of spontaneous mutation causing resistance to both isoniazid and rifampicin would be $10^8 \times 10^8 = 10^{16}$.

Acquired resistance is responsible for MDR-TB. In tuberculosis bacilli, resistance is by means of genetic mutations: (a) Codon 531 of the *rpoB* gene (rpoB531) is found to be the most frequent mutation associated with rifampicin resistance. (b) Codon 315 of the *katG* gene (katG315) is found to be the most frequent mutation associated with isoniazid resistance. (c) Six codons: rpoB531, rpoB526, rrs513, rpsL43, embB306, and katG315 are the main locations responsible for MDR-TB.

Treatment regimens

Treatment regimens [1] should contain at least four drugs with certain effectiveness. After confirmatory diagnosis of MDR-TB, patients can be treated with either standard MDR regimen or by individually tailored regimen which is based on the drug sensitivity test (DST). Any patient who does not respond to the treatment of Category first or third; any category second patient who remains smear positive at the end of fourth month treatment; contacts of MDR-TB cases will be identified as MDR-TB suspect. These will be tested by culture sensitivity and drug resistance tests. If a patient is confirmed as a non-MDR-TB case; continue Category second or Category first regimen but if MDR-TB is confirmed then Cat. fourth regimen should be started. Revised National Tuberculosis Control Programme (RNTCP) uses Category fourth regimen as the standard regimen for treatment of MDR-TB. Category fourth regimen includes: six drugs—four bactericidal: Ofloxacin (Ofx) or Levofloxacin (Lfx); Kanamycin; ethionamide; pyrazinamide and two bacteriostatic drugs: Ethambutol; cycloserine (Cs) during 6–9 months of the intensive phase (IP) and four drugs: ofloxacin (levofloxacin), ethionamide, ethambutol, and cycloserine during the 18 months of the continuation phase (CP). PAS is included in the regimen as a substitute if any drug among ofloxacin (Ofx) or levofloxacin (Lfx); kanamycin; ethionamide; pyrazinamide is not tolerated or any drug among two bacteriostatic drugs is not tolerated.

Duration of treatment

The treatment duration is divided into two phases: initial intensive phase (IP for 6 months and the continuation phase (CP) for 18 months. After 6 months of treatment, the patient reviewed and the treatment changed to CP if the fourth month culture result is negative (fourth month culture results are available at the end of the sixth month). If the 4-month culture result remains positive, the treatment is extended by 1 month duration. Extension of IP beyond 1 month will be decided on the results of sputum culture of fifth (available at the end of seventh month) and sixth months. The IP can be extended up to a maximum of 3 months duration based on culture results (i.e. maximum duration of IP is 9 months); after which the patient will be initiated on the CP irrespective of the culture result (either it is +ve or –ve). The duration for CP is 18 months. [1]

General guidelines to treat MDR-TB

(a) Use at least four drugs with certain effectiveness. (b) Do not use drugs for which there is a possibility of cross resistance. (c) Use drugs from group 1 to 4 in hierarchical basis of their potency and (d) eliminate drugs that are not safe, i.e. known severe allergy/high risk of severe adverse drug reactions (using two aminoglycosides drugs simultaneously). Preferably the standardized regimen as recommended in the national DOTS-Plus guidelines should be used: [6 or 9 kanamycin, ofloxacin, ethionamide, cycloserine, pyrazinamide, ethambutol/18 ofloxacin, ethionamide, cycloserine, ethambutol]. If the results of second line DST are available, an individualized regimen may be used in such patients after obtaining a detailed history of previous anti-TB treatment [Tables 2-5].

Role of immunomodulators in MDR-TB

Immunomodulators available are:

- Levamisole[8]

Table 2: Drugs, their chemical structure and mechanism of action[1,4-7]

Drugs	Chemical structure	Mechanism of action
Ofloxacin (Ofx)	Fluoroquinolone (bactericidal)	Inhibits bacterial DNA gyrase; inhibits protein synthesis
Kanamycin	Aminoglycoside (bactericidal)	By binding to 30s subunit; causes misreading of m-RNA and disturbances in initiation of protein synthesis
Ethambutol	A derivative of ethylenediamine, ethambutol, is active only against mycobacteria (bacteriostatic)	Inhibits arabinosyl transferase that mediates the polymerization of arabinose into arabinogalactan within the cell wall
Cycloserine	(4-amino-3-iso-oxazolidinone) Analogue of d-alanine (bacteriostatic)	Inhibits alanin ligase and alanine racemose; inhibits cell wall synthesis
Ethionamide	Introduced in 1956; like isoniazid and pyrazinamide, ethionamide is a derivative of isonicotinic acid. (bactericidal)	Interfere with mycobacterial cell wall synthesis
PAS	Tuberculostatic drug introduced in 1946; structurally related to PABA and sulfonamide	A folate synthesis antagonist
Pyrazinamide	Chemically similar to isoniazid; developed in 1952; weak tuberculocidal	More active intracellulary and in acidic medium; inhibits mycobacterial cell wall synthesis by interacting gene encoding fatty acid synthesis

Table 3: Pharmacokinetic properties of drugs used for treatment of MDR-TB[1,4-7]

Drug	Route of administration and absorption	Inhibitory concentration for M. TB	Plasma protien binding, tissue distribution, metabolism and $T_{½}$	Excretion	Dose
Ofloxacin (Ofx)	Oral; well absorbed; oral absorption is interfered by di/tri valent cations and antacids but not by food	<2 μg/ml	Widely distributed in tissues, average $T_{½}$ = 3 to 10 h	Largely as unchanged by the renal route	Bw < 45 kg = 600 mg; Bw > 45 kg = 800 mg [7.5–15 mg/kg]
Kanamycin	Intravenous; aminoglycosides are very poorly absorbed from whole GIT, almost entire oral dose is excreted in faeces	<1 μg/ml	Concentration-dependant killing; postantibiotic effect +ve; do not enter cells due to polarity	Renal route	Bw < 45 kg = 500 mg; Bw > 45 kg = 700 mg [15 mg/kg]
Ethionamide	Oral; well absorbed orally but poor GIT tolerance	2.5–10 μg/ml	Widely distributed throughout the body, including the CSF. $T_{1/2}$ = 2–3 h		BW < 45 kg to 500 mg BW > 45 kg to 750 mg [10–20 mg/kg]
Pyrazinamide	Oral; good absorption	20 μg/ml	Converted in pyrazinoic acid (active form of drug) by mycobacterial pyrazinaminidase; widely distributed throughout the body, including the CSF. $T_{½}$ = 8–11 h	Renal route	BW < 45 kg to 10 g BW > 45 kg to 12 g [20–30 mg/kg]
PAS	Oral; completely absorbed from GIT	1–5 μg/ml	Widely distributed in tissues and body fluids except CSF. Metabolizes by acetylation; short half-life (1 h)	80% of the dose is excreted in urine	BW < 45 kg–1250 mg BW > 45 kg1500 mg [150–200 mg/kg]
Cycloserine	Well absorbed after oral administration	15–20 μg/ml	widely distributed throughout body fluids, including the CSF	About 2/3 of dose as unchanged by the renal route	BW < 45 kg to 500 mg BW > 45 kg to 750 mg [10–20 mg/kg]
Ethambutol	Oral administration, 75–80% of a dose of ethambutol is absorbed		Widely distributed throughout the body except in the CSF, $T_{½}$ = 3–4 h	Renal route	BW < 45 kg to 800 mg BW > 45 kg to 1000 mg [15–20 mg/kg]

Table 4: Formulation and characteristics of anti-tubercular drugs available for MDR-TB[1,4-7]

Drugs	Formulation	Acceptability	Tolerance	Toxicity
Aminoglycosides Streptomycin; Amikacin; Kanamycin Capreomycin	Vial 0.75 and 1 g	Injection (painful)	Moderate to poor	Medium
Ethionamide and prothionamide	Tab; 250 mg	Good	Moderate	Medium
Fluoroquinolones Ofloxacin	Tab; 200 and 400 mg	Good	Good	Low
PAS	Tab; 500 mg Granules	Bad (bulk and taste)	Poor	Low
Cycloserine	Tab; 250 mg	Good	Moderate	High
Pyrazinamide	Tab; 500 and 750 mg, 1 g	Good	Moderate	Low
Ethambutol	Tab; 800 mg	Good	Good	Low

Table 5: Common adverse reactions encountered to drugs used in MDR-TB treatment[1,4-7]

Drugs	Common ADRs
Cycloserine	Peripheral neuropathy; CNS depression and psychotic reactions
Pyrazinamide	Hepatotoxicity (1–5%); nausea; vomiting; drug fever; hyperuricemia; acute gouty arthritis; non-gouty polyarthralgia; transient morbilliform rash; dermatitis
PAS	GIT symptoms; peptic ulceration and hemmorrhage; hypersensitivity reactions; skin rashes; hypokalemia; liver dysfunctions; hypothyroidism and goitre on prolonged administration
Ethambutol	Visual disturbances
Ethionamide	Intense GIT irritation; hypothyroidism with goitre on long duration treatment; liver dysfunctions; peripheral neuropathy; psychiatric symptoms; gynecomastia; menstrual disturbances; impotence; acne; headache
Fluoroquinolones	GIT disturbances, dizziness and convulsions; tendinitis and tendon rupture; arthralgia; rashes; dizziness; hypersensitivity; increase in SGPT and SGOT level, serum creatinine; photoxicity and photosensitivity (sparfloxacin); cardiotoxicity
Kanamycin (aminoglycosides)	Nephrotoxicity; ototoxicity; vertigo; hypocalcemia; hypomagnesemia, hypokalemia; local pain and induration

- Cytokines/leukotrienes[9]
- Mycobacterium vaccae vaccine:[10] It works by redirecting host cellular response from a Th-2 dominant to a Th-1 dominant pathway.
- Thalidomide:[11] This drug act by inhibiting proinflamatory cytokines IL-12 (interleukin-12)
- Interleukin-2:[12] IL-2 stimulates expansion and enhanced functional capacity of natural killer cells, which can eliminate intracellular M. TB
- Immunoglobulins—IgG
  - Polyclonal
  - Monoclonal
- Herbomineral drugs—Reimun
- Donor lymphocyte infusion
- Synergic bone marrow transplant

These immunomodulators are useful in preventing infections to proceed to the disease state; preventing the occurrence of secondary infections; achieving early control of infections in conjunction with specific chemotherapy; achieve early clinical response in terms of weight gain and reduction in toxemia. *Aerosolized IFN-γ* two million international units inhalation therapy; three times a week for 6 months plus Class I anti-tuberculous chemotherapy.[13] Isofon proved effective for MDR-TB but having a significant number of adverse effects.[14]

New alternative therapies for MDR TB

Some other drugs with initial promising results

- β-Lactam antibiotics and β-lactamase inhibitors.[16]
- Linezolid (Lzd)[17]
- Phenothiazines:[18,19] Thioridazine, chlorpromazine; 3,5-disubsituted thiadiazine thiones.
- Antimalarial agents: Ethyl-5-phenyl-6-oxa-1-azabicyclohexane-2-carbopxylate derivative.[20]
- Nitric oxide donors: DETA-NO[21]
- Plant extracts: the hexane extract from Lantana hispida.[22]
- Snake venom: Small peptide vgf-1 from Naja-atra, a snake isolated from the Yunnan province of China.[23]
- Azoles: Having Cyp-450 inhibiting activity.[24]
- Tuberactinomycin: Tuberactinomycin resembles viomycin structurally as well as in its mode of action. It acts by inhibiting protein synthesis[25]
- Riminophenazines: B 746, B 4157, and Clofazimine (Cfz): Cfz is a substituted iminophenazine bright-red dye that inhibits mycobacterial growth and binds preferentially to mycobacterial DNA causing inhibition of transcription [Tables 6 and 7].[26]

Monitoring the MDR-TB

Close monitoring of MDR-TB patients is essential. Sputum smear and culture should be performed monthly until smear and culture conversion. (*Conversion is defined as two consecutive negative smear and culture taken 30 days apart.) After conversion, the minimum frequency recommended for bacteriological monitoring is monthly for smears and quarterly for cultures. Monitoring of MDR-TB patients by a clinician should be at least monthly until sputum conversion, then every 2–3 months. Each patient's weight should be monitored monthly. Timely and intensive monitoring and management of adverse effects caused by second-line drugs are essential for MDR-TB treatment.

Table 6: Some other promising anti-tubercular drugs in various stages of development[15]

Potential drug	Active or pro-drug	Description	Cellular process inhibited
PA-824	Pro-drug	Nitroimidazo-oxazine	Mycolic acid synthesis
OPC-67683	Pro-drug	Nitroimidazo-oxazine	Mycolic acid synthesis
R207910	Active	Diarylquinoline	ATP synthesis
SQ109	Active	Ethylenediamine derivative	Lipid/cell wall synthesis
Compound 5	Pro-drug	Quinoxaline-oxide derivative	Unidentified
Compound 7g	Unknown	Quinoxaline-oxide derivative	Unidentified

Table 7: Potential regimens for the treatment of patients with MDR-TB and XDR-TB[15]

Different patterns of resistance to anti-TB drugs	Appropriate therapy regimens	Total duration of treatment, months	Desirable number of active drugs for favorable outcome
INH, RIF	PZA, EMB, FQ, INJ SLD	18–24	5–6
INH, RIF, EMB	PZA, FQ, INJ SLD	18–24	5–6
INH, RIF, PZA	EMB, FQ, INJ SLD	24	5–7
INH, RIF, PZA, EMB	FQ, INJ + SLD	24	5–7
INH, RIF, PZA, EMB, FQ	INJ* + SLD + TLD	>24	5–7
INH, RIF, PZA, EMB, INJ	FQ + INJ*+ SLD + TLD	>24	5–7
INH, RIF, PZA, EMB, FQ, INJ	INJ* + SLD + TLD	>24	5–7

INH: Isoniazid; RIF: Rifampicin, PZA: Pyrazinamide, EMB: Ethambutol, SM: Streptomycin, FQ: Flouroquinolone - ciprofloxacin or ofloxacin or levofloxacin or moxifloxacin or gatifloxacin, INJ: Injectable agents such as streptomycin or kanamycin or amikacin or capreomycin or viomycin, SLD: Second-line drugs such as rifabutin, ethionamide, prothionamide, para-amino salicylic acid, d-cycloserine and thiacetazone,TLD: Third-line drugs such as, CLR: Clarithromycin, AMX-CLA: amoxicillin b-lactam antibiotic with clavulanate β-lacatamase inhibitor, CFZ: clofazimine and LZD: linezolid.; *Capreomycin or viomycin may be used for kanamycin or amikacin or vice versa if no cross-resistance is observed.

Management of adverse reactions[1,4-7]

Liver disease

Causative drugs may be Isoniazid, Pyrazinamide and Ethionamide. However because of effectiveness of these drugs (particularly INH and RIF), they should be used even in the presence of existing liver disease. If there is clinical sign/symptoms then evaluate patients; if icterus is present then antitubercular drugs will be withheld; review patients for liver functions tests. If liver functions tests return to normal then treatment will be resumed. Patients should be reviewed at weekly intervals.

Arthralgia

Causative drugs can be: pyrazinamide or quinolones. Management is to initiate therapy with paracetamol or aspirin; if no improvement occurs, then a NSAID will be prescribed and the S. uric acid level should be monitored. If no improvement or worsening of arthralgia then either reduce the doses of offending drugs or withhold temporarily.

Hypersensitivity reactions

Hypersensitivity reactions are usually manageable with antihistaminics; if severe reactions not respond to antihistaminics then offending drug identified by challenge/dechallange tests. If there is generalized erythematous rash associated with fever and or mucous membrane involvement, then withhold all drugs immediately.

GIT disturbances

GIT complaints are common within first few weeks of therapy. Causative drugs can be ethionamide, *para*-amino salicylic acid, PZA, and ethambutol. In the presence of GI symptoms, patient's serum bilirubin and serum aminotransferases levels (AST, ALT) should be measured. If serum aminotransferase levels are less than three times the upper limits of normal then these are not assumed due to hepatic cause. Advise the patients to take drugs embedded in banana. If vomiting persists then either domperidone or proton pump inhibitor is given 1 h before administration of drugs. Antacids interfere with absorption of fluoroquinolones so should be avoided. If severe vomiting is there, then drugs can be withheld temporarily. Other causes of vomiting as hepatitis/GERD/gastric causes should be ruled out.

Hypothyroidism

PAS and ethionamide alone or both in combination can cause hypothyroidism on prolonged duration. Drug-induced hypothyroidism can occur several months after the beginning of treatment. Drug-induced hypothyroidism may or may not be associated with goitre and can be virtually asymptomatic. Systematic monitoring of patients and their biochemical tests monitoring are mandatory. Hypothyroidism responds to thyroxine. Clinically and biochemical levels returned to normal after administration of thyroxine.

Seizures

Offending drugs can be: cycloserine, pyrazinamide, fluoroquinolones. Seizures that present for the first-time during anti-TB therapy likely to be the result of an adverse effect of one of the anti-TB drugs. Temporary withdrawal of the suspected agent and initiate anticonvulsant therapy (e.g., phenytoin, valproic acid). The dose of pyridoxine is increased to maximum daily dose (200 mg/day). If the suspected agent is essential to the regimen, then reinitiate suspected agent at lower doses. The suspected agent to be discontinued if this can be done without compromising regimen.

Psychotic symptoms

Offending drugs are: Ethionamide/prothionamide, Cycloserine, Isoniazid, and fluoroquinolones. Stop suspected agent for a short-period of time. Some patients will need to continue antipsychotic while psychotic symptoms are brought under control.

Peripheral neuropathy

Offending drugs are: Cycloserine, INH, Streptomycin, Kanamycin, Amikacin, Clarithromycin, Viomycin, and Fluoroquinolones.

Dose of pyridoxine should be increased to maximum daily dose (200 mg per day) and all injectable should be changed to capreomycin. Therapy with tricyclic antidepressants such as amitriptyline and nonsteroidal anti-inflammatory drugs or acetaminophen may help in alleviating the symptoms. Reduce the dose of the suspected agent, if this can be done without compromising the regimen or discontinue the suspected agent if this can be done without the compromising regimen.

Renal toxicity

Offending agents can be: Streptomycin, Kanamycin, Amikacin, Capreomycin, and Viomycin. Special dosing guidelines for adult patients with renal insufficiency and end-stage renal disease are given [Table 8].[7]

Management of MDR-TB in pregnancy

Pregnancy is not a contraindication for treatment of MDR-TB. Discuss the risk/benefits to the patient. Treatment is started in second/third trimester unless life threatening. Aminoglycosides are avoided until delivery. The main aim is to achieve sputum conversion before delivery. Injectable agents are also avoided, capreomycin is used if it is necessary to administer injectable agent. Avoid Eto because it is teratogenic. Cycloserine: There are limited data on the safety in pregnancy, only indication to be used in pregnancy that there are no alternatives are available.

Breast feeding

Encourage the breast feeding if sputum microscopy is negative. Chemotherapy is the best way to prevent transmission of tubercle bacilli to baby. Most anti-TB drugs are excreted and

Table 8: Recommended doses and frequency for patients with creatinine clearance <30 ml/mn or for patients receiving hemodialysis

Drug	Change in frequency	Recommended doses and frequency for patients with creatinine clearance <30 ml/mn or for patients receiving hemodialysis
Isoniazid	No change	300 mg OD or 900 mg three times per week
Rifampicin	No change	600 mg OD, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Levofloxacin	Yes	750–1000 mg per dose three times per week (not daily)
Cycloserine	Yes	250 mg OD or 500 mg/dose three times per week (careful monitoring of evidence of neurotoxicity)
Ethionamide	No change	250–500 mg/dose daily
Para-amino salicylic acid	No change	4 g/dose b.d.
Streptomycin	Yes	12–15 mg/kg per dose 2 or 3 times per week (not daily)
Capreomycin	Yes	12–15 mg/kg per dose 2 or 3 times per week (not daily)
Kanamycin	Yes	12–15 mg/kg per dose 2 or 3 times per week (not daily)
Amikacin	Yes	12–15 mg/kg per dose 2 or 3 times per week (not daily)

found in the breast milk. It is recommended to provide infant formula options.

Diabetes mellitus

Diabetes mellitus may potentiate the adverse effects of drugs, renal dysfunction, and peripheral neuropathy. Use of Eto or protionamide may make it more difficult to control insulin levels.

Substance dependence

Encourage the patients of TB for complete abstinence from alcohol or other substances If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until successful completion of treatment Cycloserine has higher incidence of adverse effects in patients dependent on alcohol or other substances, including a higher incidence of seizures.

HIV/MDR TB/Drug interactions

Nonenteric-coated didanosine contains an aluminum/magnesium-based antacid. When this given along with fluoroquinolones, it results in decreased absorption of fluoroquinolone. It should therefore be given 6 h before or 2 h after fluoroquinolone administration.

CONCLUSION

The current MDR-TB epidemic is the result of ignorance for an important infectious disease, lack of resources for TB control programs, poor case detection, and inadequate/inappropriate therapy. Optimization of treatment regimens along with rapid diagnosis and DST for first- and second-line drugs, greatly improved the clinical outcome. Recent advances in diagnosis of MDR-TB and empirical treatment of patients with several drugs in the initial phase of treatment have further improved the prognosis of MDR-TB. The new anti-TB drugs that are in various stages of development also offer hope that we will not soon run out of treatment options against TB and MDR-TB. This review has summarized the drugs used to treat MDR-TB, common adverse drug reactions occurring during MDR-TB treatment and their management and has highlighted the importance of preventing the development and dissemination of this man-made disease.

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