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Adverse Drug Reactions with First-Line and Second-Line Drugs in Treatment of Tuberculosis

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Abstract

Drug-susceptible tuberculosis (DS-TB) requires treatment with first-line drugs (FLDs) whereas drug-resistant TB (DR-TB) are treated with combination of second-line drugs (SLDs) and fewer FLDs. Adverse drug reactions (ADRs) to these drugs are quite evident as they are being used for longer duration. The overall prevalence of ADRs with FLDs and SLDs are estimated to vary from 8.0 to 85 and 69 to 96%, respectively. Most ADRs are observed in the intensive phase as compared to continuation phase. Major concerns exist regarding treatment of DR-TB patients, especially with SLDs having lower efficacy more toxicity and high cost as compared to FLDs. A variety of ADRs may be produced by anti-TB drugs ranging from mild or minor to severe or major like gastrointestinal toxicity (nausea/vomiting, diarrhoea, and hepatotoxicity), ototoxicity, neurotoxicity (peripheral neuropathy and seizures), nephrotoxicity, cutaneous toxicity, and cardiotoxicity. Most of ADRs are minor and can be managed without discontinuation of treatment. Few ADRs' can be major causing life-threatening experience leading to either modification or discontinuation of regimen and even mortality. A careful monitoring of ADRs during the treatment with anti-TB drugs and early recognition and appropriate management of these ADRs might improve adherence leading to favorable outcome.

Keywords
- tuberculosis
- adverse drug reactions
- drug-resistant TB
- drug-sensitive TB
- first-line drugs
- second-line drugs
- anti-TB drugs

Introduction

India features among the 30 high-tuberculosis (TB) burden countries and has accounted for an estimated one-quarter (27%) of all TB cases worldwide.[1] Drug-susceptible TB (DS-TB) is treated with regimens containing multiple first-line drugs (FLDs') such as isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E), whereas second-line drugs (SLDs') and few FLDs' are reserved for treatment of drug-resistant TB (DR-TB). Good bacteriological diagnosis and compliance to treatment remains two main pillars of successful treatment of TB. An adverse drug reaction (ADR) has been defined as "a response to a drug which is noxious and unintended and which occurs at doses normally used in human for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[2] Patients may encounter with a variety of ADRs' when managed with anti-TB drugs. ADRs cause significant morbidity and even sometimes mortality if not detected early.[3-5] Major concerns exist regarding treatment of DR-TB patients, especially with

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SLDs having lower efficacy, costly and more toxic as compared to FLDs. Most of ADRs are mild or minor and can be managed without discontinuation of treatment. Few ADRs can be severe or major causing life-threatening experience leading to discontinuation or modification of treatment that may require hospitalization and even mortality if unrecognized and untreated promptly. Various factors, such as timing of occurrence of ADR, pattern of illness, results of laboratory tests, rechalle.g., with type, dosing or timing of drugs administration, patient age, nutritional status, the presence of preexisting diseases, or dysfunctions (such as impaired liver function, impaired kidney function, human immunodeficiency virus (HIV) coinfection, and alcoholism), might be attributed to causality of ADRs.[6] Therefore, continued surveillance of ADRs is essential particularly in DR-TB cases where early detection and timely management of ADRs might determine successful outcome. This review aims to highlight the estimated burden and management strategies of various ADRs associated with anti-TB drugs among patients undergoing treatment of TB.

Epidemiology of Adverse Drug Reactions with First-Line Anti-TB Drugs

The data on global prevalence of ADRs with FLDs is scarce. The global prevalence of ADRs is variable ranging from 8 to 85%.[3,7-13] The reasons for the difference in the prevalence of ADRs might be related to several possible factors, such as differences in definitions of ADRs terminologies, as adopted by physicians, whether the ADRs were reported by patient (subjective) or detected by clinician (objective) on the basis of clinical evidence along with feasibility of monitoring with serial laboratory investigations, whether all or only the major ADRs were studied, associated comorbidities, such as diabetes and HIV coinfection and variations in the use of specific anti-TB drugs including dosage, and also pharmacological interactions with other group of drugs comprising antiretroviral therapy (ART), oral hypoglycemic agents, and also ancillary medications used for management of ADRs. A study conducted in Nigeria observed that around 14 and 13% incidences of ADRs at 6 and 8 months, respectively. among patients receiving directly observed treatment and short-course (DOTS).[10] Brazilian National Ministry of Health reported the incidence of minor or mild ADRs in patients treated with the former FLDs to range from 5 to 20%.[11] It was also observed that major or severe ADRs' were less common (occurring in approximately 2% of the cases, reaching 8% in specialized clinics) and led to the discontinuation or alteration of the treatment. There were no difference in incidence of ADRs among patients having intermittent and daily intake of anti-TB drugs.[14] ADRs were more prevalent in intensive phase than continuation phase. The overall prevalence of ADRs with FLDs is estimated to vary from 2.3 to 17% in various Indian studies.[7,15-17] A study conducted by Mehrotra observed that the prevalence of ADRs in the initial intensive phase was 17.39%.[15] Another study conducted at a tertiary institute in Calcutta observed that the overall toxicity was found in 35% cases in the daily regimen group, whereas it was found to be 27.9% in the intermittent regimen group.[18] Data regarding prevalence of ADRs are still scarce and further surveys are required from different geographical areas of India in near future.

Epidemiology of ADRs Treated with Second-Line Anti-TB Drugs

The management of multidrug resistant (MDR)-TB patients has been considered to be complicated and challenging because of prolonged duration of 24 to 27 months of treatment and high-toxicity profile of SLDs. The prevalence of ADRs observed in various studies conducted worldwide ranged from 69 to 96%.[19-23] Reasons for the difference in the prevalence of ADRs are almost similar to that of FLDs except the fact that regimens for DR-TB contains repurposed drugs like linezolid (Lzd) and clofazimine (Cfz), as well as newer drugs such as bedaquiline (Bdq) and delamanid (Dlm). The observed frequency of specific gastrointestinal (GI) ADRs (0.5–100%) followed by ototoxicity (12–70%) among patients receiving SLDs. Tinnitus has been reported in 5 to 45% of patients whereas deafness in 6.7 to 33% patients. Ototoxicity is predominantly associated with the use of injectable aminoglycosides such as kanamycin (Km). There is possibility of additive effects of interaction with other concomitant and potentially ototoxic drugs that were used in the regimen such as ofloxacin (Ofx) and cycloserine (Cs). This warrants further investigation to uncover the possibility of these interactive effects. SLDs have reported to cause severe ADRs that have led to interruption of treatment in 19 to 60% of MDR-TB patients.[19-23] The estimated high prevalence was due to early identification and aggressive management strategies adopted by national health programs. A study from Iran reported deafness and headache/psychosis occurring due to injectable Km and Cs, respectively, as major ADRs that required frequent discontinuation and/or substitution.[23] MDR-TB patients should be managed aggressively for ADRs during therapy, especially for ototoxicity and psychiatric disorders. Very few have specifically reported frequency of ADRs in India.[19,24-28] A study conducted in Tamil Nadu reported ADRs associated with standardized treatment in 86.8% patients.[25] Severe ADRs' requiring either a reduction of dosage or termination of the offending drug(s), such as ethionamide (Eto), Ofx, Km, and Cs were observed in 58% patients. Higher incidence of ADRs associated with SLDs has been reported in HIV patients with MDR-TB coinfection. A study conducted in Mumbai among 67 HIV and MDR-TB coinfected patients treated with anti-TB treatment, as well as ART, and reported that ADRs were more frequent in this cohort with 71, 63, and 40% of patients experiencing one or more mild, moderate, or severe ADRs, respectively.[26] ADRs, such as GI disturbances (45%), peripheral neuropathy (38%), hypothyroidism (32%), psychiatric symptoms (29%), and hypokalemia (23%) were reported more frequently among this cohort. Eleven patients required hospitalization and permanent discontinuation of one or more offending drugs that were observed in 40% patients. No ADRs led to indefinite suspension of an entire MDR-TB or ART regimen. A study reported 46.9% of

98 MDR-TB patients experiencing at least one ADRs.[28] ADRs observed most frequently were nausea/vomiting in 24 (24.5%) patients, hearing disturbances in 12 (12.3%) patients, dizziness/vertigo in 10 (10.2%) patients, and arthralgia in 9 (9.2%) patients. Seventeen (17.4%) patients had major ADRs requiring change or stoppage of drugs that included ototoxicity (6.1%), headache and psychosis (4.1%), GI intolerance and hypothyroidism (3.1%), as well as arthralgia and hepatitis (4.1%).[28] Agents responsible for these ADRs were Km (ototoxicity), Cs (headache/psychosis), Eto (GI tolerance/hypothyroidism), and Z (arthralgia/hepatitis). However, no mortality was observed due to occurrence of ADRs. Further studies are required for prevalence of ADRs' in near future.

Specific Adverse Drug Reactions Associated with Anti-TB Drugs

Nausea/Vomiting

GI symptoms are one of the most common ADRs seen with intake of anti-TB drugs. Its severity can range from mild symptoms like nausea and vomiting to life-threatening complications. All the FLDs can cause mild GI upsets that can be managed symptomatically without change in dosage of drugs. In a study of 893 patients by Shinde et al, it was found that GI upset with nausea, vomiting, and abdominal pain were the most common ADRs seen in 12.5% of patients.[29] In another prospective study from China, it was found that GI ADRs were seen in 3.74% of 4,304 patients and only 7 patients required hospital admissions.[30]

Hepatotoxicity

The clinical presentation of anti-TB drug associated hepatitis is similar to that of acute viral hepatitis. Anti-TB drug-induced hepatotoxicity can manifest as transitory asymptomatic rise in transaminases or acute liver failure. The frequency of hepatotoxicity ranges from 2 to 39% in different countries.[31] An increased incidence of hepatotoxicity has been observed in Indian subpopulation when compared to Western population.[32,33] The occurrence of drug-induced hepatotoxicity is unpredictable though certain patients are at a relatively higher risk than other populations. The incidence has been reported to be higher in developing countries and factors, such as advanced age, acute or chronic liver disease, alcoholism, HIV, indiscriminate use of drugs, malnutrition, hypoproteinemia, hypoalbuminemia, anemia, and prior history of jaundice, and more advanced TB has been implicated.[34,35] Isolated H administration resulted in a three-fold increase in alanine aminotransferase levels over the normal in 10 to 20% of these patients.[33,36] Transitory and asymptomatic increases in the serum levels of bilirubin and hepatic enzymes occurred in 5% of patients with R. When H was used in combination with R, the incidence of hepatitis was observed to be 2.7%. Cholestatic hepatitis occurred in 2.7% of the patients receiving R in combination with H and was 1.1% when R was received in combination with anti-TB drugs other than H.[33] Z is the most hepatotoxic drug with toxicity being either dose-dependent or idiosyncratic.[37,38] Hepatotoxicity has also been reported with SLDs but with lesser frequency as compared to FLDs. The incidence of hepatotoxicity is 2 to 3% with fluoroquinolones (FQs) with fulminant involvement <1%, whereas it is 1 to 2% with Eto/prothionamide (Pto) and 0.3% with para-amino salicylic (PAS) acid.[39,40] Hepatitis has been rarely reported with Lzd, Cfz, and newer drugs such as Bdq and Dlm.[41]

Peripheral Neuropathy

Peripheral neuropathy occurs in approximately 20% of patients treated with H.[42] The other anti-TB drug known to cause peripheral neuropathy is E, but very rare in comparison to H. In the existing literatures also, occurrence of peripheral neuropathy is considered rare with the recommended doses of H used in DOTS strategy. Peripheral neuropathy has also been associated with Lzd, Eto, Cs, and rarely FQs.[43]

Psychiatric Disorders

H-related psychiatric disorders can manifest as psychosis, obsessive-compulsive neurosis, seizure, mania, loss of memory, and death.[44] The mechanism of production of H-related psychiatric disorders is not clearly known, but H is known to interfere with several metabolic processes essential for the normal functioning of the neuron. H causes deficiency of vitamin B6 by causing excessive excretion of the vitamin, which in turn leads to a disturbance of normal tryptophan metabolism. There is great variability in the clinical features of H-induced psychosis in the various reported cases. Jackson, in 1957, reported five cases of H-induced psychosis that presented with excessive argumentation, mental depression, euphoria, grandiose ideas, and complex delusions; none of these patients had any previous history of mental illness.[45] Cs has been associated with diverse neuropsychiatric ADRs most common being psychosis reported in >10% patients. Other ADRs, such as anxiety, headaches, and seizures, were reported in 1 to 10% of patients and insomnia, suicidal ideation in <1% of patients. Eto has reported to cause giddiness and headache in 1 to 10% of patients and rarely mental disturbances in <1% of patients. FQs has reported to cause dizziness, headaches, and insomnia in 1 to 10%, whereas it can cause or lower threshold for seizures in <1% patients.[46]

Optic/Retrobulbar Neuritis

E is one of the important FLDs in the treatment of TB. Retrobulbar neuritis is the most important potential ADR from E. It is reversible in most cases and is related to the dose and duration of treatment, but may occasionally become irreversible resulting in permanent visual disability, especially in the older population.[47] The reported incidence of retrobulbar neuritis when E is taken for more than 2 months is 18% in patients receiving greater than 35 mg/kg/day, 5 to 6% with 25 mg/kg/day, and <1% with 15 mg/kg/day.[48] Optic neuritis is observed rarely with H and SLDs such as Lzd and capreomycin (Cm).[49,50] Lzd induced optic neuritis is usually irreversible.

Ototoxicity

Streptomycin (S) predominantly affects the vestibular system, whereas Km and Cm affects predominantly cochlear

apparatus. Audiometry data suggest that the incidence of S associated ototoxicity may be as high as 25%.[51] In a large Indian study with short course chemotherapy regimes in the treatment of patients with pulmonary TB, 16.1% of the patients given S developed vertigo which was severe in 5% cases.[52] In 10% of these patients, the drug had to be stopped. Reduction of dosage was needed in about 20% cases. Ototoxicity was observed in 10.12% patients within 3.8 ± 2.6 months of treatment initiation with or without audiometry assessment.[53] High prevalence of ototoxicity (27.01%) was reported in Indian patients with DR-TB treated with injectable drugs when ototoxicity was monitored regularly using pure tone audiometry.

Immunological and Hematological Adverse Drug Reactions

R has been associated with immune mediated thrombocytopenic purpura and hemolytic anemia, especially with intermittent dosing. In a Brazilian study, R-induced thrombocytopenia, leukopenia, eosinophilia, hemolytic anemia, agranulocytosis, vasculitis, acute interstitial nephritis, and septic shock occurred in 0.1% of the patients.[33,54] However, a few Asian studies reported allergic reactions with FLDs to be between 2.02 and 2.35% and hematological ADRs to be 0.1 to 0.7%. Author in his work on hematological abnormalities during therapy found that thrombocytopenia, characterized by a rapid lowering of the platelet count in sensitive individuals was observed. Generally, the most common offending agent for the causation of thrombocytopenia secondary to anti-TB drug is R.[54,55] Isolated case reports showing thrombocytopenia following administration of Z, H, and E are found in literature and are attributed to an immunological phenomenon.[54-57] S is very rarely implicated as a cause of thrombocytopenia. Lzd has reported to be associated with hematological ADRs most common being thrombocytopenia with reported incidence as high as 11.8%.[58] Other ADRs like pancytopenia and myelosuppression are less common as compared to thrombocytopenia. These hematological ADRs are dose-dependent and usually reversible with clinical management.

Arthralgia

Z and E are two anti-TB drugs that have been reported to induce hyperuricemia in nongouty patients leading to arthralgia.[59] The metabolite pyrazinoic acid is likely responsible for the hyperuricemic effect. The mechanism is related to pyrazinoic acid, the principal metabolite of *Z* getting further oxidized by xanthine oxidase that inhibits the renal tubular secretion of uric acid. Hyperuricemia has been reported in 43 to 100% of patients treated with Z (alone or in combination).[60] Gouty attacks have also been associated with patients taking Z and E, as this combination can also cause hyperuricemia by decreasing renal uric acid clearance, but it does so less consistently and to a lesser degree than Z alone. Arthralgia has been reported with FQs particularly Lfx and Bdq containing regimens for DR-TB.[61,62]

Renal Toxicity

Aminoglycosides produce renal toxic effects due to their accumulation in the renal tubules. Such effects are more common in elderly individuals and in patients with a history of kidney disease. Prolonged use of aminoglycosides, hepatotoxicity, dehydration, hypotension, and concurrent use of nephrotoxic drugs are other risk factors for renal toxicity. The risk of nephrotoxicity is less and range around 2% while using S.[63,64] Injectable drugs such as Km and Am, as well as Cm are more nephrotoxic as compared to S making treatment for DR-TB cases challenging with reported incidence of 1.2 to 6.7%.[65] E, Z, and Cs have been reported to cause renal toxicity. Newer drugs such as Bdq and Dlm can be used safely in DR-TB patients with renal failure.

Cutaneous Adverse Drug Reactions (CADRs)

Z has been described to cause various skin reactions like maculopapular rash, erythema multiforme, exfoliative dermatitis, drug rash, and eosinophilia with systemic symptoms (DRESS) syndrome. Among the FLDs, Z is the commonest cause of CADRs (2.38%), followed by S (1.45%), E (1.44%), R (1.23%), and Z (0.98%).[66] It is not uncommon for exfoliative dermatitis to occur with more than one of the four above drugs. The incidence of E-induced rash is found to be 0.5%. The author (R.P.) reported a rare occurrence of exfoliative dermatitis secondary to E and Z in an 18-year-old female.[67] Patients receiving H can develop antinuclear antibodies during the use of the drug. Less than 1% develops systemic lupus erythematosus (SLE), the incidence of which is the same in both genders. H administration can also worsen preexisting lupus. Rash has also been reported with any SLDs including newer ones Bdq and Dlm.[68]

Cardiotoxicity (QTc Prolongation)

QTc prolongation on electrocardiogram (ECG) has been reported with FQs particularly moxifloxacin (Mfx), macrolides such as clarithromycin (Clr), Cfz, Bdq, and Dlm.[69] Risk factors for QTc prolongation include elderly, female sex, underlying cardiac disorder including congenital and acquired, electrolyte imbalance, and concurrent use of ancillary medications. A systematic search showed that Bdq is a relatively well-tolerated drug, as its discontinuation occurred in only 3.4 and 0.6% of patients due to ADRs' and QTc prolongation, respectively.[69]

Miscellaneous Adverse Drug Reactions

Few case reports on H and Eto/Pto induced gynecomastia and alopecia among patients treated with anti-TB therapy.[70] A rare

occurrence of anaphylactic shock due to S was also reported.[71] Metallic taste has been reported with Eto/Pto and FQs.[33,43] Lactic acidosis has been associated with Lzd.[33,43]

Management of Adverse Drug Reactions

Management of ADRs associated with anti-TB drugs is considered to be an essential component in order to achieve adequate adherence leading to favorable outcome particularly for DR-TB patients treated with toxic SLDs. Principles of pharmacovigilance have been adopted by the National TB Control Programmes all over the world. Pharmacovigilance is defined by the World Health Organization (WHO) as the "science and activities relating to the detection, assessment, understanding, and prevention of ADRs or any other drug-related problem."[72] 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 the 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/alle.g., and use of ancillary medications, and ART 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.[73] This system includes five grades as follows: (1) grade 1: mild symptoms requiring only observation and no intervention; (2) grade 2: moderate symptoms requiring medical intervention such as ancillary drugs; (3) grade 3: severe symptoms with inability to carry social or functional activities requiring medical intervention or even hospitalization; (4) 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 deaths; and (5) 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.[74,75] Symptoms-based approach to management of minor and major ADRs to FLDs are tabulated in ►**Tables 1–3**. ADRs of second line anti-TB drugs is tabulated in ►**Table 4** and management strategy of common ADRs are tabulated in ►**Table 5**.

Management of Adverse Drug Reactions in TB and HIV Coinfection

HIV patients experience more frequent ADRs to both anti-TB and other non-TB medications for other opportunistic infections, and the risk of ADRs enhances with the degree of immunosuppression.[20,21,26] Identifying one or more offending drugs responsible for ADRs in patients receiving concomitant therapy for DR-TB and HIV is very challenging. Many of the medications used to treat coinfection have overlapping or additive ADRs, as mentioned in ►**Table 6**.[75] The typical strategy of stopping all medications and rechallenging them one by one is not possible in these patients, as the risk of emergence of resistance, especially for ART, is very high. It should be noted that information regarding the frequency of ADRs is relatively scarce. Most of drugs have to be included in the regimens outweighing the benefit over risk despite of awareness regarding high probability of overlapping ADRs. If two drugs with overlapping toxicities are considered to be essential for therapy, intense monitoring of ADRs is to be considered rather than disallowing a certain combination. The treating physician, whether working in public or private sector, must notify all diagnosed cases to concerned DOTS center and can refer for further management.

Conclusion

The treatment of TB can cause a variety of ADRs. ADRs of varying severity are common during treatment of DS-TB and DR-TB, particularly in the intensive phase of therapy. Some ADRs become more prevalent in DR-TB patients coinfected with HIV. 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 knowle.g., of the pharmacological properties of the drugs involved will allow professionals to tailor their approach to each individual case in near future.

Conflict of Interest
None declared.

Table 1 Adverse drug reactions of first line antitubercular drugs

Drug	Common adverse drug reactions	Rare adverse drug reactions
Isoniazid (H)	• Peripheral neuropathy • Hepatotoxicity • Cutaneous reaction • Nausea and vomiting	• Anemia • Arthralgia • Dysarthria • Irritability • Seizure • Psychosis • Depression • Dysphoria • Lupoid reaction • Pellagra • Vasculitis • Thrombocytopenia • Optic neuritis
Rifampicin (R)	• Anorexia/nausea/vomiting • Hepatitis • Isolated jaundice • Sub-clinical unconjugated hyperbilirubinemia • Orange staining of body fluids	• Flu-like syndrome • Thrombocytopenia • Hemolytic anemia • Acute renal failure (majority with intermittent dosing) • Pseudomembranous colitis • Pseudoadrenal crisis • Cutaneous reaction
Ethambutol (E)	• Retrobulbar/optic neuritis • Nausea and vomiting	• Arthralgia • Peripheral neuropathy • Thrombocytopenia • Cutaneous reaction • Acute renal failure
Pyrazinamide (Z)	• Arthralgia • Hepatotoxicity • Nausea and vomiting	• Gastrointestinal reaction • Cutaneous reaction • Sideroblastic anemia • Thrombocytopenia • Photosensitivity
Streptomycin (S)	• Vestibular and auditory nerve damage • Nephrotoxicity • Cutaneous reaction • Pain, induration at site of injection	• Hypersensitivity reaction • Anaphylactic shock • Hemolytic anemia • Aplastic anemia • Agranulocytosis • Thrombocytopenia • Electrolyte abnormalities including hypokalemia, hypocalcemia, and hypomagnesemia

Table 2 Symptoms based approach to the management of minor adverse drug reaction to first line antitubercular drugs not requiring stoppage of treatment

Symptoms	Drug	Management
Abdominal pain, nausea	• Related to rifampicin	• Reassure the patients
Burning of the Feet	• Related to isoniazid • Peripheral neuropathy	• Continue isoniazid, and give pyridoxine 50–100 mg daily • Large dose of pyridoxine, may interfere the action of isoniazid
Drowsiness	• Related to isoniazid	• Reassure the patients
Gastrointestinal Upset	• Any oral medications	• 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 • If these measure fails, provide antiemetic
Joint pains	• Related to pyrazinamide	• Continue pyrazinamide • Use aspirin or nonsteroidal anti-inflammatory drugs • Use intermittent directly observed treatment if possible
Red urine	• Related to rifampicin	• Reassure the patients
Women on rifampicin	• Rifampicin may reduce the effectiveness of oral contraceptive pills	• Alternative method of contraception should be provided

Table 3 Symptoms based approach to major adverse drug reactions 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 • Stop streptomycin if no other explanation
Dizziness	• If true vertigo and nystagmus, related to streptomycin	• Stop streptomycin • If just dizziness with no nystagmus, try dose reduction for 1 week • If there is no improvement stop streptomycin
Generalized reactions including shock and purpura	• May be due to rifampicin, pyrazinamide and/ or streptomycin, thiacetazone	• Stop all medications • Use different combination of drugs
Jaundice/hepatitis	• 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 (bilirubin >2 mg/dL)	• Stop all antitubercular drugs until jaundice resolves and liver enzyme revert to baseline levels or < times of upper limit of normal • Rule out other causes/predisposing 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 • Rifampicin should be reintroduced followed by isoniazid in increasing dosages under regular Liver function test monitoring • Pyrazinamide should not be necessarily reintroduced and regimen should be continued for at least 9 months
Moderate to severe skin rash	• Related to all first line anti-tubercular drugs	• Stop all antitubercular drugs • Reintroduce drug one by one once the rash has subsided
Visual impairment	• Related to ethambutol	• Visual examination/ophthalmologist opinion • Stop ethambutol
Vomiting/confusion	• Suspect drug induced hepatitis	• Urgent liver function test • If liver enzyme test unavailable, observe

Table 4 Adverse drug reactions associated with second line antitubercular drugs

Drug	Frequent	Occasional	Rare
Amikacin	• Pain at injection site • Proteinuria	• Cochlear ototoxicity • Vestibular toxicity • Nephrotoxicity • Peripheral neuropathy • Rash • Eosinophilia	• Fever
Kanamycin	• Pain at injection site • Renal damage (usually reversible)	• Cochlear and vestibular ototoxicity (usually irreversible) • Peripheral neuropathy • Rash • Nephrotoxicity (dose related to cumulative and peak concentration, often irreversible)	• Fever
Capreomycin	• Nephrotoxicity • Tubular dysfunction • Urticaria • Maculopapular rash	• Cochlear ototoxicity • Vestibular toxicity • Electrolyte disturbances (hypokalemia, hypomagnesemia and hypocalcemia) • Pain at injection site, induration and sterile abscesses at site of injection • Neurotoxicity	• Rash
Clofazimine	• Ichthyosis • Dry skin • Pink to brown black discoloration of skin, cornea, retina, and urine • Nausea • Vomiting • Anorexia • Abdominal pain	• Hepatitis • Hypersensitivity reaction • Nephrotoxicity • Acneiform eruption	• Phototoxicity
Cycloserine and terizidone	• Neurological disturbances (headache and tremors) • Psychiatric disturbances (sleep disturbances, • anxiety, depression, irritability, confusion, and drowsiness) • Inflammation of gums • Pale skin	• Visual changes and eye pain • Skin rash • Jaundice (hepatitis) • Burning, tingling, and numbness in hands and feet	• Seizures • Suicidal thoughts • Impaired hearing in fetus • Hypersensitivity reaction

Table 4 (*continued*)

Drug	Frequent	Occasional	Rare
Ethionamide and prothionamide	• Severe gastrointestinal intolerance (including nausea, vomiting, • diarrhea, abdominal • pain, excessive salivation metallic taste) • Dose related headache • Anorexia and weight loss • Stomatitis	• Neurological disturbances • Psychiatric disturbances (depression, restlessness, drowsiness) • Allergic reactions • Postural hypotension • Reversible hepatitis (transient increase in serum bilirubin) • Hypothyroidism (especially when combined with PAS) • Menstrual irregularity • Gynecomastia • Arthralgia • Leukopenia	• Peripheral neuritis • Optic neuritis • Pellagra-like syndrome • Rash • Photosensitivity • Thrombocytopenia • Alopecia • Impotence • Purpura
Gatifloxacin	• Generally well tolerated	• Gastrointestinal Intolerance	• Headache • Malaise • Insomnia • Restlessness • Dizziness • Diarrhea • Photosensitivity • Tendon rupture • Dysglycemia • Hepatotoxicity
Levofloxacin	• Generally well tolerated	• Gastrointestinal intolerance (diarrhea) • Neurological disturbances (insomnia, restlessness, dizziness, and seizure) • Allergic reactions • Photosensitivity	• QT prolongation • Peripheral neuropathy • Tendon rupture • Rash
Moxifloxacin	• Generally well tolerated	• Gastrointestinal intolerance (diarrhea) • Neurological disturbances (insomnia, restlessness, and dizziness) • Allergic reactions • Photosensitivity	• QT prolongation (in isolated cases) • Rash
Ofloxacin	• Generally well tolerated	• Gastrointestinal intolerance (diarrhea) • Neurological disturbances (headache, insomnia, and restlessness)	• Allergic reactions • Photosensitivity • Peripheral neuropathy • Tendon rupture/tendinitis • Increased liver function tests
PAS	• Gastrointestinal intolerance (including metallic taste, anorexia, diarrhea) • Hypothyroidism especially when • Combined with ethionamide	• Hepatitis • Thyroid enlargement • Allergic reactions • Fever • Increased prothrombin time • Malabsorption syndrome (e.g., steatorrhea and low serum folate level)	

Table 4 (*continued*)

Drug	Frequent	Occasional	Rare
Linezolid	• Gastrointestinal intolerance • Rash • Headache	• Myelosuppression • Peripheral neuropathy • Optic neuropathy • Lactic acidosis	
Clarithromycin	• Gastrointestinal intolerance (abdominal pain, nausea, vomiting, and diarrhea) • Hepatitis • Ventricular arrhythmias	•	• Hypersensitivity reaction • Pseudomembranous colitis • Fever • Rash
Rifabutin	• Hepatitis • Lukopenia • Rashes	• Skin discoloration (Bronzing or pseudojaundice)	• Thrombocytopenia • Anterior uveitis
Imipenem/ cilastatin	• Gastrointestinal intolerance • Hypersensitivity reaction • Palpitation • Tachycardia	• Seizure • Hypotension • Anemia • Thrombophlebitis	• Renal failure • Hemorrhagic colitis • Pseudomembranous colitis
Meropenem	• Diarrhea • Nausea • Vomiting	• Seizure (in CNS infection)	• Elevated Liver function test • Hematologic Toxicity
Thiacetazone	• Gastrointestinal intolerance • Skin rash • Anemia	• Hepatitis • Exfoliative dermatitis • Stevens–Johnson syndrome	• Bone marrow depression • Ototoxicity
Amoxicillin/ clavulanate	• Diarrhea • Skin rash • Hypersensitivity reaction	• Candida stomatitis • Vaginitis	• Hepatic injury
Bedaquiline	• Nausea • Vomiting • Abdominal pain • Anorexia • Joint pain • Headache	• QT prolongation • Hyperuricemia • Hepatotoxicity	
Delamanid	• Nausea • Vomiting • Dizziness	• QT prolongation	

Abbreviations: CNS, central nervous system; PAS, Para-amino salicylic acid.

Table 5 Common adverse drug reactions, suspected agent(s) and management strategies of antitubercular drugs used in drug resistant tuberculosis

Adverse drug reaction	Suspected agent	Suggested management strategies
Neurological		
Seizures	CS H All FQs'	• Suspend suspected agent pending resolution of seizures • Initiate anticonvulsant therapy (e.g., phenytoin, carbamazepine, and valproic acid) • Valproic acid preferred in patients taking Bdq • Increase pyridoxine to maximum daily dose (200 mg per day) • Restart suspected agent or reintroduce suspected agent at lower dose, if essential to the regimen • Discontinue suspected agent if this can be done without compromising regimen • Anticonvulsant is generally continued until DR-TB treatment is completed or suspected agent discontinued • Monitor dosing of drugs according to creatinine clearance • History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant • Patients with history of previous seizures may be at increased risk for development of seizures during DR-TB treatment
Peripheral neuropathy	Lzd Cs H S Km Am Cm Eto/Pto FQs'	• Increase pyridoxine to maximum daily dose (200 mg per day) • Change injectable to capreomycin if patient has documented susceptibility to capreomycin • Initiate therapy with tricyclic antidepressants such as amitriptyline 25–50 mg • Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms • Lower dose of suspected agent, if this can be done without compromising regimen • Discontinue suspected agent if this can be done without compromising regimen • Patients with comorbid disease (e.g., diabetes, HIV, alcohol neuropathy dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents • Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended
Headache	Cs Bdq	• Rule out other neurological diagnoses including migraine • Often self-limiting • Maintain adequate hydration • NSAIDs to be used in mild cases and tricyclic antidepressants in refractory cases • Pyridoxine supplementation to patients on Cs therapy • Precaution not to compromise the regimen • Initiation with lower dose of Cs and increase subsequently over weeks if regression of symptoms

(*continued*)

Table 5 (*continued*)

Adverse drug reaction	Suspected agent	Suggested management strategies
Psychiatric		
Psychotic symptoms	Cs H FQs' Eto/Pto	• Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control • Initiate antipsychotic therapy • Lower dose of suspected agent if this can be done without compromising regimen • Discontinue suspected agent if this can be done without compromising regimen • Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy • Previous history of psychiatric disease is not a contraindication to the use of agents listed here but may increase the likelihood of psychotic symptoms developing during treatment • Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent
Depression and suicidal ideation	Cs FQ Eto/Pto H	• Offer group or individual counseling • Initiate antidepressant therapy • Lower dose of suspected agent if this can be done without compromising regimen • Discontinue suspected agent if this can be done without compromising regimen • Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression • Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated • History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment
Ototoxicity		
Hearing loss/deafness	S Km Am	• Monitoring with audiometry every month during intensive phase when treated with injectable aminoglycosides • - Document hearing loss and compare with baseline audiometry if
	Cm Clr	• Available • Rule out alternative diagnoses • Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin • Decrease frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week) • Discontinue suspected agent if this can be done without compromising the regimen • Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy • Hearing loss is generally not reversible • The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen • While the benefit of hearing aids is minimal to moderate in auditory • Toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use

(*continued*)

Table 5 (*continued*)

Adverse drug reaction	Suspected agent	Suggested management strategies
Vestibulotoxicity		
Tinnitus dizziness	Km Am Cm S Cs FQs' Eto/Pto Lzd H	• Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen • Consider dosing 2–3 times a week if drug is essential to the regimen and patient can tolerate • Discontinue suspected agent if persistence of symptoms in view of residual effect • Precaution to be taken in elderly • Weekly monitoring after having symptoms
Gastrointestinal		
Nausea and vomiting	Eto/Pto PAS H, E, Z Bdq Dlm	• Assess for dehydration; initiate rehydration if indicated in case of severe vomiting • Initiate antiemetic therapy like metoclopramide and ondansetron • Changing the dose timing, splitting of dose or supplementation along with or after food particularly for Eto, PAS • Lower dose of suspected agent if this can be done without compromising regimen • Discontinue suspected agent if this can be done without compromising regimen rarely necessary • Nausea and vomiting frequently observed in early weeks of therapy but abate with time on treatment and adjunctive therapy • Electrolytes should be monitored if vomiting is severe • Reversible upon discontinuation of suspected agent • Avoid ondansetron in patients taking Mfx, Bdq, and Dlm in view of QT prolongation
Gastritis and abdominal pain/acute abdomen	PAS Eto/Pto Cfz All FQs' Lzd Bdq Dlm	• H2-blockers, proton-pump inhibitors, or other antacids • Stop suspected agent(s) for short periods of time (e.g., 1–7 days) • Lower dose of suspected agent, if this can be done without compromising regimen • Discontinue suspected agent if this can be done without compromising regimen • Severe gastritis, as manifested by hematemesis, melena or hematochezia, is rare • Dosing of antacids should be carefully timed so as to not interfere with the absorption of anti-tubercular drugs like FQs' and Bdq (take 2 hours before or 3 hours after medications) • Reversible upon discontinuation of suspected agent(s) • Lzd and Bdq can cause pancreatitis and work up required if suspected • Severe abdominal distress and acute abdomen have been reported with the use of clofazimine • Although these reports are rare, if this effect occurs, clofazimine should be suspended

(*continued*)

Table 5 (*continued*)

Adverse drug reaction	Suspected agent	Suggested management strategies
Hepatitis	Z, H, R Bdq Eto/Pto PAS FQs'	• Stop all therapy pending resolution of hepatitis • Switch to three drug regimen S, FQ, and Cs in critically ill or extensive disease • Eliminate other potential causes of hepatitis including viral and alcoholism • History of previous hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens • Conditions to stop therapy: AST or ALT elevation ≥5 times ULN with normal bilirubin/AST or ALT elevation ≥3 times ULN with bilirubin ≥2 times ULN or symptoms of jaundice/isolated total bilirubin ≥2 times ULN • Consider suspending most likely agent permanently (H, Eto, Z, FQs' in case of shorter regimen and Eto, Z, Bdq, FQs' in case of longer regimens) • Reintroduce remaining drugs when AST and ALT elevation < 2 times ULN, one at a time while monitoring liver function every 3 days in the following sequence (FQs', Eto, H, Z in case of shorter regimen and FQs', Bdq, Eto, Z in case of longer regimens) • Generally reversible upon discontinuation of suspected agent • N-acetyl cysteine can be prescribed but evidence is uncertain • Gastroenterologist consult in complicated cases such as hepatic encephalopathy or portal hypertension
Diarrhea	PAS Eto/Pto	• Reassurance and observation in mild cases • Maintain hydration in severe cases • Monitor electrolytes in severe cases • Rule out any infectious etiology or dysentery or lactose intolerance • Use of loperamide in case of non-infectious etiology
Renal		
Nephrotoxicity	S Km Am	• Discontinue suspected agent • - Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen
	Cm	• Consider dosing 2–3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine) • Adjust all anti-tubercular medications according to the creatinine clearance • History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these comorbidities may be at increased risk for developing renal failure • Renal impairment may be permanent • Creatinine monitoring every month for first three months and then every three months when SLID continued during intensive phase • Creatinine monitoring every 1 to 3 weeks in case of HIV, DM and other high risk cases
Electrolyte disturbances (hypokalemia and hypomagnesemia)	Cm Km Am S	• Check potassium • If potassium is low, also check magnesium (and calcium if hypocalcemia is suspected) • Replace electrolytes as needed • If severe hypokalemia is present, consider hospitalization • Amiloride 5–10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases • Oral potassium replacements can cause significant nausea and vomiting. • Oral magnesium may cause diarrhea • Electrolyte monitoring every 1 to 3 weeks in case of HIV, DM and other high risk cases • Monitoring of calcium and magnesium levels in case of QTc prolongation on ECG

(*continued*)

Table 5 (*continued*)

Adverse drug reaction	Suspected agent	Suggested management strategies
Ophthalmological		
Optic neuritis	E Eto/Pto Lzd	• Visual acuity test and color vision at baseline and on occurrence of symptoms when treated with E and Lzd • Stop offending drug • Refer patient to an ophthalmologist if persistence of symptoms
		• Usually reverses with cessation of drug
Musculoskeletal		
Arthralgia	Z FQs' Bdq	• Initiate therapy with nonsteroidal anti-inflammatory drugs • Lower dose of suspected agent if this can be done without compromising regimen • Discontinue suspected agent if this can be done without compromising regimen • Symptoms of arthralgia generally diminish over time, even without intervention • Uric acid levels may be elevated in patients on Z • Allopurinol appears not to correct the uric acid levels in such cases
Tendonitis	FQs	• NSAIDS to be used • Provide rest to joints • Dose of FQ to be either reduced or stopped • Bdq to be considered • Care should be taken in diabetics
Hematological		
Myelosuppression thrombocytopenia	Lzd	• Discontinuation of offending drug in severe cases and substitution with other drugs • Exclude other causes • Blood or platelet transfusion in few cases depending on involvement of cell lineage • Dose can be reduced to either 300 mg daily or 600 mg thrice weekly if there is recovery with serial complete blood count monitoring every week for first month and then every month
Metabolic		
Hypothyroidism	PAS Eto/Pto	• Initiate thyroxine therapy and titration according to serial thyroid function tests
		• Completely reversible upon discontinuation of PAS or ethionamide/ prothionamide • The combination of ethionamide/ prothionamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug • Monitoring of TSH or complete thyroid profile if possible every three months when both PAS and Eto/Pto included in regimen or every six • Months when any one of them used in regimen
Dysglycemia	Gfx Mfx Eto/Pto	• Monitor blood sugars and strict control particularly in diabetics • Monthly monitoring of blood glucose • Treat hyperglycemia or hypoglycemia • Gfx can be replaced with other FQs • Insulin based regimens should be preferred over oral hypoglycemics

(*continued*)

Table 5 (*continued*)

Adverse drug reaction	Suspected agent	Suggested management strategies
Dermatological		
Rash itching Allergic reaction anaphylaxis	All FLDs and SLDs	• Reassurance and conservative treatment for mild dermatological reactions • Exclusion of other diagnoses of skin disorders • Antihistaminics and corticosteroid ointments to be used • Oral steroids in refractory cases • Order of reintroduction will be H, R, Z, Eto, Cs, E, PAS, FQ, and Km • Discontinue offending drug responsible for severe reactions such as Steven–Johnson syndrome
Cardiac		
QTc interval prolongation	Bdq Dlm FQs' especially Mfx Cfz Clr	• Serial monitoring with ECG and look for changes • If QTc interval 480–500 ms • Offending drugs should be continued under serial ECG monitoring (at least twice a week) • Exclude congenital or acquired cardiac disorders and other comorbidities • Monitor electrolytes (Na, K, Ca, and Mg) and creatinine routinely • - Precautions when used with Cm, Am, or other ancillary medications
		• Such as diuretics/macrolide antibiotics • If low electrolytes, discontinue drug temporarily till levels get corrected • If QTc interval ≥500 ms • Offending drugs should be immediately stopped temporarily till interval goes <470 ms • Mfx should be replaced with Lfx preferably • Subsequently, Cfz then Bdq and Dlm if there is persistent prolongation • Avoid Bdq and Dlm combination containing regimens if there is cardiotoxicity • Reintroduction in following sequence till there is QT interval <470 ms-Bdq, Mfx in case of Lfx resistance, Cfz, and Dlm

Abbreviations: ALT, alanine transaminase; Am, amikacin; AST, aspartate transaminase; Bdq, bedaquiline; Cfz, clofazimine; Clr, clarithromycin; Cm, capreomycin; Cs, cycloserine; Dlm, delamanid; DR-TB, drug resistant tuberculosis; E, ethambutol; ECG, electrocardiogram; Eto, ethionamide; FLD, first-line drug; FQ, fluoroquinolones; Gfx, Gatifloxacin; Km, kanamycin; H, isoniazid; Lfx, Levofloxacin; Lzd, linezolid; MDR, multi-DR; Mfx, Moxifloxacin; NSAID, nonsteroidal anti-inflammatory drug; PAS, para-amino salicylic acid; Pto, prothionamide; QD, once daily; R, rifampicin; S, streptomycin; SLD, second-line drug; TSH, thyroid stimulating hormone; Z, pyrazinamide.
Note: Drugs that the strongly associated with adverse effects shown in bold.

Table 6 Common adverse drug reactions of antiretroviral and antitubercular drugs

Toxicity	Antiretroviral agent	Antituberculosis agent	Comments
Peripheral neuropathy	D4T, ddI, ddC	Lzd, Cs, H, Sm, Km, Am, Eto/Pto, E	• Avoid use of D4T, ddI and ddC in combination with Cs or Lzd because of increased peripheral neuropathy • If these agents must be used and peripheral neuropathy develops, replace the ART with a less neurotoxic agent
Central nervous system (CNS) toxicity	EFV	Cs, H, Eto/Pto, Ofx, Lfx, Mfx, Lzd	• EFV has a high rate of CNS adverse drug reactions (confusion, impaired concentration, depersonalization, abnormal dreams, insomnia and dizziness) in the first 2 to 3 weeks, which typically resolve on their own. • If these effects do not resolve on their own, consider substitution of the agent
Depression/psychosis	EFV	Cs, Tzd, Ofx, Lfx, Mfx, H, Eto/Pto	• Severe depression can be seen in 2.4% of patients receiving EFV • Consider substituting for EFV if severe depression develops

(*continued*)

Table 6 (*continued*)

Toxicity	Antiretroviral agent	Antituberculosis agent	Comments
Headache	AZT, EFV, all integrase inhibitors	Cs, Bdq	• Rule out more serious causes of headache such as bacterial meningitis, cryptococcal meningitis, CNS toxoplasmosis, etc. • Use of analgesics (ibuprofen and paracetamol) and good hydration may help. • Headache secondary to AZT, EFV, and Cs is usually self-limited
Nausea and vomiting	RTV, D4T, NVP, RGV	Eto/Pto, PAS, H, E, Z, Bdq	• Nausea and vomiting are common adverse drug reactions and can be managed. • Persistent vomiting and abdominal pain may be a result of developing lactic acidosis and/or hepatitis secondary to medications
Abdominal pain	All ART treatments have been associated with abdominal pain	Cfz, Eto/Pto, PAS	• Abdominal pain is a common adverse drug reaction and often benign • Abdominal pain may be an early symptom of severe adverse drug reactions, such as pancreatitis, hepatitis or lactic acidosis
Pancreatitis	D4T, ddI, ddC	Lzd	• Avoid use of these agents together. • If an agent causes pancreatitis, suspend it permanently and do not use any of the pancreatitis-producing ART (D4T, ddI, or ddC) in the future. • Also consider gallstones or alcohol as a potential cause of pancreatitis
Diarrhea	All protease inhibitors, ddI (buffered formula), RGV	Eto/Pto, PAS, Ofx, Lfx, Mfx	• Diarrhea is a common adverse drug reaction • Also consider opportunistic infections as a cause of diarrhea, or clostridium difficile (a cause of pseudomembranous colitis).
Hepatotoxicity	NVP, EFV, all PIs, all NsRTIs, all integrase inhibitors, maraviroc	H, R, E, Z, PAS, Eto/Pto, Ofx, Lfx, Mfx, Bdq	• Also consider TMP/SMX as a cause of hepatotoxicity if the patient is receiving this medication • Also rule out viral etiologies such as cause of hepatitis (Hepatitis A, B, C and CMV)
Skin rash	ABC, NVP, EFV, D4T, maraviroc	H, R, Z, PAS, Am, Km, Ofx, Lfx, Mfx, Amx-Clv, T	• Do not rechalle.g., with ABC (can result in life-threatening anaphylaxis) • Do not re-challe.g., with an agent that causes Stevens–Johnson syndrome • Also consider TMP/SMX as a cause of skin rash if the patient is receiving this medication. • T is contraindicated in HIV because of life-threatening rash.
Lactic acidosis	D4T, ddI, AZT, 3TC	Lzd	• If an agent causes lactic acidosis, replace it with an agent less likely to cause lactic acidosis
Nephrotoxicity	TDF	Sm, Km, Am, Cm, Lfx	• TDF may cause renal injury with the characteristic features of Fanconi's syndrome, hypophosphatemia, hypouricemia, proteinuria, normoglycemic glycosuria and in some cases, acute renal failure
			• Use TDF with caution in patients receiving aminoglycosides or Cm and Lfx • Mfx should be preferred when ART contains TDF • Frequent creatinine and electrolyte monitoring every 1 to 3 weeks is recommended

(*continued*)

Table 6 (*continued*)

Toxicity	Antiretroviral agent	Antituberculosis agent	Comments
Nephrolithiasis	IDV	None	• No overlapping toxicities regarding nephrolithiasis have been documented between ART and anti-TB medications • Adequate hydration prevents nephrolithiasis in patients taking IDV • If nephrolithiasis develops while on IDV, substitute with another PI if possible
Electrolyte disturbances	TDF	Cm, Sm, Km, Am	• Diarrhea and/or vomiting can contribute to electrolyte disturbances • Even without the concurrent use of TDF, HIV-infected patients have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm
Bone marrow suppression	AZT	Lzd, R, Rfb, H	• Monitor blood counts regularly • -Replace AZT if bone marrow suppression develops. • Consider suspension of Lzd • Also consider TMP/SMX as a cause if the patient is receiving this medication • Consider adding folinic acid supplements, especially if receiving TMP/SMX
Optic neuritis	ddI	E, Eto/Pto (rare)	• Suspend agent responsible for optic neuritis permanently • Replace with an agent that does not cause optic neuritis
Hyperlipidemia	PIs, EFV	None	• No overlapping toxicities regarding hyperlipidemia have been documented between ART and anti- TB medications
Lipodystrophy	NRTIs (especially D4T and ddI)	None	• No overlapping toxicities regarding lipodystrophy have been documented between ART and anti-TB medications
Dysglycemia (disturbed blood sugar regulation)	PIs	Gfx, Eto/Pto	• PIs tend to cause insulin resistance and hyperglycemia • Eto/Pto tend to make insulin control in diabetics more difficult, and can result in hypoglycemia and poor glucose regulation
Hypothyroidism	D4T	Eto/Pto, PAS	• There is potential for overlying toxicity, but evidence is mixed • Several studies show sub-clinical hypothyroidism associated with ART particularly d4T • PAS and Eto/Pto, especially in combination, can commonly cause hypothyroidism
Myopathy rhabdomyolysis	AZT, RGV	E, Z	• Clinical correlation to rule out offending drug • Monitoring with creatine phosphokinase • Thorough clinical evaluation to rule out HIV associated myopathy • Muscle biopsy can be performed • AZT associated mitochondrial myopathy
QT prolongation	EFV, All PIs	Lfx, Mfx, Cfz, Bdq, Dlm	• Close monitoring to be done by ECG • Mfx is more commonly associated with QT prolongation • Lfx to be preferred over Mfx

Abbreviations: 3TC, lamivudine; ABC, abacavir; Am, amikacin; ALT, alanine transaminase; ART, antiretroviral therapy; AST, aspartate transaminase; AZT/ZDV, zidovudine; Bdq, bedaquiline; Cfz, clofazimine; Clr, clarithromycin; Cm, capreomycin; CMV, cytomegalovirus; CNS, central nervous system; Cs, cycloserine; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; Dlm, delamanid; DLV, delavirdine; DR-TB, drug resistant tuberculosis; DTG, dolutegravir; E, ethambutol; ECG, electrocardiogram; EFV, efavirenz; Eto, ethionamide; ETV, eltravirine; EVG, elvitegravir; FQ, fluoroquinolones; FTC, emtricitabine; Gfx, Gatifloxacin; Km, kanamycin; H, isoniazid; IDV, Indinavir; INV, indinavir; Lfx, Levofloxacin; Lzd, linezolid; MDR, multi-DR; NSAID, nonsteroidal anti-inflammatory drug; NsRTIs, Nucleoside reverse transcriptase inhibitors; NVP, nevirapine; Mfx, Moxifloxacin; PAS, para-amino salicylic acid; PI, protease inhibitor; Pto, prothionamide; R, rifampicin; RPV, rilpivirine; RTV, ritonavir; RGV, raltegravir; S, streptomycin; TDF, tenofovir; TMP/SMX, Trimethoprim/Sulphamethoxazole; TSH, thyroid stimulating hormone; Z, pyrazinamide.

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