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ARTICLE REVIEW: THE TREATMENT PROBLEM AND ADVERSE DRUG REACTIONS IN THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) is the resistance of Mycobacterium tuberculosis to at least two tuberculosis (TB) drugs, rifampicin and isoniazid. The disease requires a long treatment duration with several second-line drugs. This leads to a globally low success rate of approximately 56% for MDR-TB treatment. Studies have reported that adverse drug reactions (ADRs) contribute to high rates of non-compliance, treatment discontinuation, and failure. This narrative review aimed to provide information about MDR-TB treatment modalities, various ADRs, challenges encountered in MDR-TB treatment, and instances of ADRs that can impact treatment success. This narrative review study was conducted by searching for scientific information from the primary electronic databases PubMed and Google Scholar, covering 2012-2022. Based on the literature search results, 14 studies were identified, demonstrating challenges in TB and MDR-TB treatment, along with 6 ADRs that can influence treatment success in MDR-TB patients. ADRs during MDR-TB treatment can affect patients' physical, mental, and social well-being as well as their beliefs and behaviors related to treatment. Comprehensive support from families, communities, and healthcare providers is essential to assist patients in addressing treatment challenges and adverse ADRs. Rapid identification and strategies for monitoring and managing treatment challenges and ADRs can improve compliance and success of MDR-TB treatment.

Keywords: Adverse Drug Reactions, Drug Side Effects, Multi Drug-Resistant Tuberculosis (MDR-TB), Treatment Success

INTRODUCTION

Multiple-drug resistant tuberculosis (MDR-TB) is a disease caused by Mycobacterium tuberculosis strains of bacteria that are resistant to at least two anti-tuberculosis drugs, isoniazid and rifampicin. According to World Health Organization (WHO) data in 2021, the number of people diagnosed with TB globally has increased to 10.6 million cases. Cases that have been reported and undergoing treatment are 6.4 million (60.3%) people and cases that have not been reported and discovered/diagnosed are 4.2 million (39.7%) (WHO, 2022). The distribution of MDR-TB cases in developing countries makes it challenging to control and successfully eradicate TB. Despite all the efforts made by the WHO worldwide, the success rate of MDR-TB treatment remains low. The WHO targets the treatment success rate for MDR-TB patients to reach at least 80%; however, the latest

data show that the treatment success rate is currently approximately 59% (Baluku et al., 2021; Yang et al., 2017).

MDR-TB risk factors include human immunodeficiency virus (HIV) infection, low socioeconomic status, poverty, alcoholism, homelessness, crowded living conditions, and diseases that damage the immune system. Ineffective anti-TB drugs can prolong and worsen the disease and increase mortality, the spread of the disease, and the likelihood of developing resistance to treatment. These consequences significantly influence the financial impact on individuals and the healthcare system (Tola et al., 2015).

Based on WHO policy, there are currently several treatment regimens used for MDR-TB patients, namely BpaLM and BpaL regimens for 6 months, short-term regimens (STR) for 9−11 months, and individual long-term regimens (LTR) for 18–24 months. The MDR-TB treatment regimen is expensive, prolonged, and complex, and tends to cause unwanted drug reactions (ADRs). ADRs play an important role in treatment discontinuation, resulting in a high rate of treatment failure and non-adherence to treatment (Pradipta et al., 2018). A high rate of treatment failure has the potential to increase MDR-TB transmission in the community (Khan et al., 2022).

Indonesia is one of the countries with a high TB burden. One study in Indonesia stated that medication non-adherence is a complex picture of the patient's personality and attitudes, as well as the ability of health services, especially in Indonesia, where the quality of health services is not evenly distributed. Patients who come from outside the city may have additional indirect health costs, such as transportation and accommodation costs. Patients living in rural areas are also more likely to have a delayed diagnosis and treatment. Poverty, lack of access to health services, low education, and the absence of a support system (e.g., family) can delay patients from undergoing further treatment, thereby causing treatment failure. The stigma experienced by society can also result in loss of motivation (Soeroto et al., 2022).

Comprehensive management of MDR-TB that involves a multidisciplinary approach is very important. Some of them include providing financial support to patients so that they can undergo treatment to completion. The impact of MDR-TB treatment can be classified into three categories: costs associated with medical expenses (such as drug costs, examinations, doctor, and nurse services), direct nonmedical costs (including transportation to the hospital, food, and drink), and indirect costs (such as loss of income). ADRs from drugs used by MDR-TB patients include nausea, vomiting, hyperuricemia, allergies, fever, and many other effects. Treatment and ADRs problems experienced by MDR-TB patients require comprehensive identification of problems that will affect the success of treatment (Nimah et al., 2023).

Several national TB programs have attempted to increase the treatment success. Some of them include providing financial support to patients so that they can undergo treatment to completion. Treatment and ADRs problems experienced by MDR-TB patients require comprehensive identification of the problems that will affect the success of treatment.

ADRs have also been identified as contributing to patient noncompliance, resulting in poor treatment outcomes. Noncompliance with tuberculosis treatment can lead to prolonged transmission time, recurrence, emergence of drug resistance, and increased morbidity and mortality. The ADRs experienced by patients with MDR-TB are mostly mild or moderate and can be treated with additional treatment. In some cases, ADRs disappear with time and the patient tries to tolerate them until the effects subside (Khan et al., 2022). ADRs are potentially life-threatening and require temporary discontinuation of the offending drug or dose modification or drug change.

Based on this description, it is necessary to understand the problems associated with ADRs in the success of MDR-TB treatment. Therefore, this study aimed to describe the types of MDR-TB treatment, problems with MDR-TB treatment types, and the incidence of ADRs, which can influence the success of treatment in MDR-TB patients. This narrative review study aims to provide scientific information on MDR-TB treatment problems and ADRs events in MDR-TB patients as an important modality in patient-centered care to increase compliance and success of MDR-TB treatment.

RESEARCH METHODS

A literature search was conducted using the electronic databases PubMed and Google Scholar, covering the period from 2012 to 2022. In the article search process, the keywords used were "adverse drug reactions," "multidrug-resistant tuberculosis," "adherence," "medication compliance," and "barriers." The inclusion criteria were data from MDR-TB research articles on selected adult patients. A study was conducted on the type of MDR-TB treatment, ADRs, MDR-TB treatment problems, and ADRs events that could influence the success of treatment in MDR-TB patients. The exclusion criterion for the study was research article data with a period earlier than 2012.

RESULTS AND DISCUSSION

Types of Treatment for MultiDrug-Resistant Tuberculosis (MDR-TB)

A high incidence of MDR-TB is a health problem currently being faced. Drug resistance can be caused by incorrect management of TB treatment, the use of antimicrobial drugs and inappropriate formulations, non-compliance with treatment, and early discontinuation of treatment. Resistance of M. tuberculosis bacteria to anti-tuberculosis drugs (OAT) is a condition where the bacteria are so resistant that they can no longer be killed by anti-tuberculosis drugs. Drug resistance in TB is caused by several factors, including health workers, inappropriate diagnosis and treatment, inadequate treatment duration, and inadequate patient education. Patients can also develop drug resistance by not following health recommendations, irregularly taking medication, prematurely discontinuing treatment, and experiencing impaired drug absorption. The drug resistance factor is also caused by tuberculosis control programs, namely insufficient drug supplies and the low quality of anti-tuberculosis drugs provided (Kemenkes, 2020). The cure rate for drug-resistant tuberculosis is much lower than that for drug-sensitive tuberculosis. Additionally, MDR-TB treatment is more expensive, and many patients experience side effects during treatment (Soeroto et al., 2022). Table I and Table II present treatment recommendations for MDR-TB and TB RR as well as the grouping of drugs in determining the treatment mix for MDR-TB patients based on the criteria and condition of the patient.

Table I. Short-Term and Long-Term Treatment Recommendations for MDR-TB and TB-RR (WHO, 2020)

Regimen	Composition	Duration	Monitoring
Short Term MDR-TB	4–6 Bdq (6m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto/5 Lfx/Mfx-Cfz-Z-E Initial phase: 4–6 Bdq (6m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto Continuation phase: 5 Lfx/Mfx-Cfz-Z-E (Ethionamide variation)	9–11	Response to treatment was monitored by monthly sputum microscopy and culture and routine clinical assessment of signs and symptoms of disease
	4–6Bdq(6m)-Lzd(2m)-Lfx/Mfx-Cfz-Z-E-Hh/5 Lfx/Mfx-Cfz-Z-E Initial phase: 4–6 Bdq (6m)-Lzd(2m)-Lfx/Mfx-Cfz-Z-E-	9–11	Linezolid is only given for the first 2 months of treatment. Clinical and hematological monitoring is essential

	Hh Continuation phase: 5 Lfx/Mfx-Cfz-Z-E (linezolid variation)		for early detection of linezolid-related side effects, especially hematological events (sudden or significant decrease in hemoglobin, neutrophils, or platelets).
Long term MDR-TB	Starting with 5 drugs from Group A/B/C, continue with 3-4 drugs after Bdq is stopped	18–24 *	Monthly sputum microscopic examination, sputum culture test results, clinical response to treatment

Information: Bdq: Bedaquilin, Am: Amikacin, In: Delamanid, Mfx: Moxifloxacin, Cfz: Clofazimine, Eto: Ethionamide, Z: Pyrazinamide, E: Ethambutol, Hh: isoniazid high dose, TB: tuberculosis, HIV: human immunodeficiency virus, Lzd: linezolid. * Children with non-severe disease can be treated for 9–12 months, while children with severe disease require 12–18 months. ** Bdq and Dlm can be considered for use beyond 6 months.

Table II. Grouping of Drugs Recommended in The Long-Term Regimen MDR-TB (WHO, 2020)

Treatment Group	Type of Medicine	Drug Abbreviation
Group A Select all (three) drugs	Levofloxacin/Moxifloxacin Bedaquiline Linezolid	Lfx/Mfx Bdq Lzd
Group B Select all (two) drugs	Clofazimine Cycloserine or Terizidone	Cfz Cs Trd
Group C If the number of drugs from groups A+B is not sufficient for 5 types of drugs, then add 1 or more drugs from group C to complete the treatment mix	Ethambutol Delamanid Pyrazinamide Imipenem–Cilastatin Meropenem Amikacin or Streptomycin Ethionamide or Prothionamide p-aminosalicylic acid	E Dlm Z Ipm-Cln Mpm Amk S Eto Pto PAS

Short-term treatment regimens (STR) with a duration of Bdq 9−11 months (used for 6 months), levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid high-dose, pyrazinamide, and clofazimine for 4 months (possibly extended to 6 months if the patient remained BTA positive at the end of 4 months), followed by 5 months of treatment with levofloxacin, moxifloxacin, clofazimine, ethambutol, and pyrazinamide. Ethionamide can be replaced within 2 months with linezolid (600 mg daily) (Tack et al., 2021).

Long-term treatment regimens of 18–24 months consisted of a Group A agent (Bdq, levofloxacin/moxifloxacin, and Lzd) and at least one Group B agent (cycloserine and Cfz). This choice of regimen was made to ensure that at least four TB agents were likely to be effective, and that at least three agents were included for the remainder of the treatment if Bdq was discontinued. Group B agents must be included if only one or two Group A agents are used. If these two regimens are not effective, then Group C agents (ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, meropenem, amikacin (or streptomycin), ethionamide or prothionamide, and p-aminosalicylic acid) are used to complete MDR-TB treatment (WHO, 2020).

Based on the WHO policy, there is currently one regimen that can be used in addition to the short-term and long-term regimens in MDR-TB patients. The latest WHO recommendations suggest the use of a 6 month duration BPaLM and BPaL treatment regimen consisting of 100 mg bedaquiline, 200 mg pretomanid, 600 mg linezolid, and 400 mg moxifloxacin, rather than a 9 month or more regimen (18 months) in MDR-TB patients (WHO, 2022). Key factors determining the choice of treatment regimen include drug resistance profile, previous exposure to TB drugs, patient history, drug resistance profile of close contacts, patient age, extent of pulmonary TB disease, and localization of extrapulmonary TB lesions (WHO, 2022). Health workers must ensure that patients with confirmed MDR-TB can access treatment according to standards and quality quickly and precisely as an important strategy in the treatment of MDR-TB patients (WHO, 2020).

BPaL Regimen (Bedaquiline, Pretomanid and Linezolid, and Moxifloxacin)

A treatment regimen lasting 6–9 months, consisting of bedaquiline (Bdq), pretomanid (Pa), linezolid (Lzd), and moxifloxacin, can be used in MDR-TB patients with fluoroquinolone-resistant TB, who have never been previously exposed to bedaquiline and linezolid, pretomanid, or delamanid for more than 1 month. All components of the BpaLM regimen have bactericidal activity, making them effective mycobacterial drugs when used in combination. Bedaquiline, a diarylquinoline that inhibits the synthesis of adenosine triphosphate (ATP), is a nitroimidazole that inhibits cell wall biosynthesis; linezolid is an oxazolidinone that inhibits protein synthesis; and moxifloxacin is a fluoroquinolone that inhibits mycobacterial topoisomerase (WHO, 2022).

Dosage modifications with bedaquiline, moxifloxacin, and pretomanid were not permitted. Therefore, it is preferable to continue linezolid at a full dose for the entire duration. The linezolid dose may be reduced to 300 mg or discontinued (and restarted if possible) if there is significant toxicity (depending on the severity of the specific side effect or serious side effects) associated with linezolid, including optic neuritis, peripheral neuropathy, or myelosuppression (WHO, 2022). Figure 1 and Table III present the latest treatment recommendations for MDR-TB and RR-TB, as well as the drug doses for the BpaLM and BpaL regimens based on various criteria and patient conditions.

BPaLM regimen: 6–9 Bdq- Pa-Lzd-Mfx

Figure 1. Recommended treatment regimen for BPaLM (WHO, 2022)

Table III. Drug Dosage for Adults and Adolescents (Aged 14 Years) for The BPaLM Regimen (WHO, 2022)

Drug	Dose
Bedaquiline (Bdq) 100 mg tablets	400 mg (1x4 tablets) every day for the first two (2) weeks; continued 200 mg (1x2 tablets), 3x a week for 24 weeks thereafter or 200 mg daily for 8 weeks, then 100 mg
Pretomanid (Pa) 200 mg tablets	200 mg (1 x 1 tablet) every day

Linezolid (Lzd) 600 mg tablets	600 mg (1x 1 tablet) every day
Moxifloxacin (Mfx) 400 mg tablets	400 mg (1x 1 tablet) every day

BPaL Regimen (Bedaquiline, Pretomanid, and Linezolid)

The BPaL regimen may be prescribed for patients resistant to fluoroquinolones. In cases of possible fluoroquinolone resistance (e.g., history of fluoroquinolone use >4 weeks or close contact with a person infected with a fluoroquinolone-resistant strain), it is best to use the BPaLM regimen until a DST for a fluoroquinolone is available to decide whether moxifloxacin should be continued. If DST results are delayed, BPaLM can be initiated, and moxifloxacin can be discontinued from the regimen once fluoroquinolone resistance is confirmed. The BPaL regimen used the same doses of pretomanid, bedaquiline, and linezolid as the BPaLM regimen. If fluoroquinolone resistance is acquired while a person is on a BPaLM regimen, moxifloxacin can be omitted and BPaL should be continued in the absence of evidence of acquired resistance to other drugs, as there is no additional benefit to continuing an ineffective drug that may be toxic. If resistance to bedaquiline, linezolid, or pretomanid is confirmed or suspected, treatment is considered a failure, and the individual should be referred to a longer individualized regimen (WHO, 2022).

Types of Adverse Drug Reactions in MDR-TB Treatment

Adverse drug reactions (ADRs) are defined as “an undesirable and dangerous reaction occurring at normal doses used for prophylaxis, diagnosis, therapy of a disease, and improvement of the physiological system (Sant´Anna et al., 2022). Management of MDR-TB using the LTR regimen is almost always associated with higher rates of ADRs, and requires effective and timely management of ADRs. ADRs can hinder therapeutic success by causing non-compliance among patients with MDR-TB. ADRs are classified as minor reactions that do not result in immediate modification of the standard treatment regimen, and major reactions that result in a change or even discontinuation of the treatment regimen. ADRs in MDR-TB patients can occur in minor and major categories (clinically more severe), resulting in increased morbidity and a longer duration of treatment (Baluku et al., 2021).

A study reported that approximately 64% of MDR-TB patients experienced ADRs, and most cases were manageable with doctor intervention, preventing permanent regimen discontinuation (Atif et al., 2022). Two studies from Pakistan reported that 72.3−77% of patients with MDR-TB experienced at least one side effect during treatment (Nafees et al., 2016; Javaid et al., 2018). Several countries have reported a low frequency of ADRs, including India (46.9 %) (Prasad et al., 2016), Ethiopia (51 %) (Merid et al., 2019), and Nigeria (44 %) (Avong et al., 2015). The rate of frequency of ADRs resulting in differences is due to differences in health system and patient factors, the ability of physicians to detect ADRs, attitudes and practices of health workers regarding ADRs, patterns of drug use, variations in dosing regimens of antituberculosis drugs, and timely administration of antituberculosis drugs and additional drugs to reduce adverse drug reactions (Atif et al., 2022).

The most significant ADRs occurring in the majority of patients was psychiatric disorders (depression, 33%; psychosis, 7.3%). Other ADRs were musculoskeletal pain (arthralgia = 27.4%), dyspnea, peripheral neuropathy, headache, dizziness and vertigo, rash, pruritus, and visual disturbances, although this was rare (Atif et al., 2022). Treatment outcomes in patients who reported ADRs tended to be better than those in patients with MDR-TB who did not report ADRs. A possible cause is that when a patient experiences ADRs, the patient is given more intensive care and supervision so that adverse events

experienced by the patient can be prevented. Pharmacist-led patient-centered care is necessary because pharmacists have the skills to provide effective counseling and information regarding MDR-TB treatment and management of ADRs (Atif et al., 2022).

ADRs management strategies vary based on patient needs, including nonpharmacological and pharmacological interventions. Non-pharmacological interventions include counseling, whereas pharmacological interventions include adding symptomatic treatment, reducing the dose, or temporarily stopping the drug that causes ADRs. In the initial stage of MDR-TB treatment, the patient will be examined for symptoms that have occurred previously. All patients were evaluated monthly by doctors and psychologists. Patients who do not report their ADRs symptoms will be identified for evaluation based on the doctor's assessment, laboratory results, and/or the patient self-reporting the symptoms they are experiencing. Experience with and knowledge of ADRs are necessary to identify ADRs and provide appropriate care to patients (Nafees et al., 2016). Table IV shows the identification of ADRs during MDR-TB treatment.

Table IV. Types of Adverse Drug Reactions when Using MDR-TB Drugs (Nafees et al., 2016; Akshata et al., 2015; Atif et al., 2022; Zhang et al., 2017)

Adverse Drug Reactions	Signs and Symptoms
Hepatotoxicity	Increased serum transaminases more than 3 times the upper limit of normal with symptoms; increased serum bilirubin more than 2 times the upper limit of normal with symptoms; increased serum transaminase or serum bilirubin more than 5 times the upper limit of normal with or without symptom
Nephrotoxicity	Symptoms of hyperkalemia and an increase in at least one serum creatinine value greater than 1.3 mg/dL
Ototoxicity	Tinnitus, hearing loss confirmed by physical examination or audiometry, presence of imbalance, persistent ringing in the ears based on patient report
Peripheral neuropathy	Numbness, weakness, tingling, burning/pain in the extremities as diagnosed by a doctor or electromyography
Central nervous system disorders	Headache, dizziness, and seizure activity as reported by the patient or witness and documented by the physician
Psychiatric disorders	Presence of depression, anxiety, psychosis, suicidality, nightmares, and seizures as diagnosed by a doctor
Dermatological disorders	Skin changes include rash, itching, bronzing, black pigmentation, and photosensitivity reactions as reported by the patient and documented by the physician
Arthralgia	Pain in the joints as reported by the patient and documented by the doctor with or without the presence of arthritis and an increase in uric acid >7 mg/dL*
Gastrointestinal disorders	Presence of nausea, vomiting, anorexia, abdominal pain, diarrhea, epigastric discomfort, hematemesis, melena, positive endoscopic findings, as reported by the patient and documented by the physician
Hypothyroidism	At least one serum thyroid-stimulating hormone measurement is greater than the upper limit of normal, as documented by a physician
Hypokalemia	Weakness and fatigue, at least one serum potassium value < 3.5 mmol/L, as reported by the patient and documented by the physician
Fever	Fever fluctuates with a high temperature of 37,2 C in the

Adverse Drug Reactions	Signs and Symptoms
	afternoon and evening accompanied by sweat
Dyspnea	Respiratory frequency increases if damage to the lung parenchyma is widespread or accompanied by pleural effusion, pneumothorax, anemia, and others.
Hematological disorders	Decrease in the number of hemoglobin, leukocytes, or platelets to less than the lower limit of normal
*Normal range: SGOT= 5−40 IU/L; SGPT = 7−56 IU/L; total bilirubin = up to 1 mg/dL; serum creatinine = 0,6−1,3 mg/dL; uric acid = 2.5–7 mg/dL.	

To prevent and manage ADRs, it is crucial to identify drugs responsible for these reactions. ADRs that occurred during MDR-TB treatment had at least one unannounced and unreported event due to a minor or low-frequency reaction (Valadares et al., 2020) Table V presents an explanation of ADRs and drugs suspected of causing ADRs.

Table V. Adverse Drug Reactions Leading to Permanent Discontinuation of The Drug in The Treatment of Patients with MDR-TB (Lan et al., 2021)

Drug	Incident	Frequency of Adverse Drug Reactions
Levofloxacin	1.3%	Musculoskeletal (64%), peripheral neuropathy (14%), rash (14%)
Clofazimine	1.6%	Hyperpigmentation (42%), cardiovascular (33%), rash (17%), gastrointestinal (8%)
Bedaquiline	1.7%	Cardiovascular (56%), hepatotoxicity (22%), CNS Toxicity (11%), musculoskeletal (11%)
Ethambutol	1.8%	Visual disturbances (70%), gastrointestinal (17%), musculoskeletal (3%), rash (3%)
Moxifloxacin	2.9%	Cardiovascular (21%), hepatotoxicity (17%), gastrointestinal (13%), peripheral neuropathy (13%), musculoskeletal (8%)
Imipenem, Meropenem	4.9%	Hepatotoxicity (50%), rash (17%), fatigue (17%)
Pyrazinamide	5.1%	Musculoskeletal (33%), gastrointestinal (23%), hepatotoxicity (20%), rash (13%), hyperuricemia (6%)
Cycloserine, Terizidone	5.7%	Psychiatric (66%), CNS toxicity (25%), gastrointestinal (4%)
Ethionamide, Prothionamide	6.5%	Gastrointestinal (48%), hepatotoxicity (22%), psychiatry (6%), gynecomastia (5%), musculoskeletal (5%)
Kanamycin	7.5%	Ototoxicity (75%), musculoskeletal (5%), CNS toxicity (4%), gastrointestinal (4%), hypotension (4%)
Capreomycin	8.2%	Nephrotoxicity (51%), ototoxicity (17%), rash (11%), gastrointestinal (7%), hypotension (3%)
Amikacin	10.2%	Ototoxicity (87%), nephrotoxicity (10%)
Para-aminosalicylic acid	11.6%	Gastrointestinal (79%), hypothyroidism (5%), hepatotoxicity (4%), rash (4%), nephrotoxicity (3%)
Linezolid	14.1%	Peripheral neuropathy (64%), myelosuppression (22%), optic neuritis (5%)

The incidence of ADRs for MDR-TB treatment in Indonesia according to Minister of Health Regulation Number 67 is as follows: peripheral neuropathy (peripheral nerve disorders), toxic psychosis, liver disorders, seizures and digestive tract disorders, liver function disorders, anemia, gouty arthritis, vision problems (Dinkes Surabaya, 2017).

Meanwhile, according to the type of Drug-Resistant TB, the 2020 Ministry of Health Technical Guidelines, ADRs that may occur include teratogenicity, heart problems, peripheral neuropathy, hearing loss, depression, hypothyroidism, sleep disorders, digestive disorders, liver, functional disorders, kidney function disorders, optic neuritis, arthralgia arthritis, skin discoloration, tendinopathy, tendon rupture, hematological disorders, lactic acidosis, seizures, vestibular disorders (Kemkes, 2020).

A study in Indonesia found that 281 patients experienced ADRs (79.2%), 33.2% experienced drug withdrawal, and 74 patients (20.84%) experienced side effects and drug withdrawal. Common ADRs reported by patients undergoing treatment include nausea, dizziness, hearing loss, blurred vision, vomiting and hallucinations. (Windiyaningsih et al., 2021). The second study in Indonesia found that of the total characteristics of ADRs that occurred, 83 cases, the majority of ADRs that occurred were hyperuricemia (52.5%), gastrointestinal (GI) disorders (40%), ototoxicity (37.5%), and hypokalemia (27.5%). The less frequently reported ADRs were arthralgia (12.5%), rash (12.5%), headache (10%), psychiatric disorders (7.5%), visual disturbances (5%), and nephrotoxicity (2.5%). Management of ADRs plays a very important role, requiring all professional health workers, especially in the TB department, to be aware of the adverse effects of ADRs that can be life-threatening, such as hypokalemia and nephrotoxicity. ADRs are one of the most important factors causing MDR-TB patient dropout (Nilamsari et al., 2021).

MDR-TB Treatment Problems

ADRs play a significant role in treatment noncompliance, affecting the success of MDR-TB treatment. Patients with ADRs may undergo symptomatic treatment, necessitating adjustments to the MDR-TB treatment regimen. Most patients undergo dose reduction, changes in drug administration, or temporary discontinuation of the causative drug or treatment (Zhang et al., 2017). Apart from the impact of ADRs on MDR-TB treatment, other problems have been found, such as financial problems, health care, treatment burden (including the number of drugs taken), social problems, and lifestyle changes (Ridgeway et al., 2014). Prolonged duration of MDR-TB treatment significantly affects the lives of patients. Problems during MDR-TB treatment may lead to boredom, depression, a lack of self-confidence, and self-acceptance issues among patients. These problems may persist from the onset of treatment until completion. Effective management of ADRs in MDR-TB patients is crucial for enhancing treatment success and minimizing the impact on their daily lives (Ting et al., 2020).

ADRs during MDR-TB treatment significantly impact the daily routines of patients, hindering socialization and causing physical and psychological burden. The influence of ADRs and perceptions on physiological problems is noteworthy, especially considering the potential psychiatric effects of treatments, such as high-dose isoniazid, ethambutol, fluoroquinolones, and cycloserine. Patient knowledge plays a crucial role in managing physiological problems, excluding ADRs (Pradipta et al., 2021).

In Indonesia, the majority of MDR-TB patients have a history of TB treatment. MDR-TB treatment involves the use of second-line OAT, although more complex, and is associated with more severe side effects than first-line OAT, contributing to a higher dropout rate (Farihatun et al., 2018). A research study in Indonesia indicated a 91.1% compliance rate influenced by patient-related factors, condition-related factors, and treatment-related factors, including ADRs, socio-economic factors, and health service system factors (Yani et al., 2022).

Another tuberculosis study in Bengkulu, Indonesia, found that problems in TB treatment were directly and positively influenced by factors such as age, gender, education, income, knowledge, the role of the medication supervisor, drug accessibility, and family support. These factors have a direct and beneficial impact on adherence to anti-TB treatment. Conversely, the presence of drug side effects, long distances to the nearest health facility, and work commitments have negative effects (Hamidi et al., 2019). Qualitative research in Surabaya also identified problems in MDR-TB treatment related to the outcomes of

interactions between healthcare providers and patients, shortage of human resources, and inadequate health service facilities. Patient satisfaction with health services has emerged as a crucial factor for MDR-TB treatment. The role of health workers in comprehending patients' challenges is vital to enhancing patient satisfaction in delivering health services, particularly concerning ADRs (Nimah et al., 2023).

In urban areas of Indonesia, significant declines and delays in the MDR-TB service chain have been identified. Only 57% of the patients who initiated treatment successfully completed it, aligning with the global MDR-TB treatment success rate of 59%. ADRs lack financial and/or social support, initial comorbidities with increased pill counts, early discontinuation of treatment after symptoms disappear, long distance to health facilities, and other factors that may impede the success of MDR treatment (Lestari et al., 2023).

However, the success rate of TB treatment in Indonesia has not yet met the national target. Of the 90% target, treatment success is projected to reach 73% by 2021. A qualitative study conducted in Indonesia revealed several factual problems faced by patients with TB in Indonesia, leading to treatment failure. The three factors that influence TB treatment failure in Indonesia are Socio-Demographic and Economic Factors, Understanding and Perception Factors, and TB Treatment Effect Factors. Full support is essential for successful recovery from disease (Pradipta et al., 2021).

Several studies have shown that ADRs are one of the reasons for problems in TB treatment and MDR-TB. MDR-TB patients reported discontinuing treatment due to ADRs, while others did not receive information about ADRs or what to do about them. In some cases, patients received no communication from providers regarding the ADRs. Other research has also shown that health workers do not pay attention when patients report ADRs. The research studies in Table VI summarize the problems of TB treatment and MDR-TB. In this study summary, 14 studies were identified, highlighting problems with TB and MDR-TB treatment conducted in various regions between 2012 and 2022. The factors causing problems in MDR-TB treatment are shown in Figure 2.

Table VI. Research Study on TB Treatment Problems and MDR-TB

Researcher	Region	Study Design	Total Subject	Population	TB and MDR-TB Treatment Problems
(Woimo et al., 2017)	Ethiopia	Cross-sectional study	261	Active TB patient	1. Insufficient knowledge about TB and its treatment 2. Health information at each medication refill visit 3. Long distance from health facilities (more than 10 km) 4. Transportation costs 5. Cost of drugs other than anti-TB
(Gugssa Boru et al., 2017)	Ethiopia	Qualitative study	22	Active TB patient	1. Lack of adequate food 2. Poor communication between healthcare providers and patients 3. Belief in traditional medicine 4. Unavailability of nearby health services 5. Adverse drug reactions 6. Pill Burden 7. Stigma

Researcher	Region	Study Design	Total Subject	Population	TB and MDR-TB Treatment Problems
					8. Discrimination
(Ayele et al., 2017)	Amhara	Cross-sectional study	154	Latent TB-HIV patients	1. Lack of information about isoniazid preventive therapy (IPT) 2. Adverse drug reactions
(Daksa et al., 2016)	Oromia	Cross-sectional study	67	Active TB patient	1. Lack of family support 2. Health facilities are far away 3. Adverse drug reactions 4. Feel better 5. Level of education, 6. HIV positive
(van den Hof et al., 2016)	Ethiopia, Indonesia, and Kazakhstan	Cross-sectional study	406	TB Patients and MDR-TB Patients	1. High socio-economic impact 2. Job Loss due to MDR-TB treatment
(Sanchez-Padilla et al., 2014)	Armenia	Cohort and qualitative retrospective studies	381	MDR-TB patients	1. Adverse drug reactions 2. Poor patient response Respon 3. Ineffective treatment 4. Less specific information 5. Duration of treatment 6. Social problem
(Gualano et al., 2019)	Italy	Retrospective cohort study	74	MDR-TB patients	1. Adverse drug reactions 2. Patient education about drug side effects
(Santos et al., 2021)	Brazil	Qualitative study	7	MDR-TB patients	1. The impact of social determinant 2. Barriers to accessing services 3. Adverse Drug Reactions
(Deshmukh et al., 2015)	India	Qualitative study	20	MDR-TB patients	1. Adverse Drug Reactions 2. Lack of provider support 3. Social support 4. Economic support 5. Pill burden 6. Motivational counseling 7. Social stigma 8. Treatment service time
(Bhering et al., 2021)	Portugal	Qualitative study	8	MDR-TB patients	1. Depression 2. Social discrimination 3. Adverse Drug Reactions 4. Emotional support 5. Treatment monitoring

Researcher	Region	Study Design	Total Subject	Population	TB and MDR-TB Treatment Problems
(Mpagama et al., 2020)	Tanzania	Qualitative study	40	MDR-TB patients	1. Different patients understanding of MDR-TB 2. Socioeconomic difficulties 3. Availability of MDR-TB diagnostic center 4. Lack of knowledge of health care providers
(Gebreweld et al., 2018)	Asmara	Qualitative study	12	Active TB patient	1. Lack of patient knowledge regarding TB treatment 2. Access services 3. Social support 4. Stigma 5. Adverse Drug Reactions 6. Duration of treatment
(Schacht et al., 2019)	Manica and Sofala	Qualitative study	51	Patients with DS-TB, TB/HIV and MDR-TB	1. Delay in diagnosis 2. Stigma related to diagnosis and treatment 3. Long wait at the health facility 4. No nutritional support 5. There is no comprehensive psychosocial support program 6. Overall lack of knowledge about TB or resistant TB
(Nigam et al., 2021)	Saharia	Qualitative study	16	XDR/MDR-TB patients	1. Lack of education and awareness 2. Poor living conditions 3. Lack of health facilities 4. Poor access to health facilities 5. High pill burden 6. Drug side effects 7. Longer duration of treatment 8. Financial burden

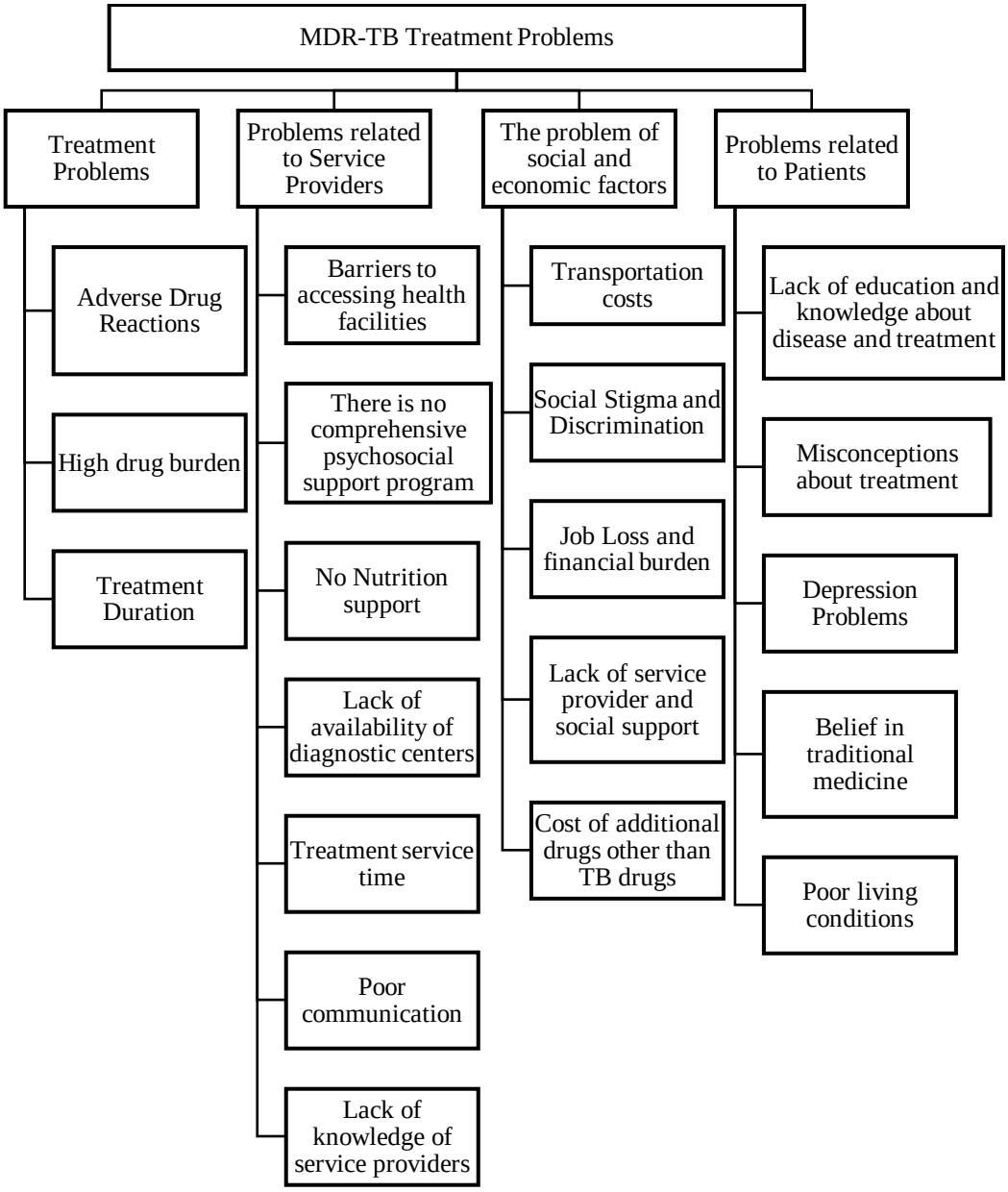

Figure 2. Chart of MDR-TB treatment problems (Deshmukh et al., 2015; Gugssa Boru et al., 2017; Nigam et al., 2021; Sanchez-Padilla et al., 2014; Schacht et al., 2019; Woimo et al., 2017)

ADRs can influence treatment adherence in MDR-TB patients. Frequently reported ADRs, such as vomiting, severe headache, vertigo, restlessness, and psychiatric conditions, are important reasons for discontinuing treatment (Deshmukh et al., 2015). ADRs can affect treatment adherence in patients with MDR-TB Commonly reported symptoms, including vomiting, severe headaches, vertigo, restlessness, and psychiatric conditions, are significant factors for treatment discontinuation (Morris et al., 2013). Perceived barriers arise when patients believe that taking TB drugs requires effort, time, effort, and money owing to ADRs. Patients with poor physical health may face more obstacles during the completion of the MDR-TB treatment regimen, affecting their lives conceptually, both directly and indirectly (Tola et al., 2017).

This review also identified another factor associated with non-adherence related to adverse drug reactions: the healthcare system. Poor healthcare provider relationships with communication gaps, disrespect for patients, and a lack of professional commitment affect the success of tuberculosis treatment. The perceived quality of health services and patient satisfaction also influence noncompliance with MDR-TB treatment. Patients lacking health information/education about treatment and ADRs are more likely to be noncompliant (Mpagama et al., 2020).

The problem of providing better health services and access was also perceived as lacking. When patients experience ADRs, those in need of additional medication to alleviate the ADR face difficulties due to distant service access, leading them to self-administer treatment at home. Healthcare providers should provide access to health services, especially ADR issues, and enhance patient education (prior to treatment initiation) regarding the potential impact of MDR-TB treatment on their daily lives (Ting et al., 2020).

ADRs are exacerbated by the large number of drugs used for an extended period during MDR-TB treatment, making treatment completion challenging for patients. A large amount of medication is a factor in non-adherence to MDR-TB treatment, often associated with potential damage to the body and a higher risk of not tolerating medication (Deshmukh et al., 2018; Nigam et al., 2021; Ting et al., 2020). The average patient took 10 tablets per daily dose. The high number of tablets combined with an unpleasant taste creates difficulties for drug administration. The development of strategies for shorter treatment regimens can reduce ADRs, thereby enhancing treatment efficacy. Providing health information on MDR-TB, its treatment, and side effects can contribute to treatment success in patients with MDR-TB (Deshmukh et al., 2018).

The impact of ADRs also affects financial burden, including meeting nutritional needs, transportation costs, and medical expenses beyond antituberculosis drugs during MDR-TB treatment (Morris et al., 2013). Most patients believe that inadequate dietary intake is associated with more severe side effects and difficulty in tolerating the drug. Insufficient food intake can pose a treatment problem, especially for patients with insufficient income. ADRs can affect the success of treatment, leading to patients being unable to work optimally, resulting in income loss, and becoming the primary obstacle to treatment (Deshmukh et al., 2018; Nigam et al., 2021).

Social stigma and discrimination act as obstacles to completing treatment for MDR-TB patients. Many patients are unable to engage in social activities because they feel too weak to socialize. The effects of ADRs on MDR-TB treatment can make them feel embarrassed, they cannot do household work well, and they are isolated from friends and family. Psychosocial problems, including real or perceived stigma, hospital anxiety, loss of income, and isolation from family and friends, require further monitoring of treatment policies and creating the best strategy to increase the success of treatment for MDR-TB patients (Oladimeji et al., 2016).

One reason for discontinuing treatment was that the patient felt cured. Healthcare providers must be trained and motivated to provide appropriate counseling before and during MDR-TB treatment (Gebreweld et al. 2018). Lack of awareness about MDR-TB and its treatment can affect treatment, because lack of awareness often leads patients to stop treatment and fail to complete the treatment.

The Incidence of ROTD Affects the Success of MDR-TB Treatment

Extended MDR-TB treatment often leads to ADRs. If these drug reactions are not managed optimally, poor treatment outcomes can be achieved. Most ADRs associated with this treatment are mild or moderate, and can be effectively addressed with adequate supervision and monitoring. MDR-TB patients with comorbidities undergoing treatment may experience interactions with anti-TB drugs, necessitating dose modifications or changes. Ensuring patient compliance and appropriate handling of side effects and drug interactions by health workers is crucial for favorable TB treatment outcomes (Gupta et al., 2020). The summary of research studies in Table VII highlights the incidence of ADRs, which can affect the success of MDR-TB treatment. This study identified 6 studies conducted in various regions between 2012 and 2022.

Table VII. The Incidence of ROTD Affects the Success of MDR-TB Treatment

Researcher	Region	Design Studies	Total Subject	Population	Adverse Drug Reaction
(Akshata et al., 2015)	India	Retrospective cohort study	607	MDR-TB	1. Gastritis (71.7%), 2. Visual impairment (0.2%)
(Dela et al., 2017)	Rajkot	Retrospective study	147	MDR-TB	1. Gastrointestinal (24.5%) 2. Weakness (21.23%) 3. Psychological (14.38%) 4. Joint pain (14.38%)
(Ngoc et al., 2021)	Vietnam	Prospective cohort study	659	MDR-TB	1. Gastrointestinal (38.5%) 2. Arthralgia (34.7%) 3. Psychiatric disorders (30.0%) 4. Nephrotoxicity (7.4%) 5. Hearing loss (15.2%)
(Wang et al., 2019)	China	Retrospective study	316	MDR-TB	1. Hyperuricemia (31.9%), 2. Hepatotoxicity (26.3 %) 3. Kidney damage (8.3%) 4. Psychiatric symptoms (4.3%)
(Massud et al., 2022)	Pakistan	Prospective observational study	271	MDR-TB	1. Gastrointestinal (66.7%) 2. Nervous system disorders (59.4%) 3. Electrolyte disorders (55.7%) 4. Artralgia (49.1%) 5. Ototoxicity (24%) 6. Pruritic reaction/rash (12.9%) 7. Dyspnea (12.5%) 8. Tinnitus (8.8%)

Researcher	Region	Design Studies	Total Subject	Population	Adverse Drug Reaction
(Gualano et al., 2019)	Italy	Retrospective cohort study	74	MDR-TB	1. Gastrointestinal (32.8%) 2. Ototoxicity (11.5%) 3. Central nervous system disorders (8.6%) 4. Liver disorders (8.1%)

ADRs are an obstacle to completing treatment and can adversely affect treatment outcomes. Documenting, assessing, and managing ADRs are crucial for achieving better patient compliance and improving treatment outcomes (Shean et al., 2013). Patient education about ADRs and a standardized approach to each clinical evaluation can help complete treatment successfully and reduce the risk of severe ADR events. Patients must understand MDR-TB treatment and the possibility of ADRs occurring frequently during MDR-TB treatment. One of our goals is to promptly address ADR incidents and guide patients on appropriate actions where they occur (Gualano et al., 2019).

Monitoring and managing ADRs, particularly severe ones, are useful for providing appropriate clinical decisions and improving patient care. Active pharmacovigilance is an effective approach for detecting ADRs during MDR-TB treatment (Ngoc et al., 2021). ADRs significantly influenced adherence to MDR-TB treatment. The management of ADRs, along with additional treatment costs, plays a crucial role in improving the success rate of MDR-TB treatments. Treatment outcomes demonstrate a significant improvement in patients who experience ADRs (Dela et al., 2017). TB providers prioritize patients with ADRs, increasing treatment adherence and the likelihood of positive treatment outcomes. Symptom-based ADR management includes adjusting the dose of the causative drug or temporary discontinuation if an alternative drug replacement is necessary (Dela et al., 2017).

The target success rate for MDR-TB treatment in Indonesia in 2021 has not yet reached 75%. Health workers involved in the National TB program require experience and expertise in finding and contact tracing active cases. They serve as a reference source for providing information, knowledge, and support, including technical and logistical support, to ensure drug availability to address ADRs in MDR-TB treatment. Electronic treatment monitoring, conducted through non-face-to-face methods via video call facilities from mobile applications, has proven effective in assisting patients in completing MDR-TB treatments (Depkes, 2022).

One of the results of research in Surakarta, Indonesia, revealed that counseling efforts enhance ADR monitoring and increase TB treatment compliance. This provides an opportunity for pharmacists to provide beneficial clinical services that leverage pharmacists' strengths and guarantee positive therapeutic outcomes for patients. One of the pharmacist's services is to provide education about TB drugs. Additional media such as leaflets were used to enhance patient compliance. Increasing treatment success requires good cooperation between fellow patients, the government, health workers, the community, and the patient's family to achieve therapeutic goals (Karuniawati et al., 2019).

Early detection of side effects during treatment is crucial because the sooner they are identified and addressed, the better their prognosis. Health workers should consistently monitor the emergence of ADRs and provide treatment as soon as possible. In Indonesia, monitoring and managing ADRs are conducted in all MDR-TB health-service facilities. The collection and reporting of ADR monitoring data are performed by health workers available in all health service facilities using the Tuberculosis Information System (SITB) (Kemkes, 2020).

CONCLUSIONS

The MDR-TB treatment regimen requires a relatively long duration, necessitating daily medication and substantial effort and expense from public health support services to ensure treatment adherence. The success of MDR-TB treatment depends on the level of treatment compliance: in the event of failure, the risk of treatment failure, relapse, and increased drug resistance. There are 3 factors that influence TB treatment failure in Indonesia: Socio-Demographic and Economic Factors, Understanding and Perception Factors, and TB Treatment Effect Factors. Full support is imperative for successful recovery from the disease.

ADRs are a significant factor influencing treatment compliance, alongside social and economic factors, and have a considerable psychological impact on the lives of MDR-TB patients. Identifying ADR issues in designing patient-centered care and treatment is expected to enhance compliance and treatment success. Nonadherence to treatment for any reason has a negative impact on treatment outcomes. The management of ADRs and the additional treatment costs to address them are crucial components that need consideration as they affect the success rate of MDR-TB treatment. Rapid identification and strategies for monitoring and managing ADRs are key to successful treatment outcomes, enabling appropriate clinical decisions, and improving the care of MDR-TB patients.

Monitoring the occurrence of drug side effects during MDR-TB treatment is crucial. Therefore, health workers must consistently monitor their side effects. Good and adequate management of the side effects is paramount for successful treatment. Clinical pharmacy services are offered as additional services to enhance the TB care programs. Treatment adherence interventions such as patient education, counseling, patient support (material or psychological), and digital technology improve TB treatment outcomes. Drug information or patient counseling is the most frequently carried out activity in clinical pharmacy services to influence and change patient knowledge about TB, support patient-centered care practices, and increase the success of MDR-TB treatment.

REFERENCES

Akshata, J. S., Anushree Chakrabarthy, R. Swapna, Shashidhar Buggi, and M. Somashekar. 2015. "Adverse Drug Reactions in Management of Multi Drug Resistant Tuberculosis, in Tertiary Chest Institute". *Journal of Tuberculosis Research, 03*(02): 27–33. doi: 10.4236/jtr.2015.32004.

Anon. 2020. *WHO Consolidated Guidelines on Tuberculosis Module 4: Treatment Drug-Resistant Tuberculosis Treatment Module 4: Treatment WHO Operational Handbook on Tuberculosis Drug-Resistant Tuberculosis Treatment*.

Atif, Muhammad, Waqar Ahmed, Muhammad Nouman Iqbal, Nafees Ahmad, Wajiha Ahmad, Iram Malik, and Yaser Mohammed Al-Worafi. 2022. "Frequency and Factors Associated With Adverse Events Among Multi-Drug Resistant Tuberculosis Patients in Pakistan: A Retrospective Study". *Frontiers in Medicine* 8. doi: 10.3389/fmed.2021.790718.

Avong, Yohanna Kamabi, Petros Isaakidis, Sven Gudmund Hinderaker, Rafael Van Den Bergh, Engy Ali, Bolajoko Oladunni Obembe, Ernest Ekong, Clement Adebamowo, Nicaise Ndembi, James Okuma, Adeline Osakwe, Olanrewaju Oladimeji, Gabriel Akang, Joshua Olusegun Obasanya, Osman Eltayeb, Aderonke Vivian Agbaje, Alas H. L. Abimiku, Charles Olalekan Mensah, and Patrick Sunday Dakum. 2015. "Doing No Harm? Adverse Events in a Nation-Wide Cohort of Patients with Multidrug-Resistant Tuberculosis in Nigeria." *PLoS ONE, 10*(3): 1–15. doi: 10.1371/journal.pone.0120161.

Ayele, Asnakew Achaw, Seyfe Asrade Atnafie, Demis Driba Balcha, Asegedech Tsegaw Weredekal, Birhanu Alemayehu Woldegiorgis, Mulgeta Melaku Wotte, and Begashaw Melaku Gebresillasie. 2017. "Self-Reported Adherence and Associated Factors to Isoniazid Preventive Therapy for Latent Tuberculosis among People Living with HIV/AIDS at Health Centers in Gondar Town, North West Ethiopia". *Patient Preference and Adherence*, 11: 743–49. doi: 10.2147/PPA.S131314.

Baluku, Joseph Baruch, Bridget Nakazibwe, Joshua Naloka, Martin Nabwana, Sarah Mwanja, Rose Mulwana, Mike Sempiira, Sylvia Nassozi, Febronius Babirye, Carol Namugenyi, Samuel Ntambi, Sharon Namiiro, Felix Bongomin, Richard Katuramu, Irene Andia-Biraro, and William Worodria. 2021. "Treatment Outcomes of Drug Resistant Tuberculosis Patients with Multiple Poor Prognostic Indicators in Uganda: A Countrywide 5-Year Retrospective Study". *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, 23: 100221. doi: 10.1016/j.jctube.2021.100221.

Bhering, Marcela, Vicente Sarubbi Junior, Afrânio Kritski, Fabiana Barbosa Assumpção Souza, and Raquel Duarte. 2021. "Multidrug-Resistant Tuberculosis in Portugal: Patients' Perception of the Challenges Faced during Treatment". *Portuguese Journal of Public Health, 38*(2): 62–70. doi: 10.1159/000511198.

Daksa, Misganu Diriba, Tsegaye Melaku Kebede, Desta Assefa, and H. /. Mariam. 2016. "Patients' Adherence to Anti-Tuberculosis Medicines and Associated Factors for Non-Adherence at a Tertiary Teaching Hospital, South West Ethiopia". *Gaziantep Medical Journal, 22*(2): 55–62. doi: 10.5578/GMJ.32149.

Dela, Arif I., Nitish Kumar D. Tank, Anil P. Singh, and Kiran G. Piparva. 2017. "Adverse Drug Reactions and Treatment Outcome Analysis of DOTS-plus Therapy of MDR-TB Patients at District Tuberculosis Centre: A Four Year Retrospective Study". *Lung India*, *34*(6): 522–26. doi: 10.4103/0970-2113.217569.

Departemen Kesehatan Republik Indonesia. 2022. "Tuberculosis Control In Indonesia 2022". 1–4.

Deshmukh, Rajesh D., D. J. Dhande, Kuldeep Singh Sachdeva, Achuthan Sreenivas, A. M. V. Kumar, Srinath Satyanarayana, Malik Parmar, Patrick K. Moonan, and Terrence Q. Lo. 2015. "Patient and Provider Reported Reasons for Lost to Follow up in MDRTB Treatment: A Qualitative Study from a Drug Resistant TB Centre in India". *PLoS ONE, 10*(8). doi: 10.1371/journal.pone.0135802.

Deshmukh, R. D., D. J. Dhande, K. S. Sachdeva, A. N. Sreenivas, A. M. V. Kumar, and M. Parmar. 2018. "Social Support a Key Factor for Adherence to Multidrug-Resistant

Tuberculosis Treatment". *Indian Journal of Tuberculosis, 65*(1): 41–47. doi: 10.1016/j.ijtb.2017.05.003.

Dinas Kesehatan Kota Surabaya. 2017. "Profil Dinas Kesehatan Kota Surabaya". *Dinas Kesehatan* 163.

Farihatun, Sitti, and Putri Bungsu Machmud. 2018. "Determinant Factors of Drop Out (Do) Among Multi Drugs Resistance Tuberculosis (Mdr Tb) Patients At Jakarta Province in 2011 To 2015". *Indonesian Journal of Tropical and Infectious Disease, 7*(3): 87. doi: 10.20473/ijtid.v7i3.7793.

Gebreweld, Frezghi Hidray, Meron Mehari Kifle, Fitusm Eyob Gebremicheal, Leban Lebahati Simel, Meron Mebrahtu Gezae, Shewit Sibhatu Ghebreyesus, Yordanos Tesfamariam Mengsteab, and Nebiat Ghirmay Wahd. 2018. "Factors Influencing Adherence to Tuberculosis Treatment in Asmara, Eritrea: A Qualitative Study". *Journal of Health, Population, and Nutrition, 37*(1): 1–9. doi: 10.1186/s41043-017-0132-y.

Gualano, Gina, Paola Mencarini, Maria Musso, Silvia Mosti, Laura Santangelo, Silvia Murachelli, Angela Cannas, Antonino Di Caro, Assunta Navarra, Delia Goletti, Enrico Girardi, and Fabrizio Palmieri. 2019. "Putting in Harm to Cure: Drug Related Adverse Events Do Not Affect Outcome of Patients Receiving Treatment for Multidrug-Resistant Tuberculosis. Experience from a Tertiary Hospital in Italy". *PLoS ONE, 14*(2): 1–14. doi: 10.1371/journal.pone.0212948.

Gugssa Boru, Cherinet, Tariku Shimels, and Arebu I. Bilal. 2017. "Factors Contributing to Non-Adherence with Treatment among TB Patients in Sodo Woreda, Gurage Zone, Southern Ethiopia: A Qualitative Study". *Journal of Infection and Public Health, 10*(5): 527–33. doi: 10.1016/j.jiph.2016.11.018.

Gupta, Amitesh, Vikas Kumar, Sekar Natarajan, and Rupak Singla. 2020. "Adverse Drug Reactions & Drug Interactions in MDR-TB Patients". *Indian Journal of Tuberculosis, 67*(4): S69–78.

Hamidi, Surahman, Setyo Sri Raharjo, and Mahendra Wijaya. 2019. "Path Analysis on the Determinants of Adherence to Anti Tuberculosis Drug Treatment in Kaur District, Bengkulu, Indonesia". *Journal of Epidemiology and Public Health, 4*(3): 205–14. doi: 10.26911/jepublichealth.2019.04.03.08.

Javaid, Arshad, Mazhar Ali Khan, Faheem Jan, Mifra Rauf, Mir Azam Khan, Anila Basit, and Sumaira Mehreen. 2018. "Occurrence of Adverse Events in Patient Receiving Community-Based Therapy for Multidrug-Resistant Tuberculosis in Pakistan". *Tuberkuloz ve Toraks, 66*(1): 16–25. doi: 10.5578/tt.64054.

Karuniawati, Hidayah, Okta Nama Putra, and Erindyah Retno Wikantyasning. 2019. "Impact of Pharmacist Counseling and Leaflet on the Adherence of Pulmonary Tuberculosis Patients in Lungs Hospital in Indonesia". *Indian Journal of Tuberculosis, 66*(3): 364–69. doi: 10.1016/j.ijtb.2019.02.015.

Kemenkes. 2020. *Temukan TB Obati Sampai Sembuh Penatalaksanaan Tuberkulosis Resisten Obat Di Indonesia*.

Khan, Farman Ullah, Amjad Khan, Faiz Ullah Khan, Khezar Hayat, Asim ur Rehman, Jie Chang, Waseem Khalid, Sidra Noor, Asad Khan, and Yu Fang. 2022. "Assessment of Adverse Drug Events, Their Risk Factors, and Management Among Patients Treated for Multidrug-Resistant TB: A Prospective Cohort Study From Pakistan". *Frontiers in Pharmacology, 13*(May): 1–10. doi: 10.3389/fphar.2022.876955.

Lan, Zhiyi, Nafees Ahmad, Parvaneh Baghaei, Linda Barkane, Andrea Benedetti, K. Sarah, James C. M. Brust, Jonathon R. Campbell, Vicky Wai, Lai Chang, Dennis Falzon, Lorenzo Guglielmetti, Petros Isaakidis, Russell R. Kempker, Maia Kipiani, Liga Kuksa, Christoph Lange, Rafael Laniado-laborín, Payam Nahid, Denise Rodrigues, and Rupak Singla. 2021. "HHS Public Access". *8*(4): 383–94. doi: 10.1016/S2213-2600(20)30047-3.Drug-associated.

Lestari, Bony Wiem, Gerine Nijman, Alamanda Larasmanah, Yuwono Soeroto, Prayudi Santoso, and Bachti Alisjahbana. 2023. "Articles Management of Drug-Resistant

Tuberculosis in Indonesia : A Four-Year Cascade of Care Analysis". *The Lancet Regional Health - Southeast Asia,* (38): 100294. doi: 10.1016/j.lansea.2023.100294.

Massud, Asif, Syed Azhar Syed Sulaiman, Nafees Ahmad, Muhammad Shafqat, Long Chiau Ming, and Amer Hayat Khan. 2022. "Frequency and Management of Adverse Drug Reactions Among Drug-Resistant Tuberculosis Patients: Analysis From a Prospective Study". *Frontiers in Pharmacology*, 13. doi: 10.3389/fphar.2022.883483.

Merid, Mehari Woldemariam, Lemma Derseh Gezie, Getahun Molla Kassa, Atalay Goshu Muluneh, Temesgen Yihunie Akalu, and Melaku Kindie Yenit. 2019. "Incidence and Predictors of Major Adverse Drug Events among Drug-Resistant Tuberculosis Patients on Second-Line Anti-Tuberculosis Treatment in Amhara Regional State Public Hospitals; Ethiopia: A Retrospective Cohort Study". *BMC Infectious Diseases, 19*(1): 1–12. doi: 10.1186/s12879-019-3919-1.

Morris, M. D., L. Quezada, P. Bhat, K. Moser, J. Smith, H. Perez, R. Laniado-Laborin, J. Estrada-Guzman, and Timothy C. Rodwell. 2013. "Social, Economic, and Psychological Impacts of MDR-TB Treatment in Tijuana, Mexico: A Patient's Perspective". *International Journal of Tuberculosis and Lung Disease, 17*(7): 954–60. doi: 10.5588/ijtld.12.0480.

Mpagama, Stellah G., Mangi J. Ezekiel, Peter M. Mbelele, Anna M. Chongolo, Gibson S. Kibiki, Kristen Petros de Guex, and Scott K. Heysell. 2020. "Gridlock from Diagnosis to Treatment of Multidrug Resistant Tuberculosis (MDR-TB) in Tanzania: Patients' Perspectives from a Focus Group Discussion". *BMC Public Health, 20*(1): 1–10. doi: 10.1186/s12889-020-09774-3.

Nafees, A., Arshad Javaid, Syed Azhar Syed Sulaiman, Afsar Khan Afridi, Zainab, and Amer Hayat Khan. 2016. "*Occurrence, Management, and Risk Factors for Adverse Drug Reactions in Multidrug Resistant Tuberculosis Patients*".

Ngoc, Nguyen Bao, Hoa Vu Dinh, Nguyen Thi Thuy, Duong Van Quang, Cao Thi Thu Huyen, Nguyen Mai Hoa, Nguyen Hoang Anh, Phan Thuong Dat, Nguyen Binh Hoa, Edine Tiemersma, and Nguyen Viet Nhung. 2021. "Active Surveillance for Adverse Events in Patients on Longer Treatment Regimens for Multidrug-Resistant Tuberculosis in Viet Nam". *PLoS ONE, 16*(9 September): 1–13.

Nigam, Samridhi, Ravendra K. Sharma, Rajiv Yadav, Vikas Gangadhar Rao, Prashant Mishra, Mercy Aparna Lingala, and Jyothi Bhat. 2021. "Experiences and Needs of Patients with MDR/XDR-TB: A Qualitative Study among Saharia Tribe in Madhya Pradesh, Central India". *BMJ Open, 11*(8). doi: 10.1136/bmjopen-2020-044698.

Nilamsari, Wenny Putri, Muhammad Fajar Rizqi, Natasya Olga Regina, Prastuti Asta Wulaningrum, and Umi Fatmawati. 2021. "Adverse Drug Reaction and Its Management in Tuberculosis Patients with Multidrug Resistance: A Retrospective Study". *Journal of Basic and Clinical Physiology and Pharmacology, 32*(4): 783–87. doi: 10.1515/jbcpp-2020-0447.

Nimah, Lailatun, Rr Dian Tristiana, Nursalam Nursalam, Laily Hidayati, R. Endro Sulistyono, and Kittisak Kumpeera. 2023. "Patients' Perceptions of Multi Drug Resistant Tuberculosis Outpatient in Healthcare Services: A Qualitative Study". *Malaysian Journal of Medicine and Health Sciences, 19*(May): 9–15.

Oladimeji, Olanrewaju, Boniface Ayanbekongshie Ushie, Ekerette Emmanuel Udoh, Kelechi Elizabeth Oladimeji, Olusoji Mayowa Ige, Olusegun Obasanya, Daisy Lekharu, Olayinka Atilola, Lovett Lawson, Osman Eltayeb, Mustapha Gidado, Joyce M. Tsoka-Gwegweni, Chikwe A. Ihekweazu, and Charles S. Chasela. 2016. "Psychosocial Wellbeing of Patients with Multidrug Resistant Tuberculosis Voluntarily Confined to Long-Term Hospitalisation in Nigeria". *BMJ Global Health, 1*(3). doi: 10.1136/bmjgh-2015-000006.

Pradipta, Ivan Surya, Lina Davies Forsman, Judith Bruchfeld, Eelko Hak, and Jan Willem Alffenaar. 2018. "*Risk Factors of Multidrug-Resistant Tuberculosis: A Global Systematic Review and Meta-Analysis*". Vol. 77. Elsevier Ltd.

Pradipta, Ivan S., Lusiana R. Idrus, Ari Probandari, Bony W. Lestari, Ajeng Diantini, Jan

Willem C. Alffenaar, and Eelko Hak. 2021. "Barriers and Strategies to Successful Tuberculosis Treatment in a High-Burden Tuberculosis Setting: A Qualitative Study from the Patient's Perspective". *BMC Public Health 21*(1). doi: 10.1186/s12889-021-12005-y.

Prasad, Rajendra, Abhijeet Singh, Rahul Srivastava, Giridhar B. Hosmane, Ram Awadh Singh Kushwaha, and Amita Jain. 2016. "Frequency of Adverse Events Observed with Second-Line Drugs among Patients Treated for Multidrug-Resistant Tuberculosis". *Indian Journal of Tuberculosis, 63*(2): 106–14. doi: 10.1016/j.ijtb.2016.01.031.

Ridgeway, Jennifer L., Jason S. Egginton, Kristina Tiedje, Mark Linzer, Deborah Boehm, Sara Poplau, Djenane Ramalho de Oliveira, Laura Odell, Victor M. Montori, and David T. Eton. 2014. "Factors That Lessen the Burden of Treatment in Complex Patients with Chronic Conditions: A Qualitative Study". *Patient Preference and Adherence, 8*: 339–51. doi: 10.2147/PPA.S58014.

Sanchez-Padilla, Elisabeth, C. Marquer, S. Kalon, S. Qayyum, A. Hayrapetyan, F. Varaine, M. Bastard, and M. Bonnet. 2014. "Reasons for Defaulting from Drug-Resistant Tuberculosis Treatment in Armenia: A Quantitative and Qualitative Study". *International Journal of Tuberculosis and Lung Disease, 18*(2): 160–67. doi: 10.5588/ijtld.13.0369.

Sant´Anna, Flávia M., Mariana Araújo-Pereira, Carolina A. S. Schmaltz, María B. Arriaga, Raquel V. C. de Oliveira, Bruno B. Andrade, and Valeria C. Rolla. 2022. "Adverse Drug Reactions Related to Treatment of Drug-Susceptible Tuberculosis in Brazil: A Prospective Cohort Study". *Frontiers in Tropical Diseases, 2*(January): 1–10. doi: 10.3389/fitd.2021.748310.

Santos, Felipe Lima Dos, Ludmilla Leidianne Limirio Souza, Alexandre Tadashi Inomata Bruce, Juliane De Almeida Crispim, Luiz Henrique Arroyo, Antônio Carlos Vieira Ramos, Thaís Zamboni Berra, Yan Mathias Alves, Alessandro Rolim Scholze, Fernanda Bruzadelli Paulino Da Costa, José Francisco Martoreli, Ana Carolina Scarpel Moncaio, Ione Carvalho Pinto, and Ricardo Alexandre Arcêncio. 2021. "Patients' Perceptions Regarding Multidrugresistant Tuberculosis and Barriers to Seeking Care in a Priority City in Brazil during COVID-19 Pandemic: A Qualitative Study". *PLoS ONE, 16*(4 April): 1–19. doi: 10.1371/journal.pone.0249822.

Schacht, Caroline De, Cláudia Mutaquiha, Felicidade Faria, Georgina Castro, Nélia Manaca, Ivan Manhiça, and James Cowan. 2019. "Barriers to Access and Adherence to Tuberculosis Services, as Perceived by Patients: A Qualitative Study in Mozambique". *PLoS ONE, 14*(7). doi: 10.1371/journal.pone.0219470.

Shean, Karen, Elizabeth Streicher, Elize Pieterson, Greg Symons, Richard Van Zyl Smit, Grant Theron, Rannakoe Lehloenya, Xavier Padanilam, Paul Wilcox, Tommie C. Victor, Paul Van, Martin Groubusch, Robin Warren, Motasim Badri, and Keertan Dheda. 2013. "Drug-Associated Adverse Events and Their Relationship with Outcomes in Patients Receiving Treatment for Extensively Drug-Resistant Tuberculosis in South Africa". *8*(5). doi: 10.1371/journal.pone.0063057.

Soeroto, Arto Yuwono, Raden Desy Nurhayati, Aga Purwiga, Bony Wiem Lestari, Chica Pratiwi, Prayudi Santoso, Iceu Dimas Kulsum, Hendarsyah Suryadinata, and Ferdy Ferdian. 2022. "Factors Associated with Treatment Outcome of MDR/RR-TB Patients Treated with Shorter Injectable Based Regimen in West Java Indonesia". *PLoS ONE, 17*(1 January). doi: 10.1371/journal.pone.0263304.

Tack, Ilse, Asnake Dumicho, Liesbet Ohler, Altynay Shigayeva, Abera Balcha Bulti, Kenneth White, Mduduzi Mbatha, Jennifer Furin, and Petros Isaakidis. 2021. "Safety and Effectiveness of an All-Oral, Bedaquiline-Based, Shorter Treatment Regimen for Rifampicin-Resistant Tuberculosis in High Human Immunodeficiency Virus (HIV) Burden Rural South Africa: A Retrospective Cohort Analysis". *Clinical Infectious Diseases, 73*(9): E3563–71. doi: 10.1093/cid/ciaa1894.

Ting, Natasha C. H., Nicole El-Turk, Michael S. H. Chou, and Claudia C. Dobler. 2020. "Patient-Perceived Treatment Burden of Tuberculosis Treatment". *PLoS ONE, 15*(10

October). doi: 10.1371/journal.pone.0241124.

Tola, Habteyes Hailu, Azar Tol, Davoud Shojaeizadeh, and Gholamreza Garmaroudi. 2015. "Tuberculosis Treatment Non-Adherence and Lost to Follow up among TB Patients with or without HIV in Developing Countries: A Systematic Review". *Iranian Journal of Public Health, 44*(1): 1–11.

Tola, Habteyes Hailu, Mehrdad Karimi, and Mir Saeed Yekaninejad. 2017. "Effects of Sociodemographic Characteristics and Patients' Health Beliefs on Tuberculosis Treatment Adherence in Ethiopia: A Structural Equation Modelling Approach". *Infectious Diseases of Poverty, 6*(1): 1–10. doi: 10.1186/s40249-017-0380-5.

Valadares, Ronise Malaquias Carlos, Wânia da Silva Carvalho, and Silvana Spíndola de Miranda. 2020. "Association of Adverse Drug Reaction to Anti-Tuberculosis Medication with Quality of Life in Patients in a Tertiary Referral Hospital". *Revista Da Sociedade Brasileira de Medicina Tropical, 53*(August): 0–1. doi: 10.1590/0037-8682-0207-2019.

van den Hof, Susan, David Collins, Firdaus Hafidz, Demissew Beyene, Aigul Tursynbayeva, and Edine Tiemersma. 2016. "The Socioeconomic Impact of Multidrug Resistant Tuberculosis on Patients: Results from Ethiopia, Indonesia and Kazakhstan". *BMC Infectious Diseases, 16*(1). doi: 10.1186/s12879-016-1802-x.

Wang, Jing, Yu Pang, Wei Jing, Wei Chen, Ru Guo, Xiqin Han, Limin Wu, Guangxu Yang, Kunyun Yang, Cong Chen, Lin Jiang, Chunkui Cai, Zhi Dou, Lijuan Diao, Hongqiu Pan, Jianyun Wang, Feifei Du, Tao Xu, Lixia Wang, Renzhong Li, and Naihui Chu. 2019. "Efficacy and Safety of Cycloserine-Containing Regimens in the Treatment of Multidrug-Resistant Tuberculosis: A Nationwide Retrospective Cohort Study in China". *Infection and Drug Resistance, 12*: 763–70. doi: 10.2147/IDR.S194484.

WHO. 2020. *WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment - Drug-Resistant Tuberculosis Treatment. Online Annexes.*

WHO. 2022. *WHO: Operational Handbook on Tuberculosis*.

Windiyaningsih, Cicilia, Eneng Nurulaini, Anisa Prihartini, and Ignatius Erik Sapta Yanuar. 2021. "Factors Influence Side Effects and Withdrawal in TB Patients Resistant to Banten Province and West Java. In 2018─2020". *Medicine and Clinical Science, 3*(4): 1–6. doi: 10.33425/2690-5191.1046.

Woimo, Tadele Teshome, Wondwossen Kassahun Yimer, Temesgen Bati, and Hailay Abrha Gesesew. 2017. "The Prevalence and Factors Associated for Anti-Tuberculosis Treatment Non-Adherence among Pulmonary Tuberculosis Patients in Public Health Care Facilities in South Ethiopia: A Cross-Sectional Study". *BMC Public Health, 17*(1). doi: 10.1186/s12889-017-4188-9.

Yang, Tae Won, Hyun Oh Park, Ha Nee Jang, Jun Ho Yang, Sung Hwan Kim, Seong Ho Moon, Joung Hun Byun, Chung Eun Lee, Jong Woo Kim, and Dong Hun Kang. 2017. "Side Effects Associated with the Treatment of Multidrug-Resistant Tuberculosis at a Tuberculosis Referral Hospital in South Korea". *Medicine (United States), 96*(28). doi: 10.1097/MD.0000000000007482.

Yani, Desy Indra, Neti Juniarti, and Mamat Lukman. 2022. "Factors Related to Complying with Anti-TB Medications Among Drug-Resistant Tuberculosis Patients in Indonesia". *Patient Preference and Adherence, 16*: 3319–27. doi: 10.2147/PPA.S388989.

Zhang, Yang, Shanshan Wu, Yinyin Xia, Ni Wang, Lin Zhou, Jing Wang, Renfei Fang, Feng Sun, Mingting Chen, and Siyan Zhan. 2017. "Adverse Events Associated with Treatment of Multidrug-Resistant Tuberculosis in China: An Ambispective Cohort Study". *Medical Science Monitor, 23*: 2348–56. doi: 10.12659/MSM.904682.