ORIGINAL ARTICLE

Outcome and Adverse Drug Reactions of Shorter Versus Longer Regimen of Drug-Resistant Tuberculosis Treatment in a Tertiary Care Respiratory Centre.

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Abstract

Drug-resistant tuberculosis (DR-TB) remains a global threat. Evidence on the outcomes and adverse drug reactions (ADRs) of DR-TB management with shorter (STR) or longer (LTR) treatment regimens is limited. This study characterised the outcomes and ADRs of STR and LTR for DR-TB patients at a tertiary care respiratory centre. A retrospective cross-sectional study was conducted among adult DR-TB patients attending the Respiratory Clinic of the Institute of Respiratory Medicine, Malaysia from January 2015 to January 2021. Medical records and ADR forms were screened for DR-TB treatment outcome and ADR information. Treatment outcomes were classified as successful or unsuccessful. Descriptive analysis was performed using SPSS version 20. Eighty-four patients aged 18 to 68 years old (41.2±14.2) were included. The DR-TB treatment consists of 42.9% (n = 36) patients in STR and 57.1% (n = 48) patients in LTR. Overall, 52.8% (n = 19) and 54.2% (n = 26) patients were categorised as having successful outcomes in the STR and LTR, respectively. Sixty-two (73.8%) patients experienced at least one ADR resulting in 110 ADR cases. Most ADRs (n = 80, 72.7%) were reported among LTR patients. The suspected drugs were mostly kanamycin (n = 32, 29.1%), cycloserine (n = 22, 20%) and ethambutol (n = 20, 18.2%). The most common ADRs involved the gastrointestinal disorders (n = 40, 36.4%). Majority of serious ADRs (n = 46/55, 83.6%) were observed in the LTR. Treatment success and occurrence of ADRs were higher in the DR-TB patients on LTR. Assessment of key factors that influence treatment decisions should be explored to guide the selection of appropriate treatment regimens.

Keywords: *Adverse drug reactions; drug-resistant tuberculosis; Malaysia; treatment outcome.*

Introduction

Tuberculosis (TB) is a curable and treatable communicable disease, ranking among the top ten causes of death worldwide. In 2019, 7.1 million new TB cases were reported globally, indicating a significant increase of about 1.4 million people since 2009 [1]. Drug-resistant TB (DR-TB) refers to TB caused by a strain of the *Mycobacterium tuberculosis* complex resistant to any TB medicines [2]. Drug-resistant TB includes, among others, multidrug-resistant TB (MDR-TB), rifampicin-resistant TB (RR-TB), and isoniazid-resistant TB (IR-TB). Globally, a total of 206,030 people with MDR-TB or RR-TB were detected and notified in 2019, marking a 10% increase from 2018. However, only about 85% were enrolled in treatment each year [1]. According to the World Health Organisation (WHO) Global Tuberculosis Report 2014, approximately 9% of estimated MDR-TB patients failed to complete treatment successfully, leading to the progression of the disease to extensively drug-resistant TB (XDR-TB). In the battle against DR-TB, the fundamental approach remains the use of combination anti-TB drugs in several DR-TB treatment regimens. In 2011, the WHO guidelines for the programmatic management of DR-TB recommended an intensive treatment phase of 8 months and longer treatment regimens (LTR) lasting 20 months and longer, containing pyrazinamide, a fluoroquinolone, a second-line injectable drug, ethionamide (or prothionamide), and either cycloserine or p-aminosalicylic acid [3]. In a 2016 update, the WHO recommended the use of a shorter treatment regimen (STR) for MDR-TB which was aimed to reduce cost, improve compliance and cure rate [4]. Previous findings comparing the treatment outcomes and occurrence of ADRs between STR and LTR revealed variations in the results. In a multicentre study conducted in Pakistan, the time to achieve sputum smear conversion was shorter, and treatment success was higher in the STR group than in the LTR group [5]. However, a study conducted in Indonesia reported the opposite, with a greater overall treatment success rate in the LTR group compared to the STR group [6]. The study also reported smear and sputum culture status as the factors associated with MDR-TB treatment outcome [6]. Pooled findings from individual studies and public data concluded that treatment success was higher with STR than with LTR [7]. Adverse drug reactions (ADRs) were reported to occur in approximately 85% of patients undergoing treatment for DR-TB [8], even in settings with a high prevalence of human immunodeficiency virus (HIV) patients [9]. The most common ADRs were gastrointestinal disorders, ototoxicity, and psychiatric disorders [10].

In 2015, Malaysia's TB mortality rate increased from 5.5 to 7.1 per 100,000 population by 2020, despite a decrease in TB incidence during the same period [11]. Aligned with the WHO End TB Strategy [12], Malaysia aims to reduce TB deaths to fewer than 85 per year [11]. The latest edition of the Malaysian Clinical Practice Guideline (CPG) on tuberculosis management excluded evidence related to DR-TB as it is addressed in separate guidelines [11]. However, the Malaysian DR-TB CPG 2016 highlighted a scarcity of evidence regarding the comparison of the effectiveness and ADRs associated with DR-TB management with STR or LTR [13]. This study utilised real-world data to compare the outcome and ADRs of STR versus LTR DR-TB management in Malaysian patients. The findings from this study can serve as a basis for developing or updating treatment guidelines, creating decision support tools for clinical practice, and offering safety-related insights for regulatory recommendations and decisions.

Materials and methods

Ethical consideration

The study obtained approval from the ethics committee for Ministry of Health (MOH) facilities in Malaysia, Medical Research and Ethics Committee (MREC) (NMRR-19-4051-48045). Additionally, approval to conduct the

study was obtained from the hospital director and the head of the department. The patient identifiers were kept confidential. Reporting of the study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [14].

Study setting

This study was conducted at the Respiratory Clinic of the Institute of Respiratory Medicine, locally referred to as IPR, Malaysia. The IPR is located in the central region of Peninsular Malaysia, where it provides expert inpatient and outpatient services in respiratory medicine and receives nationwide referrals. The IPR currently has 118 beds and is visited by approximately 250 patients daily in the outpatient setting.

Eligibility Criteria

Medical records of patients aged 18 years and older with confirmed DR-TB who attended the study site from January 2015 to January 2021 were included. The medical records of pregnant women, XDR-TB, extrapulmonary tuberculosis (EPTB), and drug-susceptible TB were excluded from the study. Additionally, patients still undergoing treatment at the end of the study duration (January 2021) were excluded.

Sampling method

A total sampling technique used in a previous study [6] was employed in this study. Data collected from eligible patients using the total sampling technique were then divided into two groups, i.e., the STR and LTR groups.

Data collection

During the study period, medical records of eligible patients were reviewed to obtain socio-demographic (age, gender, ethnicity, and smoking status), clinical (presence of co-morbidity, mode of transmission, relevant laboratory findings, and types of DR-TB), and treatment (drugs prescribed, treatment regimen, and ADR information) data.

Based on the data gathered, the treatment outcome and ADRs were classified as stated below:

a. Treatment outcomes

The DR-TB treatment outcome was classified as successful outcomes (cured and completed treatment) and unsuccessful outcomes (death, lost to follow up and treatment failed). The categories of DR-TB treatment outcome used in this study was in accordance with the standard criteria as per the WHO recommendations [16], as stated below:

i. Cured: Treatment completed as recommended by national policy without evidence of failure, and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
ii. Treatment complete: Treatment completed as recommended by national policy without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
iii. Treatment failed: Treatment was terminated or necessitated a permanent regimen change of at least 2 anti-TB drugs due to either a lack of conversion by the end of the intensive phase or bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second line injectable drugs, or ADRs.
iv. Death: A patient who dies for any reason during the course of treatment.
v. Lost to follow-up: A patient whose treatment was interrupted for 2 or more consecutive months.
vi. Not evaluated: A patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit and those whose treatment outcome is unknown.

b. Adverse drug reactions

The DR-TB treatment related ADRs reported by healthcare providers and their

corresponding laboratory findings (for example renal profile, liver function test and full blood count) were recorded. Among others, the ADRs data collected were the type of reactions, suspected drugs and the drug-reaction relationship i.e., the causality assessment based on the WHO-UMC causality assessment system [17]. In line with the national pharmacovigilance practice, the WHO Adverse Drug Reactions Terminology (WHO-ART) was used for system organ class (SOC) categorisation [18]. The medical records of the patients were reviewed to complete the ADR report forms with any missing information.

The extracted data were cross-checked by members of the research team. Any discrepancies encountered during data extraction were resolved through discussions among research team members, and consensus was reached to finalise the agreement.

Statistical Analysis

Data were analysed by using SPSS version 20. (IBM SPSS Statistics, IBM, New York, US). Categorical data were presented as frequencies and percentages, whereas continuous data were presented as mean ± standard deviations. To calculate the percentages of sociodemographic, clinical, and ADR characteristics among DR-TB patients, the numerator comprised the frequencies of the relevant parameters. The denominator, respectively, was the total number of patients for sociodemographic and clinical characteristics and the total number of reported ADRs for ADR characteristics in each regimen. A p-value < 0.05 was set as a significant result.

Results

A total of 84 patients aged 18 to 68 years old were included in the study. Among the 84 eligible patients, 42.9% (n = 36) and 57.1% (n = 48) were in the STR and LTR group, respectively. Demographic data of the eligible patients are shown in Table 1.

Treatment outcomes

The characteristics of treatment outcomes are shown in Table 2. Overall, the treatment outcome was classified as 'successful' (i.e. cured and treatment complete) for 45 (53.6%) patients. The proportion of patients with successful treatment outcome was higher in the LTR (n = 26, 54.2%) as compared to the STR (n = 19, 52.8%) group. However, this difference was not statistically significant. About 8.3% (n = 3) and 16.7% (n = 8) patients in the STR and LTR group, respectively, were lost to follow-up. The proportion of patients with treatment failure was higher in the STR group (n = 5, 13.9%).

Adverse Drug Reactions

A total of 110 ADR cases were evaluated among 62 patients (73.8%) who experienced at least one ADR related to DR-TB treatment (Figure 1). Most of the ADRs (n = 80, 72.7%) were reported among patients (n = 35, 61.4%) in the LTR. Overall, kanamycin (n = 32, 29.1%) was the most commonly suspected drug to cause ADR, followed by cycloserine (n = 22, 20%) and ethambutol (n = 20, 18.2%). The extent of reaction was mild in 56.7% (n = 17) and 46.3% (n = 37) of the ADRs that occurred in the STR and LTR, respectively. Gastrointestinal system disorders (n = 31, 28.2%), hearing and vestibular disorders (n = 14, 12.7%), and psychiatric disorders (n = 11, 10%) were the highest SOC involved in the reported ADRs during DR-TB treatment. The most common description of reactions associated with gastrointestinal system disorders were vomiting (n = 19, 61.3%), nausea (n = 7, 22.6%), and epigastric pain (n = 5, 16.1%). Additional details regarding the ADRs reported in relation to the treatment regimens are presented in Table 3.

Discussion

This study aimed to compare the treatment outcome and ADRs between STR and LTR for DR-TB management in patients attending the National Respiratory Centre in Malaysia. An

overall successful treatment outcome was found in 53.6% of the patients included in this study. The proportion of successful treatment outcomes was higher in the LTR (n = 26, 54.2%) group as compared to the STR (n = 19, 52.8%) group. Although the WHO guidelines recommended the STR as the first choice for DR-TB patients who met treatment requirements, the newer guidelines advocate that the LTR remains a valid option if the STR cannot be implemented [19]. To guide decisions on appropriate regimens, determinant factors defining treatment regimen choice, such as efficacy, safety, patient preference, clinical judgment, results of susceptibility testing, patient treatment history, age, severity, and site of the disease [20], should be carefully and systematically considered.

Unsuccessful treatment outcome was observed in 46.4% of DR-TB patients, with proportions of 47.2% and 45.8% noted for STR and LTR, respectively. Lost to follow-up and patient being transferred out to another health facility were the main reasons for unsuccessful treatment. The proportion of patients who were lost to follow up was lower (8.3%) in the STR as compared to the LTR (16.7%) group. Similar findings were reported in a study conducted in Indonesia [6]. The prevalence of lost to follow-up was found to be relatively lower in the STR, likely attributed to its shorter treatment duration, which reduces patients' exposure to undesirable side effects, minimises pill burden, and shortens the duration of injectable administrations. While the current study did not evaluate the determinant factors of loss to follow-up among DR-TB patients, evidence from the literature suggests that psychosocial and economic aspects are correlated with an increased number of loss to follow-up cases [21].

In this study, 73.8% of patients undergoing DR-TB treatment experienced at least one ADR, with 56.5% occurring in patients on the LTR. The prevalence of ADRs reported in this study aligns with the findings of previous studies conducted among DR-TB patients [22] [23]. However, the prevalence of ADRs reported among DR-TB patients in this study was higher than the rate (35.7%) reported in another local study conducted among newly diagnosed pulmonary TB patients [24]. Despite only about 1% of national ADR reports involving anti-TB drugs [25], the occurrence of ADRs among DR-TB patients warrants attention due to its impact on the treatment plan [26], patients' quality of life [27], and cost of DR-TB treatment [28].

Adverse drug reactions involving the gastrointestinal system disorders were the most commonly observed ADRs in both the STR (53.3%) and LTR (18.8%) group. The proportion of ADRs involving gastrointestinal system disorders fell within the range of proportions (5.98% to 66.7%) reported in previous studies, where gastrointestinal system disorders were observed as the most common ADRs in DR-TB patients [8] [29] [30]. The management of gastrointestinal system disorders due to DR-TB treatment was not assessed in this study. However, the local clinical practice guidelines recommend symptomatic treatments as ADR management strategy for patients experiencing gastrointestinal system disorders due to DR-TB treatment [13]. This strategy has also been successfully applied in other studies, where temporary or permanent suspension of the causative agents was avoided, thereby facilitating the continuity of treatment [8] [31]). Pharmacists can play a vital role in identification, management and reporting of ADRs by providing customised patient education and addressing pharmaceutical care issues in DR-TB patients [32]. Locally, the Medication Therapy Adherence Clinic (MTAC) is an existing service provided by pharmacists to monitor drug therapy and offer information to patients, enhancing their understanding of pharmacotherapy treatments. A similar approach could be employed to establish a Tuberculosis Medication Therapy Adherence Clinic (TB MTAC) for this purpose.

The primary strength of this study lies in presenting findings based on real-world data. Nevertheless, the study has several limitations, mainly associated with its retrospective design.

Firstly, the completeness of available data posed a significant challenge during the data collection phase. This challenge was addressed by clarifying data with treating physicians and retrieving pertinent information from source documents other than the patients' medical records available at the study site. Furthermore, the study is limited in reporting patients' compliance, a factor known to influence treatment outcomes [33]. Considering these limitations, future studies evaluating comparisons of treatment outcomes and ADRs among STR and LTR DR-TB patients should consider a prospective cohort study design to enhance the completeness of data collection, including information on patients' compliance. Additionally, areas scarcely explored in the management of DR-TB, such as the cost-effectiveness of treatment and the development of an ADR trigger tool specific to TB management, could be subjects for exploration in future research.

Conclusion

This study revealed a higher proportion of successful treatment outcomes and occurrences of ADRs in the LTR group compared to the STR group. Future studies could focus on a well-designed prospective studies to confirm the observed findings from this retrospective analysis, thus facilitating treatment decisions and enabling a deliberate choice of appropriate treatment regimens.

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Declaration of conflicting interests

The authors declares that there is no conflict of interest.

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Table 1. Sociodemographic and clinical characteristics of drug-resistant tuberculosis patients

Characteristics		STR, n (%)	LTR, n (%)	Total, n (%)	*p* - value
Number of patients		36 (42.9)	48 (57.1)	84	-
Age (years), mean ± SD		37.8 ± 14.6	43.8 ± 13.5	41.2 ± 14.2	*p*=0.053
Weight (kg), mean ± SD		54.9 ± 13.4	54.8 ± 10.3	54.8 ± 11.7	*p*=0.971
Gender					
	Male	22 (61.1)	37 (77.1)	59 (70.2)	*p*=0.113
	Female	14 (38.9)	11 (22.9)	25 (29.8)	
Citizenship					
	Malaysian	28 (77.8)	41 (85.4)	69 (82.1)	*p*=0.366
	Non-Malaysian	8 (22.2)	7 (14.6)	15 (17.9)	
Ethnicity					
	Malay	13 (36.1)	25 (52.1)	38 (45.2)	*p*=0.537
	Chinese	10 (27.8)	8 (16.7)	18 (21.4)	
	Indian	3 (8.3)	5 (10.4)	8 (9.5)	
	Others	2 (5.6)	3 (6.3)	5 (6)	
	Foreigner	8 (22.2)	7 (14.6)	15 (17.9)	
Co-morbidities					
	Yes	20 (55.6)	34 (70.8)	54 (64.3)	*p*=0.148
	No	16 (44.4)	14 (29.2)	30 (35.7)	
Smoking status					
	Smoker	7 (19.4)	13 (27.1)	20 (23.8)	*p*=0.128
	Ex-smoker	7 (19.4)	18 (37.5)	25 (29.7)	
	Non-smoker	17 (47.2)	13 (27.1)	30 (35.7)	
	Unknown	5 (13.9)	4 (8.3)	9 (10.7)	
Mode of transmission					
	Primary	9 (25)	15 (31.3)	24 (28.6)	*p*=0.53
	Acquired	27 (75)	33 (68.8)	60 (71.4)	
Types of DR-TB					
	MDR-TB	9 (25)	25 (52.1)	34 (40.5)	*p*=0.012
	RR/IR - TB	27 (75)	23 (47.9)	50 (59.5)	

DR-TB=drug-resistant tuberculosis; IR-TB=Isoniazid-resistant tuberculosis; LTR=Longer treatment regimen; MDR-TB=Multidrug-resistant tuberculosis; RR-TB=Rifampicin-resistant tuberculosis; SD=Standard deviation; STR=Shorter treatment regimen.

Table 2. Treatment outcome characteristics and culture smear conversion of drug-resistant tuberculosis patients

Characteristics	STR, n = 36 (%)	LTR, n = 48 (%)	Total, n=84 (%)	*p*-value
Treatment outcome classifications				
Successful	19 (52.8)	26 (54.2)	45 (53.6)	*p*=0.899
Unsuccessful	17 (47.2)	22 (45.8)	39 (46.4)	
Treatment outcome*				
Cured	22 (61.1)	29 (60.4)	51 (60.7)	Not evaluated**
Treatment complete	18 (50)	29 (60.4)	47 (55.9)	
Treatment failure	5 (13.9)	3 (6.3)	8 (9.5)	
Death	0 (0)	3 (6.3)	3 (3.6)	
Lost to follow-up	3 (8.3)	8 (16.7)	11 (13.1)	
Not evaluated	7 (19.4)	5 (10.4)	12 (14.3)	
Sputum smear conversion time				
1-3 months	22 (61.1)	27 (56.3)	49 (58.3)	*p*=0.727
4-6 months	1 (2.8)	1 (2.1)	2 (2.4)	
>6 months	0 (0)	1 (2.1)	1 (1.2)	
Unknown	13 (36.1)	19 (39.5)	32 (38.1)	

*Patients may have more than one type of treatment outcome
**The data was analysed descriptively due to the absence of statistical difference in the treatment outcome classification between STR and LTR and the treatment outcome data are not mutually exclusive.
LTR=Longer treatment regimen; STR=Shorter treatment regimen.

Table 3. Characteristics of Adverse Drug Reactions Reported among Patients with Drug-resistant Tuberculosis

Characteristics	**STR, n (%)**	**LTR, n (%)**	**Total, n (%)**
No. of pts experienced ADR	27 (75)	35 (72.9)	62 (73.8)
No. of ADR reported	30 (27.3)	80 (72.7)	110 (100)
Top three SOC			
Gastrointestinal system disorders	16 (53.3)	15 (18.8)	31 (28.2)
Hearing and vestibular disorders	2* (6.7)	12 (15)	14 (12.7)
Psychiatric disorders	3 (10)	8 (10)	11 (10)
Top three suspected drugs			
Kanamycin	9† (30)	23‡ (28.8)	32 (29.1)
Ethambutol	9† (30)	11 (13.8)	20 (18.2)
Cycloserine	8† (26.7)	14‡ (17.5)	22 (20)
Ethionamide	6 (20)	13‡ (16.3)	13 (11.8)
Extent of reaction			
Mild	17 (56.7)	37 (46.3)	54 (49.1)
Moderate	10 (33.3)	41 (51.2)	51 (46.4)
Severe	3 (10)	2 (2.5)	5 (4.5)
Seriousness of reaction			
Life threatening	1 (3.3)	2 (2.5)	3 (2.7)
Caused or prolonged hospitalisation	6 (20)	23 (28.7)	29 (26.4)
Caused disability or incapacity	2 (6.7)	21 (26.3)	23 (20.9)
Caused birth defect	0	0	0
Not serious	21 (70)	34 (42.5)	55 (50)
Outcome			
Recovered fully	21 (70)	33 (41.2)	54 (49.1)
Recovering	4 (13.3)	19 (23.8)	23 (20.9)
Not recovered	0	8 (10)	8 (7.3)
Unknown	5 (16.7)	19 (23.8)	24 (21.8)
Fatal	0	1 (1.2)	1 (0.9)
Causality			
Certain	7 (23.3)	37 (46.3)	44 (40)
Probable	4 (13.3)	20 (25)	24 (21.8)
Possible	18 (60)	18 (22.5)	36 (32.7)
Unlikely	1 (3.3)	2 (2.5)	3 (2.7)
Unclassifiable	0	3 (3.7)	3 (2.7)

ADR=Adverse Drug Reactions; LTR=Longer Treatment Regimen; SOC=System Organ Class; STR=Shorter Treatment Regimen.

The extent and nature of adverse drug reactions between the STR and LTR group was descriptively analysed as about 50% of the data contained minimum cell values <5.

*Application site disorders, cardiovascular disorders, and investigations were also identified as top three SOC in STR, each associated with two reported cases

†Top three suspected drugs causing ADR in STR group

‡Top three suspected drugs causing ADR in LTR group

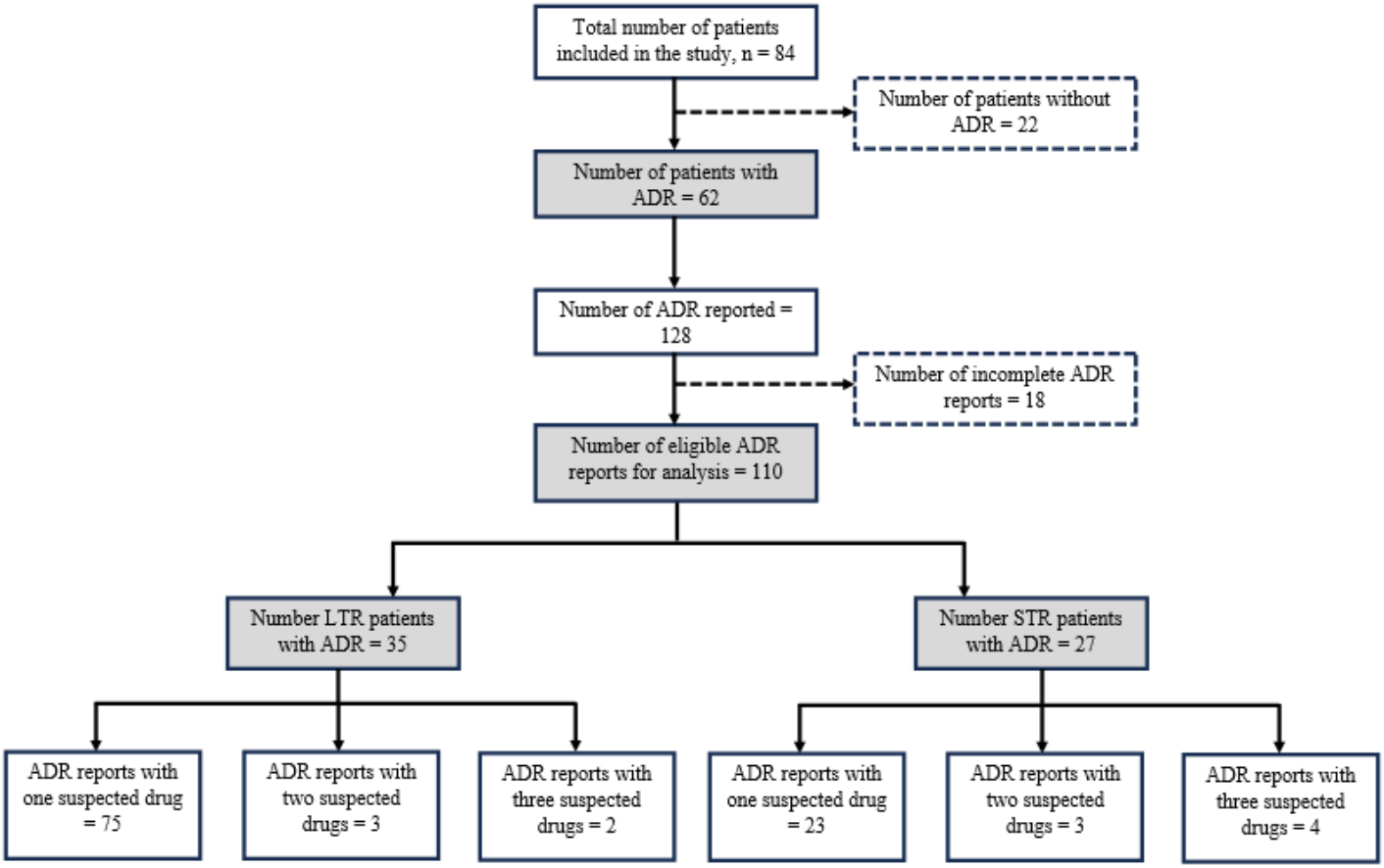

Figure 1. Adverse drug reaction reports included in the study.
ADR=Adverse Drug Reaction, LTR=Longer treatment Regimen, STR=Shorter Treatment Regimen

References

[1]. World Health Organization. Global Tuberculosis Report. 2020.

[2]. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. 2022.

[3]. Falzon D, Jaramillo E, Schünemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J. 2011 Sep 1;38(3):516 LP – 528.

[4]. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J. 2017 Mar 1;49(3):1602308.

[5]. Wahid A, Ghafoor A, Khan AW, Al-Worafi YM, Latif A, Shahwani NA, et al. Comparative effectiveness of individualized longer and standardized shorter regimens

in the treatment of multidrug resistant tuberculosis in a high burden country. Front Pharmacol. 2022;13:973713.

[6]. Indarti HT, Kristin E, Soedarsono S, Endarti D. Treatment Outcomes of Multidrug-Resistant Tuberculosis Patients in East Java, Indonesia: A Retrospective Cohort Analysis. Int J Mycobacteriology. 2022;11(3).

[7]. Abidi S, Achar J, Assao Neino MM, Bang D, Benedetti A, Brode S, et al. Standardised shorter regimens versus individualised longer regimens for rifampin- or multidrug-resistant tuberculosis. Eur Respir J. 2020 Mar;55(3).

[8]. Massud A, Syed Sulaiman SA, Ahmad N, Shafqat M, Chiau Ming L, Khan AH. Frequency and Management of Adverse Drug Reactions Among Drug-Resistant Tuberculosis Patients: Analysis From a Prospective Study. Front Pharmacol. 2022 Jun 2;13:883483. https://doi.org/10.3389/fphar.2022.883483.

[9]. Schnippel K, Firnhaber C, Berhanu R, Page-Shipp L, Sinanovic E. Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings: a systematic review and meta-analysis. J Antimicrob Chemother. 2017 Jul 1;72(7):1871–9. https://doi.org/10.1093/jac/dkx107

[10]. Wu S, Zhang Y, Sun F, Chen M, Zhou L, Wang N, et al. Adverse Events Associated With the Treatment of Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-analysis. Am J Ther. 2016 Mar-Apr;23(2):e521-30. https://doi.org/10.1097/01.mjt.0000433951.09030.5a.

[11]. Malaysian Health Technology Assessment Section (MaHTAS), Ministry of Health Malaysia. Clinical Practice Guideline. Management of Tuberculosis, 4th Edition. 2021.

[12]. World Health Organization. The End TB Strategy. 2015.

[13]. Ministry of Health Malaysia. Clinical Practice Guideline, Management of Drug-Resustant Tuberculosis, 1st Edition. 2016 https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG Management of Drug Resistant TB.pdf [accessed 27 March 2021].

[14]. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med. 2007 Oct 16;147(8):W163-94. https://doi.org/10.7326/0003-4819-147-8-200710160-00010-w1.

[15]. Malaysian Pharmacovigilance Guidelines, 2nd Edition 2016. National Pharmaceutical Regulatory Agency.

[16]. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 and January 2020). 2013. https://apps.who.int/iris/bitstream/handle/10665/79199/9789241505345_eng.pdf?sequence=1&isAllowed=y [accessed 11 December 2023].

[17]. The Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf [accessed 27 December 2022].

[18]. Rosli R, Ming LC, Aziz NA, Manan MM, Abd Aziz N, Manan MM. A Retrospective Analysis of Spontaneous Adverse Drug Reactions Reports Relating to Paediatric Patients. PLoS One. 2016;11(6):e0155385. https://doi.org/10.1371/journal.pone.0155385.

[19]. Vanino E, Granozzi B, Akkerman OW, Munoz-Torrico M, Palmieri F, Seaworth B, et al. Update of drug-resistant tuberculosis treatment guidelines: A turning point. Int J Infect Dis. 2023;130:S12–5. https://doi.org/10.1016/j.ijid.2023.03.013.

[20]. Organization WH. WHO operational handbook on tuberculosis. Module 4: treatment-drug-resistant tuberculosis treatment, 2022 update. World Health Organization; 2022.

[21]. Soedarsono S, Mertaniasih NM, Kusmiati T, Permatasari A, Juliasih NN, Hadi C, et al. Determinant factors for loss to follow-up in drug-resistant tuberculosis patients: the importance of psycho-social and economic aspects. BMC Pulm Med]. 2021;21(1):360. https://doi.org/10.1186/s12890-021-01735-9

[22]. Babu LP, Robin N, Babu J V, Jose J, George S. Adverse drug reactions among drug-resistant tuberculosis treatment: An observational cohort study. Int J Pharm Pharm Sci. 2021;13:50–5.

[23]. Unar AA, Dayo A, Ghoto MA, Unar K, Khokhar MA. Evaluation of treatment outcomes and adverse effects of drug resistant tuberculosis patients at Larkana and Sukkur tuberculosis centres. Pakistan J Physiol. 2020;16(2):17–20.

[24]. Fei CM, Hadzliana Z, Ali I, A H, Zainal H, Hyder Ali IA. Evaluation of adverse reactions induced by anti-tuberculosis drugs in hospital Pulau Pinang. Malaysian J Med Sci. 2018;25(5):103–14.

[25]. Ministry of Health Malaysia National Pharmaceutical Regulatory Agency. Malaysian Adverse Drug Reactions Newsletter 2015. https://www.npra.gov.my/images/Publications/Newsletter_MADRAC_Bulletin/Bulletin_MADRAC_April_2015.pdf

[26]. Gualano G, Mencarini P, Musso M, Mosti S, Santangelo L, Murachelli S, et al. 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 [Internet]. 2019 Feb 28;14(2):e0212948. https://doi.org/10.1371/journal.pone.0212948

[27]. Ausi Y, Santoso P, Sunjaya DK, Barliana MI. Between curing and torturing: burden of adverse reaction in drug-resistant tuberculosis therapy. Patient Prefer Adherence. 2021;2597–607.

[28]. Schnippel K, Firnhaber C, Berhanu R, Page-Shipp L, Sinanovic E. Direct costs of managing adverse drug reactions during rifampicin-resistant tuberculosis treatment in South Africa. Int J Tuberc Lung Dis. 2018;22(4):393–8.

[29]. Khan FU, Khan A, Khan FU, Hayat K, Chang J, Khalid W, et al. Assessment of adverse drug events, their risk factors, and management among patients treated for multidrug-resistant TB: A prospective cohort study from Pakistan. Front Pharmacol. 2022;13:876955.

[30]. Shinde MP, Halasawadekar NR, Ramanand SJ, Pore SM, Ramanand JB, Patil PT, et al. A study of adverse drug reactions in patients receiving treatment for multi-drug resistant tuberculosis. Int J Basic Clin Pharmacol. 2017;6(2):354–9.

[31]. Prasad R, Singh A, Gupta N. Adverse drug reactions in tuberculosis and management. indian J Tuberc. 2019;66(4):520–32.

[32]. Nasir M, Khan MA, Ashiq N, Haroon M, Rukh L, Farooq U. Role of the Clinical Pharmacist in adherence to the treatment of Multidrug-Resistant and Extensively Drug Resistant Tuberculosis. Pakistan J Chest Med. 2019;25(1):11–6.

[33]. Tesfahuneygn G, Medhin G, Legesse M. Adherence to Anti-tuberculosis treatment and treatment outcomes among tuberculosis patients in Alamata District, northeast Ethiopia. BMC Res Notes. 2015;8:1–11.