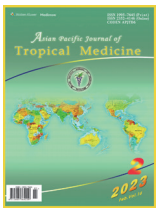

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Treatment outcomes and adverse drug reactions among patients with drug-resistant tuberculosis receiving all-oral, long-term regimens: First record viewing report from Pakistan

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ABSTRACT

Objective: To assess the effectiveness and adverse drug reactions of all-oral regimens for patients with multidrug-resistant tuberculosis.

Methods: This retrospective study was conducted at 10 Programmatic Management of Drug Resistant Tuberculosis sites in Punjab province of Pakistan. Patients receiving treatment for drug resistant tuberculosis from July 2019 to December 2020 with at least interim result *i.e.* 6th month culture conversion or final outcomes (cured, complete, lost to follow-up, failure, death) available, were included in the study. Data was extracted from electronic data management system. For the reporting and management of adverse drug events, active tuberculosis drug safety monitoring and management was implemented across all sites. All the data was analyzed using SPSS version 22.

Results: Out of 947 drug resistant tuberculosis patients included in this study, 579 (68%) of the patients had final outcomes available. Of these, 384 (67.9%) successfully completed their treatment. Out of 368 (32%) patients who had their interim results available, all had their 6th month culture negative. Combining new medications was thought to result in serious adverse outcomes such as QT prolongation. However, this study did not record any severe adverse events among patients.

Conclusions: All-oral regimens formulation guided by overall treatment effectiveness resulted in treatment outcomes comparable to those obtained with traditional injectable treatment.

KEYWORDS: All-oral long-term regimens; Long-term regimens; Bedaquiline; Linezolid; Clofazimine; Drug resistant tuberculosis; Treatment outcomes; aDSM

Significance

The World Health Organization (WHO) shifted conventional injectable regimens to all-oral regimens for the management of tuberculosis in early 2019. Pakistan implemented new regimens in July 2019. WHO claimed oral regimens to be safer and acceptable, with minimal side effects resulting in favorable outcomes. However, there is a scarcity of data in Pakistan to confirm these claims of the WHO. This study was conducted to ascertain the safety and efficacy of all oral regimens in Pakistan. The findings of this study will significantly add to the local literature and enable the National Tuberculosis Control Program to roll out oral regimens safely and confidently.

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1. Introduction

Tuberculosis (TB) is recognized as the tenth most common cause of mortality around the globe. Multidrug-resistant tuberculosis (MDR) is still a severe global public health concern. According to the World Health Organization (WHO), there were approximately 500 000 cases of rifampicin-resistant tuberculosis (RR) worldwide in 2019, of which 78% were MDR-TB. Pakistan ranks fourth in the world for drug-resistant tuberculosis (DR-TB), with an estimated 25 000 cases of rifampicin-resistant tuberculosis (RR-TB), of which 89% are MDR-TB. Pakistan accounts for 5.7% of all TB cases, making it the fifth largest TB burden country in the world[1,2]. According to an estimate, 4.2% of newly diagnosed cases and 7.3% of individuals who had already received treatment are predicted to have drug-resistant tuberculosis[3].

The typical 20-month treatment plan for DR-TB includes fluoroquinolones and an injectable drug for 8 months[4]. This treatment approach has been accompanied by significant side effects, including irreversible hearing loss caused by the injectables, which could have detrimental impacts on patients such as mortality or loss of follow-up[5]. A new drug, Bedaquillin was added to the treatment plan for tuberculosis in 2016[2,6]. Subsequently, an all-oral short regimen and an all-oral long-term regimen were included in the national TB treatment guidelines of Pakistan in 2018 and 2019, respectively. The Directly Observed Treatment Strategy-Plus, which emphasizes the use of second-line drugs in low- and middle-income settings, was one of the strategies the WHO employed in recent decades to facilitate and improve the treatment of patients with MDR-TB in high burden countries, but the cure rate remained below the WHO's target[4]. The treatment success rate for MDR/RR-TB has improved to 59% globally in 2018 as compared to 50% in 2012 when standard regimens was primarily utilized[7].

There have been significant advancements in the treatment of DR-TB with the introduction of new oral drugs (bedaquiline, delamanid, and linezolid). The WHO has revised the treatment guidelines for DR-TB in response to the availability of three additional medications in addition to clofazimine[6]. However, the effectiveness of these medications has been investigated in few studies[5,7]. In efforts to improve the treatment success, the WHO released a new drug classification and recommendations for the treatment of MDR-TB in March 2019. The second-line drugs were reorganized into three groups, including priority drugs (Group A: levofloxacin or moxifloxacin, bedaquiline, linezolid), preferentially used drugs (Group B: Clofazimine, cycloserine or terizidone), and other drugs (Group C: Ethambutol, delamanid, Pyrazinamide, imipenem-cilastatin or meropenem (administered with clavulanic acid), AM or streptomycin, ethionamide or protionamide, para-aminosalicylic acid)[15–17]. In 2018, the WHO approved an injection-free therapy using medications from group A and B for the treatment of MDR-TB. Group C agents (oral and parenteral) were reserved for the cases where group A and group B treatments cannot be used. Three widely used injectable second-line drugs (AM, KM, and CM) are no longer recommended for the treatment of MDR-TB due to their association with subpar outcomes[4,6,8].

The recommendation to deploy all-oral long-term regimens (LTR) in Pakistan was published by the National Tuberculosis Program (NTP) of Pakistan in July 2019[7]. There is a dearth of data from Pakistan about the implementation process, desired effects, and safety profile of all-oral LTR. In this context, a retrospective study was conducted to assess interim treatment outcomes and safety profile among DR-TB patients receiving all-oral regimens at the PMDT sites in Pakistan.

2. Subjects and methods

2.1. Ethical approval

The ethical approval of the study was obtained from Ethical Review Board of Combined Management Unit Tuberculosis, AIDS, Malaria, Islamabad Pakistan with IRB number F. NO.IRB-CMU-2021-20. The ethics committee waived the need for informed consent due to observational nature of the study. The patient identifiers were required for record linkage.

2.2. Study design

This retrospective record viewing study was conducted among DR-TB patients receiving all-oral LTR during July 2019 to December 2020 at 10 PMDT sites in Pakistan.

2.3. Study setting

Programmatic Management of Drug resistant Tuberculosis (PMDT) in Pakistan was started in 2010 and currently, there are 33 PMDT sites all over the country[2]. Punjab is the most populous province of the country, accounting for 56% of the total reported TB cases[8]. Currently there are 10 PMDT sites in Punjab located in tertiary care hospitals (Jinnah Hospital Lahore, Mayo Hospital Lahore, District Head Quarter Hospital Sialkot, District Head Quarter hospital Sargodha, District Head Quarter hospital Faisalabad, Nishtar Hospital Multan, Bahawal Victoria Hospital Bahawalpur, Sheikh Ziad Hospital Rahim Yar khan, Rawalpindi Leprosy Hospital Rawalpindi, Samli Sanitorium Samli Muree). Each PMDT site consisted of eight staff members (a physician, a pharmacist and other allied health care providers) with different roles and responsibilities. Each DR-TB clinic has a separate, well-equipped laboratory for TB-related blood tests. Sputum samples were sent to provincial reference labs in four different cities for line probe assay and *Mycobacterium tuberculosis* culture, and patient samples were sent to the national reference laboratory in Islamabad

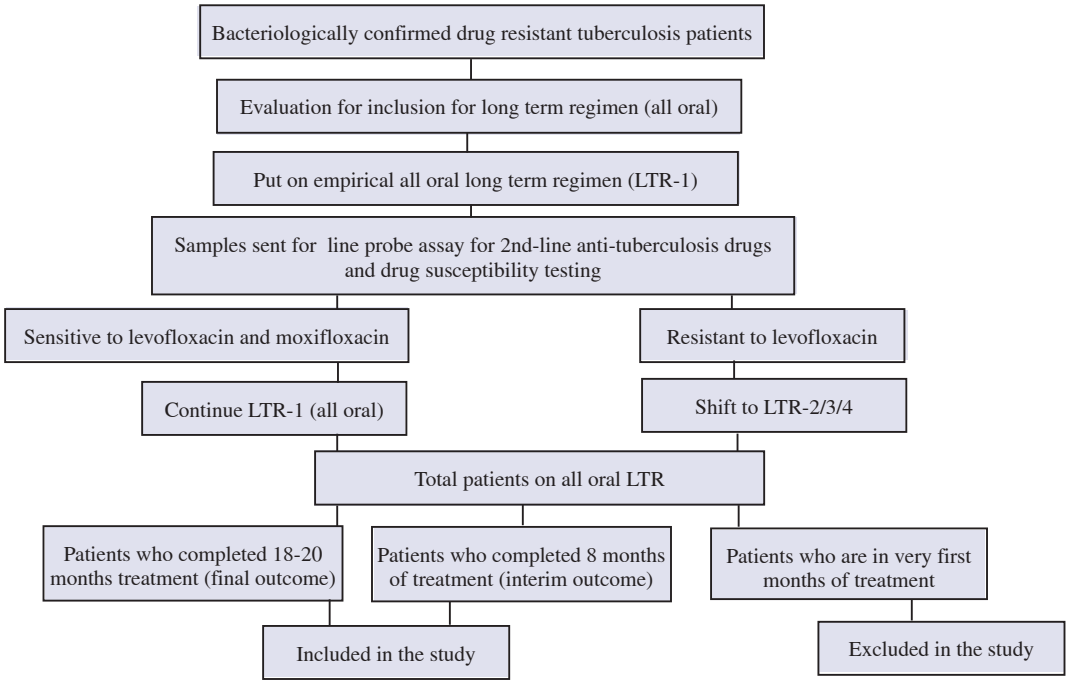

Figure 1. Study flowchart.

Table 1. Drug regimens categories in all-oral, long-term regimens[6,9].

Category	Indication	Regimens with duration
LTR-1	Who do not opt for STR **OR** Who do not qualify for STR (pregnancy, drug intolerance, HIV, disseminated CNS TB, EP with HIV)	6 Lfx, Bdq, Lzd, Cfz, Cs, Z/12 Lfx, Cfz, Cs, Z
LTR-2a	Who are confirmed with levofloxacin resistance by LPA or DST	6 Bdq, Mfx, Lzd, Cfz, Cs, Z/12 Mfx, Cfz, Cs, Z
LTR-3	Who are declared as "Treatment Failure" either on previous or newly proposed treatments	Individualized salvage regimens advised by national/provincial expert panel. For instance: 0 Bdq (9), LZd, Cfz, Cs, Eto, Z, PAS, Dlm (9) (for failures); Depending on culture conversion, BDQ & Dlm can be continued for 12 months & beyond if there is need (3 negative cultures not available)
LRT-4	Who are declared XDR on DST	20 Bdq, Dlm, Lzd, Cfz, Cs, Eto, Z, PAS (XDR confirmed)

STR: Short-term regimens; LTR: Long-term regimens; LPA: Line probe assay; DST: Drug susceptibility test; XDR: Extensive drug resistance.

Table 2. Multidrug-resistant tuberculosis treatment outcomes for all-oral, long-term regimens[2].

Interim outcome	
Culture conversion	When two successive cultures, taken at least 30 days apart, are found to be negative, the culture is deemed to have converted. The date of conversion in this situation is the specimen collection date of the first negative culture.
Final outcomes	
Cured	Treatment has been completed in accordance with National Policy (minimum 18 months, including 16 months since culture conversion), without signs of failure, and three or more consecutive cultures taken at least 30 days apart have returned negative results (after intensive phase in cases where injectable is used)
Treatment completed	Treatment finished as advised by National Policy (minimum 18 months with 16 months since culture conversion) without signs of failure BUT no evidence that three or more consecutive cultures obtained at least 30 days apart are negative.
Treatment failed	At least two anti-TB medications must be changed permanently, or treatment must be discontinued due to: • Lack of conversion1 by the end of the intensive phase; • Bacteriological reversion2 in the continuation phase after conversion to negative; • Evidence of additional acquired resistance; • Adverse drug reactions
Died	A patient who passes away during therapy, regardless of the cause.
Lost to follow-up	A patient whose therapy was stopped for more than two months in a row.
Not evaluated	Patient for whom no assigned treatment outcome exists. This includes patients who have been "transferred out" to another treatment facility and whose prognosis is uncertain.
Treatment success	The sum of treatment completed and cured

(capital of Pakistan) for drug susceptibility testing. All these sites follow a uniform prescription practice of all-oral regimens as per the national guidelines.

2.4. Study population, inclusion and exclusion criteria

All RR/MDR-TB patients receiving all-oral LTR from July 2019 to December 2020 were included in this study. Patients with DR-TB who exhibited additional forms of drug resistance, such as substantial drug resistance, poly-resistance, or mono-resistance, were not included in this study. Of all patients, there was one subgroup of the patients who had completed 18-20 months of treatment for whom final treatment outcomes were declared. Another subgroup of the patients was those who had completed 8 months of treatment for whom interim outcomes were available. Both subgroups were included in study. However, the group of patients for which outcome data was not available, was not included in this study (Figure 1).

2.5. Drugs regimens in all–oral LTR

Table 1 indicates four regimens included in all-oral LTR along with duration for treatment.

2.6. Treatment outcomes

The treatment outcomes among patients were reported in accordance with the WHO recommendations and national guidelines for the uniform recording of treatment outcomes among MDR-TB patients (Table 2)[2]. By the end of the eighth month, the 6th month culture conversion was the primary interim result. When two successive cultures, taken at least 30 days apart, are found to be negative, the culture is deemed to have converted. The date of conversion in this situation is the specimen collection date of the first negative culture. Gaining weight, a reduction in TB symptoms, and an improvement in chest X-rays were among the other interim results.

2.7. Data collection and management

The data of DR-TB patients at PMDT were extracted from Electronic Nominal Record System (ENRS). The ENRS contains information about sociodemographic, clinical conditions, and medical therapies. During the monitoring and evaluation visits, the patients' TB treatment cards and medical records were randomly checked against the retrieved data to ensure its accuracy. Data was entered in a pre-designed structured data collection form. The data regarding adverse drug reactions (ADRs) were extracted from Active Tuberculosis Drug Safety Monitoring and Management (aDSM). The aDSM is a newly established system by the National Tuberculosis Control Program in Pakistan for monitoring ADRs among DR-TB patients. It includes active screening and diagnosis of ADRs. The aDSM is a part of ENRS[2]. Patients were anonymized before extraction of data. All the physical and electronic data of the patients were lock/key and password protected, respectively. Only authorized investigators had access to patients' data.

2.8. Data analysis

All the data were analyzed through EpiData software. The data were initially prepared in spreadsheet for cleaning purposes. Subsequently, the data were transferred to software for descriptive analysis. The categorical variables were presented in counts and proportions (%). On the other hand, the continuous data were presented as mean and standard deviations.

3. Results

A total of 947 DR-TB patients were included in this study (Table 3) and 56.0% of them were males. Most of the participants (42.2%) aged 15 to 54 years and 75.7% of the patients were from all-oral LRT-1 group, followed by LTR-2a (21.4%). The majority of the patients (97%) had pulmonary TB. Nearly two thirds (68.0%) of the patients had previously received treatment for TB. Diabetes (16.0%) was the most prevalent co-morbid condition, while only 0.6% patients had HIV positive. The average body weight of the patients was (47.5±12.8) kg at the beginning of the treatment and (49.0±12.9) kg at the end of the therapy. At the outset, 720 (76.0%) patients had a positive sputum smear for AFB, while 924 (97.0%) patients had their Gene Xpert available. Likewise, 700 (73.9%) had positive cultures at baseline (Table 3).

Arthralgias was the most frequent (18.4%) ADR among the study participants, followed by myelosuppression (12.4%), allergic response (11.0%), gastro-intestinal toxicity (9.9%), and hepatotoxicity (9.7%). Most of these ADRs were minor and did not cause any interruption or alteration in the treatment (Table 4). The frequency distribution of ADRs was similar in sub-groups of patients.

The interim therapy results were available for 368 patients and their final results were pending. Of these, sputum conversion (*via* smear and culture) at the end of the eighth month of treatment was recorded in 248 individuals (67.4%), which is indicative of a successful interim treatment outcome. Additionally, 579 patients had final results available at the time of data collection. Of these, 361 (62.3%) were cured, and 23 (4%) had outcome as treatment completed. Of 195 patients with unfavorable treatment outcomes, 144 died, 45 lost the follow-up, and two patients experienced the treatment failure (Table 5).

Table 3. Socio-demographics and clinical characteristics of drug resistant tuberculosis patients on all-oral, long-term regimens registered at 10 programmatic management of drug resistant tuberculosis sites of Punjab from 2019 to 2020 [*n* (%)].

Characteristics	LTR (*n*=947)	LTR-1 (*n*=717)	LTR-2a (*n*=203)	LTR-3 (*n*=6)	LTR-4 (*n*=21)
Sex					
Male	530 (56.0)	397 (55.4)	117 (57.6)	3 (50.0)	13 (61.9)
Female	417 (44.0)	320 (44.6)	86 (42.4)	3 (50.0)	8 (38.1)
Age, years					
<15	28 (3.0)	24 (3.3)	4 (2.0)	0	1 (4.8)
15-34	399 (42.2)	291 (40.6)	99 (48.8)	1 (16.7)	8 (38.1)
35-54	303 (32.3)	223 (31.1)	69 (34.0)	4 (66.7)	7 (33.3)
>54	217 (23.9)	179 (25.0)	31 (15.3)	1 (16.7)	6 (28.6)
Residence					
Urban	455 (48.4)	353(49.2)	92 (45.3)	1 (16.7)	9 (42.9)
Rural	492 (52.3)	364 (50.8)	111 (54.7)	5 (83.3)	12 (57.1)
Smokers	132 (14.0)	96 (13.4)	29 (14.3)	3 (50.0)	4 (19.0)
Diagnostic tests					
Xpert MTB					
MTB and RR detected	924 (97.6)	701 (97.8)	198 (97.5)	6 (100.0)	19 (90.5)
Not available	23 (2.4)	16 (2.2)	5 (2.5)	0	2 (9.5)
AFB smear microscopy					
Positive	720 (76)	522 (72.8)	175 (86.2)	4 (66.7)	19 (90.5)
Negative	193 (20.4)	162 (22.6)	27 (13.3)	2 (33.3)	2 (9.5)
Not done	34 (3.6)	33 (4.6)	1 (0.5)	0	0
LPA-2					
Isoniazid and rifampicin	490 (51.7)	442 (61.6)	45 (22.2)	2 (33.3)	1 (4.8)
Isoniazid and rifampicin & levofloxacin	179 (18.9)	34 (4.7)	139 (68.5)	3 (50.0)	3 (14.3)
Isoniazid and rifampicin, levofloxacin & second line injectable	23 (2.4)	10 (43.5)	0	0	13(61.9)
Not available	255 (26.9)	231 (32.3)	19 (9.4)	1 (16.7)	4 (19.0)
Culture					
Positive	700 (73.9)	497 (69.3)	183 (90.1)	4 (66.7)	16 (76.2)
Negative	126 (13.3)	115 (16.0)	6 (3)	2 (33.3)	3 (14.3)
Not available	121 (12.8)	105 (14.6)	14 (6.9)	0	2 (9.5)
DST					
Isoniazid and rifampicin	314 (33.2)	285 (39.7)	27 (13.3)	2 (33.3)	0
Isoniazid and rifampicin & levofloxacin	155 (16.4)	27 (3.8)	117 (57.6)	3 (50.0)	8 (38.1)
Isoniazid and rifampicin, levofloxacin & second line injectable	31 (3.3)	11 (1.5)	17 (8.4)	0	3 (14.3)
Not available	429 (45.3)	376 (52.4)	42 (20.7)	1 (16.7)	10 (47.6)
Sensitive to all	18 (1.9)	18 (2.5)	0	0	0
Basis of diagnosis					
Bacteriological	944 (99.7)	714 (99.6)	203 (100.0)	6 (100.0)	21 (100.0)
Clinical	3 (0.3)	3 (0.4)	0	0	0

LTR: Long term regimen; HIV/AIDS: Human immune deficiency virus/acquired immune deficiency disease; Xpert MTB: Xpert *Mycobacterium tuberculosis*; RR: Rifampicin resistant; LPA: Line probe assay; DST: Drug susceptibility test; AFB: Acid fast bacilli.

Table 4. Adverse drug reactions reporting among drug resistant tuberculosis patients registered on all-oral long-term regimens at 10 programmatic management of drug resistant tuberculosis sites of Punjab from July 2019 to December 2020 [*n* (%)].

Adverse drug reactions	LTR (*n*=947)	LTR-1 (*n*=717)	LTR-2a (*n*=203)	LTR-3 (*n*=6)	LTR-4 (*n*=21)
Allergic reaction	104 (11.0)	78 (10.9)	22 (10.8)	1 (16.7)	3 (14.3)
GI irritation	94 (9.9)	74 (10.3)	18 (8.9)	0	3 (14.3)
Hepatitis	92 (9.7)	69 (9.6)	21 (10.3)	0	2 (9.5)
QT prolongation	57 (6.0)	39 (5.4)	18 (8.9)	0	0
Palpitations	18 (1.9)	15 (2.1)	3 (1.5)	0	0
Arthralgias	174 (18.4)	138 (19.2)	32 (15.8)	1 (16.7)	3 (14.3)
Myelosuppression	117 (12.4)	89 (12.4)	24 (11.8)	1 (16.7)	3 (14.3)
Peripheral neuropathy	88 (9.3)	71 (9.9)	18 (8.9)	1 (16.7)	0
Renal injury	21 (2.2)	15 (2.1)	6 (3.0)	0	0
Depression	60 (6.3)	51 (7.1)	9 (4.4)	0	0
Anxiety	42 (4.4)	36 (5.0)	6 (3.0)	0	0
Psychosis	25 (2.6)	19 (2.6)	5 (2.5)	0	1 (4.8)
Retinopathy	69 (7.3)	61 (8.5)	6 (3.0)	1 (16.7)	1 (4.8)

LTR: Long term regimen, GI: Gastro-intestinal, QT: QT wave.

Table 5. Treatment outcomes of drug resistant tuberculosis patients on all-oral long-term regimens registered at 10 programmatic management of drug resistant tuberculosis sites of Punjab from 2019 to 2020 [*n* (%)].

Treatment outcomes	LTR	LTR-1	LTR-2a	LTR-3	LTR-4
Interim outcomes (*n*=368)					
Sputum conversion by the end of 8th months (smear + culture)	248 (47.4)	198 (53.8)	44 (21.7)	0	6 (1.6)
Weight gain	214 (58.2)	169 (45.9)	38 (18.7)	1 (0.3)	6 (1.6)
Improvement in CXR	313 (85.1)	236 (64.1)	68 (33.5)	1 (0.3)	8 (2.2)
Final outcomes (*n*=579)					
Favorable					
Cured	361 (62.3)	269 (46.5)	79 (13.6)	3 (0.5)	10 (1.7)
Treatment completed	23 (4.0)	18 (3.1)	5 (0.9)	0	0
Unfavorable					
Lost to follow-up	45 (7.8)	36 (6.2)	8 (1.4)	0	1 (0.2)
Died	144 (24.9)	113 (19.5)	28 (4.8)	2 (0.3)	1 (0.2)
Treatment failure	2 (0.3)	1 (0.2)	1 (0.2)	0	0
Not evaluated	4 (0.7)	0	3 (0.5)	0	1 (0.2)

LTR: Long term regimen.

4. Discussion

The evaluation of patients' cohort is a useful modality for assessing the effectiveness of a program-recommended new all-oral WHO treatment regimens[9]. To the best of our knowledge, this is the first study to ascertain safety profile and outcomes among DR-TB patients receiving all-oral LTR.

This large-scale, multi-center retrospective study provides information on safety of new all-oral regimens, frequency and severity of ADRs with novel anti-TB drugs *i.e.*, bedaquiline, delamanid and linezolid containing regimens in Pakistan. Our research revealed a 67.9% treatment success rate among study participants whose final outcomes were available. Only 4.7% of patients lost the follow-up, as compared to 8.45% of patients on conventional therapy in 2018[3]. The case fatality rate was 15% in our study. After the addition of new medications to the all-oral LTR, significant ADRs were not observed during our analysis. The severity of ADRs was mild to moderate in nature. Only 9.2% of patients were found to have peripheral neuropathy that is very common with the use of linezolid[18]. Only 6% of the individuals had QT prolongation with long-term bedaquiline containing regimens.

According to the WHO's Global Tuberculosis Report 2021[3], the treatment success rate for DR-TB patients in the cohort of 2015-2018 (who were on a standard regimens including injectables) was 70%. A previous investigation conducted on conventional injectable regimens from Kenya (9%) and two sites in Ethiopia (11% and 12%) revealed a higher rate of lost to follow-up among MDR-TB patients receiving old conventional therapy[10].

This study is primarily strengthened by a large number of participants enrolled in a national setting to evaluate the outcomes and success of all-oral LTR after exclusion of injectables. The second most important contribution of this study is demonstration of the initial steps and efforts by PMDT sites of Punjab Pakistan in implementing aDSM in practice. Last but not least, programmatic data has been used during the analysis that is validated on different levels and authenticated via monitoring and evaluation visits. In this context, the findings of this study carry pivotal implications for future research and practice.

This study is accompanied by a few limitations. First of all, due to the study's cohort being conducted from July 2019 to December 2020, we were unable to obtain the final results for all patients enrolled in this study. The results are presented in a descriptive way, necessitating the need for inferential analysis in future research. Since the data was obtained from a record system, the clinicians' bias may present during the observation of outcomes and ADRs. The selection bias in this study is minimum as all consecutive patients were included in the analysis. The study design limits the exploration of causal relationship between the outcomes and demographics. The sample size in four sub-groups was not similar as last two groups has very less representation in the analysis. However, in the absence of inferential analysis, the impact of less sample in sub-groups will be minimal, but future studies should consider a higher number of samples in each group in order to increase the power of the study. The National Tuberculosis Program should take effective prospective measures to evaluate the patients on all-oral LTR for factors associated with successful and unsuccessful outcomes. There is a little evidence on the safety and efficacy of novel medications in all-oral LTR[1,12], the future research should consider this objective in detailed way. The aDSM system is still not robust enough to rule out the possibility that serious ADRs contribute to the failure of the treatment. The National Tuberculosis Program focus on more active pharmacovigilance surveillance and its relationship with the treatment outcomes.

There is a need to design and implement patient-centered interventions to reduce the influence of various factors associated with the quality-of-life following among DR-TB patients[13]. The introduction of oral regimens present an opportunity to improve the medication adherence among DR-TB patients. A good indicator of projecting progress as well as the efficacy and success of treatment might be found in the interim treatment results among MDR-TB

patients[14]. In addition, these findings support the importance of examining interim treatment outcomes to gauge the efficacy of anti-TB therapy.

The findings of this study confirm the relative safety of new drugs (bedaquiline. linezolid and delamanid) among patients with DR-TB patients receiving all-oral LTR. These results indicate support the WHO's recent recommendations for the widespread use of new regimens for patients with DR-TB. In addition, this study underscores the effectiveness of aDSM system at PMDT sites. The aDSM provides a standardized, regular, close, and active recording and reporting model with a common protocol that is practical and helpful for monitoring of safety of anti-TB medications.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

HA: Principal investigator, study concept and design, data analysis and interpretation, paper preparation, and final manuscript version approval. AO, RF, AY, WU, AK, UR, YHK, THM: Study conception and design, data analysis and interpretation, preparation of the paper, and approval of the final manuscript version.

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