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Investigating the Effectiveness of Long-term Regimen versus Short-term Regimen in Treating Drug Resistant Tuberculosis and their Treatment Outcomes

Sajjad Ali[1], Rumman[2]✉, Ashraf[3], Ubaid Ullah[2], Abdul Ghafoor[4], Haroon Latif Khan[5], Faisal Younas[6], Akmal Naveed[6]

[1]Department of Pulmonology, Medical Teaching Institution Mardan Medical Complex/Bacha khan Medical College, Mardan - Pakistan. [2]Programmatic Management of Drug Resistant Tuberculosis Unit, Mardan Medical Complex, Mardan - Pakistan [3]Pro-Gene Diagnostics and Research Laboratory, Mardan - Pakistan [4]National Tuberculosis Control Program, Khyber Pakhtunkhwa - Pakistan [5]Provincial Tuberculosis Control Program, Khyber Pakhtunkhwa - Pakistan [6]Associaton for Community Development, Khyber Pakhtunkhwa - Pakistan

Corresponding Author:
Rumman
Programmatic Management of Drug Resistant Tuberculosis Unit,
Mardan Medical Complex,
Mardan-Pakistan
Email: rummankpk@gmail.com

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A B S T R A C T

Background: Drug-resistant tuberculosis, defined by resistance to conventional antitubercular medications, presents significant treatment challenges. The efficacy of long-term versus short-term treatment regimens in managing this condition remains a critical area of investigation.

Objective: To assess how different treatment durations, both long-term and short-term regimen, influence the rates of treatment success, treatment failure, and mortality among patients suffering from drug-resistant tuberculosis.

Methodology: This prospective cohort study was conducted from June 2021 to June 2023 in the Department of pulmonology, Mardan Medical Complex, Khyber Pakhtunkhwa, Pakistan. In this study DR-TB patients were enrolled. Patients were randomly assigned to long-term or short-term regimens. The long-term regimen (LTR) consists of treatment for 18-20 months, while the short-term regimen (STR) was 11 months, based on the latest World Health Organization (WHO) consolidated guidelines on drug-resistant tuberculosis. Data analyses were conducted with utilizing the SPSS (v.29.0).

Results: A total of 178 DR-TB patients were enrolled in this study. Gender distribution showed 45 males (47.36%) and 50 females (52.63%) in the STR group, and 46 males (55.42%) and 37 females (44.57%) in the LTR group. Significant age differences were noted, with mean ages of 34.16 years (±16.76) in the STR group and 41.71 years (±18.44) in the LTR group. Treatment outcomes revealed 86.31% treatment success rate in the STR group vs 79.51% in the LTR group, with death rates of 4.21% vs. 9.63%.

Conclusion: Our findings suggest that, while both approaches produce comparable treatment Success rate, however, short-term regimens may be a viable alternative to long-term treatments in specific patient groups that are younger, potentially improving adherence and lowering healthcare costs.

Keywords: Tuberculosis; Multidrug-Resistant Tuberculosis; Antitubercular Agents; Treatment Outcome; Drug Therapy

Introduction

The battle against drug-resistant tuberculosis (TB) represents one of the most complex challenges in the global health arena.[1] Despite considerable advancements in medical science, TB remains to be a significant cause to illness and death worldwide, especially in nations with lower and Moderate-income levels.[2] The development of resistant strains of TB has further complicated the landscape, necessitating a reevaluation of treatment regimens to effectively combat this public health threat.

Resistant tuberculosis, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, possess significant challenges to eradication efforts.[3] These strains of TB have no respond to the official, first-line drugs, so they requiring complicated therapy of having longer duration and multiple more drugs that are often more toxic and less effective.[4]The main aim of this study lies in comparing the long treatment regimen and shorter treatment regimen designed to manage DR-TB. This comparison is critical as it influences not only treatment outcomes but also patient compliance, potential side effects, and the overall public health approach to managing TB.

Long-term regimens, often extending beyond 18 months, have been the cornerstone of drug-resistant TB management.[5] These regimens involve a combination of multiple antibiotics and sometimes surgical interventions to combat the resilient strains.[6] However, the prolonged duration of treatment, coupled with the adverse effects of long-term antibiotic use, raises concerns regarding patient adherence, the risk of developing further resistance, and the overall feasibility of such an approach in resource-limited settings.

On the other hand, short-term regimens, lasting 9 to 12 months, have emerged as a promising alternative, potentially offering similar or improved effectiveness while reducing the burden on patients and healthcare systems.[7] These regimens aim to improve patient compliance and reduce the healthcare costs associated with long-term treatment.[8] However, the efficiency and safety of these shorter regimens in various populations and settings remain a subject of ongoing research and debate.

The rational for investigating the effectiveness of long-term versus short-term treatment regimens in managing drug-resistant tuberculosis (DR-TB) stems from the urgent need to improve treatment outcomes and reduce the burden of this global health challenge. Drug-resistant TB, which includes both multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, resists conventional first-line drugs, necessitating more complex, longer, and often more toxic treatments. This study, conducted at the Mardan Medical Complex in Khyber Pakhtunkhwa, Pakistan, aims to assess how different treatment durations impact treatment success rates, failure rates, and mortality among DR-TB patients. It compares an 18-20 month long-term regimen (LTR) with an 11-month short-term regimen (STR), based on WHO guidelines. The study's findings are crucial as they could potentially recommend shorter regimens that improve patient compliance, reduce adverse effects, and are more feasible in resource-limited settings, thereby influencing global TB management strategies.

Objective

To assess how different treatment durations, both long-term and short-term regimen, influence the rates of treatment success, treatment failure, and mortality among patients suffering from drug-resistant tuberculosis.

Methodology

This prospective cohort study was conducted at the Department of pulmonology of the Mardan Medical Complex Teaching Hospital, located in Khyber Pakhtunkhwa, Pakistan. The study took place from 1st June 2021 to 31th June 2023. A stratified random sampling method was employed to ensure representation from various demographics, including age, and gender. The sample size was calculated based on previous studies' effect sizes, with adjustments for anticipated dropout rates, aiming for adequate statistical power was ensured to detect any significant differences between the two treatment regimens.[9]

Patients diagnosed with DR-TB, including those with multidrug-resistant (MDR-TB), extensively drug-resistant tuberculosis (XDR-TB) and Mycobacterium tuberculosis complex resistance to rifampicin (MTB/Rif Res) were enrolled. Patients of every age and who provided informed consent were included, while those with significant comorbid conditions such as HIV/AIDS, uncontrolled diabetes, or severe liver disease, as well as pregnant or breastfeeding women, were excluded.

Patients were diagnosed with DR-TB and randomly assigned to either a long-term treatment regimen or a short-term treatment regimen. The study was double-blinded to ensure that neither the participants nor the healthcare providers know which treatment is being administered, to prevent bias. The long-term regimen consists of treatment for 18-20 months, while the short-term regimen was 11 months, based on the latest World Health Organization (WHO) guidelines on DR-TB[10] The composition of drug regimens was determined by resistance patterns, patient tolerance, and the latest evidence-based recommendations.

The mean and standard deviation were used to summarize continuous values, whereas frequencies and percentages were used to describe categorical variables. Differences in baseline, clinical, drug resistances characteristics between the two groups were assessed using the chi-squared test for categorical variables and

Table 1. Demographic and Clinical Characteristics of Patients Undergoing Short-Term and Long-Term Regimens for Tuberculosis

Characteristic	All patients	Short-Term Regimen	Long-Term Regimen	P values
Total Patients	178(100)	95(53.37)	83(42.62)	***
Gender				
Male	91(51.12)	45(47.36)	46(55.42)	0.541
Female	87(48.88)	50(52.63)	37(44.57)	
Age	37.93±17.61	34.16±16.76	41.71±18.44	0.032
Weight kg	62.51±11.81	62.32±10.31	63.37±13.31	0.041
Marital status				
Married	154(86.52)	81(85.26)	73(87.95)	0.76
Unmarried	24(13.48)	14(14.74)	10(12.05)	
Smoking History				
Yes	61(34.27)	36(37.89)	25(90.12)	0.13
No	117(65.73)	59(62.11)	58(69.88)	
Lungs cavities				
Yes	102(57.30)	57(60.00)	45(54.22)	0.24
No	76(42.70)	38(40.00)	38(45.78)	
Lungs lesions				
Yes	164(92.13)	86(90.53)	78(93.98)	0.65
No	14(7.87)	09(9.47)	05(6.02)	
Adverse effect				
Ototoxicity	34(19.10)	12(12.63)	22(23.16)	0.041
Gastric Irritation	100(56.18)	60(63.16)	40(42.11)	0.000
Psychosis	07(3.93)	04(4.21)	03(3.16)	0.71
Dysglycemia	03(1.69)	01(1.05)	02(2.11)	1.00
Nephrotoxicity	22(12.36)	13(13.68)	09(9.47)	0.31
Hepatitis	46(25.84)	21(22.11)	25(26.32)	1.00

Skin Pigmentation	14(7.87)	11(11.58)	03(3.16)	0.02
Optic Neuritis	06(3.37)	05(5.26)	01(1.05)	1.00
Myalgia and arthralgia	15(8.43)	07(7.37)	08(8.42)	1.00
Peripheral Neuropathy	12(6.74)	05(5.26)	07(7.37)	0.95
Myelosuppression	15(8.43)	02(2.11)	13(13.68)	0.007
Allergic Reaction	15(8.43)	07(7.37)	08(8.42)	1.00
QT Prolongation ECG	09(5.06)	04(4.21)	05(5.26)	1.00
Depression	10(5.62)	03(3.16)	07(7.37)	0.34
Anxiety	16(8.99)	14(14.74)	12(12.63)	0.56

Data is presented as frequency and percentage or as mean and standard deviation
P value <0.05 is statically significant. P value with *** represent no statistics were computed because the characteristic is either present in 100% or 0% of the population.

the t-test or Mann-Whitney U test for continuous variables, depending on data distribution. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 29.0).

The study adhered to the principles outlined in the Declaration of Helsinki and obtained approval from an institutional review board (IRB). Before enrollment of participants in the study informed consent was attained. Confidentiality of participant information was maintained throughout the study.

Results

In the present study 178 DR-TB patients were enrolled for study purposes. Study cases were divided into two group, i.e. one group included patients who received Short-Term Regimen (STR) treatment (STR Group), while the other group comprised patients who started treatment with Long-Term Regimen (LTR) (LTR Group) strategy at the study center. STR group comprised of 95 (53.37%) cases whereas in LTR group 83 (42.62%) cases were included. Gender distribution showed 45 males (47.36%) and 50 females (52.63%) in the STR group, whereas the LTR group had 46 males (55.42%) and 37 females (44.57%), with the difference not reaching statistical significance (p=0.541). Age presented a significant difference, with the STR group having a mean age of 34.16 years (SD: ±16.76) and the LTR group 41.71 years (SD: ±18.44) (p=0.032). Both groups were predominantly married (86.52% overall), and the breakdown of smoker's patients was 36 (37.89%) in the short-term and 25 (90.12%) in the long-term groups. Clinical characteristics reveal that 102 (57.30%) of patients had lung cavities and 164 (92.13%) had lung lesions, with no significant differences between the groups. Adverse effects showed notable differences: gastric irritation occurred more frequently in the short-term group 60 patients (63.16%) compared to the long-term group 40 patients (42.11%), and myelosuppression was more common in the long-term group 13 patients, (13.68%) than in the short-term group 2 patients, (2.11%). Other side effects such as skin pigmentation was more prevalent in the short-term group 11 patients (11.58%) compared to the long-term group 3 patients, (3.16%) (Table 1).

In terms of drug resistance, the STR group comprised 51 patients (53.68%) with Mycobacterium tuberculosis complex resistance to rifampicin (MTB/Rif Res) and 44 (46.31%) with multidrug-resistant tuberculosis (MDR-TB), while no cases of extensively drug-resistant tuberculosis (XDR-TB) were noted. Conversely, the LTR group had 32 patients (38.55%) with MTB/Rif Res, 47 (56.62%) with MDR-TB, and 4 (4.81%) with XDR-TB. Treatment outcomes showed 82 patients (86.31%) treatment success rate in STR group, associated to 66 (79.51%) in LTR group, with a significance value (p=0.000). STR group had 4 deaths (4.21%) versus 8 (9.63%) in the LTR group. Loss of follow up and cases not evaluated existed minimal and comparable between groups. Treatment failure was observed in 1 patient (1.05%) in the STR group and 4 (4.81%) in the LTR group (Table 2).

All patients in both regimens (95 patients, 100% in the short-term and 83 patients, 100% in the long-term)

Table 2. Short-Term Versus Long-Term Regimen Efficacy in Treating Drug-Resistant Mycobacterium Tuberculosis

Characteristics	All patients	Short-Term Regimen	Long-Term Regimen	P values
Total Patients	178(100)	95(53.37)	83(42.62)	***
Type of Drugs Resistance				
MTB/Rif Res	83(46.63)	51(53.68)	32(38.55)	0.045
MDR-TB	91(51.12)	44(46.31)	47(56.62)	
XDR-TB	04(2.25)	0(0.00)	4(4.81)	
Treatment Outcome				
Cured	68(38.20)	32(33.68)	36(43.37)	0.000
Completed	80(44.94)	50(52.36)	30(36.14)	
Died	12(6.74)	4(4.21)	8(9.63)	
Loss of follow up	07(3.93)	4(4.21)	3(3.61)	
Not evaluated	06(3.37)	4(4.21)	2(2.40)	
Failed	05(2.81)	1(1.05)	4(4.81)	
Treatment Success Rate				
Cured + Completed	148(83.15)	82(86.31)	66(79.51)	0.000

Data is presented as frequency and percentage.
MDR-TB: Multidrug-Resistant tuberculosis, XDR-TB: Extensively Drug-Resistant tuberculosis, MTB/Rif Res: Mycobacterium tuberculosis complex resistance to rifampicin.
P value <0.05 is statically significant. P value with *** represent no statistics were computed because the characteristic is either present in 100% or 0% of the population.

exhibited resistance to Rifampicin, with no cases showing sensitivity, indicating no statistical difference. Significant differences in drug susceptibility were noted for several medications. For Ethambutol, resistance was observed in 4 patients (4.21%) in the short-term regimen compared to 18 patients (21.69%) in the long-term, with 95.79% and 78.31% sensitivity respectively (p=0.000). Pyrazinamide showed resistance in 11 patients (11.58%) in the short-term regimen versus 24 patients (28.92%) in the long-term, with 88.42% and 71.08% sensitivity respectively (p=0.000). Similarly, Streptomycin resistance was lower in the short-term (15 patients, 15.79%) compared to the long-term (25 patients, 30.12%), though sensitivity was comparable (p=0.030). Kanamycin, Amikacin, Ofloxacin, Levofloxacin, and Moxifloxacin all demonstrated a 100% sensitivity rate in the short-term regimen, contrasting with varying degrees of resistance in the long-term regimen 4 patients (4.28%) for Kanamycin, 5 patients (6.02%) for Amikacin, and 31 patients (37.35%), 33 patients (39.76%), and 29 patients (34.94%) respectively for the fluoroquinolones, each showing statistically significant differences (Table 3).

Discussion

The present study aimed to investigate the effectiveness of long-term versus short-term treatment regimens in managing drug-resistant tuberculosis (TB), focusing on treatment outcomes and overall patient health. Drug-resistant TB, a growing public health concern globally, presents significant challenges in treatment, necessitating a comparison of different treatment durations to

Table 3. Comparative Analysis of Phenotypic Drugs Susceptibility Results Across Long-term and Short-term Treatment Regimens

Characteristics	All patients		Short-Term Regimen		Long-Term Regimen		P values	
Total Patients	178(100)		95(53.37)		83(42.62)		***	***
Drugs susceptibility	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive
Rifampicin	95 (53.37)	83 (46.63)	95 (100)	-	83 (100)	-	1.000	1.000
Isoniazid	118 (66.29)	60 (3.71)	67 (70.53)	28 (29.47)	51 (61.45)	32 (38.55)	0.210	0.261
Ethambutol	22 (12.36)	156 (87.64)	04 (4.21)	91 (95.79)	18 (21.69)	65 (78.31)	0.000	0.000
Pyrazinamide	35 (19.66)	143 (80.34)	11 (11.58)	84 (88.42)	24 (28.92)	59 (71.08)	0.000	0.000
Streptomycin	40 (22.47)	126 (70.79)	15 (15.79)	68 (71.58)	25 (30.12)	58 (69.88)	0.030	0.931
Kanamycin	04 (2.25)	174 (97.75)	-	95 (100)	04 (4.28)	79 (95.18)	0.045	0.041
Amikacin	05 (2.81)	173 (97.19)	-	95 (100)	05 (6.02)	78 (93.98)	0.021	0.029
Capreomycin	02 (1.12)	176 (98.88)	-	95 (100)	02 (2.41)	81 (97.59)	0.222	0.221
Ofloxacin	31 (17.42)	144 (80.90)	-	95 (100)	31 (37.35)	52 (62.65)	0.000	0.000
Levofloxacin	33 (18.54)	145 (81.46)	-	95 (100)	33 (39.76)	50 (60.24)	0.000	0.000
Moxifloxacin	29 (16.29)	149 (83.71)	-	95 (100)	29 (34.94)	54 (65.06)	0.000	0.000
Ethionamide	02 (1.12)	176 (98.88)	-	95 (100)	02 (2.41)	81 (97.59)	0.222	0.232
Clofazamine	02 (1.12)	176 (98.88)	-	95 (100)	02 (2.41)	81 (97.59)	0.222	0.232

Data is presented as frequency and percentage.
P value <0.05 is statically significant. P value with *** represent no statistics were computed because the characteristic is either present in 100% or 0% of the population.

optimize patient care and minimize resistance development. Our findings suggest that short-term regimens, while more demanding on patients and healthcare systems, lead to higher rates of treatment success and lower mortality rates compared to long-term regimens. These outcomes align with the hypothesis that extended exposure to antibiotics, under strict compliance, is crucial in combating mycobacteria with developed resistance.

The comparison of short-term (STR) and long-term (LTR) treatment regimens for drug-resistant Mycobacterium tuberculosis revealed not at all significant variance in gender distribution among the two groups, representing that gender does not significantly influence the selection or outcome of treatment regimen in this study population. This aligns with previous studies indicating that treatment efficacy is generally consistent across genders.[11]

However, the age difference between the STR and LTR groups was statistically significant, suggesting older patients might be preferentially selected for, or might require, longer treatment durations due to factors such as comorbidities, slower metabolic rates affecting drug processing, or potentially more advanced stages of disease at diagnosis.[12] This finding raises important considerations for treatment planning and highlights the need for personalized treatment strategies that take patient age into account.

The distribution of drug resistance types in the study revealed that while the majority of patients in both the short-term and long-term regimen groups had MDR-TB, XDR-TB was exclusively found in the long-term regimen (LTR) group. This pattern suggests that the most resistant forms of tuberculosis may require longer treatment durations. A related study by Tang et al. examined the prevalence of MDR-TB and XDR-TB among patients in China, confirming that XDR-TB occurred only in patients undergoing longer treatment regimens. This emphasizes the need for tailored treatment strategies based on the degree of drug resistance.[13] The absence of significant differences in other resistance types between the two groups, except for the presence of XDR-TB in the LTR group, suggests that the severity of drug resistance might not significantly affect the choice between short-term and long-term treatments within the parameters of this study.

Nunn et al. conducted a trial comparing the treatment outcomes of shorter treatment regimen for MDR-TB. The study revealed that mortality rates were 8.5% patients in the short-regimen group and 6.4% in the long treatment regimen group. Furthermore, acquired resistance to Levofloxacin/Moxifloxacin or Injectable (Amikacin, Capreomycin) was reported in 3.3% and 2.3% of patients.[14] In our study, the comparison of treatment outcomes, specifically the treatment success and death rates, showed a difference between the short-term regimen (STR) and long-term regimen (LTR). The STR had a success rate with 82 patients (86.31%) and a death rate involving 4 patients (4.21%), whereas the LTR observed a success rate in 66 patients (79.51%) and a higher death rate with 8 patients (9.63%). This finding is crucial as it suggests that, for a considerable portion of drug-resistant TB patients, shorter treatment regimens could be as effective as longer ones, potentially reducing the burden of treatment on patients and healthcare systems. However, the higher Treatment Success rate in the STR group suggests that shorter regimens might be associated with better adherence, a critical factor in TB management.

Our findings resonate with a growing body of research indicating that shorter TB treatment regimens can be effective and have comparable outcomes to longer regimens.[15] Studies have shown that adherence improves with shorter treatment durations, which can lead to better patient outcomes.[16] However, the challenge of treating XDR-TB, as seen in the presence of this condition exclusively in the LTR group emphasizing the complexity and difficulty of managing the most drug-resistant forms of TB.

This study has limitations, including its observational design and the potential for selection bias in treatment regimen assignment. The variability in drug resistance types, particularly the small number of XDR-TB cases, limits the ability to draw broad conclusions about the most resistant TB forms. Furthermore, the impact of comorbidities and social determinants of health on treatment outcomes was not explored in depth, representing an area for future research. Future studies should investigate the role of patient comorbidities, genetic factors, and social determinants in influencing treatment outcomes for drug-resistant TB. Additionally, research into personalized treatment regimens, based on factors such as age, gender, and specific drug resistance profiles, could further optimize TB management strategies. The development and testing of new TB drugs and treatment regimens, especially for XDR-TB, remain a priority.

Conclusion

This study's findings contribute to the evolving understanding of TB treatment, particularly the management of drug-resistant forms. The results suggest that short-term treatment regimens could offer a viable alternative to long-term treatments for certain patient populations, with implications for improving treatment adherence and reducing healthcare costs. However, the treatment of drug-resistant TB remains complex, requiring a nuanced, patient-centered approach that considers individual patient characteristics and the specificities of their disease.

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