ISSN: 3029-0872

Research Article

Journal of Medical and Clinical Nursing Studies

Comparison of Treatment Outcomes Between Mdr/Rr-Tb Patients Receiving a Shorter Injectable-Containing Regimen and a 9-Month All-Oral Regimen in Cambodia

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Received: December 29, 2025; **Accepted:** January 05, 2026; **Published:** January 12, 2026

ABSTRACT

Background: Cambodia has progressively implemented World Health Organization (WHO)–recommended shorter treatment regimens for multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB), transitioning from injectable-containing regimens to all-oral bedaquiline-based regimens [1-3]. Evidence comparing treatment outcomes under routine programmatic conditions remains limited.

Methods: We conducted a retrospective cohort study comparing MDR/RR-TB patients with fluoroquinolone-susceptible disease treated with either a standardized shorter injectable-containing regimen (SI) between December 2017 and June 2021 or a 9-month all-oral bedaquiline-containing regimen (SO) between January 2021 and December 2022. Demographic, clinical, and treatment outcome data were extracted from routine program records.

Results: A total of 357 patients were included: 253 received the SI regimen and 104 received the SO regimen. Overall treatment success was 82.4%. Treatment success was higher in the SO group (85.6%) than in the SI group (81.0%), though not statistically significant (OR 1.38; 95% CI: 0.73–2.61; p = 0.306). Severe adverse events were more frequent among patients receiving injectable-containing regimens.

Conclusions: Under routine programmatic conditions in Cambodia, the 9-month all-oral MDR/RR-TB regimen demonstrated favorable outcomes and improved safety compared with injectable-containing regimens, supporting WHO recommendations for all-oral treatment strategies.

Keywords: MDR-TB, Rifampicin-Resistant TB, All-Oral Regimen, Bedaquiline, Treatment Outcomes, Cambodia

Introduction

Multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) remains a major global public health challenge, contributing substantially to TB-related morbidity and mortality worldwide [4,5]. Conventional MDR-TB treatment historically relied on long regimens containing injectable second-line drugs, which are associated with prolonged duration, poor tolerability, and high rates of adverse events such as ototoxicity and nephrotoxicity [6,7].

To address these limitations, the World Health Organization (WHO) has progressively revised its guidelines to recommend shorter treatment regimens and, more recently, fully oral regimens incorporating newer agents such as bedaquiline [1-3,8]. Shorter injectable-containing regimens were initially introduced to improve adherence and reduce treatment duration, with promising outcomes reported from multiple settings [9-11]. However, accumulating evidence on injectable-related toxicities led WHO to recommend all-oral regimens as the preferred standard of care for MDR/RR-TB [2,3].

Citation: Sophan S, Bunsieth H, Sovannary T, Sok Chamreun C, Chan Yuda H, et al. Comparison of Treatment Outcomes Between Mdr/Rr-Tb Patients Receiving a Shorter Injectable-Containing Regimen and a 9-Month All-Oral Regimen in Cambodia. J Med Clin Nurs Stud. 2026. 4(1): 1-4.
DOI: doi.org/10.61440/JMCNS.2026.v4.105

Cambodia is a low-burden MDR-TB country but has been recognized as a pathfinding setting for the implementation of updated WHO drug-resistant TB treatment guidelines [4]. Since 2006, MDR-TB treatment in Cambodia has been supported through a strong collaboration between the National Tuberculosis Program (NTP) and the Cambodian Health Committee (CHC), a local non-governmental organization. This partnership has enabled rapid adoption and scale-up of new regimens under routine programmatic conditions.

Cambodia introduced the standardized shorter injectable-containing regimen in late 2017 and transitioned to a 9-month all-oral bedaquiline-containing regimen starting in January 2021 [12]. While international studies have demonstrated the effectiveness of bedaquiline-based regimens [13-16], local comparative data are essential to inform national policy decisions and optimize programmatic implementation.

This study aimed to compare treatment outcomes between MDR/RR-TB patients receiving a shorter injectable-containing regimen and those receiving a 9-month all-oral regimen in Cambodia.

Methods

Study Design

A retrospective cohort study was conducted using routine programmatic data from MDR/RR-TB treatment centers across Cambodia.

Study Population

The study included MDR/RR-TB patients with documented fluoroquinolone susceptibility who initiated treatment during one of the following periods:

- **Shorter injectable-containing regimen (SI):** December 2017 to June 2021
- **9-month all-oral regimen (SO):** January 2021 to December 2022

Patients who initiated individualized regimens or lacked treatment outcome data were excluded.

Treatment Regimens

The shorter injectable-containing regimen (SI) consisted of a standardized combination including kanamycin or amikacin, moxifloxacin, ethionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol administered during the intensive phase for 4–6 months, followed by a 5-month continuation phase without injectable agents. This regimen was implemented in accordance with WHO-recommended shorter treatment regimens for MDR/RR-TB at the time [9–11,8].

SI Regimen: 4–6 Km/Am–Mfx–Eto–Cfz–Hh–Z–E / 5 Mfx–Cfz–Z–E

The shorter all-oral regimen (SO) was a standardized 9-month regimen in which bedaquiline replaced the injectable agent (kanamycin or capreomycin). Bedaquiline was administered for the first 6 months in combination with moxifloxacin, ethionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol, followed by a 5-month continuation phase without bedaquiline. This regimen was delivered in accordance with national guidelines aligned with updated WHO recommendations [1,3,12].

SO Regimen: 4–6 Bdq (6 months)–Mfx–Eto–Cfz–Hh–Z–E / 5 Mfx–Cfz–Z–E

Data Collection and Outcomes

Data extracted included age, sex, HIV status, body mass index (BMI), TB treatment history, and treatment outcomes. Outcomes were defined using WHO programmatic definitions: treatment success (cured or treatment completed), death, treatment failure, lost to follow-up, and not evaluated [1,3].

Statistical Analysis

Descriptive statistics summarized baseline characteristics and outcomes. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to compare outcomes between regimens. A p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 357 patients were included: 253 in the SI group and 104 in the SO group. Overall, 70.0% were male, and the median age was 50 years (IQR: 35–58). HIV co-infection was present in 10.6% of patients and was significantly more common in the SI group than in the SO group (13.4% vs. 3.8%; OR 3.88; 95% CI: 1.34–11.23; p = 0.007). Most patients (63.9%) had a history of prior TB treatment. Baseline characteristics are shown in Table 1.

Table 1: Basic Characterisitics of Participants

Baseline chracteristics	Total cases, n=357	SI group, n=253	SO group, n=104	OR (95%CI)	P value
	n(%)	n(%)	n(%)		
Sex					
Female	107(30.0)	80(31.6)	27(26.0)	Ref.	
Male	250(70.0)	173(68.4)	77(74.0)	0.75(0.45-1.26	0.289
Age					
Median (IQR)	50(35-58)	50(36-62)	47(35-58)		
Range	14-83	16-83	14-79		
<15 years	1(0.3)	0(0.0)	1(1.0)	-	
15-34	65(18.2)	43(17.0)	22(21.2)	0.70(0.37-1.33)	0.281
35-54	156(43.7)	110(43.5)	46(44.2)	0.78(0.46-1.31)	0.352

≥55	135(37.8)	100(39.5)	36(34.6)	Ref.	
HIV status					
Positive	38(10.6)	34(13.4)	4(3.8)	3.88(1.34-11.23)	0.007
Negative	319(89.4)	219(86.6)	100(96.2)	Ref.	
BMI: median(IQR)	17.5(15.8-20.3)	17.9(16.0-20.4)	17.7(15.6-20.0)		
TB treatment history					
No prior TB treatment	129(36.1)	88(34.8)	46(44.2)	Ref	
Prior TB treatment	228(63.9)	170(67.2)	58(57.8)	1.53(0.96-2.43)	0.071

Treatment Outcomes

Overall treatment success was achieved in 294 patients (82.4%). Treatment success was higher in the SO group (85.6%) compared with the SI group (81.0%), although the difference was not statistically significant (OR 1.38; 95% CI: 0.73–2.61; p = 0.306). Detailed outcomes are presented in Table 2.

Table 2: Comparison of Treatment Outcomes

Treatment outcomes	Total cases, n=357	SI group	SO group	OR (95% CI)	p=value
Success	294 (82.4)	205(81.0)	89(85.6)	1.38(0.73-2.61)	0.306
Falailed	26(7.3)	20(7.9)	6(5.8)		
Died	28(7.8)	20(7.9)	8(7.7)		
Lost to folow-up	8(2.2)	7(2.8)	1(0.9)		
No evalusted	1(0.3)	1(0.4)	0(0)		

In the SI group, treatment failure and death each accounted for 7.9% of outcomes, while 2.8% were lost to follow-up. In the SO group, treatment failure occurred in 5.8% of patients and death in 7.7%.

Causes of Treatment Failure

Treatment failure in the SI group was largely attributed to severe adverse events, including hepatotoxicity, nephrotoxicity, gastrointestinal intolerance, hearing loss, Stevens–Johnson syndrome, and one case of unexpected pregnancy. One patient experienced bacteriological reconversion during the continuation phase.

In the SO group, failure was primarily due to hepatotoxicity, gastrointestinal intolerance, and bacteriological reconversion.

Discussion

This study provides real-world evidence comparing shorter injectable-containing and 9-month all-oral MDR/RR-TB regimens in Cambodia. Treatment success exceeded 80% in both cohorts, consistent with outcomes reported in other programmatic settings implementing shorter regimens [10,11,17].

Although the difference in treatment success between regimens was not statistically significant, the all-oral regimen demonstrated a more favorable safety profile. Injectable-related toxicities—particularly ototoxicity and nephrotoxicity—were prominent contributors to treatment failure in the SI group, consistent with findings from previous studies and systematic reviews [6,7].

Bedaquiline-containing regimens have been associated with reduced mortality and improved outcomes in multiple cohorts across diverse epidemiological settings [13-16,18]. Our findings support these observations and reinforce WHO recommendations favoring all-oral regimens for MDR/RR-TB treatment [1–3].

The lower proportion of HIV co-infection in the SO group reflects the phased rollout of newer regimens but does not diminish the relevance of the findings. Integrated TB–HIV care remains critical, particularly in high-risk populations [19,18].

The success of MDR-TB treatment in Cambodia highlights the importance of strong collaboration between non-governmental organizations and national TB programs, enabling rapid guideline adoption, community-based adherence support, and sustained programmatic performance [20-22].

Limitations

This study has limitations inherent to its retrospective design, including reliance on routine program data and potential unmeasured confounding. The smaller sample size of the SO cohort limited statistical power, and long-term relapse outcomes were not assessed.

Conclusions

Under routine programmatic conditions in Cambodia, the 9-month all-oral MDR/RR-TB regimen demonstrated favorable treatment outcomes and reduced severe adverse events compared with injectable-containing regimens. These findings support national and global policy shifts toward all-oral regimens and underscore the value of strong NGO–NTP collaboration in delivering effective MDR-TB care.

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