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Minerva Respiratory Medicine 2024 March; 63(1):16-24
DOI: 10.23736/S2784-8477.23.02066-1

REVIEW

Bedaquiline and delamanid treatment outcomes among patients with drug-resistant tuberculosis: a systematic review and meta-analysis

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ABSTRACT

INTRODUCTION: Drug-resistant tuberculosis (DR-TB) remains a leading global health priority worldwide. The main problem for designing an effective regimen is the identification of active drugs. Two novel available drugs, delamanid and bedaquiline, are presently pivotal in ongoing scientific debates.

EVIDENCE ACQUISITION: We selected published studies reporting data on the treatment outcomes of delamanid and bedaquiline for treating DR-TB cases in humans involving adult populations.

EVIDENCE SYNTHESIS: A total of 38 studies provided outcomes for 4926 DR-TB patients across 16 countries. Sputum culture conversion rates to bedaquiline and delamanid-containing regimens were 75% and 71%. In addition, median (IQR) time to sputum culture conversion for delamanid plus bedaquiline was ~24 days. Treatment success of bedaquiline ranged from 47% to 100%, with an overall pooled proportion of 63% achieving treatment success. Overall pooled proportion of 78% achieving delamanid plus bedaquiline treatment success (95% CI: 61-92%). Cure rate, death and treatment failure for bedaquiline with a proportion of 58% (95% CI: 45-71%), 8% (95% CI: 3-15%), and 6% (95% CI: 2-12%) were reported, respectively. Median (IQR) time to sputum culture conversion for delamanid and bedaquiline was ~20.50 days and ~18 days, respectively. The most commonly reported adverse events were gastrointestinal side-effects, and QT prolongation.

CONCLUSIONS: Treatment outcomes may suggest that the addition of delamanid and bedaquiline to DR-TB regimens may improve treatment outcomes, although associated with significant adverse events.

(*Cite this article as:* Heidari H, Moradkasani S, Ghanavati R, Kalantar-Neyestanaki M, Kouhsari E, Ghafourian S, *et al.* Bedaquiline and delamanid treatment outcomes among patients with drug-resistant tuberculosis: a systematic review and meta-analysis. Minerva Respir Med 2023;62:000-000. DOI: 10.23736/S2784-8477.23.02066-1)

Key words: Tuberculosis; Drug resistance, multiple; OPC-67683; Bedaquiline.

Introduction

Globally, tuberculosis (TB) is the 13th important cause of mortality, with the death of 1.5 million people in 2020, and the second leading infectious killer following coronavirus disease (COVID-19).[1-3] The continuing spread of drug-resistant-TB is one of the most challenges and concerns worldwide.[4, 5] Elimination of TB by 2035 will be possible only if countries effective-

ly address the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis*.[2, 3] The mismanagement of TB treatment (such as inappropriate or incorrect use of antimicrobial drugs, or application of ineffective formulations of drugs, and premature treatment interruption) and person-to-person transmission a number of reasons why MDR- and XDR-TB continues to emerge and spread.[1-3] Treatment options for MDR- and XDR-TB are limited, long, and expensive, and recommended medicines are often unavailable and associated with many adverse events.[6-8] The main problem for designing an efficient regimen is the identification of active drugs.[7] The World Health Organization (WHO) 2016 has recently suggested a revision of the classification of novel anti-TB drugs based on current evidence on each drug for the treatment of MDR-TB. In the revised WHO classification, exclusively aimed at managing drug-resistant cases, medicines are again listed in hierarchical order from group A to group D (D1, D2, and D3).[8] Two novel available drugs, delamanid and bedaquiline, are presently pivotal in ongoing scientific discussions and delamanid/bedaquiline are included in the D2 group.[9] The primary aim of the present systemic review and meta-analysis was to assess all available data on the efficacy and safety of delamanid and bedaquiline for the treatment of DR-TB cases.

Evidence acquisition

Design

We conducted a systematic review and meta-analysis to assess the efficacy of delamanid and bedaquiline against DR-TB cases. This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[10] This study was approved by the Ethics committee of Ilam University of Medical Sciences (reference n. IR. MEDILAM. REC. 1400.147).

Search strategy

We used the databases MEDLINE [PubMed], Scopus, and Embase to identify any relevant full-text English articles without any time constraints until June 2020. The article screening was performed by using the following keywords: ("Tuberculosis" OR "drug resistant tuberculosis" OR "DR-TB" OR "drug-resistant tuberculosis" OR "multidrug resistant tuberculosis" OR "MDR-TB" OR "MDRTB" OR "extensively drug-resistant tuberculosis" OR "extensively drug resistant tuberculosis" OR "XDR-TB" OR "XDRTB") AND ("delamanid" OR "bedaquiline") in the Title/Abstract/Keywords fields. The records found through database searching were merged, and the duplicates were removed using EndNote X8 (Thomson Reuters, New York, NY, USA). One of the team researchers randomly evaluated the search results and confirmed that no relevant study had been ignored. All these steps were carried out by three authors (R.G.H., H.H., and H.K.), and any disagreements over article selection were resolved by discussion. A fourth author (E.K.) also acted as arbiter. The three reviewers screened all titles and abstracts independently and excluded irrelevant or duplicate articles. Then all four reviewers separately assessed the remaining articles (full text screening) for inclusion. Any discrepancies were resolved by consensus. The flow chart of the selected studies is shown in Figure 1.

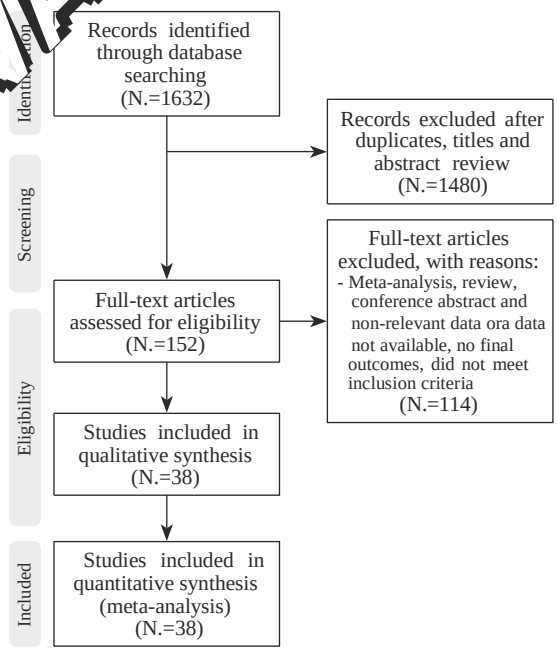

Figure 1.—Flow chart of study selection.

Study selection

We selected published studies reporting data on the treatment outcomes of delamanid and bedaquiline in treating DR-TB cases in humans involving adult populations of ≥5 patients. The following studies were excluded: 1) case reports fewer than five DR-TB cases, letters to the editor, abstracts commentaries, editorials, and reviews on delamanid and bedaquiline in DR-TB; 2) *in vitro* and *in vivo* studies; 3) studies without full texts, or those did not report a main outcome; and 4) studies with unclear/unconfirmed diagnosis of treated DR-TB patients. Inclusion criteria included original studies (retrospective or prospective Cohort, Case Series, randomized trials) that reported (1) treatment outcomes in a population of adults, and (2) at least one outcome according to WHO classifications of success (*e.g.*, cure or treatment completion), failure, death, and treatment adverse events related to DR-TB therapy.

Data extraction

Data were collected using a standardized data extraction form, comprising of first author name, publication year, duration of study, type of study design, age and gender, number and characteristics of treated DR-TB patients, dose and duration of treatment, and treatment outcomes recorded in conformity with the WHO classification,[1] sputum smear, and time and rate of culture conversion and adverse events.

Participants

Patients diagnosed with DR-TB and treated with delamanid and/or bedaquiline and both. There were no restrictions on sex and ethnicity.

Interventions

Treatment containing delamanid and/or bedaquiline and both served as the intervention in the observation group. Placebo or other treatments that did not contain delamanid and/or bedaquiline and both served as the interventions in the control groups.

Outcomes

The main outcomes included the sputum culture conversion and treatment success, and the secondary outcomes included the cure rate, death, and adverse events.

Quality assessment

The quality of the included studies was assessed by two independent reviewers (M.SH. and H.K.) using an adapted version of the tool proposed by the Newcastle-Ottawa Quality Assessment Form for cohort, non-randomized, and case series studies.[1,2] A score ranging from 0 to 9 points was allocated to each study. Articles with scores ≥5 points and <4 points were considered as high and low quality, respectively. A third reviewer (E.K.), as an arbiter, adjudicated in any case where there was disagreement.

Statistical analysis

We performed all statistical analyses using statistical software Stata SE Software, v.14.1 (StataCorp, College Station, TX, USA). The Score (Wilson) confidence intervals (CIs) were used to compute the CIs for the individual studies. We also carried out the random effects model using the DerSimonian and Laird method, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model. We also expressed our results by the aid of forest plots. Publication bias was assessed using Egger's test. The P value ≤0.05 was considered statistically significant. All statistical interpretations were reported on a 95% CI: basis.

Evidence synthesis

Selection of the studies

A total of 1632 records were identified in our initial electronic database search. From these records, after an initial screening of the title and abstract, 1480 articles were excluded due to their irrelevance and duplication. The full texts of the remaining 152 articles were reviewed. Of the 152 articles, 114 were excluded for being meta-analysis, review, and conference abstract, as well as for irrelevant or unavailable data, no final outcomes, and the lack of necessary criteria for reporting treatment outcomes. The full texts of the remaining 38 studies[7, 11, 13-48] (3896 cases on bedaquiline, 789 cases on delamanid,

and 241 cases on delamanid plus bedaquiline) were identified as eligible for inclusion in the meta-analysis (Supplementary Digital Material 1: Supplementary Table I).

Characteristics of included studies

The 38 studies selected for this work were performed on 4926 patients (47.09% males and 52.90% females, with the mean age of 32 years) in more than 16 countries across the globe. Per regional distribution, more than half (N.=18; 31.57%) were conducted in Asia. The rest of the studies were conducted in Africa (N.=13) and Europe (N.=12). None of the selected studies was conducted in USA. In addition, nine of the selected studies were from multinationals. Except two studies,[4][6, 47] 36 (<96%) studies were performed in the years between 2015 and 2020. The epidemiological design of the studies was retrospective in 28 out of 38 (53.8%) cases. Also, only two clinical trials[1][7, 42] were performed. One study enrolled children,[1][1] and four studies included a control group. All the DR-TB patients in the selected studies, except one study, were received a single daily dose of bedaquiline (400 mg). Daily dosage of delamanid was the same as bedaquiline in the selected studies, but the individuals with DR-TB were given a daily dose of 200 mg of delamanid. All the 38 studies were reported in English and included studies that received treatment between 1996 and 2018. About 1702 and 1506 of patients enrolled were tested positive for MDR-TB and XDR-TB, respectively. The average study population (range) was 10[illegible] (24-620), and the duration of treatment ranged from 24 to 120 days.

Treatment outcomes

Sputum culture conversion

Median (IQR) time to sputum culture conversion for delamanid and bedaquiline was ~20.50 (11) days and ~18 (12) days, respectively. In addition, median (IQR) time to sputum culture conversion for delamanid plus bedaquiline was ~24 (10) days.

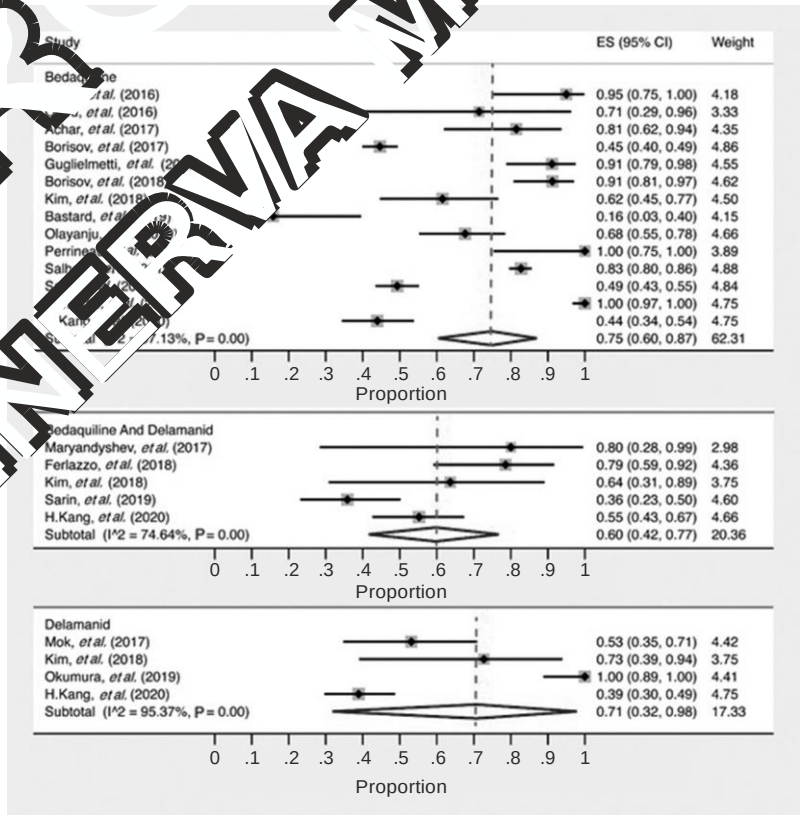

Figure 2.—Forest plot for the (A) bedaquiline, (B) bedaquiline plus delamanid, and (C) delamanid culture conversion of positive sputum to negative.[7, 11-14, 17, [illegible], 20, 22, 24, 27, 31, 34, 37-39, 41, 43, 44]

Fourteen studies reported sputum culture conversion to bedaquiline-containing regimens, with a pooled proportion of 75% (95% CI: 60-87%) and heterogeneity across studies (I^2=97.13%), as shown in Figure 2.[7, 11, 14, 17, 18, 20, 22, 24, 27, 31, 34, 37-39, 41, 43, 44] No statistical significance was detected between the time conversion of positive and negative sputum culture among drugs. Four studies reported sputum culture conversion to delamanid-containing regimens, with a pooled proportion of 71% (95% CI: 32-98%; I^2=95.37%), which was higher than the rate reported for delamanid plus bedaquiline-containing regimens (60% (95% CI: 42-77%; I^2=74.64%; Figure 2).

Treatment success

A total of 809 patients achieved treatment success of bedaquiline with a combined proportion of 63% (95% CI: 48-78%) and a significant heterogeneity (I^2=97.29%; Figure 3).[7, 11, 13-15, 18, 20, 21, 25, 28, 30, 21, 33, 25, 42, 46-48] Two studies[14, 47] reported 100% treatment success (95% CI: 48-100 and 82-100, respectively). For delamanid plus bedaquiline, the treatment success was 78% (95% CI: 61-92%) among 241 patients (Figure 3).

Cure rate and death

A total of 663 patients achieved bedaquiline cure rate, with a proportion of 58% (95% CI: 45-71%; Figure 4)[7, 14, 15, 21, 24, 25, 29, 31, 35, 39, 42, 46-48] and a significant heterogeneity (I^2=94.88%). The cure rate of delamanid treatment was 53% (95% CI: 48-59%; Figure 4). Death and treatment failure were observed in 8% (95% CI: 3-15%) and 6% (95% CI: 2-12%) and in 4% (95% CI: 2-7%) and 2% (95% CI: 0-14%) of the enrolled subjects treated with bedaquiline and delamanid, respectively.

Adverse events

The incidence of adverse events related to bedaquiline and delamanid described in 32 studies. The most common significant adverse events were gastrointestinal and dermatological side effects, QT prolongation, neurological disorders, headache,

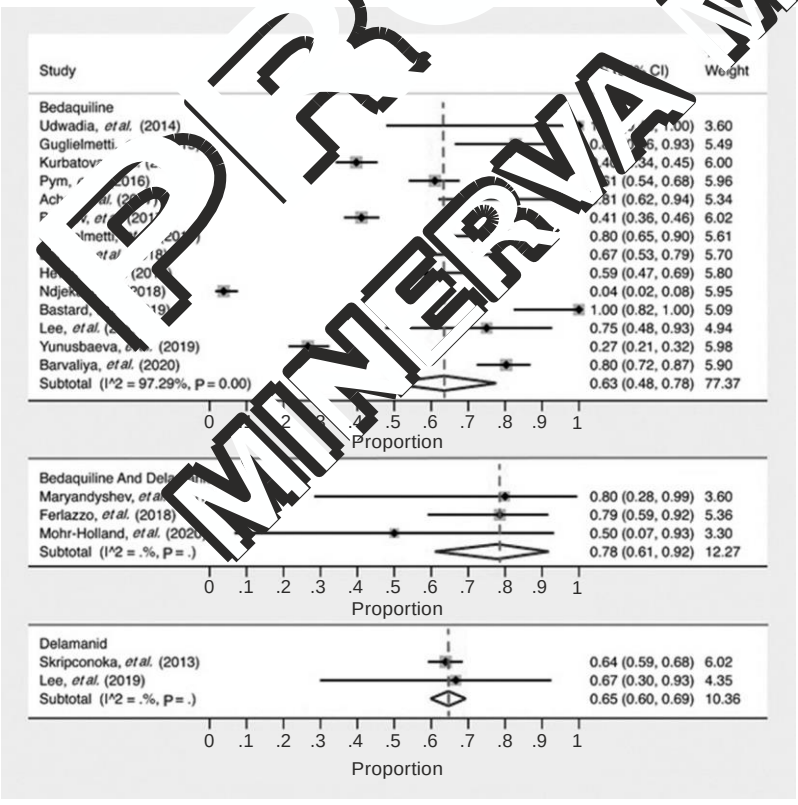

Figure 3.—Forest plot for the (A) bedaquiline, (B) bedaquiline plus delamanid, and (C) delamanid treatment success.[7, 11, 13-15, 18, 20, 21, 25, 28, 30, 21, 33, 25, 42, 46-48]

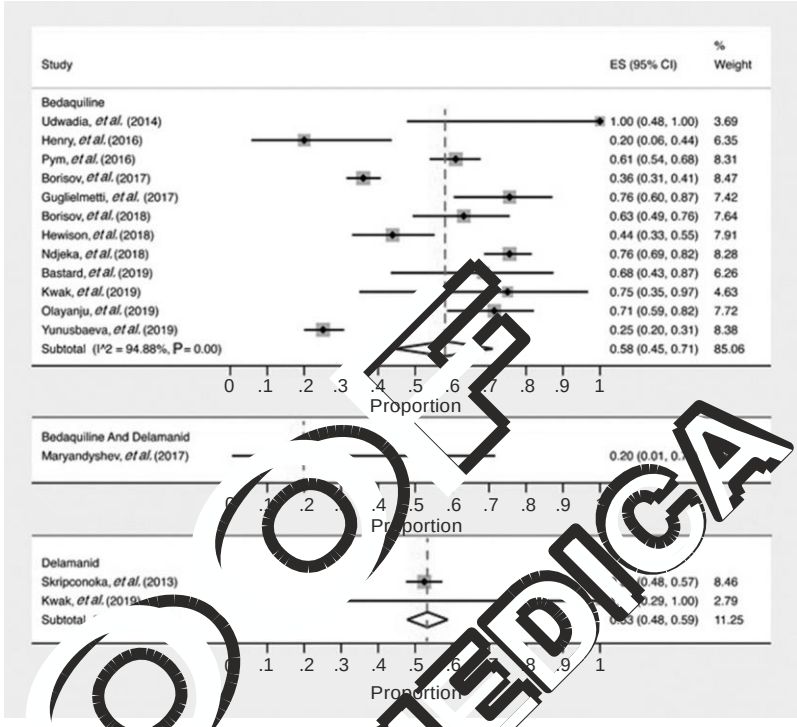

Figure 4.—Forest plot cure rates for the (A) bedaquiline, (B) bedaquiline plus delamanid, and (C) delamanid.[7, 14, 15, 21, 24, 25, 29, 31, 35, 39, 42, 46-48]

fatigue, and anorexia. Serious adverse events, including cardiac arrhythmia, peripheral neuropathy, and renal failure, were observed in 21 studies that were used bedaquiline and delamanid treatments.

Publication bias

Begg's and Egger's regression tests were performed to assess the publication bias. The shapes of the funnel plots do not show obvious evidence of asymmetry. However, the P value of Egger's test confirmed the existence of publication bias for all the outcomes evaluated, with the P values of 0.33, 0.22, and 0.54 for cure rate, death, and treatment failure (P=0.54), respectively (Supplementary Digital Material 2: Supplementary Figure 1, Supplementary Figure 2, Supplementary Figure 3).

Discussion

The current study systematically reviewed the available scientific evidence to support the development of future evidence-based guidance on using delamanid or bedaquiline in difficult-to-treat DR-TB cases. However, only one study is available on bedaquiline treatment in DR-TB children.[1] This systematic review was conducted with a sample size of 4926 cases collected from different continents.

The findings from this study showed that bedaquiline or delamanid has no statistically significant difference in the time/rate of positive conversion culture relative to negative culture. Due to the novelty of the drug data on patients treated with bedaquiline, outside clinical trials are still infrequent. Herein, we provide evidence for the effectiveness of bedaquiline- or delamanid-based regimens in clinical practices. This systematic review and meta-analysis included a larger number of observational studies and suggested that the two mentioned medications are increasingly being used off-label in the management of DR-TB. Notably, most of the patients in our study received bedaquiline, a drug shown to improve treatment outcomes of DR-TB patients. Similar treatment outcomes are described in other high-resource settings, but these studies included fewer XDR-TB patients.[4] [2, 49-51] The routine or broad off-label use of delamanid in combination with bedaquiline is not recommended by WHO.[5] [2] Therefore, this

issue necessitates more support to protect patients from potential adverse events related to the combination of the two new drugs in addition to that deriving from the drugs used in the background regimen. In our study, sputum culture conversion rates of bedaquiline and delamanid were 75% and 71% for DR-TB patients, which were relatively lower than DR-TB patient prospective[42, 53, 54] and retrospective[20, 55-57] clinical studies. This review identified 38 studies, with 28 distinct cohorts published since 2013 that reported treatment regimens and outcomes in 1602 MDR-TB and 1318 XDR-TB patients. The included studies reported adverse events, sputum culture conversion, and treatment outcomes. The pooled overall treatment success in DR-TB patients to bedaquiline was 63%, similar to a previously reported study (61% treatment success rate),[58] as well as well below the WHO (75% treatment success rate) and results from a large global prospective cohort (74.2% treatment success rate).[59] In our review, delamanid and bedaquiline were administered in combination with other antitubercular drugs to achieve treatment success. Thus, treatment success may not be exclusively attributed to delamanid and bedaquiline. The pooled overall cure rates of DR-TB patients treated with bedaquiline and delamanid were 58% and 53%, respectively, which was lower than those stated in the 2015 WHO Global TB report[6] *i.e.* cure rates in 2014 from 13 countries as 75% with global average cure rate of 50%. The lack of association in many treatment parameters (use of any individual drugs, treatment length, and number of drugs), and clinical characteristics (such as human immunodeficiency viruses' coinfection) observed in our included studies may reflect the limitations and difficulties of pooling the data rather than a true lack of differences in efficacy of regimens or individual drugs. The treatment success proportion obtained in the present study in comparison with the culture conversion pointedly implies that most of the DR-TB patients who achieve sputum culture conversion do not obtain treatment success. This unsuccessful outcome may arise from treatment failure, and also treatment discontinuation due to adverse effects or relapse. The major adverse events identified in our review were gastrointestinal and dermatological side effects, as well as QT prolongation.

Limitations of the study

Our systematic review has several limitations. First, the included studies were mostly retrospective. The relatively insufficient information of these studies can lead to an increase in the rate of patients' withdrawal to follow-up and consequently less report adverse events. Second, none of the control group of patients received bedaquiline or delamanid. Indeed, the results of the case group have not been compared properly with the control group, which causes confounding in our pooled analysis because crude outcomes, rather than adjusted odds ratios, were reported for most trials. Hence, results should be evaluated cautiously given the small number of trials and unclear risk of bias as determined according to the reporting. Third, significant heterogeneity, including presence of publication bias, is evident among studies. Further and more trials are necessary on the use of delamanid and bedaquiline in TB patients to ensure reproducibility.

Conclusions

While data on the clinical outcomes in DR-TB patients treated with bedaquiline and delamanid are observational and limited, these two agents appear beneficial drugs. Moreover, the addition of delamanid and bedaquiline to MDR- and XDR-TB regimens, though is associated with significant adverse events, may improve treatment outcomes. However, this surmise needs to be systematically evaluated in well-designed clinical trials.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding
This study was supported by Ilam University of Medial Sciences (Project no: 1459).

Authors' contributions
Hamid Heidari and Safoura Moradkasani contributed equally to this work and share first authorship. Hamid Heidari, Safoura Moradkasani, Roya Ghanavati, Mahshid Kalantar-Neyestanaki, Seifu Gizaw Feyisa and Hossein Kazemian participated in the conception, design, and drafting the manuscript; Ebrahim Kouhsari and Sobhan Ghafourian carried out analysis of the work. Ebrahim Kouhsari and Hossein Kazemian conceived of the study, and participated in its design and coordination and helped to draft, revising and final approval the manuscript. All authors read and approved the final version of the manuscript.

History
Manuscript accepted: March 17, 2023. - Manuscript received: March 4, 2023.

Supplementary data
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