

Interventions to Improve Adherence to Medication on Multidrug-Resistant Tuberculosis Patients: A Scoping Review

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ABSTRACT

Introduction: Inappropriate treatment and non-adherence use of anti-tuberculosis (TB) drugs trigger the spread of multidrug-resistant tuberculosis (MDR-TB) strains and causes an emerging public health threat worldwide. Therefore, non-adherence to MDR-TB treatment leading to prolonged medication period, increase incidence of adverse event and financial burden, thus it requires interventions to achieve a therapeutic outcome.

Objective: This scoping review aims to provide an overview of interventions to improve the adherence level to medication of MDR-TB patients.

Materials and Methods: A review of observational studies was conducted to discuss the accuracy, tolerability and ease of use of tonometers in measuring IOP in children with glaucoma.

Three databases (PubMed, Web of Science, Scopus) were used in a scoping review. The data were synthesised using Rayyan AI. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to guide this review.

Results: A total of 11 articles were included in this review to describe the various interventions in MDR-TB treatment adherence. Psychological counselling or education intervention was the most popular intervention, and it significantly increased adherence levels among MDR-TB patients. Increased adherence level patients also reported by interventions with Medication Event Reminder Monitor (MERM), Video Directly Observed Therapy (VDOT), 30-day recall and Visual Analogue Scale (VAS), Financial Support, mHealth Application and directly observed therapy, short course (DOTS) and DOTS-Plus programs. However, we found that Electronic Dose Monitoring (EDM) device intervention has less effect on MDR-TB patients' adherence. **Conclusion:** The recovery of patients can be facilitated through MDR-TB treatment adherence interventions. It is acknowledged that the studies included in this review exhibit heterogeneity, with a majority showing significant

improvement. Therefore, further study was required to investigate the specific on developing highly personalised interventions tailored to specific population or context, as well as to assess the cost-effectiveness of such interventions.

KEYWORDS:

Adherence intervention, scoping review, therapy MDR-TB

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* which has existed for millennia and remains a major global health problem for approximately 10 million people each year, and is one of the top 10 causes of death worldwide.¹ Treatment of TB is even more complex and challenging with the emergence of multidrug-resistant tuberculosis (MDR-TB).^{2,3} Multidrug-resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* strains resistant to at least isoniazid and rifampicin, two first-line medicines used to treat TB.⁴

The prevalence of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) was estimated to be 3.3% in new cases and 18% in previously treated cases globally in 2020. Overall, an estimated 465,000 incident cases of MDR/RR-TB were reported, and the global proportion of RR-TB cases estimated to have MDR-TB was 78%.¹ Despite considerable advances in therapy in the last decade, treatment outcomes remain poor for individuals with MDR-TB, with treatment success rates of 56% worldwide and 48% in India for the 2017 patient cohort.⁵ Although some of the variability in treatment outcomes may be attributable to the composition of the patient's drug regimen,^{7,8} suboptimal medication adherence may be another critical problem contributing to poor MDR-TB treatment outcomes.⁹

Medication non-adherence is well recognised as a leading cause of health problems and a financial burden.¹⁰⁻¹² Therefore, a robust assessment of adherence to the treatment regimen MDR-TB is needed to assess progress towards the treatment goals and inform policy and practice.¹³ Recent data

This article was accepted: 13 March 2024

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Table I: Keywords used in each database

No.	Database	Keywords
1	PubMed	(intervention program) AND (multidrug resistant tuberculosis) AND (adherence)

from a global meta-analysis explained that non-adherence to treatment regimens was associated with a higher prevalence of MDR-TB and poor treatment outcomes.^{14,15} Socioeconomic, health care systems, conditions, treatment and patient knowledge factors are closely related to adherence level.^{16,17} Previous studies on interventions to increase adherence in TB patients have outlined various approaches.¹⁸⁻²² These encompass TB interventions, education, counselling, incentives, community-based initiatives, and mixed interventions, all linked to several active TB care cascade outcomes. However, the selection of strategies requires accounting for cost-effectiveness and local contexts due to their substantial diversity. Despite these investigations, there is not comprehensively review study addressing interventions targeted specifically at MDR-TB patients. This scoping review aims to provide an overview of interventions to improve the adherence level of MDR-TB patients.

MATERIALS AND METHODS

A scoping review was conducted to assess the articles interventions to improve adherence among MDR-TB patients. The review encompassed articles published between January 2012 to November 2022. This period was specifically chosen to encompass the latest advancements and initiatives in MDR-TB treatment and adherence strategies, reflecting a decade of significant progress and innovation in this field. This scoping review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²³ The review specifically emphasised the PICOS criteria which included the population (patient with MDR-TB, infected with strains resistant to isoniazid and rifampicin), intervention, comparator, outcomes and study design. Only interventions specifically targeting medication adherence and treatment outcomes for MDR-TB were considered in this review. The intervention included in this review required a comparison group to assess their effectiveness of the intervention, such as a comparison between intervention groups or a control group. Additionally, the review examined treatment outcome in relation to improvements in adherence level or the absence of no impact after the intervention.

Searching Strategy

Initial searches were conducted using three electronic databases (PubMed, Web of Science, and Scopus). A broad literature search was undertaken to identify keywords in the field. Literature search uses the primary term to expand the search. Key terms used for the search were as follows (Table I).

Eligibility Criteria

This review uses inclusion and exclusion criteria for specific journals as material for this review. The inclusion criteria included an original study with adult MDR-TB patients receiving continuous anti-TB treatment, supplemented with adherence tools interventions. The exclusion criteria were

review articles, commentary articles, handbooks, guidelines and study protocol.

Study Selection

The title and abstract of the articles were screened by the authors, and then the full text of the articles was assessed for eligibility and quality by the authors. Data screening was conducted using Rayyan Intelligent Systematic Review software (<https://www.rayyan.ai/>). Duplicate papers were excluded from the study. Abstracts were read, and relevant full articles were reviewed for data extraction. Any uncertainty or conflict was discussed at regular check-ins until a consensus was reached among the authors. While Rayyan's AI screening and highlighting feature were utilised, each record was still individually screened. In cases of uncertainty, a more inclusive approach was adopted. Independent screening of full-text articles was conducted by at least two researchers, and conflicts or uncertainties were resolved through further discussions until a consensus was reached among all researchers conflicts and uncertainties were resolved through further discussion until a consensus was reached among all researchers.

Charting the Data

We developed data extraction templates to map data to each research question. To define these conceptual areas, we adopted the World Health Organisation's guidance on ethics and governance of MDR-TB for health definitions (based on the recommendations of the Artificial Intelligence Council of the Organization for Economic Cooperation and Development states.^{5,6} The following data were extracted:

- General information: Authors, publication year, country, intervention, participants, duration of intervention, outcome measurement and conclusion of the intervention effect.
- Types of intervention: Psychological Counselling or Educational Intervention, Medication Event Reminder Monitor (MERM)/Electronic Dose Monitoring (EDM), Video Directly Observed Therapy (VDOT), 30 day recall and Visual Analogue Scale (VAS), Financial Support, mHealth Application, directly observed therapy, short course (DOTS) and DOTS-Plus program.

Collating, Summarising, and Reporting the Results

The analysis used data related to the research questions to summarise implementation motives and elements in the implementation process. Articles were read and re-read, with initial ideas sorted into domains of explanations for improved adherence for MDR-TB patients. Next, initial codes were identified within each article. The codes were compared based on similarities and differences and organised into potential themes, which were then compared to generate the interventions used to come up with clear definitions and names for each intervention in each of the domains of adherence levels of MDR-TB patients. Data analysis was conducted in pairs, and any uncertainties or differences were discussed among all authors until a consensus was reached.

Table II: Overview of articles included in the scoping review (N = 11)

No	Author	Year	Country	Intervention	Participants	Participants type	Duration of intervention	Outcome measurement	Conclusion of the interventions effect
1	Baral et al. ²⁵	2014	Nepal	A mixed-method study comprising a qualitative formative survey, pilot intervention study, and explanatory qualitative study better to understand barriers to completion of treatment for MDR-TB	49 registered people with MDR-TB for interview	Patients	18 months	The MDR-TB treatment causes extreme social, financial, and employment difficulties. The pilot intervention study resulted in cure rates for those receiving counselling, combined support, and no support of 85%, 76% and 67%, respectively. Compared with no support, the (adjusted) risk ratios of a cure for those receiving counselling and receiving combined support were 1.2 (95% CI 1.0 to 1.6) and 1.2 (95% CI 0.9 to 1.6), respectively.	Financial and counselling support appear to improve MDR-TB treatment outcomes and cure rates.
2	Tola, et al. ³³	2016	Ethiopia	A structured questionnaire, psychological counselling, and adherence education.	698 TB patients, who were in treatment	Patients	30 minutes	Non-adherence level decreased among the intervention group from 19.4 (at baseline) to 9.5% (at endpoint), while it increased among the control group from 19.4% (baseline) to 25.4% (endpoint).	Psychological counselling and educational interventions, which were guided by HBM (Health Belief Model), significantly decreased treatment non-adherence levels among the intervention group
3	Malini et al. ²⁸	2021	Indonesia	The study used a quasi-experimental design with a pretest-post-test without a control group. The program intervention of health education uses with lecture method and group discussion using flipcharts and video as media	29 respondents	Patients	4 months	The result of this study shows that 65.5% of patients take medication regularly. The provision of health education on MDR-TB prevention behaviour emphasises motivation and self-efficacy.	The effect of health education in improving respondents' knowledge of MDR-TB preventive health behaviour.
4	Calligaro et al. ³¹	2021	South Africa	questionnaires and conducting qualitative interviews	60 patients	Patients	3 months	Qualitative interviews revealed participants' perceptions of the value of the intervention. From baseline to follow-up, patients reported reductions in substance use severity, symptoms of depression, distress, and functional impairment.	Participant retention in the study was moderate. Randomized studies are needed to demonstrate the efficacy of this intervention before considering the potential for wider implementation.
5	Walker et al. ²⁶	2018	Nepal	This feasibility study used a mixed quantitative and qualitative approach. Counselling, using educational materials and group interaction	135 patients	Patient	30 to 60 minutes	All aspects of the intervention package were acceptable to patients. Researchers successfully trained individuals with no psychological counselling experience to deliver HAP (Health Activity Program).	This psychosocial support package is acceptable to patients.

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No	Author	Year	Country	Intervention	Participants	Participants type	Duration of intervention	Outcome measurement	Conclusion of the interventions effect
6	Thomas et al. ⁹	2021	India, US	Interviews with patients (MDR-TB) multidrug resistance-tuberculosis and health care providers (HCPs)	65 patients with MDR-TB and 10 HCPs.	Patients and HCPs	45 minutes	HCPs reported that MERM implementation resulted in fewer in-person interactions with patients and thus allowed HCPs to dedicate more time to other tasks, which improved job satisfaction.	Adherence to ART was independently associated with ART resistance and mortality
7	Bateman et al. ³⁰	2022	South Africa	Patients on ART and starting MDR-TB treatment with bedaquiline were enrolled at a public hospital in KwaZulu-Natal, South Africa (PRAXIS Study). Participants received separate EDM tools measuring adherence to bedaquiline and ART (nevirapine or lopinavir/ritonavir).	198 persons with MDR-TB and HIV	Patients	6 month	A total 11% of people with MDR-TB and HIV had multiple resistance at baseline, and 7.5% developed ART resistance.	
8	Casalme et al. ²⁹	2022	Philippines	Healthcare workers (HCWs) monitored adherence by watching videos via a web-based dashboard with the VOT (video-observed therapy) mobile app.	308 patients converted to MDR-TB cases	Patients and treatment providers	-	The treatment success rate was 88%, and the loss to follow-up rate was 8.1%. All HCWs agreed that VOT data accurately reflect the medication intake of the patients; 88/89 (99%) mentioned benefits of VOT, notably convenience, sense of comfort, privacy, and security	VOT (video-observed therapy) is feasible and acceptable for both patients and HCWs (Healthcare workers)
9	Stephens et al. ³²	2019	South Africa	3-day recall, 30-day recall, and Visual Analogue Scale (VAS) and examined adherence to monthly study visits (months 0–12).	200 patients	Patients	30 days	Adherence to medications (81–98% fully adherent across all measures) and clinic visits (80% missed ≤1 visit) were high, irrespective of HIV status. Adherence to antiretroviral therapy (ART) was significantly higher than to MDR-TB treatment by all self-reported measures (3-day recall: 92% vs. 84%, respectively. Adjusted risk ratio (aRR) of unsuccessful MDR-TB treatment increased with every missed visit: 1.50, 2.25, and 3.37 for unsuccessful treatment, for 1, 2, ≥3 missed visits.	Adherence to ART was significantly higher than MDR-TB treatment by all self-reported measures. Less effect of the intervention on MDR-TB patients.
10	Chaiyachatt ³⁴	2013	South Africa	Trained five Health Care Workers (HCWs) in one location and given mobile phone HCWs' mobile usage patterns were electronically tracked for seven months and analysed	Five HCWs (one of five HCWs is female, two mobile HCWs were nurses; three completed secondary schooling without additional training)	Healthcare Workers and patients	7 months	Mobile HCWs submitted nine of 33 (27%) expected adverse events forms, conflicting with qualitative results in which mobile HCWs stated that mobilise improved adverse events communication, helped their daily workflow, and could be successfully expanded to other health interventions.	Explore the motivations of HCWs in the context of the limitations of their workflow and better technology for closer and real-time performance monitoring to create scalable interventions
11	Chien et al. ²⁷	2013	Taiwan	Researchers conducted a retrospective analysis of resistance profiles among MTB isolates obtained from 2160 consecutive patients with culture-confirmed pulmonary tuberculosis (pulmonary TB).	2160 patients	Patients	month	Trend analysis revealed that the rates of acquired MDR-TB were significantly lower after implementing the DOTS and DOTS-Plus programs (p < 0.01). The rates of resistance to rifampicin, isoniazid, ofloxacin, and para-aminosalicylic acid decreased significantly during the study period.	DOTS and DOTS-Plus are both effective at preventing the acquisition of MDR-TB in Taiwan

Table II: Study interventions characteristics

Intervention	Studies
1 Psychological counselling or educational intervention	Baral et al. 2014; ²⁵ Tola et al., 2016; ³³ Walker et al, 2018; ²⁶ Malini et al., 2021; ²⁸ Calligaro et al., 2021 ³¹
2 Medication event reminder monitor (MERM)/electronic dose monitoring (EDM)	Thomas, et.al, 2021; ⁹ Bateman, et al., 2022 ³⁰
3 Video Directly Observed Therapy (VDOT)	Casalme et al., 2022; ²⁹ Malini et al., 2021 ²⁸
4 30-day recall and VAS	Stephens et al., 2019 ³²
5 Financial Support	Baral et al., 2014 ²⁵
6 mHealth Application	Chaiyachati et al, 2013 ³⁴
7 Directly observed therapy, short course (DOTS) and DOTS-Plus programmes	Chien et al, 2013 ²⁷

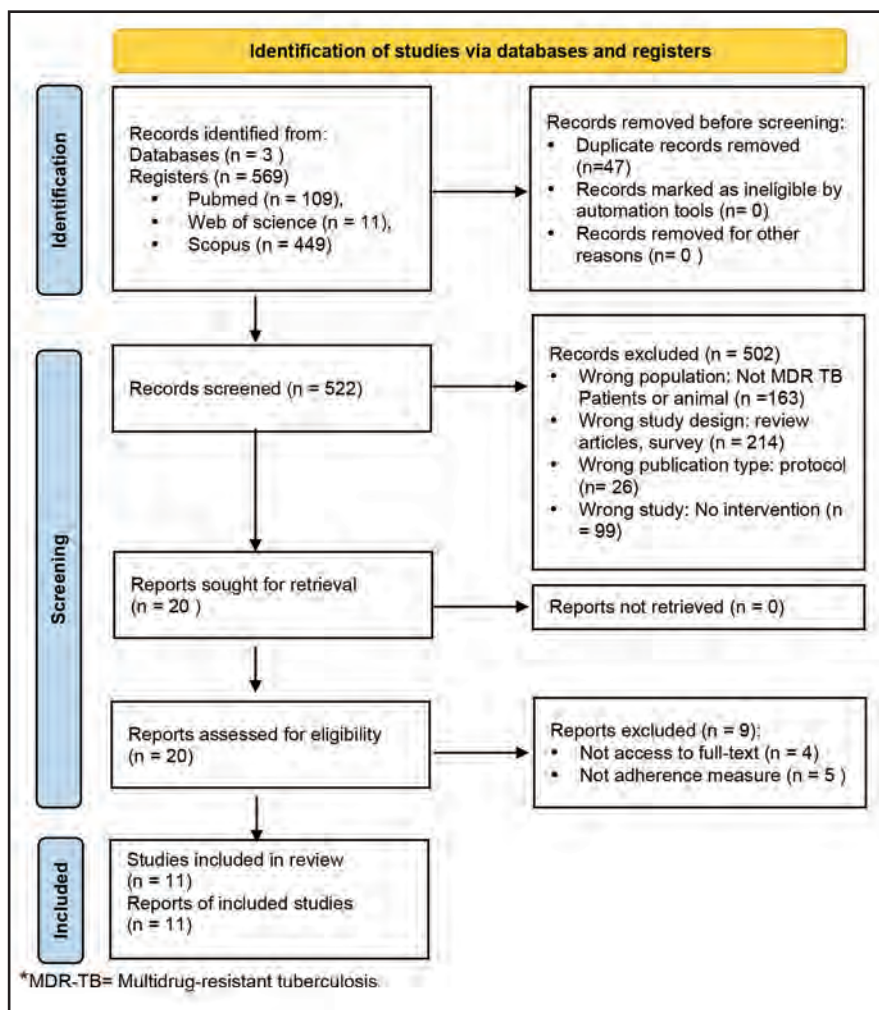


Fig. 1: PRISMA diagram of this review.

RESULTS

Study Selection

All original studies are assessing the intervention to improve adherence to medication MDR-TB. We use journals published for the period January 2012 and November 2022 that were selected for this systematic review. During the search, we found 569 articles divided into 109 articles from the PubMed database, 11 articles from the WoS database and 449 articles from Scopus. We identified 47 duplicate articles using the Rayyan AI® software.²⁴ A total of 522 articles were screened for the title and abstract. This initial screening excluded 502 irrelevant articles then, the full-text screening process was

continued for 20 articles. In the full-text screening, nine articles were excluded, consisting of no access to full-text articles (n = 4) and no adherence measure (n = 5). We finally analysed 11 articles for qualitative synthesis. The flow diagram, literature search and screening process following the inclusion and exclusion criteria using the PRISMA diagram²³ can be seen in Figure 1.

Study Characteristic

We found 11 studies related to improving the adherence in MDR-TB patients. In this review, we included studies on two continents, i.e. Asia and Africa. The studies from Asian

countries, i.e., India,⁹ Nepal,^{25,26} Taiwan,²⁷ Indonesia²⁸ and Philippines,²⁹ while the African studies from South Africa,³⁰⁻³² and Ethiopia³³ (Table II).

Study Interventions

The implementation of an intervention for MDR-TB patients is essential to improve adherence (20). Some interventions are very influential in improving the adherence level of MDR-TB patients. The results of the intervention can be seen in Table II.

From all the intervention studies we identified, psychological counselling or educational interventions were found to be the most popular interventions for improving adherence in MDR-TB patients because as indicated by several.^{25,26,28,31,33} It has been shown that psychological counselling increases the adherence rate of MDR-TB patients and promotes regular medication intake.

Furthermore, the electronic-based monitoring system using specifically MERM/EDM has also garnered. The implementation of MERM has been demonstrated to improve adherence in MDR-TB patients⁹, while EDM had less effect on adherence levels in the same patient group.³⁰ VDOT is also one of the effective methods to improve adherence levels in MDR-TB patients. Recent study show that VDOT methods enhance the adherence of MDR-TB patients because it provides a sense of ease, comfort, privacy and safety.^{28,29} Recent study with interventions such as 30 day recall and VAS,³² Financial,²⁵ mHealth application,³⁴ DOTS and DOTS-Plus programs²⁷ also had a significant in improving adherence to MDR-TB patients.

DISCUSSION

Principal Findings

To the best of our knowledge, this is the first study of adherence to explore the adherence level of MDR-TB patients. We found eleven intervention studies in the research literature that mostly supported adherence rates in MDR-TB patients. Some intervention studies, such as psychological counselling and educational intervention, were more widely used by researchers in the literature sources. Focusing on the implementation process of adherence in MDR-TB patients still seems to be an important topic in research.

Study Characteristics

Regarding our findings, based on the studies published in 2012 to 2022, the research on the intervention to increase the adherence level of MDR-TB patients were dominated by lower-middle countries such as South Africa (four studies). In low- and middle-income countries, TB is often linked to poverty, poor living conditions and lack of access to healthcare.³⁵ Our findings are supported by the fact that more than 90% of notified tuberculosis infections occur in low-income and middle-income countries. Two-thirds of the estimated 10 million new active tuberculosis cases globally are accounted for by eight countries: India (26% of global cases), Indonesia (9%), China (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (4%).³⁶

Study Interventions

Interventions aimed at improving to treatment adherence in patients with multi-drug resistant tuberculosis (MDR-TB) in low- and middle-income countries can pose challenges due to various factors such as poverty, lack of access to healthcare, and poor understanding of the disease.³⁶ Regarding our findings, psychological counselling or education intervention were identified as the most popular interventions, especially in low- and middle-income countries. MDR-TB treatment is a long and complex process that often leads to psychological distress for patients, including anxiety, depression and stigma.³⁵ The implementation of psychological counselling and health education interventions resulted in a significantly reduction in non-adherence levels among the intervention group. Moreover, unlike those studies that reported contradictory results, our findings were consistent with many other studies findings. For instance, Liefoghe et al. reported limited impact on adherence improvement despite intensive patient counselling.³⁷ However based on the evidence from five studies using psychosocial were found to be the most effective, efficient and cost-effective making them suitable for implementation in low-income countries. This conclusion with the study conducted by Kaliakbarova et al. which revealed significant decrease in treatment non-adherence levels with the provision of psychological support to MDR-TB patients.³⁸ Furthermore, Lee et al. found that physical education significantly reduced cumulative non-adherence levels among the intervention group compared with the control group.³⁹ Thiam et al. also reported an improvement in TB treatment adherence levels following an intervention focused on enhancing communication between health care workers and patients.⁴⁰

Psychological and social factors that can affect treatment adherence can be addressed through counselling which provides emotional support, coping strategies and disease-related information to patients.^{9,41} One approach utilised is cognitive-behavioural therapy (CBT), which assists patients in identifying and modifying thought patterns and behaviours affecting their adherence to treatment. CBT also in the development of coping strategies for managing medication side effects and the physical and emotional impacts of the disease.⁴² Another approach is motivational interviewing (MI), an employs patient-centred counselling method to helps patients explore and resolve ambivalence about treatment adherence. MI also facilitates the identification of personal motivations for adherence and the establishment of treatment goals.^{25,33} Group counselling can also prove effective for MDR-TB patients, as it allows patients to share their experiences with others facing similar challenges. Offering emotional support and reducing feelings of isolation and stigmatisation.^{26,28} It is important to note that psychological counselling should be provided by trained professionals and integrated into the comprehensive treatment plan for MDR-TB patients. In summary, psychological counselling was valuable intervention for increasing treatment adherence in MDR-TB patient by addressing psychological and social factors, providing emotional support, coping strategies and disease related information.^{9,40,41}

The improvement of MDR-TB adherence can be achieved through the utilisation of MERM. Positive outcomes were observed in studies conducted by Thomas et al., demonstrating the effectiveness of MERM in improving treatment adherence among MDR-TB patients.⁹ MERMs serve as reminders for patients to take their medication at the designated time and generate electronic records of medication adherence. Patients greatly appreciated the reduction in clinic visits, resulting in time and cost savings, as the frequency of routine clinic visits for patients with MDR-TB was reduced during the pilot implementation of MERM.⁴¹ Despite the decreased in face-to-face interactions with healthcare providers (HCPs), some patients expressed a feeling more cared for. This feeling stemmed from the perception that HCPs were remotely monitoring their clinical progress and the from positive responses to receive through actual phone or in-person outreach based on adherence data. The study also highlights the advantage of MERM as the reminders prompt patient to access their medication storage area, increasing the likelihood of prompt medication intake and promote habit-forming medication-taking behaviour.^{45,46}

Furthermore, the impact of MERM monitoring in this population will contingent upon the development of interventions to address issues such as drug toxicity, depression, stigma and substance use disorders, which frequently contribute to non-adherence.⁴⁵ Therefore, the utilisation MERMs is deemed to have a good impact on adherence in MDR-TB patients. In a study conducted in India, the implementation of a mobile phone-based system with text message reminders improved treatment adherence among MDR-TB patients by more than 20%.⁴¹ However, a study on EDM in South Africa³⁰ shows that EDM has less effect on improving adherence among MDR-TB patients, and there are several reasons why studies on EDM may have indicated limited effectiveness. One reason is the potential inadequate utilisation of EDM systems by patients, healthcare providers or both. For example, patients may forget to use the device or may not understand how to use it properly. Similarly, healthcare providers may not properly integrate the device into their care and follow-up practices.⁴⁷ Another reason is that EDM systems may not be appropriate or feasible for all patients, especially those residing in low- and middle-income countries with limited access to technology.

Additionally, some patients may not have access to the necessary infrastructure to support EDM, such as electricity or mobile phone networks.⁴⁸ Another reason is that EDM systems alone may not improve adherence in patients with MDR-TB. Treatment adherence is a complex issue influenced by many psychological, social, and economic factors. Therefore, it's important to consider a multifaceted approach that includes psychological counselling, social support, and financial support.^{39,40} Finally, some studies may have limitations that affect the results' accuracy and generalisability of the findings. Therefore, it's important to consider the design and methodology of studies when interpreting their results. While EDM systems such as MERMs can be an effective approach to improve adherence to treatment in patients with MDR-TB, they may not be as effective in specific populations or when used in isolation. It's important to consider the context and the patient's needs and

to use a multifaceted approach when addressing adherence to treatment in MDR-TB patients.

VDOT is a technology-based approach that can improve adherence to treatment in patients with MDR-TB. VDOT involves video conferencing technology, allowing healthcare workers to observe patients taking their medication remotely. Additionally, it allows for more frequent monitoring of medication adherence, which can improve treatment outcomes. Our findings show this approach positively enhanced the adherence of MDR-TB patients to treatment who have difficulty attending in-person clinic visits, such as those who live in remote areas or have mobility limitations.^{28,29} Garfein and Doshi⁵⁰ and Chen et al.⁵¹ stated that the combination of media (audio-visual) and effective communication while delivering health education programs could be effective in improving knowledge and behaviour for TB control.⁵²⁻⁵⁴ A randomised clinical trial in Moldova showed that VOT increased adherence to TB treatment.⁵⁵ A much earlier study on asynchronous VOT at five sites in California showed that VOT reduced stress on the TB programs and enabled a quicker return to daily activities. It also reported that VOT was beneficial for patients in remote areas as it does not require consistent network connectivity.⁵⁶ VDOT can effectively improve adherence to treatment in patients with MDR-TB by increasing accessibility to care, allowing healthcare workers to observe patients taking their medication remotely, and providing more frequent monitoring of medication adherence.

The 30-day recall method and VAS are two methods that can be used as interventions to improve adherence to treatment in patients with multi-drug resistant tuberculosis (MDR-TB).³² Both methods can be used with other interventions, such as directly observed therapy (DOT) and psychological counselling to improve treatment adherence. For example, the 30-day recall method can monitor medication adherence over time, while VAS can assess patients' attitudes and beliefs about their treatment and adherence.³² However, a study conducted by Wilson et al. stated that the closer correlation between the 3-day recall measure and TB treatment outcomes compared to the 30-day recall measure is consistent with evidence suggesting that self-reports during shorter recall periods (2 to 4 days) tend to be more accurate compared to more extended recall periods.⁵⁷ We agree that in addition to more accurate results with shorter recall periods, the results may also provide adherence for MDR-TB patients.^{57,58} The 30-day recall method and VAS are two methods that can be used as interventions to improve adherence to treatment in patients with MDR-TB. Still, they should be used in conjunction with EDM or DOT to get a more comprehensive picture of a patient's adherence.

Another approach is financial support, which can help to reduce the burden of treatment-related costs and increase treatment adherence. Providing counselling and financial support reduces their vulnerability and increases recovery rates.²⁵ Another study in India showed that providing financial support through transportation vouchers improved treatment adherence among MDR-TB patients by more than 15%.⁵⁹ A recent study in Thailand shows no significant difference in medication adherence rates after financial

support.⁶⁰ It is important to note that financial support should be provided in a way sensitive to the patient's needs and cultural context. It can be an effective intervention for improving adherence to treatment in patients with MDR-TB by reducing the burden of treatment-related costs and making it easier for patients to adhere to their treatment regimen.

Furthermore, an approach through mHealth applications is mobile phone-based health interventions that can provide patients with reminders to take their medication, information about the disease and its treatment, and the ability to communicate with healthcare providers.³⁴ Additionally, mHealth applications can be integrated with financial incentives for adherence, such as mobile phone credit or other rewards, to motivate patients to adhere to their treatment regimen.²⁵ The mHealth applications should be designed with the patient's needs and cultural context in mind, and they should be easy to use and accessible to patients with limited literacy and technology skills.⁶¹

The classical way to improve the adherence level of MDR-TB patients was DOTS and DOTS-Plus program approaches.²⁷ DOTS is a World Health Organisation (WHO) recommended strategy for the treatment of TB, which involves providing patients with daily supervised therapy.⁶² DOTS-Plus is an extension of the DOTS strategy that includes using second-line drugs to treat MDR-TB. It is a comprehensive package of care that provides for the provision of medicines, diagnostic services, and other support services. DOTS-plus also includes components such as psychological counselling, social support, and financial assistance, which can help to improve adherence to treatment.⁶³ The rationale is that the social interaction and peer pressure involved in DOT can motivate patients to more adhere to prescribed treatment.⁶⁴ However, DOT raises several ethical and legal issues.^{65,66} Some studies have shown that frequent DOT can reveal a patient's TB status, which is stigmatised in many cultures.^{67,68} Despite the unfavourable stigma, continued use of DOTs will yield positive results. This is because, in some countries, DOT is provided by trained private observers such as volunteers or specialized DOT providers employed by the government.^{69,70}

There are several limitations that may be encountered when studying interventions to improve adherence to treatment in patients with multi-drug resistant tuberculosis (MDR-TB). The results of studies may not be generalisable to other populations or settings. The interventions may be effective in specific contexts but may not be appropriate or feasible in others. MDR-TB is a complex disease that requires a multifaceted approach to address treatment adherence. It's important to consider the length of treatment and side effects when addressing adherence to treatment in patients with MDR-TB. In addition, it's important to acknowledge the challenges associated with different interventions to study limitations. These include scalability, cost-effectiveness, cultural considerations and implementation barriers. However, similar evaluation should apply to other interventions to comprehensively understand their real-world impact.

CONCLUSION

Our review implies that interventions to improve adherence to treatment for multidrug-resistant tuberculosis (MDR-TB) are essential for successful outcomes. These interventions can include directly observed therapy (DOT), counselling, education and provision of social support. Additionally, involving community members and traditional healers in the care and treatment of patients with MDR-TB can increase trust and understanding, leading to better adherence. Overall, a combination of interventions tailored to the patient's and community's specific needs and cultural context is likely to be most effective in improving adherence to treatment for MDR-TB. Further study is required to investigate the specific on developing highly personalized interventions for a particular population or context, and examining the cost-effectiveness of interventions to help policymakers, and health systems make informed decisions about which interventions to implement.

ACKNOWLEDGMENT

This study is supported by Indonesian Education Scholarship and Harapan Bangsa University Purwokerto.

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