ORIGINAL RESEARCH

Barriers and Enablers to All-Oral Multi-Drug Resistance Tuberculosis Treatment Adherence in Traditional Authorities Chimwala and Chowe, Mangochi District, Malawi

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Abstract

Background

The Malawi National Tuberculosis Program (MNTP) switched the MDR-TB treatment regimen from a combination of injectable and oral anti-TB drugs to an all-oral regimen in 2018. This has increased the pill burden and increased the treatment period from 12 to 18 months. The change was necessitated by the need to minimize amikacin-induced side effects which include vertigo, convulsions, and numbness. However, the longer treatment period and pill burden may affect treatment adherence.

Objective

The purpose of the study was to assess factors that influence adherence to the all-oral drugs for MDR-TB.

Methods

This descriptive qualitative study employed 10 in-depth interviews, 2 focus group discussions and 7 key informant interviews with patients, guardians and health workers. Participants were identified through purposive sampling from Traditional Authorities Chowe and Chimwala in Mangochi district. Data analysis was done through a thematic approach.

Results:

Patients expressed satisfaction with the newly-introduced oral treatment for MDR-TB owing to the fewer side effects the treatment has, absence of pain from injections, desire to accomplish plans, delivery of drugs close to patients through drones, and home visits by health care workers. However, some patients highlighted barriers to adherence such as delayed food provision, and delayed transport refunds by the Malawi National Tuberculosis Control Program through its partners. Other barriers were medication stockouts, bad weather, and traveling away from home. Participants recommended that to improve adherence, interventions should include involving ex-MDR-TB patients and guardians in giving out MDR-TB adherence messages, and intensifying community sensitisation on MDR-TB.

Conclusion

MDR-TB treatment non-adherence is associated with patient factors, economic factors, access to health facility factors and environmental factors. Addressing the barriers is key to preventing MDR-TB relapse and new infections.

Introduction

Malawi has known system challenges in treating Multidrug Resistant Tuberculosis (MDR-TB). These include funding limitations, delays in diagnosis, prolonged treatment duration, failure to initiate treatment for all diagnosed patients, and a lack of transport from patients, homes to the health facilities, among others[1]. MDR-TB is resistant to rifampicin and isoniazid, the first line of anti-TB drugs[2]. This resistance is facilitated by mismanaged tuberculosis treatment and person-to-person transfer of TB strains[2]. (1) Treatment of MDR-TB initially combined injectable and oral anti-TB drugs, one of which was amikacin. In 2018, following World Health Organisation (WHO) recommendations, the Malawi National Tuberculosis Program (MNTP) switched the MDR-TB treatment regimen from a combination of injectable and oral anti-TB drugs to an all-oral regimen to minimise amikacin-induced side effects such as hearing loss[3]. This means patients with MDR-TB now take all their medication from home. One concern with this shift is treatment adherence due to the high pill burden, longer treatment duration (18-24 months), limited opportunities for direct observed treatment by the health worker and socioeconomic factors.

Medication adherence is a crucial determinant for improved MDR-TB outcomes[4]. It is the extent to which a patient's behaviour corresponds to the prescribed medication dosing regimen, including time, dosing and interval of medication intake[5]. There is literature indicating that MDR-TB treatment adherence is affected by patient factors, social, economic, health system, therapy, lifestyle and geographical factors[6]. These factors can be barriers or facilitators to treatment adherence.

Some documented factors to MDR treatment adherence include patients' knowledge about TB and its treatment, beliefs about TB, trust that patients have in healthcare providers, sense of responsibility to adhere to treatment

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and support from healthcare providers, family and friends[2]. (1) Other factors are stigma associated with MDR-TB, tolerance to medication, simplicity or complexity of the regimen, and accessibility and affordability of MDR-TB services[7], perception of care[8]. While studies in several countries document enablers and barriers to MDR treatment adherence, data on factors influencing adherence in Malawi are scanty. Therefore, this study aimed to examine factors influencing the all-oral MDR-TB treatment adherence from the patients' perspective in Mangochi, Malawi. Furthermore, the study explored barriers to adherence to the all-oral drug regimen for MDR-TB patients and enablers to an all-oral drug regimen for MDR-TB patients.

Materials and Methods

Study design

A descriptive qualitative design was used to explore in-depth the barriers and enablers of MDRTB treatment adherence.

Setting

The study was carried out in Mangochi district, in the Traditional Authorities Chimwala and Chowe.

Participants

The study population comprised previously treated MDR-TB patients at Mangochi District Hospital who switched from injectable to all-oral treatment, their caretakers and healthcare workers as key informants.

Study size and sampling technique

We conducted 10 in-depth interviews with MDR-TB patients, 2 focus group discussions with patients' caretakers, each group comprising 4 participants, and 9 key informant interviews with health workers. Purposive sampling was used to select participants.

Variables

Our independent variable was MDR-TB treatment adherence. Dependent variables were enabling factors and challenges to MDR-TB treatment adherence, such as fewer medication side effects and barriers to the uptake of MDR-TB treatment. For example, medication access challenges and financial constraints.

Data collection procedures

In the investigation, the study team used questions that were developed by using data objectives and literature. Originally, questions were in English. During data collection, a Yao-speaking interpreter translated for only Yao-speaking participants. Patient participants were interviewed in their homes, while in-depth interviews for health workers and focus group discussions with the patient's caregivers were conducted at the hospital. Open-ended questions were used, accompanied by follow-up questions to get clarification.

Data analysis

The researcher transcribed digitally recorded data by listening and typing the exact words recorded. Then the investigators reviewed the transcripts separately. Being health personnel with previous client experience on medication adherence, the investigators made sure that their prior knowledge and experience would not influence the interpretation of study results. The investigators therefore did counter-examination of the interpretations before agreeing on themes and subthemes. The researcher developed a coding template with key themes generated from the interviews and focus group discussions. This was done manually. A thematic analysis process was employed to analyse the data into general themes relative to enablers and barriers to adherence to anti-TB-resistant drugs.

Five steps were performed during this process. The first was familiarisation, in which the investigator was involved in the repeated and active reading of data to better understand the participants' responses. The second step generated initial codes using a deductive approach, whereby the investigator took notes on data items of potential interest, questions, and observed connections between data items and other preliminary items. This marked the beginning of coding. The codes that were developed were fitted into coding frameworks that were connected to develop the themes. Thematic maps were used to visually show the connections between concepts, main themes, and sub-themes[9].

The third step was to build the themes. This entailed examining the coded and collated data extracts to build themes. This was done by analysing, comparing, combining, and mapping the relationships among the codes. The fourth step was to review the themes.

Each theme was checked to see if it fitted meaningfully into each dataset, and whether the thematic map accurately represented the entire body of the data. This process was iterative.

In the fifth step, each theme was defined and described. The researcher also explained why each theme was important to the broader research question and which aspect of the dataset it covered. The researcher looked for overlap between themes while still identifying the emerging sub-themes. Furthermore, the extracted data were presented in the final report to represent the selected themes. The final step was to write the final analysis and description of the findings. The findings are presented as themes and subthemes with their corresponding quotations[9]

Ethical approval

Approval for the study was obtained from the Kamuzu University of Health Sciences Research and Ethics Committee. The ethical approval number was U.04/22/3604. In addition, authorities from the Mangochi District Research Committee were informed and written informed consent was sought from participants before enrolment.

Summary of results

This study found three themes on barriers and three themes on enablers of MDR-TB treatment adherence. Each theme had an average of two subthemes. Enablers included fewer side effects to the medication, positive rapid response to the treatment, absence of pain from injections, and home visits by health care workers. On the other hand, barriers to treatment adherence were bad weather, transport challenges, lack of food, and drug stock-outs at the health facility. In the figure below, themes are presented in rectangles and subthemes are in circles.

Barriers to adherence to all-oral MDR-TB treatment adherence

A. Financial constraints

1. Lack of food

The study found that the National Tuberculosis Program (NTP) provided food for the patients to encourage treatment adherence, since the drugs induce hunger. However, this

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Summary of study participants

TYPE	NUMBER OF PARTICIPANTS	GENDER	AGE RANGE
IN-DEPTH INTERVIEW	10 ex-MDR-TB patients who were switched from injectable to all-oral regimen.	4 females, 6 males	18-45 years
FOCUS GROUP DISCUSSIONS	2 groups, each consisting of 4 patient caretakers	4 males, 4 females	23-50 years
KEY INFORMANTS	7 health workers from the TB department	3 females, 4 males	30-44 years

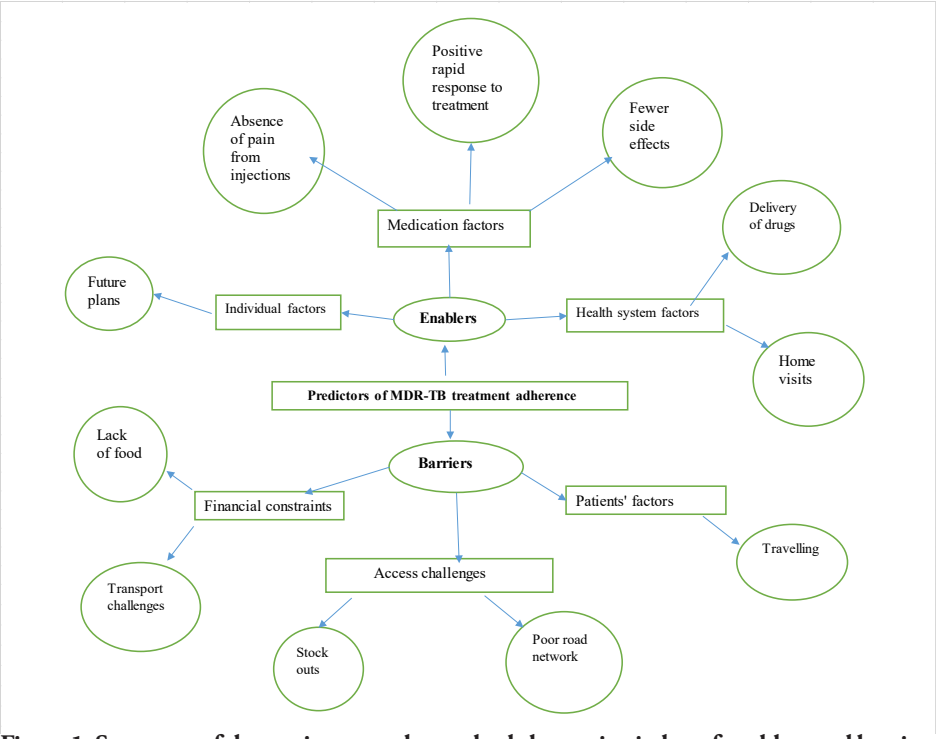

Figure 1: Summary of themes in rectangles, and subthemes in circles, of enablers and barriers

food was shared among family members, since most of the families were struggling financially. Therefore, the provided food did not last the entire quarter. As a result, patients skipped their medications. Below are some quotations from what some participants had to say:

'The NTP provided food for the patient who is our family's breadwinner. Since he was not able to provide due to his ill condition, our whole family was relying on his food handout from NTP for survival.' Mother, FGD 2

'There is this one patient in particular; he has nothing…no money to buy food. This prevents him from taking medication because one side effect of these drugs is intense hunger.' KII 6, clinician.

2. Transport challenges

Most clients reported transport as a barrier to adherence. Transport money was refunded by NTP, via mobile money transfer after a patient visited the clinic for follow-up and refill of medications. Sometimes it would take months before the money was refunded, such that by the time the next date for a subsequent medication refill visit arrives, the patient would have no money to use for transport to the hospital. Sometimes own efforts to get to the hospital through family or friends' support would prove futile. When asked, they narrated:

'Transport refunds via mobile wallets take a long time, sometimes months. We missed subsequent visits because we did not have money. Even neighbours refused to borrow us'. Interview 2.

'I relied on someone to take me to the hospital on his bicycle. Sometimes this person gave lame excuses at the last minute, so I had to struggle to find money for a cyclist to take me to the hospital. Sometimes I could miss my appointment' Interview 4.

B. Access challenges

1. Stock outs

Some participants reported to have been non-adherent because, at some point, there was a stock out of the drugs at the health facility. Aside the active drugs that target the bacteria, patients are also prescribed other drugs that work to alleviate side effects. It was these supportive drugs that were sometimes not available at the hospital. As such, patients missed those drugs. Some had this to say:

'Some supporting drugs were not available at times, but the actual MDR-TB drugs were always available. In such cases, I could not take the supporting drugs.' Interview 4.

'*There were some days when other types of drugs were not available at the facility. As a result, my patient did not take those drugs on those days. But when all the drugs were available, my patient would take all of them without any problem.'* Spouse, FGD 1

2. Poor road network

Participants explained that during heavy downpours, the roads were poor, and the rivers were flooded. Most of the rivers do not have proper bridges. As such, they are inaccessible mostly during the rainy season. This was also reported as a barrier to adherence. Patients found it difficult to travel to the hospital for medication refills during heavy rainfall. Some of the participants had this to say:

'During the rainy season, for example, during the recent cyclone Fred, it was difficult for our patients to come to the hospital to access the medication'. KII 5 nurse.

'When rivers are flooding, we don't cross. Therefore, we wait until crossing is safe again for us to go and collect medications from the health facility.' Interview 10

C. Patient factors

1. Travelling away from home

It also was reported that participants could miss drugs when they travelled on business trips, or other social functions, especially when they spent the night away from home. Apparently, the drugs were not part of their travel package, either forgotten, overlooked, or voluntarily left at home. This also resulted in medication non-adherence. Here is what some of them had to say:

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'Sometimes I could go on a business trip, hoping that I would come back the next day. But for some reason, I would extend my trip, so I missed my drugs on those extra days.' Interview 4.

'*It's difficult to take medication when I attend family gatherings such as funeral. I skip medication because I don't want people to ask why I am taking them.'* Interview 9

C. Enablers to adherence to introduced oral drugs for MDR-TB.

A. Medication factors

Most clients rated their adherence to the treatment at a scale of 90-100%, citing the following factors as motivators:

1. Few side effects as compared to the previous injectable method

Clients stated that they were happy with all oral MDR-TB medication use because there were fewer and bearable side effects compared to the previous regimen. They also expressed that they can persevere side effects, as they are part of the medications. As such, they were able to take the medication daily, as prescribed. Below are some of their narratives:

'Pills brought joint pains, but they were better. The side effects were more tolerable than those from injections.' In-depth interview 2.

Drugs fight off infections in a person's body. The side effects were fewer as compared to the injectable drugs. Therefore, I only focused not on side effects, but on getting better.' In-depth interview 4.

2. Medication's rapid positive effect

Clients reported that they noticed a rapid improvement in their health condition the time they were switched to all-oral drugs. This was because they noticed a rapid subsiding of symptoms and signs of MDR-TB. This gave them the courage to go on with the drugs, because they could see or feel the positive effects that the medication had on their bodies. Below are some of the quotations on what they had to say:

'When I started taking the pills, I noticed a fast improvement in my health, unlike the time I was being injected'. Interview 7

'*During the time my son was being injected, I could not see much improvement. But once the tablets were introduced, I noticed that there was a quick improvement in his health*.' Mother, FGD 1.

3. Absence of pain from injections

Most clients expressed a preference for all-orals to injectable drugs because there was no pain from injections. The injections were overwhelming to the patients, because they were very painful. As a result, the pain distracted their activities of daily living, such as sitting down properly. The oral medication was free from such pain, so patients were encouraged to adhere. This is what some of them said:

'Getting daily injections was very challenging and painful; I couldn't sit. As time passed, I couldn't tell which buttock was injected the previous day to alternate.' Interview 2.

Oral drugs are too much, but the burden cannot be compared with injections. Sometimes I felt like I was getting crazy with the injections. I like the tablets better, unlike injections.' Interview 6

B. Health system factors

1. Home visits by healthcare providers

Most clients reported that they were adherent to the medication because healthcare workers used to visit them in their homes to check how they were doing, and how they were taking their medications. They also offered words of encouragement on such visits. This brought them so much encouragement and eventually led to adherence.

'Health workers used to come to visit me every week to check how I was doing, how I was taking my drugs. Those people were so caring.' Interview 8

'Most of my relatives shunned away from us, so the health care providers helped us a lot with their words of encouragement during the home visits until my patient improved.' Spouse, FGD 1.

2. Delivery of drugs to the nearest health facility

Another factor that contributed to patient adherence was the delivery of medicine to patients who come from hard-to-reach areas. Drugs were delivered to the patient's nearest facility through a drone. The use of these drones was a pilot project. Sometimes, medication was brought to the nearest health centre through a health worker who visited the district hospital for other reasons. MDR-TB medication was therefore easily accessible within the patients' locality.

'Some patients come from afar. For such patients, we would send them drugs at times through a drone, or a health worker from their nearest facility who came to the district hospital.' KII 1.

'It was easy for me to get my drugs from the (nearest) health centre. I had the medication. If it were not for this, I would have to travel to the boma (district hospital) to refill my drugs, of which I doubt if I could manage" Interview 8.

C. Individual factors

1. Plans

The patient's intrinsic desire for recovery was also reported as a motivator for adherence to the oral MDR-TB drugs. Some patients had plans for the future, which they wanted to accomplish once they were in good health. They understood that the only way to regain their health was through taking medication as prescribed. Therefore, they chose to be adherent, as they were quoted as saying below:

'I was being adherent so that I could be cured, and if God still gives me life, I should go to "theba" (Johannesburg)'. Interview 6.

'I get motivated to adhere to treatment when I think of my children; I don't want to leave them orphans if I die. I take medication to resume my normal activities for generating money and taking care of my family.' Interview 6

2. Fear of disease complications

Fear was also reported as an enabler of adherence. Patients feared the complications of the disease, especially death, and they feared treatment failure. This is what they said:

'I was advised beforehand that if one is being non-adherent, he can lose his life, or fall sick again into a more serious TB than this. So I was being adherent because I knew what would follow if I did not adhere to the treatment plan.' Interview 2.

'I learned from other clients who were not adherent; they were not improving in their health. I didn't want my condition to deteriorate or to die.' Interview 8.

Discussion

In this investigation, factors that influence MDR-TB treatment adherence were patient, economic, access to health services and environmental factors. The enablers, such as fewer side effects and a positive, rapid response to treatment upon initiation, should be made known to the communities to increase adherence. Similarly, barriers such as drug stock-

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outs and lack of food should be addressed to minimise non-adherence. These efforts combined can improve MDR-TB patients' treatment outcomes. However, this study did not ascertain whether these factors prevail only in the all-oral regimen, or were prevalent also in the previous injectable regimen.

Barriers to MDR-TB treatment adherence

This study identified financial burden as a barrier to treatment adherence. For instance, there was a delayed transport refund by the Malawi NTP. Participants did not have a reliable source of income due to their ill state and did not have relatives who were financially capable of providing them with transportation money. These patients were previously running businesses, such as selling fish or selling goods from South Africa. Once they suffered from MDR-TB, they were not able to work and secure money for supporting their lives and for travelling to the hospital. As was the case in other studies, lack of transportation money coupled with long distance deterred them from accessing healthcare[9-11]. Long distances to health facilities are already a hindrance to accessing healthcare, and presents a double burden to MDR-TB patients who experience side effects from medication. As such patients encounter a life-threatening situation in the treatment process.

Another finance-related factor that hindered MDR-TB treatment adherence was the lack of food and the lack of money to get to the hospital for a refill of drugs. The Malawi NTP supplied patients with food, but this could not last until the next stock, because they were sharing it with everyone in the family. This was especially common where the patient was a breadwinner or the patient did not have a stable means of income. For those who were breadwinners, the illness meant a break in their income-generating activities (IGA) in the initial weeks of initiating treatment. As a result, essential commodities, including food and money, were scarce in the homes. This forced the whole family to rely on the food that was provided by NTP. Once this food was finished, it was challenging for the MDR-TB patient to adhere to medication on an empty stomach, since the drugs are intolerable without food. Conversely, sufficient food provision in the United States of America was shown to improve adherence to TB treatment[12]. Incorporating MDR-TB patients and family in social cash-transfer activities may be some of the recommendations for addressing these challenges, particularly after a few weeks of starting treatment, when the patient can manage small income generating activities (IGAs). In other countries, engaging MDR-TB patients in vocational training skills also lessens the burden[13]. Patients can utilise these skills while still sick because normally patients stabilize once they start MDR-TB treatment. As such, they resume light activities, which can include vocation skills such as tailoring. This assures that in Malawi adherence can be promoted if MDR-TB patients are empowered with skills that they can utilise to earn money to support their lives. In the course, the lack of money for transport to the hospital for subsequent visits can also be solved.

Patient factor was also identified as a barrier to treatment adherence. The majority of the patients reported travelling away from home as a barrier. These were business people who would travel several days to purchase goods for sale. It was uncomfortable for them to take medications during this time because they were afraid of stigma. This aligns with a systematic review that was conducted to determine patient characteristics associated with TB treatment adherence[14]. Mass sensitisation, advocacy by influential leaders and social contact are recommended to reduce stigma in business places[15]. This will provide a sense of security to MDR-TB patients and permit adherence regardless of where they are. In Malawi, the NTP may adopt the named initiatives that were used to reduce stigma according to literature since mass sensitization can be achieved using outlets such as radio ads as radios are widely used. Again, leaders are very influential in facilitating community behavior and social contacts influence peers.

Our study revealed access challenges as a barrier to treatment. For example, participants reported that sometimes-accompanying drugs to MDR-TB drugs were not available. These drugs help to alleviate or lessen the side effects of the active MDR-TB drugs. Without these supportive drugs, the side effects of active MDR-TB drugs become intolerable. As a result, they miss doses. This finding is consistent with other findings, which showed that drug shortages affected medication adherence[16]. Identification of the causes of a drug shortage, namely supply issues, demand issues and regulatory issues[17] can serve to mitigate drug stock-outs. The NTP and its partners must address the supply, demand and regulatory issues to enable unlimited access to treatment by strengthening the logistics management information system (LMIS).

Again, poor road network and weak bridges that become impassable during bad weather hindered the MDR-TB patients from going to the health facility to collect drugs. For example, cyclone Fred that hit Malawi in 2024 destroyed weak bridges and roads, which prevented treatment access and led to non-adherence. Similar findings were observed in other studies[18]. During the rainy season, clinic visits and hospital deliveries decreased significantly, resulting in low health service utilisation[19]. We recommend construction of climate-resilient, as well as timely maintenance of roads and bridges by the local district councils to ease mobility for MDR-TB patients to the hospital during all seasons of the year.

Enablers to MDR-TB treatment adherence

This study identified fewer and less severe drug side effects and no exposure to injection pain as enablers of treatment adherence. Apparently, the previous regimen was less tolerable due to the painful injections, and severe medication side effects. The new regimen, on the other hand, does not require injections, and its side effects are less severe. Thus, many welcomed the new regimen, leading to medication adherence. Contrary to this, studies found that perceived drug side effects and pill burden prevented patients from complying with treatment[11,20]. The difference between Mangochi setting and other places could be from use of different types or drugs and number of pills per dose. However, this study did not ascertain the reason for the difference because the investigators did not find the specific type of drugs that are used in the other settings as all oral drugs for MDR-TB to make a good comparison.

In addition, patients reported that quick positive responses to drugs facilitated adherence. The majority of participants reported a quick improvement in their health condition once they were switched from injectable to all-oral treatment. The rapid subsiding of signs and symptoms evidenced this. In other studies on TB regimen adherence, patients were recovering following treatment adherence which was

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promoted by persuasive guardians[14]. The treatment's less severe side effects, coupled with patients' positive rapid response is an advantage to the Malawi TB control program. Health workers should incorporate these messages in patient education and mass sensitisation campaigns to encourage more patients to adhere to the treatment. Health workers can easily educate patients on adherence because they routinely give health education during MDR-TB clinics and conduct home visit, which allows provision of health information to patients in their frequent contacts.

We found that patients' adherence was influenced by health system factors, one of which is home visits by healthcare workers. During visits, they provided counselling and encouragement. Sometimes they would re-fill the patient's drugs. Literature reveals a correlation between home visits and increased treatment adherence. This reduced hospitalisation rates[21]. As such home visits need to be promoted by scheduling frequent visits and supporting health workers with required resources such as motorcycles for transportation.

Additionally, the delivery of drugs by drones was influencing adherence, as there was a timely and continuous supply of drugs. The use of drones to deliver drugs to the hard to reach facilities was a pilot project by NTP. While some literature attests to good adherence when there is a shorter distance to the health facility[22,23], other literature suggests that medication adherence is not directly influenced by distance to the health facility[24,25]. Nonetheless, the Malawi NTP should further explore this option in other parts of the country, and scale it up if it continues to give good results on patients' adherence to MDR-TB treatment.

Our study revealed that patients were taking treatment because they were focusing on goals they wanted to achieve in life. This was an inspiration such that they disregarded side effects. However, in Ethiopia and India, patients were not complying with treatment because they were experiencing severe side effects, and they were taking a high number of pills[26,27]. To encourage adherence among MDR-TB patients, we suggest continued psychosocial counselling to MDR-TB patients during routine clinic visits as part of care, so that they can still find life meaningful despite being sick.

Limitation

While the study provided important insights on enablers and challenges of the all-oral MDR -TB treatment and care of patients with MDR TB, collection of data was only from one small area and it was purely qualitative. It does not compare with quantitative data. There is a need for more comprehensive studies to correlate the qualitative and quantitative findings of the level of adherence. Larger-scale studies should further investigate the whole district to generalise results and develop district-specific interventions to address the barriers to treatment adherence.

Conclusion

MDR-TB treatment non-adherence is associated with patient factors, economic factors, access to health facility factors and environmental factors. Addressing the barriers is key to preventing MDR-TB relapse and new infections.

References

1.Charlie Loveness, Amanuel Hanna, Said Bibie GE. Programmatic Challenges in Managing Multidrug-Resistant Tuberculosis in Malawi. Res Int J Mycobacteriology. 2021;6(3):239–45. doi: 10.4103/ijmy.ijmy

2.Yani DI, Juniarti N, Lukman M. Factors Related to Complying with Anti-TB Medications Among Drug-Resistant Tuberculosis Patients in Indonesia. Patient Prefer Adherence. 2022;16(December):3319–27. doi: 10.2147/PPA.S388989

3.Arnold A, Cooke GS, Kon OM, Dedicoat M, Lipman M, Loyse A, et.al. Adverse Effects and Choice between the Injectable Agents Amikacin and Capreomycin in Multidrug-Resistant Tuberculosis. Antimicrob Agents Chemother. 2017 Aug 24;61(9):e02586-16. doi: 10.1128/AAC.02586-16.

4.Folkvord F, Würth ARU, van Houten K, Liefveld AR, Carlson JI, Bol N, et al. A systematic review on experimental studies about patient adherence to treatment. Pharmacol Res Perspect. 2024;12(1):1–11. doi: 10.1002/prp2.1166

5.Gast A, Mathes T. Medication adherence influencing factors - An (updated) overview of systematic reviews. Syst Rev. 2019;8(1):1–17. doi: 10.1186/s13643-019-1014-8

6.Nezenega ZS, Perimal-lewis L, Maeder AJ. Factors influencing patient adherence to tuberculosis treatment in ethiopia: A literature review. Int J Environ Res Public Health. 2020;17(15):1–12. doi: 10.3390/ijerph17155626

7.Grigoryan Z, McPherson R, Harutyunyan T, Truzyan N, Sahakyan S. Factors Influencing Treatment Adherence Among Drug-Sensitive Tuberculosis (DS-TB) Patients in Armenia: A Qualitative Study. Patient Prefer Adherence. 2022;16(September):2399–408. doi: 10.2147/PPA.S370520

8.Endo Y, Jaramillo J, Yadav RPH. Patient- and Health-System-Related Barriers to Treatment Adherence for Patients with Drug-Resistant Tuberculosis in the Philippines: A Mixed-Methods Study. Tuberc Res Treat. 2022;2022:1–11. doi: 10.1155/2022/6466960

9.Kiger ME, Varpio L. Thematic analysis of qualitative data: AMEE Guide No. 131. Med Teach [Internet]. 2020;42(8):846–54. Available from: https://doi.org/10.1080/0142159X.2020.1755030

10.Lipato M. Socio-Cultural and Behavioural Factors affecting adherence to Tuberculosis treatment in Malawi. 2021; https://researchspace.ukzn.ac.za/handle/10413/19706

11.Shringarpure K, Gurumurthy M, Sagili KD, Taylor M, Garner P, Tonsing J, et al. Patient adherence to tuberculosis treatment in the Indian subcontinent: Systematic review and meta-synthesis of qualitative research. BMJ Open. 2023;13(5):1–12. doi: 10.1136/bmjopen-2022-063926

12.Wagnew F, Gray D, Tsheten T, Alene KA, Kelly M, Clements ACA. Effectiveness of nutritional support to improve treatment adherence in patients with tuberculosis : a systematic review. 2023;00(0):1–10. doi 10.1093/nutrit/nuad120

13.Paz-Soldan VA, Alban RE, Jones CD, Oberhelman RA. The provision of and need for social support among adult and pediatric patients with tuberculosis in Lima, Peru: a qualitative study. BMC Health Serv Res. 2013;13:(290). https://doi.org/10.1186/1472-6963-13-290

14.Appiah MA, Arthur JA, Gborgblorvor D, Asampong E, Kye-Duodu G, Kamau EM, et al. Barriers to tuberculosis treatment adherence in high-burden tuberculosis settings in Ashanti region, Ghana: a qualitative study from patient's perspective. BMC Public Health. 2023;23(1):1–12. doi: 10.1186/s12889-023-16259-6

15.Shahwan S, Goh CMJ, Tan GTH, Ong WJ, Chong SA, Subramaniam M. Strategies to Reduce Mental Illness Stigma: Perspectives of People with Lived Experience and Caregivers. Int J Environ Res Public Health. 2022;19(3). doi: 10.3390/ijerph19031632

16.Malhab B, Malhab SB, Haddad C, Sacre H, Hajj A, Zeenny RM. Adherence to treatment and harmful effects of medication shortages in the context of severe crises : scale validation and correlates. J Pharm Policy Pract. 2023;5:1–9. doi: 10.1186/s40545-023-00667-5

17.Shukar S, Zahoor F, Hayat K, Saeed A, Gillani AH, Omer S, et al. Drug Shortage: Causes, Impact, and Mitigation Strategies. Front

Pharmacol. 2021;12(July):1–18. doi: 10.3389/fphar.2021.693426

18.Samano D, Saha S, Kot TC, Potter JE, Duthely LM. Impact of Extreme Weather on Healthcare Utilization by People with HIV in Metropolitan Miami. Int J Environ Res Public Health. 2021 Mar 2;18(5):2442. doi: 10.3390/ijerph18052442.

19.Stone B, Sambo J, Sawadogo-lewis T, Roberton T. When it rains , it pours : detecting seasonal patterns in utilization of maternal healthcare in Mozambique using routine data. BMC Health Serv Res 2020;20(950). https://doi.org/10.1186/s12913-020-05807-0

20. Hutchison C, Khan MS, Yoong J, Lin X, Coker RJ. Financial barriers and coping strategies: a qualitative study of accessing multidrug-resistant tuberculosis and tuberculosis care in Yunnan, China. BMC Public Health. 2017;17(1):1–11. doi: 10.1186/s12889-017-4089-y

21.Ghimire A, Allison R, Lichtemberg Y, Joseph J, Jain V. Respiratory Medicine : X A single home visit improves adherence and reduces healthcare utilization in patients with frequent exacerbations of Severe Asthma and COPD. Respir Med X. 2021;3(March):100026. doi: 10.1016/j.yrmex.2021.100026

22.Dhar L, Dantas J, Ali M. A Systematic Review of Factors Influencing Medication Adherence to Hypertension Treatment in Developing Countries. 2017;211–50. doi:10.4236/OJEPI.2017.73018

23.Amram O, Shoveller J, Hogg R, Wang L, Sereda P, Barrios R, et al. Spatial and Spatio-temporal Epidemiology Distance to HIV care and treatment adherence : Adjusting for socio-demographic and geographical heterogeneity. Spat Spatiotemporal Epidemiol. 2018;27:29–35. doi: 10.1016/j.sste.2018.08.001

24.Yan LD, Pierre-louis D, Isaac BD, Jean-baptiste W, Vertilus S, Fenelon D, et al. Does distance from a clinic and poverty impact visit adherence for noncommunicable diseases ? A retrospective cohort study using electronic medical records in rural Haiti. BMC Public Health. 2020 Oct 14;20(1):1545. doi: 10.1186/s12889-020-09652-y.

25.Syed ST, Sharp LK, Kim Y, Jentleson A, Lora CM, Touchette DR, et al. Relationship Between Medication Adherence and Distance to Dispensing Pharmacies and Prescribers Among an Urban Medicaid Population with Diabetes Mellitus. Pharmacotherapy. 2016 Jun;36(6):590-7. doi: 10.1002/phar.1757.

26.Ali AOA, Prins MH. Patient Characteristics Associated with Non-Adherence to Tuberculosis Treatment: A Systematic Review. J Tuberc Res. 2020;08(02):73–92. doi: 10.4236/jtr.2020.82008

27.Naidoo P, Peltzer K, Louw J, Matseke G, McHunu G, Tutshana B. Predictors of tuberculosis (TB) and antiretroviral (ARV) medication non-adherence in public primary care patients in South Africa: A cross sectional study. BMC Public Health. 2013;13(1). doi: 10.1186/1471-2458-13-396