CASE REPORT

# The First Extensively Drug-Resistant (XDR) Tuberculosis Patient Diagnosed in Malawi – a Case Report

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## Abstract

We report the first case of extensively drug-resistant (XDR) TB diagnosed in Malawi. A 43-year-old female living with HIV, on tenofovir-lamivudine-dolutegravir antiretroviral therapy, with long-term viral suppression, accumulated resistance to rifampicin, levofloxacin, and linezolid on successive TB treatment regimens between 2018 and 2024, qualifying as XDR-TB. Throughout treatment as an outpatient, she regularly missed TB visits and reported poor TB drug adherence, mainly related to alcohol abuse and inconsistent availability of funds for transport. After XDR-TB diagnosis, the patient, guardians, treatment providers, and health facility leadership agreed to management as an inpatient in August 2024, when she started an 18-month regimen of bedaquiline-delamanid-cycloserine-clofazimine-pyrazinamide, with good treatment outcome. The emergence of XDR-TB in Malawi calls for further scale-up of TB resistance testing and structured approaches to improving drug adherence among drug-resistant TB patients.

**Keywords:** Tuberculosis, Drug-resistance, XDR-TB, Adherence, Malawi

## Introduction

Tuberculosis (TB) remains a major global public health problem. It was estimated that in 2023, there were 10.8 million TB cases with 1.25 million deaths[1]. Drug resistance against TB drugs has become an increasing problem that threatens the success of the World Health Organization (WHO)'s End TB strategy, which aims to achieve a 90% reduction in TB incidence and a 95% reduction in TB mortality by 2035[2]. TB drug resistance is commonly categorized as mono-resistance (including rifampicin-resistance [RR]), poly- and multidrug-resistance (MDR), pre-extensive drug resistance (pre-XDR), and extensive drug resistance (XDR)[3]. According to the WHO's updated definition from 2021, XDR-TB is defined as TB that fulfils the definition of MDR or RR, plus resistance to any fluoroquinolone, and to at least one of bedaquiline and linezolid[4]. In 2023, WHO reported that 159,684 (1.9%) people had MDR or RR-TB and 28,982 (0.4%) people had pre-XDR-TB or XDR-TB worldwide[1].

Based on the last published national TB drug resistance survey conducted in 2011, Malawi has a low prevalence of drug-resistant (DR-) TB with MDR prevalence of 0.4% among new cases and 4.8% among retreatment cases[5]. According to a more recent but unpublished national TB drug resistance survey conducted in 2018/19, MDR/RR prevalence was 2.3% among new cases and 6.1% among retreatment cases (internal National TB and Leprosy Elimination Program data). More recent, routinely collected, data from 2023 indicate that 18,784 TB cases were notified in Malawi, with an estimated TB incidence of 119 per 100,000 population. MDR or RR-TB prevalence and incidence were estimated at 0.6% and 3.2 cases per 100 000, respectively [6]. A total of 113 people had resistance to at least rifampicin, and 4 had pre-XDR TB[6]. TB treatment success rates for drug-susceptible TB and DR-TB were 90% and 66%, respectively[6]. In this report, we present the first XDR-TB case diagnosed in Malawi, describe the challenges faced with its management, and discuss some public health implications.

## Case presentation

A 43-year-old HIV-positive female on antiretroviral therapy (ART) was diagnosed with TB through fluorescent smear microscopy (acid-alcohol fast bacilli [AAFB] positive) in 2018, and she was initiated on standardized first-line TB treatment (rifampicin, isoniazid, pyrazinamide, and ethambutol). TB diagnosis was based solely on smear microscopy, as Mycobacterium tuberculosis (MTB) GeneXpert testing could not be performed due to a stockout of MTB GeneXpert/Rif/Ultra cartridges. Drug resistance was first suspected after noticing persistent sputum smear AAFB-positive microscopy results upon treatment completion. GeneXpert testing was done in March 2020 and demonstrated MTB sputum positivity with rifampicin resistance. In May 2020, she was initiated on the then standardized second-line, longer all-oral regimen consisting of bedaquiline, levofloxacin, linezolid, cycloserine, and clofazimine, to be taken for 18 months. Monthly follow-up sputum microscopy testing was negative until the 14th month, but became AAFB smear positive in June 2021. With delays in getting phenotypic drug sensitivity testing (DST) results from the national TB reference laboratory (NTRL), she continued on the same regimen and had a sputum smear AAFB-positive result again

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https://dx.doi.org/10.4314/mmj.v38i3.11

in December 2021. Another sputum sample was collected in June 2022 and examined via Line Probe Assay (LPA) conducted at NTRL showed resistance to levofloxacin and moxifloxacin, thus qualifying as pre-XDR TB. In August 2022, she was therefore switched to an individualized TB treatment regimen consisting of bedaquiline, delamanid, linezolid, cycloserine, and clofazimine. On clinical review, it was noted that she had lost weight and had a body mass index (BMI) of 16 kg/m$^2$ (weight 40 kg; height 158 cm). The health facility started providing food supplements, which were provided sparingly due to limited availability. A routine monthly sputum culture result from December 2023, whose result was received in July 2024, showed resistance to linezolid. At this point, the patient was diagnosed with XDR-TB given the combined resistance to rifampicin, levofloxacin, and linezolid[4]. When she came to the health facility in August 2024, an individualized TB treatment regimen consisting of bedaquiline, delamanid, cycloserine, clofazimine, and pyrazinamide was initiated.

The patient had been diagnosed with HIV in January 2014 and had started antiretroviral therapy with tenofovir disoproxil fumarate/lamivudine/efavirenz on the same day. In April 2019, she was transitioned to tenofovir disoproxil fumarate / lamivudine/dolutegravir due to a change in the standardized first-line antiretroviral therapy regimen in national HIV management guidelines and she remains on this regimen to date. She had suppressed HIV viral load results throughout her TB treatment period (Table 1). Complete blood counts, liver enzyme tests, and random blood glucose concentration results were obtained regularly over the course of the treatment for RR-TB and pre-XDR-TB and had not shown significant abnormalities. Electrocardiography was done during the initial months of second-line treatment, mainly to determine the QT time, and appeared normal. Chest X-ray imaging could not be done due to a non-functioning X-ray machine at the district hospital until repairs in July 2025, when a chest radiograph showed bilateral infiltrations (Figure 1).

**Table 1. Trend of HIV viral load results in relation to ART and TB treatment regimens**

| Month of sample collection | VL result | ART regimen | TB regimen |
|---|---|---|---|
| June 2018 | <839 copies/mL | TDF/3TC/EFV | RHZE |
| September 2021 | Undetectable | TDF/3TC/DTG | bedaquiline, levofloxacin, linezolid, cycloserine, clofazimine |
| April 2023 | Undetectable | TDF/3TC/DTG | bedaquiline, delamanid, linezolid, cycloserine, clofazimine |
| March 2024 | Undetectable | TDF/3TC/DTG | bedaquiline, delamanid, linezolid, cycloserine, clofazimine |

VL, viral load; mL, milliliter; ART, anti-retroviral therapy; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine; EFV, efavirenz; DTG, dolutegravir; R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol

**Figure 1. Chest radiograph taken in July 2025**

The patient had not experienced any side effects from the TB treatment regimens; however, she reported cough and night sweats at follow-up visits throughout the TB treatment duration. Before the XDR-TB diagnosis, she had been treated as an outpatient and never required hospital admissions. While honoring all 3-monthly ART clinic visits, she missed several monthly TB clinic visits that were not aligned with ART follow-up. When asked, she mentioned a lack of transport funds and TB-associated stigmatizing comments from relatives as reasons for missing visits. Several initiatives were taken to improve TB treatment adherence, including assignment of an individual treatment supporter, provision of psychosocial support, home visits, and involvement of community leaders, with little success. She reported harmful alcohol use, missing TB doses when she got drunk, and sometimes selling household items to source money for alcohol, but stopped taking alcohol in 2022. The patient was not employed, but her husband works as a tenant at a farm. He is the only household member, and they have no children. He is also living with HIV and on ART. Upon TB contact investigation, TB symptom screening was negative, and a chest X-ray was unremarkable. TB preventive treatment was not provided to the husband as national guidelines do not recommend it for contacts of DR-TB cases, in line with WHO guidance stating lack of evidence for its benefit in this scenario[7].

At the start of XDR-TB treatment, renewed, intensive

https://dx.doi.org/10.4314/mmj.v38i3.11

engagement of health facility staff and community leadership with the patient led to a mutually agreed management plan, where patient would receive daily, directly observed treatment (DOT) at the hospital premises from a nurse, with food for patient and husband provided free of charge. This initiative started in August 2024 and led to good treatment adherence and to regular monthly sampling for scheduled routine treatment monitoring. She completed XDR-TB treatment in February 2026. Her phenotypic DST result from a sputum sample submitted in March 2026 was negative, and she was clinically stable without major side effects.

## Discussion

This is the first XDR-TB case diagnosed in Malawi. The patient had not been in contact with known DR-TB patients, nor had she ever travelled to a high-prevalence DR-TB country. Taken together with the treatment history, it is likely that resistance was not transmitted, but acquired and accumulated on TB treatment due to poor adherence and treatment interruptions.

Our patient had successive TB treatment failures while having excellent long-term HIV virologic control, including during TB treatment. This indicates differential adherence to ART and TB treatment, a phenomenon that has been well-described previously, in particular among patients on older DR-TB regimens that are more complicated. A South African study found that adherence to ART was significantly higher than to MDR-TB treatment (92% vs. 84% respectively; p=0.003)[8]. In another study from South Africa, six-month adherence was higher for ART than for XDR-TB medications (88.2% vs. 67.7%; p<0.001)[9]. Causes of this differential adherence were explored in qualitative studies among South African patients with drug-resistant TB, who expressed a preference to ART as a result of greater tolerability, lower pill burden, and higher commitment to HIV treatment[10]. Barriers to DR-TB treatment adherence included side effects, pill burden, economic constraints, lack of food, stigma with lack of disclosure, and limited communication with health professionals[8,11]. Our patient did not report any serious side effects of TB medications, but many of the other barriers likely affected her TB drug adherence. The frequent, monthly TB clinic visits were challenging for her, in particular due to economic hardships, while multi-month ART dispensing helped limiting travel and opportunity costs[12]. Several risk factors contributed to the accumulation of drug resistance in our patient, including previous TB treatment, HIV co-infection, and alcohol dependence. Prior TB treatment is a well-known risk for DR-TB, particularly in combination with poor adherence[13]. Poor clinic visit attendance is strongly associated with poor TB treatment outcomes and is a predictor of MDR-TB treatment failure[8]. Malawi is a high HIV prevalence country with a high HIV-TB co-infection rate of 47%[6]. HIV complicates TB management in several ways, including compromising immunity, increasing pill burden and side effects. HIV positivity increased the odds of XDR-TB diagnosis 2.5 times among South African and Portuguese TB patients[14]. Harmful alcohol use affected TB treatment adherence among South African XDR-TB patients[14]. In addition, alcohol affects the immune response to TB and lowers the bioavailability of anti-tuberculous drugs, resulting in poor clinical outcomes among heavy alcohol consumers[15].

While DR-TB management can be challenging in any setting[16], it is particularly difficult in Malawi, due to several local barriers, including long turnaround time (TAT) of culture results, delays in diagnosis, lack of transport means for home visits, and long treatment duration[16]. There are only three public laboratories where MTB culture and sensitivity testing can be done. The availability of a few technicians with the expertise to process samples at these laboratories leads to a high workload and contributes to TATs of MTB culture and sensitivity results. Challenges in sample transportation from the health facility to the central culture laboratories add to a prolonged TAT. For our patient, it took close to 7 months from sample collection to receiving the linezolid resistance result, which led to delayed drug resistance diagnosis, persistence on a failing regimen, and consequent risk of resistance development to additional drugs. Of note is that, contrary to rifampicin, isoniazid, fluoroquinolones, and older injectable drugs, linezolid resistance cannot currently be tested with regularly available molecular methods and therefore relies on phenotypic culture and sensitivity testing. The often months-long TAT of phenotypic DST results limits their practicality for diagnostic confirmation and monitoring treatment of DR-TB.

National TB management guidelines prescribe monthly clinic visits for TB for review and drug refill[7]. The Ministry of Health, through NTLEP, reimburses transport costs of clients with drug-resistant TB; however, delays in processing payments often affect patients with weak socio-economic backgrounds. The longer duration of DR-TB treatment can contribute to losses to follow-up, poor treatment outcomes, and further transmission[16]. Our patient could not yet benefit from the effective, much shorter regimens that are now available for RR-TB and MDR-TB in Malawi[1,7,17].

Given the low national coverage of molecular and of conventional phenotypic DST, this first XDR-TB case may be the tip of an iceberg of DR-TB cases in Malawi that is higher than presumed on the basis of older national data. Further improvements may therefore be needed for the prevention, detection, and management of DR-TB. Improvements in the drug-resistant TB diagnostic network are needed for early drug resistance diagnosis and improved treatment monitoring, including increasing the coverage of molecular testing at health facilities, adding to the number of laboratories with phenotypic drug sensitivity testing capacity, and improving the efficiency of the sample transport network. Strategies to improve management of DR-TB patients include expansion of the availability of short DR-TB regimens, decentralizing care and treatment, adequate provision of transport remuneration, empowering clients and communities to take control of their own health, aligning ART and TB clinic visits, and innovative solutions for other drug adherence challenges.

Limitations in this case report include lack of access to whole-genome sequencing for comprehensive molecular drug resistance testing and having no information on the follow-up for post TB lung disease after XDR-TB treatment. The preparation of the case report was also affected by some missing data.

## Conclusion

We describe the first XDR-TB case diagnosed in Malawi. Resistance accumulated during sequential TB treatment episodes, hallmarked by persistently poor adherence to TB treatment regimens, while adherence to ART was adequate, given long-term undetectable viral load results. Individual risk factors for DR-TB were harmful alcohol use, HIV

https://dx.doi.org/10.4314/mmj.v38i3.11

infection, and poor socioeconomic status. Limited availability of molecular resistance testing and delayed phenotypic DST results hampered management. Eventually, an individualized, intensive management plan was successful and XDR-TB treatment led to a successful outcome.

## Ethical considerations

Written informed consent was obtained and is available on request from the first author. All personal data were de-identified and anonymized. The report was reviewed by the National Health Sciences Research Committee and approved for publication.

## Conflict of Interest: None declared

Author contributions: GCT and JvO conceptualized the case report. GCT, BK and CK collected the data. GCT wrote the first draft. All authors provided feedback and approved the final manuscript for submission.

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