Literature Review: Impact of Multidrug-resistant Tuberculosis Treatment on Hemoglobin Levels

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Abstract. Multidrug-resistant tuberculosis (MDR-TB) requires complex treatment regimens that are frequently associated with hematological adverse effects, particularly due to the use of linezolid. This literature review aims to evaluate the impact of MDR-TB treatment regimens on hemoglobin (Hb) levels. A narrative review was conducted using studies retrieved from electronic databases, including PubMed, Google Scholar, and Scopus, which examined hemoglobin changes and anemia in patients receiving MDR-TB therapy. The reviewed literature consistently demonstrates that MDR-TB treatment significantly affects hemoglobin levels. Long-term and short-term regimens are associated with a higher risk of hemoglobin reduction and anemia, mainly due to prolonged exposure to linezolid. In contrast, shorter regimens such as BPaL/M tend to show a more favorable hematological profile. This benefit is attributable not only to the shorter duration of therapy but also to simpler and less complex drug combinations, which may reduce cumulative hematological toxicity. Mitochondrial dysfunction leading to impaired erythropoiesis is identified as the primary mechanism underlying linezolid-associated anemia. These findings highlight the importance of selecting treatment regimens that balance therapeutic efficacy with hematological safety and underscore the need for regular hemoglobin monitoring during MDR-TB treatment.

Keywords: *Hemoglobin, Linezolid, MDR-TB.*

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A. Introduction

Multidrug-resistant tuberculosis (MDR-TB), remains a major challenge in global tuberculosis control.[1] In 2023, an estimated 175,923 MDR/RR-TB cases were reported worldwide, with Indonesia contributing approximately 7.4% of the global burden.[2],[3] MDR-TB treatment is complex, prolonged, and associated with a high risk of adverse drug reactions, which may compromise treatment outcomes.[4],[5]

In 2020, the World Health Organization (WHO) recommended two main therapeutic approaches for MDR-TB: long-term and short-term regimens.[6],[7] The long-term regimen, lasting 18–20 months, consists of three Group A drugs bedaquiline, levofloxacin or moxifloxacin, and linezolid as the core agents, supported by at least one Group B drug such as cycloserine or clofazimine during the intensive phase.[6] The short-term regimen has two variations: a linezolid-based regimen and an ethionamide-based regimen, with a treatment duration of 9–12 months. To improve treatment effectiveness and tolerability, WHO later introduced a shorter, fully oral regimen.[6],[8],[9] The BPaL/M regimen, combining bedaquiline, pretomanid, and linezolid with or without moxifloxacin, has demonstrated favorable treatment outcomes with a duration of six months.[8],[9],[10] Indonesia began implementing this regimen in 2024.[11]

Despite its shorter duration, careful monitoring of adverse events remains essential, particularly due to linezolid-associated hematological toxicity.[12],[13],[14] A decrease in hemoglobin levels is a common manifestation of linezolid-induced myelosuppression.[10],[14],[15] Linezolid inhibits mitochondrial protein synthesis and reduces ATP production in bone marrow precursor cells, leading to hematological toxicity, including anemia.[14],[16],[17] Several studies have reported that factors such as organ dysfunction and higher cumulative doses of linezolid may increase the risk of anemia.[18],[19]. Therefore, this literature review aims to summarize and critically analyze existing evidence on hemoglobin changes and anemia associated with linezolid-containing regimens in MDR-TB treatment.

B. Method

This study was conducted as a narrative literature review aimed at summarizing and critically analyzing published evidence on hemoglobin changes and anemia among patients with MDR-TB receiving linezolid-containing regimens. A literature search was performed using electronic databases including PubMed, Google Scholar, and Scopus. Relevant studies were selected based on predefined eligibility criteria and synthesized narratively according to thematic relevance.

C. Result and Discussion

Multidrug-resistant Tuberculosis (MDR-TB)

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis resistant to at least rifampicin and isoniazid, the two most potent first-line anti-tuberculosis drugs, thereby requiring treatment with second-line regimens.[6],[20],[21] In 2023, an estimated 175,923 cases of multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) were diagnosed and treated globally, representing approximately 44% of the estimated total burden.[2] Indonesia accounted for around 7.4% of global MDR/RR-TB cases, placing the country among those with a high MDR-TB burden.[2] MDR-TB may arise through primary transmission of drug-resistant Mycobacterium tuberculosis (Mtb) strains or develop as secondary resistance due to inadequate treatment regimens, poor adherence, impaired drug absorption, or drug interactions leading to subtherapeutic serum concentrations.[21]

Several risk factors contribute to the development of MDR-TB, including previous exposure to anti-tuberculosis drugs, younger and economically productive age groups, low socioeconomic status, and limited access to quality healthcare services.[21] Comorbid conditions such as HIV infection and diabetes mellitus have also been associated with MDR-TB, although their impact varies across studies and is often influenced by underlying clinical and metabolic factors.[21] From a pathogenetic perspective, drug resistance in Mycobacterium tuberculosis is primarily driven by spontaneous chromosomal mutations, notably mutations in the *rpoB* gene associated with rifampicin resistance and mutations in the *katG* and *inhA* genes related to isoniazid resistance.[22],[23] Additional resistance mechanisms include increased efflux pump activity,

alterations in drug targets, biofilm formation, bacterial cell heterogeneity, and toxin–antitoxin systems, all of which enhance bacterial survival under antibiotic pressure.[20],[7]

Clinically, tuberculosis (TB) presents with insidious and non-specific symptoms such as diurnal fever, night sweats, weight loss, anorexia, and generalized weakness.[24] Cough is reported in approximately 90% of cases, initially non-productive and later becoming productive, with hemoptysis occurring in about 20–30% of patients.[24] Other respiratory manifestations include pleuritic chest pain, dyspnea, and abnormal breath sounds.[24] Physical examination may reveal fine crackles, rhonchi, or amphoric breath sounds in the presence of pulmonary cavitation.[24]

The diagnosis of MDR-TB relies on rapid and accurate drug susceptibility testing to guide appropriate treatment selection.[22] Drug susceptibility testing includes phenotypic methods that assess bacterial growth in the presence of anti-tuberculosis drugs and molecular methods that detect genetic mutations associated with drug resistance.[22] Molecular diagnostics, such as line probe assays (LPA) for first- and second-line drugs and rapid molecular tests including GeneXpert MTB/RIF, play a crucial role in national TB control programs due to their ability to rapidly identify Mycobacterium tuberculosis and detect rifampicin resistance.[11],[13]

Management of MDR-TB

Since 2023, Indonesia has implemented several treatment regimens for patients with MDR-TB, with varying durations tailored to disease characteristics and drug susceptibility profiles.[11] A 6 month regimen includes the BPaL/M combination, consisting of bedaquiline, pretomanid, and linezolid, with or without moxifloxacin, as well as a specific regimen for isoniazid-monoresistant tuberculosis (Hr-TB).[11] In addition, a 9 month treatment option is available, comprising regimens with ethionamide-based or linezolid-based variations.[11] For patients requiring prolonged therapy, conventional long-term regimens with a duration of 18 to 20 months remain available.[11]

The World Health Organization (WHO) recommends the BPaL/M regimen comprising bedaquiline, pretomanid, and linezolid, with or without moxifloxacin as a 6-month treatment for multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB).[8] This regimen has demonstrated high efficacy with an acceptable safety profile and represents a significant advance in the management of MDR-TB.[8] It is indicated for patients aged over 14 years with MDR/RR-TB, excluding those with central nervous system, osteoarticular, or disseminated disease.[11],[25] Prior prolonged exposure to key drugs and pregnancy or breastfeeding are generally considered contraindications.[11],[25] The inclusion of moxifloxacin is guided by fluoroquinolone susceptibility testing, and resistance to any core drug requires transition to longer treatment regimens.[11],[25]

Bedaquiline exerts bactericidal activity by inhibiting mycobacterial ATP synthase, while pretomanid disrupts mycolic acid biosynthesis.[22] Linezolid, a key component of the regimen, inhibits bacterial protein synthesis but is associated with hematological toxicity due to myelosuppression.[14],[22] Moxifloxacin enhances bactericidal activity through inhibition of DNA gyrase.[7],[22] Standard dosing includes bedaquiline 400 mg daily for two weeks followed by 200 mg three times weekly, pretomanid 200 mg daily, linezolid 600 mg daily, and moxifloxacin 400 mg daily.[11] Given the risk of linezolid-associated anemia and thrombocytopenia, close monitoring is essential, with dose reduction or discontinuation as clinically indicated.[11] The regimen is administered for a fixed duration of six months, with limited extension only in cases of treatment interruption.[25]

The 9-month short-course regimen for MDR-TB is intended for patients without documented resistance to bedaquiline, clofazimine, high-dose isoniazid, ethionamide, or linezolid, and without prior prolonged exposure to these drugs. This regimen is not recommended for patients with extensive pulmonary disease, defined as cavitary lesions larger than 4 cm, or severe extrapulmonary tuberculosis, including central nervous system, osteoarticular, spinal, miliary, pericardial, or abdominal involvement. Both HIV-negative individuals and people living with HIV may receive this regimen, while pregnant and breastfeeding women are eligible for the linezolid-based variation.[11]

Since 2024, two variations of the 9-month regimen have been implemented: an ethionamide-based variation and a linezolid-based variation. The ethionamide-based regimen is preferred in patients with baseline anemia, neutropenia, thrombocytopenia, or pre-existing peripheral neuropathy or visual impairment. In contrast, the linezolid-based variation is reserved

for patients with adequate baseline hematological parameters and no evidence of peripheral or optic neuropathy prior to treatment initiation.[11]

The regimen consists of an intensive phase lasting 4–6 months, followed by a 5-month continuation phase. Bedaquiline is administered for 6 months in both variations, combined with levofloxacin, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol, with either ethionamide or linezolid added during the intensive phase. Treatment progression is guided by sputum conversion, and failure to achieve conversion by six months necessitates transition to a longer or individualized MDR-TB regimen.[11]

The long-term treatment regimen for MDR-TB is indicated for patients with severe extrapulmonary disease, resistance to key drugs used in the BPaL/M or short-term regimens, or intolerance to these treatment options.[11] It is also required for patients with poor treatment response, including failure of sputum conversion, lack of clinical improvement, emergence of additional drug resistance, or treatment interruption.[11] Pregnant or breastfeeding women who are ineligible for the nine-month linezolid-based regimen, children under 14 years who are unsuitable for short-course therapy, and other patients unable to receive the nine-month regimen for clinical or programmatic reasons are also candidates for long-term treatment.[11]

The long-term regimen is administered for 18–20 months and is constructed to include at least four effective anti-tuberculosis agents. It typically comprises three Group A drugs bedaquiline, levofloxacin or moxifloxacin, and linezolid combined with at least one; Group B drug, such as cycloserine or clofazimine.[6] If bedaquiline is discontinued, a minimum of three effective agents is maintained.[6] When fewer Group A drugs are available, both Group B drugs are included, and additional agents from Group C may be added as needed to ensure regimen adequacy.[6] In pediatric patients, treatment duration varies according to disease severity, ranging from 9–12 months for mild disease to 12–18 months for severe disease, with routine supplementation of pyridoxine.[6]

Adverse Drug Reactions Associated with MDR-TB Management

Management of MDR-TB is frequently challenged by drug-related toxicities, as individual components of contemporary regimens possess distinct pharmacological properties and characteristic safety profiles. Newer and repurposed agents, including bedaquiline, linezolid, pretomanid, moxifloxacin, delamanid, and tedizolid, have been associated with hematological, cardiac, neurological, and hepatic adverse effects, largely reflecting their mechanisms of action and pharmacokinetic interactions.[10]

Bedaquiline inhibits mycobacterial ATP synthase and exerts potent bactericidal activity; however, its interaction with cardiac ion channels can result in QT interval prolongation, increasing the risk of ventricular arrhythmias, particularly when co-administered with other QT-prolonging agents such as fluoroquinolones or in the presence of CYP3A4 inhibitors. Moxifloxacin, a fluoroquinolone, also contributes to QT prolongation through effects on cardiac repolarization and may increase the risk of tendinopathy, especially when combined with corticosteroids. Reduced plasma concentrations due to drug interactions may further complicate dosing and resistance risk.[10]

Nitroimidazole derivatives, including delamanid and pretomanid, disrupt mycolic acid synthesis after activation within Mycobacterium tuberculosis. Delamanid is associated with QT prolongation, whereas pretomanid is more frequently linked to hepatotoxicity, particularly in the context of drug interactions that increase systemic exposure. Linezolid, an oxazolidinone, plays a critical role in MDR-TB regimens but is strongly associated with mitochondrial protein synthesis inhibition, leading to myelosuppression such as anemia, thrombocytopenia, and leukopenia, especially with prolonged use. Its monoamine oxidase inhibitory properties also increase the risk of serotonin syndrome when combined with serotonergic agents. Tedizolid, a newer oxazolidinone, demonstrates a more favorable safety profile; however, hematological toxicity and neuropathy may still occur with long-term exposure.[10]

Hemoglobin and Anemia as Hematological Indicators

Hemoglobin (Hb) is the principal protein component of erythrocytes and plays a central role in human physiology. Approximately 95% of the erythrocyte cytoplasmic content consists of

hemoglobin, which is efficiently compartmentalized within red blood cells to prevent plasma degradation and renal excretion. The intracellular concentration of hemoglobin reaches approximately 34 g/dL, with a molecular weight of about 64,000 Daltons.[26]

The primary function of hemoglobin is the transport of oxygen from the lungs to peripheral tissues and the return of carbon dioxide from tissues to the lungs for elimination. In addition, hemoglobin contributes to the maintenance of acid–base homeostasis by buffering hydrogen ions and modulates vascular tone through interactions with nitric oxide. Free hemoglobin released during hemolysis has a short half-life in the circulation and is rapidly cleared to prevent renal toxicity.[26]

Normal hemoglobin levels vary according to age, sex, and physiological conditions. In adults, reference ranges are generally 14–18 g/dL in men and 12–15 g/dL in women, while neonates exhibit higher levels ranging from 16.5 to 21.5 g/dL. Individuals residing at high altitudes typically demonstrate elevated hemoglobin concentrations as a compensatory response to reduced ambient oxygen tension.[26]

Anemia is defined as a reduction in hemoglobin concentration below established reference values for healthy individuals of comparable age and sex under similar environmental conditions.[26] Functionally, anemia represents a diminished oxygen-carrying capacity of the blood, leading to tissue hypoxia.[27] Globally, anemia remains a major public health concern, affecting approximately 40% of children aged 6–59 months, 37% of pregnant women, and 30% of women of reproductive age, and contributing substantially to years lived with disability.[28]

The pathogenesis of anemia involves ineffective or insufficient erythropoiesis, blood loss, or increased red blood cell destruction. Ineffective erythropoiesis occurs when erythroid precursors undergo premature apoptosis, as observed in megaloblastic anemia, thalassemia, and sideroblastic anemia. Insufficient erythropoiesis results from reduced erythroid precursor production due to iron deficiency, erythropoietin deficiency in chronic kidney disease, bone marrow failure, infections, or marrow infiltration. Anemia may also arise from acute or chronic blood loss or hemolysis, which shortens erythrocyte lifespan beyond the compensatory capacity of the bone marrow.[26]

Risk factors for anemia include nutritional deficiencies, chronic inflammation, genetic disorders, pregnancy, blood loss, impaired erythropoiesis, and exposure to medications that suppress bone marrow function or accelerate erythrocyte destruction. Clinically, anemia commonly presents with fatigue, reduced exercise tolerance, pallor, dyspnea, and palpitations, while severe anemia may lead to dizziness, syncope, or cardiovascular complications.[19],[29] Diagnosis relies on a combination of clinical assessment and laboratory evaluation, particularly complete blood count and red blood cell indices, supported by additional investigations to determine the underlying cause.[27]

Association Between MDR-TB Treatment Regimens and Changes in Hemoglobin Levels

Contemporary MDR-TB treatment regimens incorporate potent agents with proven efficacy but are frequently associated with hematological adverse effects.[14] Among these, linezolid is a cornerstone drug due to its strong bactericidal activity and excellent tissue penetration; however, its use is closely linked to the development of anemia and other forms of myelosuppression.[12]

Clinical studies have consistently reported a high incidence of hematological toxicity during linezolid-containing regimens.[12] Previous investigations have demonstrated that a substantial proportion of severe adverse events in MDR-TB patients are attributable to linezolid-induced anemia, with higher rates observed among patients requiring drug discontinuation. Severe anemia, commonly defined as hemoglobin levels below 8 g/dL, represents a potentially life-threatening condition requiring prompt clinical intervention.[12]

The mechanism underlying linezolid-associated anemia is primarily related to mitochondrial toxicity. Linezolid inhibits bacterial protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit, thereby preventing formation of the functional 70S initiation complex. However, human mitochondrial ribosomes share structural similarities with bacterial ribosomes, allowing linezolid to bind mitochondrial 16S rRNA and disrupt mitochondrial protein synthesis. This effect is particularly pronounced in hematopoietic progenitor cells within the bone marrow, leading to impaired erythropoiesis and subsequent anemia.[12]

Mitochondrial dysfunction induced by linezolid has been supported by biochemical markers such as elevated growth differentiation factor-15 (GDF-15), which has been proposed as a predictive biomarker for anemia during prolonged therapy. The risk of hematological toxicity increases with treatment duration, cumulative dose, renal impairment, and concomitant conditions that affect mitochondrial function.[14],[12]

Given the central role of linezolid in modern MDR-TB regimens, careful monitoring of hemoglobin levels and early recognition of hematological toxicity are essential to balance therapeutic efficacy against drug-related adverse effects. Understanding the mechanistic link between MDR-TB treatment and anemia is therefore critical in optimizing patient outcomes and informing clinical decision-making.

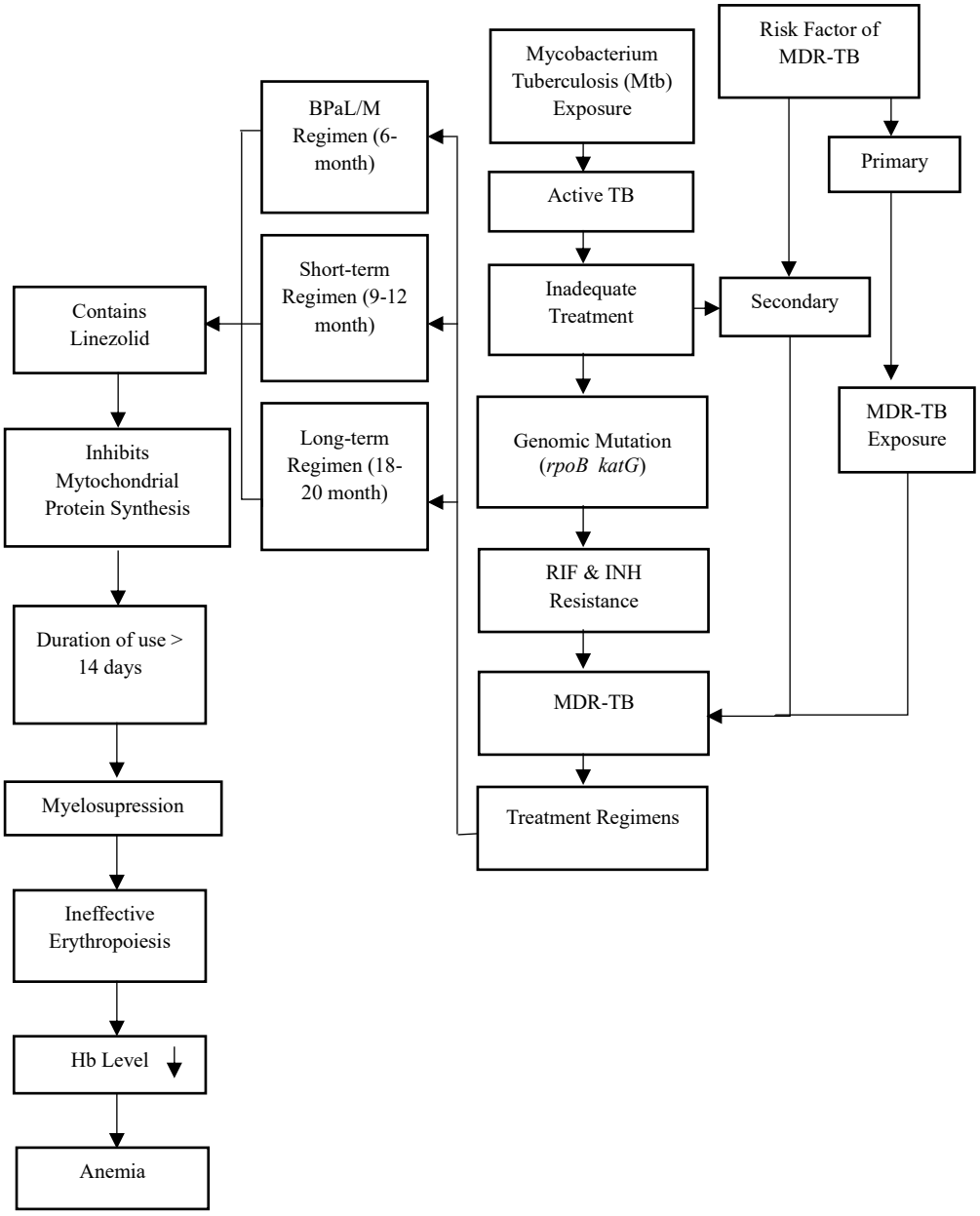

Figure 1. Impact of MDR-TB Treatment Regimens on Hemoglobin Levels

Analysis and Discussion

Based on the reviewed literature, anemia is one of the most frequently reported hematological adverse effects in the treatment of MDR-TB, particularly in regimens containing linezolid.[12],[30],[31] Changes in hemoglobin levels among MDR-TB patients are influenced by a combination of disease-related factors and drug-induced toxicity, with the duration of linezolid exposure emerging as the most consistent determinant of anemia.[5]

Most studies indicate that long-term MDR-TB regimens are associated with a higher risk of anemia compared to shorter regimens such as BPaL/M.[5],[8],[32] This difference is primarily attributed to prolonged exposure to linezolid, as its hematological toxicity is considered time-dependent.[5],[32],[33] From a biological perspective, linezolid inhibits mitochondrial protein synthesis in hematopoietic cells, leading to impaired erythropoiesis and ineffective red blood cell production.[18],[15] These effects become more pronounced with increasing treatment duration and cumulative dose.[18]

In addition to this mechanism, recent literature has highlighted the role of GDF-15 as a potential biomarker associated with linezolid-induced anemia.[14],[16] Elevated GDF-15 levels have been reported to reflect mitochondrial dysfunction and cellular stress and have been shown to correlate with declining hemoglobin levels in MDR-TB patients receiving prolonged linezolid therapy.[14],[16] These findings suggest that GDF-15 may serve as an early indicator of hematological toxicity before clinically significant anemia develops.[14],[16]

Other factors contributing to anemia in MDR-TB patients include poor nutritional status, chronic inflammation related to active tuberculosis, impaired renal function, and comorbid conditions such as HIV infection and diabetes mellitus.[1],[19] Variability in findings across studies may be explained by differences in study design, population characteristics, definitions of anemia, and strategies for linezolid dose adjustment and monitoring.

Overall, the literature suggests that the BPaL/M regimen has a more favorable hematological safety profile compared to long-term regimens due to its shorter treatment duration and reduced mitochondrial exposure to linezolid.[9],[33] However, as most available evidence is derived from observational studies with inherent limitations, regular hemoglobin monitoring remains essential for all MDR-TB patients receiving linezolid-based regimens. Further research is warranted to clarify the clinical utility of biomarkers such as GDF-15 in predicting and managing anemia during MDR-TB treatment.

D. Conclusion

This literature review demonstrates that MDR-TB treatment has a significant impact on Hb levels, particularly in regimens containing linezolid. The evidence indicates that a higher risk of Hb reduction is associated with long-term treatment regimens, whereas shorter regimens such as BPaL/M tend to have a more favorable effect on Hb levels. This improved hematological profile is attributable not only to the shorter duration of therapy but also to the simpler and less complex drug combinations, which may reduce cumulative hematological toxicity. Regular monitoring of Hb levels remains essential to minimize anemia-related complications and optimize patient outcomes during MDR-TB treatment.

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