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REVIEW

Combating drug-resistant tuberculosis in South Africa: strategies, challenges, and progress

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South Africa faces a critical challenge with drug-resistant tuberculosis (DR-TB), which includes high rates of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Recent innovations in treatment, particularly the all-oral bedaquiline, pretomanid, linezolid (BPaL) and bedaquiline, pretomanid, linezolid, moxifloxacin (BPaLM) regimens, and evidence from studies on extended bedaquiline use and paediatric therapies, show promise in enhancing patient outcomes and reducing treatment duration. This review explores South Africa's approach to DR-TB treatment, diagnostics, and strategic initiatives, examining challenges such as patient adherence, infrastructure limitations, and socioeconomic obstacles. We highlight the progress made and the potential for further advances through collaborative research and supportive healthcare policies.

Keywords: drug-resistant tuberculosis, strategies, challenges, progress

Introduction

According to reports from The Union World Conference on Lung Health 2024, 8.2 million new tuberculosis (TB) cases were diagnosed globally in 2023, an increase from 7.5 million in 2022 and 7.1 million in 2019. TB was responsible for approximately 1.25 million deaths in 2023, including 1.09 million among HIV-negative individuals and 161 000 among people living with HIV. TB treatment coverage reached 75% in 2023, falling short of the World Health Organization's (WHO) End TB Strategy 90% target. Funding for TB prevention, diagnosis, and treatment services amounted to USD 5.7 billion in 2023. Drug-resistant tuberculosis (DR-TB) presents a significant public health threat globally, with South Africa among the countries hardest hit due to high rates of rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant tuberculosis (XDR-TB).[1] Factors such as high HIV prevalence and socioeconomic disparities exacerbate the TB epidemic. Over the past decade, South Africa has prioritised innovative treatment options and diagnostics, aligning its strategies with WHO recommendations to combat DR-TB.[2]

Recently, new regimens such as BPaL (bedaquiline, pretomanid, and linezolid), BPaLM (bedaquiline, pretomanid, linezolid, and moxifloxacin), BEAT-TB (6 months of bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine), and EndTB (6 months of bedaquiline, delamanid, clofazimine, and linezolid) have demonstrated promise in offering shorter and more effective treatment courses.[3,4] Studies exploring extended use of bedaquiline, paediatric adaptations, and economic evaluations of these shorter regimens further support their potential as viable treatment strategies.[5,6] This review examines South Africa's approach to drug-resistant tuberculosis (DR-TB), assessing current practices, recent advances, and ongoing challenges in implementing these regimens. While these new options show progress, treatment duration remains lengthy, toxicities—particularly those associated with linezolid—are still common, and tolerability requires significant improvement.

Epidemiology of drug-resistant tuberculosis in South Africa

South Africa reports some of the highest DR-TB rates worldwide, with a significant proportion of MDR-TB and XDR-TB cases. According to WHO estimates, approximately 410 000 individuals developed MDR-TB or RR-TB globally in 2022, with South Africa contributing 11 000 cases, making it the second-highest globally and the first in terms of the population incidence of RR-TB among African nations. The intersection of TB and HIV in South Africa intensifies these rates, complicating patient outcomes and leading to higher mortality and treatment attrition rates.[7] The DR-TB epidemic in South Africa has transitioned from being dominated by acquired resistance during inadequate treatment to being driven by community transmission of resistant strains .[8] Studies indicate that 70–80% of MDR-TB or XDR-TB cases in high-burden settings arise from direct transmission rather than treatment failure. Key aspects of the RR-TB landscape in South Africa, based on recent surveillance data, include genetic diversity of RR-TB strains, geographic variation in transmission and control measures in place.[9] In South Africa, the most dominant RR-TB strain is the Beijing genotype (Lineage 2), primarily found in the Western and Eastern Cape provinces, where it is associated with large outbreaks and increased transmissibility. The strain accounts for 67–71% of RR-TB cases in the Western Cape, with both typical and atypical variants circulating in the region. Other prevalent strains include those from the Euro-American genotypes (Lineage 4), such as LAM, T, S, and X, with LAM4 (F15) being especially common in KwaZulu-Natal and Gauteng, and linked to MDR-TB. The EAI genotype (Lineage 1), while

primarily restricted to Mpumalanga and less transmissible, is also significant, with a strong association to cross-border migration from neighbouring Mozambique.

Geographically, high RR-TB transmission rates are observed in the Western and Eastern Cape, where clustering rates are as high as 64% and 42%, respectively, indicating rapid local transmission. Small clusters (2–5 cases) dominate, but larger clusters (more than 26 cases) have also been reported in these provinces and Mpumalanga, suggesting possible community transmission. Factors contributing to these transmission dynamics include overcrowding, inadequate TB control measures, high HIV prevalence, and poor living conditions, such as inadequate ventilation, particularly in the Western Cape. Targeted interventions, such as contact investigations and infection control measures, are essential for reducing transmission rates, alongside stronger district-level health systems and broader community-wide interventions in high-transmission areas. However, challenges such as biased surveillance data, which may underestimate the RR-TB burden, and the limitations of traditional genotyping methods (e.g. spoligotyping), suggest that newer technologies like whole-genome sequencing may provide a more accurate picture of transmission dynamics.

Despite South Africa's leadership in adopting rapid diagnostic tools like the Xpert MTB/RIF assay, which has been scaled up since 2011, a significant portion of DR-TB cases remains undiagnosed or misdiagnosed, contributing to ongoing transmission. Challenges persist in diagnosing resistance to newer drugs such as bedaquiline, with only limited tools available for pre-treatment susceptibility testing. Furthermore, the COVID-19 pandemic strained TB services, leading to delayed diagnoses and disrupted treatment across South Africa. The National Strategic Plan for 2023–2028 seeks to recover from these setbacks, enhancing the TB care continuum through expanded testing, community-based care initiatives, and preventive measures.[2]

This holistic approach underscores South Africa's commitment to mitigating DR-TB and improving patient access to timely care, although significant structural challenges like poverty, stigma, and under-resourced healthcare infrastructure remain hurdles in achieving optimal outcomes.

Prevention of DR-TB

Preventing the spread of MDR-TB requires a multifaceted approach. Rapid identification of infected individuals, effective treatment, and provision of preventative therapy to at-risk populations are crucial components of this strategy.[10] At-risk groups include household contacts of TB patients, healthcare workers, and individuals with conditions that compromise their immune systems, such as HIV infection, diabetes, or cancer.

The WHO's updated recommendations for the prevention of MDR-TB emphasise the use of targeted preventive treatment strategies to address this significant public health challenge. A key recommendation is the inclusion of six months of daily levofloxacin (6Lfx) as a tuberculosis preventive treatment (TPT) for individuals exposed to MDR- or rifampicin-resistant TB (MDR/RR-TB). This approach is strongly advised based on moderate evidence of effectiveness, supported by findings from recent trials such as TB CHAMP and V-QUIN, which demonstrated that 6Lfx significantly reduces the risk of TB disease in household contacts of MDR/RR-TB cases.[11,12]

Another critical element of the recommendations is the integration of systematic screening and testing for TB infection in high-risk populations, particularly household contacts of confirmed MDR/RR-TB cases. Ensuring that these individuals receive appropriate preventive care is central to reducing transmission and progression to active disease. The guidelines also highlight the importance of monitoring drug susceptibility in source TB strains to guide effective regimen selection, particularly in regions with high background resistance.

To enhance programmatic implementation, the guidelines propose supportive measures such as adherence strategies tailored to local contexts, operational research to optimise delivery models, and equity-focused interventions to ensure accessibility in remote areas. Ongoing studies are recommended to refine the composition and duration of preventive regimens, improve safety profiles, and address specific challenges such as drug resistance and comorbidities. This comprehensive approach aims to support global efforts to scale up TPT and achieve the goals of the End TB Strategy. To this end, the ACTG has an ongoing Phase III multicentre trial comparing the efficacy and safety of delamanid vs. isoniazid for preventing active TB among high-risk household contacts of MDR-TB patients (PHOENIx, clinicaltrials.gov: NCT03568383).[13] Results are expected in 2025.

Advances in DR-TB treatment regimens

South Africa has been at the forefront of introducing innovative approaches to managing RR-TB, and its contributions have significantly influenced global policy.[14] Recent advances in DR-TB treatment regimens have offered alternatives to the lengthy and complex courses previously recommended, enabling shorter, all-oral treatments that improve patient adherence and outcomes.

BPaL and BPaLM regimens

These regimens have transformed DR-TB management by shortening treatment duration to six months for MDR-TB and XDR-TB patients. The TB-PRACTECAL trial (Clinicaltrials.gov: NCT02589782) demonstrated that a 24-week BPaLM regimen was non-inferior to the standard 9- to 20-month regimens, with better safety profiles and fewer adverse events.[7] This regimen includes bedaquiline, pretomanid, linezolid (600 mg), with or without moxifloxacin, and can replace longer regimens (nine months or more) in eligible patients. Emerging evidence suggests that similar outcomes can be achieved in real-world programmatic settings. In South Africa, national guidelines recommend levofloxacin as an alternative to moxifloxacin, making the regimen adaptable to local settings.

Patients with more than one month of exposure to certain second-line drugs will receive the BPaL-L regimen, provided they test negative for resistance to bedaquiline and linezolid. Treatment initiation should not be delayed pending resistance test results.

In cases of documented resistance to fluoroquinolones (in patients with pre-extensively drug-resistant (pre-XDR-TB), the BPaL regimen, excluding levofloxacin, may be utilised. While drug susceptibility testing (DST) to fluoroquinolones is recommended, it should not hinder treatment initiation. Linezolid is the most toxic drug in the regimen, necessitating vigilant monitoring by healthcare providers to detect and manage adverse events promptly. Early identification of adverse events, particularly in primary care settings, is crucial for preventing complications and reducing morbidity and mortality.

Confirmed resistance to any component of the regimen, except levofloxacin, is a contraindication, as is severe extrapulmonary TB. Healthcare providers must exercise caution and adhere to guidelines when prescribing and monitoring patients on the BPaLM regimen to ensure optimal treatment outcomes while minimising risks.

Understanding the mechanisms of action and pharmacokinetic properties of these medications is essential for tailoring treatment regimens to individual patients, minimising adverse effects, and optimising therapeutic outcomes in the management of DR-TB.[15] Close monitoring of patients for drug efficacy and toxicity is also crucial throughout the treatment course to ensure successful outcomes and prevent the development of further drug resistance.

Pediatric use of delamanid

Delamanid has been approved for paediatric MDR-TB patients weighing at least 10 kg, following evidence from a phase I/II study demonstrating its safety and efficacy in children up to 17 years of age. With a 24-month follow-up, 89.2% of paediatric participants had successful outcomes, making delamanid a viable option for children and adolescents who previously had limited treatment options.[16]

Economic benefits of shorter regimens

The STREAM trial showed that nine-month bedaquiline-based regimens significantly reduced healthcare costs in South Africa compared to traditional long-term regimens.[6] The reduced duration lowered the economic burden for patients and healthcare systems, supporting the use of short-course regimens as both clinically effective and cost-efficient. Furthermore, a study by Trevisi et al.[17] investigated the effectiveness of bedaquiline use beyond the typical six-month duration. Results indicated that extending bedaquiline use beyond six months did not significantly improve treatment outcomes when used in conjunction with potent regimens containing new and repurposed drugs. This finding suggests that while bedaquiline is crucial, its extended use may not provide additional benefits under well-optimised regimens.[18] In line with the new South African Treatment Guidelines for Drug Resistant Tuberculosis.

New treatment regimens, including BPaL and BPaLM, have significantly shortened treatment duration to six months while maintaining high efficacy. However, emerging resistance to bedaquiline poses a serious threat to these advances. Current estimates suggest that phenotypic resistance to bedaquiline exists in 3–5% of MDR-TB cases in South Africa.[8]

Diagnostic innovations and supportive measures

Improvements in diagnostics have facilitated the rapid detection and targeted treatment of DR-TB, crucial for optimising patient outcomes in South Africa.

GeneXpert XDR and phenotypic testing

The GeneXpert XDR cartridge provides a quick assessment of drug resistance profiles, allowing clinicians to tailor regimens based on specific resistance patterns. This tool has largely replaced traditional line probe assays, improving the speed and accuracy of DR-TB diagnosis.[19]

Extended drug susceptibility testing (DST)

Phenotypic DST for bedaquiline, linezolid, and other drugs enables the personalisation of regimens for patients with complex resistance profiles. This testing supports South Africa's individualised care approach, ensuring that patients receive effective treatments according to their resistance patterns.[2]

Challenges in laboratory capacity and accessibility

Despite improvements, laboratory resource limitations and delays persist, particularly in rural areas. Addressing these gaps is essential to support rapid diagnosis and treatment initiation across the country, a critical component of the National Strategic Plan's goals.

The recent implementation of the BD MAX MDR-TB assay in South Africa's regional laboratories offers a promising tool for detecting Mycobacterium tuberculosis complex and associated drug resistance. This fully automated system has demonstrated high sensitivity and specificity for both rifampin and isoniazid resistance, making it a valuable addition to diagnostic workflows. However, its integration has faced challenges, such as the need for stable power, sufficient laboratory infrastructure, and trained personnel. The assay's capability to process 24 samples in under four hours highlights its potential for centralised, high-volume testing. Despite these strengths, addressing issues like workflow optimisation and resistance mutation coverage is critical to fully leverage this technology in closing existing diagnostic gaps.[20]

Challenges in the management of DR-TB

Managing DR-TB in South Africa involves navigating adherence issues, healthcare resource limitations, and socioeconomic barriers that affect patient access and outcomes.

Patient adherence

The lengthy and complex treatment regimens for DR-TB, coupled with significant side effects, often challenge patient adherence, particularly in South Africa, where DR-TB and HIV co-infection rates are high. Barriers to adherence include high pill burdens, overlapping toxicities from DR-TB and antiretroviral therapies (ART), and frequent clinic visits. Patients often prioritise ART adherence over DR-TB treatment, influenced by better support systems and perceptions of HIV treatment outcomes. Solutions

to improve adherence include adopting shorter, all-oral regimens for DR-TB, enhancing patient education, addressing stigma, and strengthening clinic visit attendance through interventions like appointment reminders and follow-ups. Utilising lessons from HIV care to provide more patient-centred and integrated support can improve outcomes for DR-TB patients.[21] Once diagnosed, children require individualised, all-oral regimens that prioritise effective medications, child-friendly formulations, and close monitoring for adverse effects. Treatment adherence is influenced by caregiver education, training, and support, ensuring proper medication administration and dose adjustments for weight gain. Socioeconomic factors, including financial strain and food insecurity, exacerbate adherence challenges, necessitating nutritional and financial assistance for affected families. Regular follow-up, typically monthly, helps monitor clinical progress and address side effects promptly, preventing non-adherence. Emerging technologies, such as video observed therapy (VOT) and digital adherence tools, alongside traditional directly observed therapy (DOT), offer innovative methods to enhance adherence monitoring. With targeted interventions, comprehensive support systems, and a focus on minimising treatment barriers, South Africa can improve outcomes for children with MDR-TB, contributing to broader TB control efforts.[2,18,22]

Bedaquiline resistance

There has been a reported increase in resistance to bedaquiline, despite most DR-TB regimens relying on this medication. It is crucial to begin considering alternative treatment options. For instance, in the Western Cape, bedaquiline resistance rates have been reported as high as 20%, although in most other parts of the country, the rates remain at 5% or lower.

Tolerability of available regimens

Current regimens are also associated with significant toxicities, including anaemia, other bone marrow toxicities, neuropathy (e.g. from linezolid), and skin discolouration caused by clofazimine. Additionally, poor tolerability due to adverse events and the high pill burden further challenge the success of these treatment approaches.

Healthcare system constraints

Under-resourced healthcare facilities and workforce shortages remain significant challenges. The DR-TB epidemic is compounded by poverty, stigma, and limited healthcare resources, which disrupt patient care and treatment adherence.[8] Decentralised models, allowing nurses to initiate DR-TB care at primary health clinics, have improved access but require additional resources to sustain. The National Strategic Plan for 2023–2028 emphasises expanding community-based care to improve access and reduce treatment barriers in underserved area.[23]

Socioeconomic barriers

Poverty, stigma, and limited healthcare access hinder TB treatment, especially in rural areas.

Economic evaluations of shorter tuberculosis treatment regimens, as demonstrated in the STREAM and Nix-TB trials, reveal substantial potential for cost savings and improved accessibility. These findings highlight the economic and health benefits of transitioning from standard regimens to shorter, bedaquiline-containing therapies.

The STREAM Stage 2 trial assessed a nine-month all-oral regimen, a nine-month injectable-containing regimen (control), and a six-month regimen that included an injectable for the first two months. The six-month regimen emerged as highly cost-effective, particularly in Ethiopia and India, where it was projected to reduce total healthcare costs for tuberculosis programmes and patients by approximately 20–30% compared to the control regimen. Moreover, price reductions in bedaquiline, from $1.81 to $1.00 per tablet, further enhanced the cost-effectiveness of the nine-month all-oral regimen, allowing it to dominate in India from a provider-perspective cost-effectiveness analysis.[24]

The trial, conducted in South Africa, evaluated a six-month regimen combining bedaquiline, pretomanid, and linezolid for treating highly drug-resistant tuberculosis, including XDR-TB and MDR-TB unresponsive to standard treatments. The regimen achieved a 90% favourable outcome rate (95% confidence interval, 83–95) at six months post-treatment, demonstrating resolution of clinical disease and sustained negative culture status in the majority of patients.

This regimen not only maintained high efficacy but also presented advantages in reducing the treatment burden. Its all-oral format eliminated the need for prolonged hospital stays, while the shorter duration minimised indirect costs such as lost wages for patients. Despite common toxic effects associated with linezolid, such as peripheral neuropathy (81%) and myelosuppression (48%), these were generally manageable through dose adjustments or temporary discontinuation.

Patients benefitted from the streamlined therapy, which also reduced health system expenditures by limiting the extended outpatient follow-ups often required for traditional regimens. This approach highlights the potential of innovative drug combinations to address the challenges of managing DR-TB effectively.[25]

Additionally, modelling studies reinforce these findings by suggesting that a universally applicable, pan-tuberculosis regimen could yield further cost savings and health improvements by eliminating the need for drug susceptibility testing and streamlining treatment protocols. For instance, a pan-tuberculosis regimen with a 3.5-month duration could reduce non-drug costs by 32–42% and avert up to 30–32% of tuberculosis-related deaths compared to standard care regimens.[26] These findings support the adoption of short-course regimens as economically and clinically viable solutions.[6]

Progress and future directions

South Africa's commitment to controlling DR-TB is evident through policy shifts, research, and collaborative efforts that

continue to strengthen its healthcare infrastructure and treatment options.

Policy and programmatic shifts

The 2023–2028 National Strategic Plan's focus on patient-centred, community-based care aligns with WHO's End TB Strategy. This plan prioritises shorter regimens, expanded diagnostic networks, and the involvement of community health workers in TB care to meet local needs and improve outcomes.[2]

Ongoing research and clinical trials

Recent studies conducted in South Africa highlight promising avenues for curbing TB transmission and improving resource allocation. Strategies such as spatial monitoring and targeted interventions show the potential to mitigate the spread of DR-TB.[12] While progress has been made, sustained efforts and collaboration are necessary to achieve global TB reduction targets. Interim results from a phase IIb/c study of quabodepistat in combination with delamanid and bedaquiline indicated that the four-month regimen is safe and effective against drug-sensitive TB. Quabodepistat, a DprE1 inhibitor developed by Otsuka, targets an enzyme involved in cell wall synthesis. The trial showed that 96% of participants in the QBD arms and 91% in the HRZE arm achieved sputum culture conversion by the end of the four-month treatment. Adverse events of grade 3 or higher occurred in 15%, 12%, and 11% of participants. Further research is necessary to determine the optimal dose, drug combinations, and duration for quabodepistat.[27]

A study on pretomanid's effects on sperm count in males with MDR-TB found that the drug does not adversely affect male reproductive function. The study involved 26 males from South Africa and Georgia and measured changes in total sperm count, sperm concentration, sperm volume, and male reproductive hormones. Results indicated improved gonadal status, with pretomanid not affecting male reproductive function. The US FDA will review the data to decide on including male children in future pretomanid studies. Currently, the TB Alliance and IMPAACT network are restricted by the FDA to a single-dose study of pretomanid in female children only.[28]

Host directed therapies (HDTs)

Emerging evidence highlights the potential of small-molecule and soluble host-directed therapies (HDTs) as adjuncts to conventional MDR-TB treatments. Drugs like metformin, originally an anti-diabetic medication, have demonstrated promising anti-tubercular effects, such as reducing pulmonary bacterial load and enhancing CD8+ T-cell responses. Clinical data indicate that metformin shortens hospital stays, decreases relapse rates, and lowers mortality among TB patients with diabetes, although further randomised trials are needed to confirm these benefits for MDR/XDR-TB cases. Other potential HDTs include nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and indomethacin, which limit TB-associated pathology in preclinical models,[29] and vitamin D supplementation,[30] which has shown mixed results in clinical trials but warrants further investigation. Additionally, cytokine-targeted therapies, such as anti-TNF-α and anti-IL-6 antibodies,[31] offer potential for reducing immunopathology in severe TB cases. However, drug-drug interactions, such as the impact of isoniazid on vitamin D metabolism, underline the need for careful dosing and timing of HDT interventions.

Personalised cell-based therapies are being explored to complement existing TB regimens, drawing lessons from cancer immunotherapy.[32] Techniques such as adoptive T-cell therapy involve isolating, expanding, and modifying TB-specific T cells or NK cells for reinfusion,[33] potentially enhancing pathogen clearance while mitigating immunopathology. Mesenchymal stromal cells (MSCs) have also shown promise, with clinical studies reporting reduced bacterial loads, radiological improvements, and immune modulation in MDR/XDR-TB patients.[34] Despite these advances, resource limitations in high-burden TB settings pose challenges to implementing personalised HDTs. The use of allogeneic cell sources and mobile, GMP-compliant laboratories could expand access to advanced therapies in these regions.[35] While personalised HDTs remain a complement rather than a replacement for standard therapies, their integration could improve treatment outcomes and inform future therapeutic strategies.

Continued investment in research, innovation, and healthcare infrastructure is imperative to address the persistent burden of DR-TB effectively.

Collaborative efforts

Partnerships with global health organisations, such as the WHO, TB Alliance, and Médecins Sans Frontières, are instrumental in providing resources, treatment options, and updated guidelines. Collaborative trials, including endTB and TB-PRACTECAL (Clinicaltrials.gov: NCT02589782), support South Africa's goals to refine and expand DR-TB treatment options and diagnostic access, aligning local practices with global standards.[7]

Conclusion

South Africa has made substantial strides in managing DR-TB through novel treatment regimens, advanced diagnostics, and policy improvements. Challenges remain, especially regarding adherence, healthcare infrastructure, and socioeconomic disparities. With continued research, collaborative efforts, and increased funding, South Africa can improve DR-TB outcomes and support the WHO's goal of ending TB as a public health threat.

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