

Implementing novel regimens for drug-resistant TB in South Africa: what can the world learn?

N. Ndjeka,¹ J. Hughes,² A. Reuter,³ F. Conradie,⁴ M. Enwerem,⁵ H. Ferreira,⁶ N. Ismail,⁷ Y. Kock,¹ I. Master,⁸ G. Meintjes,⁹ X. Padanilam,¹⁰ R. Romero,¹¹ H. S. Schaaf,² J. te Riele,¹² G. Maartens⁸

¹Drug-resistant TB Directorate, National Department of Health, Pretoria, ²Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, ³Médecins Sans Frontières, Khayelitsha, ⁴University of Witwatersrand, Faculty of Health Sciences, Department of Clinical Medicine, Johannesburg, ⁵Amity Health Consortium, Johannesburg, ⁶Klerksdorp/Tshepong Hospital Complex MDR/XDR TB Unit, North West Provincial Department of Health, Perinatal HIV Research Unit, ⁷Centre for Tuberculosis, National Institute for Communicable Diseases, Johannesburg, ⁸King Dinuzulu Hospital, Kwazulu Natal Provincial Department of Health, ⁹Department of Medicine and Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, ¹⁰Sizwe Tropical Disease Hospital, Department of Health, Gauteng, ¹¹District Clinical Specialist Team, Namakwa, Northern Cape, ¹²Metro TB Hospital Centre, Brooklyn Chest Hospital, Western Cape

SUMMARY

Worldwide uptake of new drugs in the treatment of rifampicin-resistant tuberculosis (RR-TB) has been extremely low. In June 2018, ahead of the release of the updated WHO guidelines for the management of RR-TB, South Africa announced that bedaquiline (BDQ) would be provided to virtually all RR-TB patients on shorter or longer regimens. South Africa has been the global leader in accessing BDQ for patients with RR-TB, who now represent 60% of the global BDQ cohort. The use of BDQ within a shorter modified regimen has generated the programmatic data underpinning the most recent change in WHO guidelines endorsing a shorter, injectable-free regimen. Progressive policies on access to new drugs have resulted in

improved favourable outcomes and a reduction in mortality among RR-TB patients in South Africa. This supported global policy change. The strategies underpinning these bold actions include close collaboration between the South African National TB Programme and partners, introduction of new TB diagnostic tools in closely monitored conditions and the use of locally generated programmatic evidence to inform country policy changes. In this paper, we summarise a decade's work that led to the bold decision to use a modified, short, injectable-free regimen with BDQ and linezolid under carefully monitored programmatic conditions.

KEY WORDS: TB; drug resistance; bedaquiline; shorter treatment regimen; injectable-free regimens

SOUTH AFRICA HAS BEEN fighting an epidemic of rifampicin-resistant tuberculosis (RR-TB), with 13 005 patients diagnosed in 2019. In response to this deadly threat, the National TB Programme (NTP) has implemented ambitious new policies to programmatically introduce novel and repurposed drugs, including bedaquiline (BDQ), delamanid (DLM) and linezolid (LZD) for the treatment of RR-TB. Expanded access to BDQ—approximately 62% of the 37 157 people who have received BDQ globally are from South Africa¹—has resulted in a reduction in RR-TB mortality in South Africa.² In June 2018, ahead of the WHO's consolidated guidance on the management of RR-TB, South Africa was the first country to announce that people diagnosed with RR-TB would receive an injectable-

free treatment regimen that includes BDQ, either within a shorter or a longer treatment regimen. This programmatic data on a BDQ-containing, shorter modified regimen subsequently led to the WHO's December 2019 Rapid Communication endorsing the use of an injectable-free, shorter regimen for eligible patients with RR-TB.

Here, we describe the roll-out of newer drugs in South Africa over the last decade, the aspects which have led to the success of the RR-TB programme and the reasons for the NTP's decision to use a modified, short, injectable-free RR-TB treatment regimen with BDQ and LZD under carefully monitored programmatic conditions (see Figure 1 for timelines).

SETTING

In 2010, the South African National Department of

NN, AR and JH contributed equally.

Correspondence to: Norbert Ndjeka, Drug-resistant TB Directorate, National Department of Health, e-mail: Norbert.Ndjeka@health.gov.za

Article submitted 29 March 2020. Final version accepted 15 June 2020.

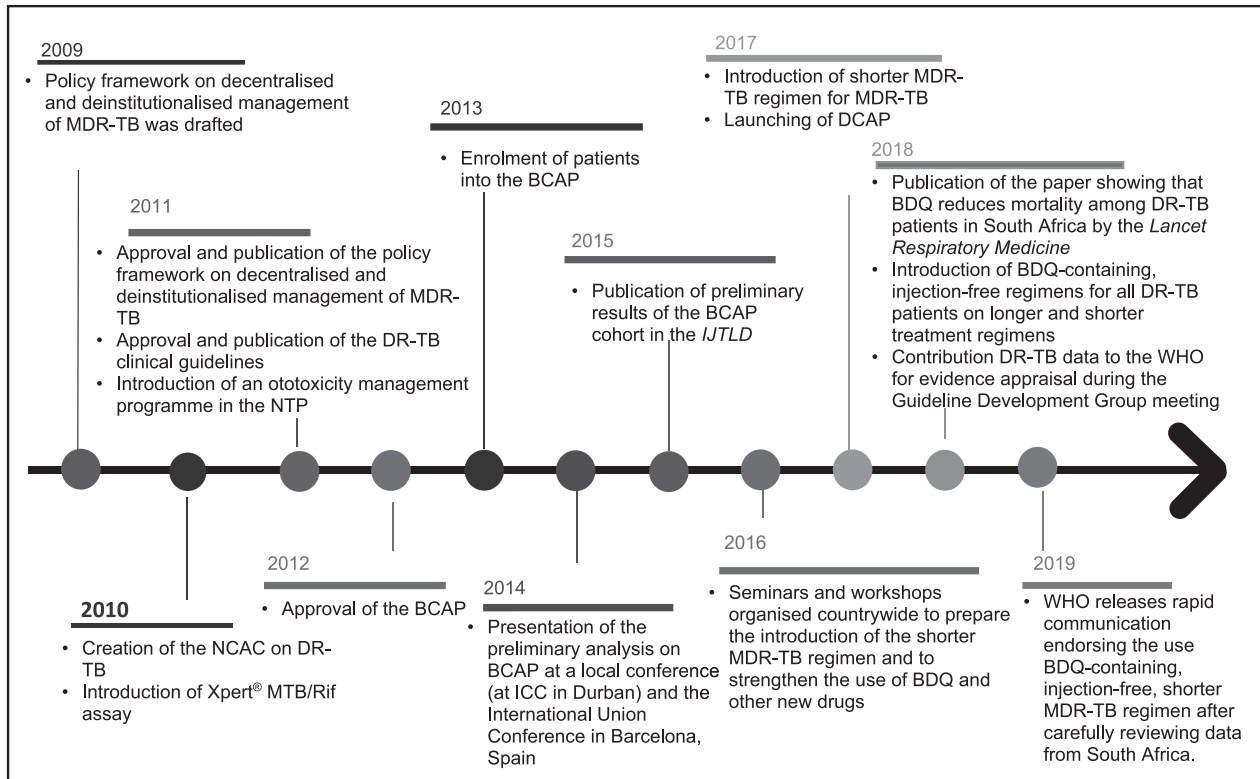


Figure 1 Timelines of key policy changes and updated treatment recommendations for management of drug-resistant tuberculosis in South Africa. MDR-TB = multidrug-resistant tuberculosis; NTP = National Tuberculosis Programme; BCAP = Bedaquiline Clinical Access Programme; IJTL D = International Journal of Tuberculosis and Lung Diseases; DCAP = Delamanid Clinical Access Programme; DR-TB = drug-resistant tuberculosis; BDQ = bedaquiline; WHO = World Health Organization; NCAC = National Clinical Advisory Committee; ICC = International Convention Centre.

Health introduced the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) as the primary diagnostic test for TB and RR-TB. The implementation of this technology, in addition to the use of other molecular diagnostic tests, notably GenoType MTBDR*plus* and GenoType MTBDR*sl* line-probe assays (Hain Lifescience, Nehren, Germany), has facilitated increased and earlier RR-TB case detection. A national population representative survey conducted in South Africa between 2012 and 2014 showed high levels of resistance to second-line drugs in 13% of cases of multidrug-resistant tuberculosis (MDR-TB; defined as demonstrated resistance to rifampicin and isoniazid [INH]).³ Programmatic treatment outcomes at the time were poor, with only 51% and 20% treatment success and mortality rates of 19% and 44%, respectively, for MDR-TB and extensively drug-resistant TB (XDR-TB; defined as MDR-TB, plus any fluoroquinolone [FQ] and at least one of three injectable second-line drugs, i.e., amikacin, kanamycin [KM] or capreomycin) in the 2012 cohort.⁴ The South African Drug-Resistant TB Directorate conducted several studies to unpack predictors of treatment outcomes and mortality,^{5,6} with the aim to raise visibility and plan actionable steps to mitigate poor treatment outcomes. The need for the decentralisation of services and introduction

of new drugs were identified as key to improving treatment outcomes. Introduction of new DR-TB drugs such as BDQ has been found to be safe⁷ and cost-effective⁸ by other studies.

EARLY ACCESS TO BEDAQUILINE THROUGH A CLINICAL ACCESS PROGRAMME

Implementation of decentralised RR-TB care at the district level and later, at the sub-district level began in 2009. This was formalised and further strengthened by the formulation and approval of MDR-TB treatment guidelines and policy framework on the decentralised management of MDR-TB in 2011,⁹ including the establishment of a decentralised ototoxicity monitoring programme.¹⁰ A national clinical advisory committee (NCAC) consisting of experienced RR-TB clinicians, researchers and infectious disease specialists (all working in a voluntary capacity) was formed in 2010 to support the NTP in guidelines formulation and clinical decision-making regarding complex DR-TB patients. The decentralisation of RR-TB care, the ototoxicity programme and the NCAC played a vital supporting role in the roll-out of new drugs. The number of RR-TB treatment initiation sites increased from 17 in 2011 to 655 in 2020.

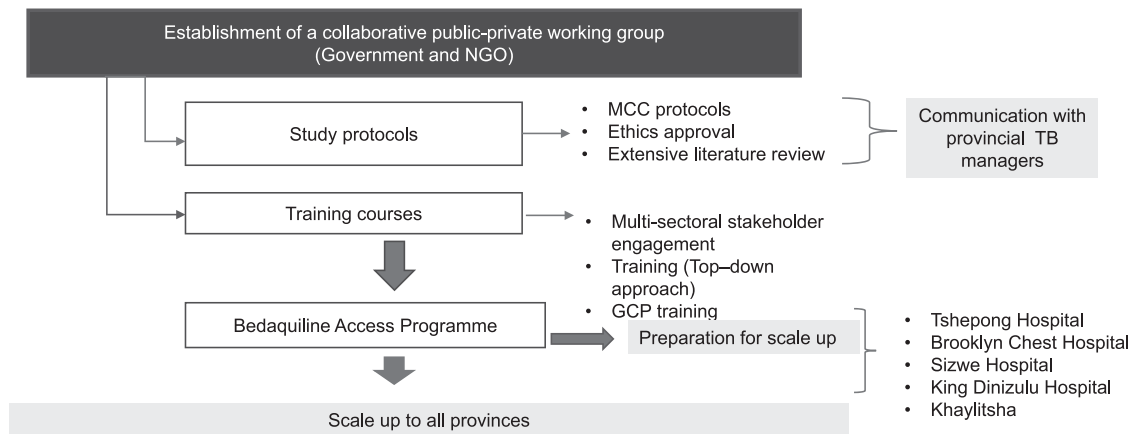


Figure 2 Planning and implementing Bedaquiline Clinical Access Programme in South Africa: from 2011 to 2015. NGO = non-governmental organisation; MCC = Medicines Control Council; TB = tuberculosis; GCP = good clinical practice.

In 2012, the newly developed diarylquinolone, BDQ, showed promising results in Phase II clinical trials. This included faster sputum culture conversion and higher rates of treatment success with BDQ than in the placebo group. This offered some hope for patients with limited treatment options.¹¹ Following accelerated approval of BDQ by the Food and Drug Administration in December 2012, the drug manufacturer, Janssen Pharmaceutica (Beerse, Belgium), facilitated international access to BDQ under an expanded access programme model. Through this mechanism, South Africa began using BDQ via the national Bedaquiline Clinical Access Programme (BCAP),¹² which was established through the collaboration between the South African NTP and various national partners after a long planning phase from November 2011 to December 2012. A protocol outlining patient eligibility for BDQ, i.e., clinically stable pulmonary DR-TB adult patients who were laboratory-confirmed, along with patient safety monitoring guidance and a prospective data collection plan, was approved by the Medicines Control Council (MCC) in December 2012. BCAP was initially implemented at four sites across South Africa following ethics approval from three institutions. Patient enrolment started in March 2013, and at the end of the BCAP on 15 March 2015, there were a total of seven sites with 200 patients enrolled on BDQ using Janssen's BDQ donation.

NCAC, which had already been established, was used to provide clinical governance to BCAP site clinicians. All patients were presented electronically to this committee and to Janssen for approval to use BDQ within an optimised background regimen; this included LZD in most cases (128/200 patients, 64%).¹³

A description and preliminary analysis of the first 91 patients enrolled on BCAP was published in 2015, with promising results.¹⁴ Final treatment outcomes of the entire BCAP cohort of 200 patients, all with

MDR-TB with additional second-line drug resistance, was published subsequently and showed a high proportion of favourable outcomes (146/200, 73%).¹³ Of the 603 adverse events reported, most were mild or moderate (507/603, 84.1%) and only 19 (3.2%) were attributed to BDQ. A summary of planning activities is given in Figure 2.

FURTHER ROLL-OUT OF BEDAQUILINE INTO THE SOUTH AFRICAN NATIONAL TUBERCULOSIS PROGRAMME

BDQ was registered in South Africa in October 2014. A national framework was developed to support the BDQ scale-up phase that started on 16 March 2015 in all provinces and later, all districts.¹⁵ During this phase, BDQ was purchased by various provinces using a conditional grant allocated to them by the National Department of Health. Under this framework, patients eligible to receive BDQ included those with MDR-TB strains with both *inhA* and *katG* mutations, MDR-TB with additional resistance to the FQs and/or injectable agents, and patients with RR-TB and intolerance or toxicity (e.g., ototoxicity, renal dysfunction, psychosis) to drugs in the standard injectable-based RR-TB treatment regimen. By 31 December 2016, a total of 4212 patients were enrolled on a BDQ-containing treatment regimen.

Provincial departments elaborated plans that were aligned with the national plan to scale up BDQ (including for all pregnant women pending NCAC approval). Key aspects included capacity building and effective data collection using the national Electronic Drug-Resistant TB Register (EDR Web), which was modified to incorporate BDQ-specific variables. Active drug safety monitoring (aDSM) was an important component of the implementation plan, as highlighted by a multicentre study on the effectiveness and safety of BDQ-containing regimens for DR-TB.⁷ Provincial advisory committees and task

teams were set up to support the NCAC. The scale-up process led to wider access to ECG machines at primary and secondary care facilities, and enhanced monitoring and pharmacovigilance among all RR-TB patients. In view of the concerns related to acquisition of BDQ resistance, nationwide laboratory surveillance for BDQ resistance was implemented. By September 2015, 598 patients had received BDQ in South Africa.¹⁶

IMPLEMENTATION OF THE SHORTER RIFAMPICIN-RESISTANT TUBERCULOSIS REGIMEN

In the 2016 update of the WHO treatment guidelines for RR-TB, it was recommended that selected patients (i.e., those without previous exposure to second-line drugs and in whom, resistance to FQs and injectables has been excluded) be treated using a shorter regimen of 9–11 months instead of the conventional longer regimen of 18–20 months. Following 9 months of preparation, South Africa progressively implemented the shorter regimen (comprised of clofazimine [CFZ], a FQ, KM, ethionamide [ETH], high-dose isoniazid, pyrazinamide and ethambutol) for eligible patients with RR-TB during 2017. The policy decision of substituting injectable with BDQ in selected patients was also applied to patients on the shorter regimen. This practice was supported by the NCAC and the NTP, as the toxicity associated with injectable agents was becoming increasingly unacceptable to patients, clinicians and civil society alike.¹⁷

IMPACT OF BEDAQUILINE ON MORTALITY, AND ITS INTRODUCTION INTO INJECTABLE-FREE REGIMENS

Wider use of BDQ at a programmatic level was carefully monitored through the EDR.Web. A retrospective cohort analysis of 19 617 patients starting treatment for RR-TB in South Africa between July 2014 and March 2016 was carried out, comparing outcomes of all 1016 patients who received BDQ with those who did not; the adjusted analysis demonstrated a three-fold reduction in all-cause mortality in patients who received BDQ compared to those who did not (adjusted hazard ratio 0.35, 95% confidence interval [CI] 0.28–0.46) for MDR-TB and 0.26, 95%CI 0.18–0.38 for XDR-TB) (see Figure 3).² While acknowledging the limitations of these observational data, it is notable that the data did meet high-quality standards and were used in the individual patient data meta-analysis by Menzies et al.¹⁸ Data from South Africa was also used among the data from 25 countries (with the largest contribution coming from South Africa) and informed the radical

changes in the 2018 WHO RR-TB treatment guidance.¹⁹

Another study from South Africa comparing treatment outcomes of 162 patients who received BDQ as a substitute for the injectable agent in the conventional longer regimen with those of a matched control group that did not receive BDQ found that BDQ use in the conventional longer regimen resulted in a lower risk of death.²⁰ Similar data supporting the efficacy and safety of BDQ in programmatic contexts have been reported from other countries.²¹ In contrast, the commonly used injectable agents (KM, amikacin, capreomycin) have limited evidence of efficacy (KM specifically has been found to increase mortality among RR-TB patients¹⁸), and are associated with significant morbidity, including renal impairment, electrolyte disturbances and irreversible hearing loss.²²

Mounting evidence began to emerge that patients with XDR-TB treated with BDQ were more likely to survive than patients with MDR-TB treated without BDQ.¹⁷ Further supporting this were experiences from the NTP's decentralised ototoxicity monitoring programme demonstrating high incidences of hearing loss as a result of injectable agent use.²³ This led to the announcement by the National Department of Health in June 2018 that the injectable agent would be dropped and replaced by BDQ in the shorter 9–11-month regimen, as well as in the conventional longer treatment regimens for RR-TB.²⁴ Although BDQ had not yet been approved for use in children under the age of 12 years, the recommendation for injectable-free RR-TB treatment for adolescents and children of all ages was strongly supported by paediatric clinicians and researchers.¹⁷

THE MODIFIED SHORTER REGIMEN FOR TREATMENT OF RIFAMPICIN-RESISTANT TUBERCULOSIS WITHOUT SECOND-LINE DRUG RESISTANCE

In addition to BDQ replacing the injectable agent, further modifications to the shorter 9–11-month RR-TB regimen were decided upon following discussions between the NCAC and the NTP. Published and unpublished evidence were reviewed, including locally generated programmatic data evaluating the efficacy of national RR-TB treatment recommendations over the years. As a result of these discussions, in September 2018, a modified, shorter, injectable-free RR-TB regimen containing CFZ, levofloxacin, BDQ, LZD, high-dose INH, pyrazinamide and ethambutol was recommended for patients with RR-TB, and subsequently implemented across South Africa.²⁴ The South African clinical decision-making algorithm used to decide on the shorter or longer regimen for adults and children is given in Figure 4.

Classified by the WHO as a Group A drug for RR-

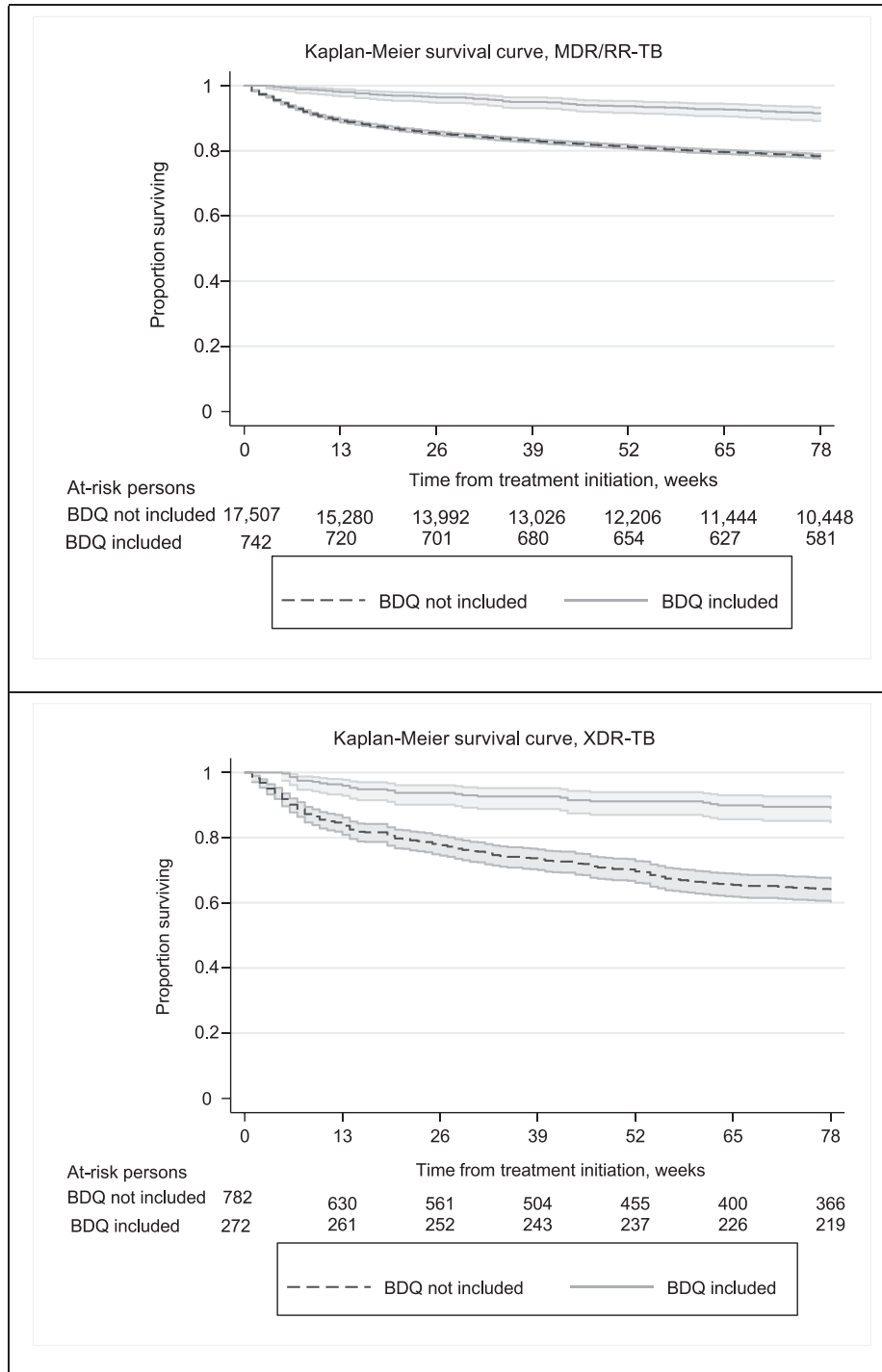


Figure 3 Kaplan-Meier survival curves for MDR/RR-TB and XDR-TB by regimen inclusive of BDQ, with 95% confidence intervals, for patients started on treatment 1 July 2014 and 31 March 2016. MDR/RR-TB = multidrug/rifampicin-resistant tuberculosis; XDR-TB = extensively drug-resistant tuberculosis.

TB,²⁵ LZD was incorporated into the modified, shorter regimen for the first 2 months of treatment with careful adverse event monitoring. Up to 13% of RR-TB cases across South Africa demonstrate additional resistance to FQs but in many provinces, there is a delay in accessing second-line drug-susceptibility testing (DST) results. The inclusion of LZD at the

start of treatment helps to protect against the acquisition of BDQ resistance while awaiting FQ susceptibility results. Detection of FQ resistance after initiation of a shorter modified regimen necessitates a switch to an individualised longer regimen. LZD has been associated with improved RR-TB treatment outcomes and a reduction in the risk of RR-TB-

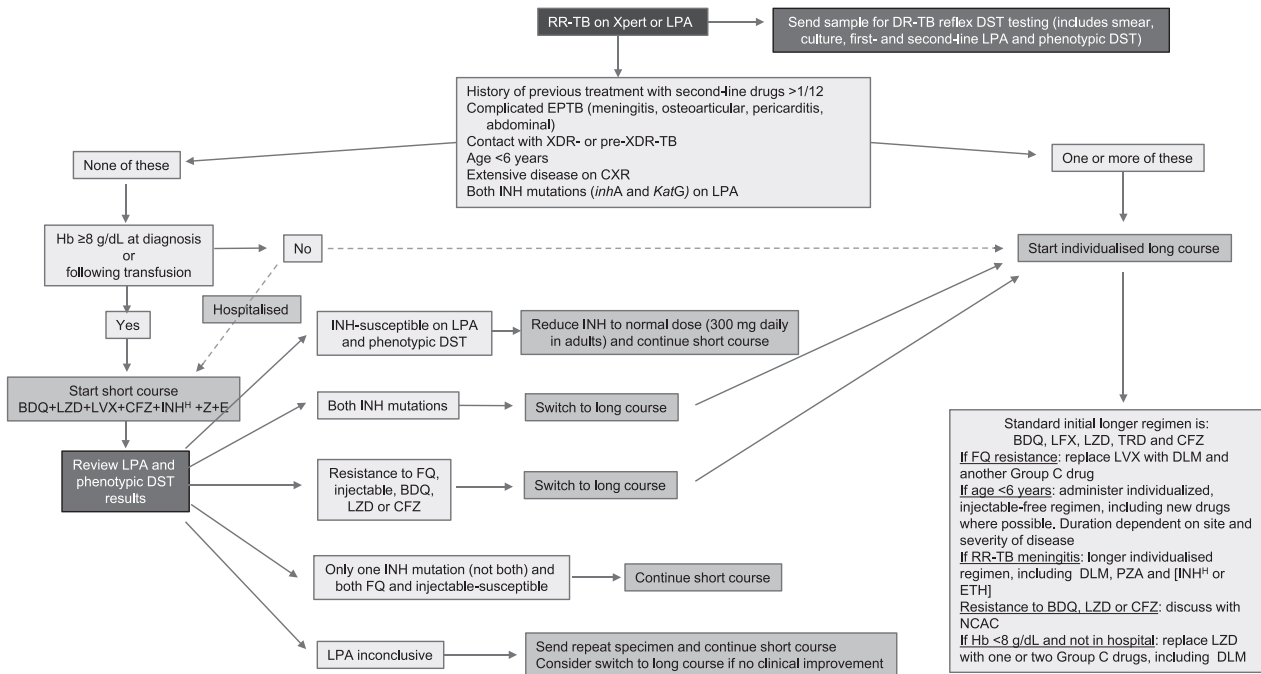


Figure 4 Overall flow diagram for RR-TB patients in South Africa. RR-TB = rifampicin-resistant tuberculosis; LPA = line-probe assay; DR-TB = drug-resistant tuberculosis; DST = drug susceptibility testing; EPTB = extrapulmonary TB; XDR-TB = extensively drug-resistant TB; CXR = chest X-ray; Hb = haemoglobin; BDQ = bedaquiline; LZD = linezolid; LVX = levofloxacin; CFZ = clofazimine; INH^H = high-dose INH; Z = pyrazinamide; E = ethambutol; INH = isoniazid; FQ = fluoroquinolone; TRD = terizidone; DLM = delamanid; ETH = ethionamide; NCAC = National Clinical Advisory Committee.

related mortality.¹⁸ LZD is a key agent in ongoing clinical trials, such as NIX-TB that has proved to be very promising.²⁶

The decision to exclude ETH from the shorter regimen was based on concerns about its efficacy and tolerability. There are limited data on ETH efficacy. ETH commonly causes severe gastrointestinal adverse effects, which can result in both patient morbidity and poor adherence. Furthermore, ETH resistance among MDR-TB strains is as high as 44.7% (95%CI 25.9–63.6) in South Africa.³

SUBSEQUENT CONSIDERATIONS FOLLOWING IMPLEMENTATION OF THE MODIFIED SHORTER REGIMEN

Patient eligibility to receive the modified, South African shorter regimen was based on inclusion and exclusion criteria similar to those for the WHO-recommended shorter regimen; however, it was agreed that pregnant women and their infants were also likely to benefit from a shorter, effective and more tolerable treatment regimen during pregnancy and post-partum. Children were also able to benefit from modified shorter regimens, and subsequent to the 2018 WHO rapid communication, BDQ was recommended as part of an injectable-free, shorter regimen for children above the age of 6.¹⁹ This recommendation was based on interim pharmacokinetic and safety data from unpublished and ongoing

BDQ paediatric studies. Similarly, DLM was recommended for children aged ≥ 3 years based on available dosing data.¹⁹ DLM is considered along with LZD and para-aminosalicylic acid as alternative second-line drug options to replace the injectable agent in RR-TB treatment regimens for younger children until dosing and safety data on BDQ becomes available for children aged < 6 years.^{27,28}

The modified shorter regimen is being implemented programmatically in South Africa with rigorous monitoring and evaluation, updated training for clinicians, national aDSM, patient education and counselling, laboratory surveillance to detect emerging resistance to new drugs and strong clinical governance through regular clinical audits. The NCAC continues to provide oversight to the NTP and offers clinical support to clinicians, in a role similar to the Global TB Consilium which operates at a supra-national level and may be useful for second opinions.²⁹ Several other organisations have also commended such an approach in managing DR-TB.³⁰ The NTP is equipped to conduct regular interim analyses of routinely available data and can respond quickly to any unexpected safety concerns. Extended phenotypic DST includes resistance testing for LZD, CFZ and BDQ are routinely carried out on all RR-TB isolates with second-line drug resistance, treatment failures and upon request from clinicians.

CONCLUSION

The South African NTP, supported by an outstanding laboratory service and strong collaboration from stakeholders, has progressively implemented changes in RR-TB treatment recommendations in line with emerging evidence on efficacy and safety of second-line TB drugs;⁷ this has generated compelling evidence to inform guidelines for other NTPs and the WHO. The introduction of rapid diagnostics and new medications under carefully monitored conditions and ongoing evaluation of programmatic data to iteratively inform changes in treatment guidance is an approach that has revolutionised the TB landscape and improved RR-TB treatment outcomes in South Africa.³¹ This approach has catalysed the most recent changes in the 2019 WHO RR-TB treatment guidance,^{32,33} and has the capacity to shift the current 55% global MDR-TB treatment success rates closer to the goals set by the EndTB initiatives.³⁴

Conflicts of interest: FC was/is an investigator for the trials STREAM and TMC-207 (BDQ). The other authors declare no conflict of interest.

References

- DR-TB STAT. DR-TB scale-up treatment action teams country updates, 2019. <http://drtb-stat.org/country-updates/>.
- Schnippel K, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med* 2018; 6(9): 699–706.
- Ismail N A, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. *Lancet Infect Dis* 2018; 18(7): 779–787.
- National Department of Health, South Africa. Electronic Drug-Resistant Tuberculosis Register. Pretoria, South Africa: NDoH, 2012.
- Schnippel K, et al. Predictors of mortality and treatment success during treatment for rifampicin-resistant tuberculosis within the South African National TB Programme, 2009 to 2011: a cohort analysis of the national case register. *Int J Infect Dis* 2015; 39: 89–94.
- Ndjeka N, Dlamini S S, Bantubani N, Schnippel K. Mortality during XDR-TB treatment in South Africa, 2007–2009: a retrospective cohort analysis. *Union World Conference on Lung Health, Cape Town, South Africa, 2–6 December 2015*. [OA-346-04] *Int J Tuberc Lung Dis* 2019; 12(Suppl 2): S130.
- Borisov S E, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J* 2017; 49(5): 1700387.
- Schnippel K, et al. Incremental cost effectiveness of bedaquiline for the treatment of rifampicin-resistant tuberculosis in South Africa: model-based analysis. *Appl Health Econ Health Policy* 2018; 16(1): 43–54.
- National Department of Health, South Africa. MDR-TB: policy framework on decentralized and deinstitutionalised management for South Africa. Pretoria, South Africa: NDoH, 2011.
- National Department of Health, South Africa. Management of drug-resistant tuberculosis—policy guidelines: 2013 update. Pretoria, South Africa: NDoH, 2013.
- Diacon A H, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *antimicrobial agents and chemotherapy*. 2012; 56(6): 3271–3276.
- Conradie F, et al. Clinical access program for bedaquiline for the treatment of drug-resistant tuberculosis. *S Afr Med J* 2014; 104(3): 164.
- Ndjeka N, et al. High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. *Eur Respir J* 2018; 52(6): 1801528.
- Ndjeka N, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *Int J Tuberc Lung Dis* 2015; 19(8): 979–985.
- National Department of Health, South Africa. Introduction of new drugs and drug regimens for the management of drug-resistant tuberculosis in South Africa: policy framework. Pretoria, South Africa: NDoH, 2015. <https://www.nicd.ac.za/assets/files/Introduction%20of%20new%20drugs%20and%20drug%20regimens%20for%20the%20management%20of%20drug%20resistant%20TB%20in%20SA%20-%202015.pdf>.
- Ndjeka N. Incorporation of bedaquiline in the South African National TB Programme. in *Conference on Retroviruses and Opportunistic Infections*. 2016.
- Reuter A, et al. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? *Int J Tuberc Lung Dis* 2017; 21(11): 1114–1126.
- Ahmad N, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018; 392(10150): 821–834.
- World Health Organization. Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis. Geneva, Switzerland: WHO, 2018. http://apps.who.int/bookorders.%0Ahttp://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf?ua=1.
- Zhao Y, et al. Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug-resistant tuberculosis: a retrospective cohort study. *Clin Infect Dis* 2019; 68(9): 1522–1529.
- Borisov S, et al. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report. *Eur Respir J* 2019; 54(6): 1901522.
- Seddon J A, et al. Hearing loss in patients on treatment for drug-resistant tuberculosis. *Eur Respir J* 2012; 40(5): 1277–1286.
- National Department of Health, South Africa. Electronic Drug-Resistant Tuberculosis Register. Pretoria, South Africa: NDoH, 2017.
- National Department of Health, South Africa. Interim clinical guidance for the implementation of injectable-free regimens for rifampicin-resistant tuberculosis in adults, adolescents and children. Pretoria, South Africa: NDoH, 2018.
- World Health Organization. Treatment guidelines for multidrug and rifampicin-resistant tuberculosis: 2018 update. Geneva, Switzerland: WHO, 2018; <https://www.who.int/tb/publications/2018/WHO.2018.MDR-TB.Rx.Guidelines.prefinal.text.pdf>.
- Conradie F, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020; 382(10): 893–902.
- Seddon J A, et al. Time to act on injectable-free regimens for children with multidrug-resistant tuberculosis. *Lancet Respir Med* 2018; 6(9): 662–664.
- Treatment Action Group. Statement on injectable-free regimens for children under the age of 12 years with rifampicin-resistant tuberculosis. New York, NY, USA: TAG, 2018. <https://www.treatmentactiongroup.org/wp-content/uploads/2018/08/recs-for-injectable-free-regimens-children-with-rr-tb.pdf>.

- 29 Tiberi S, et al. Challenging MDR-TB clinical problems—the case for a new Global TB Consilium supporting the compassionate use of new anti-TB drugs. *Int J Infect Dis* 2019; 80: S68–S72.
- 30 Nahid P, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med* 2019; 200(10): e93–e142.
- 31 World Health Organization. Global tuberculosis report, 2018. WHO/CDS/TB/2018.20. Geneva, Switzerland: WHO, 2018. <https://www.who.int/tb/publications/en/>.
- 32 World Health Organization. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva, Switzerland: WHO, 2019. https://www.who.int/tb/publications/2019/WHO_RapidCommunicationMDR_TB2019.pdf?ua=1.
- 33 World Health Organization. Consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, Switzerland: WHO, 2019.
- 34 World Health Organization. The End TB Strategy. Geneva, Switzerland: WHO, 2015.

R É S U M É

L'adoption des nouveaux médicaments du traitement de la tuberculose résistante à la rifampicine (RR-TB) a été très médiocre dans le monde. En juin 2018, avant la publication des directives mises à jour de l'OMS pour la prise en charge de la RR-TB, l'Afrique du Sud a annoncé que la bédaquiline (BDQ) serait fournie à pratiquement tous les patients RR-TB sous protocole plus court ou plus long. L'Afrique du Sud a été le leader mondial dans l'accès à la BDQ pour les patients atteints de RR-TB constituant 60% de la cohorte de BDQ. L'utilisation de la BDQ au sein d'un protocole modifié plus court a généré les données de programme étayant les modifications les plus récentes des directives de l'OMS, approuvant un protocole injectable plus court et gratuit. Les politiques progressives relatives à l'accès aux nouveaux médicaments ont abouti à une

amélioration des résultats favorables et à une réduction de la mortalité parmi les patients RR-TB en Afrique du Sud. Ceci a soutenu le changement de politique mondiale. Les stratégies soutenant ces actions audacieuses incluent une étroite collaboration entre le Programme national de la lutte contre la tuberculose et ses partenaires, l'introduction de nouveaux outils de diagnostic de la TB dans des conditions de suivi étroit et l'utilisation de preuves programmatiques générées localement pour élaborer les changements de politique dans le pays. Dans cet article, nous résumons le travail d'une décennie qui a abouti à la décision audacieuse d'utiliser un protocole modifié court injectable et gratuit comportant de la BDQ et du linézolide, soigneusement suivi dans des conditions de programme.

R E S U M E N

La aceptación de nuevos fármacos para el tratamiento de la tuberculosis resistente a la rifampicina (TB-RR) ha sido demasiado baja en todo el mundo. En junio del 2018, antes de la publicación de la actualización de las directrices de la OMS sobre el tratamiento de la TB-RR, se anunció en Suráfrica que la bedaquilina (BDQ) se administraría prácticamente a todos los pacientes con TB-RR en un esquema acortado o un esquema más largo. Suráfrica ha sido pionera mundial del acceso a la BDQ para los pacientes con TB-RR y constituye el 60% de la cohorte mundial de BDQ. El uso de BDQ en un esquema terapéutico modificado, más corto, generó datos programáticos que respaldan la modificación más reciente de las directrices de la OMS, que aprueban un régimen acortado sin inyectables. Las políticas progresivas en materia de acceso a los nuevos fármacos

han llevado a aumentar los desenlaces favorables y disminuir la mortalidad de los pacientes con TB-RR en Suráfrica. Estos resultados respaldaron la modificación de la política mundial. Entre las estrategias que apoyan estas medidas innovadoras se cuentan la colaboración estrecha entre el Programa Nacional de Tuberculosis y sus asociados, la introducción de nuevas herramientas diagnósticas de la TB en condiciones de supervisión cuidadosa y la utilización de la evidencia programática generada localmente para fundamentar los cambios de políticas en el país. En el presente artículo se sintetiza un decenio de trabajos que condujeron a la decisión audaz de utilizar un régimen terapéutico modificado, más corto y sin inyectables, a base de BDQ y linezolid en condiciones programáticas con una supervisión estrecha.