South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Respiratory

MDR TUBERCULOSIS TREATMENT OVERVIEW:

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The following narrative provides an overview of MDR Tuberculosis pharmacological management and should be reviewed together with the individual medicine reviews for bedaquiline, linezolid, delaminid and clofazimine.

Multidrug resistant (MDR) tuberculosis (TB) is defined as tuberculosis with resistance to both rifampicin and isoniazid. In 2017, the World Health Organization (WHO) estimated that the incidence of TB in South Africa was 322,000.[1] Approximately 2.8% of these are MDR TB cases.[2] Outcomes for rifampicin-resistant TB in South Africa with traditional injectable-agent-based regimens are poor, with only 22% of such patients successfully completing treatment.[3] In addition to their poor efficacy, the traditional MDR regimens required approximately 20-24 months of therapy, and were also associated with substantial toxicities, including ototoxicity, renal failure, neuropsychiatric abnormalities, and frequent gastrointestinal symptoms. Thus, the development and introduction of regimens that were more efficacious, shorter, and/or better tolerated has been a priority. In addition, a more secure evidence base for MDR TB regimens was desired, with previous WHO recommendations and South African guidelines being based on "very low quality" observational evidence at high risk of bias.[4]

STREAM I trial

The STREAM I trial was a randomized phase 3 non-inferiority trial that compared a shorter 9-11 month regimen that had appeared promising in an earlier observational study (the so-called "Bangladesh regimen") with the standard-of-care 20 month MDR TB regimen (as per the WHO 2011 MDR TB guidelines).[5, 6]

Shorter regimen	**Example of standard-of-care regimen** (as used in South Africa)
For 40 weeks: • Clofazimine • Ethambutol • Pyrazinamide • Moxifloxacin **AND** *For the first 16-24 weeks:* • Kanamycin • Isoniazid • Prothionamide	*For 18 months after culture conversion:* • Terizidone • Ethionamide • Pyrazinamide • Moxifloxacin **AND** *For the first 6 or more months, until culture conversion* • Kanamycin

The primary outcome was a favourable status, defined as cultures negative for M. tuberculosis at 132 weeks and on 1 previous occasion, with no intervening positive culture, and a pre-specified non-inferiority margin of 10% was chosen. A favourable outcome was achieved in 79.8% of participants in the long regimen group and in 78.8% of those in the short-regimen group (95% CI for difference: -7.5 to 9.5%, p=0.02), and thus non-inferiority was established. Adverse events were similar between the two regimens, though again there was trend towards increased safety with the long regimen.

2019 World Health Organization consolidated guidelines on drug-resistant tuberculosis treatment[7]

Following data from the STREAM trial and other data from trials relating to bedaquiline, etc., the WHO has endorsed two main regimens:

1. A shorter (9-12 month) regimen, based on the shorter regimen in the STREAM 1 trial.
2. A longer (18 to 20 month regimen), based on at least 4 TB drugs likely to be effective, which should ideally be:

- Bedaquiline (usually for the first 6 months only)
- Linezolid
- Levofloxacin or moxifloxacin
- Clofazimine and/or terizidone/cycloserine
- With or without additional drugs such as pyrazinamide, ethambutol, delaminid, terizidone, imipenem/meropenem, etc.

The choice between the shorter and the longer regimen would be based on several factors, including previous exposure to second-line medications, the exclusion of resistance to fluoroquinolone and injectable agents, pregnancy, complicated extra-pulmonary TB, etc. In a first for MDR TB treatment regimen, the longer regimen allowed for an all-oral regimen that did not require an injectable agent, thereby potentially avoiding many of the toxicities historically associated with MDR treatment.

South African Department of Health Interim Clinical Guidance for rifampicin-resistant tuberculosis: 2018[8]

SA National Department of Health (NDoH) guidelines were released in 2018, and also recommended two regimens for MDR TB (and a third regimen for MDR TB involving the central nervous system).

Short regimen (9-11 months)	Longer regimen (18-20 months)
• Linezolid (first 2 months only) • High-dose isoniazid* (first 4 months) • Bedaquiline (first 6 months usually) • Levofloxacin • Clofazimine • Pyrazinamide • Ethambutol	• Linezolid (first 6-8 months only) • Bedaquiline (first 6-8 months only) • Levofloxacin • Clofazimine • Terizidone

**INH 15mg/kg*

The long regimen is broadly concordant with the WHO guidelines above. The NDoH short regimen differs from WHO guidance in the following ways:

- *Bedaquiline replaces the injectable agent*
- *High-dose isoniazid is used regardless of INH genotypic resistance status*

Assessment of evidence base for WHO and SA NDoH regimens

- The STREAM trial has provided good evidence that a shorter injectable-based regimen (à la the "Bangladesh regimen") is non-inferior to the older injectable-based longer regimens.[6]
- The longer bedaquiline-based regimen (as recommended by the WHO and NDoH) has not been directly compared in a randomized control trial with an injectable-based longer regimen, or any shorter regimen (either injectable or all-oral). However, other observational data and RCTs for individual drugs do exist, and on the basis of this data, WHO currently finds there to be sufficient evidence to justify recommending the regimen (albeit the estimates of effect were classified as between "very low" and "moderate" certainty, depending on the specific recommendations).[7] The absence of an injectable agent was thought to offer significant toxicity advantages.
- The decision by the NDoH to use bedaquiline instead of the injectable agent is at odds with WHO guidance currently. In preparing their latest guidelines, WHO state that *"no data from variants of the shorter regimen in which the injectable agent was replaced by bedaquiline were reported to WHO*", and thus the regimen could not be recommended.[7] The report further states that such regimens "***can be explored under operational research conditions***."[7] To date, there is considerable observational data supporting bedaquiline's use in longer regimens, though not in short regimens. The STREAM 2 RCT, currently underway and expected to complete enrollment in 2022, will compare an all-oral regimen very similar to the proposed NDoH short-course regimen to other regimens, and it is anticipated that this will provide further guidance as to the efficacy of this regimen. Pending that, the evidence for replacing the injectable agent with bedaquiline in the short-course regimen is currently weak, though it may be argued that the improved side-effect profile may justify this at a programmatic level.
- The decision by the NDoH to recommend high-dose isoniazid regardless of INH resistance status is also broadly at odds with the WHO guidelines, which state that "high-dose isoniazid may have a role in patients with <u>*confirmed susceptibility*</u> to isoniazid" (emphasis added).[7] Previous guidelines have recommended high-dose INH in MDR TB regimens only if the *inhA* mutation was present, since this mutation causes only low-level resistance that can be overcome with higher doses of INH. By contrast, the *katG* mutation generally precludes INH use given the high level of resistance to INH that this causes. Though the routine addition of high-dose INH to MDR TB cases was shown in one RCT to be beneficial, this trial did not establish which of the INH mutations was present at what proportions in the population, and MIC data from the trial suggested that much of the resistance was low grade (and thus likely caused by *inhA*).[9] The evidence for administering INH even when the *katG* mutation is known to be present is therefore very weak, and may well be outweighed by the associated toxicities of the drug in this scenario.

References

1. WHO. Global Tuberculosis Control 2018 2018 [Available from: http://www.who.int/tb/publications/global_report/en/
2. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S, 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):779-87.
3. Naidoo P, Theron G, Rangaka MX, Chihota VN, Vaughan L, Brey ZO, et al. The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. J Infect Dis. 2017;216(suppl_7):S702-S13.
4. Falzon D, Jaramillo E, Schunemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J. 2011;38(3):516-28.
5. Van Deun A, Maug AK, Salim MA, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010;182(5):684-92.
6. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med. 2019;380(13):1201-13.
7. WHO. WHO consolidated guidelines on drug-resistant tuberculosis 2019. https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1.
8. South African National Department of Health. Interim Clinical Guidance for the Implementation of Injectable-free Regimens for Rifampicin-resistant Tuberculosis in Adults, Adolscents and Children 2018. http://www.tbonline.info/media/uploads/documents/dr_tb_clinical_guidelines_for_rsa_september_2018.pdf.
9. Katiyar SK, Bihari S, Prakash S, Mamtani M, Kulkarni H. A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2008;12(2):139-45.