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

MEDICINE REVIEW:

1. Executive Summary

Date: 17th September 2019
Medicine (INN): Levofloxacin, oral (in addition to rifampicin, pyrazinamide, and ethambutol)
Medicine (ATC): J01MA12
Indication (ICD10 code): U50.1
Patient population: Adults with isoniazid-resistant, rifampicin-susceptible tuberculosis
Prevalence of condition: 6.1% of new TB cases are isoniazid-resistant in South Africa[1]
Level of Care: Secondary level of care
Prescriber Level: Medical officer
Current standard of Care: Combination therapy with rifampicin, pyrazinamide and ethambutol
Efficacy estimates: aOR for treatment success of 2.8 (95% CI 1.1 to7.3); Risk Difference per 1,000 treated: 50 more treatment successes per 1,000 (95% CI: 0 to 90) (Fregonese et al, 2018; WHO, 2018)
Motivator/reviewer name(s): Dr. J. Nel; Dr H Dawood
PTC affiliation: Dr H Dawood: KZN Provincial PTC

2. Name of author(s)/motivator(s)

Primary reviewer: Dr Jeremy Nel (assisted by TD Leong – costing analysis)
Secondary reviewer: Dr H Dawood

3. Author affiliation and conflict of interest details

Dr J Nel:

- *Affiliation:* University of the Witwatersrand; Co-opted expert to the Adult Hospital Level Committee (2017-2020)
- *Conflict of interests:* AbbVie (Consultation on ARV study); Helen Joseph Hospital (Cryptococcal meningitis research); Mylan (Consultation on ART regimens); SA HIV Clinician Society Cryptococcal meningitis Guidelines.

Dr H Dawood:

- *Affiliation:* Greys hospital, KZN Department of health; Caprisa, UKZN; Member of the Adult Hospital Level Committee.
- *Conflict of interests:* MSD: ECMID 2018 - Conference attendance; ACTA study - DSMB member (crypto meningitis); Adcock Ingram - HIV discussion with general practitioners; President elect: IDSSA; SA HIV Clinician Society Cryptococcal meningitis Guidelines.

Ms TD Leong:

- *Affiliation:* National Department of Health, Essential Drugs Programme; Secreteriat to the Adult Hospital Level Committee; no conflicts of interest declared.

4. Introduction/ Background

Isoniazid mono-resistant TB is defined as tuberculosis resistant to isoniazid but susceptible to rifampicin. A 2018 study estimated that 6.1% of tuberculosis cases in South Africa were isoniazid-mono-resistant in the 2012-2014 period, ranging from 5.3% to 8.1% across South Africa's nine provinces.[1] Despite the relatively high prevalence both nationally and internationally (substantially higher than MDR prevalence, for instance), the optimal regimen and therapeutic duration for this condition is not well studied.

Traditionally, the standard of care in South Africa has been a combination of rifampicin, pyrazinamide, and ethambutol (for ease of administration, usually administered co-formulated with isoniazid as a fixed dose combination product for a period of 6 months).[2] However, this treatment was not based on high quality evidence, and it is possible that alternative regimens may be more efficacious. Recently, the WHO recommended adding levofloxacin to the standard of care regimen in those with proven INH mono-resistant TB.[3]

Levofloxacin, a fluoroquinolone, has in vitro activity against *M. tuberculosis* and represents the initial category of second-line anti-tuberculous drugs in the setting of resistance and/or intolerance to first-line TB drugs. Levofloxacin is associated with less frequent events of QT prolongation and therefore is for patients on a regimen including other agents associated with QT prolongation or when ECG monitoring is not easily available. However, levofloxacin requires dose adjustment in those with renal impairment.

5. Purpose/Objective i.e. PICO

-P: adult patients with isoniazid monoresistant, rifampicin-susceptible tuberculosis

-I: use of levofloxacin in addition to rifampicin, pyrazinamide, and ethambutol +/- isoniazid.

-C: standard of care: rifampicin, pyrazinamide, and ethambutol +/- isoniazid.

-O: efficacy: culture conversion, treatment success rate; safety: grade 3 and 4 adverse events, mortality rate

6. Methods:

a. Data sources: PubMed, World Health Organization Consolidated Guidelines on Drug-resistant Tuberculosis Treatment. Only Randomized controlled trials, systematic reviews and meta-analyses were included.

b. Search strategy

PubMed: (("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields]) AND isoniazid-resistant[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND (systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp])

c. Excluded studies:

PMID	*Type of study*	*Reason for exclusion*
766340	RCT	Did not study levofloxacin
3051607	RCT	Did not study levofloxacin
9487448	RCT	Did not study levofloxacin
11931398	RCT	Did not study levofloxacin
16704830	Systematic review	Review of isoniazid-preventative therapy, not treatment
17135182	Meta-analysis	Meta-analysis of colorimetric diagnostic methods
21575299	Clinical trial	Trial of TB acquisition risk
23348808	Systematic review	Children only, study looked at prevalence rather than treatment
26034243	Systematic review	Children only, study looked at prevalence rather than treatment
26760084	RCT	Trial of TB meningitis, did not look specifically at isoniazid-resistant TB
27156625	Systematic review	Systematic review of INH resistance prevalence
30462960	Meta-analysis	Meta-analysis of the diagnostic accuracy of line probe assays. Not relevant to PICO analysis.
27865891	Systematic review and meta-analysis	Data entirely incorporated into a later meta-analysis (PMID: 29595509)
31142548	Systematic review	Systematic review of reviews. Comment re: INH resistance limited to single sentence without quantification.

d. Evidence synthesis

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Stagg et al., 2016[4]	Systematic review and meta-analysis	59 RCTs (patient numbers unclear)	Patients with INH resistance (MDR excluded)	Rifampicin-containing regimens using <3 effective drugs at 4 months, in which RIF was protected by another effective drug at 6 months, and RIF taken for 6 months.	Unfavourable outcome (definition: treatment failure or lack of microbiological cure, relapse post-treatment, death due to TB)	Fixed effects model: regimens with ≥3 effective drugs at 4 months plus a duration of >6 months had lower odds of an unfavourable outcome (OR 0.31, 95% CI 0.12 to 0.81). In random effects model, all effect estimates crossed the null.	INH mono-resistance itself couldn't be assessed. "In a network restricted to patients with INH-mono-resistant disease data sparsity made conclusions difficult to draw." In some studies unfavourable outcome frequencies had to be estimated from reported favourable outcomes. Not all studies reported all three of the unfavourable outcomes assessed. Few HIV-positive patients.
Heemskerk AD et al., 2017[5]	Subgroup analysis of a RCT	86 with INH-resistance	Patients with TB meningitis	Intensified regimen (incl. high dose RIF, 15 mg/kg/day, + levofloxacin, 20 mg/kg/day, for 1st 8 weeks) vs standard regimen (incl. standard-dose RIF, 10 mg/ kg/day).	Death during 9 months of follow-up	In Cox regression model, INH-resistant group had a HR of 0.38 (95% CI 0.18 to0.80) for death (i.e. improved survival) when treated with a fluoroquinolone.	Patients limited to TB meningitis. INH-resistant(INH-R) group included INH mono (n=24), INH + streptomycin resistant (n=59), and INH + ethambutol resistant (n=3). Fluoroquinolones could be added early (as per randomization) or late (once INH-R identified), though benefit appeared to come from the first category rather than the second. Can't disentangle benefit of fluoroquinolones from benefit of high-dose RIF.
Fregonese F et al., 2018[6]	Individual patient data meta-analysis	3923 patients, from 23	Isoniazid-resistant,	Addition of fluoroquinolone to RIF+PZA+EMB	Treatment success (cure or completion), death	Addition of fluoroquinolone had aOR 2.8 (95% CI 1.1-	Quality of evidence classified as "very low" due to "the observational nature of most

		cohort studies and 17 randomised trials	rifampicin-sensitive TB	vs no fluoroquinolone.	during treatment, acquired RIF resistance.	7.3) for treatment success, but no statistically significant difference in mortality (aOR 0.7; 95% CI 0.4-1.1) or acquired RIF resistance (aOR 0.1, 95% CI 0.0-1.2), though trend towards better outcomes in both these outcomes also.	of the data, the diverse settings, and the imprecision of estimates." Study unable to define the best quinolone, or the optimal duration of quinolone. Unclear whether quinolones were being used at beginning of treatment or only once drug-susceptibility testing results were available. Adverse events could not be analysed because these were either not reported or lacked standardized reporting.

e. **Evidence quality:** Low. No RTC specifically devoted to optimal regimen for INH-resistant, RIF-sensitive TB cases. WHO summary recommendation for levofloxacin states "very low certainty in the estimates of effect". However, it must also be noted that the standard of care regimen has an even lower evidence base in terms of efficacy and outcomes, and the evidence available points to the standard of care regimen being inferior. See evidence synthesis table above.

7. **Alternative agents:** Standard of care: rifampicin + pyrazinamide + ethambutol

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [ ] Not confident [x] Uncertain [ ]	See evidence quality above. It is unlikely that there will be a RCT to answer the PICO question as the detection rate and numbers are low.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [x]	See evidence synthesis table, above. Levofloxacin's rate of adverse events was relatively low: 4.1% (95% CI 1.9 to 8.8%) in an individual patient data meta-analysis of MDR regimens. However, adverse event rate specifically for adding levofloxacin to standard of care regimen for INH-resistant, RIF-susceptible TB is unknown (Ahmad et al, 2018)
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group: n/a List specific exclusion from the group: n/a	
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [x] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	Levofloxacin included in most guidelines for management INH-mono-resistant TB.
RESOURCE USE	**How large are the resource requirements?** More intensive [X] Less intensive [ ] Uncertain [ ]	**Price of medicines/ treatment course** – 6/12s (168 days) *Dose of levofloxacin:* • >50 kg: 1000 mg daily • ≤50 kg: 750 mg daily **Medicine** / **Cost (ZAR)*** 1) Levofloxacin 500mg, oral daily, 168 tabs – 829.20 2) RHZE, oral 4 tablets daily (70 kg adult), 672 tabs** – 752.76** Levofloxacin 1000 mg, oral daily + RHZE (1+2) – 1581.96 *Contract circular HP01-2019TB: Levofloxacin 500mg, 28 tablets=R69.10; RHZE 112 tablets=125.46. **Combination of rifampicin 10mg/kg/daily, pyrazinamide 25mg/kg/daily, and ethambutol 15mg/kg/daily (for ease of administration, usually administered co-formulated with isoniazid as a fixed dose combination product - RHZE). **Estimated budget impact:** • Reported TB cases in 2018: 227 999 (WHO) • INH-R TB cases: 6.1% (5.3% to 8.1%) [1] • Estimated INH-R TB cases in 2018: 13908 (12084 to 18468).

		• Treatment course for a 70 kg adult = R1,581.96. • Estimated budget impact: R22,001,803 (R19,116,321 to R29,215,509) • Incremental cost for adding levofloxacin to current regimen for 70 kg adult = R 829.20 • Estimated incremental budget: R11,532,463 (R10,020,009 to R15,313,598) **Additional resources:** N/A
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[ ]	[ ]	[ ]	[X]	[ ]

Recommendation: Based on this evidence review, the Adult Hospital Committee reccomends a levofloxacin-based regimen for treatment of INH-monoresistant TB, for a duration of 6 months. To assist with adherence, a fixed dose combination (FDC) product is preferred. Rifampicin, pyrazinamide and ethambutol are only available in a fixed dose combination product co-formulated with isoniazid. It is noted that this FDC is routinely prescribed in clinical practice for ease of administration by the patient, and levofloxacin can be added to this.

Rationale: Aligned with WHO conditional reccomendation with very low quality evidence[3].

The Adult Hospital Committee notes that the upcoming updated draft NDoH DR-TB Guidelines also recommends adding high dose INH regardless of INH resistance subtype (*inhA* and/or *katG* mutations). Although the addition of high-dose INH can be expected to increase the effectiveness of the regimen when the INH resistance is caused by the *inhA* mutation alone, the high-level resistance typically caused by the *katG* mutation likely renders the addition of isoniazid futile. There is no evidence that adding high-dose INH in the presence of the *katG* mutation is beneficial. In addition, it contradicts WHO guidance, which states that "[in the presence of a *katG* mutation], the inclusion of isoniazid in the regimen, even at a higher dose, is unlikely to increase its effectiveness."[7] Furthermore, in South Africa, INH-resistance is initially determined genotypically, so the subtype of INH resistance (*inhA* vs *katG*) is almost always available to the clinician, allowing him/her to easily determine the appropriateness of adding high dose INH. *katG* mutations are also more common than *inhA* mutations in any case at the population level. Lastly, the addition of extra INH to the FDC adds to the pill burden and increases the risk of adverse events due to isoniazid.

Level of Evidence: III Individual patient data meta-analysis (observational data)

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
[x]	[x]	[ ]

VEN status:

Vital	Essential	Necessary
[ ]	[x]	[ ]

NEMLC MEETING OF 5 DECEMBER 2019:

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, above.

The Global TB Programme report of 78.6% of 1174 isolates of rifampicin susceptible, isoniazid resistant TB presenting with mutations in the katG gene was noted (article pending publication).

Monitoring and evaluation considerations: Ongoing prevalence of INH mono-resistance and medicine utilisation for this indication**.**

Research priorities: Need RCT-level data showing benefit.

References:

1. 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.
2. South African National Department of Health. National Tuberculosis Management Guidelines 2014 2014 [Available from: http://www.tbonline.info/media/uploads/documents/ntcp_adult_tb-guidelines-27.5.2014.pdf.
3. World Health Organization. WHO Consolidated Guidelines on Drug-resistant Tuberculosis Treatment 2019 [Available from: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/.
4. Stagg HR, Harris RJ, Hatherell HA, Obach D, Zhao H, Tsuchiya N, et al. What are the most efficacious treatment regimens for isoniazid-resistant tuberculosis? A systematic review and network meta-analysis. Thorax. 2016;71(10):940-9.
5. Heemskerk AD, Nguyen MTH, Dang HTM, Vinh Nguyen CV, Nguyen LH, Do TDA, et al. Clinical Outcomes of Patients With Drug-Resistant Tuberculous Meningitis Treated With an Intensified Antituberculosis Regimen. Clin Infect Dis. 2017;65(1):20-8.
6. Fregonese F, Ahuja SD, Akkerman OW, Arakaki-Sanchez D, Ayakaka I, Baghaei P, et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2018;6(4):265-75. https://www.ncbi.nlm.nih.gov/pubmed/29595509
7. World Health Organization. Frequently asked questions on the WHO treatment guidelines for isoniazid-resistant tuberculosis. 2018. Available from: https://www.who.int/tb/publications/2018/FAQ_TB_policy_recommendations_guidelines.pdf?ua=1.