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

This version is an update of the previous review, dated 9 April 2019. The cost of a treatment course of 3HP has been updated, as the tender price of rifapentine has been published on contract circular HP01-2019TB on the 7 November 2019.

MEDICINE REVIEW:

1. Executive Summary

Date: 14 November 2019
Medicine (INN): Rifapentine (as part of Isoniazid-rifapentine short course TLTBI regimen)
Medicine (ATC): J04AB05
Indication (ICD10 code): LTBI preventive therapy (Z79.2)
Patient population: Adult persons living with HIV (PLHIV) on ART in a high burden TB country
Prevalence of condition:
Level of Care: Primary Level
Prescriber Level: Nurse practitioner
Current standard of Care: 12 months INH for all PLHIV on initiation of ART
Efficacy estimates: (preferably NNT) 3HP and 1HP shown to be comparable to 6- and 9-month isoniazid monotherapy in preventing TB disease.
Motivator/reviewer name(s): TD Leong, A Black
PTC affiliation: A Black: Helen Joseph PTC; AG Parrish: Frere and Cecilia Makiwane Hospitals PTCs

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

Primary review: TD Leong (initial review, 2018); A Black (updated review, 2019)
Secondary reviewer: A Black (initial review, 2018); AG Parrish (updated review, 2019)

3. Author affiliation and conflict of interest details

TD Leong: NDoH, EDP, Secretariat to Adult Hospital level Committee and National Essential Medicine List Committee (2017-2020); no conflicts of interest declared.
A Black: Department of Medicine Helen Joseph Hospital and University of the Witwatersrand; Adult Hospital Level Committee (2017-2019); National Essential Medicine List Committee; Conflicts of interest: Astra Zeneca - Attendance and accommodation to attend industry funded Pulmonology Update; Pfizer - Sponsorship to attend Pneumococcal weekend summit.
AG Parrish: Frere and Cecilia Makiwane Hospitals; National Essential Medicine List Committee; no conflicts of interest declared.

4. Introduction/ Background

Treatment of latent tuberculosis infection (LTBI is an important strategy to decrease active TB disease[i]. Currently, South Africa uses isoniazid in its TB programme to treat latent TB infection and prevent reinfection with TB.

PLHIV with LTBI have been shown to be at a higher risk for progressing to active TB[ii]; and are more likely to reactivate with TB[iii] compared to the HIV-uninfected. Systematic review of RCTs showed that treating LTBI (any anti-TB medicine) in PLHIV reduces the risk for active TB disease by 32% (RR 0.68; 95% CI 0.54 to 0.85) with a greater benefit amongst those who tested positive for LTBI[iv]. However, many of these RCTs were

from the pre-ART era. PLHIV on ART the benefit of INH appears to extend to include persons testing negative for LTBI[v]; whilst INH prophylaxis in PLHIV initiating ART or on ART decreases incident TB[iv, x] and all cause mortality[xi]. The National Department of Health's Universal Test and Treat (UTT) strategy is noteworthy, as ART has been shown to reduce the risk of developing active TB disease[vi]. The NDoH Consolidated HIV Guidelines[vii] and PHC STGs and EML, 2018[viii] recommends 12 months IPT in PLHIV, irrespective of TST status.

Recently, the World Health Organisation published Guidelines for LTBI (April 2018)i that recommends various options for LTBI in countries of high TB incidence, including:

- 'Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence. *(Strong recommendation, high-quality evidence. Existing WHO recommendation).*

Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence. (Conditional recommendation, moderate-quality evidence. New WHO recommendation)'.

Previous EML 25 October 2018 assessed the available evidence for 3-months of weekly rifapentine and isoniazid. The reviewers concluded that 3HP was neither inferior nor superior to INH in both efficacy (prevention of active TB and mortality) or safety. Concern was expressed at the early termination of a study aimed to examine pharmacokinetic drug-drug interactions between HP and dolutegravir[ix]. 3HP was considered to be an alternative to INH for TLTBI with the reservation that cost was comparable given the comparable efficacy and safety. Safety of HP and dolutegravir co administration was to be revisited once the results of an ongoing Phase I/II study in PLHIV were available.

5. Purpose/Objective i.e. PICO

P All PLHIV on ART in a high burden TB country
I: Short duration INH-rifapentine regimen
C: 12 months INH for all PLHIV on initiation of ART
O: TB disease post completion of TLTBI. All-cause mortality

6. Methods:

Search strategy:

A: October 2018 (initial):

i. *Search strategy A:*

- **a. Data sources:** World Health Organisation Guidelines website https://www.who.int/medicines/publications/en/
- **b. Search strategy** *'latent TB Guidelines'*

ii. *Search strategy B:*

- **c. Data sources: PUBMED**
- **d. Search strategy:** (Isoniazid-Rifapentine[All Fields] AND ("latent tuberculosis"[MeSH Terms] OR ("latent"[All Fields] AND "tuberculosis"[All Fields]) OR "latent tuberculosis"[All Fields] OR ("latent"[All Fields] AND "tuberculosis"[All Fields] AND "infection"[All Fields]) OR "latent tuberculosis infection"[All Fields])) AND Systematic Review[All Fields]

Two articles retrieved: i) systematic review/meta-analysis and ii) CDC summary update of recommendations – the latter was excluded as it was merely an overview of the systematic review/meta-analysis.

B: April 2019 (update):

a. *Since the previous review no new studies were found on PUBMED however we identified one recently published RCT [x], one new conference abstract[xi] and one review[xii].*

b. *Unlike the initial review that considered all 3HP TLTBI infections regardless of HIV status this review only considered studies of short course HP in PLHIV, 3 studies were considered, 2 which were included in the previous review and 1 new study.*

c. *Another systematic review and network meta-analysis looking at TB prophylaxis in general also addressed the role of rifapentine-based regimens.*

d. Evidence synthesis

Initial:

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Njie et al, 2018[ix]	Systematic review and meta-analysis	15 studies (RCTs, Observational studies)	Adults ≥ 12 years; children aged 2-11 years; PLWHVA	3HP vs other LTBI regimens: i.e.: 4-/6-/9-mo or continuous daily INH; 4-month RIF-INH; 4-moRIF; 2-3 mo RIF-PZA	<u>*Primary outcomes:*</u> •Prevention of TB disease. •Treatment completion <u>*Other outcomes:*</u> •Adverse events •Treatment discontinuation •Deaths	**<u>Primary outcomes:</u>** •*Prevention of TB disease:* 3HP vs other ltBI regimens – OR 0.89 (0.46, 1.70); I2=38% •*Treatment completion:* 3HP vs other LTBI regimens – OR 2.97 (2.10, 4.21);I2=63% **<u>Subgroup analyses:</u>** <u>Prevention of TB disease:</u> - PLWHA (2 RCTS): OR 0.74 (0.23, 43). **<u>Stratified analyses:</u>** <u>Prevention of TB disease:</u> - 3HP vs 6-mo INH: OR 1.09 (0.60, 1.99) - 3HP vs 9-mo INH: OR 0.47 (0.20, 1.12); I2=0% <u>Treatment completion</u> - 3HP vs 6-mo INH: OR 4.34 (2.36, 7.99) - 3HP vs 9-mo INH: OR 5.06 (2.31, 11.1); I2=92% <u>Adverse events:</u> - 3HP vs 6-mo INH: RR 0.68 (0.40, 1.15) - 3HP vs 9-mo INH: RR 0.46 (0.02, 1.71); I2=75%	Systematic review and meta-analysis showed that 3HP was as safe and effective as other LTBI regimens (including 9-mo INH). However, 3HP achieved higher treatment completion rates. Review had an '*a priori*' design and addressed series of clear questions. Analytical framework described the search strategy of a number of databases, though restricted to English language. Statistical analysis was appropriate. Review methodology, including the quality assessment of included studies, performed by 2 reviewers with disputes resolved through consensus, minimizing the potential for error and/or bias. Identified studies eligible for inclusion were reported, though most of the studies were observational cohort designs, increasing the risk of bias. There was significant heterogeneity between the studies with possible publication bias for studies assessing treatment completion. Other study limitations include: - most studies was for 3HP by DOT' - patient follow-up durations varied and long term durability not assessed. - most studies only assessed use in persons testing positive for LTBI. -confounding factors contributing to completion rates of shorter course 3HP not analysed (e.g.: socio-economic status; level of education; substance and drug abuse; etc).

						Treatment discontinuation: - 3HP vs 6-mo INH: RR 1.00 (0.25, 3.95) - 3HP vs 9-mo INH: RR 1.08 (0.66, 1.76); I2=28% Deaths: - 3HP vs 6-mo INH: RR 0.68 (0.37, 1.23) - 3HP vs 9-mo INH: RR 0.75 (0.47, 1.20); I2=0%	Overall, studies were of low to moderate methodological quality and should be interpreted with a degree of caution.
Pease et al, 2017[xii]	Systematic review with network meta-analysis	30 RCTs + 5 companion studies	Patients with confirmed LTBI Median value of average patient age was 34.7 (range 3.6–59.7) 2 RCTs enrolled only children 5 RCTs amongst HIV-infected 1 RCT in transplant patients 2 in patients with silicosis	3-4 H vs 6 H vs 9 H vs 12-72 H vs 3 HP vs 2/12's RIF+PZA vs 3/12's HR + PZA vs 3-4HR vs Placebo/no treatment	• *Treatment efficacy;* • *Treatment completion*	*Treatment efficacy:* - RE informative model suggested lower rate of active TB with each of the active regimens vs. control group, with benefits reaching statistical significance for all but 9 H and 3-4H.. - Comparisons between active regimens summarized in league table tabulated in order of decreasing SUCRA value, below (with no statistically significant differences between regimens); - Univariate meta-regression sensitivity analyses adjusting for average patient age, year of study publication, HIV infection, silicosis, transplantation; showed that the effect estimates were relatively unchanged.	Populations studied probably heterogeneous in their baseline risk of reactivation (Authors state that RCTs including 9 H had low rates of active TB in all arms suggesting a lower baseline risk of TB reactivation with a possible lower benefit from 9 H treatment). Acceptance rates amongst study participants not reported, noting that real-world data would be more informative. Assessment of treatment adherence varied between RCTs – methods included DOT, pill counts with/without self-reporting, electronic devices measuring timing of opening pill bottles and in some RCTs assessment modes differed in the comparator vs control arms. Few RCTs used DOT, except with 3HP, and thus treatment completion rates should be interpreted with caution. Adverse effects between treatments not analysed in this study.

			2 RCTs in prisoners			*Treatment completion* - RE informative model showed that overall, regimens of shorter duration more likely to show higher completion rates vs longer treatment courses.	

INH=isoniazid; RPT=rifapentine; RFMP=rifampin; PZA=pyrazinamide; RE=random effects; SUCRA= Surface Under the Cumulative Ranking.

INH 12-72mon								
0.83 (0.43 – 1.61)	**RIF/PZA-2**							
0.80 (0.44 – 1.50)	0.97 (0.44 – 2.16)	**INH/RIF-3/4**						
0.78 (0.35 – 1.66)	0.95 (0.36 – 2.30)	0.97 (0.44 – 2.03)	**INH/RIF/PZA-3**					
0.77 (0.36 – 1.72)	0.94 (0.40 – 2.28)	0.97 (0.46 – 2.07)	0.99 (0.40 – 2.70)	**INH/RPT-3**				
0.70 (0.41 – 1.16)	0.84 (0.42 – 1.61)	0.87 (0.49 – 1.47)	0.89 (0.44 – 1.83)	0.90 (0.42 – 1.82)	**INH-6**			
0.53 (0.18 – 1.91)	0.65 (0.20 – 2.49)	0.66 (0.23 – 2.30)	0.68 (0.21 – 2.84)	0.69 (0.28 – 1.97)	0.77 (0.27 – 2.73)	**INH-9**		
0.34 (0.16 – 0.67)	**0.41 (0.16 – 0.96)**	**0.42 (0.18 – 0.91)**	0.43 (0.18 – 1.07)	0.44 (0.16 – 1.07)	**0.49 (0.24 – 0.96)**	0.64 (0.15 – 2.04)	**INH 3/4**	
0.29 (0.17 – 0.49)	**0.36 (0.16 – 0.73)**	**0.37 (0.19 – 0.65)**	**0.38 (0.20 – 0.72)**	**0.38 (0.16 – 0.81)**	**0.42 (0.25 – 0.69)**	0.55 (0.15 – 1.63)	0.87 (0.44 – 1.73)	**PL / no trt**

League table comparing treatment efficacy of regimens from the RE informative model (Pease et al, 2017)
(Efficacy was treated as a binary endpoint (as opposed to a rate). Statistically significant differences between regimens are shown in bold, underlined font. Treatments are ordered from upper left to lower right in order of decreasing SUCRA value).

Guidelines:

WHO, 2018[i]	Guidelines for LTBI	AGREE II assessment of this Guideline showed general agreement between reviewers AB and TL of most domains. Consensus reached on using the guidelines (with possible adaptation).

Studies:

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**	**Effect sizes**	**Comments**
Martinson et al, 2011[xiii]	RCT	n=1 150 3 HP =328 6 H = 327	Adult PLHIV CD4> 200 Not on ART TST positive South Africa	3HP vs 3 RH vs 6H vs Continuous	*Primary outcomes:* • Active tuberculosis • Death *Other outcomes:* •Adverse events •Adherence	Active Tuberculosis: 3HP vs 6H RR= 1.05 (0.56-1.97) p=0.87 Death : 3HP vs 6H RR=0.66 (0.33-1.26) p=0.18 SAEs: 3HP 8.7%, 6H 15.4% p <0.05 Adherence 3HP 95.7% 6H 83.8%	Unblinded 3HP (900/900) administered via DOTS 6H (300) self-administered Uncertain how adherence to 6H was determined. Unusually high rate of SAEs in INH group Mean BMI = average weight (24.9) Post hoc analysis suggested INH provided protection for the total time on INH in the continuous INH arm which decreased shortly after INH stopped. All participants TST positive. Not on ART. 3 year follow up
Sterling et al, 2016 [xiv]	Unrestricted randomized open label non-inferiority trial	3HP =206 9H =193	PLHIV >2yrs, TST positive or close TB contact. USA, Spain, Brazil, Canada, Hong Kong, Peru	3 months of once-weekly rifapentine 600–900 mg (adjusted by weight above or below 50 kg) and isoniazid 15 mg/kg DOTS versus daily self-administrated isoniazid 5mg/kg for 9 months	*Primary outcomes:* •Active tuberculosis •Death *Other outcomes:* •Adverse events •Adherence	Active Tuberculosis: Per protocol analysis failed to show non-inferiority of 3HP. MITT demonstrated non- inferiority of 3HP Death : No difference p=1 AEs: Grade 3 p=0.36 Grade 4 p=0.1 Completion 3HP 89% 9H 64% % difference 25.0 (17.0. 33); p<0.001	Unblinded 3HP administered via DOTS 9H self-administered All participants TST positive or close contact. Not on ART while taking 3HP. Randomisation unrestricted. Included children (only 4 participants <18) Unable to recruit pre-determined numbers 33 months follow up Non-inferiority study showing that 3HP is not non-inferior to 9H, though only for the MITT analysis (minimizing attrition bias).

Swindells et al, 2019x	Randomized open label phase 3 non inferiority trial	2986 1HP = 1488 9H = 1498	PLHIV Age > 13yrs Africa, Asia, South America, North America Living in area TB prevalence > 60: 100 000 or positive for LTBI Neveripine or efavirenz based ART allowed	1 month daily H 300) P(300-600) versus 9H	Active TB. Death TB or unknown death Secondary outcomes Safety Side effects All cause mortality	MITT <u>TB incident rate/100 person yrs</u> HP 0.65 H 0.67 Difference -0,02 (-0.35 to 0.3) non inferiority upper limit <1.25 <u>Discontinuation or withholding due to toxicity</u> Prop OR favoring HP 2.09 (1.32 to3.33) <u>SAE Grade 3-5</u> p=0.07 HP NNH 20 H NNH 17 An analysis of the rates of combined grade 3 and 4 serious adverse events and targeted safety events over the entire follow-up period showed that fewer events occurred in the 1-month group than in the 9-month group (2.9 vs. 4.6 events per 100 person-years)(p = 0.01). <u>Completion</u> 1HP 97% 9H 90% p<0,01	Open label Adherence self-reported. 3.3 year follow up

The reviewed studies demonstrated short course HP either weekly for 12 weeks or daily for 1 month was non inferior to 6-9 months daily INH for the prevention of active TB and death, over approximately 3 year follow up. In the populations studied serious adverse events were more common in participants who received INH. INH safety data from South African studies: Thibela 24221 participants started INH: possible study defined AEs 0.54%. Rangaka no difference in number stopping study drug when comparing INH to placebo[v].

Recent updated review and network meta-analysis evaluated both comparative efficacy and safety of LTBI treatment regimens. However, evidence for hepatotoxicity was very limited and risk of bias very high or uncertain in many of the RCTs; so the table below should be interpreted with caution (suggesting that rifamycin/ rifamycin+isoniazid regimens had lower rates of hepatotoxicity)[x].

Table 2. ORs and Treatment Rankings for Hepatotoxicity, Derived From the Network Meta-analysis

Regimen	OR vs. Placebo (95% CrI)	OR vs. No Treatment (95% CrI)	Rank (95% CrI)
No treatment	0.24 (0.06-0.75)	1.00 (reference)	4 (2-7)
Placebo	1.00 (reference)	4.12 (1.33-15.88)	9 (7-10)
INH 6 mo	0.27 (0.10-0.60)	1.10 (0.40-3.17)	5 (3-7)
INH 9 mo	0.41 (0.08-1.62)	1.70 (0.35-8.05)	6 (3-10)
INH 12-72 mo	0.66 (0.26-1.32)	2.72 (0.96-7.44)	8 (6-10)
RPT-INH	0.13 (0.03-0.42)	0.52 (0.13-2.15)	2 (1-5)
RMP	0.03 (<0.02-0.16)	0.14 (0.02-0.81)	1 (1-2)
RMP-INH 3-4 mo	0.17 (0.05-0.46)	0.72 (0.21-2.37)	3 (2-6)
RMP-INH-PZA	0.58 (0.07-3.72)	2.41 (0.25-20.02)	7 (2-10)
RMP-PZA	0.80 (0.25-2.17)	3.32 (0.99-11.23)	9 (6-10)

CrI = credible interval; INH = isoniazid; OR = odds ratio; PZA = pyrazinamide; RMP = rifampicin; RPT = rifapentine.

Completion rates were higher for HP, MITT analysis factors the improved completion rates into the final results and while completion rates may be a process indicator, they are not, and should not be used as a surrogate for clinical outcomes.

The 3HP trials only included participants that were positive for LTBI or who were a close contact with a tuberculosis case, efficacy in LTBI negative persons unknown.

Pragmatic considerations:
Rifapentine induces CYP450 enzymes which may cause important drug interactions with multiple medicines, training on possible common drug interactions and alternatives will be essential prior to considering a roll-out of rifapentine. The DOLPHIN trial evaluated the safety and pharmacokinetics of DTG with 3HP in HIV-infected persons with latent TB infection, interim results were presented at CROI 2019 and it appears that the co-administration of DTG and HP may be safe, published final results are awaited[xi].

Rifapentine dosage needs to be weight adjusted and is not simply one dosage for all.

Fixed dose combination (FDC) formulation of rifapentine with isoniazid is not yet available as a registered product in South Africa, and pill burden may affect treatment adherence. Rifampicin and isoniazid is available locally as a FDC formulation and 3HR may be considered as an option to longer 12H[xiii].
There is currently one supplier of rifapentine, globally, but generic products are currently in development.

There is limited data of the safety of rifamycins in pregnancy.

Of the current short course HP regimens daily HP for 1 month is the simplest regimen.

Summary: There is reasonable evidence of comparable efficacy and safety of 3HP compared to current standard of care (12 H). However, rifapentine is expensive and price parity of 3HP to 12 H is recommended. Furthermore, preliminary data presented at CROI suggests that rifapentine is safe to administer with dolutegravir, but more data is required for drug-drug interactions of ARVs and rifapentine.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: x Not confident: Uncertain:	Randomised trials of moderate quality show HP to be non inferior to 6-9H
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: X Harms outweigh benefits: Benefits = harms or Uncertain:	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: No: X List the members of the group. n/a List specific exclusion from the group: n/a	Rationale for therapeutic alternatives included: 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:	
RESOURCE USE	**How large are the resource requirements?** More intensive: X Less intensive: Uncertain: *Incremental price = R 139.40 per patient*	**Price of medicines:** (1/12 = 28 days) **Medicine** / **Cost (ZAR)*** INH 300 mg daily x 9/12s — 158.58 INH 300 mg daily x12/12s — 211.44 INH-Rifapentine 900/900mg weekly x3months — 350.84** * Contract circular HP01-2019TB: INH 300 mg tablet, 28 = R17.62; Rifapentine 150mg tablet, 24 = R109.40, single 150 mg tablet = R4.558 ** Rifapentine 150 mg tablets, 72: R328.20 + INH 300 mg tablets, 36: R22.64 = R350.84 **Additional resources:** *n/a*
EQUITY	**Would there be an impact on health inequity?** Yes: No: Uncertain: X	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: No: Uncertain: X	

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 Level Committee recommended that a rifapentine-isoniazid regimen probably has similar efficacy and safety to the current INH recommendation and could be considered as an alternative TLTBI option in PLHIV on an efavirenz or raltegravir based ART regimen. Given the non-inferiority in efficacy and slightly improved safety profile, cost would need to be comparable to the current recommendation of 12H.

Rationale: Current evidence does not show superior efficacy of short course HP to 6-12H.

HP showed decreased adverse events when compared to 6-9H, the adverse event rates reported for INH in these populations are not consistent with the adverse event rates reported from other South African studies. The improved completion rates are already factored into the efficacy results for HP owing to MITT analysis, the improved rates shown did not translate into superior efficacy of HP over 6-9H.

Level of Evidence: I RCTs (moderate quality).

Review indicator: *Reduction in price*

Evidence of efficacy	Evidence of harm	Price reduction
x	x	X

VEN status:

Vital	Essential	Necessary

NEMLC MEETING OF 5 DECEMBER 2019

NEMLC accepted the proposal as reccomended by the Adult Hospital Level Committee, above. Until there is a reduction in price of rifapentine resulted in price parity between treatment regimens 12H and 3HP, rifapentine is considered unaffordable to include on the EML.

Monitoring and evaluation considerations:

- Completion rate in programmatic setting as a process indicator.
- Drug-drug interactions.
- TB incidence in PLHIV

Research priorities

- Results of ongoing trial looking at safety with dolutegravir.
- Durability of protective effect in high tuberculosis areas.
- Efficacy in persons on ART testing negative for LTBI.

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