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

EVIDENCE SUMMARY:

1. Executive Summary

Date: 11 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 DTG-containing regimen in a high burden TB country
Prevalence of condition: n/a
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): Dr J Nel
PTC affiliation: n/a

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

Jeremy Nel

3. Author affiliation and conflict of interest details

- *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.

4. Introduction/ Background

Latent TB affects approximately one third of the world, and 36-89% of South Africans, depending on precise exposure risk.[1-3] Treatment of latent TB can reduce the chances of developing active TB by 60-90% in HIV-negative patients, and by 32% in HIV-positive patients overall (and 72% in HIV-positive patients with a positive tuberculin skin test).[4, 5] While taking treatment for latent TB, the patient is also likely offered a degree of protection against developing active TB following a new exposure. One of the recommended regimens to treat latent TB is a combination of rifapentine and isoniazid, both given weekly.[6] However, there are concerns about possibly clinically-significant drug-drug interactions between rifapentine and dolutegravir. Dolutegravir is metabolised by CYP3A and UGT1A1, both enzymes that are induced by rifamycins such as rifapentine.

5. PICO analysis

-P *(patient/population): Adults taking dolutegravir (DTG)-based antiretroviral therapy*
-I *(intervention): Rifapentine + isoniazid weekly for 12 weeks ("3HP regimen").*
-C *(comparator): None.*
-O *(outcome):* dolutegravir drug level, rifapentine drug level, HIV viral failure rates, adverse events.

6. Methods:

a. Data sources *PubMed, CROI abstracts.*

b. Search strategy:

i. PubMed: ((Drug-Drug[All Fields] AND Interactions[All Fields]) AND ("dolutegravir"[Supplementary Concept] OR "dolutegravir"[All Fields])) AND ("rifapentine"[Supplementary Concept] OR "rifapentine"[All Fields])

1 study retrieved (Brooks et al, 2018)

c. Evidence synthesis –

Author, date	*Type of study*	n	Population	Methods	Outcome	Comments
Brooks KM et al., 2018[7]	Phase I clinical trial	4 (before study termination)	Healthy volunteers	DTG 50mg daily for 4 days, then DTG (daily) + isoniazid and rifapentine (HP) + pyridoxine (weekly). PK analysis on days 4, 14, 18 & 19.	DTG area under the curve (AUC) after HP initiation decreased by 46% (90% CI 27-110%) on day 14 at 14% (55-129%) on day 19. Study stopped due to cytokine-mediated serious adverse events in 2/4 subjects (fever, hypotension, elevated transaminases).	Due to early termination, study underpowered, and AUC differences were not statistically significant. The 2 patients who developed the adverse events were both slow acetylateors of INH, and their INH AUC was 67-92% greater than historic controls.
Dooley KE, et al.[8] (DOLPHIN study)	Phase I/II	61 (in three groups).	HIV positive patients on efavirenz- or DTG-based ART with undetectable viral loads.	Patients switched to TLD (tenofovir, lamivudine, dolutegravir) if on efavirenz-based regimen, then given weekly HP for 12 weeks (INH dose = 900mg). DTG dose was 50mg daily for all participants. DTG drug levels measured at various time intervals (baseline, after 3rd HP dose, after 8th HP dose, additional sparse sampling). HIV viral load at baseline (DTG alone) week 11 (DTG+HP) and week 24 (4 weeks post-HP)	DTG trough concentrations were reduced by ~60%, but geometric means were all >300 ng/mL. AUC at weeks 3 and 8 were each 29% lower. Viral load at week 9 <40 copies/mL in all participants. One participant had 2,300 copies/mL at week 24, but resuppressed after adherence counselling. Drugs well tolerated overall. Only three grade 2/3 AEs, and no grade 4 AEs.	Target trough concentration for DTG likely >300 ng/mL – the mean was above this threshold at all times, though a minority of patients did fall below this. No patient fell below the IC_{90} for DTG, 64 ng/mL. Patient who had an unsuppressed viral load on one occasion did not have trough concentrations <300 at all. The syndrome of serious AEs described by Brooks et al. was not seen in this study. One patient developed a similar syndrome after the 3rd HP dose, but this quickly settled and did not recur on subsequent HP doses. This reaction was thought to possibly be a viral upper respiratory tract illness rather than a true hypersensitivity. Trial conducted in South Africa.

Evidence summary:

DOLPHIN trial's PK data suggests modest decreases in DTG AUC and trough concentrations. There were no episodes of raised viral loads while taking the HP, and the single patient who developed a raised viral load 1 month after completing HP was able to resuppress their viral load after counselling, suggesting that no clinically significant HIV resistance had developed. Importantly, all patients enrolling in the trial started with a suppressed HIV viral load, and so the effect of the modest reductions in DTG drug levels cannot be extrapolated to those with high viral loads. Patients with high HIV viral loads may require higher DTG levels to suppress their virus compared to the DTG level that patients with undetectable viral loads require to maintain their viral suppression. Longer-term follow-up (e.g. 12 months, 24 months) would additionally be helpful in helping to reassure that the modest DTG level reductions seen have no significant clinical outcomes.

The serious adverse event syndrome that stopped the initial study by Brooks et al was not seen in the later DOLPHIN study.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?
Confident [ ] Not confident [ ] Uncertain [X]</td><td>Preliminary results of the DOLPHIN study as a conference abstract was reviewed. Publication of the DOLPHIN study in peer reviewed journal would increase confidence in the study results.</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?
Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [X]</td><td>Long-term safety and efficacy data required.</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [X] No [ ]
List the members of the group.
12H</td><td>Rationale for therapeutic alternatives included:
References:</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>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 [ ] No [ ] Uncertain [X]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [X] Less intensive [ ] Uncertain [ ]
Incremental price = R 139.40 per patient</td><td>Price of medicines: (1/12 = 28 days)
<table><tr><th>Medicine</th><th>Cost (ZAR)*</th></tr><tr><td>INH 300 mg daily x 9/12s</td><td>158.58</td></tr><tr><td>INH 300 mg daily x12/12s</td><td>211.44</td></tr><tr><td>INH-Rifapentine 900/900mg weekly x3months</td><td>350.84**</td></tr></table>* Contract circular HP01-2019TB: INH 300 mg tablet, 28 = R17.62; Rifapentine 150mg tablet, 24 = R109.40</td></tr>
</table>

		** 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 [X] Uncertain [ ]	
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 concludes that in patients with suppressed viral load on DTG, 3HP could be considered as an alternative TLTBI option in PLHIV that are virally suppressed on a DTG-containing 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: Preliminary data, suggests that rifapentine has no impact on patients who are already virally suppressed. Co-administration of DTG and HP was well tolerated with no HP-related adverse effects of ≥ grade 3. Although HP decreased DTG bioavailability, which was associated with a modest decrease in trough levels, all trough levels but one were above the DTG IC90. All viral loads were suppressed and DTG can be co-administered with HP without dose-adjustment.

Level of Evidence: III Phase I/II study

Review indicator: *Reduction in price; evidence of efficacy and safety*

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:

Research priorities:

3HP in ART-naïve PLHIV iniated on DTG-containing regimen.Long-term studies investigating safety and efficacy.

References

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2. Ncayiyana JR, Bassett J, West N, Westreich D, Musenge E, Emch M, et al. Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study. BMC Infect Dis. 2016;16(1):661.
3. Hanifa Y, Grant AD, Lewis J, Corbett EL, Fielding K, Churchyard G. Prevalence of latent tuberculosis infection among gold miners in South Africa. Int J Tuberc Lung Dis. 2009;13(1):39-46.
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7. Brooks KM, George JM, Pau AK, Rupert A, Mehaffy C, De P, et al. Cytokine-Mediated Systemic Adverse Drug Reactions in a Drug-Drug Interaction Study of Dolutegravir With Once-Weekly Isoniazid and Rifapentine. Clin Infect Dis. 2018;67(2):193-201.
8. Dooley KE CG, Savic RM, Gupta A, Marzinke M, Zhang N, Edward V, Wolf L, Sebe M, Likoti M, Fyvie M, Shibambo I, Beattie T, Chaisson RE. Safety & PK of weekly rifapentine/isoniazid (3HP) in adults wiht HIV on dolutegravir. CROI; Seattle, USA. 2019.