South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Isoniazid Preventive Therapy

1. Executive Summary

Date: 11 November 2018
Medicine (INN): Isoniazid
Medicine (ATC): J04AC01
Indication (ICD10 code): Isoniazid preventive therapy (Z79.2)
Patient population: Persons living with HIV on antiretroviral therapy
Level of Care: Primary level of care
Prescriber Level: Nurse practitioner
Current standard of Care: 12 months INH for all PLHIV on initiation of ART
Efficacy estimates: (preferably NNT)
- *NNT to avert 1 TB case= 33*[6]
- *NNT to avert 1 death= 32*[7]

Motivator/reviewer name(s): Andrew Black, Halima Dawood
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2. Name of author(s)/motivator(s) Andrew Black

Primary reviewer: Andrew Black
Secondary reviewer: Halima Dawood

3. Author affiliation and conflict of interest details:

Primary reviewer: Department of Medicine Helen Joseph Hospital and University of the Witwatersrand; Adult Hospital Level Committee (2017-2019). No conflict of interest to declare.
Secondary reviewer: Greys hospital and Caprisa, UKZN; Adult Hospital Level Committee (2017-2020). Conflict of interests: Pfizer- SA Pneumococcal summit attendance; MSD: SAASP - Attendance of meetings; MSD: ECMID - Conference attendance; ACTA study- DSMB member; Adcock Ingram & Novartis - Speaker fees; IDSSA – President elect; HpCA – Ethics Committee member.

4. Background

Tuberculosis is the leading cause of morbidity and mortality in South Africa. HIV infection is a strong risk factor for TB disease, and active TB increases viral replication with resultant progression of HIV disease. Isoniazid preventive therapy (IPT) has been shown to reduce active TB disease in PLHIV[1].

Current guidelines are based on evidence developed prior to the widespread and early use of ART in PLHIV. The evidence from randomized controlled trials is consistent and shows an overall 35% risk reduction (RR 0.65; 95% CI (0.51,0.84)). The benefit of IPT in PLHIV not on ART has only been found to be significant in Tuberculin Skin Test (TST) positive patients, (pooled RR 0.48; 95% CI (0.29,0.82)) with no significant effect of IPT being shown in TST negative or TST status unknown patients[2].

The lack of information on efficacy of IPT in TST negative PLHIV not on long term ART has complicated IPT guidelines. Shortages of PPD and other health system issues as to why a TST cannot be done has resulted in a treat all strategy. IPT while having a clear benefit to the individual has not been shown to have any long term population effect even when used as a mass preventative therapy.[3] The cost effectiveness and ethics of giving a treatment with known adverse effects (no matter how rare) to a majority of PLHIV where there is no proven individual benefit may be one of the reasons that IPT roll out has been slow.

Another confounding factor has been the variable durability of the benefit of IPT once the course is completed with the protective effect waning with time which may be related to the burden of TB and risk of re infection[1]. In pre HIV studies the protective effect of IPT has been shown to persist for up to 19 years despite very high TB incidence[4].

With immune restoration following ART initiation there is a decrease in the risk of TB disease in PLHIV, the decreased risk is related to the degree of immune restoration although it never returns to the background population risk even at CD 4 cell counts >500 cells/ul [5].

The roll out of ART for all PLHIV and the resultant improved immunity may influence the efficacy and durability of IPT.

This review aims to determine the evidence for IPT and its administration in PLHIV either starting or already on ART.

5. Purpose/Objective i.e. PICO question

P: All PLHIV on ART or starting ART (IPT naïve)
I: INH of any duration
C: 12 months INH treatment
O: All cause mortality, TB disease.

6. Methods:

a. Search strategy:

Medline via Pubmed and the Central Cochrane library were searched, with the following search terms.

(((((((("hiv"[MeSH Terms] OR "hiv"[All Fields]) OR human immunodeficiency virus [Abstract]) AND tuberculosis[Abstract]) AND inh[Abstract]) OR isoniazid[Abstract]) AND preventive therapy[Abstract]) OR ipt[Abstract]) AND ART[Abstract]) OR antiretrovirals[Abstract] AND randomized

251 articles were identified by the search terms. The titles were reviewed to identify relevant articles. 20 full text articles were reviewed of which 4 met the inclusion criteria – randomized controlled trials, PLHIV on ART, IPT and outcomes of either: TB incidence, TB mortality or all-cause mortality.

b. Evidence synthesis and quality

Table 1: Summary of included studies/systematic reviews and meta-analysis: Active medicine compared to placebo and head to head

Author, date	Type of study	n	Population	Comparators	Outcomes: primary and secondary	Effect sizes	Comments
Rangaka et al, 2014[6]	Randomised double-blind placebo-controlled trial	n=1 329 (3 227 person years)	Adult ART clinic attendees either established on ART or newly on ART. CD4 count 216; IQR 152 to 360	Daily self-administered INH versus placebo	*Primary:* • All TB incidence. • Effect by TB infection status at enrolment. *Secondary:* • All-cause mortality. • Drug toxicity.	*Primary:* • Incident TB: aHR 0.64, (95% CI 0.42 to 0.96) *Secondary:* • All-cause mortality: HR 0.72, (95% CI 0.34 to 1.34) NNT to prevent 1 case TB: 25 (as reported in the paper however this could not be reproduced with the reported data **NNT = 33** (see appendix 1) **NNH: 100**	Modified ITT analysis. Conducted in South Africa Sufficient power for difference detected in incident TB. Reported NNT not reproducible with reported data Under powered for effect by TB infection status at enrolment. No follow up of negative TB status tests to distinguish between immunodeficiency related anergy or "true" negative Insufficient power to demonstrate formal interaction by time period LTF was 11% in each arm. Number lost to follow up ((n=142) was greater than the number of participants who developed incident TB (n=95) No statistically significant difference in adverse events between INH and placebo groups. Follow up of 2.5 yrs (IQR 2.1 to 3.1) **Note**: This study was done in local setting.
Danel,2015[7]	Unblinded, multicenter, individual-randomised, controlled, 2-by-2 factorial, 1:1 superiority trial	n = 2076 2383 and 2375 person years	Adults HIV infected. CD4 < 800 not eligible for ART under WHO guidelines at the time. Attending 9 care centers in Abidjan	<u>Group 1:</u> Deferred ART <u>Group 2:</u> Deferred ART plus IPT <u>Group 3:</u> Early ART <u>Group 4:</u> Early ART plus IPT	• Composite end point: AIDS diseases, non-AIDS defining cancer, non AIDS defining invasive bacterial disease or death from any cause. • Grade 3 or 4 adverse events.	• Incident TB :IPT vs no IPT aHR 0.44; 95% CI 0.28 to 0.69 **NNT to prevent 1 case of TB = 33** (26 events in 1030 participants receiving IPT vs 57 events in 1026 participants not on IPT) • Death: IPT vs no IPT aHR 0.60 (0.34-1.09)Grade 3 or 4 adverse events IPT vs no IPT HR 0.86; 95% CI 0.52 to 1.42	Open label study. Follow up of 30 months. LTFU 3% with no differences between arms. Composite end point but most frequent primary end point event was TB: 42% IPT and ART had an additive efficacy with respect to the prevention of TB No significant interaction between ART and IPT (p=0.45) First 936 participants randomized underwent IGRA tests as per protocol. Statistical

							significant efficacy of IPT against incident TB was limited to the IGRA positive participants
Badje et al, 2017[8]	Post-trial follow up of Temprano RCT (5 above)	n= 2056 (9404 person years)	Post 30 month follow up of patients from Temprano	<u>Group 1:</u> Deferred ART <u>Group 2:</u> Deferred ART plus IPT <u>Group 3</u>: Early ART <u>Group 4:</u> Early ART plus IPT	All-cause mortality	• aHR for death IPT vs no IPT 0.61; 95% CI 0.39 to 0.94 (adjusted for ART strategy, baseline CD4 cell count and other key characteristics) **NNT to avert 1 death= 58** (34 out of 1030 in IPT groups vs 54 out of 1026 in no IPT groups)	LTFU overall 14.7% no difference between IPT vs no IPT strategy Background incident TB: • Cote d'Ivoire 159/100000 • No evidence for statistical interaction between IPT and ART (P= 0.077) or IPT and time (P=0.94). Benefit persisted for up to 6 years. • Sub analysis based on QTF-GIT status no statistical interaction between result of QTF-GIT test at baseline and IPT strategy with regards to mortality P = 0.96 • Efficacy of IPT on mortality maximal during early follow-up in QTF-GIT positive, and during late follow-up in those with negative QTF-GIT tests. • Overall mortality appeared to be lower in patients who had a positive baseline QTF-GIT test. (QTF-GIF test = QuantiFERON-TB Gold In-Tube test)
Hakim et al, 2017[9]	Open – label factorial design 1:1 randomisation	n=1805	HIV infected adults and children> 5yrs of age, from 8 periurban and urban centres. ART naïve. CD4<100	ART and CTX vs ART, INH (12/52) fluconazole (12/52), azithromycin 5/7, albendazole stat and CTX	*<u>Primary:</u>* 24 week mortality *<u>Secondary:</u>* • TB mortality • TB incidence • Adverse reactions	• 24 week mortality enhanced prophylaxis vs standard prophylaxis: HR 0.73; 95% CI 0.55 to 0.98) (effect of each individual component could not be assessed. • TB incidence lower in enhanced prophylaxis group (p=0.02) • TB mortality 48 weeks no difference between groups (p=0.72) • Adverse events no difference between groups (p=0.08)	Open label multicenter trial. Intervention: package of prophylaxis, and benefit of INH specifically cannot be clearly assessed. Short duration of INH therapy and short period of follow up time.

7. Discussion:

Benefit of IPT: The current evidence from randomized control trials demonstrates that IPT in conjunction with ART is protective against incident TB across the ranges of CD4 cell counts[6,7,9] . A mortality benefit was shown for persons with high CD4 cell counts receiving IPT, this mortality benefit only became statistically significant after long term follow up, the mortality benefit was seen in in both baseline IGRA positive and IGRA negative participants[8]

Adverse events: There was no significant increase in drug related adverse events seen in patients receiving both INH and ART[6,7,8,9].

Duration of IPT: The exact duration of INH and the durability of IPT remains uncertain. In an area with high TB incidence 6 months INH offered durable efficacy (measured as mortality benefit) up to 6 years[8]. In an area with "very" high incident TB;, efficacy appeared to wane over time however this trial was not powered to determine treatment duration effect[6]. In the Rangaka paper the majority of participants were already on ART at the time of starting IPT and it can not be determined if a PLHIV requires ART for a certain period of time to restore immunity in order to receive maximal benefit of IPT.

Timing of IPT: Rangaka et al started IPT in persons established on ART (median days on ART 357 IQR 139-798) and soon after in persons starting ART (median days on ART 14 IQR 4-25)[6], in the Temprano trial persons start IPT after 30 days on ART[7], in the Reality trial IPT was started with ART[9].

TST/IGRA status: The study by Rangaka et al, was not powered for this analysis, although significant benefit for protection against incident TB was seen in the TST and IGRA negative participants the finding that no significant benefit was seen in IGRA and TST positive participants suggests this finding is due to chance.

Danel et showed the efficacy of IPT in prevented incident TB was restricted to the IGRA positive participants. However in the long term follow up of the Temprano participants the mortality benefit of IPT was shown for both IGRA positive and IGRA negative participants[8].

Given the mortality benefit demonstrated for IPT despite baseline TB infection status, as measured by TST or IGRA, baseline TB status testing may not need not be a prerequisite for IPT in PLHIV on ART.

Repeat courses: No evidence for repeat courses of IPT was found in the literature.

Secondary prophylaxis: No evidence for secondary prophylaxis in PLHIV on ART was found.

8. Conclusion:

INH prophylaxis decreases incident TB[6,7] and all cause mortality[8] in PLHIV starting ART or on ART across the spectrum of CD4 cell counts. IPT has been shown to decrease long term mortality independent of baseline TB status[8]. The combination of IPT and ART did not cause a significant increase in adverse events in the reviewed trials. The only trial that had sufficient statistical power to comment on durability showed a mortality benefit up to 6 years post 6 months of INH, a limitation of this study for decision making in South Africa is the lower rate of TB in the study population and higher CD4 cell counts[7,8]. Despite this limitation there is currently no robust RCT evidence for a longer course of IPT in PLHIV on ART.

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:	IPT has been shown to decrease incident TB in PLHIV on ART across the CD4 cell count range. Mortality benefit at higher CD4 cell counts. No increase in adverse events. Not confident of ideal duration in a high TB incident population.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: x Harms outweigh benefits: Benefits = harms or Uncertain:	No increased adverse effects shown in the reviewed trials although monitoring recommended.
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the outcomes?** Minor: Major: Uncertain: X **Is the option acceptable to key stakeholders?** Yes: No: Uncertain: x	
RESOURCE USE	**How large are the resource requirements?** More intensive: Less intensive: x Uncertain:	**Cost of medicines:** Medicine: INH 300 mg daily x 6/12's — Cost (ZAR): 109.10 Medicine: INH 300 mg daily x 12/12's — Cost (ZAR): 218.19 * Contract circular RT278-2017: INH 300 mg tablet = R0.6061 **Additional resources:** n/a
EQUITY	**What would be the 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 Level Committee recommends a single six month course of INH within one month of initiating ART independent of CD4 cell count or TST status. However, NEMLC did not accept this recommendation (see below), and the previous NEMLC recommendation of 12 months IPT in PLHIV was retained, until further evidence is forthcoming.

Rationale: Evidence of efficacy and safety with decreased TB incidence rate[6,7,9]. Patients already on ART who have never received IPT have also been shown to benefit from IPT[6] (see discussion section above: benefit of IPT). Badie *et al* showed that 6 months provided sustained mortality benefit up to 6 years post treatment, and this benefit was shown in both IGRA positive and IGRA negative patients.[8] As the mortality benefit was shown in patients with high CD4 cell counts[8] a cut off CD4 cell count above which IPT is not required can not be given.

Level of evidence: I RCTs

NEMLC MEETING OF 21 FEBRUARY 2019:

Isoniazid Monotherapy

Available evidence for IPT in PLHIV: Most of the evidence for isoniazid prevention therapy (IPT) in people living with HIV (PLHIV) was from the pre-ART era. Two RCTs done in PLHIV: i) RCT in Khayelitsha by Rangaka et al, 2014[6] of PLHIV either starting or established on ART comparing 12 months of isoniazid vs placebo; ii) Temprano RCT by Danel et al, 2015[7], where IPT; ART and IPT+ART were evaluated either starting early or late.

Previous NEMLC recommendation: In the PHC STGs and EML, 2018 IPT was simplified to 12 months, from the previous complex algorithm requiring TST, based on the Khayelitsha RCT.
Evidence for 6 months IPT: The Adult Hospital Level Committee's recommendation to change duration of IPT to 6 months based on a mortality benefit from the Temprano RCT, raised a concern. The Temprano RCT was done in West Africa, where the incidence of TB is lower compared to South Africa. It was stated that greater mortality benefit of 6 months IPT compared to 12 months IPT was biologically implausible, unless IPT is very toxic, however this is not the case.
Network meta-analysis of individual patient data (including South African data) is currently underway in the USA which should further inform decision-making on duration of IPT in PLHIV.
WHO recommendation of 36 months was discussed, noting that the evidence base was from the pre-ART era. IPT with ART was reported to be more durable than IPT without ART.

Recommendation: Previous NEMLC recommendation of IPT in PLHIV be retained as 12 months duration, until further evidence is forthcoming.
Rationale: Biologically plausible that 12 months rather than six months IPT would have greater benefit. Despite the lack of data comparing duration of IPT therapy, available evidence in the local South African setting suggests that 12 months IPT would be reasonable.
Level of Evidence: I RCT

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	x	

VEN status:

Vital	Essential	Necessary
	X	

M & E considerations: Adverse events

Further research needed:

1) Timing of IPT
2) Duration of IPT in high TB incident areas
3) Durability of IPT in high TB incident areas
4) IPT post TB treatment in PLHIV on ART

References

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APPENDIX I

Table S4 Number needed to treat to benefit vs. harm

Endpoint	Non-cases	Cases	Absolute Risk	Absolute Risk Difference (95% CI)	Number needed to treat
All tuberculosis					
Placebo	609	58	0.10		
Isoniazid	625	37	0.06	0.04 0.03-0.06	*25
§Stopping drug for adverse events					
Placebo	649	18	0.03		
Isoniazid	635	27	0.04	0.01 0.004 - 0.04	**100

*Number needed to treat to benefit one individual and **Number needed to treat to harm one individual: [1 / Absolute Risk Difference]. §Stopping for any of grade 3/4 ALT, clinical hepatitis, new or worsening grade 2 or more rash or peripheral neuropathy

	E (IPT)	**C (no IPT)**
Events	EE = 37	CE = 58
No event	EN = 625	CN = 609
Total (S)	ES = EE+EN ES = 37 + 625 ES = 662	CS = CE + CN CS = 58 + 609 CS = 667
Event rate (ER)	EER = EE/ES EER = 37/662 EER = 0.0558912387 EET rounded to two decimal points = 0.06	CER = CE/CS CER = 58/667 CER = 0.0869565217 CER rounded to two decimal points = 0.09
ARR	ARR = CER – EER ARR = 0.09 – 0.06 ARR = 0.03	
NNT	NNT = 1/ARR NNT = 1/0.03 NNT = 33.33 NNT nearest whole number = 33	