The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis

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Studies report conflicting links between isoniazid preventive therapy (IPT) and adverse pregnancy outcomes. Given known harms of active TB in pregnancy, the findings do not support systematic deferral of IPT until postpartum. We need more safety research. http://bit.ly/2R0Wc3G

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ABSTRACT

Background: The World Health Organization (WHO) recommends tuberculosis (TB) preventive treatment for high-risk groups. Isoniazid preventive therapy (IPT) has been used globally for this purpose for many years, including in pregnancy. This review assessed current knowledge about the safety of IPT in pregnancy.

Methods: We searched PubMed, Embase, CENTRAL, Global Health Library and HIV and TB-related conference abstracts, until May 15, 2019, for randomised controlled trials (RCTs) and non-randomised studies (NRS) where IPT was administered to pregnant women. Outcomes of interest were: 1) maternal outcomes, including permanent drug discontinuation due to adverse drug reactions, any grade 3 or 4 drug-related toxic effects, death from any cause and hepatotoxicity; and 2) pregnancy outcomes, including *in utero* fetal death, neonatal death or stillbirth, preterm delivery/prematurity, intrauterine growth restriction, low birth weight and congenital anomalies. Meta-analyses were conducted using a random-effects model.

Results: After screening 1342 citations, nine studies (of 34 to 51 942 participants) met inclusion criteria. We found an increased likelihood of hepatotoxicity among pregnant women given IPT (risk ratio 1.64, 95% CI 0.78–3.44) compared with no IPT exposure in one RCT. Four studies reported on pregnancy outcomes comparing IPT exposure to no exposure among pregnant women with HIV. In one RCT, adverse pregnancy outcomes were associated with IPT exposure during pregnancy (odds ratio (OR) 1.51, 95% CI 1.09–2.10), but three NRS showed a protective effect.

Conclusions: We found inconsistent associations between IPT and adverse pregnancy outcomes. Considering the grave consequences of active TB in pregnancy, current evidence does not support systematic deferral of IPT until postpartum. Research on safety is needed.

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Introduction

Pregnant women with HIV have a high risk of acquiring tuberculosis (TB), which can have severe consequences for both mother and fetus [1]. Isoniazid has a well-documented safety profile established from its long history of use in pregnant and breastfeeding mothers treated for both latent and active TB.

The 2011 World Health Organization (WHO) guidelines recommend isoniazid preventive therapy (IPT) in people living with HIV regardless of pregnancy [2]. These guidelines and the 2018 guideline on latent tuberculosis infection (LTBI) advise caution and clinical judgement when deciding the best time to start LTBI treatment in pregnant women [3]. Pregnancy and the postpartum period is a risk factor for drug-induced hepatotoxicity [4] and, although evidence is insufficient, the WHO encourages clinical monitoring as well as baseline liver function tests where feasible for these groups [3].

A recent clinical trial reported more frequent adverse pregnancy outcomes among women with HIV exposed to IPT during gestation [5]. The study also reported higher frequency of maternal adverse events (AEs) than expected. To date there has been no systematic review which has investigated the safety of IPT among pregnant women. Therefore, we have conducted this systematic review to assess the safety of IPT in pregnant and postpartum women compared to other preventive treatment regimens or no treatment.

Material and methods

Search strategy

We performed a systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [6] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [7]. The protocol for this review is registered on PROSPERO (CRD42019136065, www.crd.york.ac.uk/prospero/).

We searched the following databases from inception to May 15, 2019: MEDLINE (PubMed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Global Health Library. Furthermore, we reviewed databases listing ongoing randomised controlled trials (RCTs) through ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. We developed the search strategy in consultation with a librarian (see appendix 1 in the supplementary material) and searched the following major HIV and TB conferences: the International AIDS Conference, the International AIDS Society (IAS) Conference on HIV Science, the Conference on Retroviruses and Opportunistic Infections, the UNION World Conference on Lung Health, the European Respiratory Society (ERS) Congress and the American Thoracic Society (ATS) Conference. The International AIDS Conference and the IAS Conference of HIV Science were searched for all available years (2002–2019), while, for the Conference on Retroviruses and Opportunistic Infections, the UNION World Conference on Lung Health, the ERS Congress and the ATS Conference, only conferences from the last 3 years were searched. We did not impose any language or geographic restrictions. Bibliographies of included articles were screened and we contacted experts and authors of relevant studies to retrieve relevant study information.

Study eligibility and data extraction

Two reviewers independently screened study titles and abstracts identified by the search for inclusion. The full text was then screened by the same pair of reviewers and eligibility was assessed. Any disagreements were resolved through discussion.

Studies were included when 1) the study population included pregnant or postpartum women (defined as within 12 months of delivery) regardless of HIV status; 2) the intervention was preventive treatment with daily isoniazid alone for 6 months or longer; 3) the comparator was another preventive treatment regimen or no preventive treatment (including deferred provision until postpartum in a comparison group); 4) the outcomes included permanent drug discontinuation due to an adverse drug reaction, any Grade 3 or 4 drug-related toxic effect, death from any cause, hepatotoxicity, *in utero* fetal death, neonatal death, preterm delivery/prematurity, intrauterine growth restriction, low birth weight or congenital anomalies; and 5) the study design was an RCT or a non-randomised study (NRS). We initially intended to exclude studies without a comparison group; however, we eventually included them due to the limited number of studies identified. We excluded studies that included participants with active TB or those who were exposed to multidrug-resistant TB (MDR-TB) or isoniazid-resistant TB.

Data were extracted independently by two reviewers using standardised extraction forms, as follows: study design, total duration and date of study, and study context (setting, location); number of participants, age, race, ethnicity, body mass index (BMI), body weight, education history, HIV status (plus antiretroviral status, CD4 count and viral load), obstetric history, inclusion criteria, exclusion criteria, comorbidities, results of tuberculin skin tests and interferon-γ releasing assays, and contact history; type of intervention,

comparison, concomitant medications and outcomes. Any disagreements were resolved by consensus and authors were contacted for missing data.

Quality of individual studies and evidence assessment

For the risk of bias in individual studies, we used the revised Cochrane Risk-of-Bias tool (RoB2) for RCTs [8] and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for NRS [9]. Grading of recommendations assessment, development, and evaluation (GRADE) methodology was used to assess and appraise the quality of evidence for each outcome across all studies [10]. We made an overall judgement on the quality of evidence across RCTs and NRS separately. When ROBINS-I was used, the initial rating of the certainty of evidence was assigned as high rather than low and was subsequently rated down, as recently recommended by the GRADE working group [11].

Statistical analysis and meta-analysis

Relative risks for dichotomous data were presented with 95% confidence intervals (CI). Meta-analysis was conducted with a random effects model using the method of DerSimonian and Laird [12] if the included studies were sufficiently clinically homogenous. When at least one study included zero events in one group, the Mantel–Haenszel method was used without continuity correction. Due to inconsistency in the direction of effect indicating a significant heterogeneity by study type, data from RCTs and NRS was not pooled. For NRS, adjusted estimates were pooled and, if unavailable, unadjusted estimates were pooled; however, unadjusted and adjusted estimates were not pooled together. Data was presented by HIV status, by pregnancy or postpartum status and by preventive treatment regimen given to the control group; however, the limited number of studies precluded meta-analysis by subgroup. Forest plots were used to visually assess heterogeneity among the included trials. Unfortunately, the small number of studies precluded a sensitivity analysis.

Results

From 1342 records identified, nine studies met our inclusion criteria, including two conference abstracts (figure 1) [4, 5, 13–19]. Six studies included only women with HIV [5, 13, 15–17, 19] and three included very few or no HIV-positive women [4, 14, 18]. Of the six studies among HIV-positive women, five were conducted in African countries [13, 15–17, 19] and one was conducted in multiple countries with high TB prevalence (⩾60 per 100 000 population) [5]. Eight studies were NRS, with three reporting data among women who were enrolled in trials of different preventive treatment regimens and who became pregnant during those trials [14, 17, 19]. Four included pregnant women started on IPT [4, 13, 15, 16] and one included postpartum women [18]. The remaining study was a RCT comparing pregnant women with HIV who started 6 months of IPT immediately upon enrolment and those who deferred it until 12 weeks postpartum [5]. Study characteristics are summarised in table 1.

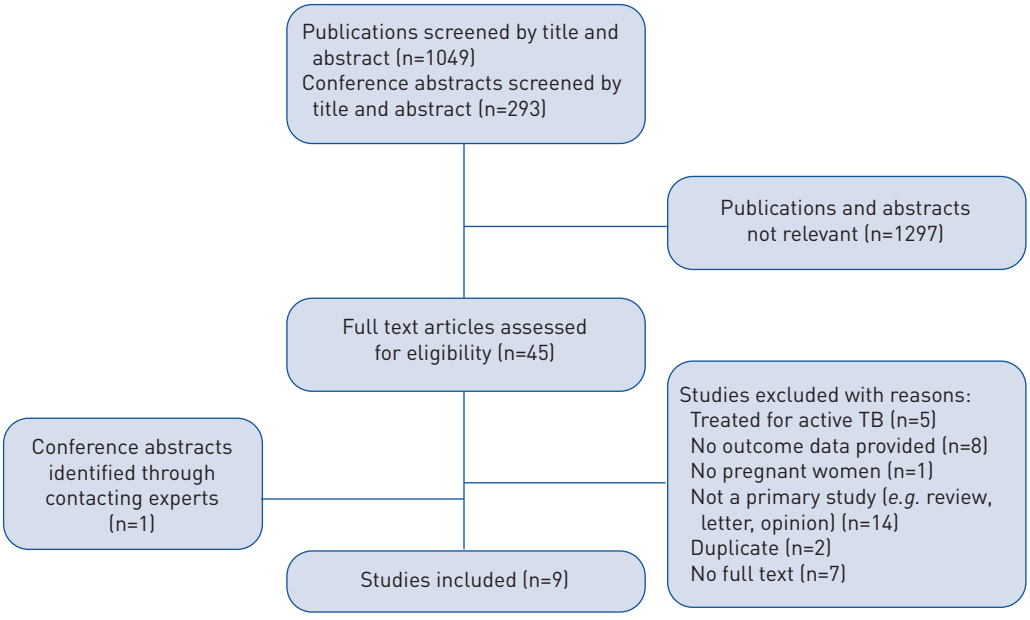

FIGURE 1 PRISMA flow diagram for the review.

TABLE 1 Characteristics of included studies

First author	Study design	Setting	Population	Isoniazid arm	Comparison
Chang *et al.* [18]	Retrospective cohort	A TB referral centre, USA	LTBI patients who began isoniazid treatment (including 228 postpartum women)	6–9 months of isoniazid (n=228)	No control group who were given no or other regimens
Gupta *et al.* [5]	RCT	Eight countries with high TB prevalence (⩾60 per 100 000 population)	HIV-infected pregnant women (⩾18 years old, 14–34 weeks gestation and 99.8–100% on cART)	Immediate isoniazid, started at study entry and continued for 28 weeks (n=477)	Deferred isoniazid, started at 12 weeks postpartum and continued for 28 weeks (n=479)
Franks *et al.* [4]	Retrospective cohort	A clinic, USA	Women enrolled during the first 18 months of the prenatal IPT programme	6–12 months of isoniazid (n=3681)	No control group who were given no or other regimens
Kalk *et al.* [15]#	Retrospective cohort	Routine electronic clinical information systems from public sector health facilities, Western Cape, South Africa	HIV-infected women on or initiating cART during pregnancy (41.8% newly initiated on cART and the rest already on cART)	Isoniazid duration unknown, based on "prescription" in the electronic record (n=10 715)	No treatment (n=41 227)
Msandiwa *et al.* [19]#	Sub-analysis of RCT	A hospital, South Africa	Women with HIV who became pregnant during the trial	6 months or continuous isoniazid (n=26)	3-month rifampicin or 3HP (n=8). Switched to isoniazid alone or discontinued
Moro *et al.* [14]	Sub-analysis of two RCTs	TBTC 26 and 33 (USA, Canada, Brazil, Spain, Peru, South Africa and Hong Kong)	Women who became pregnant during the trial	9 months isoniazid (n=56)	3HP (n=31), no exposure (n=39)
Salazar-Austin *et al.* [13]	Prospective cohort	Antenatal clinics and obstetrics wards at a Hospital, South Africa	Pregnant women with HIV (⩾18 years old, 66–78% on cART)	6 months isoniazid (median gestational age at initiation 25 weeks, IQR 20–30 weeks) (n=71)	No isoniazid (n=84)
Taylor *et al.* [17]	Sub-analysis of RCT	Clinics, Botswana	Women with HIV (⩾18 years old, became pregnant during the trial, 37% on cART and the rest on AZT or AZT/3TC)	6–36 months isoniazid (n=103)	No exposure (n=93)
Tiam *et al.* [16]	Prospective cohort	Two hospital-based maternal and child health clinics, Lesotho	Pregnant women (⩾14 years old with HIV, presented for their first antenatal clinic visit irrespective of their gestational age, 36.2% on cART and the rest on AZT prophylaxis)	6 months of isoniazid (n=124)	No control group who were given no or other regimens

RCT: randomised controlled trial; TB: tuberculosis; TBTC: Tuberculosis Trials Consortium; LTBI: latent tuberculosis infection; IPT: isoniazid preventive therapy; cART: combination antiretroviral therapy; AZT: zidovudine; 3TC: lamivudine; IQR: interquartile range; 3HP: 3-month weekly rifapentine plus isoniazid. #: conference abstracts.

Maternal outcomes

Four studies reported data on hepatotoxicity in pregnant women with HIV [5, 15–17], five studies reported deaths [5, 13, 15–17], two studies reported Grade 3 or 4 AEs [5, 16] and one study reported treatment discontinuations [5] (supplementary tables S3–S5). The RCT by Gupta *et al.* [5] reported the highest frequency of hepatotoxicity (6.1% in the immediate IPT arm and 7.1% in the deferred IPT arm), while Karl *et al.* [15] reported only 0.3% and two other NRS reported none. Frequency of deaths ranged from none to 2% across studies.

Gupta *et al.* [5] provided data on hepatotoxicity compared to placebo by restricting to "events that occurred until 3 months postpartum", before the control group was started on IPT (table 2). On analysis, the frequency of hepatotoxicity was higher in women living with HIV who were given IPT during

TABLE 2 Hepatotoxicity in pregnant women living with HIV

Study	IPT	Control	Risk ratio (95% CI)
Gupta *et al.* [5]	18 out of 477 (3.8%)#	Placebo 11 out of 479 (2.3%)#	1.64 (0.78–3.44)
Kalk *et al.* [15]	30 out of 10715 (0.3%)	No treatment 114 out of 41227 (0.3%)	1.01 (0.68–1.51)
Tiam *et al.* [16]	0 out of 124 (0%)	NA	NA
Taylor *et al.* [17]	0 out of 103 (0%)	NA	NA

IPT: isoniazid preventive therapy; CI: confidence interval; NA: not available. #: the analysis was restricted to events that occurred until 3 months postpartum. Some women were still on IPT and were censored.

pregnancy (18 out of 477, 3.8%) compared to those given a placebo (11 out of 479, 2.3%); however, this difference was not statistically significant (risk ratio 1.64, 95% CI 0.78–3.44) [5]. Kalk *et al.* [15] did not find any difference in frequency of hepatotoxicity between the two groups.

Three studies reported maternal death in pregnant women with HIV who received IPT compared to those who did not [5, 13, 17] (table 3). The RCT did not show a statistically significant difference in the risk of death between the two groups [5]. Meta-analysis of two NRS suggested a lower risk of death in pregnant women with HIV given IPT (risk ratio 0.65, 95% CI 0.39–1.07).

The RCT [5] provided data on Grade 3 or 4 AEs and treatment discontinuations in pregnant women with HIV given IPT compared to those given a placebo. There was no statistical difference in the frequency of treatment discontinuation between the two groups (2.3% *versus* 1.7%; risk ratio 1.38, 95% CI 0.56–3.40). However, there was a higher risk of Grade 3 or 4 AEs in participants given IPT (7.1% *versus* 4.6%; risk ratio 1.55, 95% CI 0.92–2.61).

For HIV-negative pregnant women, Moro *et al.* [14] reported data on Grade 3 or 4 AEs, hepatotoxicity and deaths in pregnant women on IPT (n=56) and those on 3-month weekly rifapentine plus isoniazid (3HP; n=31) without a significant difference between the two groups. Other studies did not provide data with a control group [4, 16–18].

Pregnancy outcomes

Four studies provided data on the comparison between IPT and no treatment or a placebo among pregnant women living with HIV (supplementary table S6). All of them reported composite pregnancy outcomes including at least low birth weight, preterm delivery, spontaneous abortion, stillbirth and major congenital anomaly in the composite. Kalk *et al.* [15] additionally included termination of pregnancy and neonatal death, while Taylor *et al.* [17] included neonatal death. The frequency of these composite pregnancy outcomes among women given IPT ranged from 15.0% to 31.1%. In three studies reporting the frequency of individual outcomes, prematurity and low birth weight were commonly observed in women given IPT (10.1–13.4% for prematurity and 8.7–14.9% for low birth weight) [5, 13, 15]. Results were similar in women not exposed to IPT (supplementary table S6).

Results from the one RCT and three NRS were inconsistent (figure 2). The RCT showed a significantly higher risk of composite adverse pregnancy outcomes in those who initiated IPT during pregnancy

TABLE 3 Maternal deaths in pregnant women living with HIV

Study	IPT	Control	Risk ratio (95% CI)
Gupta *et al.* [5]	1 out of 477 (0.2%)	Placebo 3 out of 479 (0.6%)	0.33 (0.03–3.21)
Kalk *et al.* [15]	18 out of 10715 (0.2%)	No treatment 103 out of 41227 (0.3%)	0.67 (0.41–1.11)
Salazar-Austin *et al.* [13]	0 out of 71 (0%)	No isoniazid exposure 2 out of 84 (2%)	0.24 (0.01–4.84)
Tiam *et al.* [16]	2 out of 124 (1.6%)	NA	NA
Taylor *et al.* [17]	0 out of 103 (0%)	No isoniazid exposure 0 out of 93 (0%)	NA

IPT: isoniazid preventive therapy; CI: confidence interval; NA: not available.

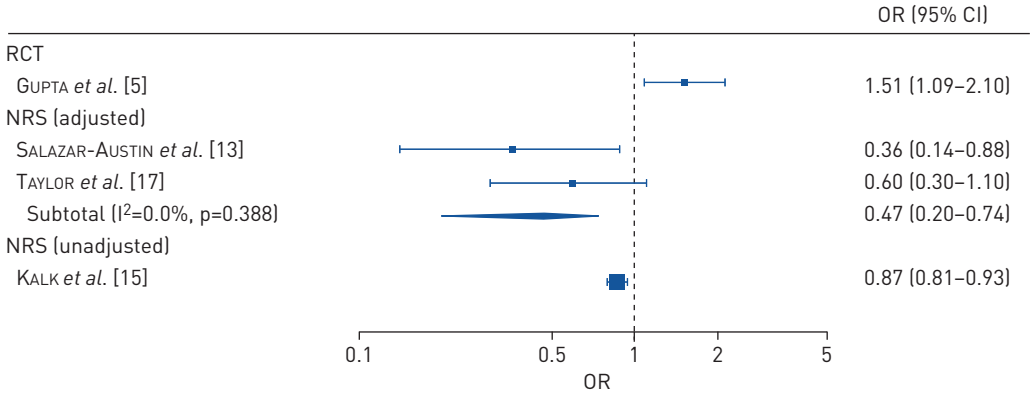

FIGURE 2 Composite pregnancy outcomes in pregnant women with HIV. A meta-analysis conducted using adjusted odds ratios (ORs). RCT: randomised controlled trial; NRS: non-randomised study; CI: confidence interval.

(Mantel–Haenszel odds ratio (OR) stratified by gestational age; OR 1.51, 95% CI 1.09–2.10), while a meta-analysis of composite outcomes using adjusted estimates from two NRS suggested a significantly lower risk of adverse pregnancy outcomes (OR 0.47, 95% CI 0.20–0.74) (figure 2). Due to substantial heterogeneity (I^2=80%, p=0.002), we did not pool data from the RCT and NRS.

A similar trend was observed when individual outcomes were analysed (figure 3 and supplementary tables S7–S10). In the RCT [5], women on IPT were more likely to experience still birth, spontaneous abortion, neonatal death, preterm birth, low birth weight, or congenital anomaly, although none of these were statistically significant. Salazar-Austin *et al.* [13] reported a lower risk of low birth weight and preterm delivery in those given IPT, while, in the study by Kalk *et al.* [15], IPT was significantly associated with lower risk of individual adverse pregnancy outcomes.

In HIV-negative pregnant women, only one study reported data on pregnancy outcomes (still birth, spontaneous abortion, neonatal death and congenital anomaly) [14]. This study did not find a statistical difference between pregnant women exposed to IPT, 3HP, or no treatment; however, the number of women in each group was very small (n=56, n=31 and n=39, respectively).

Quality of evidence assessment

Supplementary tables S1 and S2 in appendix 2 present the results of a risk of bias assessment. The risk of bias in the RCT by Gupta *et al.* [5] was considered to be of some concern due to missing outcome data

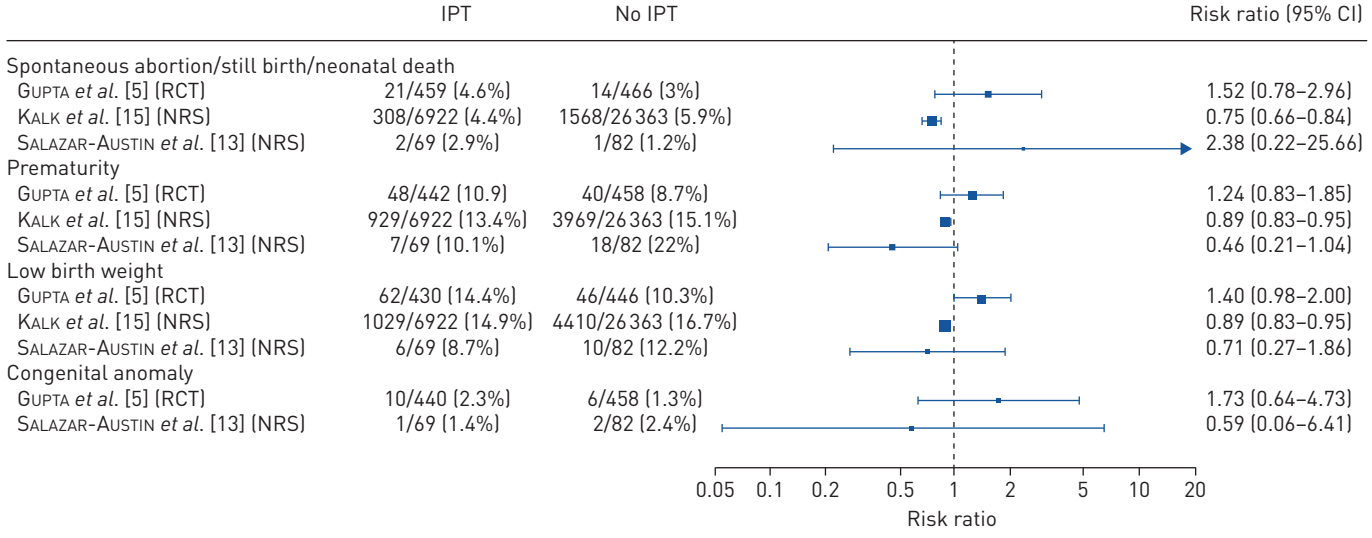

FIGURE 3 Individual pregnancy outcomes in pregnant women with HIV. IPT: isoniazid preventive therapy; CI: confidence interval; RCT: randomised controlled trial; NRS: non-randomised study.

(15.9% in the immediate IPT arm and 17.3% in the deferred IPT arm). Of the four NRS with a control group that reported pregnancy outcomes, all were considered at serious risk of bias.

Quality of evidence was rated on a comparison between IPT and no preventive treatment or placebo among pregnant women with HIV (table 4). Certainty of evidence ranged from low to moderate for the one RCT and from very low to low for two NRS.

Discussion

This is the first systematic review that has evaluated the safety of IPT among pregnant women. Our review found inconsistent associations between IPT and adverse pregnancy outcomes among pregnant women with HIV in different studies. IPT was associated with more adverse pregnancy outcomes in one RCT while it was protective in three NRS. Frequency of hepatotoxicity was higher in the RCT than NRS.

There are several possible reasons for the discrepancy. First, it may be explained by differences in participant characteristics and settings. In the RCT, almost all of the participants (99.8% in the immediate IPT arm and 100% in the delayed IPT arm) were already on combination antiretroviral therapy (cART) at baseline. However, this was not the case in the three NRS. In the study by Salazar-Austin *et al.*, 72% of women were on antiretroviral therapy (ART) at delivery, while in the study by Taylor *et al.*, only 37%

TABLE 4 Grading of recommendations assessment, development, and evaluation (GRADE) methodology in assessment of evidence regarding isoniazid preventive therapy (IPT) compared to no IPT or placebo for pregnant women living with HIV

Outcomes	Studies	Anticipated absolute effects (95% CI)[¶¶]		Relative effect (95% CI)	Participants	Certainty of the evidence (GRADE)
		Risk with no IPT or a placebo	Risk with IPT			
Composite pregnancy outcomes (low birth weight, preterm delivery, spontaneous abortion, stillbirth, or congenital anomaly	One RCT: Gupta *et al.* [5]	170 per 1000	236 per 1000 (182–300)	OR 1.51 (1.09–2.10)	909	⊕⊕⊕◯ (Moderate)[#]
Composite pregnancy outcomes (low birth weight, preterm delivery, spontaneous abortion, stillbirth, neonatal mortality, or congenital anomaly)	Two observational studies: Salazar-Austin *et al.* [13] Taylor *et al.* [17]	360 per 1000	209 per 1000 (101–294)	OR 0.471 (0.199–0.742)	347	⊕◯◯◯ (Very low)[#,¶]
Maternal death	One RCT: Gupta *et al.* [5]	6 per 1000	2 per 1000 (0–20)	Risk ratio 0.33 (0.03–3.21)	956	⊕⊕◯◯ (Low)[+]
Maternal death	Two observational studies: Salazar-Austin *et al.* [13] Taylor *et al.* [17]	3 per 1000	2 per 1000 (1–3)	Risk ratio 0.65 (0.39–1.07)	52 097	⊕⊕◯◯ (Low)[¶]
Grade 3 or 4 AEs related to study treatment	One RCT: Gupta *et al.* [5]	46 per 1000	71 per 1000 (42–120)	Risk ratio 1.55 (0.92–2.61)	956	⊕⊕⊕◯ (Moderate)[#]
Hepatotoxicity	One RCT: Gupta *et al.* [5]	23 per 1000	38 per 1000 (18–79)	Risk ratio 1.64 (0.78–3.44)	956	⊕⊕⊕◯ (Moderate)[#,§]
Hepatotoxicity	One observational study: Kalk *et al.* [15]	3 per 1000	3 per 1000 (2–4)	Risk ratio 1.01 (0.68–1.51)	58 242	⊕⊕◯◯ (Low)[f,##]
Discontinuation of study drug due to toxicity	One RCT: Gupta *et al.* [5]	17 per 1000	23 per 1000 (9–57)	Risk ratio 1.38 (0.56–3.40)	956	⊕⊕⊕◯ (Moderate)[§]

CI: confidence interval; RCT: randomised controlled trial; OR: odds ratio; AE: adverse event. [#]: optimal information size was not met; [¶]: bias due to confounding was considered serious (important confounders were not fully accounted for); [+]: large CI, including both appreciable benefits and harms, and very few events; [§]: CI included both appreciable benefits and harms; [f]: confounding was not accounted for and bias due to measurement of hepatotoxicity was considered serious (since liver function tests were performed only if clinically indicated, which was likely to be influenced by knowledge of the receipt of IPT); [##]: very large sample size and CI of absolute effect was very narrow; [¶¶]: the risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

received cART during pregnancy. In the study by KALK *et al.*, although all women were on cART, 41.8% of them started it during pregnancy. In fact, median CD4 counts were higher in the RCT study (491 cells·mm^{-3} in the immediate IPT arm and 496 cells·mm^{-3} in the deferred IPT arm) compared to the other studies with median CD4 counts ranging from 364–424 cells·mm^{-3}. Furthermore, the three NRS were conducted in South Africa and Botswana, where TB incidence is estimated to be amongst the highest in the world [20]. In contrast, only one third of the RCT study subjects were enrolled in South Africa and Botswana and the remaining participants were from countries with a lower TB incidence. Women in the NRS may thus have been at a higher risk of TB than those in the RCT. In fact, KALK *et al.* reported a 1.5-fold higher risk of TB in those not given IPT. It is therefore possible that IPT reduced adverse pregnancy outcomes by averting more active TB during gestation. However, SALAZAR-AUSTIN *et al.* reported no TB cases in the control group during pregnancy and the reason for reduction of adverse pregnancy outcomes in the IPT group thus remains unclear [13]. Secondly, NRS were at higher risk of bias. For example, they did not control for all important confounders such as history of liver disease, alcohol use and pregnancy history. Thirdly, it is possible that the RCT found more adverse pregnancy outcomes by chance.

The higher frequency of hepatotoxicity observed in the RCT could also be explained by a difference in the uptake of ART. ART causes hepatotoxicity and drug interactions while IPT may increase the risk further [21, 22]. In addition, due to its study design, the RCT measured events that developed while participants were on placebo. Therefore, as the authors discuss, not all hepatotoxic events are attributable to IPT [5]. It is also likely that rigorous monitoring and systematic laboratory testing during follow-up may have detected more events than would be observed under routine programmatic conditions. The NRS performed liver function tests only when clinically indicated, in accordance with the standard practice recommended by the WHO [13, 15, 17]. Asymptomatic liver enzyme elevation may be transient or resolve after completion of treatment without causing clinically significant effects. It is unknown whether routine liver function testing actually prevents clinically significant hepatotoxicity through earlier cessation of a medicine in the field.

Given the findings from the one RCT, deferral of preventive TB treatment may be justifiable in those with low risk for TB after careful consideration of benefits and harms and informed choice of the woman. However, this needs caution as multiple studies have reported loss to HIV-care after delivery [23–25]. Therefore, deferral of IPT may lead to a missed opportunity to protect women and their babies from TB and death. Although data on IPT are limited in pregnant women, this should not be an impediment to giving preventive TB treatment to pregnant women at high risk for progression to active TB. To strengthen confidence in initiating preventive TB treatment during pregnancy, safety studies are needed in both HIV-positive and HIV-negative pregnant women. These studies should include different regimens and would preferably be designed as RCTs of appropriate power to measure key pregnancy and maternal outcomes individually. Pooled meta-analysis from person-level data that includes longer-term postpartum surveillance for AEs in infants would also be helpful.

The strengths of this review include the use of a comprehensive search strategy, explicit inclusion criteria, a systematic approach to data collection and an independent assessment for study inclusion and data extraction. This enabled the first comprehensive assessment of the body of evidence on the safety of IPT among pregnant women. Our review revealed that the increased risk of adverse pregnancy outcomes due to IPT in a single RCT was not supported by multiple NRS, although their risk of bias was serious. This finding and the limited number of studies available signal an urgent need for more research on this important clinical and public health issue.

This review has several limitations. First, the majority of studies that met the inclusion criteria were among pregnant women living with HIV and who were aware of their status. Only three studies provided data on IPT safety among HIV-negative pregnant women and pregnant women living with HIV who were unaware of their status. Of these, two did not include a control group that was not given IPT. Furthermore, the associations observed among HIV-positive pregnant women are likely to be influenced by the concurrent use of ART and the increased risk of developing TB in these women and thus the findings are not fully generalisable to HIV-negative pregnant women. Secondly, limited data were available on the safety of IPT compared to rifamycin-containing preventive TB regimens among pregnant women. Thirdly, our primary analysis focused on composite adverse pregnancy outcomes because adjusted ORs were not available for individual outcomes. The composite outcome was driven by preterm delivery and low birth weight. The frequency of other outcomes (*e.g.* congenital anomaly and still birth) is usually much lower than those outcomes [26–29]. This was also the case in our review and hence less evidence is available on the impact of IPT on the other outcomes.

In conclusion, a single RCT showed an increased risk of adverse pregnancy outcomes due to IPT, while three NRS suggested it has a protective effect. The benefits of IPT may outweigh its potential AEs in

women at high risk of TB. Therefore, our findings do not support systematic deferral of IPT until postpartum regardless of the risk of TB.

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Conflict of interest: None declared.

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