**PHC/Adult Hospital Expert Review Committee: Evidence Summary Isoniazid Preventive Therapy in Pregnancy**

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**Reviewer(s):** Dr Jessica Taylor, Prof. Karen Cohen
**Affiliation:** University of Cape Town, Groote Schuur Hospital
**Author affiliation and conflict of interest details:** JT and KC have no interests pertaining to isoniazid. KC is a co-author on the paper by Kalk et al.

**Oversight Group Support:** Zahiera Adam

**Research Question: What is the efficacy and safety of isoniazid preventive therapy in pregnant women?**

## 1. Background and timeline of NEMLC recommendations

Tuberculosis disease during pregnancy and the post-partum period is associated with adverse maternal, pregnancy, infant outcomes.(1) There is consensus regarding the benefit of treating active tuberculosis disease during pregnancy. Additionally, there is consensus regarding the benefit of isoniazid preventive therapy (IPT) in non-pregnant people living with HIV (PLWHIV) to prevent tuberculosis disease.(1)

In PLWHIV not on ART, tuberculosis preventive therapy is reported to reduce the risk of tuberculosis disease by 33% (RR 0.67; 95% CI 0.51 to 0.87), with the reduction in risk reaching 64% in those with proven latent tuberculosis infection on skin testing (RR 0.36; 95% CI 0.22 to 0.61)(2). In a South African study of PLWHIV who were predominantly on ART, 12 months of IPT was associated with 37% reduction in risk of tuberculosis (3226.5 person-years of follow up; HR 0.63; 95% CI 0.41 to 0.94). This protective effect was demonstrated even in those with negative tuberculin skin tests (TST)(aHR 0.43; 95% 0.21 to 0.86) or interferon gamma release assays (IGRA)(aHR 0.43; 95% CI 0.20 to 0.96). However, no difference in all-cause mortality was reported (IPT 0.9 per 100 person-years vs. placebo 1.2 per 100 person-years; HR 0.72; 95% CI 0.34 to 1.34; p = 0.32).(3) The 2018 NEMLC medicine review titled "Isoniazid Preventive Therapy" reported a number needed to treat (NNT) to avert 1 case of tuberculosis disease of 33 in non-pregnant PLWHIV.(4) Additionally, this review indicated that IPT is associated with a mortality benefit in a long-term follow-up study across all $CD_4$ counts and irrespective of baseline latent tuberculosis infection (aHR 0.61; 95% CI 0.39 to 0.94; NNT 57).(4, 5) However, there remains a lack of consensus regarding the safety and efficacy of IPT in pregnant women living with HIV. Safety is of particular importance in the setting of prophylactic treatment, where the acceptable threshold for potential harm is much lower.

In the 2014 primary healthcare (PHC) standard treatment guidelines (STG), IPT was recommended for all PLWHIV. The duration of IPT recommended, ranged from 6 – 36 months depending on the results and availability of TST and whether or not the patient was taking highly active antiretroviral therapy (HAART). In addition, 12 months of IPT was recommend for all HIV positive pregnant women.(6)

In 2018, the decision was taken to simplify this recommendation to 12 months of IPT for all PLWHIV regardless of TST testing or HAART, based on the results of the locally conducted clinical trial of IPT versus placebo in participants on ART mentioned previously.(3) In the same year preliminary data from the TB APPRISE randomized controlled trial (RCT) reported increased adverse pregnancy outcomes associated with IPT use during pregnancy as compared to the post-partum period, and no difference in tuberculosis disease or mortality. As a result, NEMLC recommended that a caution be added to the STG regarding the use of IPT in pregnant women living with HIV with high $CD_4$ counts. (1)

After further deliberation, based on the evidence of potential harm associated with IPT use in pregnancy, and after consideration of the potential benefit of IPT in the high tuberculosis prevalence setting of South Africa, a $CD_4$ cut off for IPT initiation in pregnancy was recommended. The recommendation was that IPT be deferred until after delivery in women living with HIV with $CD_4$ counts of < 100 cells/$mm^3$. This $CD_4$ count was extrapolated from the REALITY RCT, which showed an association between IPT and a reduction in incident tuberculosis disease in non-pregnant patients with advanced HIV ($CD_4$ < 100 cells/$mm^3$) starting ART. (7)

Following this, data emerged from a locally conducted, retrospective cohort study in the Western Cape, which reported the benefit of antenatal IPT in preventing incident tuberculosis in women living with HIV with $CD_4$ counts ≤ 350 cells/$mm^3$, as well as encouraging safety data, leading to a change in the previously recommended $CD_4$ count criteria. In the Adult Hospital HIV Chapter (2017 – 2019) and the Primary Healthcare HIV Chapter (2020), it was recommended that pregnant women living with HIV and with a $CD_4$ count cells/$mm^3$ < 350 receive 12 months of IPT, while in those with $CD_4$ counts ≥ 350 cells/$mm^3$, IPT be deferred till after delivery (see Appendix 1 Textbox 1). (8)

Currently, in high tuberculosis incidence settings, the World Health Organisation (WHO) recommends 36 months of IPT in PLWHIV with unknown or positive TST, irrespective of $CD_4$ count, history of previous treatment for tuberculosis or pregnancy (conditional recommendation, low quality evidence).(9) This recommendation is based on data from non-pregnant population.

In February 2023, the South African Tuberculosis programme released national guidelines for the treatment of tuberculosis infection, recommending 12 months of IPT for all HIV positive pregnant women, irrespective of $CD_4$ count. Additionally in these programmatic guidelines, in HIV negative pregnant women, with a history of close contact with a person with active tuberculosis disease, a 3-month treatment regimen consisting of isoniazid and rifampicin is recommended. (10) A CD4 count-based risk stratified approach was assessed by the NDoH TB program as not feasible to implement. Therefore NEMLC and the NDoH TB program jointly decided in March 2024 to defer TPT in all pregnant women with HIV (See Appendix 1 Textbox 2).

Local clinicians raised concerns about deferring TPT in pregnant women living with HIV (PWLHIV), particularly women with advanced HIV and a higher risk of incident TB. In August 2025, a debate on use of IPT in pregnancy was held at the SA HIV Clinicians Society Conference. A poll taken after the debate indicated strong support from clinicians for a CD4 count-guided approach to IPT initiation in pregnancy. The 2023 update of the Consolidated ART Guideline[1] clearly outlines a specific package of care for people with Advanced HIV Disease, defined as any client (including pregnant women) with a CD4 count < 200 cells/$mm^3$, or WHO Stage 3 or 4 clinical conditions. This comprehensive package of care now provides opportunity to reconsider a CD4 count risk stratification approach to IPT in PWLHIV, in line with the latest available evidence for benefit and harms. After collaborative engagement between the NDoH TB program, the HIV program and NEMLC, joint recommendation was made, as follows:

- PWLHIV with CD4 counts ≤ 200 cells/$mm^3$ and starting ART should receive 12 months of TPT after exclusion of active tuberculosis disease.
- In PWH with CD4 counts > 200 cells/mm3 and starting ART, TPT should be deferred to the post-partum period.

This document aims summarizes evidence for safety and efficacy of IPT to date, as well as programmatic implementation feasibility concerns to inform recommendations and decision-making.

## 2. Literature Search

A rapid review of the literature was conducted. PubMed was searched with the following search terms:

("isoniazid"[MeSH Terms] OR "isoniazid"[All Fields] OR "isoniazide"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR ("preventive"[All Fields] AND "therapy"[All Fields]) OR "preventive therapy"[All Fields])

[1] NDoH. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. Accessible online https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields])

One hundred and thirty-two articles were identified in the initial search. Systematic reviews, randomized clinical trials, and observational studies with comparator groups, published in English, were eligible for inclusion. Furthermore, studies were required to compare isoniazid monotherapy in pregnant women to placebo/no treatment/delayed treatment, and report on safety (adverse pregnancy outcomes, infant outcomes, hepatotoxicity) and/or efficacy (tuberculosis disease and mortality), to be included.

In the screening stage, only 3 studies conducted in HIV-negative populations were identified. Two of these were single-arm retrospective cohort studies comparing outcomes to historical cohorts only, and were therefore not eligible for inclusion.(11, 12) The third study conducted in HIV-negative women examined pregnancy outcomes in women who became pregnant in RCT's that compared weekly rifapentine-isoniazid (3-HP) to IPT, or self-administered 3-HP to directly observed 3-HP. In this study, rates of fetal loss in IPT and 3-HP exposed pregnancies were compared to each other, and overall, to a historical American cohort.(11) This study was also not considered for further inclusion.

Therefore, after screening of the titles and abstracts, 8 studies were identified, none of which were conducted in pregnant women without HIV.

The relevant studies identified for inclusion are summarized in table 1.

*Table 1.*

| | Study Name/Author | Study Type | Name of Publication | Year of Publication |
|---|---|---|---|---|
| 1. | Hamada et al. | Systematic Review | The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis(13) | 2020 |
| 2. | Gupta et al. (TB-APPRISE) | Randomized Controlled Trial | Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women(1) | 2019 |
| 2.1 | Theron et al. (TB-APPRISE) | Randomized Controlled Trial | Individual and Composite Adverse Pregnancy Outcomes in a Randomized Trial on Isoniazid Preventative Therapy Among Women Living with Human Immunodeficiency Virus(14) | 2020 |
| 2.2 | Cherkos et al. (TB-APPRISE) | Randomized Controlled Trial | Effect of pregnancy versus postpartum maternal isoniazid preventive therapy on infant growth in HIV-exposed uninfected infants: a post-hoc analysis of the TB APPRISE trial(15) | 2023 |
| 3. | Taylor et al. | Prospective cohort study nested in randomized controlled trial. | Pregnancy Outcomes in HIV-Infected Women Receiving Long-Term Isoniazid Prophylaxis for Tuberculosis and Antiretroviral Therapy(16) | 2013 |
| 4. | Gupta et al. (BRIEF-TB) | Prospective cohort study nested in randomized controlled trial. | Adverse Pregnancy Outcomes Among Women with Human Immunodeficiency Virus Taking Isoniazid Preventive Therapy During the First Trimester(17) | 2023 |
| 5. | Salazar-Austin et al. (TSHEPISO) | Prospective cohort study | Isoniazid Preventive Therapy and Pregnancy Outcomes in Women Living with Human Immunodeficiency Virus in the Tshepiso Cohort (18) | 2020 |
| 6. | Kalk et al. | Retrospective cohort study | Safety and Effectiveness of Isoniazid Preventive Therapy in Pregnant Women Living with Human Immunodeficiency Virus on Antiretroviral Therapy: An Observational Study Using Linked Population Data(8) | 2020 |

## 3. Evidence Summary

### 3.1 TB-APPRISE(1, 14, 15)

TB-APPRISE was a multicenter, double-blind, placebo controlled non-inferiority trial that enrolled pregnant women living with HIV between 14 – 34 weeks' gestation. All women were enrolled from high tuberculosis prevalence countries, defined as ≥ 60 cases per 100 000. However, only 20% of participants were enrolled from South Africa, which has twice the tuberculosis prevalence than some of the other countries of enrollment. Women were randomized to receive either IPT immediately for 28 weeks followed by placebo, or placebo immediately followed by IPT initiated from 12-weeks post-partum. Women with a recent exposure to a close contact with active tuberculosis, and therefore at higher risk of progression to tuberculosis disease, were excluded.

A total of 956 women were enrolled in the study with 477 randomized to the immediate IPT group and 479 to the deferred IPT group. The median $CD_4$ count was 493 cells/$mm^3$ and all but one of the participants were receiving HAART[2]. The HAART regimen included efavirenz in 85.1% of all participants and 63.1% of participants had an undetectable HIV viral load at enrollment. Thirty percent of the enrolled study participants had positive IGRA results indicative of latent tuberculosis infection.

A relatively high attrition rate was reported with 171 women (17.9%) discontinuing the trial prematurely, 88 in the immediate IPT group and 83 in the deferred IPT group. No significant difference in patient-reported adherence or by assessment of pill count were noted between the immediate and deferred groups.

Approximately, one third of participants were exposed to IPT or placebo from the second trimester into the third trimester. The remaining two thirds of participants were exposed to IPT or placebo in third trimester only.

The primary outcome was a composite safety outcome of maternal adverse events of grade 3 or higher that were possibly, probably, or related to isoniazid or placebo or permanent discontinuation of the trial due to toxic effects. The primary outcome event occurred at an incidence rate of 15.03 events per 100 person-years in the immediate IPT group as compared to 14.93 events per 100 person-years in the deferred group (rate difference 0.10; 95% CI -4.77 to 4.98). The predefined noninferiority criterion was met for the primary outcome event.

In terms of efficacy, only 6 cases of incident tuberculosis were reported throughout the trial, 3 cases in each arm. As a result, no significant difference in incident tuberculosis between the immediate IPT and the deferred group was reported (incidence rate: 0.60 vs. 0.59 per 100 person-years; rate difference 0.01; 95% CI -0.94 to 0.96). Six deaths occurred during the trial, 2 in the immediate IPT group and 4 in the deferred group. A large proportion of the deaths occurred due to liver failure (66.67%). No significant difference in mortality rate between the immediate IPT group and the deferred group was reported (incidence rate 0.40 vs. 0.78 per 100 person-years; rate difference -0.39; 95% CI -1.33 to 0.5).

Of the 956 women enrolled in the study, 926 women had pregnancy outcome data. The composite adverse pregnancy outcome included stillbirth (fetal death ≥ 20 weeks' gestation), spontaneous abortion (pregnancy loss <20 weeks' gestation), low birth weight (<2500 g), preterm delivery (delivery < 37 weeks' gestation), or major congenital anomalies in an infant. The composite adverse pregnancy outcome occurred more frequently in the immediate IPT group as compared to the deferred group (23.6% vs. 17.0%; risk difference 6.7 percentage points; 95% CI 0.8 to 11.9; p = 0.01). Individually, the outcomes of stillbirth, spontaneous abortion, and low birth weight infant occurred more frequently in the immediate IPT group than in the deferred group, but the between group differences failed to reach statistical significance.

Theron et al. conducted a secondary analysis of the pregnancy outcome data from 925 mother-infant pairs[3] from the TB-APPRISE study.(14) Important covariates adjusted for in the multivariable logistic regression models included maternal age at delivery, $CD_4$ quartile, suppressed HIV viral load, timing of ART initiation, HBsAg status,

[2] HAART refers to treatment regimens consisting of three or more antiretroviral drugs.

[3] 926 women with pregnancy outcome and excluding 1 induced abortion. Therefore, 925 women who had at least 1 live birth or fetal demise were analysed.

maternal mid upper arm circumference (MUAC), IGRA status, noninfectious pregnancy complications, infectious pregnancy complications, twin versus singleton pregnancy, current smoking status, and hospitalization.

The study reported that the adjusted odds of a composite of fetal demise, preterm delivery, low birth weight infant or congenital anomaly were 1.63 times higher among women randomized to immediate IPT arm (23.6% vs. 17.0%; aOR 1.63; 95% CI 1.15 to 2.31; p = 0.007; NNTH 16) (refer Table 2). Immediate IPT was also associated with increase odds of composite adverse outcomes that included neonatal death (composite 2) and early neonatal death (composite 3). When examining the individual components of the composite outcomes, no association was detected between IPT study arm and perinatal mortality or preterm delivery. However, after adjusting for other covariates, immediate IPT was associated with a 58% increase in the odds of a low-birth-weight infant (14.4% vs. 10.3%; aOR 1.58; 95% CI 1.02 to 2.46; p = 0.041; NNTH 25).

*Table 2. Summary of Composite Adverse Pregnancy Outcomes by Treatment Group and Adjusted Odds Ratio Estimates from Theron et al.*

| Outcome | Immediate INH, n/N (%) | Deferred INH, n/N (%) | Unadjusted OR (95% CI), by study arm | Adjusted OR (95% CI), by study arm |
|---|---|---|---|---|
| Composite 1: fetal demise, PTD, LBW, or congenital anomaly | 106/449 (23.6) | 78/460 (17.0) | 1.51 (1.09–2.10) | 1.63 (1.15–2.31) |
| Composite 2: fetal demise, PTD, LBW, or neonatal death (<28 days) | 105/450 (23.3) | 78/459 (17.0) | 1.48 (1.07–2.06) | 1.62 (1.14–2.30) |
| Composite 3: fetal demise, PTD, LBW, or early neonatal death (<7 days) | 105/450 (23.3) | 73/459 (15.9) | 1.61 (1.15–2.24) | 1.74 (1.22–2.49) |
| Perinatal death 1: fetal demise or neonatal death | 23/459 (5.0) | 20/466 (4.3) | 1.18 (.64–2.17) | 1.32 (.69–2.53) |
| Perinatal death 2: fetal demise or early neonatal death | 21/459 (4.6) | 13/466 (2.8) | 1.67 (.83–3.38) | 1.84 (.87–3.85) |
| LBW: <2500 grams at birth | 62/430 (14.4) | 46/446 (10.3) | 1.46 (.97–2.20) | 1.58 (1.02–2.46) |
| PTD: <37 weeks gestation at delivery | 48/442 (10.9) | 40/458 (8.7) | 1.27 (.82–1.98) | 1.35 (.85–2.15) |

Multivariable model for composite outcomes by study arm.

Abbreviations: CI, confidence interval; LBW, low birth weight; OR, odds ratio; PTD, preterm delivery.

Cherkos et al. conducted a post hoc analysis of data from the TB APPRISE RCT, analyzing only 898 HIV-exposed but uninfected live born babies with at least one follow-up after birth.(15) After adjusting for maternal BMI, maternal age, HAART regimen, HIV viral load, $CD_4$ count, level of education, and household food security, they reported that infants born to mothers randomized to the immediate IPT arm had a 1.60 times greater risk of low birth weight than infants born to mothers in the deferred IPT arm (aRR 1.60; 95% CI 1.07 to 2.41). No significant association between treatment arm and preterm birth (aRR 1.31; 95% CI 0.87 to 1.97) or small-for-gestational-age was reported (aRR 0.97; 95% CI 0.71 to 1.32). Additionally, infants born to mothers randomized to immediate IPT experienced a 47% increased risk of becoming underweight in the first 12 weeks of life (aHR 1.47; 95% CI 1.06 to 2.03), and a 34% increased risk of becoming underweight in the first 48 weeks of life (aHR 1.34; 95% CI 1.01 to 1.78). No association between IPT treatment arm and stunting or wasting was reported. These findings were particularly pronounced in male infants, suggesting modification of the effect of antenatal IPT by sex.

Pertinent results from all 3 publications arising from the TB-APPRISE RCT are summarized in Table 3 below.

*Table 3. Summary of all publications arising from TB-APPRISE RCT*

| Efficacy(1) | Maternal Adverse Events(1) | Adverse pregnancy outcomes(1, 14) | Infant Growth(15) |
|---|---|---|---|
| **INCIDENT TB:**<br>IG 0.60 vs. DG 0.59<br>Rate difference: 0.01 per 100 person-years<br>(95% CI -0.94 to 0.96)<br><br>**MORTALITY:**<br>IG 0.40 vs. DG 0.78<br>Rate difference: -0.39 per 100 person-years<br>(95% -1.33 to 0.56) | **≥ GRADE 3 AE OR AE LEADING TO TREATMENT DISCONTINUATION:**<br><br>IG 15.03 vs. DG 14.93<br>Rate difference: 0.10 per 100 person-years<br>(95% CI -4.77 to 4.98) | **STILLBIRTH, SPONT. ABORTION, LBW, PRETERM, CONGENTIAL ANOMALIES**<br>IG 23.6% vs DG 17%<br><br>Risk difference: 6.7<br>(95% CI 0.8 to 11.9)<br><br>aOR 1.63 (95% CI 1.15 to 2.31) | **LBW:**<br>aRR 1.60 (95% CI 1.07 to 2.41)<br><br>**PRETERM:**<br>aRR 1.31 (95% CI 0.87 to 1.97)<br><br>**SGA:**<br>aRR 0.97 (95% CI 0.71 to 1.32)<br><br>**UNDERWEIGHT by 12 weeks:**<br>aHR 1.47 (95% CI 1.06 to 2.03) |

| | | | |
|---|---|---|---|
| | | **STILLBIRTH, SPONT. ABORTION, LBW, PRETERM, NEONATAL DEATH (28 days):** aOR 1.62 (95% CI 1.14 to 2.30)<br><br>**STILLBIRTH, SPONT. ABORTION, LBW, PRETERM, NEONATAL DEATH (7 days):** aOR 1.74 (95% CI 1.22 to 2.49) | **UNDERWEIGHT by 48 weeks:** aHR 1.34 (95% CI 1.01 to 1.78) |
| *IG – immediate group; DG – deferred group; SGA – small for gestational age; LBW – birth weight < 2.5kg; SGA –small for gestational age or weight < 10th percentile for gestational age; aOR – adjusted odds ratio; CI – confidence interval* | | | |

### 3.2. Taylor et al. (16)

Taylor et al. conducted a nested cohort study of women living with HIV who became pregnant while enrolled in a double-blind, randomized, placebo-controlled tuberculosis prevention trial. In the trial, conducted in Botswana, all participants received 6 months of IPT, after which they were randomized to either continue IPT or changed to placebo for a further 30 months. Women, not yet on HAART[4], who became pregnant during the trial with $CD_4$ counts of > 200 cells/$mm^3$ received zidovudine prophylaxis from 34 weeks' gestation. Whereas those who became pregnant $CD_4$ counts ≤ 200 cells/$mm^3$ were referred to initiate HAART.

One hundred and ninety-six pregnancies occurred during the trial, of which 103 pregnancies[5] were exposed to isoniazid (52.6%) and 93 were not. Almost all (99%) of IPT-exposed pregnancies were exposed from the first trimester, with only 68% of women having ongoing exposure throughout the pregnancy. Thirty seven percent of pregnant women received HAART during pregnancy, with the remainder receiving only zidovudine-based prophylaxis. The median $CD_4$ count at baseline for women who became pregnant during the trial was 368 cells/$mm^3$. Approximately 16% of the cohort had $CD_4$ counts below 200 cells/$mm^3$. No statistical comparison of the baseline characteristics of the pregnancies exposed to IPT compared to those unexposed was provided.

In this study, adverse pregnancy outcome was defined as preterm delivery (≤ 37 weeks' gestation), low birth weight (<2500g), stillbirth (delivery of an infant with no signs of life at ≥ 28 weeks' gestation), spontaneous abortion (spontaneous termination of pregnancy < 24 weeks' gestation), neonatal mortality (death of a term infant within 28 days of delivery), or any noted congenital abnormality. Isoniazid exposure during pregnancy was not associated with increased odds of an adverse pregnancy outcome (aOR 0.6; 95% CI 0.3 to 1.1), after adjusting for ART regimen, maternal $CD_4$ count, maternal age, and BMI. Furthermore, no maternal deaths, isoniazid-associated hepatitis or other severe isoniazid-associated events were reported in the 103 women who were exposed to IPT in pregnancy during the trial.

### 3.3. Gupta et al. (BRIEF-TB trial)(17)

BRIEF-TB was an open-label, randomized, non-inferiority trial, comparing a weight-based 1-month isoniazid plus rifapentine regimen (1HP) with the standard 9-month IPT for tuberculosis prevention among PLWHIV. The trial was conducted from 2012 to 2017, and enrolled participants from ten high tuberculosis prevalence countries[6] (including South Africa). All those who were randomized to receive IPT and became pregnant during the trial were analysed as part of the planned secondary analysis by Gupta et al. Pregnancies were classified as being unexposed[7] (n = 89) or exposed to IPT (possibly or definitely)(n = 39)[8]. Based on the study definition of exposure, all pregnancies exposed to IPT were conceived while taking IPT, with fewer women having ongoing exposure in the second and third trimesters. To note, although the data that informed this study was collected prospectively under trial conditions, which pregnancies were exposed or not exposed to IPT was not determined by randomization.

[4] HAART refers to treatment regimens consisting of three or more antiretroviral drugs.

[5] In 103 women

[6] High tuberculosis prevalence defined as ≥ 60 cases per 100 000 population.

[7] Pregnancies were classified as IPT unexposed if pregnancy outcome occurred > 45 weeks after the final isoniazid dose.

[8] Pregnancies were classified as definitely exposed to IPT if the positive pregnancy test, pregnancy outcome, or estimated date of conception based on gestational age at birth occurred on or before the date of last dose of isoniazid.

Once again a composite adverse pregnancy outcome of spontaneous abortion (fetal demise before 20 weeks' gestation), ectopic pregnancy, or stillbirth (fetal demise at or beyond 20 weeks' gestation) was defined. For live births, low birth weight (< 2500 g) and preterm delivery (delivery before 37 weeks gestational age) were outcomes of interest. Analyses were adjusted for maternal $CD_4$ count, ART use, hepatitis B surface antigen positivity, age, and latent tuberculosis infection. However, other important confounders associated with poor pregnancy outcomes such as maternal smoking status, BMI or obstetric history were not measured or adjusted for. The median $CD_4$ count for the cohort was 534 cells/$mm^{3.}$ Thirty eight percent of the IPT-exposed women were receiving HAART at enrolment, increasing to 79% by pregnancy outcome. Thirty four percent of the unexposed women were receiving HAART at enrolment, increasing to 96% at pregnancy outcome. The difference in proportion of women receiving HAART at pregnancy outcome by IPT exposure was statistically significant (79% vs. 96%; p = 0.007).

A total of 29 pregnancies ended in an adverse pregnancy outcome: 25 spontaneous abortions, 2 stillbirths and 2 ectopic pregnancies. The composite pregnancy outcome occurred in 33% of pregnancies exposed to IPT and 18% of pregnancies not exposed to IPT. Crudely, the proportion of spontaneous abortions and stillbirths was 2-fold higher in the pregnancies exposed to IPT as compared to those unexposed. When adjusted for baseline covariates mentioned previously, IPT exposure in pregnancy was associated with an almost 2-fold increased risk of the adverse composite outcome (aRR 1.90; 95% CI 1.01 to 3.54; p = 0.04)(Refer Table 4). In an analysis adjusted for the same covariates, but measured closest to the pregnancy outcome, the association was no longer statistically significant (aRR 1.45; 95% CI 0.75 to 2.80; p = 0.27). No association was reported between IPT exposure in pregnancy and low birth weight (RR 1.01; 95% CI 0.29 to 3.56) or preterm delivery (RR 0.87; 95% CI 0.32 to 2.42).

*Table 4. Results from Regression Model of Relative Risk of Adverse Pregnancy Outcome by IPT exposure from Gupta et al. 2023.*

| | No./Total N (%) | | Unadjusted | | Adjusted for Covariates Measured at Enrollment | | Adjusted for Covariates Measured at Pregnancy Outcome | |
|---|---|---|---|---|---|---|---|---|
| Outcome | IPT-exposed | Unexposed | RR (95% CI) | *P* | aRR (95% CI) | *P* | aRR (95% CI) | *P* |
| Composite adverse outcome[a] (excludes induced abortion as adverse outcome) | | | | | | | | |
| Primary analysis (n = 128) | 13/39 (33) | 16/89 (18) | 1.85 (.99, 3.47) | .05 | 1.90 (1.01, 3.54) | .04 | 1.45 (.75, 2.80) | .27 |
| Restricted risk set analysis (n = 122[b]) | 13/36 (36) | 16/86 (19) | 1.94 (1.04, 3.61) | .04 | 1.98 (1.08, 3.65) | .03 | 1.52 (.83, 2.81) | .18 |
| Extended composite adverse outcome (includes induced abortion as adverse outcome) | 16/39 (41) | 19/89 (21) | 1.92 (1.11, 3.33) | .02 | 1.98 (1.15, 3.41) | .01 | 1.47 (.84, 2.55) | .18 |
| Preterm delivery <37 wks gestational age (n = 68[c]) | 4/20 (20) | 11/48 (23) | 0.87 (.32, 2.42) | .80 | … | … | … | … |
| Low birth weight <2500 g (n = 74[c]) | 3/22 (14) | 7/52 (13) | 1.01 (.29, 3.56) | .98 | … | … | … | … |

Models adjusted for maternal age, CD4 count, antiretroviral use and latent tuberculosis status.

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; IPT, isoniazid prevention therapy; RR, relative risk.

[a]Any event resulting in a non-live birth, other than induced abortion; individual component outcomes were spontaneous abortion (<20 wks), stillbirth (≥20 wks), and ectopic pregnancy.

[b]Excluded six pregnancies that ended in induced abortion (3 in each exposure group).

[c]Assessed among live births for which data were available; adjusted analyses not undertaken because of small number of events.

### 3.4. Salazar- Austin et al. TSHEPISO Cohort(18)

Salazar-Austin et al. conducted a secondary analysis of data collected prospectively from a cohort of pregnant women living with HIV in Soweto (TSHEPISO cohort), between 2011 and 2014. The study enrolled pregnant women of at least 18 years of age living with HIV, and of at least 13 weeks' gestation. As part of the study, enrolled women who were investigated for and identified as having tuberculosis disease were subsequently matched to 2 pregnant women living with HIV but without tuberculosis. All pregnant women enrolled without tuberculosis disease were offered IPT. In this study, maternal, pregnancy, and infant outcomes among those women living with HIV without tuberculosis disease, who did or did not use IPT for tuberculosis prevention during pregnancy, were analyzed.

All outcomes assessed in the study were self-reported but confirmed using clinic and hospital records or the road-to-health-chart where available. A participant was considered exposed to IPT if she self-reported use of isoniazid for tuberculosis prevention for any duration while pregnant. A large proportion of the study was conducted during the

time when according to South African guidelines pregnant women were only eligible for efavirenz-based HAART if their $CD_4$ count was less than 350 cells/$mm^3$.

The study enrolled 155 women without tuberculosis disease, and 71 were considered IPT exposed (46%) and 84 (54%) unexposed. Pregnancy outcomes were available for 69 of the women exposed to IPT (97%) and 82 (98%) of women unexposed to IPT. Significantly less long-term outcome data, relating to tuberculosis disease and mortality, were available for women unexposed to IPT (76%), as compared to the IPT exposed group (92%), and only a complete case analysis was performed.

Baseline characteristics were similar between the two groups. The $CD_4$ count at enrollment for the IPT exposed participants was 373 cells/$mm^3$ compared to 364 cells/$mm^3$ in the unexposed group. Approximately 26.49% of the cohort received zidovudine with or without single dose nevirapine at delivery for prevention of mother to child transmission. In the unexposed group, 87% were receiving HAART at delivery, compared to only 65% of the IPT exposed group (although this difference was not statistically significantly). As a result, only 39% of the IPT exposed group were virally suppressed, as compared to 55% of the unexposed group, prior to delivery. Almost all participants initiated IPT in the second or third trimester, with only 2 participants reporting initiation in the first trimester. No participants were taking IPT at the time of conception.

In this study the composite adverse pregnancy outcome consisted of fetal demise (spontaneous abortion < 28 weeks or stillbirth ≥ 28 weeks gestational age), low birth weight (< 2500g), prematurity (<37 weeks) and/or major congenital abnormality). Crudely, this outcome occurred less frequently in the IPT-exposed pregnancies, but the difference was not statistically significant (IPT exposed 16% vs. unexposed 28%; p = 0.08). The absolute increase in the composite adverse pregnancy outcome in the unexposed group was driven by preterm delivery (IPT exposed 10% vs. unexposed 22%, p = 0.06).

There was no difference in the composite outcome consisting of maternal, fetal, or infant death, or tuberculosis disease occurring within 1 year of delivery between those exposed to IPT and those unexposed (IPT exposed 3% vs. unexposed 4%; p = 1.0). In the adjusted logistic regression, women unexposed to IPT had 2.5-fold greater odds of having an adverse pregnancy outcome after controlling for $CD_4$ count at baseline, ARV regimen, HIV viral load, maternal age, BMI, and anemia (aOR 2.5; 95% CI 1.0 to 6.5; p = 0.048).

In this non-randomized study, it is possible that women who opted to take IPT were healthier with better health-seeking behavior than those who declined IPT, impacting on the association of IPT with decreased adverse pregnancy outcomes. This is illustrated by the greater proportion of missing outcome events for the unexposed group, and the larger number of participants in the unexposed group qualifying for HAART at the time. Additional, important confounders of adverse pregnancy outcomes such as maternal smoking status, alcohol use, and obstetric history and risk factors were not measured or adjusted for. Additionally, the self-reported measure of exposure to IPT does not exclude participants prescribed IPT, who did not take the treatment, contributing to misclassification bias.

### 3.5 Kalk et al.

Kalk et al. conducted a large retrospective cohort study in the Western Cape, using routine electronic health data from the public sector. The cohort comprised 43 971 pregnant women living with HIV who initiated ART during or prior to a pregnancy between 1 January 2015 and 31 December 2017. The objective of the study was to analyze differences in tuberculosis incidence, mortality, and pregnancy outcomes between those women who received IPT during pregnancy and those who did not, over 12 months of post pregnancy outcome follow-up. At the time, South African guidelines recommended 12 months of IPT for all PLWHIV regardless of $CD_4$ count and including pregnant women. Additionally, all pregnant women living with HIV were eligible for HAART.

IPT was dispensed during pregnancy in 16.6% of the cohort. The median $CD_4$ count for the cohort was 422, with only 9.7% of the cohort having $CD_4$ counts <200. At antenatal presentation, there were noteworthy and statistically significant differences in the characteristics of women by antenatal IPT exposure. More women exposed to antenatal IPT group were receiving HAART prior to falling pregnant (77.9% vs 71.6%; p < 0.001). A larger proportion of women exposed to antenatal IPT group had $CD_4$ counts greater than 500 cells/$mm^3$ compared to those who were not exposed to IPT (29.1% vs 26.7%). Similarly, a greater proportion of the antenatal IPT exposed group were virologically

suppressed (63.9% vs. 56.1%; p < 0.001). A history of previous tuberculosis disease was also less common in the IPT exposed women (10.6% vs. 13.0%; p < 0.001). These differences may indicate that the cohort that received IPT antenatally was more clinically stable, healthier, or at lower risk of tuberculosis disease than those who did not.

Tuberculosis developed in 1 002 (2.3%) women across the cohort. Only 1% of the women that received antenatal IPT developed tuberculosis, compared to 2.5% of the women who did not receive IPT (Risk difference -1 518 cases per 100 000; 95% CI -1 799 to -1 238 per 100 000). Furthermore, antenatal IPT was associated with a 29% reduction in risk of tuberculosis (aHR 0.71; 95% CI 0.63 to 0.81) after adjusting for maternal age, $CD_4$ count, history of tuberculosis disease, HIV viral load, and duration of HAART prior to delivery. When stratified by $CD_4$ count, the benefit of IPT in terms of reduction in incident tuberculosis was greatest in those with $CD_4 \leq 350$ cells/$mm^3$ (aHR 0.51; 95% CI 0.41 to 0.63), with no reduction in risk of tuberculosis in those with $CD_4 > 350$ cells/$mm^3$ (aHR 0.93; 95% CI 0.76 to 1.13). Additionally, the reduction in tuberculosis risk persisted even when IPT was started after 14 weeks gestation compared to no IPT (aHR 0.63; 95% CI 0.54 to 0.74). In 75.7% of those that developed tuberculosis during the study, the diagnosis occurred close to the time of the pregnancy outcome or soon thereafter, with 35.6% occurring within 3 months following the pregnancy outcome. After adjustment for covariates listed previously, IPT was not associated with a reduction in maternal mortality (aHR 0.75; 95% CI 0.46 to 1.22) but was associated with severe liver injury (aHR 1.51; 95% CI 1.18 to 1.93).

In the study, the composite adverse pregnancy outcome included miscarriage (loss of products of conception before 27 weeks' gestation), stillbirth (delivery of a fetus with no signs of life after 27 completed weeks' gestation), neonatal death (death of an infant within 28 days of birth), or low birth weight (< 2500 g). Antenatal IPT exposure was associated with a 17% reduction in the odds of adverse pregnancy outcome in the adjusted analysis (aOR 0.83; 95% CI 0.78 to 0.87). The mechanism of this protective effect is postulated to be related to the reduction in tuberculosis disease. However, other important confounders of adverse pregnancy outcomes, such as maternal BMI, smoking status, alcohol use and obstetric history were not adjusted for. When components of the composite outcome were examined individually, stillbirth (aOR 0.80; 95% CI 0.63 to 1.00) and miscarriage (aOR 0.83; 95% CI 0.68 to 1.00) appeared to be largely responsible for the effect.

When analyzed by timing of IPT exposure in pregnancy, IPT exposure starting after 14 weeks gestation was associated with reduced adverse pregnancy outcomes as compared to no IPT exposure (refer Table 5). This effect was driven largely by the reduction in miscarriage, with much smaller reductions in low birth weight and stillbirth.

*Table 5. Multivariable analysis for individual pregnancy outcomes by timing of IPT exposure in pregnancy from Kalk et al.*

| | aOR (95% CI)<br>IPT < 14 weeks versus none | aOR (95% CI)<br>IPT > 14 weeks versus none | aOR (95% CI)<br>IPT < 14weeks versus IPT > 14weeks (<14weeks=ref) |
|---|---|---|---|
| Poor outcome composite | 1.04 (0.94 – 1.16) | 0.71 (0.65 – 0.79) | 0.64 (0.55 – 0.75) |
| Misc | 1.39 (1.11 – 1.75) | 0.33 (0.22 – 0.48) | 0.21 (0.13 – 0.35) |
| SB | 0.97 (0.68 – 1.37) | 0.71 (0.53 – 0.94) | 0.73 (0.44 – 1.19) |
| NND | 1.16 (0.76 – 1.77) | 0.83 (0.56 – 1.21) | 0.84 (0.45 – 1.56) |
| LBW (livebirths) | 1.10 (0.97 – 1.18) | 0.90 (0.83 – 0.98) | 0.91 (0.79 – 1.04) |

IPT – INH preventive therapy; LBW – Low birth weight < 2500g; Misc – miscarriage; NND – neonatal death; SB – stillbirth

Adjusted for maternal age, first recorded pregnancy, ART prior to pregnancy, history of TB disease, CD category, VL suppression category, booking and/or delivery in primary care.

IPT exposure from after 14 weeks of gestation compared to IPT exposure prior 14 weeks gestation was also associated with a reduction in odds of an adverse pregnancy outcome (aOR 0.64; 95% CI 0.55 to 0.75). Again, this reduction in adverse outcome was driven by the reduction in miscarriage (refer Table 5). However, although the study defined any loss before 27 weeks as a miscarriage, risk of miscarriage decreases significantly with advancing gestation. (19) Therefore, survival bias is introduced in the cohort of women exposed to IPT after 14 weeks of gestation. For any women to be classified as IPT exposed after 14 weeks gestation, the pregnancy must have been viable and survived

until 14 weeks gestation. These pregnancies would have therefore, already passed the period of greatest risk, explaining the apparent reduction in miscarriage events reported when compared to no IPT or IPT initiated prior to 14 weeks.

In those exposed to IPT prior to 14 weeks gestation compared to no IPT exposure, no significant difference in the composite adverse pregnancy outcome were reported (aOR 1.04; 95% CI 0.94 to 1.16)(refer Table 3). However, examination of the individual components of the composite outcome, reveal a statistically significantly increased odds of miscarriage associated with first trimester exposure to IPT (aOR 1.39; 95% CI 1.11 to 1.75).

### 3.6. Hamada et al.

Hamada et al. conducted a systematic review and meta-analysis of the safety of IPT in pregnancy. Randomized and non-randomized studies of pregnant or postpartum women, regardless of HIV status, where the intervention was preventive treatment with daily isoniazid alone for 6 months or longer, and the comparator was another preventive treatment regimen or no preventive treatment (including deferred provision until postpartum in the comparison group) were included. Additionally, to be included, studies needed to have reported on the following outcomes: permanent drug discontinuation due to adverse drug reaction; grade 3 or grade 4 drug related toxic effects; death from any cause; hepatotoxicity; in utero fetal death; neonatal death; preterm delivery/prematurity; intrauterine growth restriction; low birth weight or congenital anomalies. In the systematic review, randomized and non-randomized studies, including those without a comparator group were eligible for inclusion.

The systematic review was assessed as "low quality", using the AMSTAR 2 appraisal tool as the description of the included studies did not contain adequate detail (e.g. duration of follow up), as sources of funding for studies included in the review were not reported, and as they did not provide a list of excluded studies (although the reasons for exclusion were described).

Databases were searched from inception until 15 May 2019. Nine studies were included after full text review(1, 11, 12, 16, 18, 20-23), of which only 1 study was a randomized controlled trial.(1) This RCT was assessed to have some concern for bias due to missing outcome data, and is previously summarized in section 3.1. The outcomes from this RCT relating to infant growth emerged after this systematic review was conducted, and were not included in this analysis. (15)

Of the 8 non-randomized studies included, three had no control/comparator arm and did not contribute to any of the pooled analyses.(12, 21, 23) Another 2 non-randomized studies conducted comparisons between IPT and other preventive regimens, rather than placebo/no treatment/deferred treatment, and are not summarized further here. (11, 20). The three remaining non-randomized studies were considered to be at serious risk of bias, specifically related to confounding.(8, 16, 18) These three studies are summarized in sections 3.2, 3.4 and 3.5 above. Notably, the data included in the systematic review from the study by Kalk et al. was derived from the analysis of the same cohort data published in 2020, but from a conference abstract presented in 2018.(8, 22) Furthermore, the analysis of the BRIEF-TB trial is not included in this systematic review as it was published in 2023. (17)

Due to significant heterogeneity between study types, data from the RCT and non-randomized studies could not be pooled for the outcome hepatotoxicity. Similarly, for maternal death, the RCT by Gupta et al. and pooled analysis of 2 non-randomized studies by Kalk et al. and Salazar-Austin et al. are reported separately and indicated no association with IPT use in pregnancy (Refer Table 6).

*Table 6. Summary of evidence regarding IPT use in pregnant women living with HIV with GRADE assessment by Hamada et al.*[9]

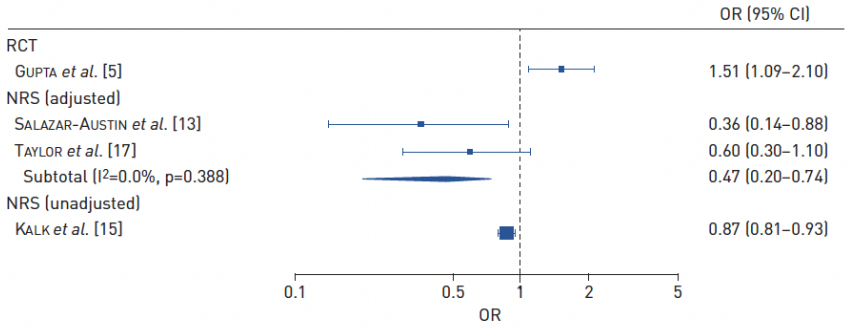
[9] The table contains a correction of an error detected in the review process and confirmed with the primary author of the systematic review.

| 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] Kalk et al. [15] | 3 per 1000 | 2 per 1000 (1 3) | Risk ratio 0.65 (0.39 1.07) | 52097 | ⊕⊕◯◯ (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) | 58242 | ⊕⊕◯◯ (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).

The results for adverse pregnancy outcomes were inconsistent across the included studies. Once again, due to significant heterogeneity, data from the RCT could not be pooled with the non-randomized studies. However, the adjusted estimates from the studies by Taylor et al. and Salazar-Austin et al. were pooled, and suggested that IPT use in pregnancy is associated with a reduction in adverse pregnancy outcomes (OR 0.47; 95% CI 0.20 to 0.74).(16, 18) The estimates from the study by Kalk et al. were unadjusted and could not be pooled with the other non-randomized studies, but suggested the same direction of effect (Refer figure 1 and table 6).

*Figure 1. Forest plot for composite adverse pregnancy outcomes in pregnant women with HIV by IPT exposure from Hamada et al.*




A summary of evidence for the safety of IPT use in pregnant women with HIV is presented in Table 6 with accompanying GRADE certainty of evidence assessment.

## 4 Summary of Evidence

Important differences in study design, population and tuberculosis prevalence between the studies discussed are summarized in Table 7. Key points to note from the evidence

- There is a signal of increased spontaneous miscarriage after first trimester exposure to IPT, compared to no exposure in pregnant women living with HIV on HAART, with relatively high $CD_4$ counts, in some observational studies. (8, 17)

- In an RCT, there was an association between IPT exposure in second and third trimester and low birth weight (<2500g), that may continue to impact infant growth at week 12 and week 48 of life in pregnant women living with HIV on HAART and with relatively high $CD_4$ counts.(1, 14, 15)
- In an RCT of women living with HIV on ART, with high $CD_4$ counts, and without recent close contact to an active tuberculosis case, the risk of developing tuberculosis is similar when IPT is given antenatally versus delayed to 12 weeks post-partum.(1)
- In observational data from a high TB prevalence setting, there is a reduction in incident tuberculosis disease in pregnant women on ART with $CD_4$ counts ≤ 350 cells/$mm^3$ who received IPT during pregnancy, but not for those with CD4 counts >350 cells//$mm^3$. (8)
- Antenatal IPT did not reduce in maternal mortality in the RCT or observational studies.(1, 8, 18)
- Risk of IPT-associated hepatotoxicity may be higher during pregnancy and the postpartum period than in non-pregnant woman (1).
- The reduction in tuberculosis disease seen with antenatal IPT use in women with low $CD_4$ counts may be an explanation for the better pregnancy outcomes seen in observational studies. None of the observational studies were adjusted for important confounders of adverse pregnancy outcomes. (8, 16, 18)
- All the above data were from women living with HIV, and the majority of those on ART were on efavirenz containing regimens.
- We found no comparative data exploring benefits and risks of IPT in HIV-negative pregnant women.

**5. Feasibility considerations**

5.1 Deliberations with the NDoH TB program in March 2024

Following engagement with the NDoH program guideline team and other stakeholders on the 7th March 2024, the following matters were raised for local consideration:

- The TB program team raised concerns with the complexity of multiple guidance for pregnant women at various CD4 counts initiating ART and for pregnant women already established on ART.
    - Especially considering the number of pregnant women starting ART below various CD4 thresholds has not yet been determined.
    - A simplified recommendation applicable to all pregnant patients with HIV would be preferred for ease of implementation.
- It was noted that the evidence of benefit in terms of reduction of TB disease was demonstrated in low-quality observational data from South Africa. But that there was no difference in reduction of TB disease between antenatal IPT and IPT deferred to the postpartum period in data from an RCT. However, it was highlighted that the median CD4 from this RCT was 500, which is much higher than what is observed locally
- The strong signals of harm highlighted by the review were noted.

In light of the above, the group proposed that the following recommendation be considered by NEMLC:

> - Initiation of IPT should be deferred in all pregnant patients until after delivery
> - In the absence of IPT initiation, the importance of ART and continued active screening for TB throughout pregnancy was emphasized.

This recommendation was adopted by NEMLC in November 2024.

5.2 Deliberations with the NDoH TB program in October 2025

In 2023 the NDoH HIV Programme updated the Consolidated ART Guideline10 to clearly outline a specific package of care for people with Advanced HIV Disease (AHD), defined as any client (including pregnant women) with a CD4 count < 200 cells/mm3, or WHO Stage 3 or 4 clinical conditions. This package contains several elements, including:

- systematic TB screening and investigation, and IPT if TB is excluded,

[10] NDoH. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. Accessible online https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

- screening for cryptococcal antigenaemia,
- screening and management of serious bacterial infections,
- CPT prophylaxis,
- ART,
- Adherence support, and
- Intensified follow-up.

Pregnant women with CD4<200 cells/$mm^3$ are also eligible for this package of care for advanced HIV disease. As this package includes IPT, this provides an opportunity to reconsider CD4 count-based stratification to inform the administration of IPT in pregnancy, aligned with the AHD definition (i.e., CD4 < 200). This would allow the benefit of IPT for PWH at higher risk of TB, while minimising the programmatic complexity as the intervention will be nested within the newly established AHD programme, rather than a stand-alone intervention.

The TB programme have therefore suggested revisiting inclusion of a CD4 cut off, but used the AHD definition i.e. CD4<200 to guide initiation of IPT, so that IPT is administered to PWLWHA as part of the AHD package of care.

*Table 7. Summary of important differences between studies reviewed.*

| Study Author, Study Type | N | % on HAART on entry into study | Median CD4 (cells/mm$^3$) | % Viral Load Suppressed | % on efavirenz based HAART | % participants confirmed with latent TB infection | TB Prevalence by Geographic Location of enrolment | % participants initiated on IPT by trimester | Effect |
|---|---|---|---|---|---|---|---|---|---|
| Gupta et al.<br><br>Randomized controlled trial | 956 | 100% | 493 | 62.83% | 85.1% | 30% positive IGRA | Zimbabwe: 33.37% (344 per 100 000) (24)<br><br>South Africa: 19% (681 per 100 000)(8)<br><br>Uganda 17.36% (401 per 100 000)(24)<br><br>Botswana: 12.55% (305 per 100 000)(25) | No 1st trimester IPT initiation.<br><br>IPT initiation between 14 – 24 weeks: 33.6%<br><br>IPT initiation >24 weeks: 66.4% | Increased adverse pregnancy outcome, specifically low birth weight, after second/third trimester exposure.<br><br>Increased risk of underweight for infant exposed antenatally. |
| Kalk et al.<br><br>Retrospective cohort study | 43 971 | 76.8% | 422<br>$CD_4$ < 200: 9.7% | 57.4% | Not reported | Not reported. | South Africa: 100% (681 per 100 000)(8) | IPT initiation < 14 weeks: 36.2%<br><br>IPT initiation ≥ 14 weeks: 63.8% | Decreased adverse pregnancy outcomes.<br><br>IPT < 14 weeks associated with increased miscarriage compared to no IPT. |
| Taylor et al.<br><br>Nested prospective cohort study | 196 | (Pre-universal ART) 37% | 368<br>$CD_4$< 200: 16% | Not reported | Not reported | Not reported. | Botswana: 100% (305 per 100 000)(25) | 1st trimester IPT initiation: 99% | No association. |
| Gupta et al. 2023<br><br>Nested prospective cohort study | 128 | (Pre-universal ART) 35% | 534 | Not reported | 64% in IPT exposed group at pregnancy outcome<br><br>87% in unexposed group at pregnancy outcome. | 20% positive TST (but testing limited by shortage of reagents) | South Africa: 28.12% (681 per 100 000)(8)<br><br>Botswana: 26.56% (305 per 100 000)(25)<br><br>Haiti: 18.75% (254 per 100 000)(26)<br><br>Kenya: 10.16% (558 per 100 000)(24) | 1st trimester IPT initiation: 100%<br><br>(All IPT exposed pregnancies were conceived while taking isoniazid.) | Increased adverse pregnancy outcomes, specifically miscarriage, after first trimester exposure. |
| Salazar Austin et al.<br><br>Prospective cohort study | 155 | 71.52% on HAART | 364 - 373<br>(No IPT vs. IPT) | 47.68% | 60.26 % | Not reported. | South Africa: 100% (681 per 100 000)(8) | 1st trimester IPT initiation: 3%<br>2nd trimester IPT initiation: 48%<br>3rd trimester IPT initiation: 49% | Decreased adverse pregnancy outcomes. |

| PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION: | | | | | |
|---|---|---|---|---|---|
| **Type of recommendation** | We recommend against the option and for the alternative **(strong)** | We suggest not to use the option **(conditional)** | We suggest using either the option or the alternative **(conditional)** | We suggest using the option **(conditional)** | We recommend the option **(strong)** |
| | | | | **X** | |

**ERC Recommendation 13 November 2025:** We recommend that pregnant women living with HIV, with:

- $CD_4$ counts ≤ 200 cells/$mm^3$ and starting ART, receive 12 months of IPT after exclusion of active tuberculosis disease.
- $CD_4$ counts > 200 cells/$mm^3$ and starting ART, IPT should be deferred to the post-partum period.

*Rationale: The benefit of IPT in preventing tuberculosis disease at CD4 counts ≤ 350 cells/$m^3$(low certainty evidence) outweighs the increased risk of adverse pregnancy outcomes. However, in pregnant women with higher $CD_4$ counts, the increased risk of miscarriage after first trimester IPT exposure (low certainty evidence) and increased risk of low birth weight and underweight for age after second trimester IPT exposure (moderate certainty evidence) outweighs any potential benefit (moderate certainty evidence). However, a CD4 cut off of 350 was not deemed programmatically feasible. The current programmatic "package of care" for patients with advanced HIV (CD4< 200), for which. pregnant women are eligible, includes IPT. The ERC therefore suggests administering 12 months of IPT for all pregnant women with newly diagnosed HIV with a CD4< 200, co-initiated with ART, after screening for active TB, as part of the AHD package of care*

**Level of Evidence:**

Risk of adverse pregnancy outcomes after first trimester exposure (low certainty evidence from observational studies and cohort studies nested in randomised controlled trials)

Risk of adverse pregnancy outcomes after second trimester exposure (moderate certainty evidence from a randomized controlled trial)

Evidence of benefit at $CD_4$ ≤ 350 cells/$mm^3$ (low certainty evidence from an observational study)

**Review indicator:** New high quality evidence of benefit or harm.

**NEMLC RECOMMENDATION (MEETING 27 November 2025): NEMLC supports the ERC recommendation as detailed above (dated 13 Nov 2025).**

**Monitoring and evaluation considerations, and research priorities:**

Pregnant women should be routinely screened for TB at every antenatal visit.

Strenthening of pharmacovigilance systems, with implementaiton of measures for identifying signals of drug-related harm in pregnant women.

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**APPENDIX 1: HISTORIC ERC/NEMLC RECOMMENDATIONS**

**Textbox 1: ERC/NEMLC Recommendation (2017-2019 review cycle)**

**NEMLC Recommendation:** *IPT deferral if CD4 ≥350 in pregnant women; whilst where CD4<350, active TB to be excluded with symptom screen and then IPT given.*

**Rationale:**

*A RCT of immediate versus delayed IPT initiation in pregnant woman found that isoniazid exposure in pregnancy was associated with increased risk of adverse pregnancy outcome (fetal demise, low birth weight, preterm delivery and congenital anomaly). Isoniazid should therefore be deferred until after delivery, except in women who are severely immunocompromised and have low CD4s. Subsequently, a local retrospective cohort study[31] (n= 43 971) showed that antenatal IPT is safe with greatest benefit against active TB when CD4 ≤350 cells/mm3.*

**Level of Evidence: II Cohort Study**

**Textbox 2: ERC/NEMLC Recommendation (2020-2024 review cycle)**

**Multi stakeholder engagement meeting recommendation- 7 March 2024:**

The consensus recommendation from a multi stakeholder engagement meeting, which included representatives from the NEMLC, NDOH TB and maternal healthcare programs and South African Medical Research Council (SAMRC) with reference to local feasibility considerations, is as follows:

- Initiation of IPT should be deferred in all pregnant patients until after delivery
- In the absence of IPT initiation, the importance of ART and continued active screening for TB throughout pregnancy must be emphasized.

*Rationale: While the evidence in support of the ERC recommendation dated 9 November 2023 above was not in dispute, concern was expressed with the complexity of multiple guidance for pregnant women at various CD4 counts initiating ART and for pregnant women already established on ART. The consensus recommendation from the multi stakeholder group was therefore for a less complex recommendation to avoid IPT in pregnancy in all pregnant women, regardless of HIV status or CD4 count. It was noted at the meeting that screening for TB as part of routine antenatal care is already included in programmatic guidance, to identify pregnant women with tuberculosis disease timeously and initiate appropriate antituberculosis treatment.*

**ERC Recommendation: Mar 2024**

The ERC recommends that pregnant women living with HIV, with:

- $CD_4$ counts ≤ 350/mm$^3$ and starting ART, receive 12 months of IPT after exclusion of active tuberculosis disease.
- $CD_4$ counts > 350 cells/mm$^3$ and starting ART, IPT should be deferred to the post-partum period.

*Rationale: The benefit of IPT in preventing tuberculosis disease at CD4 counts ≤ 350 cells/m$^3$(low certainty evidence) outweighs the increased risk of adverse pregnancy outcomes. However, in pregnant women with higher $CD_4$ counts, the increased risk of miscarriage after first trimester IPT exposure (low certainty evidence) and increased risk of low birth weight and underweight for age after second trimester IPT exposure (moderate certainty evidence) outweighs any potential benefit (moderate certainty evidence).*

**Level of Evidence:**

Risk of adverse pregnancy outcomes after first trimester exposure (low certainty evidence from observational studies and cohort studies nested in randomised controlled trials)

Risk of adverse pregnancy outcomes after second trimester exposure (moderate certainty evidence from a randomized controlled trial)

Evidence of benefit at $CD_4$ ≤ 350 cells/mm$^3$ (low certainty evidence from an observational study)

**Review indicator:** New high quality evidence of benefit or harm.

**NEMLC RECOMMENDATION (MEETING OF 14 March 2024):** NEMLC supported the multi stakeholder recommendation that IPT be avoided during pregnancy.