

ICAP Journal Club

ICAP's Journal Club is designed to inform ICAP staff and colleagues of the latest scientific literature by providing a succinct summary and critical analysis of important studies, and by discussing the implications of the research on clinical work.

Article

Gupta A, Montepiedra G, Aaron L, et al for the IMPAACT P1078 TB APPRISE Study Team. **Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women.** *N Engl J Med.* 2019;381(14):1333-1346. <https://www.nejm.org/doi/10.1056/NEJMoa1813060>

Study Summary

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network P1078 TB APPRISE trial (TB Ante vs. Postpartum Prevention with INH in HIV Seropositive Mothers and Their Exposed Infants) was a multicenter, double-blind, placebo-controlled, randomized non-inferiority trial that evaluated the safety and efficacy of initiating isoniazid preventive therapy (IPT) in pregnant women living with HIV.

Study Setting

- Thirteen sites in eight countries that have a high prevalence of tuberculosis (TB), defined as ≥ 60 cases per 100,000 population.

Methods

- Pregnant women were eligible to participate if they were ≥ 18 years old, living with HIV, between 14 weeks and 34 weeks of gestation, weighed ≥ 35 kilograms, had an absolute neutrophil count of ≥ 750 cells/cubic millimeter, a hemoglobin of ≥ 7.5 grams/deciliter, a platelet count of $\geq 50,000$ per/cubic millimeter, and levels of aspartate aminotransferase, alanine aminotransferase, and total bilirubin ≤ 1.25 times the upper limit of the normal range.
- Women were excluded for suspected active TB, recent known TB exposure, treatment for TB for >30 days in the previous year, evidence of recent acute hepatitis, or peripheral neuropathy of grade 1 or higher.
- Participants were randomly assigned (1:1) to begin taking oral isoniazid (300 mg daily) either during pregnancy (immediate group) or at week 12 after delivery (deferred group).
 - The immediate group received isoniazid for 28 weeks and then received placebo until week 40 after delivery.
 - The deferred group received placebo from the time of trial entry until week 12 after delivery and then received isoniazid for 28 weeks.
- All women received open-label pyridoxine and a prenatal multivitamin from the time of trial entry until week 40 after delivery.
- Randomization was stratified by duration of gestation at trial entry (≥ 14 weeks to <24 weeks or ≥ 24 weeks to ≤ 34 weeks).

- The primary outcome was a composite safety outcome of maternal adverse events of grade 3 or higher or permanent discontinuation of the trial regimen because of toxic effects, through week 48 after delivery.
- Secondary maternal outcomes included adverse events of grade 3 or higher from any cause, hepatotoxicity, death, and TB.
- Secondary infant outcomes included adverse events of grade 3 or higher, TB, and death, assessed through week 48 after birth.
- The composite adverse pregnancy outcome was stillbirth (fetal death ≥ 20 weeks) or spontaneous abortion (loss of pregnancy before 20 weeks), low birth weight (< 2500 g), preterm delivery (before 37 weeks of gestation), or major congenital anomalies.
- The composite severe adverse pregnancy outcome was stillbirth or spontaneous abortion, very low birth weight (< 1500 g), very preterm delivery (before 34 weeks), or major congenital anomalies.
- Non-inferiority was defined as the upper boundary of the 95% confidence interval (CI) for the between-group difference in the incidence rate of < 5 events per 100 person-years.

Study Population and Follow-up

- From August 2014 through April 2016, a total of 956 participants were enrolled, with 477 women assigned to the immediate group and 479 to the deferred group.
- The median age of participants was 29 years, 90.5% were black African, and 33.6% had a duration of gestation between 14 weeks and < 24 weeks.
- Participants had a median CD4 count of 493 cells/cubic millimeter; all participants except one were receiving antiretroviral therapy (ART), and the majority (85.1%) were on a regimen that included efavirenz (EFV).
- In total 17.9% of women discontinued the trial prematurely, with the most common reason being participant was lost to follow-up (8.9%), followed by withdrawal of consent (8.2%).
- Of the 879 participants with available adherence data, 85.8% in the immediate group and 87.9% in the deferred group completed at least 90% of the treatment per self-report, and 88.1% in the immediate group and 91.0% in the deferred group completed at least 90% of the treatment according to pill counts.
- There were 926 deliveries, and 909 infants were born alive.

Primary Outcome

- In the intent-to-treat population, a primary outcome event occurred in 15.1% of women in the immediate group and 15.2% in the deferred group (incidence rate, 15.03 and 14.93 events per 100 person-years, respectively; rate difference, 0.10; 95% CI, -4.77 to 4.98), which met the criterion for non-inferiority of immediate treatment to deferred treatment.

Maternal Secondary Outcomes

- There was no significant difference between the groups in incidence of any adverse event of grade 3 or higher, peripheral neuropathy, or hepatotoxicity (incidence rate 5.80 per 100 person-years in immediate group and 6.69 per 100 person-years in deferred group; rate difference, -0.89 ; 95% CI, -3.98 to 2.19).
- Six women died in the postpartum period, two in the immediate group and four in the deferred group. The primary cause of death in four of the women (one in the immediate

group and three in the deferred group) was liver failure; two of the four had received isoniazid and all were on EFV-based ART.

- TB developed in three women in each group, and all cases occurred during the postpartum period. The incidence rate of maternal TB was 0.60 and 0.59 per 100 person-years in the immediate and deferred group, respectively (rate difference, 0.01; 95% CI, -0.94 to 0.96).

Pregnancy and Infant Secondary Outcomes

- A greater percentage of women in the immediate group than in the deferred group had a composite adverse pregnancy outcome event (23.6% vs. 17.0%; difference, 6.7%; 95% CI, 0.8 to 11.9; $p=0.01$).
- There was a higher frequency of each of the individual adverse pregnancy outcomes in the immediate group than in the deferred group, but none of the between-group differences were significant.
- No significant difference was observed between the immediate group and the deferred group in the composite severe adverse pregnancy outcome (6.3% vs. 4.6%; difference, 1.7%; 95% CI, -1.3 to 4.8).
- No difference in grade 3 or 4 adverse events, HIV infection, TB infection or death assessed through week 48 after birth were found among the infants in each group.

Critical Analysis

This multicenter, double-blind, placebo-controlled randomized trial found that IPT initiated during the second and third trimester of pregnancy in women living with HIV was non-inferior to initiation at three months after delivery with respect to maternal adverse events. However, a higher incidence of adverse pregnancy outcomes was observed in the immediate group than in the deferred group, and there was no difference in maternal TB incidence between the two groups.

The following points should be considered when interpreting the study findings:

- Although the incidence of individual adverse pregnancy outcomes was not significantly different between the groups, the study was not powered to detect a difference in these individual outcomes.
- Participants had relatively high CD4 cell counts, and only 30.0% had documented latent TB infection at enrollment, which may have contributed to low TB incidence rates observed in both groups.
- The trial excluded women with recent TB exposure, a population that may have benefited more from IPT.
- Women were also excluded if they were in their first trimester, therefore the effect of isoniazid on organogenesis was not evaluated.
- The trial included monthly monitoring of liver enzymes, which is not the standard of care in most settings, and may reduce the generalizability of the safety findings.
- The majority of women were on EFV, which is also known for hepatotoxicity, making it difficult to isolate effects of isoniazid on hepatic safety outcomes.

Implications

This multicenter, double-blind, placebo-controlled, randomized, non-inferiority trial found that IPT initiation during pregnancy in women with HIV living in areas with a high TB prevalence was as safe as deferring IPT to three months after delivery with respect to maternal treatment-related adverse events. However, evidence of an increased rate of adverse pregnancy outcomes in women who initiated IPT during pregnancy was found, and no added benefit with respect to risk of TB was observed. Currently the World Health Organization recommends IPT during pregnancy¹, but these results suggest that the risks may outweigh the benefits in pregnant women living with HIV, and further investigation is warranted to determine the optimal timing of TB preventive treatment initiation in this population.

This article synopsis was written by Cassia Wells. Share your thoughts on this article or suggest an article for Journal Club by emailing her at caw2208@columbia.edu.

Reference

- 1) World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018. <https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/>