Clinical Infectious Diseases

MAJOR ARTICLE

Individual and Composite Adverse Pregnancy Outcomes in a Randomized Trial on Isoniazid Preventative Therapy Among Women Living With Human Immunodeficiency Virus

Gerhard Theron,[1] Grace Montepiedra,[2] Lisa Aaron,[2] Katie McCarthy,[3] Nahida Chakhtoura,[4] Patrick Jean-Philippe,[5] Bonnie Zimmer,[6] Amy James Loftis,[7] Tsungai Chipato,[8] Teacler Nematadzira,[9] Mandisa Nyati,[10] Carolyne Onyango-Makumbi,[11] Gaerolwe Masheto,[12] James Ngocho,[13] Fuanglada Tongprasert,[14,15] Sandesh Patil,[16] Dominique Lespinasse,[17] Adriana Weinberg,[18] and Amita Gupta[19]; for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1078 Tuberculosis (TB) APPRISE Study Team.

[1]Department of Obstetrics and Gynaecology, Stellenbosch University, Cape Town, South Africa, [2]Center for Biostatistics in AIDS Research, Harvard TH Chan School of Public Health, Boston, Massachusetts, USA, [3]FHI 360, Durham, North Carolina, USA, [4]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland, USA, [5]National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA, [6]Frontier Science Foundation, Amherst, New York, USA, [7]University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, [8]Department of Obstetrics and Gynaecology, University of Zimbabwe College of Health Sciences, Harare, Zimbabwe, [9]University of Zimbabwe College of Health Sciences–Clinical Trials Research Centre, Harare, Zimbabwe, [10]Perinatal Human Immunodeficiency Virus (HIV) Research Unit, University of the Witwatersrand, Johannesburg, South Africa, [11]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [12]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, [13]Department of Epidemiology and Applied Biostatistics, Kilimanjaro Christian Medical University College, Moshi, Tanzania, [14]Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai, Thailand, [15]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand, [16]Byramjee Jeejeebhoy Government Medical College, Johns Hopkins University Clinical Research Site, Pune, India, [17]Les Centres GHESKIO, Port-au-Prince, Haiti, [18]Departments of Pediatrics, Medicine and Pathology, University of Colorado Denver Anschutz Medical Center, Aurora, Colorado, USA, and [19]Center for Clinical Global Health Education, Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Background. International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1078, a randomized noninferiority study designed to compare the safety of starting isoniazid preventive therapy (IPT) in women living with human immunodeficiency virus (HIV) either during pregnancy or after delivery, showed that IPT during pregnancy increased the risk of composite adverse pregnancy outcomes, but not individual outcomes. Many known factors are associated with adverse pregnancy outcomes: these factors' associations and effect modifications with IPT and pregnancy outcomes were examined.

Methods. Pregnant women living with HIV from 8 countries with tuberculosis incidences >60/100 000 were randomly assigned to initiate 28 weeks of IPT either during pregnancy or at 12 weeks after delivery. Using univariable and multivariable logistic regression and adjusting for factors associated with pregnancy outcomes, composite and individual adverse pregnancy outcome measures were analyzed.

Results. This secondary analysis included 925 mother-infant pairs. All mothers were receiving antiretrovirals. The adjusted odds of fetal demise, preterm delivery (PTD), low birth weight (LBW), or a congenital anomaly (composite outcome 1) were 1.63 times higher among women on immediate compared to deferred IPT (95% confidence interval [CI], 1.15–2.31). The odds of fetal demise, PTD, LBW, or neonatal death within 28 days (composite outcome 2) were 1.62 times higher among women on immediate IPT (95% CI, 1.14–2.30). The odds of early neonatal death within 7 days, fetal demise, PTD, or LBW (composite outcome 3) were 1.74 times higher among women on immediate IPT (95% CI, 1.22–2.49).

Conclusions. We confirmed higher risks of adverse pregnancy outcomes associated with the initiation of IPT during pregnancy, after adjusting for known risk factors for adverse pregnancy outcomes.

Keywords. adverse pregnancy outcomes; IPT.

Globally, an estimated 10 million people developed tuberculosis (TB) disease in 2018, with 251 000 deaths among people living with human immunodeficiency virus (HIV) [1]. Of those who developed TB, 5.7 million were men, 3.2 million women, and 1.1 million children. People living with HIV comprise 8.6% of the total, of which the vast majority are living in Africa. Active TB is particularly prevalent during pregnancy and the postpartum period [2–5]. TB disease during pregnancy or the early postpartum period is associated with adverse maternal, pregnancy, and infant outcomes [2, 6, 7]. Active TB in women

Received 19 May 2020; editorial decision 18 September 2020; published online 30 September 2020.

Correspondence: G. Theron, Department of Obstetrics and Gynaecology, Stellenbosch University, Cape Town, South Africa (gbth@sun.ac.za).

Clinical Infectious Diseases® 2021;72(11):e784–90

DOI: 10.1093/cid/ciaa1482

living with HIV is an independent risk factor for nonobstetric maternal mortality. According to national maternal mortality data in South Africa, for example, nonpregnancy related infections are the leading cause of maternal deaths, accounting for 968 (35.2%) of all maternal deaths between 2014 to 2016 [8]. The vast majority of deaths occurred in women living with HIV, and TB was the most common final cause of death in 336 (34.7%) women.

A network meta-analysis of randomized controlled trials of the treatment of latent TB infection, comparing 6 months of INH versus a placebo in adults and children, showed a reduction of active TB, with an odds ratio of 0.61 (95% confidence interval [CI], .48–.77) [9]. However, this meta-analysis did not include any safety or efficacy data for isoniazid preventive therapy (IPT) in pregnant women, including those taking combination antiretroviral therapy (ART), as pregnant women consistently have been excluded from IPT trials [10–15].

Small studies, however, involving women living with HIV, including those that became pregnant on IPT, as well as retrospective studies including pregnant women on IPT, did not identify any specific toxicity concerns or increased adverse pregnancy outcomes [16–18]. Based on these data, the World Health Organization (WHO) strongly recommends IPT for latent TB infection in people living with HIV, including pregnant women [1]. However, pregnant women living with HIV, especially if on ART, may have a higher risk of adverse events [19]. Understanding the relative risks and benefits of therapies used in pregnancy is critical.

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1078, TB APPRISE, was a Phase IV, randomized, double-blind, placebo-controlled noninferiority study to evaluate the safety of immediate (antepartum-initiated) versus deferred (postpartum-initiated) IPT among 956 pregnant women living with HIV and their infants in high–TB incidence settings [20]. IPT initiated in pregnancy was noninferior to initiation at 12 weeks postpartum with respect to adverse events—defined as Grade 3 maternal adverse events possibly, probably, or definitely related to the study drug (INH or placebo)—or permanent discontinuation of the study drug due to toxicity by Week 48 postpartum. However, surprisingly, IPT initiated during pregnancy was associated with an increased risk of the secondary endpoint of composite adverse pregnancy outcomes, defined as fetal demise (stillbirths or spontaneous abortions), preterm delivery (PTD), low birth weight (LBW), or a congenital anomaly. Given there are many known contributors to adverse pregnancy outcomes, such as twin gestation, infection, smoking, or hypertension, that could explain our initial findings, we performed an in-depth evaluation of the burdens and risk factors for adverse pregnancy outcomes, and explored the potential modification effect of these factors by IPT study arm.

METHODS

IMPAACT P1078 enrolled pregnant women living with HIV at ≥14 through to ≤34 weeks and 6 days gestation [20]. The study population was at high risk for TB infection and disease due to residing in 8 high–TB prevalence countries, defined as having 60 or more TB cases per 100 000 population in the WHO TB annual report (sub-Saharan Africa: Botswana, South Africa, Tanzania, Uganda, and Zimbabwe; Asia: India and Thailand; and Central America: Haiti) [1]. Women with suspected or confirmed TB disease were excluded.

Women were randomized to receive either 28 weeks of IPT or placebo. The immediate arm initiated IPT in pregnancy, while the deferred arm initiated IPT at 12 weeks postpartum. Women also received vitamin B6 and multivitamins from study entry until 40 weeks postpartum.

We previously published the primary outcome, defined as Grade 3 or higher maternal adverse events possibly, probably, or definitely related to the study drug (INH or placebo), or permanent discontinuation of the study drug due to toxicity by Week 48 postpartum, whichever occurred first. We also briefly reported on the secondary maternal outcomes of all-cause adverse events ≥Grade 3, hepatotoxicity, death, and TB occurring by Week 48 postpartum. We unexpectedly identified that IPT given during pregnancy was associated with a 6% increased risk difference of composite adverse pregnancy outcomes as compared to deferred IPT. We focused this analysis on the risk factors associated with adverse pregnancy outcomes, and on interactions between IPT study arm and adverse pregnancy outcomes.

Adverse pregnancy outcomes recorded in the study were PTD (gestation <37 weeks using the Ballard examination, when available, or obstetrical estimate), LBW (<2500 grams at birth), congenital anomaly (according to the Metropolitan Atlanta Congenital Defects Program of the US Centers for Disease Control and Prevention), spontaneous abortion (gestation <20 weeks), stillbirth (gestation ≥20 weeks), early neonatal death (<7 days), and neonatal death (<28 days) [21, 22]. The following were the composite outcome measures of interest used in the primary paper: spontaneous abortion, stillbirth, PTD, LBW, and congenital anomaly (composite outcome 1) [20]. For this analysis, we included neonatal death and early neonatal death in 2 additional composite outcomes (composite outcomes 2 and 3, respectively). We excluded congenital anomalies from these 2 new composite measures, as we enrolled women in their second trimester (ie, beyond the key period of exposure for risk of congenital anomalies) and because INH is not considered to be teratogenic [23]. We also evaluated perinatal mortality, defined as a composite of spontaneous abortion, stillbirth, early neonatal death, and neonatal death. Lastly, the individual outcomes of LBW and PTD were assessed.

Statistical Analysis

The analyses of composite outcomes and perinatal mortality included mother-infant (M-I) pairs with at least 1 live birth, stillbirth, or spontaneous abortion. The analyses of LBW and PTD included M-I pairs with at least 1 live birth. Twin M-I pairs where at least 1 infant has a missing outcome and the other infant(s) did not meet any of the outcomes were considered missing and were excluded.

Logistic regression models were fit to assess the association of each adverse pregnancy outcome of interest with study arm, stratified by gestational age (14 to <24 weeks vs 24–34 weeks), and adjusted for important covariates. Multiple logistic regression models included potential risk factors with $P < .15$ in the univariate analysis, with the following maternal characteristics considered: maternal age, ART regimen, timing of ART initiation, CD4 count, plasma HIV RNA, hepatitis B surface antigen (HBsAG) status, hepatitis C serology, interferon-gamma release assay (IGRA) status, mid-upper arm circumference (MUAC), twin pregnancy, current smoker, food insecurity, noninfectious pregnancy complication, infectious pregnancy complication, and maternal hospitalization. The interactions of the study arm with each of the identified significant risk factors were tested to identify potential effect modifiers of the treatment arm. *P* values less than .05 were considered statistically significant.

Trial Oversight

The trial was approved by local and collaborating institutional review boards and reviewed every 6 months by an independent data and safety monitoring board. All women provided written informed consent. In February 2016, as requested by the data and safety monitoring board, a patient safety letter was issued to all participants about potential risks of IPT and ART after 2 deaths from fulminant liver failure occurred. The data were provided by the research sites and analyzed by the IMPAACT Statistical Data Analysis Center, according to statistical analysis plans.

RESULTS

Of 956 women enrolled, 926 women had pregnancy outcome data, of which 899 had at least 1 live birth, 26 had at least 1 stillbirth or spontaneous abortion (fetal demise), and 1 had an induced abortion (Table 1). Excluding the 1 induced abortion, we analyzed 925 women who had at least 1 live birth or fetal demise. Participant sociodemographic and clinical factors are summarized in Table 2. Most women (842; 91.0%) were recruited from sub-Saharan Africa, with 32 (3.5%) from Thailand, 31 (3.4%) from India, and 20 (2.2%) from Haiti. Of these, 914 women had singletons and 11 had twins. The median CD4 count at baseline was 494 cells/mm^3, and 581 women (62.8%) had HIV RNA less than the lower limit of quantification (LLOQ). All women were receiving ART at study entry, with 85% taking an efavirenz-containing regimen and 13% taking a nevirapine-containing regimen. The median maternal age at delivery was 30 years.

Table 1. Summary of Pregnancy Outcomes Overall and by Study Arm

Pregnancy outcome	Immediate INH, n = 460	Deferred INH, n = 466	Total, n = 926
Live births			
Singletons	439 (95%)	451 (97%)	890 (96%)
Twins	3 (1%)	6 (1%)	9 (1%)
Stillbirth, IUFD ≥ 20 wks			
Singletons	15 (3%)	8 (2%)	23 (2%)
Twins	1 (<1%)	0 (0%)	1 (0%)
Spontaneous abortion, <20 wks, singletons only	1 (<1%)	0 (0%)	1 (<1%)
Induced abortion, singletons only	1 (<1%)	0 (0%)	1 (<1%)
Discordant twin birth outcome: 1 live birth, 1 stillbirth	0 (0%)	1 (<1%)	1 (<1%)

Of the women, 8% (n = 70) experienced at least 1 infectious pregnancy complication, with the most common infectious complication being vulvovaginal candidiasis (n = 63), while 18% (n = 170) experienced at least 1 noninfectious pregnancy complication. The most common noninfectious pregnancy complications were gestational hypertension (n = 24), vomiting (n = 17), vaginal hemorrhage (n = 16), and preeclampsia (n = 14). There were 6 maternal deaths: 2 in the immediate arm and 4 in the deferred arm. All the deaths occurred between 5 and 39 weeks postpartum.

The risk factors that met the criteria for inclusion in the multivariable logistic regression models were maternal age at delivery, CD4 quartile, HIV RNA < LLOQ, timing of ART initiation, HBsAg status, MUAC, IGRA status, twin versus singleton pregnancy, current smoking status, noninfectious pregnancy complications, infectious pregnancy complications, and hospitalization (7 risk factors mentioned in the subsequent paragraphs are included in Table 3). The adjusted odds ratio estimates of the risk factors significantly associated with adverse pregnancy outcomes when comparing the immediate treatment arm to the deferred arm are summarized in Table 4.

The adjusted odds of fetal demise, PTD, LBW, or congenital anomaly (composite outcome 1) were 1.63 times higher among women in the immediate IPT arm, compared to the deferred IPT arm (95% CI, 1.15–2.31; $P = .007$). HBsAg positivity, lower MUAC, twin versus singleton pregnancy, and having a noninfectious pregnancy complication were also associated with higher odds of composite outcome 1. The logistic regression analysis also found that the adjusted odds of fetal demise, PTD, LBW, or neonatal death within 28 days (composite outcome 2) were 1.62 times higher among women in the immediate IPT arm as compared to the deferred arm (95% CI, 1.14–2.30;

Table 2. Baseline Maternal Demographic Characteristics and Clinical Factors Among Women With Delivery Outcomes

Characteristic	Group	Total, n = 925
Treatment group	Immediate INH	459 (49.6%)
	Deferred INH	466 (50.4%)
Efavirenz-containing ARV regimen	Yes	784 (84.8%)
	No	141 (15.2%)
Timing of initiation of EFV	Before pregnancy	226 (24.4%)
	First trimester	102 (11.0%)
	Second or third trimester	465 (50.3%)
	Postpartum/never initiated	132 (14.3%)
Nevirapine-containing ARV regimen	Yes	121 (13.1%)
	No	804 (86.9%)
Timing of initiation of NVP	Before pregnancy	128 (13.8%)
	First trimester	7 (.8%)
	Second or third trimester	9 (1.0%)
	Postpartum/never initiated	781 (84.4%)
Timing of initiation of ART	Before pregnancy	362 (39.1%)
	First trimester	103 (11.1%)
	Second or third trimester	460 (49.7%)
Years of age at delivery	Number missing	0
	Mean (SD)	30 (6)
	Min, max	18, 46
	Median (Q1, Q3)	30 (25, 34)
Age at delivery	18 to <21	40 (4.3%)
	21 to <35	668 (72.2%)
	≥35	217 (23.5%)
Country	Botswana	118 (12.8%)
	Haiti	20 (2.2%)
	India	31 (3.4%)
	South Africa	168 (18.2%)
	Tanzania	78 (8.4%)
	Thailand	32 (3.5%)
	Uganda	164 (17.7%)
	Zimbabwe	314 (33.9%)
CD4 count, cells/mm3	Number missing	3
	Mean (SD)	523 (243)
	Range	7 to 1630
	Median (Q1, Q3)	494 (356, 673)
HIV RNA < LLOQ	Yes	581 (62.8%)
	No	342 (37.0%)
	Unknown	2 (.2%)
Mid-upper arm circumference, cm	Number missing	2
	Mean (SD)	29 (4)
	Min, max	13, 45
	Median (Q1, Q3)	28 (26, 31)
Mid-upper arm circumference, category	Severe malnutrition: <18	1 (.1%)
	Moderate malnutrition: 18–21	2 (.2%)
	Mild malnutrition: 21–23	38 (4.1%)
	Normal: >23	882 (95.4%)
	Missing	2 (.2%)
Number of fetuses	Singleton	914 (98.8%)
	Twins	11 (1.2%)
Current smoker	Yes	17 (1.8%)
	No	908 (98.2%)
Food insecurity	Yes	118 (12.8%)
	No	807 (87.2%)
Noninfectious pregnancy complication	Yes	170 (18.4%)
	No	755 (81.6%)
Infectious pregnancy complication	Yes	70 (7.6%)
	No	855 (92.4%)
Hospitalized	Yes	53 (5.7%)
	No	872 (94.3%)

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; HIV, human immunodeficiency virus; LLOQ, lower limit of quantification; Q, quarter; SD, standard deviation.

P = .007), and the adjusted odds of fetal demise, PTD, LBW, or neonatal death within 7 days (composite outcome 3) were 1.74 times higher among women in the immediate arm as compared to the deferred arm (95% CI, 1.22–2.49; P = .002).

Among mothers who had at least 1 live birth, 62 (14.0%) in the immediate arm and 46 (10.0%) in the deferred IPT arm had at least 1 infant with an LBW. This difference was not significant in the unadjusted analysis but became significant after adjustment for covariates. The adjusted odds of an LBW were 1.58 times higher in the immediate arm as compared to the deferred arm (95% CI, 1.02–2.46; P = .041). A lower MUAC, being a current smoker, and having a twin pregnancy were associated with higher odds of an LBW.

The IPT study arm was not associated with perinatal mortality or PTD in univariate or adjusted models. Having a noninfectious pregnancy complication and having a twin pregnancy were associated with higher odds of perinatal mortality. Detectable HIV RNA (with respect to the LLOQ), a lower MUAC, and having a noninfectious pregnancy complication were associated with higher odds of PTD. Infectious pregnancy complications were inversely related to PTDs.

There were no significant interactions of study arm with any of the covariates for any of the adverse pregnancy outcomes (P values ≥ .10 for all outcomes).

DISCUSSION

Until recently, limited data from small studies showed IPT to be safe, and were the basis for including pregnant women in the WHO guidelines of TB prevention. P1078 is the only randomized trial assessing IPT in pregnant women living with HIV, and found a surprising statistically significant increase of 6.7% in the absolute risk difference in composite adverse pregnancy outcomes in those who started IPT in pregnancy as compared to those who deferred to 3 months postpartum [20]. To better understand this

Table 3. Summary of Composite Adverse Pregnancy Outcomes by Treatment Group and Adjusted Odds Ratio Estimates

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.

unexpected finding, our analysis here first identified the burdens and strengths of associations between many of the known risk factors for adverse pregnancy outcomes, including twin pregnancy, maternal nutritional status (as measured by MUAC), and noninfectious complications like hypertension and preeclampsia [24]. Twin gestation was strongly associated with adverse pregnancy outcomes, but only occurred in 9 pregnancies. We also identified noninfectious complications, such as hypertension, preeclampsia, and vaginal hemorrhage, which occurred in 18% of women, as being associated with 2-fold increased odds of composite adverse pregnancy outcomes and 6-fold increased odds of perinatal mortality. Furthermore, as expected, LBW was associated with maternal nutritional status and smoking, while PTD was associated with nutritional status and noninfectious complications and was less likely in women whose HIV was virally suppressed. Secondly, we assessed the associations of IPT exposure with pregnancy and adverse pregnancy outcomes, and observed that even after adjusting for the mentioned contributors, INH use in pregnancy was independently associated with 62–74% increased odds of composite adverse pregnancy outcomes and with 58% increased odds of an LBW as compared to deferring to postpartum IPT initiation. Our analyses confirmed that IPT exposure during pregnancy has a significant, independent effect on adverse pregnancy outcomes.

Table 4. Summary of Covariates Significantly Associated With At Least 1 Adverse Pregnancy Outcome

	Adjusted OR (95% CI)						
Outcome[a]	HBsAG positive vs negative	Normal MUAC	Noninfectious pregnancy complication vs none	Infectious pregnancy complication vs none	Twin gestation vs singleton	Current smoker vs never/previous smoker	HIV RNA < LLOQ vs ≥ LLOQ
Composite 1: fetal demise, PTD, LBW, or congenital anomaly	2.32 (1.01–5.30)	.92 (.87–.96)	2.06 (1.34–3.17)	.46 (.22–1.00)	14.43 (3.35–62.08)	…	…
Composite 2: fetal demise, PTD, LBW, or neonatal death (<28 days)	…	.91 (.87–.96)	2.13 (1.39–3.28)	…	14.51 (3.38–62.29)	…	…
Composite 3: fetal demise, PTD, LBW, or early neonatal death (<7 days)	…	.91 (.87–.96)	2.06 (1.33–3.19)	…	15.02 (3.50–64.38)	…	…
Perinatal death 1: fetal demise or neonatal death	…	…	6.21 (3.14–12.31)	…	…	…	…
Perinatal death 2: fetal demise or early neonatal death	…	…	6.76 (3.18–14.36)	…	6.01 (1.08–33.55)	…	…
LBW: <2500 grams at birth	…	.88 (.83–.94)	…	…	19.09 (3.95–92.35)	3.18 (1.05–9.63)	…
PTD: <37 weeks gestation at delivery	…	.93 (.87–.99)	1.90 (1.08–3.34)	.29 (.09–.98)	…	…	.56 (.32–.97)

The multivariable model includes study arm and the following covariates: maternal age at delivery, CD4 quartiles, HIV RNA < LLOQ, timing of ART initiation, HBsAG status, MUAC, IGRA status, twin versus singleton pregnancy, current smoker, noninfectious pregnancy complications, infectious pregnancy complications, and maternal hospitalization.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HBsAG, hepatitis B surface antigen; HIV, human immunodeficiency virus; IGRA, interferon-gamma release assay; LBW, low birth weight; LLOQ, lower limit of quantification; MUAC, mid-upper arm circumference; OR, odds ratio; PTD, preterm delivery.

[a]Estimates are shown if $P < .05$.

We explored the potential modification effect of being on an ART regimen, as well as other identified risk factors, but did not find any differences. Most women in this study were on an EFV- or NVP-containing regimen. It remains important to examine the potential interactions between other ART regimens and INH exposure during pregnancy, such as the new dolutegravir-based regimen.

The analysis adjusting for important risk factors found stronger evidence for IPT study arm differences with respect to pregnancy outcomes. We found that fetal demise, PTD, LBW, or a congenital anomaly (composite outcome 1) were significantly more likely among women in the immediate arm compared to the deferred arm. Excluding congenital abnormalities and including neonatal and early neonatal deaths in the analysis (composite outcomes 2 and 3, respectively) also resulted in significantly higher risks among women in the immediate arm as compared to the deferred arm. This finding suggests that INH administration during pregnancy carries an independent risk of adverse pregnancy outcome, as compared to postpartum administration. It is challenging to study the effects of drug exposure in pregnancy, as often pregnant women are excluded from clinical trials and as the sample sizes are often too small to detect small but important effects.

Adjustment for the covariates effectively increased the precision of our estimated effects and the power to detect differences in outcomes by study arm. Interestingly, we found IPT during pregnancy to be independently associated with an LBW in our adjusted models. This is 1 of the factors, along with fetal death/stillbirth, that largely drove the increase in adverse composite pregnancy outcomes. We also found non–statistically significant increases in perinatal mortality and PTD.

In contrast, other studies have reported different findings. Taylor et al [17] found no significant association with adverse pregnancy outcomes in 196 women living with HIV, of which 103 were exposed to IPT in pregnancy, between 2004 and 2006 in Botswana. This study had only 37% of participants on combination ART, with minimal adjustments for risk factors and confounders of pregnancy outcomes.

Subsequently to P1078, a few other groups have looked retrospectively at data from Southern Africa. An observational study by Salazar-Austin et al [18] reported on 151 pregnant women in the Tshepiso cohort, of which only 69 were on IPT between 2011–2014. They reported the adjusted odds of a composite adverse pregnancy outcome as 2.5 times higher (95% CI, 1.0–6.5; $P = .048$) in IPT-unexposed women as compared with IPT-exposed women, after controlling for maternal age, CD4 count, viral load, ART regimen, body mass index, and anemia. IPT-exposed women, however, were enrolled at a significantly lower gestational age of 29 versus 31 weeks ($P = .01$), which was not adjusted for, and were less likely to be on combination ART (65% vs 77% in IPT-exposed women) suggesting that in this nonrandomized study the women who received IPT were not the same as those who did not. Furthermore, the authors found more severe pregnancy outcomes of very low PTD (<34 weeks) and very LBW in those exposed to IPT, but the opposite when assessing just for PTD (<37 weeks) and LBW (<2500 grams). The authors do mention the possibility that healthier women were initiated on IPT, which could have overestimated its effect on pregnancy outcomes.

A second study by Kalk et al [25] conducted a retrospective analysis of South African programmatic data collected between 2015 and 2017. A total of 43 971 pregnant women living with HIV were identified, of which 7310 received IPT. Significant reductions in miscarriages, stillbirths, and LBW babies were found in women commencing IPT subsequently to 14 weeks gestation (adjusted OR, 0.83; 95% CI, .78–.87); however, women who were placed on INH were more likely to be on ART and have higher CD4 counts, lower viral loads, more antenatal care, and less prior TB, and therefore were different from women not started on IPT. There may be more residual confounding and confounding by indication of receipt of IPT that may explain the differences observed, despite adjustments.

The benefits of IPT in improving maternal health by reducing active TB have been proven beyond doubt in randomized trials [9]. All women were enrolled during pregnancy in the parent study, with TB symptoms used as exclusion criterium [20]. All 6 women that developed TB became symptomatic ≥10 weeks postpartum. Our study is the only study that was a randomized trial, making the groups completely comparable between those who did and did not receive IPT in the second and third trimesters of pregnancy. Moreover, here we described the prevalences and associations of factors associated with adverse pregnancy outcomes, as well as confirmed the higher risks of adverse pregnancy outcomes associated with initiation of IPT during pregnancy, after adjusting for known risk factors of adverse pregnancy outcomes. Measures to reduce PTD and LBW rates in low- and middle-income countries are important, as these infants are at an increased mortality risk [26].

Our study does have some limitations. We only studied women living with HIV and on ART, both conditions which also contribute to adverse pregnancy outcomes. We also may have been underpowered to identify subtle effects of IPT on less common individual pregnancy outcomes, such as perinatal death.

The strengths of the study are the larger number of women included in a randomized controlled trial and the multiple logistic regression models, adjusted for covariates. Our findings provide support for deferring the initiation of IPT to 12 weeks postpartum in healthy, pregnant women living with HIV who are on antiretrovirals and are not recent contacts.

Notes

The Clinical Research sites are listed in descending order of recruitment: Makerere University–Johns Hopkins University Research Collaboration (Makerere University–Johns Hopkins University CARE LTD), Uganda; St Mary's, Zimbabwe; Seke North, Zimbabwe; Soweto International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), South Africa; Kilimanjaro Christian Medical Centre, Tanzania; FAM-CRU, South Africa; Harare Family Care, Zimbabwe; Molepolole, Botswana; Gaborone, Botswana; Byramjee Jeejeebhoy Medical College, India; Chiang Mai

University Human Immunodeficiency Virus (HIV) Treatment, Thailand; Les Centres GHESKIO Clinical Research Site, Haiti; and Desmond Tutu Tuberculosis Centre, Stellenbosch University, South Africa.

Acknowledgments. The authors thank the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network and operations staff for their support; their numerous community advisory boards; the international site investigators and research teams; the women and families who participated in the trial; Vandana Kulkarni, who served as the protocol laboratory technologist; Joan Coetzee, who was a field representative; Rebecca LeBlanc, who coordinated sample transfer and central laboratory data management; Vivian Rexroad, who assisted in pharmacy training; and Renee Browning, who was a protocol medical officer; the independent endpoint review committee members; Timothy R. Sterling, who represented scientific inputs on behalf of the US CD-funded Tuberculosis Trials Consortium. The IMPAACT P1078 TB APPRISE Study Team thanks the P1078 mothers and their infants enrolled in the study for their contributions.

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial support. This work was supported by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT), which was funded by the National Institute of Allergy and Infectious Diseases with cofunding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health, all components of the National Institutes of Health (NIH; award numbers UM1AI068632 to the IMPAACT Leadership and Operations Centre; UM1AI068616 to the IMPAACT Statistical Data Management Center; and UM1AI106716 to the IMPAACT Laboratory Center); and by the NICHD (contract number HHSN275201800001I).

Potential conflicts of interest. A. G. was supported by National Institutes of Health grant UM1AI069465. A. G. and G. M. received grant R01 AI142669, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization. Global tuberculosis report 2019 (license: CCBY-NC-SA3.oIGO). Geneva, Switzerland: World Health Organization.
2. Pillay T, Khan M, Moodley J, Adhikari M, Coovadia H. Perinatal tuberculosis and HIV-1: considerations for resource-limited settings. Lancet Infect Dis **2004**; 4:155–65.
3. Mofenson LM, Rodriguez EM, Hershow R, et al. *Mycobacterium tuberculosis* infection in pregnant and nonpregnant women infected with HIV in the Women and Infants Transmission Study. Arch Intern Med **1995**; 155:1066–72.
4. Venkatesh PA, Bosch RJ, McIntosh K, Mugusi F, Msamanga G, Fawzi WW. Predictors of incident tuberculosis among HIV-1-infected women in Tanzania. Int J Tuberc Lung Dis **2005**; 9:1105–11.
5. Vo QT, Stettler W, Crowley K. Pulmonary tuberculosis in pregnancy. Prim Care Update Ob Gyns **2000**; 7:244–9.
6. Jana N, Vasishta K, Saha SC, Ghosh K. Obstetrical outcomes among women with extrapulmonary tuberculosis. N Engl J Med **1999**; 341:645–9.
7. Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clin Infect Dis **2012**; 55:1532–49.
8. Saving mothers 2014–2016: seventh triennual report of the Confidnetila Enquiries into Maternal Deaths in South Africa. Department of Health, Pretria, **2016**.
9. Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. Ann Intern Med **2014**; 161:419–28.
10. McKenna L, Frick M, Lee C, et al. A community perspective on the inclusion of pregnant women in tuberculosis drug trials. Clin Infect Dis **2017**; 65:1383–7.
11. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med **2011**; 365:11–20.
12. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet **2014**; 384:682–90.
13. Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet **2011**; 377:1588–98.
14. Sterling TR, Villarino ME, Borisov AS, et al; Tuberculosis (TB) Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med **2011**; 365:2155–66.
15. Gupta A, Mathad JS, Abdel-Rahman SM, et al. Toward earlier inclusion of pregnant and postpartum women in tuberculosis drug trials: consensus statements from an international expert panel. Clin Infect Dis **2016**; 62:761–9.
16. Martinson N, Barnes G, Msandiwa R, et al. Novel regimens for treating latent TB in HIV-infected adults in South Africa: a randomized clinical trial [abstract #36bLB]. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections (Montreal, Canada). **2009**.
17. Taylor AW, Mosimaneotsile B, Mathebula U, et al. Pregnancy outcomes in HIV-infected women receiving long-term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. Infect Dis Obstet Gynecol **2013**; 2013:195637.
18. Salazar-Austion N, Cohn S, Lala S, et al. Isoniazid preventative therapy and pregnancy outcomes in women living with human immunodeficiency virus in the Tshepiso cohort. doi:10.1093/cid/ciz1024. Accessed 21 October 2019.
19. Ouyang DW, Shapiro DE, Lu M, et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. AIDS **2009**; 23:2425–30.
20. Gupta A, Montepiedra G, Aaron L, et al. Isoniazid preventative therapy in HIV infected pregnant and postpartum women. N Eng J Med **2019**; 381:1333–46.
21. Ballard JL, Khoury JC, Wedig K, et al. J Pediatrics **1991**; 417:417–23.
22. Metropolitan Atlanta Congenital Defects Program (MACDP). Available at https://www.cdc.gov/ncbddd/birthdefects/macdp.html
23. Bothamley G. Drug treatment for tuberculosis during pregnancy: safety considerations. Drug Saf **2001**; 24:553–65.
24. Available at https://www.nichd.nih.gov/health/topics/preterm/conditioninfo/who_risk. Accessed 12 October 2019.
25. Kalk E, Heekes A, Mehta U, et al. Safety and effectiveness of isoniazid preventative therapy in pregnant women living with human immunodeficiency virus on antiretroviral therapy: an observational study using linked population data. Clin Infect Dis [Preprint]. January 4, 2020.
26. Katz J, Lee AC, Kozuki N, et al; CHERG Small-for-Gestational-Age-Preterm Birth Working Group. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. Lancet **2013**; 382:417–25.