

Adverse Pregnancy Outcomes Among Women with Human Immunodeficiency Virus Taking Isoniazid Preventive Therapy During the First Trimester

Amita Gupta,^{1,✉} Michael D. Hughes,² Jorge Leon Cruz,² Anchalee Avihingsanon,³ Noluthando Mwelase,⁴ Patrice Severe,⁵ Ayotunde Omoz-Oarhe,⁶ Gaerolwe Masheto,⁶ Laura Moran,⁷ Constance A. Benson,⁸ Richard E. Chaisson,¹ and Susan Swindells^{9,✉}; for the ACTG 5279 BRIEF-TB study team

¹Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; ²Center for Biostatistics in AIDS Research, Harvard TH Chan School of Public Health, Boston, Massachusetts, USA; ³HIV-NAT, Thai Red Cross AIDS Research Centre and Center of Excellence in Tuberculosis, Faculty of Medicine Chulalongkorn University, Bangkok, Thailand;

⁴Department of Medicine, University of Witwatersrand, Johannesburg, South Africa; ⁵Clinical Trials Unit, Les Centres GHESKIO, Port-au-Prince, Haiti; ⁶Botswana Harvard AIDS Institute Partnership, Clinical Trials Unit, Gaborone, Botswana; ⁷Public Health and Scientific Research Unit, Social & Scientific Systems, a DLH Company, Silver Spring, Maryland, USA; ⁸Division of Infectious Diseases, University of California San Diego School of Medicine, La Jolla, California, USA; and ⁹Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

Background. Isoniazid preventive therapy (IPT) is recommended for tuberculosis prevention yet data on the safety of first-trimester pregnancy exposure are limited.

Methods. Planned secondary analysis in a TB prevention trial of adverse pregnancy outcomes among participants assigned to 9-month IPT who became pregnant during (IPT-exposed) or after (unexposed) IPT. Regression models compared binary outcomes of a composite adverse outcome (any non-live birth, excluding induced abortion); preterm delivery <37 weeks; and low birth weight <2500 g) among exposure groups. Models were adjusted for latent TB infection, maternal age, CD4 count, and antiretroviral therapy (ART).

Results. In total, 128 participants had a known pregnancy outcome; 39 IPT-exposed and 89 unexposed. At pregnancy outcome, ART use was lower in IPT-exposed (79%) than unexposed women (98%). Overall, 29 pregnancies ended in a composite adverse outcome (25 spontaneous abortions, 2 stillbirths and 2 ectopic pregnancies), 15 preterm deliveries, and 10 infants with low birth weight. IPT was associated with the composite adverse outcome adjusting for covariates at enrollment (adjusted relative risk [aRR] 1.98; 95% confidence interval [CI] 1.15, 3.41), but the effect was attenuated when adjusted for covariates at pregnancy outcome (aRR 1.47; 95% CI .84, 2.55); IPT was not associated with preterm delivery (relative risk [RR] 0.87; 95% CI .32–2.42) or low birth weight (RR 1.01; 95% CI .29, 3.56).

Conclusions. First-trimester IPT exposure was associated with nearly two-fold increased risk of fetal demise, mostly spontaneous abortion, though the association was attenuated when adjusted for covariates proximal to pregnancy outcome including ART use. Further study is needed to inform TB prevention guidelines.

Keywords. TB preventive therapy; isoniazid; HIV infection; pregnancy; adverse pregnancy outcome.

Provision of isoniazid prevention therapy (IPT) is a key global strategy for reducing tuberculosis (TB) and death in the context of human immunodeficiency virus (HIV) [1]. The World Health Organization (WHO) currently recommends IPT with antiretroviral therapy (ART) for all people with HIV, including during pregnancy [1, 2]. However, this guidance is primarily supported by safety and efficacy data from nonpregnant populations. A systematic review by Sobhy et al found that

tuberculosis in pregnancy was associated with 4-fold increased maternal mortality, 9-fold increased risk of miscarriage, 2-fold risk of preterm birth, 2-fold risk of low term birth, and 4-fold increased risk of perinatal death [3]. Pregnant women continue to be excluded from most IPT trials [4] and the limited studies of IPT during pregnancy report conflicting associations between antenatal exposure and adverse pregnancy outcomes [5, 6]. Pregnancy increases the risk of TB [7], and maternal TB is linked to poor maternal [8] and infant outcomes [9, 10], yet without high quality data, the safety of isoniazid exposure during pregnancy is uncertain. Data on IPT exposure during conception and early pregnancy are particularly limited.

Two recent systematic reviews identified inconsistent results among non-randomized and randomized studies comparing adverse pregnancy outcomes among women with HIV infection with and without antenatal IPT exposure [5, 6]. A recent large programmatic observational study included in these two reviews found that women with HIV who received IPT during pregnancy were less likely to experience poor pregnancy

Received 28 June 2023; editorial decision 15 September 2023; published online 28 September 2023

Presented in part: CROI March 6–10, 2021, virtual. Abstract 178.

Correspondence: S. Swindells, University of Nebraska Medical Center, 804 S 52nd St, 988106 Nebraska Medical Center, Omaha, NE 68198-8106 (sswindells@unmc.edu); A. Gupta, Division of Infectious Diseases, Johns Hopkins University School of Medicine, 1830 East Monument Street, Baltimore, MD 21205 (Agupta25@jhmi.edu).

Clinical Infectious Diseases® 2024;78(3):667–73

© The Author(s) 2023. Published by Oxford University Press on behalf of Infectious Diseases Society of America. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

<https://doi.org/10.1093/cid/ciad583>

outcomes than those who did not receive IPT [10]. This protective effect was primarily identified among women starting IPT during the second and third trimesters; no effect was identified among women starting IPT in the first trimester. In contrast, the multi-country International Maternal Pediatric Adolescent AIDS Clinical Trials network TB APPRISE, a randomized double-blind placebo controlled trial (IMPAACT P1078), enrolled women during the second or third trimesters and documented an increased risk of composite adverse pregnancy outcomes with antenatal IPT exposure, including stillbirth, spontaneous abortion and low birth weight [11]. Theron et al subsequently confirmed this increased risk of second- and third-trimester IPT exposure on composite adverse outcomes and low birth weight in a follow-up analysis, which identified and adjusted for multiple confounders of adverse pregnancy outcomes [12]. IPT during pregnancy was also associated with adverse longer term growth outcomes in infants born to participants receiving IPT during pregnancy compared to postpartum (especially among male infants) [13].

To address this knowledge gap, we conducted a pre-specified secondary analysis among women who became pregnant during the AIDS Clinical Trials Group Brief Rifampentine-Isoniazid Evaluation for TB Prevention trial (ACTG A5279 BRIEF-TB). This multi-country, randomized trial assessed standard nine-month IPT versus a 1-month isoniazid plus rifampentine regimen (1HP) in adolescents and adults with HIV in TB endemic settings [14]. Here, we describe and compare a composite adverse pregnancy outcome (any non-live birth) and individual adverse outcomes (preterm delivery before 37 weeks gestational age and low birth weight less than 2500 g) among trial participants with an index pregnancy during IPT (IPT-exposed) or after IPT completion (unexposed). No pregnancies occurred during receipt of 1HP. The results provide data to enhance our understanding of the potential risks of antenatal isoniazid as we advance the agenda to inform global health policy for women of reproductive age with HIV.

METHODS

Study Design and Procedures

The ACTG 5279 BRIEF-TB trial was an open-label, randomized noninferiority trial of a standard 9-month IPT regimen (IPT) and a weight-based 1-month isoniazid plus rifampentine regimen (1HP) for TB prevention among people with HIV (NCT 01404312). The trial was conducted from May 2012 to November 2017 at multiple study sites across 10 countries (Botswana, Brazil, Haiti, Kenya, Malawi, Peru, South Africa, Thailand, USA, and Zimbabwe) with TB prevalence more than 60 cases per 100 000 population. Details of the trial design and conduct have been previously described [14]. The protocol enrolled adolescents and adults aged 13 years or older with HIV and no evidence of active TB. Females of reproductive potential

(had menses within the preceding 24 months or had not undergone surgical sterilization, such as hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) were required to have a negative serum or urine pregnancy test within 7 days before enrollment and were required to use 1 reliable non-hormonal form of contraceptive (ie, condoms, with a spermicidal agent; a diaphragm or cervical cap with spermicide; or an intrauterine device [IUD]) while receiving RPT and for 6 weeks after stopping this drug. Evidence of latent TB infection (LTBI) was not required prior to study enrollment, as participants all had HIV and lived in high TB burden countries but was requested at enrollment by TB skin testing or interferon-gamma release assay (IGRA). Participants began IPT or 1HP immediately after randomization; all participants received pyridoxine with isoniazid to minimize side effects. Antiretroviral therapy (ART) was limited to the use of efavirenz or nevirapine for the first month of trial participation because of concerns about drug-drug interactions with rifampentine, with any other ART regimen permitted after the first month. Follow-up visits were at weeks 2, 4, 8, 12, 16, 20, 24, and 36, then every 12 weeks starting at week 48 and continued until 3 years after the last participant enrolled.

This planned secondary analysis included all female participants who were randomized to standard IPT (300 mg of isoniazid daily for 36 weeks), became pregnant during the trial and had a known pregnancy outcome by the end of trial follow-up. We excluded participants assigned to 1HP because no pregnancies occurred during 1HP, possibly due to the contraceptive requirement surrounding rifampentine use. The A5279 protocol required pregnancy testing as indicated during IPT (ie, through week 36) but not after IPT completion. Women who experienced pregnancy during the trial could continue IPT and were encouraged to continue study participation and complete evaluations per the schedule of events. All pregnancy outcomes, including adverse events among mothers and infants, were recorded using a dedicated Case Report Form. Pregnancies that occurred on study in female participants receiving ART were reported to the Antiretroviral Pregnancy Registry.

Ethical Approval

All participants provided written informed consent at enrollment. The trial was approved by local and collaborating institutional review boards.

Isoniazid Exposure and Study Outcomes

The pregnancy outcome analysis was restricted to the first pregnancy experienced by each participant during the trial. Exposure was evaluated using a combination of computerized and manual review. A pregnancy was considered IPT-exposed if a positive pregnancy test, pregnancy outcome, or the estimated date of conception (based on gestational age at birth) occurred on or before the date of the final isoniazid dose (definite exposure), or if the interval between the pregnancy

event and the final isoniazid dose was close but could not be definitively determined (possible exposure). A pregnancy was considered unexposed if the pregnancy outcome occurred more than 45 weeks after the date of the final isoniazid dose or within 45 weeks of the final dose and manual review determined that the pregnancy event was outside of the isoniazid exposure window.

We defined a composite adverse pregnancy outcome as any event resulting in a non-live birth other than induced abortion. This included spontaneous abortion (fetal demise before 20 weeks gestational age), ectopic pregnancy, and stillbirth (fetal demise at or beyond 20 weeks gestational age). An extended composite adverse outcome that included induced abortion was also used in the analysis. Preterm delivery (delivery before 37 weeks gestational age) and low birth weight (< 2500 g) were assessed among live births. Measured confounding variables were LTBI status at enrollment and maternal age, CD4 count (cells per microliter), and ART use at enrollment and proximal to pregnancy outcome.

Statistical Analysis

Maternal covariates were summarized using descriptive statistics and compared across exposure groups using Wilcoxon rank-sum and Fisher's exact tests, as appropriate. The association between isoniazid exposure and binary adverse pregnancy outcomes was evaluated using Poisson regression models with estimation of standard errors using robust methods [15]. Models were adjusted for potential confounders at study enrollment and separately for the same variables measured proximal to pregnancy outcome.

RESULTS

The BRIEF-TB trial enrolled 1614 nonpregnant females with HIV, including 812 assigned to IPT. No women became pregnant while taking or within 6 weeks of completing rifampentine and isoniazid (IHP), so women in this arm of the trial were not analyzed further. Among the 812 women assigned IPT, 136 (17%) became pregnant during the trial period, including 12 who became pregnant twice. We excluded 5 participants who were lost to follow-up and 3 who were still pregnant at the end of the trial. The first pregnancies of the remaining 128 participants were included in this analysis, yielding 39 IPT-exposed and 89 unexposed pregnancies (Figure 1). All were singleton pregnancies, and except for ART use, maternal characteristics were similar among exposure groups at enrollment and proximal to pregnancy outcome (Table 1). Overall, participants were predominantly recruited from sub-Saharan Africa (70% of 128); at enrollment, median age was 29 years, median CD4 count was 534 cells per microliter, and 35% were taking ART. 20% had positive test results for LTBI, but a shortage of reagents limited TB skin testing. At pregnancy

outcome, median age was 31.5 years (interquartile range [IQR] 27.1, 36.2), and median CD4 count was 552 cells per microliter (IQR 415, 706). Compared to the unexposed group, fewer IPT-exposed participants were receiving ART at pregnancy outcome (79% vs 96%, $P = .007$), and the ART regimen was less likely to include efavirenz at enrollment (23% vs 33%, $P = .010$) and pregnancy outcome (64% vs 87%, $P = .006$).

Isoniazid Exposure

By definition, IPT exposure always occurred during the first trimester (all IPT-exposed pregnancies were conceived while taking isoniazid); a smaller proportion of participants also had second-trimester exposure, and relatively few had third-trimester exposure. Based on the trial data collected, duration of IPT exposure could not be estimated for pregnancies that ended in a composite adverse outcome or induced abortion. Overall, 19 of 39 (49%) women completed IPT while pregnancy was ongoing, 9 (23%) discontinued IPT early (6 due to pregnancy, 2 due to non-compliance, and 1 withdrew consent), 8 (21%) had a pregnancy outcome while taking IPT (6 spontaneous abortions and 2 induced abortions), and 3 (8%) had possible early exposure (Table 1). We were able to estimate IPT exposure duration during pregnancy for the 19 (of 23) live births for whom data on gestational age at delivery was available; exposure duration ranged from 5.7 to 34.3 weeks with a median duration of 14.7 weeks (IQR 7.3, 24.3).

Adverse Pregnancy Outcomes

A total of 35 pregnancies (27% of 128) ended in a non-live birth outcome, including 25 spontaneous abortions (fetal demise before 20 weeks gestational age), 6 induced abortions, 2 stillbirths (fetal demise at or beyond 20 weeks gestational age), and 2 ectopic pregnancies. Aside from ectopic pregnancy, the proportion of each individual outcome was approximately 2-fold higher in IPT-exposed than unexposed pregnancies, and a greater proportion of IPT-exposed than unexposed pregnancies experienced the composite adverse outcome which excluded induced abortions (33% vs 18%), primarily spontaneous abortions (Figure 2). In regression models, antenatal IPT was associated with the composite adverse outcome in unadjusted analysis (relative risk [RR] 1.85; 95% confidence interval [CI] .99, 3.47; $P = .054$) and analysis adjusted for maternal covariates at enrollment (adjusted relative risk [aRR] 1.90; 95% CI 1.01, 3.54; $P = .04$). The effect was attenuated in separate analysis adjusted for the same covariates measured proximal to pregnancy outcome, largely driven by ART use, which increased substantially between study entry and pregnancy outcome (aRR 1.45; 95% CI .75, 2.80; $P = .27$, Table 2). We obtained a similar pattern of results in 2 separate analyses: 1 that excluded pregnancies ending in induced abortion from the risk set, and 1 that included induced abortions in the extended composite adverse outcome (Table 2).

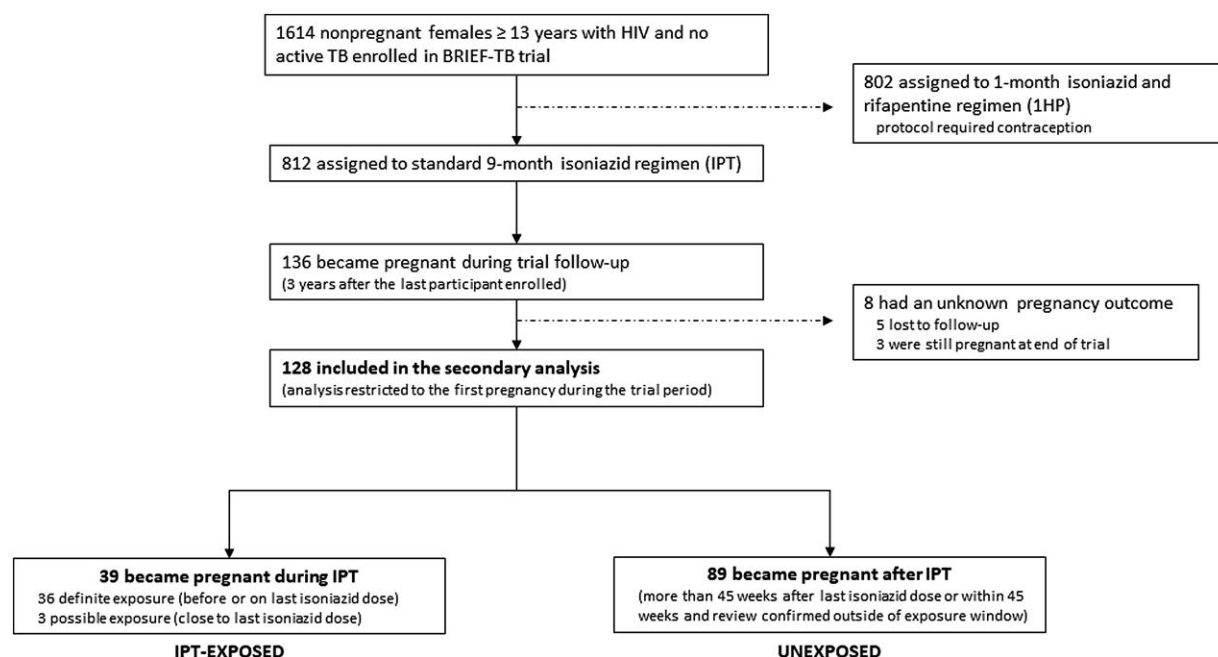


Figure 1. CONSORT diagram of female participants enrolled in BRIEF-TB. Abbreviations: HIV, human immunodeficiency virus; IPT, isoniazid.

With respect to individual adverse outcomes among live births ($n = 93$), 68 had data on gestational age at delivery (20 IPT-exposed and 48 unexposed), and 74 had data on birth weight (22 IPT-exposed and 52 unexposed). IPT-exposed and unexposed participants had similar proportions of preterm delivery (20% vs 23%) and low birth weight (14% vs 13%) (Figure 2). Antenatal IPT was not significantly associated with either outcome in unadjusted regression models (RR 0.87; 95% CI .32, 2.42 for preterm delivery and RR 1.01; 95% CI .29, 3.56 for low birth weight); adjusted analysis was not done given the small number of events (15 preterm deliveries and 10 infants with low birth weight; Table 2).

DISCUSSION

This secondary analysis of the BRIEF-TB trial shows a nearly 2-fold increased risk of fetal demise with IPT exposure at conception and continuing into at least the first trimester of pregnancy, which was largely driven by spontaneous abortions. However, there was no significant association between exposure starting during the first trimester and preterm delivery or low birth weight. Overall, our results complement the TB-APPRISE trial [11, 12], which documented increased adverse pregnancy outcomes with second- and third-trimester IPT exposure and provides possible evidence of a negative impact of isoniazid during conception and early pregnancy. The high incidence of spontaneous abortion suggests the need for contraception counseling, as women with HIV of reproductive potential may choose to take measures to avoid pregnancy while taking extended regimens isoniazid or isoniazid-containing regimens.

Our study is generally complementary to a sub-analysis of the TB-APPRISE trial, which confirms the negative impact of antenatal IPT exposure later in pregnancy among women with HIV [12]. After adjustment for multiple confounders (maternal age at delivery, CD4 quartile, plasma HIV RNA, hepatitis B surface antigen status, timing of ART initiation, mid-upper arm circumference, IGRA status, twin vs singleton pregnancy, current smoking status, noninfectious pregnancy complications, infectious pregnancy complications, and hospitalization), Theron et al report 62%–74% increased odds of 3 composite adverse outcomes, which include at least fetal demise, preterm delivery, and low birth weight. Although this effect was independently driven by low birth weight (adjusted odds ratio [aOR] 1.58, 95% CI 1.02, 2.46), antenatal IPT had an increased odds of perinatal death (fetal demise or early neonatal mortality), but this did not reach statistical significance (aOR 1.84, 95% CI .87–3.85). Notably, the TB-APPRISE trial included women with second- and third-trimester isoniazid exposure (the protocol excluded pregnant women at < 14 weeks of gestation) so the vast majority of fetal demise was due to stillbirths, whereas our analysis primarily included women with first-trimester exposure (IPT-exposed pregnancies were conceived during 36-week IPT), and the majority of fetal demise was due to spontaneous abortions (fetal demise < 20 weeks gestation). The effects of IPT exposure on fetal demise appear to vary by trimester exposure with spontaneous abortions appearing to be increased when exposure occurs during the first trimester, whereas stillbirths appearing more likely with second and third trimester exposure. Animal studies also provide

Table 1. Characteristics of Adolescent and Adult Females With an Incident Pregnancy During ACTG 5279, According to Antenatal Isoniazid Exposure Classification (n = 128)

Characteristic	IPT-Exposed N = 39	Unexposed N = 89	P
Country, n (%)	...	...	.47
Botswana	11 (28)	23 (26)	
Brazil	1 (3)	5 (6)	
Haiti	9 (23)	15 (17)	
Kenya	5 (13)	8 (9)	
Malawi	3 (8)	2 (2)	
Peru	1 (3)	3 (3)	
South Africa	7 (18)	29 (33)	
Thailand	1 (3)	3 (3)	
USA	1 (3)	0 (0)	
Zimbabwe	0 (0)	1 (1)	
Median age, y (IQR)			
At enrollment	29.2 (25.7, 35.5)	29.2 (25.0, 33.7)	.44
At pregnancy outcome	30.0 (26.4, 36.3)	31.8 (27.2, 36.0)	.54
Median CD4 count, cells/ μ L (IQR)			
At enrollment	527 (432, 735)	538 (432, 678)	.54
Closest to pregnancy outcome	522 (398, 707)	555 (420, 704)	.61
ART use, n (%)			
At enrollment	15 (38)	30 (34)	.69
EFV-based regimen	9 (23)	29 (33)	.01
Non-EFV-based regimen	6 (15)	1 (1)	
At pregnancy outcome	31 (79)	85 (96)	.007
Efavirenz-based regimen	25 (64)	77 (87)	.006
Non-efavirenz-based regimen	6 (15)	8 (9)	
LTBI-positive at enrollment	10 (26)	16 (18)	.35
Isoniazid exposure			
Completed IPT during pregnancy	19 (49)	...	
Discontinued IPT early ^a	9 (23)	...	
Pregnancy outcome occurred during IPT	8 (21)	...	
Possible exposure	3 (8)	...	
Median duration of exposure (n = 19 ^b), wks (IQR)	14.7 (7.3, 24.3)	...	

Data presented as no. (%) unless otherwise indicated.

Abbreviations: ACTG, AIDS Clinical Trials Group; ART, antiretroviral therapy; EFV, efavirenz; IPT, isoniazid prevention therapy; IQR, interquartile range; LTBI, latent tuberculosis infection.

^aBefore study week 36 due to pregnancy (n=6), non-compliance (n=2) or withdrawn consent (n=1).

^bNumber of live births for which gestational age at delivery was available; exposure duration estimated as study week off isoniazid minus (study week of birth minus gestational age at delivery).

evidence for an embryocidal effect of isoniazid, documenting small litter sizes among mice exposed to high concentrations of isoniazid during pregnancy [16].

In contrast to our findings and those from the TB-APPRISE trial, a large retrospective study of programmatic data among pregnant women with HIV in South Africa [17] provided evidence for protective effect on adverse pregnancy outcomes of IPT during the second and third trimesters with no effect of exposure in the first trimester. Overall, combining across trimesters of initial IPT exposure, Kalk et al found antenatal IPT to be protective against adverse pregnancy outcomes (composite of spontaneous

abortion, stillbirth, low birth weight or neonatal death). Consistent with our findings, this effect appeared to be driven by fetal demises. Further analysis according to trimester of start of IPT exposure showed significantly reduced risk in women who initiated IPT during the second or third trimester compared to unexposed women (aOR 0.71 95% CI .65, .79) but no difference in risk in women who initiated IPT during the first trimester compared to unexposed women in both unadjusted and adjusted analyses (aOR 1.04 95% CI .94, 1.16). It is unclear why findings related to first trimester exposure differ from this study. Possibilities include prospective versus retrospective study design which may influence ascertainment of outcomes particularly spontaneous abortions, and differences in populations studied. Perhaps of note, women in the study of Kalk et al had much more extensive antiretroviral exposure (77% were on ART prior to pregnancy for a median 175 months) than in our study (35% were on ART at enrollment, increasing to 91% at pregnancy outcome). In this respect, our findings showed attenuation of effect when adjusted for variables assessed proximal to pregnancy outcome including antiretroviral status.

Two small secondary analyses have assessed outcomes among participants who were inadvertently exposed to IPT during randomized clinical trials. In contrast to our study, Taylor et al reported reduced risk of a composite adverse outcome (spontaneous abortion, stillbirth, preterm delivery, low birth weight, neonatal death, or congenital abnormality) among HIV-infected women exposed to long-term IPT in Botswana (aOR 0.6; 95% CI, .3–1.1) [18]. Most IPT-exposed pregnancies (102 of 103) had first-trimester exposure, including a number of pregnancies conceived during IPT (median IPT initiation was 341 days [48 weeks] before pregnancy outcome). Notably, only 37% of women were on ART; there were unmeasured potential confounders and exposure groups (IPT-exposed and IPT-unexposed) were dissimilar, particularly with regard to ART use. Another sub-analysis of 2 multi-country TBTC trials reported 14% incidence of fetal loss (all spontaneous abortion) among 56 pregnancies exposed to IPT for a median 4 weeks [19]. By comparison, we observed 2-fold higher incidence of spontaneous abortion (31%, 12 of 39) in our IPT-exposed group. However, the study populations differ in important ways, as only participants without HIV from the United States and Canada became pregnant during the TBTC trials.

Limitations of our study include small sample size, and limited measurement and hence adjustment for potential confounders. Pregnancy testing in the study after entry was performed only if indicated, and some early pregnancy loss may have been missed. In addition, we could not accurately assess duration of isoniazid exposure during pregnancy except for those carried to term. Although our analyses of low birth weight and preterm delivery are limited by missing data, our study highlights a potentially important association between antenatal IPT exposure and spontaneous abortion. Lastly, this

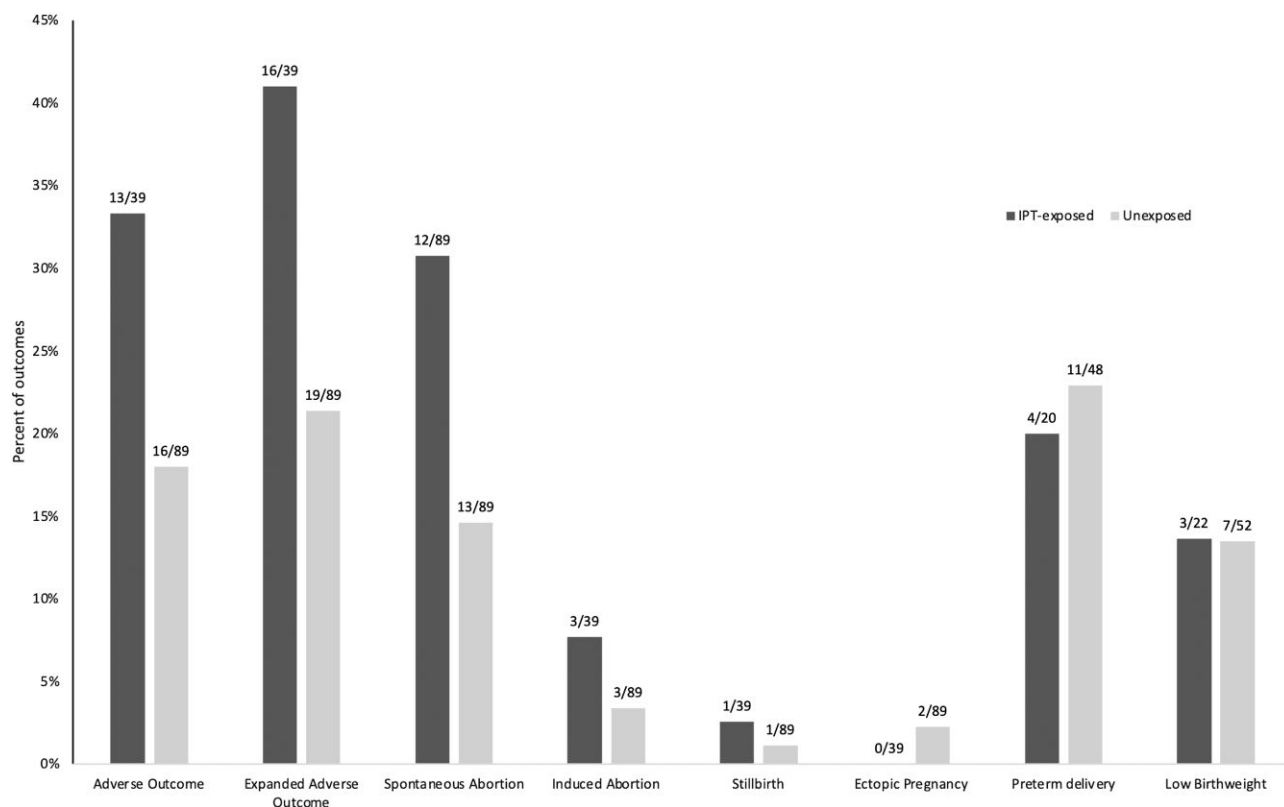


Figure 2. Final pregnancy outcomes according to antenatal isoniazid exposure classification (n = 128). Composite and individual adverse pregnancy outcomes by antenatal isoniazid therapy exposure. Adverse pregnancy outcome was a composite of any event resulting in a non-live birth, excluding induced abortion; the expanded adverse pregnancy outcome included induced abortion. Preterm delivery (<37 wks) and low birth weight (<2500 g) were assessed among live births for which data were available. Abbreviation: IPT, isoniazid prevention therapy.

Table 2. Results From Regression Models Describing Relative Risk of Adverse Outcomes Among IPT-exposed Versus Unexposed Pregnancies

Outcome	No./Total N (%)		Unadjusted		Adjusted for Covariates Measured at Enrollment		Adjusted for Covariates Measured at Pregnancy 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.

^aAny 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.

^bExcluded six pregnancies that ended in induced abortion (3 in each exposure group).

^cAssessed among live births for which data were available; adjusted analyses not undertaken because of small number of events.

study was conducted prior to the guidance that all people with HIV should receive ART, and the study did not include participants receiving integrase inhibitor therapy.

This work contributes to the existing fund of knowledge but also highlights the difficulties of generating solid evidence to inform guidelines. Overall, non-randomized studies provide some reassurance, documenting a protective effect of isoniazid during pregnancy [17, 18, 20], but pregnant women are systematically excluded from almost all randomized controlled trials of TB preventive therapy [4, 21]. As outlined above, results from prior studies are conflicting and exhibit substantial heterogeneity among study design, IPT exposure timing, ART exposure and outcomes assessed. Observational studies may also have inherent limitations such as small sample size [18, 20], confounding by indication [17, 20], and unmeasured confounding factors [17, 18]. It is also difficult to ascertain early pregnancy loss and TB trials do not routinely collect this information. In addition, programs also rarely collect data on pregnancy status or outcomes.

In summary, we apriori included a study of pregnancy outcomes in the BRIEF TB trial and observed that isoniazid exposure during conception and first trimester was associated with spontaneous abortion but not preterm birth or low birth weight. It is notable that there were no incident pregnancies during the ultrashort course therapy of 1 month of isoniazid and rifapentine. Efforts to scale up short course TB preventive therapy, where incident pregnancies are unlikely to occur, should be prioritized. Our data also highlight the critical need to ensure pregnant women have full access and inclusion in relevant TB trials, so that robust data can be generated to inform guidelines, and pregnant women and providers can have the necessary information to weigh the benefits and the risks associated with tuberculosis therapies.

Notes

Acknowledgments. The authors thank the participants and other team members, including Katherine Shin, pharmacist; Anthony T. Podany, pharmacologist; Ian Sanne, Network Leadership representative; Janet Nicotera, field representative; David L. Shugarts, laboratory technologist; Amina M. Shali, community representative; and the members of the Division of AIDS African data and safety monitoring board for their oversight of the trial; Timothy Sterling and Prudence Ive for performing the independent endpoint reviews; and Katie McIntyre for assisting with manuscript preparation.

Financial support. This work was supported by grants (grant numbers UM1AI069465, UM1 AI068634, UM1 AI068636, and UM1 AI06701) from the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The views expressed in this article are those of the authors and do not necessarily represent the official views of the NIH.

Potential conflicts of interest. A. G. reports Advisory Board roles from NIAID and Indo-US Science and Technology Forum (IUSSTF). M. H. reports institutional research and training grants related to infectious diseases from US NIH; board membership of Botswana-Harvard Partnership through employer; spouse's research grants from NIH related to infectious diseases research. C. A. B. reports institutional grant support for clinical trials from Gilead and DNAe; consulting fees (paid to author) from National Data and Analytics Platform (NDAP), Inc.; honoraria for medical education lectures and travel support (paid to author) from

International Antiviral Society–United States (IAS-USA), a non-profit medical education entity; and unpaid positions as Present of the non-profit Conference on Retroviruses and Opportunistic Infections (CROI) Foundation Board, and Secretary/Treasurer of the IAS-USA Board of Directors. R. E. C. reports spouse's stock in Merck. S. S. reports institutional research support from ViiV Healthcare and participation on a Data Safety Monitoring or Advisory board for now completed NIH coronavirus disease (COVID)-related trials. 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. Organization WH. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. 2011.
2. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization, 2018. Licence: CC BY-NC-SA 3.0 IGO.
3. Sobhy S, Babiker Z, Zamora J, Khan KS, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. *BJOG* 2017; 124:727–33.
4. 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.
5. Hamada Y, Figueroa C, Martín-Sánchez M, Falzon D, Kanchar A. The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis. *Eur Respir J* 2020; 55:1901967.
6. Zhou X, Fang G, Xie Y, Wei A, Huang F. Safety evaluation of antituberculosis drugs during pregnancy: a systematic review and meta-analysis. *Front Surg* 2022; 9:871321.
7. Gupta A, Nayak U, Ram M, et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in pune, India, 2002–2005. *Clin Infect Dis* 2007; 45:241–9.
8. Gould JM, Aronoff SC. Tuberculosis and pregnancy-maternal, fetal, and neonatal considerations. *Microbiol Spectr* 2016; 4. doi:10.1128/microbiolspec.TNM17-0016-2016.
9. Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. *Clin Infect Dis* 2012; 55:1532–49.
10. Sugarman J, Colvin C, Moran AC, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. *Lancet Glob Health* 2014; 2:e710–6.
11. Gupta A, Montepiedra G, Aaron L, et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. *N Engl J Med* 2019; 381:1333–46.
12. Theron G, Montepiedra G, Aaron L, et al. Individual and composite adverse pregnancy outcomes in a randomized trial on isoniazid preventative therapy among women living with human immunodeficiency virus. *Clin Infect Dis* 2021; 72:e784–90.
13. Cherkos AS, LaCourse SM, Enquobahrie DA, et al. 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. *EClinicalMedicine* 2023; 58:101912.
14. Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med* 2019; 380:1001–11.
15. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; 159:702–6.
16. Isoniazid product label.
17. Kalk E, Heekes A, Mehta U, et al. 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. *Clin Infect Dis* 2020; 71:e351–8.
18. 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.
19. Moro RN, Scott NA, Vernon A, et al. Exposure to latent tuberculosis treatment during pregnancy. The PREVENT TB and the iAdhere trials. *Ann Am Thorac Soc* 2018; 15:570–80.
20. Salazar-Austin N, Cohn S, Lala S, et al. Isoniazid preventive therapy and pregnancy outcomes in women living with human immunodeficiency virus in the Tshpeiso cohort. *Clin Infect Dis* 2020; 71:1419–26.
21. Gupta A, Hughes MD, Garcia-Prats AJ, McIntire K, Hesselting AC. Inclusion of key populations in clinical trials of new antituberculosis treatments: current barriers and recommendations for pregnant and lactating women, children, and HIV-infected persons. *PLoS Med* 2019; 16:e1002882.