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Pharmacokinetics and Safety of 3 Months of Weekly Rifapentine and Isoniazid for Tuberculosis Prevention in Pregnant Women

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Background. Pregnancy increases the risk of tuberculosis and its complications. A 3-month regimen of weekly isoniazid and rifapentine (3HP) is safe and effective for tuberculosis prevention in adults and children, including those with HIV, but 3HP has not been evaluated in pregnancy.

Methods. IMPAACT 2001 was a phase I/II trial evaluating the pharmacokinetics and safety of 3HP among pregnant women with indications for tuberculosis preventative therapy in Haiti, Kenya, Malawi, Thailand, and Zimbabwe (NCT02651259). Isoniazid and rifapentine were provided at standard doses (900 mg/week). Pharmacokinetic sampling was performed with the first (second/third trimester) and twelfth (third trimester/postpartum) doses. Nonlinear mixed-effects models were used to estimate drug population pharmacokinetics.

Results. Of 50 participants, 20 had HIV and were taking efavirenz-based antiretroviral therapy. Among women without HIV, clearance of rifapentine was 28% lower during pregnancy than postpartum (1.20 vs 1.53 L/hour, $P < .001$), with area under the concentration-time curve (AUC_{SS}) of 786 and 673 mg × hour/L, respectively. In pregnant women with HIV, clearance was 30% higher than women without HIV ($P < .001$), resulting in lower AUC_{ss} (522 mg × hour/L); clearance did not change significantly between pregnancy and postpartum. Pregnancy did not impact isoniazid pharmacokinetics. There were no drug-related serious adverse events, treatment discontinuations, or tuberculosis cases in women or infants.

Conclusions. 3HP does not require dose adjustment in pregnancy. Rifapentine clearance is higher among women with HIV, but all women achieved exposures of rifapentine and isoniazid associated with successful tuberculosis prevention. The data support proceeding with larger safety-focused studies of 3HP in pregnancy.

Clinical Trials Registration. NCT02651259.

Keywords. maternal health; latent tuberculosis; rifapentine; pharmacokinetics; HIV.

Active tuberculosis (TB) is twice as likely to develop postpartum than at any other time in a woman's life [1]. Every year, an estimated 200 000 pregnant women develop active TB [2], which is a leading infectious cause of maternal mortality globally [2, 3]. Infants of mothers with TB have high rates of prematurity, low birth weight, and stillbirth [4, 5]. Maternal TB more than doubles the risk of mother-to-child transmission of human immunodeficiency virus (HIV) [6] and significantly increases mortality for all children in the household [4, 7–9].

The World Health Organization (WHO) currently recommends 6–9 months of daily isoniazid (INH) preventive therapy (IPT) to prevent TB in people living with HIV, but uptake during pregnancy varies widely by country [10–12]. TB Antepartum vs Postpartum Prevention with INH in HIV Seropositive mothers and their Exposed infants (TB APPRISE)—a randomized controlled IPT trial in pregnant women living with HIV (WLHIV)—showed an increased risk of adverse pregnancy outcomes from antepartum versus postpartum IPT [13]. But a meta-analysis of 9 other studies found inconsistent associations between IPT and adverse pregnancy outcomes [14].

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Consequently, the optimal strategy for TB prevention in pregnant WLHIV remains unclear.

The WHO also endorses 3 months of weekly INH and rifapentine (3HP) for TB prevention [10]. This regimen has higher completion rates and decreased adverse events compared with IPT [15], including in people with HIV [16]. However, pregnant women were excluded from all 3HP trials. The intent of this study was to evaluate the effects of pregnancy on 3HP pharmacokinetics (PK) to generate initial safety and toxicity data in pregnancy, and to establish the appropriate rifapentine (RPT) dose in pregnant women with and without HIV.

METHODS

The International Maternal Pediatric Adolescent AIDS Clinical Trial Network (IMPAACT) 2001 study (NCT02651259) was a phase I/II, open-label, PK and safety study of 3HP among pregnant women living with and without HIV, with an indication for TB preventive therapy. Participants were enrolled in Haiti, Kenya, Malawi, Thailand, and Zimbabwe. Cohort 1 enrolled second-trimester women (≥14 to <28 weeks' gestation, n = 25), and cohort 2 enrolled third-trimester women (≥28 to ≤34 weeks' gestation, n = 25) (Figure 1). Participants received 12 directly observed, once-weekly doses of RPT (900 mg) and INH (900 mg), with pyridoxine. RPT was donated by Sanofi; INH was purchased from Macleod. Treatment completion was defined as receipt of at least 11 doses over 16 weeks [15].

Participants

Eligibility requirements included age of 18 years or older, singleton pregnancy by ultrasound with gestational age of 14–34 weeks, high risk for TB (household contact with pulmonary TB, or WLHIV with latent TB), and the following laboratory values: hemoglobin of 7.5 g/dL or greater, white blood cell count of 1500 cells/mm^3 or greater, absolute neutrophil count of 750 cells/mm^3 or greater, platelet count of 100 000/mm^3 or greater, alanine aminotransferase less than 2.5 times the upper limit of normal (ULN), and total bilirubin less than 1.6 times the ULN. Women living with HIV had to be taking an efavirenz (EFV)-based antiretroviral regimen (ART). Exclusion criteria included active TB within 2 years, treatment for latent TB, personal history or exposure to drug-resistant TB, fetal abnormality by ultrasound, liver cirrhosis, or peripheral neuropathy. Mother–infant pairs were followed until 24 weeks postpartum.

Study Procedures

At study entry, participants were screened for TB symptoms. At study visits, safety laboratory tests (complete blood count, liver function panel) were collected monthly and fetal movement and heart sounds assessed until delivery. Maternal prothrombin time (PT) was collected at baseline and at 34 or more weeks of gestation, if still taking the study drug. Intensive PK sampling was performed with the first dose (pre-dose, then 0.5, 1, 2, 4, 5, 8, 12, 24, 48, and 72 hours post-dose). Sparse PK sampling occurred with the 12th dose (1, 4, 24, and 48 post-dose) (Figure 1). Infants were assessed within 3 days of delivery. If the mother was taking the study drug at delivery, infant PT was checked. Follow-up visits assessed interim health changes and adverse events.

Oversight/Safety

All women provided written informed consent for themselves and their infants. The study was approved by local institutional review boards and/or ethics committees at participating sites. An independent Safety Monitoring Committee within the IMPAACT Network reviewed accrual, safety, PK data, and quality of study implementation. The Protocol Team reviewed PK and safety data regularly.

Primary and Secondary Outcomes

The primary outcome measures were as follows: (1) PK parameters of RPT and INH (eg, absorption, oral clearance, volume of distribution) 3 (2) maternal safety of 3HP (eg, serious adverse events [SAEs], grade 2+ drug-related adverse events [AEs], grade 3+ AEs, and permanent study drug discontinuation), and (3) infant drug-related SAEs. Attribution of AEs to the study drug was determined by the study team.

Secondary outcomes included drug tolerability, as assessed by discontinuation of the study drug regimen due to intolerance, and incidence of active TB in mother–infant pairs.

Pharmacokinetics

Drug Concentration Analysis

Plasma RPT and INH concentrations were analyzed with validated liquid chromatography–tandem mass spectrometry assays developed at the Division of Pharmacology, University of Cape Town [17] (Supplementary Methods). The lower limit of quantification (LLOQ) for rifapentine was 0.039 µg/mL.

Pharmacokinetics Analysis

Pharmacokinetics parameters for RPT were determined from plasma concentration-time profiles using a nonlinear mixed-effects model (version 7.4; ICON PLC, Dublin, Ireland). The PK model described the oral absorption of RPT and estimated antepartum RPT clearance by HIV status and the apparent volume of distribution relative to bioavailability (Vc/F). For the effect of trimester on clearance, cohort 1 intensive PK sampling was used for second-trimester analysis; sparse and intensive PK sampling from cohorts 1 and 2, respectively, were used for third-trimester analysis. For the effect of pregnancy on clearance, pooled second- and third-trimester data were compared with sparse postpartum PK sampling. Model-based secondary PK parameters included maximum concentration (C_{max}) and steady-state area under

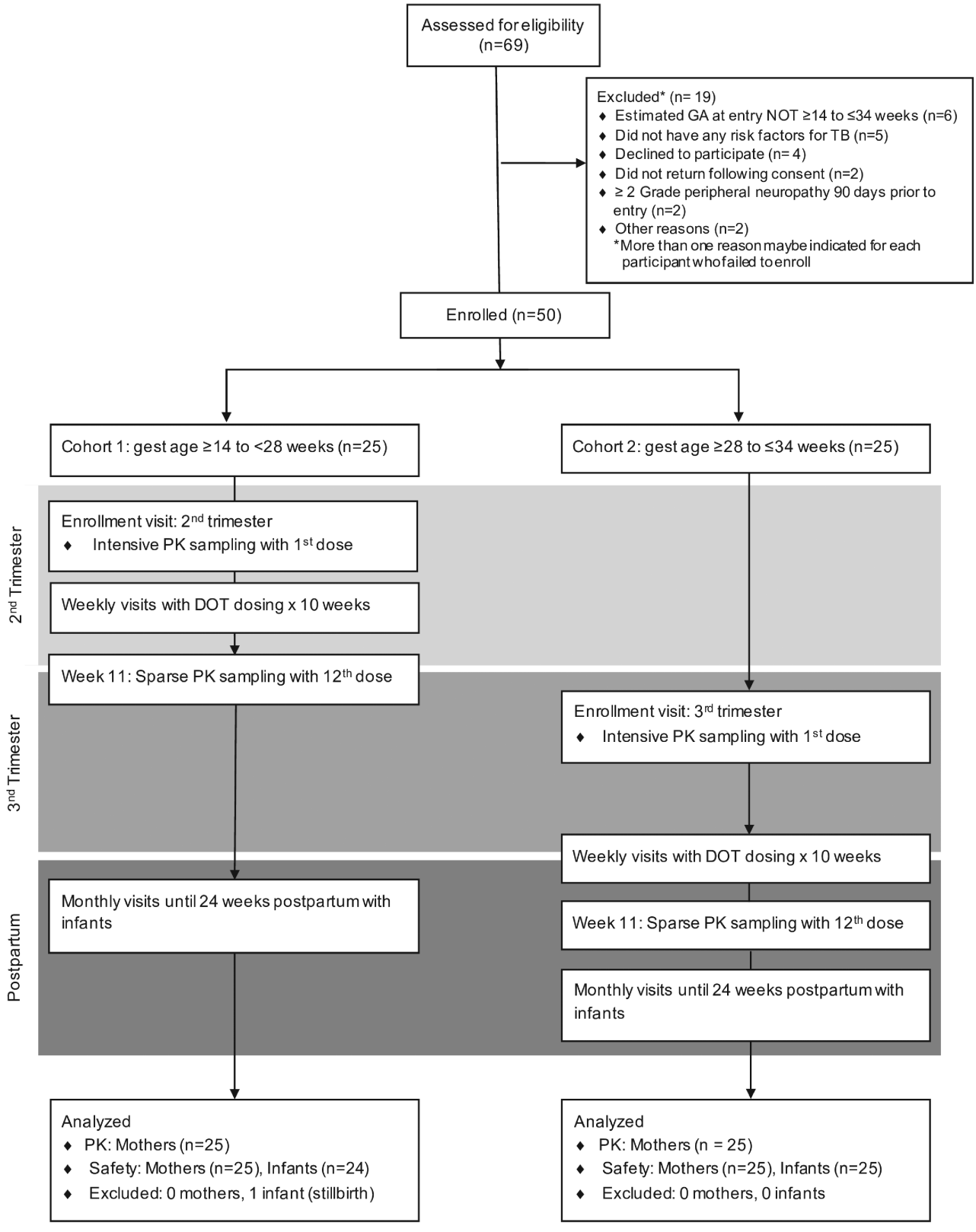


Figure 1. CONSORT diagram and study schema: CONSORT flow diagram showing participant flow through the IMPAACT 2001 trial. Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; DOT, directly observed therapy; GA/gest age, gestational age; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trial Network; PK, pharmacokinetics; TB, tuberculosis.

the concentration-time curve (AUC_{SS}), which describes drug exposure after weekly dosing. A similar model-based approach was used for INH.

An interim PK analysis was conducted after 12 participants enrolled into each cohort to determine if a dose adjustment was indicated. The median estimates were within 25% of historical controls, so no dose adjustments occurred [16].

Statistical Analysis

Sample Size

The sample size was based on precision for estimating PK parameters. The stochastic simulation-estimation (SSE) methodology for clinical trial simulation was used to determine sample sizes required to evaluate key PK parameters with adequate precision [18]. A sample size of 50 achieved a relative standard error less than 20% when comparing clearance between the second and third trimester. With this sample size we had 90% power to detect a safety event with a true occurrence of 5 per 100 women.

Safety

The safety dataset included women who had received at least 1 dose of the study drug and their infants. The proportion and exact 95% confidence interval were computed, overall and by cohort.

RESULTS

Trial Population

We enrolled 50 women from March 2017 to June 2018 (Table 1). Aside from gestational age, baseline characteristics of women in cohorts 1 and 2 were similar. The median age was 27 years (interquartile range [IQR], 20–32 years) and median weight was 61 kg (IQR, 56–67 kg), with 72% of participants of Black African, non-Hispanic race and ethnicity. Of the 20 (40%, 10 per cohort) WLHIV, median CD4 cell count was 510 cells/mm^3 (IQR, 390–877 cells/mm^3).

Pharmacokinetics Analyses

Effect of Trimester

There was no significant difference in clearance of INH (data not shown) or RPT in samples collected in the second versus the third trimesters (Figure 2). This allowed us to pool second- and third-trimester PK data to assess the impact of HIV on antepartum clearance and to compare antepartum with postpartum PK.

Effect of HIV/ART

During pregnancy, RPT clearance in WLHIV was 1.56 L/hour, 30% higher than in women without HIV (1.20 L/hour; $P < .001$). This resulted in a 34% lower AUC_{SS} of 522 mg/L × hour (5th–95th percentile: 445–664 mg/L × hour) for pregnant WLHIV, compared to 786 mg/L × hour (5th–95th percentile: 639–904 mg/L × hour) in women without HIV (Figure 2). The INH PK profiles, stratified by HIV status, were comparable to one another. The AUC_{SS} of INH was estimated to be 78.2 mg × hour/L (IQR, 21.9–78.2 mg × hour/L), with a maximum INH concentration of 7.74 mg/L (IQR, 5.68–10.6 mg/L) (Figure 3).

Effect of Pregnancy

In WLHIV, the clearance of RPT antepartum and postpartum was comparable (1.60 vs 1.56 L/hour). However, in women without HIV, clearance was 28% higher in postpartum than in antepartum samples (1.53 vs 1.20 L/hour, $P < .001$) (Figure 4). Accordingly, the AUC_{SS} for women without HIV was 786 mg/L × hour during pregnancy and 673 mg/L × hour postpartum, 21–50% higher than WLHIV at both time points (554 and 522 mg/L × hour) (Table 2). The INH PK profiles were unaffected by pregnancy status (Figure 3).

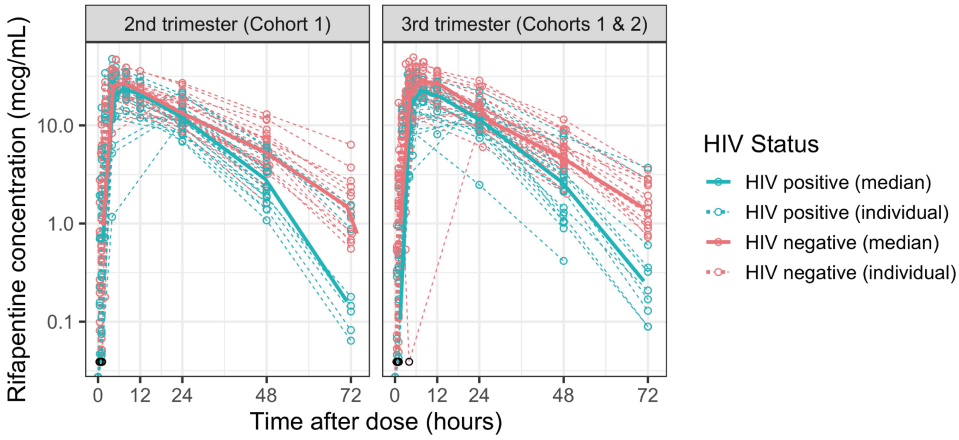
Comparison to Historic Nonpregnant Data

The clearance estimates of RPT in pregnant and postpartum women were within 25% of that reported in nonpregnant

Table 1. Baseline Maternal Characteristics

Characteristic	Overall (N = 50)	Cohort 1 (Second Trimester, n = 25)	Cohort 2 (Third Trimester, n = 25)
Race/ethnicity, n (%)			
Black African, non-Hispanic	31 (62)	13 (52)	18 (72)
Black, Caribbean, non-Hispanic	16 (32)	11 (44)	5 (20)
Asian, Pacific Islander	3 (6)	1 (4)	2 (8)
Age at study entry, median (IQR), years	27 (20–32)	26 (22–33)	27 (20–31)
HIV-positive, n (%)	20 (40)	10 (40)	10 (40)
CD4, median (IQR), cells/mm^3	510 (390–877)	586 (415–846)	489 (368–952)
Weight, median (IQR), kg	61 (56–67)	59 (55–66)	61 (58–67)
Gestational age at entry, median (IQR), weeks	26 (20–30)	20 (16–24)	30 (28–31)
Midupper arm circumference, median (IQR), cm	27 (25–30)	27 (25–31)	27 (26–29)
Prothrombin time, median (IQR), seconds	10 (10, 11)	10 (10, 11)	11 (10–12)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.



Parameter	HIV-positive	HIV-negative	% change vs. HIV-
Clearance, L/hr (RSE)	1.56 (7%)	1.20 (6%)	↑30%
AUC_{SS}, mg/L*hr (IQR)	522 (359-803)	786 (549-1171)	↓34%

Figure 2. Effect of HIV on clearance of RPT in second-trimester and third-trimester trimester. There were no differences in RPT concentration between second-trimester data (intensive PK from cohort 1; left panel) and third-trimester data (intensive PK from cohort 2, sparse PK from cohort 1; right panel). RPT clearance was 30% higher in pregnant WLHIV (blue) compared with women without HIV (pink) ($P < .001$). Data deemed to be below the LLOQ are displayed as open black circles as the LLOQ value (0.039 µg/mL). Abbreviations: AUC_{SS}, steady-state area under the concentration-time curve; HIV, human immunodeficiency virus; IQR, interquartile range; LLOQ, lower limit of quantification; PK, pharmacokinetics; RPT, rifapentine; RSE, relative standard error; WLHIV, women living with HIV.

populations. Pregnant and postpartum women also achieved drug exposures of INH and RPT comparable to exposures associated with successful TB prevention (Table 2) [19].

Maternal Safety

All enrolled women completed the study regimen. None developed active TB. There were 5 (10%; 95% confidence interval [CI]: 3–22%) women who experienced SAEs; 2 (8%) in cohort 1 and 3e (12%) in cohort 2 (Table 3). None of the SAEs were deemed to be related to the study treatment. Ten weeks after completing the study regimen, 1 woman had a grade 5 placental abruption following physical trauma and, despite emergent C-section, suffered intrauterine fetal demise and died. Another woman had a grade 4 placental abruption related to pre-eclampsia. One woman had grade 3 pregnancy-induced hypertension, one had grade 3 postpartum hemorrhage requiring surgery, and one had grade 1 pregnancy-induced hypertension.

Overall, there were 9 (18%; 95% CI: 9–31%) women who had grade 3+ AEs: 5 (20%) in cohort 1 and 4 (16%) in cohort 2. None of these AEs were assessed as being related to the study treatment (Table 3). In cohort 1, the grade 3+ hemoglobin levels all occurred postpartum; the woman with the grade 5 placental abruption accounted

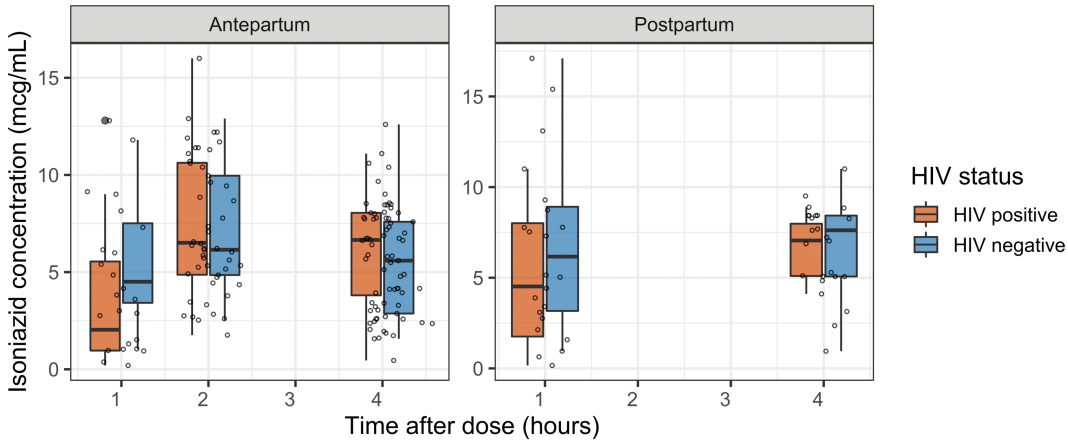
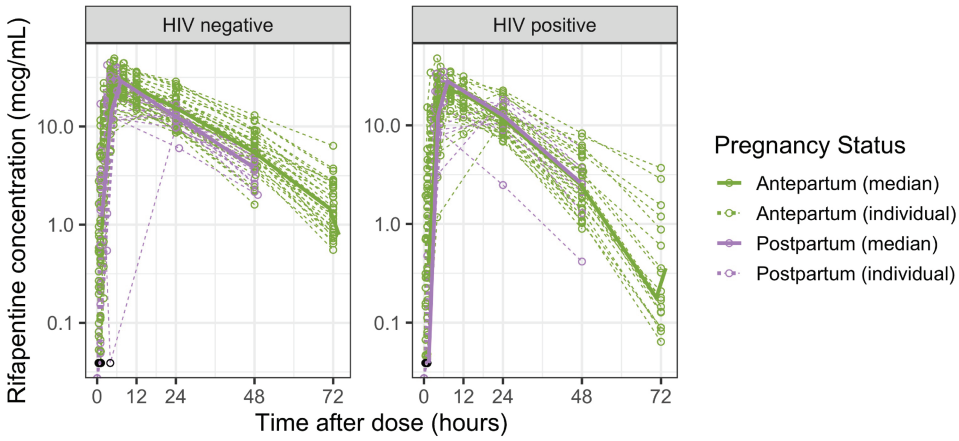


Figure 3. Effect of pregnancy and HIV on INH PK: The clearance of isoniazid was comparable between pregnant and postpartum women with HIV (orange) and without HIV (blue). The AUC_{SS} for the entire population was 78.2 mg × hour/L (IQR, 21.9–78.2) and maximum isoniazid concentration was 7.74 mg/L (IQR, 5.68–10.6). Abbreviations: AUC_{SS}, steady-state area under the concentration-time curve; HIV, human immunodeficiency virus; IQR, interquartile range.



Status	Antepartum	Postpartum	% change vs. pregnancy
HIV-positive clearance, L/hr (RSE)	1.56 (7%)	1.60 (11%)	↑ 2%
HIV-negative clearance, L/hr (RSE)	1.20 (6%)	1.53 (8%)	↑28%

Figure 4. Effect of pregnancy on clearance of RPT, by HIV status: In women without HIV (left panel), the postpartum clearance (purple) was 28% higher than antepartum clearance (green). In WLHIV, the clearance of RPT antepartum and postpartum was comparable to each other, and to postpartum clearance in women without HIV. Abbreviations: HIV, human immunodeficiency virus; RPT, rifapentine; RSE, relative standard error; WLHIV, women living with HIV.

for 2 of these events. The woman with the grade 4 placental abruption (described above) also had premature delivery and grade 3 pre-eclampsia. In cohort 2, the grade 3 hemoglobin levels also occurred after delivery, including the woman with postpartum hemorrhage described above. The other events are described in Table 3.

Only 1 (2%) participant had an AE assessed to be possibly related to the study regimen. She was in cohort 1 and had grade 2 muscle cramps of legs, feet, arms, hands, and face at week 7 of the study. She continued the study drug and her symptoms resolved within 24 hours.

Table 2. Rifapentine Pharmacokinetic Results in IMPAACT 2001 and Other Studies in Nonpregnant Populations

Rifapentine Parameter	IMPAACT 2001 (n = 50)	Weiner, JPIDS 2014 [16] (n = 80)
CL/F, L/hour (RSE)		
Antepartum[a]		
HIV-positive	1.56 (7%)	…
HIV-negative	1.20 (6%)	…
Postpartum		
HIV- positive	1.60 (11%)	…
HIV-negative	1.53 (8%)	…
Nonpregnant (HIV-negative)	…	2.32 (11%)
CL_{met}/F (RSE)	2.75 (7%)	2.05 (10%)
Median AUC_{SS} (5th–95th percentile), mg × hour/L		
Antepartum[a]		
HIV-positive	522 (359–803)	…
HIV-negative	786 (549–1171)	…
Postpartum		
HIV-positive	554 (434–751)	…
HIV-negative	673 (471–847)	…
Nonpregnant (HIV-negative)	…	553 (326–931)
Median (IQR) C_{min}, mg/L	1.05 (0.455–2.01)	…
Median (IQR) C_{max}, mg/L	27.4 (24.7–34.6)	…

Abbreviations: AUC_{SS}, steady-state area under the concentration-time curve; CL/F, clearance; CL_{met}/F, clearance of metabolite; C_{max}, observed maximum concentration; C_{min}, observed minimum concentration; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trial Network; IQR, interquartile range; JPIDS, *Journal of the Pediatric Infectious Diseases Society*; RSE, relative standard error.

[a]Includes combined second- and third-trimester data.

Table 3. Frequency [n (%)] of Maternal Adverse Events

Event	Total (N = 50)	Cohort 1 (Second Trimester, n = 25)	Cohort 2 (Third Trimester, n = 25)
Serious adverse events[a]	5 (10%); 95% CI: 3–22%	2 (8%); 95% CI: 1–26%	3 (12%); 95% CI: 3–31%
Abruptio placentae	2	2	0
Hypertensive disorders	3	1	2
Postpartum hemorrhage	1	0	1
Death	1	1	0
Grade 3–4 adverse events	9 (18%); 95% CI: 9–31%	5 (20%); 95% CI: 7–41%	4 (16%); 95% CI: 5–36%
Hematologic	5	3	2
Anemia	4	2	2
Elevated PT	1	1	0
Stillbirth	1	1	0
Premature delivery	1	1	0
Bacterial pneumonia	1	1	0
Drug-related grade 2 adverse events (muscle cramps)	1 (2%); 95% CI: .05–11%	1 (4%); 95% CI: .1–20%	0 (0%); 95% CI: 0–14%
Permanent study drug discontinuation due to toxicity	0 (0%); 95% CI: 0–7%	0 (0%); 95% CI: 0–14%	0 (0%); 95% CI: 0–14%

Abbreviations: CI, confidence interval; PT, prothrombin time.
[a]Participants could have experienced >1 of the listed events.

Infant Safety

Of the 49 liveborn infants, none developed TB or study treatment–related SAEs (95% CI: 0–7%). There were 6 (12%) infants with SAEs; 4 (17%) born to women in cohort 1 and 2 (8%) from cohort 2 (Table 4). At 8 weeks of life, 1 infant had grade 3 anemia and grade 4 total bilirubin; both resolved by 12 weeks. There were 8 (16%) infants who had at least 1 adverse birth outcome: 2 (8%) in cohort 1 and 6 (24%) in cohort 2. In cohort 1, one had premature birth (<37 weeks) and low birth weight (<2500 g). In cohort 2, one had premature and low birth weight; one had premature birth, intrauterine growth retardation and low birth weight; and one had low birth weight and was small for gestational age. The remaining events are described in Table 4.

There were 2 (4%) infants who had grade 2 or higher AEs that were assessed to be possibly related to the study drug (not shown in Table 4). One infant had a grade 4 PT value at week 0 and another had a grade 3 PT value at week 4. Both mothers were taking the study drug at delivery. Neither infant had clinical signs of bleeding and repeat PT values were normal. Overall, the proportion of infants with AEs possibly related to the study drug was 4% (95% CI: .5–14%): 0% (95% CI: 0–14%) in cohort 1 and 8% (95% CI: 1–26%) in cohort 2.

Table 4. Frequency [n (%)] of Infant Adverse Events

Event	Total (N = 49)	Cohort 1 (Second Trimester, n = 24)	Cohort 2 (Third Trimester, n = 25)
Serious adverse events[a]	6 (12%); 95% CI: 5–25%	4 (16.7%); 95% CI: 5–37%	2 (8%); 95% CI: .1–26%
Neonatal sepsis	4	3	1
Hyperbilirubin	2	1	1
Neonatal respiratory distress	1	1	0
Premature birth (<32 weeks)	1	1	0
Anemia of prematurity	1	1	0
Small for gestational age[b]	1	0	1
Subgaleal hematoma[a]	1	0	1
Adverse birth outcomes[c]	8 (16%); 95% CI: 7–30%	2 (8%); 95% CI: 1–27%	6 (24%); 95% CI: 9–45%
Premature birth (<37 weeks)	5 (10%); 95% CI: 3–22%	1 (4%); 95% CI: .01–21%	4 (16%); 95% CI: 5–36%
Low birth weight (<2500 g)	4 (8%); 95% CI: 2–20%	1 (4%); 95% CI: .01–22%	3 (12%); 95% CI: 3–31%
Small for gestational age[b]	3 (7%); 95% CI: 4–12%	1 (5%); 95% CI: .1–24%	2 (9%); 95% CI: 1–29%
Intrauterine growth retardation	1 (2%); 95% CI: .7–6%	0 (0%); 95% CI: 0–16%	1 (5%); 95% CI: .1–23%

Abbreviation: CI, confidence interval; ICH, International Conference on Harmonization.
[a]Infants could have experienced >1 of the listed events.
[b]There are 6 missing classification of newborn intrauterine growth and gestational age and only 1 of the 3 was a serious adverse event (had met ICH criteria of hospitalization).
[c]The adverse birth outcomes reported in this table are on the live born infants only, stillbirth is reported as a maternal adverse event in Table 3.

DISCUSSION

IMPAACT 2001 was the first study to evaluate 3HP in pregnancy. We found that pregnancy did not significantly impact the clearance of RPT or INH. However, clearance of RPT in pregnant WLHIV was significantly higher than that in pregnant women without HIV. This amount of change in clearance does not warrant a change in RPT dosage for pregnant WLHIV. To understand whether this is an effect of HIV or of EFV-based ART, assessment of RPT PK given together with newer antiretrovirals, such as dolutegravir (DTG), will be helpful. Our study also did not find major safety issues in mothers or infants, which provides a strong rationale for a larger safety study of this regimen.

The most important first step to extend the use of a drug to pregnant women is establishing appropriate dosage. Pregnancy increases activity of progesterone-dependent cytochromes in the liver, for example, which may necessitate modifications to dose or schedule [20, 21]. In IMPAACT 2001, RPT concentrations were higher during pregnancy compared with postpartum. These increases, however, were modest, limited to women without HIV, and resulted in exposures that were within the range seen in nonpregnant adults taking 3HP [18]. Pregnancy did not alter INH disposition, which is in agreement with some previous studies, but in contrast to TB APPRISE [13, 22, 23]. To more fully characterize INH PK in this population, acetylation status and PK data collected in the absorption and elimination phase are needed.

The second step is to evaluate safety and tolerability during pregnancy. Given that 3HP is a 12-week regimen, it can be fully completed during pregnancy if started by the early third trimester. In this study, all 50 women completed the regimen, providing initial evidence of good tolerability during pregnancy. Furthermore, there were no major drug-related toxicities. These findings provide a strong rationale to proceed with a study adequately powered to evaluate maternal safety.

In our study, HIV was associated with a 30% higher clearance and 34% lower AUC_{ss} of RPT during pregnancy compared with women without HIV. This is consistent with the effects of HIV on RPT pharmacokinetics observed in nonpregnant adults, which has been attributed to malabsorption or, possibly, ART effects [25]. However, the AUC_{ss} for pregnant WLHIV in IMPAACT 2001 was similar to mean AUC values reported in nonpregnant adults without HIV [16]. Standard dosing in pregnant WLHIV, therefore, achieves drug exposures within the range of exposures associated with successful prevention of TB in registrational trials [15].

Interestingly, women without HIV experienced a 28% decrease in clearance while pregnant. A similar effect has been seen with rifampicin [25]. The increased clearance over time may be related to physiologic changes of pregnancy but may also be partly related to auto-induction of RPT-metabolizing enzymes [26–28]. A recent meta-analysis reported that RPT clearance may increase by 20% due to auto-induction with once-weekly dosing, but effects on AUC are modest [24].

In pregnant WLHIV, however, there was no significant change in clearance between antepartum and postpartum periods. A possible explanation is that EFV had already induced the enzymes responsible for RPT metabolism by the time 3HP was started, leaving less room for RPT's induction of its own metabolism. A recent study of nonpregnant people with HIV reported decreased RPT clearance in slow N-acetyltransferase 2 acetylators taking EFV-based ART, likely because of increased INH exposure [29]. IMPAACT 2001 did not collect pharmacogenetic data to assess whether this association is present during pregnancy. As DTG replaces EFV as first-line treatment for WLHIV globally, additional PK studies during pregnancy may be useful to confirm that DTG does not significantly affect RPT PK, as has been shown in nonpregnant adults [30].

This study was designed to establish the RPT dose in pregnancy that achieves concentrations similar to those in nonpregnant adults. It was not powered to fully characterize the effect of 3HP on birth outcomes. The initial safety and tolerability data from our study, however, are encouraging, with complication rates comparable to global estimates [31–34]. The single maternal death was related to placental abruption from trauma weeks after completing the study drug. Although there were more adverse birth outcomes in those enrolled in the third trimester (cohort 2), the number of events was too small to determine their significance. One would expect similar or more adverse birth outcomes in cohort 1 because they were enrolled in the second trimester and had longer exposure to the study drug earlier in pregnancy, when most fetal development occurs. The only study drug–related AEs were grade 2 maternal muscle cramps, which resolved, and 2 grade 3/4 elevated PT in infants, which were not clinically significant.

A limitation of the study was the homogeneity of the population, both by race/ethnicity and ART used. For this initial PK study with a limited sample size, homogeneity increases statistical confidence in results. However, future safety studies should include more heterogeneous populations to increase generalizability. Rifapentine significantly decreases the plasma levels of protease inhibitors [35] (PIs); therefore, women on PIs were excluded. Dolutegravir was not approved for pregnancy at the time this study was initiated, but pregnant women on DTG will be included in future studies of 3HP. Because this is a single-arm study, we could not assess whether the shorter duration and small number of doses in 3HP is safer compared with other TB prevention regimens containing prolonged daily dosing in this population. An earlier study of 54 pregnant women who were inadvertently exposed to 3HP early in pregnancy also found no increased risk of fetal loss or congenital anomalies compared with women on nine months of daily INH or the general population [36], but it was similarly not powered for definitive

comparison. Larger, postmarketing studies are needed to thoroughly evaluate the safety before definitively recommending 3HP in pregnant and postpartum women.

Conclusions

The prevention of TB in pregnant women is an important priority for maternal-child health. Pregnant and postpartum women are at high risk of TB, which carries a serious risk of adverse outcomes for a woman and her child [5, 7, 8]. IMPAACT 2001 was the first dedicated study to evaluate the PK of 3HP in pregnancy, and it demonstrated that 3HP can be given without dose adjustment to both pregnant and postpartum women. In WLHIV taking EFV-based ART, RPT clearance was higher than in women without HIV but similar to nonpregnant populations. As 3HP was well tolerated, there is a strong rationale to proceed with a larger safety-powered study to ensure that pregnant and postpartum women have an equal opportunity to benefit from the revolutionary research occurring in TB prevention.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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