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# Population Pharmacokinetics of Rifampin in Pregnant Women with Tuberculosis and HIV Coinfection in Soweto, South Africa

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**Effective treatment of tuberculosis during pregnancy is essential for preventing maternal and fetal mortality, but little is known about the effects of pregnancy on the disposition of antituberculosis drugs. We explored the effects of pregnancy on the pharmacokinetics of rifampin, the key sterilizing drug in tuberculosis treatment, in Tshepiso, a prospective cohort study involving pregnant HIV-infected women with or without tuberculosis in Soweto, South Africa. Participants receiving standard first-line tuberculosis treatment underwent sparse sampling for rifampin at 37 weeks' gestation or delivery and then postpartum. Cord blood was collected when possible. A population pharmacokinetic model was developed to investigate the effects of pregnancy on rifampin pharmacokinetics. Among the 48 participants, median age and weight were 28 years and 67 kg, respectively. A one-compartment model with first-order elimination, transit compartment absorption, and allometric scaling described the data well. Pregnancy reduced rifampin clearance by 14%. The median (interquartile range) model-estimated rifampin area under the concentration-time curve over 24 h ($AUC_{0-24}$) during pregnancy or intrapartum was 40.8 h · mg/liter (27.1 to 54.2 h · mg/liter) compared to 37.4 h · mg/liter (26.8 to 50.3 h · mg/liter) postpartum. The maximum concentrations were similar during pregnancy and postpartum. Rifampin was detectable in 36% (8/22) of cord blood samples, and 88% (42/48) of the women had successful treatment outcomes. There was one case of perinatal tuberculosis. In conclusion, rifampin clearance is modestly reduced during the last trimester of pregnancy. Exposures are only slightly increased, so dose adjustment during pregnancy is not needed. Rifampin was detected in cord blood samples when delivery occurred soon after dosing. The consequences of exposure to this potent inducer of metabolizing enzymes among HIV-exposed infants are unclear.**

Tuberculosis (TB) remains a global public health threat, with 9 million new cases and 1.5 million TB-related deaths in 2013 (1). The first-line treatment for TB consists of four drugs, isoniazid, rifampin, pyrazinamide, and ethambutol, and the total treatment duration is 6 months. Rifampin is the key sterilizing drug in the TB treatment regimen. Several lines of evidence indicate that rifampin drives the overall treatment response in drug-sensitive TB and that the current rifampin dosing achieves exposures that are at the lower end of the dose-response curve (2–7), suggesting that modest changes in exposure to the drug might have important clinical consequences. Since inadequate rifampin exposures can lead to relapse or acquired drug resistance (8, 9), ensuring adequate dosing in all populations is essential.

Pregnant women with HIV infection are at especially high risk of progression from latent TB infection (LTBI) to TB disease, and immunologic changes related to pregnancy may enhance the risk (10, 11). In addition, TB is a significant cause of infant and maternal morbidity and mortality, especially in settings where the HIV incidence is high (12, 13). TB treatment guidelines recommend use of the same regimens and dosages for pregnant women and nonpregnant adults except that some, but not all, guidelines suggest that pyrazinamide may be withheld in pregnancy (with prolongation of treatment from 6 to 9 months) (14).

Pregnancy induces physiologic changes that affect drug absorption, distribution, metabolism, and hepatic or renal clearance (15, 16). While the impact of pregnancy on the pharmacokinetics (PK) of some commonly used antimicrobials has been well studied or can be predicted based on knowledge of the compound and the expected effects of pregnancy on drug disposition, for the majority of antibiotics, data are lacking (17). That is, there are no published studies describing the pharmacokinetics of TB drugs, including rifampin, in pregnancy. Rifampin is rapidly absorbed, with a time to maximum concentration of about 2 h. It is 80% protein bound and has a half-life of about 2.5 h at steady state. It is deacetylated in the liver and is excreted in the bile and urine (18). While hepatic cholestasis related to the use of estrogens like ethynylestradiol can interfere with the elimination of some drugs that are cleared via the biliary route (19) and may theoretically affect rifampin clearance (20), the effects of pregnancy on rifampin pharmacokinetics have not been investigated. Further, rifampin is known to cross the placenta; however, exposures of the fetus and neonate to this drug, which is a strong inducer of metabolizing enzymes that may theoretically affect exposures of drugs administered to neonates, have been poorly characterized (21, 22).

The aims of this study were to evaluate the population pharmacokinetics of rifampin among women with HIV and TB coin-

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**TABLE 1** Demographics, clinical characteristics, and TB treatment outcomes for the entire substudy population and those included in the population PK analyses

| Characteristic[a] | Full substudy population ($n = 48$) | Cohort included in population PK analysis ($n = 33$) |
|---|---|---|
| Age at enrollment (median [IQR]) (yr) | 28 (25–31) | 28 (26–30) |
| CD4 at enrollment (median [IQR]) (cells/mm$^3$) | 301 (195–439) | 300 (148–443) |
| Site of TB infection (no. [%]) | | |
| Pulmonary | 45 (94) | 31 (94) |
| Extrapulmonary | 3 (6) | 2 (6) |
| Infant weight at delivery (median [IQR]) (g) | 3,000 (2,575–3,370) | 3,000 (2,580–3,400) |
| Mother weight at delivery (median [IQR]) (kg) | 67 (60–76) | 66 (60–77) |
| Gestational age at delivery (median [IQR]) (wk) | 38 (37–40) | 38 (37–40) |
| TB treatment completed at time of delivery (median [IQR]) (wk) | 9 (7–17) | 9 (8–16) |
| TB treatment outcome (no. [%]) | | |
| Cured | 2 (4) | 2 (6) |
| Treatment completed | 40 (83) | 28 (85) |
| Death | 0 | 0 |
| Default | 1 (2) | 1 (3) |
| Failure | 0 | 0 |
| Lost to follow-up | 3 (6) | 1 (3) |
| Ongoing treatment | 2 (4) | 1 (3) |
| Concomitant ART | | |
| EFV-based HAART | 41 (85) | 28 (85) |
| NVP-based HAART | 1 (2) | 0 |
| LPV/r-based HAART | 1 (2) | 1 (3) |
| AZT until delivery + single dose NVP at delivery | 5 (10) | 4 (12) |

[a] ART, antiretroviral therapy; EFV, efavirenz; HAART, highly active antiretroviral therapy; NVP, nevirapine; LPV/r, lopinavir-ritonavir; AZT, zidovudine.

fection taking rifampin-containing TB treatment during pregnancy and postpartum and to evaluate cord blood exposures to rifampin.

## MATERIALS AND METHODS

**Study population.** Tshepiso is a prospective cohort study evaluating the effects of TB on maternal and infant outcomes in women with HIV infection. Pregnant women who were aged ≥18 years, had a gestational age of >13 weeks, and had HIV infection with or without TB were recruited from antenatal clinics and obstetrics wards at Chris Hani Baragwanath Hospital, Soweto, South Africa, between January 2011 and January 2013 (23). The subjects included in the current analysis were enrolled in a rifampin pharmacokinetic substudy within Tshepiso. The substudy included participants with confirmed or probable TB who received rifampin-containing TB treatment for ≥10 days during pregnancy or postpartum. Antiretroviral and TB treatment was dispensed by local providers outside the study. The regimens followed the national treatment guidelines. Rifampin was given as part of a fixed-dose combination tablet (Rifafour or Rifinah) at a dose of ~10 mg/kg, with most participants receiving 600 mg daily. This study was approved by the institutional review boards of Johns Hopkins Medicine, University of the Witwatersrand, and University of Cape Town. Participants provided written informed consent.

**Study protocol.** Women receiving standard first-line TB treatment underwent pharmacokinetic sampling for rifampin at 37 weeks' gestation or at delivery and then postpartum at 6 weeks after delivery. In most women, blood samples were collected predose and then 2, 4, and 6 to 8 h postdose, but the sampling schedule was pragmatic for women taking their medications just prior to arrival in the clinic or in the evening and for women presenting in labor. In the latter group, samples were collected at 3-h intervals from presentation until delivery (maximum of four samples), and a cord blood sample was collected. In all patients, the timing of rifampin doses prior to presentation to the clinic was recorded based on self-report. Maternal TB treatment outcomes (cure, treatment completion, death, default, or failure) were recorded. Successful treatment was defined as cure or treatment completion. Episodes of neonatal TB (TB within the first 6 months of life) were noted.

**Drug concentration analysis.** Rifampin plasma concentrations were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) performed in the Division of Clinical Pharmacology, University of Cape Town, as previously described (24). The method was linear over the range of 0.117 (the lower limit of quantification [LLOQ]) to 30 mg/liter. The interday accuracy of the assay ranged from 99.4% to 102.6%, and the coefficient of variation (%CV) of the precision ranged from 5.9% to 8.3%.

**Pharmacokinetic and statistical analyses.** A population PK model of steady-state rifampin was developed with NONMEM version 7.3 and first-order conditional estimation with eta-epsilon interaction (25); we also used Pirana, Perl-speaks-NONMEM, and Xpose4 to aid the modeling process and prepare model diagnostics (26). For the structural model, we started with a previously published model for rifampin pharmacokinetics (27), specifically a one-compartment model with transit compartment absorption (28). The final statistical model assumed log-normal distribution for the between-subject and between-occasion random effects, and a combined additive and proportional structure for the residual unexplained variability, with the additive component of the error bound to be at least LLOQ/2. Values below the LLOQ (BLQ) were imputed to LLOQ/2, except for consecutive values during the elimination phase of the PK profiles which were excluded from the fit, following the M6 method in Beal (29). Allometric scaling based on total body weight was applied to clearance (CL) and volume of distribution ($V$), as suggested by Anderson and Holford (30), and the effect of other covariates was tested and included in the model based on physiological plausibility and significant decreases in the objective function value (OFV). The statistical signifi-

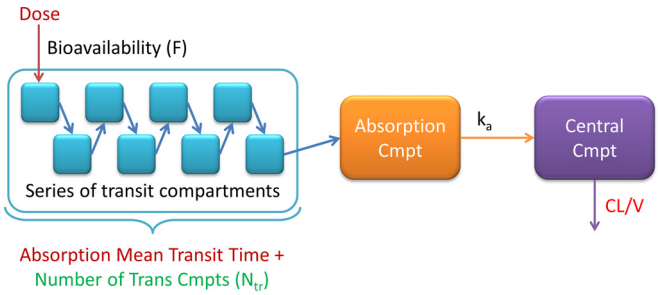


**FIG 1** Structural model. Rifampin is assumed to go through a series of transit compartments before it appears at the absorption site, from which it is absorbed into the central compartment with a first-order absorption rate ($k_a$). It is then eliminated from the central compartment with first-order kinetics. The transit compartments do not represent the physical compartments of the digestive system, but they are simply a mathematical expedient to flexibly describe drug absorption. Their number and the transit time through them are estimated from the data.

cance cutoff for an additional degree of freedom was a drop of at least 3.84 points, corresponding to a $P$ value of 0.05. Covariates tested in investigating the effects on the PK parameters were pregnancy, age, and formulation (the four-drug versus two-drug formulation for the intensive and continuation phases of the TB treatment, respectively). The OFV, goodness-of-fit plots, and visual predictive checks (31) guided model development. The robustness of the final parameter estimates was assessed with a nonparametric bootstrap.

The final population PK model was used to generate individual *post hoc* Bayesian estimates of PK parameters, which were then used to obtain the steady-state area under the concentration-time curve over 24 h ($AUC_{0-24}$) and the maximum concentration ($C_{max}$) values.

## RESULTS

**Study population.** There were 48 pregnant women with HIV/TB coinfection who received rifampin and underwent PK sampling. The median age was 28 years, the median weight at delivery was 67 kg, and most of the women (41/48) were receiving efavirenz-based antiretroviral treatment. The demographic, clinical, and laboratory characteristics of substudy participants are presented in Table 1.

**Population pharmacokinetics of rifampin during pregnancy and postpartum.** The modeling analysis was performed on 183 samples from 33 participants and 48 PK sampling visits: 20 during the third trimester, 4 peripartum, and 24 postpartum. While all the PK samples collected from patients receiving anti-TB treatment in the Tshepiso study were screened for inclusion in the current analysis, the sampling schedule was not optimized for rifampin, and the dosing of anti-TB agents was not always accurately recorded (this was an opportunistic substudy nested within Tshepiso, whose main PK focus was on antiretrovirals); PK profiles that were uninformative or had obvious inconsistencies with the recorded dosing schedule were excluded from the population PK analysis. Details about the excluded data can be found in the Appendix. The characteristics of the participants that were and were not included in the PK analyses were similar (Table 1).

The data were best fit by a one-compartment disposition model, with first-order elimination and transit compartment absorption. The model equations are presented in the Appendix, the model structure is shown in Fig. 1, the final parameter estimates are contained in Table 2, and a prediction-corrected visual predictive check (32) is shown in Fig. 2.

The inclusion of weight-based allometric scaling on CL and $V$ improved the fit (18-point improvement in OFV). Pregnancy was found to decrease CL by 14% (OFV improvement of 4.97 points, $P = 0.026$). The model detected modest between-subject variability in CL, between-occasion variability in bioavailability, and a large between-occasion variability in the other absorption parameters.

The values of $AUC_{0-24}$ and $C_{max}$ were obtained using empirical Bayesian estimates of the individual parameters, whose values of shrinkage are reported in Table 2 along with the other parameter estimates (33). The median (interquartile range [IQR]) model-estimated rifampin $AUC_{0-24}$ during pregnancy or intrapartum was 40.8 h · mg/liter (27.1 to 54.2 h · mg/liter), compared to 37.4 h · mg/liter (26.8 to 50.3 h · mg/liter) postpartum. The $C_{max}$ during pregnancy/intrapartum was 8.4 mg/liter (7.1 to 10.0 mg/liter), compared to 9.0 mg/liter (6.6 to 11.9 mg/liter) postpartum. The proportion of PK profiles with a rifampin $C_{max}$ of <8 mg/liter was similar during pregnancy and intrapartum (46%) versus postpartum (42%).

The data contained 49 BLQ samples (27%), and most of these were found, as expected, in predose samples, collected ~24 h after the previous dose. Given the large proportion of BLQ data, we assessed whether the approach chosen to handle BLQ concentrations might affect the results by reestimating the model excluding all BLQ samples. The results are not shown here for brevity, but

**TABLE 2** Final population pharmacokinetic model parameter estimates[a]

| Parameter | Typical value | Parameter variability (%)[b] (shrinkage [%]) |
|---|---|---|
| CL (liters/h)[c] | 16.2 (13.8–19.1) | BSV: 30.4 (15.7–44.3) (4) |
| $V$ (liters)[c] | 43.3 (35.6–48.5) | |
| $k_a$ (1/h) | 1.67 (1.01–2.75) | BOV: 78.2 (35.2–114.5) (54) |
| Absorption mean transit time (h) | 1.31 (1.04–1.56) | BOV: 34.4 (18.8–50.8) (47) |
| No. of absorption transit compartments, $N_{tr}$ | 54.6 (27.2–108.5) | |
| Bioavailability, $F$ | 1 fixed | BOV: 28.0 (19.4–35.5) (36) |
| Proportional error (%) | 13.1 (6.9–16.7) | |
| Additive error (mg/liter)[d] | 0.0585 fixed | |
| Pregnancy effect on CL (%) | −14.0 (−28.7 to −2.8) | |

[a] Values in parentheses are empirical 95% confidence intervals, obtained with a 500-sample nonparametric bootstrap.
[b] The parameter variability was included either as between-subject (BSV) or between-occasion (BOV) variability. It is reported here as approximate %CV.
[c] The values of CL and $V$ were allometrically scaled, so the typical values reported here refer to the median body weight (66 kg) of the cohort included in the PK model.
[d] The estimate of the additive component of the error was not significantly different from its lower boundary of LLOQ/2, so it was fixed to this value.

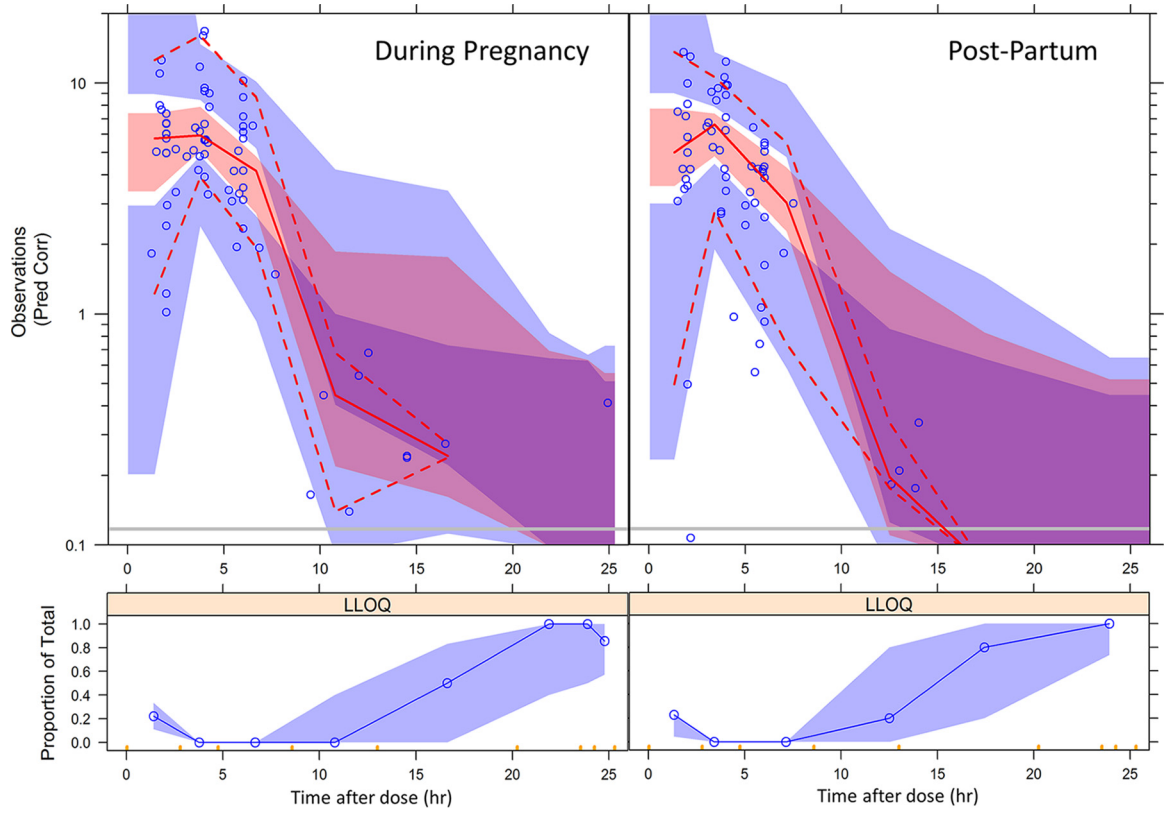


**FIG 2** Visual predictive check. Prediction-corrected visual predictive check of the final model, stratified by pregnancy status (data during pregnancy on the left and postpartum on the right). The upper panels refer to the concentrations above the limit of quantification (LLOQ): the solid and dashed lines are the 5th, 50th, and 95th percentiles of the observations, while the shaded areas represent the 95% model-predicted confidence intervals for the same percentiles. The lower panels show the proportion of data below the limit of quantification (BLQ): the solid line is the proportion observed, while the shaded area is the 95% confidence interval for the proportion predicted by the model. An appropriate model is expected to have the most percentiles observed within the simulated confidence intervals. It is important to note that both observations and model predictions in this chart are rescaled due to the prediction-correction; they can thus be used to diagnose the model, but they are not on the same scale as the original data.

none of the parameter estimates changed significantly, including the pregnancy effect on CL.

**Cord blood concentrations among infants born to women receiving rifampin-containing TB treatment.** Plasma rifampin concentrations were measured in 22 cord blood samples, 7 of which were collected concomitantly with maternal PK samples. Rifampin concentrations were BLQ in 14 of the samples, while the remaining 8 contained quantifiable concentrations, and their median time from the reported dose was 5.5 h. The information about maternal dosing peripartum was obtained by self-report from participants during labor and was sometimes, understandably, imprecise. As detailed in the previous section, some of the maternal PK curves presented obvious inconsistencies with the reported dosing history and had to be excluded. Two of these inconsistent profiles had matched cord blood samples (with BLQ concentrations), which were thus discarded. The same assessment was not possible for cord blood samples not matched with maternal PK samples, so all of the remaining samples were considered for the analysis. Figure 3 shows the measured cord blood concentrations versus the estimated time after maternal dose intake and superimposed to the model-predicted maternal concentration.

The matched mother/cord data were not sufficient to support robust and meaningful modeling. However, visual inspection of the plasma concentrations of rifampin in cord blood versus the estimated time after the maternal dose shows that all detectable concentrations in cord blood coincided with earlier times after the maternal dose and were generally lower than the expected maternal concentrations. On the other hand, a number of cord blood samples with concentrations BLQ were present even within the first hours after a reported maternal dose. No matched maternal concentrations were available for those samples to ascertain whether such low values may have been due to maternal noncompliance. All cord blood samples collected ≥15 hours after the dose were BLQ.

**Clinical outcomes.** Among 48 pregnant, HIV-infected women treated for TB during pregnancy, treatment outcomes were successful in 42 (88%) (Table 1). There was one case of antepartum hemorrhage, and no women discontinued TB treatment due to toxicity.

Among infants born to the study participants, there was one case of infant TB diagnosed at 4 months of age. The mother had pulmonary TB, and at the time of delivery she was in the continuation phase of TB treatment; her rifampin blood concentrations were similar to those of other participants taking rifampin. The mother successfully completed a full course of standard pulmonary TB treatment without interruption at 3 months postpartum and did not report relapse during the study follow-up. The neonate received 3 months of prophylaxis with rifampin and isoniazid beginning at day 8 of life and received *Mycobacterium bovis* BCG

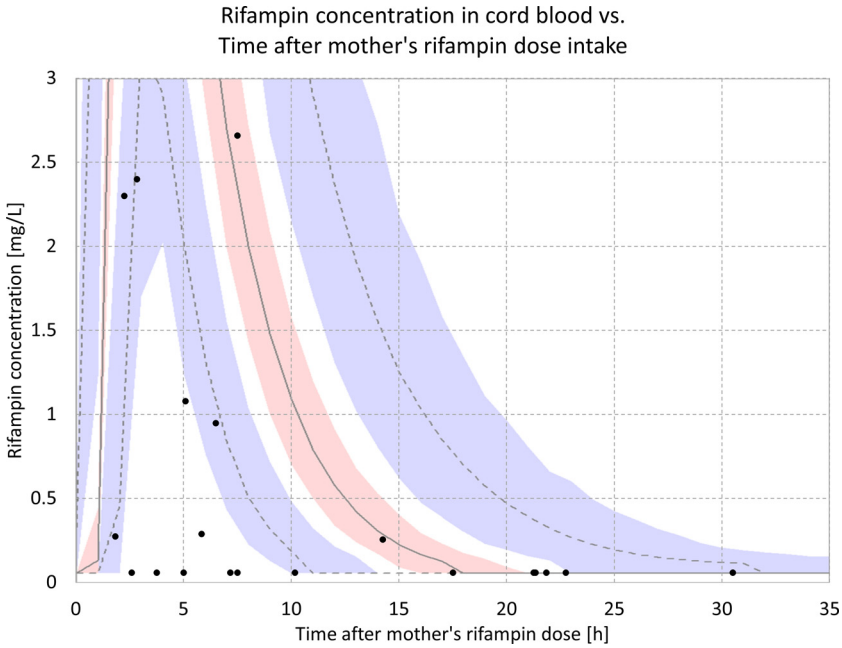


**FIG 3** Cord blood concentrations. Rifampin cord blood concentration versus time after the mother's rifampin dose intake. The black dots are the rifampin concentrations observed in cord blood, while the solid and dashed lines represent the model-simulated 5th, 50th, and 95th percentiles of rifampin concentration in this cohort of pregnant women. The shaded areas are the 95% confidence intervals of the same percentiles. BLQ concentrations are shown in the graph as LLOQ/2.

vaccine at birth. At 4 months, the infant was admitted for shortness of breath, cough, and fever and was diagnosed with pulmonary TB based on the chest X-ray findings. The infant was initiated on and completed 6 months of standard first-line treatment, with good response. It is not known whether other household contacts also had TB disease.

## DISCUSSION

Rifampin is the key sterilizing drug in the treatment regimen for drug-sensitive TB. Our study is the first to describe the pharmacokinetics of rifampin in pregnant women. Interestingly, rifampin oral clearance was reduced rather than increased during the last trimester of pregnancy. While exposures are predicted by our model to be higher in pregnant women than in nonpregnant adults, the expected increases are very modest and not likely to be clinically meaningful, so no dose adjustment is needed. The observed proportion of women achieving the target $C_{max}$ (≥8 mg/liter) was very similar in pregnancy (54%) versus postpartum (58%). Rifampin was present in cord blood, most commonly when the dose was given shortly before delivery. Overall, among pregnant women with HIV/TB coinfection, rifampin-containing TB treatment was safe and well tolerated.

For some drugs, systemic exposure in pregnancy can be predicted based on knowledge of the drug's chemical properties and pharmacokinetics and an understanding of the gestational age-dependent changes in maternal physiology and contributions of the fetal-placental unit to alterations in drug distribution (34, 35). These predictions can then be tested clinically. For a majority of drugs, concentrations are unchanged or reduced during pregnancy (16). However, clearance of some drugs, like those metabolized by cytochrome P450 (CYP) 1A2 or CYP2C19, is reduced in pregnancy, resulting in higher exposures (36, 37). Rifampin, though, is not a P450 substrate. Rifampin is largely eliminated in the bile, and pregnancy can cause estrogen-induced intrahepatic cholestasis (19). Pregnancy-induced cholestasis can theoretically result in higher concentrations of drugs that are eliminated by hepatobiliary excretion. This has rarely been reported in the literature but may occur with azithromycin (38). Interestingly, in a report from Harrison and Gibaldi in 1976, the average half-life of rifampin was 5.7 h in patients with obstructive jaundice, twice as long as that in patients without biliary obstruction (39). It is not clear if the longer half-life resulted from the competition of bilirubin and rifampin for clearance or from cholestasis itself. Nevertheless, this observation has led to the conjecture that pregnancy can induce cholestatic changes that, in turn, reduce rifampin clearance (20). Up to now, there has been no clinical evidence that this is the case, although ongoing pharmacokinetic studies in pregnant women with TB may shed further light on this topic (ClinicalTrials registration no. NCT00042289).

It is good news that rifampin exposures are not reduced in pregnant women with TB, given the negative impact that inadequate treatment can have on the health of the mother and her infant. In addition, it is fortunate that exposures to rifampin are only modestly increased in pregnancy and are, thus, unlikely to pose a safety risk. In general, rifampin is a well-tolerated antibiotic, even in clinical trials in which doses significantly exceeding those currently recommended are given (6). While maternal hemorrhage is listed as a risk in pregnancy in the package insert, this appears to be uncommon, but the true magnitude of the risk is unknown.

As highlighted in recent reviews, pharmacokinetic data for drugs in pregnancy are scarce, and there are large knowledge gaps (40). Given that "pregnant women get sick and sick women get pregnant," that pregnancy can have a significant and sometimes

unpredictable impact on drug disposition, and that pregnant women are routinely excluded from trials of new drugs (limiting our knowledge of safety and optimal dosing in this special population), assessment of drugs in pregnancy is a high priority (41). This is especially true for diseases like TB for which treatment options are extremely limited.

Rifampin crosses the placenta (21, 22), and it is present in cord blood for a short time following administration of a dose to the mother. The consequences of daily *in utero* exposure to rifampin, a potent inducer of drug-metabolizing enzymes and drug transporters, especially among HIV-exposed infants, is unclear. In pregnant rodents, rifampin has been shown to induce expression of fetal P450-metabolizing enzymes and drug transporters, such as ABCB1 (42, 43). The effects of maternal rifampin use on drug-metabolizing enzymes and transporters in developing human fetuses and neonates are unclear and require further study, especially if drugs such as antiretrovirals are given routinely to infants born to women with HIV/TB coinfection.

This study has several limitations. First, no HIV-uninfected women were included, so we could not separately evaluate the effects of pregnancy and HIV coinfection on the pharmacokinetics of rifampin. HIV infection is generally associated with low rifampin concentrations, largely owing to the reduced bioavailability of the drug in HIV-infected persons (24, 44). It is reassuring, then, that pregnancy does not appear to reduce rifampin concentrations even further in HIV-infected women. We did not measure the free concentrations of rifampin. Rifampin is moderately (80%) protein bound and pregnancy-related changes in plasma volume and circulating proteins can affect the concentrations of unbound drug and drug clearance, particularly for compounds that are highly protein bound. Third, we could not elucidate the mechanism for reduced clearance of rifampin in pregnancy, although estrogen-related cholestasis is one possibility. Finally, this study was relatively small, and there were clear challenges inherent with collecting samples from pregnant women receiving TB drugs in a program rather than in a clinical trial setting. However, PK studies of this sort must be done in patients rather than healthy volunteers, and a model-based approach allowed for assessment of the effects of pregnancy on drug disposition even when dosing times were variable and study participants were heterogeneous. Confirmatory studies in pregnant women with TB with or without HIV are needed.

In conclusion, rifampin clearance was reduced rather than increased in pregnant women, possibly owing to pregnancy-related cholestasis, although the mechanism is unknown. Concentrations were very modestly increased, so there is no need for dose adjustment in pregnancy. Rifampin is present in cord blood shortly after rifampin dosing. The clinical relevance of daily *in utero* exposure to rifampin, a potent inducer of drug-metabolizing enzymes and transporters, among HIV-exposed infants merits further study.

## APPENDIX

**Model equations.** The differential equations of the model are the following:

$$dA_{\mathrm{abs}}(t)/dt = D \cdot \frac{(k_{\mathrm{tr}} \cdot t)^{N_{\mathrm{tr}}}}{\Gamma(N_{\mathrm{tr}}+1)} \cdot e^{-k_{\mathrm{tr}} \cdot t} - k_a \cdot A_{\mathrm{abs}}(t)$$

$$dA_{\mathrm{c}}(t)/dt = k_a \cdot A_{\mathrm{abs}}(t) - \frac{\mathrm{CL}}{V} \cdot A_{\mathrm{c}}(t)$$

where $A_{\mathrm{abs}}$ and $A_{\mathrm{c}}$ represent the drug amounts in the absorption and central compartments, respectively, $D$ is the amount of the dose in milligrams, $t$ denotes the time in hours from the last dose, $k_{\mathrm{tr}}$ is the first-order rate constant between the transit compartments, $N_{\mathrm{tr}}$ is the number of transit compartments, $k_a$ is the first-order absorption rate constant, $\Gamma(.)$ is the gamma function, CL is the clearance, and $V$ is the volume of distribution of the central compartment.

**Data exclusions and cohort in the PK analysis.** After all the samples collected from patients receiving anti-TB treatment who were enrolled in the Tshepiso study were screened, data were available for 48 patients from 83 PK visits: 30 while pregnant, 8 during delivery, and 45 postpartum. The data from 21 PK visits were not included in the analysis because all concentrations from these visits were BLQ, and they would not meaningfully contribute to the model. For 9 of these visits, all samples were collected >12 h after the last rifampin dose, at a time when the rifampin concentrations are expected to be very low, while in the remaining 12 it is posited that the recorded dose time was unreliable, because concentrations were undetectable in all samples even if these were collected shortly after a reported dose. Additionally, another 14 PK profiles showed serious inconsistencies with the patient-reported dosing schedule (e.g., the participant reported taking a dose a few minutes before coming to the clinic and the drawing of the first sample, yet the concentrations were all extremely low and no absorption was detectable for the following few hours). Since no participants with observed dosing (pregnant or not) had similar issues with their PK profiles, these data were excluded from the analysis.

The demographic, clinical, and laboratory characteristics for the cohort of patients that were included in the PK analysis and those in the general cohort were similar (See Table 1).

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