Predicted Pharmacokinetic Interactions Between Hormonal Contraception and Single or Intermittently Dosed Rifampicin

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Abstract

The scale-up of rifampicin-based prevention regimens is an essential part of the global leprosy strategy. Daily rifampicin may reduce the effectiveness of the oral contraceptive pill (OCP), but little is known about the effects of rifampicin at the less frequent dosing intervals used for leprosy prophylaxis. As many women of reproductive age rely on OCP for family planning, evaluating the interaction with less-than-daily rifampicin regimens would enhance the scalability and acceptability of leprosy prophylaxis. Using a semi-mechanistic pharmacokinetic model of rifampicin induction, we simulated predicted changes in OCP clearance when coadministered with varying rifampicin dosing schedules. Rifampicin given as a single dose (600 or 1200 mg) or 600 mg every 4 weeks was not predicted to result in a clinically relevant interaction with OCP, defined as a >25% increase in clearance. Simulations of daily rifampicin were predicted to increase OCP clearance within the range of observed changes previously reported in the literature. Therefore, our findings suggest that OCP efficacy will be maintained when coadministered with rifampicin-based leprosy prophylaxis regimens of 600 mg once, 1200 mg once, and 600 mg every 4 weeks. This work provides reassurance to stakeholders that leprosy prophylaxis can be used with OCP without any additional recommendations for contraception prevention.

Keywords

contraception, drug–drug interactions, leprosy, pharmacokinetics, rifampicin

Rifamycins and hormonal contraceptives are critical to the delivery of essential health services to women globally. It is estimated that 151 million women worldwide (14%) of reproductive age with a family planning need use an oral hormonal contraceptive pill (OCP), and that a further 190 million women worldwide have an unmet need for contraception and could potentially benefit from using an OCP.[1] Moreover, rifamycins are instrumental worldwide in the treatment and prevention of tuberculosis (TB), leprosy, and other infectious diseases that together affect a substantial proportion of the population in many regions of the world.[2–6] Universal access to sexual and reproductive healthcare services as well as actions to address the global burden

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of infectious diseases are highlighted under the United Nations Sustainable Development Goals (SDGs).[7]

One complication of upscaled rifamycin use in women of reproductive age are drug–drug interactions (DDIs) between rifampicin, the most widely used rifamycin drug, and hormonal contraceptives.[8,9,10] Decreased OCP concentrations in plasma have been observed with concomitant use of daily rifampicin.[11–13] Although these concentration decreases have had varied impacts on the effectiveness of hormonal contraceptives, the general approach based on the consensus of expert advice is that women should not rely on OCPs for pregnancy prevention while taking rifampicin.[10,11] However, the DDIs between rifampicin and OCPs have largely been investigated in cases of daily rifampicin therapy, that is, the standard dosing used in the treatment and prevention of TB. Therefore, the recommendations during concomitant use are based on daily rifampicin use.

Alternative, less frequent dosing intervals of rifampicin are delivered for post-exposure prophylaxis (PEP) to contacts of people with leprosy.[5,6,14] For example, the international non-governmental organization until No Leprosy Remains (NLR) is evaluating 3 doses of rifampicin 600 mg plus clarithromycin 600 mg given at 4-weekly intervals (day 1, day 29, and day 57) over 8 weeks (PEP++); this regimen is being trialed in comparison with single-dose rifampicin (SDR).[15,16] Another group is evaluating single double-dose rifampicin (1200 mg) (PEOPLE trial),[17] and a regimen comprising 2 doses of rifampicin and bedaquiline, given 4 weeks apart (BE-PEOPLE trial).[18] The clinical recommendation for these women diagnosed with leprosy is not to rely on OCPs for pregnancy prevention, and instead use alternative birth control methods during multidrug therapy for leprosy, which may last 12 months. This recommendation places a large burden on women of childbearing age.

The DDIs between OCPs and rifampicin are unknown with rifampicin dosing schedules used in leprosy PEP. We aimed to predict the change in OCP pharmacokinetics with various rifampicin dosing frequencies (ranging from a single dose to a daily dose) using pharmacokinetic simulations. We hypothesized that, in contrast to daily rifampicin, the DDI on OCP pharmacokinetics with leprosy PEP regimens would not be clinically relevant, thus suggesting that OCPs can be safety used with rifampicin-based leprosy PEP regimens without additional or alternative pregnancy prevention methods.

Methods

We performed Monte Carlo simulations with a rifampicin pharmacokinetic model to predict the expected induction effect of rifampicin on OCP oral clearance (CL/F_{OCP}) with different dosing regimens potentially used for leprosy PEP. Rifampicin dosing schedules were selected based on recommended World Health Organization (WHO) and investigational leprosy PEP regimens. These regimens were: a single 600 mg dose, a single 1200 mg dose, and 600 mg once every 4 weeks.[5,14,15,17] Additionally, we included rifampicin 600 and 300 mg once daily and 600 mg once weekly for comparison. Rifampicin 600 mg once every 4 weeks was simulated for 1 year, to better illustrate the effect of rifampicin on CL/F_{OCP} among patients taking treatment for multibacillary leprosy, which requires a 12-month course of 450-600 mg of rifampicin once monthly. Other regimens were simulated for 3 months. Simulation outputs were summarized as medians and 90% prediction intervals, accounting for interindividual variability. A 20% or more increase in CL/F_{OCP} was considered clinically relevant.

Pharmacokinetic Model Details and Assumptions

Parameter estimates for simulation were drawn from the rifampicin autoinduction model developed by Smythe et al[19]; values are shown in Table 1. The model structure is semi-mechanistic, where metabolic enzymes increase and decrease dynamically with changing rifampicin concentration. This model was developed with clinical data collected from 174 adult participants in a TB trial conducted in South Africa, Senegal, Guinea, and Benin. The differential equations describing rifampicin enzyme induction are shown in

Table 1. Rifampicin Induction Parameter Estimates Used for Simulation

Parameter	Units	Value (% RSE)	Interindividual Variability (% CV)
Rifampicin clearance (CL)	L/h	10.0 (3.7)	30.0
Rifampicin volume of distribution (V)	L	86.7 (2.3)	19.2
Rifampicin absorption rate	/h	0.35 (1.6)	–
Enzyme turnover rate (kenz)	/h	0.00369 (5.6)	–
Maximum induction effect (E_{max})	Fold-change	1.04 (2.6)	–
Rifampicin concentration at 50% E_{max} (EC50)	mg/L	0.0705 (6.3)	49.3

CV, coefficient of variation; RSE, relative standard error.
Parameter estimates are from Smythe et al.[19]

Equations (1–3), where Equations (1) and (2) describe rifampicin pharmacokinetics and Equation (3) describes the induction enzyme kinetics.

$$dA1dt = -ka \times A1 \quad (1)$$

$$dA2dt = ka \times A1 - \frac{CL}{V} \times A2 \times ENZ \quad (2)$$

$$dENZdt = kenz \times \left(1 + \frac{E_{max} \times C_{rif}}{C_{rif} + EC50}\right) - kenz \times ENZ \quad (3)$$

In this model, rifampicin concentration in plasma (C_{rif}) increases the level of enzyme (ENZ) with a maximum induction effect (E_{max}) of 1.04-fold, and with an effective concentration at 50% E_{max} (EC_{50}) of 0.0705 mg/L. Enzyme degradation occurs at a rate (kenz) with a half-life of 7.8 days. Interindividual variability on clearance (CL), volume (V), and EC_{50} were applied exponentially, according to model estimates (Table 1).[19] The initial value for ENZ was 1 and the change in CL/F_{OCP} was calculated as (ENZ – 1). We assumed that the induction parameter estimates reported for rifampicin (E_{max}, EC_{50}, and kenz) described rifampicin induction of OCPs and that the effect is the same for all OCPs. To evaluate the validity of our assumptions, we compared the predicted versus observed change in CL/F_{OCP} with 600 mg rifampicin once daily, where observed estimates were derived from the literature.[10] The predicted change in CL/F_{OCP} was converted to area under the concentration time curve (AUC) ratios by taking the inverse of the enzyme level at a given time (ie, 1/ENZ).

Scenario Analysis

We conducted a scenario analysis to explore sources of uncertainty and assumptions in the induction model applied for predicting changes in CL/F_{OCP} with rifampicin use. In scenario 1, we assessed the uncertainty in the estimated parameter values from Smythe et al using the 5th percentile of the EC_{50} (highest potency) and the 95th percentile of the E_{max} (highest effect); this represents a scenario at the upper limit of confidence of the effect on clearance induction. In scenarios 2 and 3, we assessed the uncertainty in applying the rifampicin autoinduction estimates broadly to the induction of OCP pharmacokinetics. In these scenarios, EC_{50} was reduced to 50% (ie, rifampicin had a more potent affect) and E_{max} was increased either 2-fold (scenario 2) or 4-fold (scenario 4) (ie, a greater effect); these represent scenarios in which the induction effect of rifampicin on CL/F_{OCP} is much greater than that of rifampicin autoinduction.

Software

The simulations were performed in RStudio 1.2.5019 with "PKPDsim" and visualized with "ggplot2."

Results

Pharmacokinetic Predictions with Leprosy PEP Regimens

Oral hormonal contraceptive pill clearance (CL/F_{OCP}) was predicted to increase by a maximum of 12% with a single 600 mg rifampicin dose, 14% with a single 1200 mg rifampicin dose, and 14% with 600 mg rifampicin once every 4 weeks (Figure 1). Maximum increases were predicted on day 2 and declined to <5% by 14 days. No additional increase in CL/F_{OCP} was predicted when 600 mg rifampicin once every 4 weeks was extended for 12 doses, as used in the treatment for multibacillary leprosy (Figure 2).

In the scenario analysis of greater induction effects, clinically relevant increases were predicted for leprosy PEP regimens in the hypothetical scenarios of 2-fold (scenario 2) or 4-fold (scenario 3) greater E_{max} values (Table 2). There was no change in predictions using the upper limit of reference estimates (scenario 1). The time above the clinically relevant threshold with leprosy PEP regimens increased to 2-3 days in scenario 2 and 9-10 days in scenario 3 (Table 2).

Pharmacokinetic Predictions with Comparator Rifampicin Regimens

Clinically relevant increases (≥25%) in CL/F_{OCP} were predicted with rifampicin 600 mg given once-weekly or once-daily. CL/F_{OCP} induction accumulated with repeated dosing, rising from 12% on the day after the first dose (day 2) to 25% with once-weekly frequency, up to 80% with once-daily frequency by day 28 (Figure 1). CL/F_{OCP} was predicted to be +150% and +239% with daily rifampicin under scenarios of a higher induction effect (scenarios 2 and 3, respectively) (Table 2). The OCP AUC ratio with/without daily rifampicin observed from literature varied widely depending on the OCP drug and study (Figure 3). The observed norethindrone AUC ratios fell between the reference prediction (1-fold effect) and the scenario-2 prediction (2-fold effect). Two studies observed less pronounced ethinyl estradiol AUC reduction than predicted, and 3 studies observed AUC reductions that lay between the predictions obtained with 2- and 4-fold induction effects. The observed reductions in dienogest AUC were far lower than predicted in the most extreme (4-fold effect) scenario.

Discussion

Our model-based predictions suggest that the expected increase in OCP clearance through the rifampicin induction of metabolism is not clinically meaningful when rifampicin is dosed as 1 single dose (600 or 1200 mg) or as 600 mg once every 4 weeks, as given

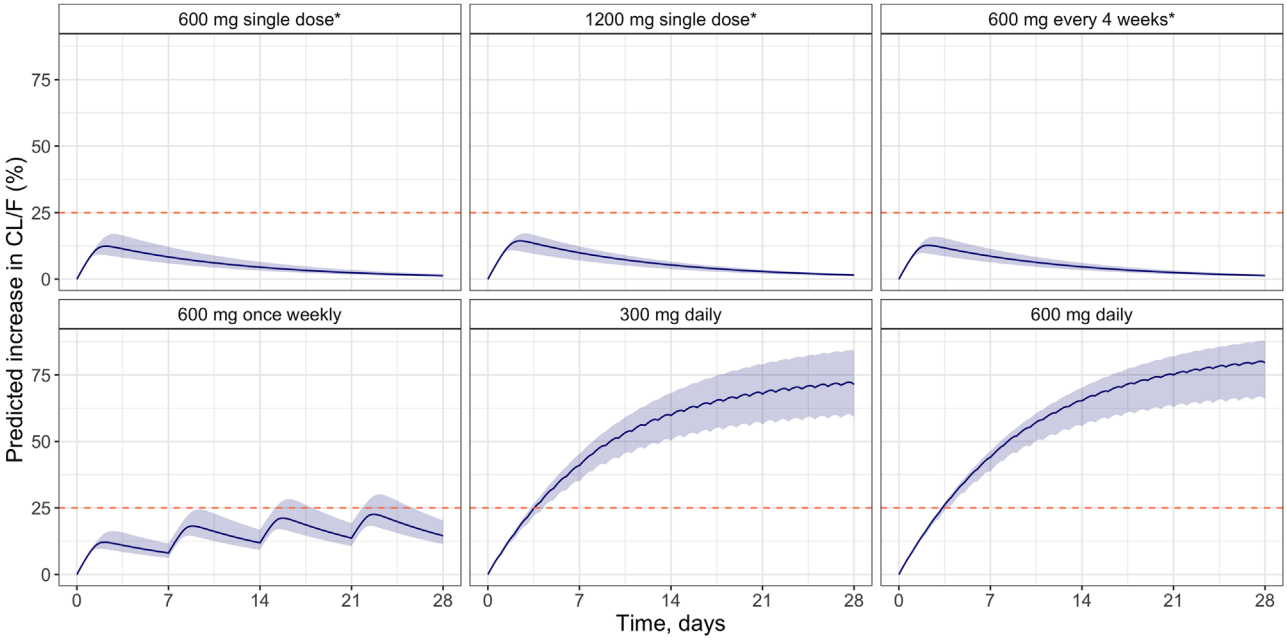

Figure 1. Predicted increase in oral clearance (CL/F) of hormonal contraceptives over time when used in combination with rifampicin under different dosing schedules. The solid line indicates the median and the shaded region indicates the 90% prediction interval in a simulated population of 100 individuals. The dashed orange line indicates a clinically relevant increase of 25%. *Leprosy post-exposure prophylaxis regimen.

for leprosy PEP. Therefore, we predict that women using OCPs can expect contraceptive efficacy to be maintained, without dose adjustment, while taking these leprosy PEP regimens.

Our results are based on an important assumption that rifampicin induction of OCP clearance follows a similar induction profile as rifampicin induction of rifampicin clearance (ie, autoinduction). To our knowledge, no data currently exist on the DDI between rifampicin and OCP when rifampicin is dosed less frequently than once daily, making it impossible to validate our predictions with literature findings. Under daily dosing of rifampicin (300-600 mg), a systematic review reported reduced ethinyl estradiol AUC by 12%-66%, estradiol valerate AUC by 44%, norethindrone AUC by 30%-60%, and dienogest AUC by 85%,[10] compared with our prediction of a 43% decrease in AUC with 600 mg daily rifampicin. The observed estimates varied widely by study, which could be linked to the small sample sizes (<10), different populations, and/or study designs. We captured the range of observed mean AUC ratios from literature for all drugs except dienogest using scenario analyses with induction effect sizes of up to 4-fold. Although these greater induction scenarios inflated the predictions for leprosy PEP regimens above the clinically relevant threshold,

Table 2. Model Predictions of Mean Changes in Hormonal Contraceptive Oral Clearance (CL/F) Under Scenarios of a Greater Induction Effect

	Maximum Increase in CL/F (%)				Time with CL/F >25% (hours)			
Regimen	Reference[a]	Scenario 1[b]	Scenario 2[c]	Scenario 3[d]	Reference[a]	Scenario 1[b]	Scenario 2[c]	Scenario 3[d]
600 mg single dose*	12.4	12.9	**26.8**	**49.3**	0	0	**41**	**221**
1200 mg single dose*	14.4	14.6	**29.8**	**54.3**	0	0	**75**	**254**
600 mg every 4 weeks*	12.7	12.9	**26.8**	**49.3**	0	0	**41**	**221**
600 mg once weekly	22.6	24.2	**47.1**	**81.0**	0	0	**534**	**654**
300 mg daily	**72.2**	**76.5**	**139.2**	**220.2**	**588**	**590**	**635**	**654**
600 mg daily	**80.1**	**83.3**	**150.7**	**238.7**	**593**	**594**	**636**	**654**

Values reflect the median prediction over a 28-day (672-hour) simulation. Bolded values indicate clinically relevant changes.

*Leprosy post-exposure prophylaxis (PEP) regimens.

[a] Model prediction using the mean parameter estimates from Smythe et al.

[b] Model prediction using the EC_{50} 0.05 percentile and E_{max} 0.95 percentile from Smythe et al, representing stronger potency and effect.

[c] Model prediction using a 50% lower EC_{50} and 2-fold higher E_{max} than Smythe et al, representing stronger potency and effect.

[d] Model prediction using a 50% lower EC_{50} and 4-fold higher E_{max} than Smythe et al, representing stronger potency and effect.

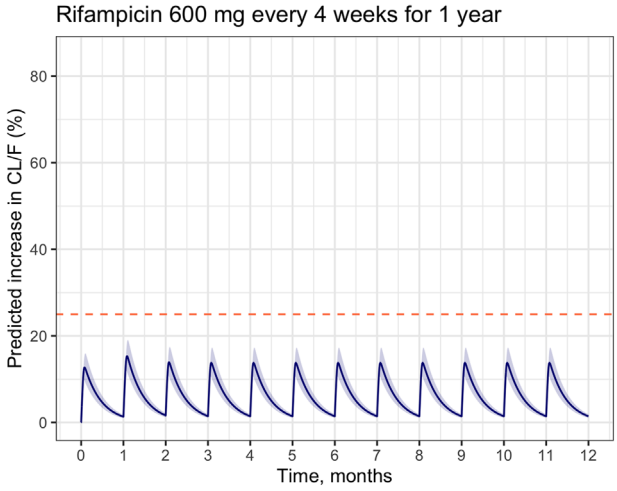

Figure 2. Predicted increase in oral clearance (CL/F) of hormonal contraceptives over 1 year when used in combination with rifampicin 1 monthly for multibacillary leprosy treatment. The solid line indicates the median and the shaded region indicates the 90% prediction interval in a simulated population of 100 individuals. The dashed orange line indicates a clinically relevant increase of 25%.

the maximum impact was a 33% decrease in OCP, which dropped below 20% after 10 days.

The clinical relevance of DDIs involving hormonal contraceptives is the primary link to clinical practice. In this study, we used a prespecified threshold of a 25% increase in clearance, corresponding to a 20% decrease in AUC, as previously suggested for clinical studies evaluating significant DDIs with hormonal contraceptives.[20] However, clinically relevant changes in pharmacokinetics do not necessarily mean clinically relevant changes in efficacy. Furthermore, the exposure–response relationship may differ for each OCP such that, for example, a 20% decrease in norethindrone AUC has a greater or lesser effect on efficacy than a 20% decrease in dienogest AUC. OCP AUC correlation with surrogate measures of contraceptive effectiveness (ie, serum progesterone levels on cycle days 19 to 23) has been reported with daily rifampicin use, with inconclusive findings[10]: 2 studies with >50% mean decrease in norithendrone AUC found no change in serum progesterone[21,22]; 1 study with 30% decrease in mean norithendrone AUC reported 2 of 7 women with increased serum progesterone, suggesting that ovulation occurred.[23] Meyer et al reported 11 of 22 women ovulated when receiving levonorgestrel/ethinyl estradiol with daily rifampicin, compared with 0 without rifampicin, but did not collect OCP concentrations.[24]

Although our study applies the rifampicin induction model to predict a different output (OCP clearance instead of rifampicin clearance), the input (dynamic rifampicin concentration) and driver of the output remains consistent with the original model and DDI mechanism.[19] Rifampicin binds to PXR, leading to the downstream upregulation of a large number of genes involved in xenobiotic metabolism and elimination, including CYP450 enzymes and P-glycoprotein transporters involved in the metabolism and elimination of OCPs.[25] The model structure is semi-mechanistic, describing both hepatic and pre-systemic induction processes, but does not describe changes to each downstream enzyme and transporter. There is some evidence that the induction of hormonal contraceptive metabolism and rifampicin autoinduction are both at least partly mediated by upregulated P-glycoprotein expression.[26,27] However, there are differences in the metabolism pathways: rifampicin is metabolized by hepatic esterases and OCPs are primarily metabolized

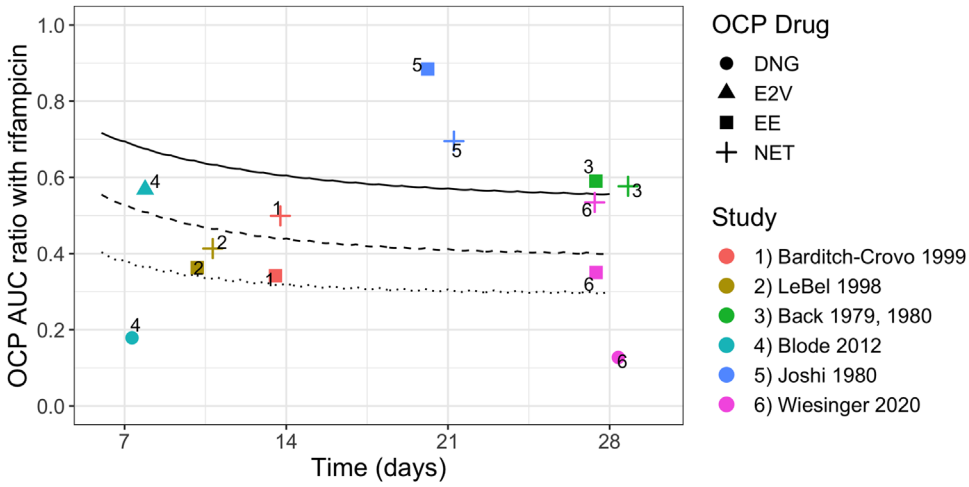

Figure 3. Predicted versus observed estimates of OCP AUC reduction with 300-600 mg rifampicin daily. Observed AUC ratios from literature are shown as points. Predicted AUC ratios from model simulations are shown for the reference scenario (solid line), the higher induction scenario 2 (dashed line), and the higher induction scenario 3 (dotted line). AUC, area under the concentration–time curve; DNG, dienogest; EE, ethinyl estradiol; E2V, estradiol valerate; NET, norethindrone; OCP, oral contraceptive pill.

by CYP450 enzymes. Moreover, the metabolic profiles of OCPs differ and so may the induction profiles. These mechanistic differences could bias the OCP induction predictions and could not be accounted for given the model structure. Nonetheless, the relative induction changes between rifampicin dosing regimens of the same victim drug should be conserved with our model structure.

The parameter estimates in Smythe et al were based on data from sub-Saharan African adult participants, so it is possible that they would not be representative of other populations. There are some known pharmacogenomic predictors that affect rifampicin pharmacokinetics (eg, *SLCO1B1*, the gene that encodes the organic anion-transporting polypeptide 1B1, OATP1B1) that are expected to vary across populations; however, studies are mixed on whether these pharmacogenetic differences explain the rifampicin pharmacokinetic variability.[28–31] Although the study conducted by Smythe et al did not include data from adolescents (12-18 years of age), it is unlikely that there are marked differences in rifampicin induction of OCP metabolism between adults and adolescents at comparable drug exposures given fully mature metabolic pathways.[32] For example, the effect of rifampicin on dolutegravir exposure was similar between adolescents and adults receiving 50 mg once daily (without rifampicin) and twice daily (with rifampicin).[33] In addition, the WHO recommends a lower leprosy SDR treatment of 450 mg for PEP in contacts aged 10-14 years old.[5,14] The scenario analysis provides some additional confidence that our clinical inferences for leprosy PEP regimens are robust, despite uncertainty in the parameter estimates that may differ in the induction of OCP clearance (E_{max}, EC_{50}, and kenz). Altering these parameter values to predict more extreme induction scenarios resulted in minimal to modest changes in clinical inference with leprosy PEP regimens. This finding confirms that even if rifampicin induction of OCPs is much greater than rifampicin autoinduction, the infrequent dosing intervals used in leprosy PEP regimens are not predicted to alter OCP pharmacokinetics to clinically meaningful levels.

Our findings are limited to predicted interactions of rifampicin with OCPs. A proportion of women eligible for leprosy PEP will be using a non-oral contraceptive method. As the model used for simulations does not distinguish between changes in systemic clearance and oral bioavailability (ie, first-pass metabolism), the predicted difference between OCPs and parenteral methods (including injectable and implant-based contraceptives) is not easily determined.[19] No DDI studies of parenteral formulations were identified in a systematic review to compare with oral OCP DDI observations.[10] Additionally, other rifamycins (rifapentine and rifabutin) are known or are expected to have a similar DDI with OCPs.[10,34] Although rifampicin is the most widely used and researched, other rifamycins such as rifapentine are increasingly being used.[35] Our methodology could be adapted easily to predict changes in OCP pharmacokinetics with rifapentine,[36] should observational data become available for validation.

Overall, our findings support the view that the DDIs between OCPs and rifampicin given as part of leprosy PEP are not clinically relevant, and supplemental contraception is not needed to prevent pregnancy. Normative guidance relating to this DDI should account for the rifampicin regimen being used as our study demonstrates that rifampicin dose and dose frequency are key drivers of induction. Importantly, our findings are based on simulations only and should be confirmed with pharmacokinetic data for OCPs when used with leprosy PEP regimens. Until observation data becomes available, results of this study can serve as an encouraging prediction for women suffering from leprosy who want to continue relying on OCPs for contraception.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Data Availability Statement

This study did not include any original data.

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