Title: Rifapentine population pharmacokinetics and dosing recommendations for latent tuberculosis infection

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Short running title: Pooled analysis of rifapentine pharmacokinetics

Impact Statement: Our model is the first to characterize rifapentine population pharmacokinetics with concentration-driven autoinduction and includes all clinically relevant patient factors. We show evidence to support removing weight band dosing from rifapentine dosing guidelines and propose increased doses for individuals with HIV. This model will serve as an important tool for determining optimal rifapentine doses for tuberculosis infection and active disease in future clinical trials and clinical practice.

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"This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org"
“At a Glance Commentary”

What is the current scientific knowledge on this subject?
Rifapentine has become a principle component of novel short-course regimens for latent tuberculosis infection and a promising agent for treatment shortening regimens for active disease. Evidence suggests that rifapentine induces its own elimination, but the implications for novel dosing strategies are not well understood. Further, the evidence supporting the current weight band dosing of rifapentine is lacking and requires further evaluation.

What does this study add to the field?
In this individual participant data meta-analysis of rifapentine pharmacokinetics, we describe the population pharmacokinetics of rifapentine, including full characterization of the autoinduction profile. We find no evidence supporting weight band dosing of rifapentine and thus, recommend all individuals receive the same dose, with the exception of HIV-positive individuals, who would benefit from higher doses. This model will serve as a valuable tool for predicting drug exposure and determining optimal rifapentine doses for future clinical trials and in clinical practice.
Abstract

Rationale: Rifampentine has been investigated at various doses, frequencies, and dosing algorithms but clarity on the optimal dosing approach is lacking.

Objectives: In this individual participant data meta-analysis of rifampentine pharmacokinetics, we characterize rifampentine population pharmacokinetics, including autoinduction, and determine optimal dosing strategies for short-course rifampentine-based regimens for latent tuberculosis infection.

Methods: Rifampetine pharmacokinetic studies were identified through a systematic review of literature. Individual plasma concentrations were pooled, and non-linear mixed effects modeling was performed. A subset of data was reserved for external validation. Simulations were performed under various dosing conditions including current weight-based methods and alternative methods driven by identified covariates.

Measurements and Main Results: We identified 9 clinical studies with a total of 863 participants with pharmacokinetic data (n=4301 plasma samples). Rifampentine population pharmacokinetics were described successfully with a one-compartment distribution model. Autoinduction of clearance was driven by rifampentine plasma concentration. The maximum effect was a 72% increase in clearance and was reached after 21 days. Drug bioavailability decreased by 27% with HIV infection, decreased by 28% with fasting, and increased by 49% with a high-fat meal. Body weight was not a clinically relevant predictor of clearance. Pharmacokinetic simulations showed that current weight-based dosing leads to lower exposures in low weight individuals, which can be overcome with flat dosing. In HIV-positive patients, 30% higher doses are required to match drug exposure in HIV-negative patients.
Conclusions: Weight-based dosing of rifapentine should be removed from clinical guidelines and higher doses for HIV-positive patients should be considered to provide equivalent efficacy.

Abstract word count: 250/250

Keywords: tuberculosis; rifapentine; rifamycins; population pharmacokinetics; latent tuberculosis
Introduction

The World Health Organization (WHO) estimates that 23% of the world’s population has latent tuberculosis infection (LTBI) and is at risk of developing active disease (1). Standard treatment for LTBI has historically been 9 months of daily isoniazid, for which patient compliance is poor and hepatotoxicity is a concern (2, 3). Recently, novel rifapentine-based regimens have demonstrated efficacy in preventing tuberculosis disease with much shorter treatment durations (4, 5). Additionally, these regimens have shown equal to better safety profiles and higher patient compliance. The first regimen was three months of once-weekly rifapentine plus isoniazid (3HP) (4); it received FDA approval in 2014 and is now recommended by the Centers for Disease Control and the WHO for individuals with LTBI (6-8). An ultra-short-course regimen, one month of daily isoniazid-rifapentine (1HP), has also shown efficacy, safety, and improved compliance in HIV-infected patients at high risk of developing tuberculosis disease (5); 1HP inclusion into WHO guidelines is under review (9).

Rifapentine has high anti-mycobacterial activity and a long elimination half-life of 15 hours that makes it an attractive candidate for treatment shortening regimens (6, 10, 11). However, unlike in LTBI, it is still unknown if rifapentine will be effective in short-course regimens for active drug-sensitive tuberculosis disease (DS-TB). The only completed Phase 3 clinical trial (Rifaquin) failed to demonstrate non-inferiority of intermittent rifapentine regimens in DS-TB patients compared to the 6-month standard of care (12).

Robust characterization of rifapentine pharmacokinetics is required to determine optimal dosing strategies for new short-course regimens and for special populations. Current rifapentine-based
regimens for LTBI use weight band dosing (6, 8). However, these recommendations are not based on pharmacokinetic evidence; rather, they are drawn from the historical mg/kg doses used in rifampin-based therapy. The influence of body weight on rifapentine clearance remains inconclusive as current studies report conflicting findings (13, 14). Meal-type, dose amount, HIV status, race, and age may also impact rifapentine concentration (14-18). Additionally, repeated dosing of twice weekly and daily administration results in lower rifapentine exposures over time, suggesting that rifapentine induces its own metabolism (19, 20).

Several Pharmacokinetic studies have been conducted with varying rifapentine doses (up to 20 mg/kg daily), frequencies (once weekly to twice daily), and methods (weight-based or flat dose) (19-22). Our aim here was to perform an individual participant data meta-analysis and pool individual pharmacokinetic data from all relevant clinical studies in various populations (healthy volunteers and LTBI and DS-TB patients with and without HIV infection). The goals are (i) to characterize rifapentine population pharmacokinetics, including the time course of autoinduction and relevant covariates that may have a significant clinical impact on rifapentine exposures and clinical efficacy, and (ii) to derive dosing recommendations to inform optimal current and future use of rifapentine in tuberculosis infection and disease.

Methods

Clinical Studies

Rifapentine pharmacokinetic studies were identified through a literature search in PubMed with the terms ‘rifapentine’ AND (‘study’ OR ‘trial’) from 1 January 1980 to 31 December 2015 according to PRISMA guidelines (23). Additional studies were identified through author
collaborations. Corresponding authors of the study were invited to contribute data if the studies
were prospective and multiple dose, pharmacokinetic measurements were available and
validated, and covariates of interest were documented (e.g., HIV status, meal-type, and weight).
All studies included in the analysis received ethical approval by their local ethical review boards.

**Population Pharmacokinetic Analysis**

Identified studies were split into an analysis cohort for structural model development and a
validation cohort for external validation. We sought to conserve 1/3 of drug concentration data
for the validation cohort and to match dosing schedules and covariates (e.g., HIV) between
cohorts when possible. Rifapentine plasma concentrations were natural log-transformed and
analyzed using non-linear mixed effects modeling with NONMEM 7.41 (ICON Development
Solutions, Elliott City, Maryland). Pharmacokinetic data without an associated dosing record
were excluded.

Population pharmacokinetic model building followed standard procedures by first characterizing
the base structural model (24). To describe rifapentine autoinduction, a semi-mechanistic
enzyme turnover model was used (25). Known covariate effects (i.e., HIV, meal-type, dose)
were incorporated into the structural model. Additional covariate effects such as weight, age,
race, BMI and sex were identified through a stepwise procedure with forward selection (p<0.05)
and backward elimination (p<0.01). Final inclusion of covariates was based on statistical
significance, scientific plausibility, and clinical relevance defined as ≥ 20% change in the
parameter estimate (26). Model development was guided by graphical assessment of goodness-
of-fit plots, condition number, and the likelihood ratio test. Simulation-based diagnostics (e.g.,
visual predictive check (VPC) were used for model validation. Detailed model building procedures are provided in the Supplemental material.

Software

R software (version 3.4.2) was used for all data management, analyses, and graphical visualization. The xpose (version 0.4.4) and vpc (version 1.0.1) packages were used for visual diagnostics. Nonparametric bootstrap and covariate modeling were performed with Perl-speaks-NONMEM (version 4.7.0).

Dosing simulations

Simulations were performed with the final model to (i) predict the autoinduction process with different doses and dosing schedules, (ii) assess the impact of clinically relevant patient factors (e.g., HIV, weight) on rifapentine exposure, and (iii) to propose pragmatic dosing for rifapentine-containing LTBI regimens. Pharmacokinetic profiles were evaluated by different drivers of pharmacodynamics, including time above minimum inhibitory concentration (MIC), area under the concentration-time curve (AUC), AUC/MIC, maximum concentration (C_max), and C_max/MIC, with MIC set to 0.06 mg/L (27). For 1HP and 3HP simulations, we predicted rifapentine exposure following current weight band dosing (1HP: 300 mg [<35 kg], 450 mg [35-45 kg], or 600 mg [>45 kg] daily; 3HP: 750 mg [<50 kg] and 900 mg [≥50 kg] once weekly) (4, 5). Alternative dosing methods were explored based on identified covariates. All simulations were performed under low-fat meal conditions (the referent, where relative bioavailability =1) given label recommendations.
Univariate analysis of month 2 culture conversion

Microbiological outcome data (i.e., liquid and solid culture data) was acquired from two Phase II clinical studies: TBTC-29 and TBTC-29x (22, 28). Participant body weight and rifapentine AUC were evaluated as predictors month 2 culture conversion by logistic regression. Body weight was categorized as < 50 kg or ≥ 50 kg, consistent with the weight band dosing strategy used in these studies. AUC was categorized at the median AUC.

Results

Clinical Studies

We identified nine clinical studies with rifapentine pharmacokinetic data for the pooled analysis (Figure 1), including Phase 3 (n=2), Phase 2 (n=4), and Phase 1 (n=3) studies (12, 14, 19-21, 28-31). Overall, 863 subjects were included: 84 healthy volunteers, 702 patients with DS-TB, and 77 persons treated for LTBI. The analysis cohort included 360 subjects (n=3273 samples) from five studies. The validation cohort included 503 subjects (n=1115 samples) from four studies. Participant and trial characteristics are shown in Table 1. The analysis and validation cohorts were similar in design and participant characteristics. Overall, the median age was 34 years, the median weight was 59 kg, 31% were men, and 9% of patients were HIV-positive. There was a wide range of rifapentine doses, dosing frequencies, and diets that were tested across studies (Table 1).

Pharmacokinetic-enzyme model
The final rifapentine pharmacokinetic-enzyme model is shown in Figure 2, and final parameter estimates are in Table 2. All pharmacokinetic parameters were well estimated with low relative standard errors. Rifapentine apparent clearance was estimated to be 1.11 L/h in the typical adult and increased up to 1.92 L/h (173%) over time as a result of autoinduction. The induction process was described using an indirect response semi-mechanistic enzyme turnover model (Figure 2). The effect (EFF) of rifapentine drug concentration on enzyme production was described through an $E_{\text{max}}$ relationship:

$$\text{EFF} = \left( \frac{E_{\text{max}} \cdot C_p^\gamma}{EC_{50}^\gamma + C_p^\gamma} \right)$$

where $EC_{50}$ is the rifapentine concentration in plasma ($C_p$) when half the maximum induction effect ($E_{\text{max}}$) is observed; $\gamma$ represents the steepness of the relationship. The maximum autoinduction effect is expected at the steady state concentrations achieved with daily doses of 300 mg or more, and clearance stabilizes by day 21 of therapy, assuming 5 half-lives to steady state (Figure 3).

**Rifapentine model evaluation and validation**

The VPC of the basic structural model (built with analysis cohort data alone) shows that the model predicted the analysis cohort raw data well: the median, $5^{\text{th}}$, and $95^{\text{th}}$ percentiles of raw data fell within or near the percentiles of model-predicted concentrations for all time points (Figure 4A). Further, we show that model-predicted concentrations matched the raw data of an external dataset (i.e., the validation cohort, which was not used in model development; Figure 4B).
After model validation, data from both cohorts were pooled and parameters re-estimated. VPCs of the final pharmacokinetic model for rifapentine and its metabolite are provided in the Supplement. The final model predicted rifapentine (Figure E2) and metabolite (Figure E3) concentrations well for all studies.

**Impact of covariates on rifapentine pharmacokinetics**

Rifapentine bioavailability was strongly (p<0.001) influenced by HIV status, food, and dose with clinically relevant effect sizes. The relative effects on bioavailability of HIV-positive status (vs. HIV-negative), high-fat meal or fasting condition (vs. low-fat meal), and dose per 100 mg above 300 mg (the referent) are shown in Table 2. Body weight was related to rifapentine clearance (p<0.001) with a 0.1 L/h (9%) increase in clearance per 10 kg increase in weight (Figure 5). However, weight explained only 2.9% of the inter-individual variability in clearance, and the effect size did not meet our criteria for clinical relevance. Further, the majority of statistical significance was from a few influential individuals over 90 kg in weight (Supplemental). Allometrically scaling clearance did not provide any additional improvement over the linear relationship, and the functions were nearly identical at relevant weight ranges (40-100 kg). Therefore, the only covariates included in the final model were HIV, food, and dose.

**Rifapentine simulations of different dosing schedules**

The effect of dose and dosing frequency on rifapentine pharmacokinetics is shown in Figure 6. With intermittent dosing, autoinduction was minimal to moderate and clearance increased slightly with larger doses (see Supplemental). With daily dosing, maximum induction was achieved with doses of 300 mg or more. All dosing schedules were able to maintain
concentrations above MIC during the dosing interval except once weekly in which concentrations fall below MIC just prior to the next dose (Figure 6B). $C_{\text{max}}$/MIC and AUC/MIC were highest with daily dosing, due to drug accumulation, and increased with increasing dose (Online data supplement, E2 Table).

Rifapentine simulations for 1HP and 3HP therapy

We simulated rifapentine drug concentrations under the 1HP and 3HP regimens for LTBI in both HIV-positive and HIV-negative adults. The typical HIV-positive patient had lower drug concentrations than the typical HIV-negative patient when given the same dose due to decreased rifapentine bioavailability (Figure 7). Lower drug concentrations are also predicted in low weight individuals with the current weight band dosing (Figure 7). Removing weight bands and administering the same flat dose to all individuals would result in equal exposures across weights; however, it did not equalize exposures by HIV status (Figure 8). With a stratified regimen, where HIV-positive individuals receive ~30% higher doses, similar exposures are expected by HIV status and weight for both 1HP and 3HP (Figure 8).

Univariate analysis of month 2 culture conversion

A total of 363 individuals treated with 10 mg/kg rifapentine had Phase II microbiological data available. Univariate logistic regression results for month 2 culture conversion of liquid media are shown in Figure 9. Month 2 culture conversion was less likely in individuals who had lower rifapentine AUC (Odds ratio = 0.49) and in those who weighed less than 50 kg (Odds ratio = 0.60).
Discussion

In this study, we used a pooled individual-data approach with an external validation to describe rifapentine population pharmacokinetics in a large cohort of subjects. This analysis included nine clinical studies with a wide range of rifapentine doses and scheduling frequencies, allowing for successful characterization of rifapentine autoinduction with respect to drug concentration. It represents the largest analysis of rifapentine population pharmacokinetics to date. Our results establish several findings that may help guide rifapentine dosing strategies: (i) pharmacokinetic data do not support dosing rifapentine by body weight; (ii) HIV-positive individuals require at least 30% higher doses to achieve equal drug exposures to HIV-negative persons; (iii) rifapentine autoinduction is strongly influenced by dosing frequency rather than dose amount.

Since rifapentine’s approval, several studies have shown evidence of rifapentine inducing its own elimination but none have characterized autoinduction with respect to rifapentine concentration (14, 16, 17, 19, 20). Previously published models have described rifapentine autoinduction empirically with time-varying clearance model (14, 17) or reduced bioavailability (16). While these approaches are adequate for describing data, they have limited utility in clinical settings and for dose determination in new clinical trials. In our analysis, we used a semi-mechanistic turnover model where rifapentine concentration was the driver of autoinduction (25). This method is advantageous in that it allows for predicting the magnitude of autoinduction with different rifapentine regimens of various doses and frequencies, including those which have not yet been tested in a clinical trial.
Rifapentine autoinduction is strongly influenced by dosing frequency. Simulated pharmacokinetic profiles showed increasing $C_{\text{max}}$ and AUC in the first week of therapy with daily dosing due to drug accumulation but decreased thereafter as a result of clearance induction. This effect was most prominent with daily dosing, moderate with thrice weekly dosing, and minimal with less frequent dosing. These findings are in agreement with previous reports from non-compartmental analyses (20, 30, 32). Dose amount had little effect on the magnitude of autoinduction (~10% higher clearance with 1200 mg vs. 600 mg), regardless of dosing frequency. A dose effect on rifapentine autoinduction has been described previously (17, 19). In our model, nonproportional increases in drug exposure with increasing dose were described through a reduction in bioavailability, consistent with saturable absorption (14). Still, as the induction process is a function of rifapentine plasma concentration in our model, any additional dose effects on clearance would be captured. While full autoinduction is predicted with daily dosing, drug accumulation was also high, leading to superior $C_{\text{max}}$/MIC and AUC/MIC compared to less frequent dosing. This confirms that daily dosing has the highest potential for concentration-dependent killing of $M. tuberculosis$. Further, this work is an important contribution to the understanding of the rifapentine dose-exposure relationship, especially in the context of DS-TB where daily dosing is likely required (15).

Currently, body weight is the only dose determining factor for rifapentine, which was not supported in our analysis. In three previously described population pharmacokinetic models, weight did not influence rifapentine pharmacokinetics (15) (14, 17). Furthermore, Savic and colleagues supported flat dosing of rifapentine, which was later implemented in a Phase 3 clinical trial for DS-TB (Study 31, Clinicaltrials.gov NCT02410772) (15). Contrarily, Langdon
and colleagues report a change in rifapentine clearance by 0.5 L/h per 10 kg of body weight in a small cohort of 46 patients (13). However, their model did not incorporate dose-dependent absorption (i.e., reduced bioavailability with increased dose), which likely would reduce the estimated weight effect on clearance since the study dosed by weight, and clearance and bioavailability are indirectly linked with oral dosing (13). Francis et al. allometrically scaled clearance by fat-free mass (16). The model’s application to rifapentine dosing, which is based on total body weight, was not described. Our study is the largest population pharmacokinetic study to-date with over 800 patients and healthy volunteers. While a small weight effect was observed (<10% change in clearance per 10 kg in body weight), it does not justify a 150 mg (~30%) change in dose as currently recommended in LTBI dosing guidelines. Weight and patient population appeared correlated in our dataset (i.e., DS-TB patients weighed less on average); therefore, we investigated the weight effect in healthy volunteers, individuals with LTBI, and DS-TB patients separately. The weight effect was comparable and remained clinically irrelevant. We conclude that weight is not a clinically relevant predictor of rifapentine clearance and that weight-based dosing should not be recommended.

Simulations of the 1HP and 3HP regimens showed lower rifapentine exposures in low weight individuals who receive lower doses with current weight band dosing. This ultimately puts the smallest, most vulnerable individuals at risk of underexposure and consequently, treatment failure (33, 34). A univariate analysis of Phase 2 culture data from two DS-TB studies showed month 2 culture conversion was less likely in low weight individuals and those with low rifapentine exposure. While the pharmacokinetic-pharmacodynamic relationships in LTBI have not been established, rifamycins show concentration-dependent killing of *M. tuberculosis* and
rifapentine AUC is a strong predictor of month 2 culture conversion (15, 35). Flat dosing of rifapentine (e.g., prescribing the same dose to all adults) ensures equal rifapentine exposure in adult patients of all sizes and thus, equal chance of successful outcome. Moreover, flat dosing simplifies the regimen in adults and encourages coformulation of rifapentine and isoniazid into a fixed-dose combination tablet, reducing pill burden and simplifying the regimen even further.

Dose discrimination may be warranted by HIV status. HIV-positive persons have 27% lower rifapentine bioavailability, resulting in lower exposures than HIV-negative adults. Reduced bioavailability of rifamycins with HIV infection has been reported previously (15, 17) and has been attributed to malabsorption (36-38). While antiretroviral drugs may also explain decreases in rifamycin concentration, the HIV-positive participants in our analysis did not receive antiretroviral therapy (12, 22, 28). Given rifapentine’s main metabolite has activity against *M. tuberculosis*, we also looked at metabolite concentrations by HIV status. It appeared that HIV-positive individuals had lower exposures of both rifapentine and its metabolite, confirming need for higher doses in HIV+ patients. Increasing the 3HP dose to 1200 mg once weekly in HIV-positive patients results in similar exposures to 900 mg once weekly in HIV-negative patients. Likewise, 750 mg daily in HIV-positive adults is similar to 600 mg daily in HIV-negative adults for the 1HP regimen. While 1HP at 600 mg daily was effective in preventing tuberculosis disease in HIV-positive individuals (5), this may reflect the minimum effective dose and higher doses may provide better protection.

The proposed dosing recommendations are limited by the lack of established pharmacokinetic targets in LTBI. We proposed doses that would match median exposures following the standard
doses tested in clinical trials with demonstrated efficacy. Given the development of tuberculosis was rare in those studies, these pharmacokinetic targets are reasonable, and we would expect the proposed doses to result in similar efficacy to that observed in clinical trial. The pharmacokinetic target for 1HP regimen reflects the median predicted exposure in a typical HIV-positive adult receiving 600 mg daily and may be on the low end. Pharmacokinetic data from BRIEF-TB and future trials are urgently needed to confirm pharmacokinetic thresholds for 1HP. Additionally, one study showed higher rifapentine bioavailability in Asians compared to Africans, which could impact dose requirement (15). This finding could not be confirmed in our study because TBTC 29X was the only study contributing substantial Asian population. Further investigation of race effects on rifapentine pharmacokinetics is required.

Our systematic review included all relevant studies published prior to 2016. Only one pharmacokinetic study was identified in more recent literature and would not have met our inclusion criteria due to non-standardized meal administration (16). Thus, our model represents the most up-to-date analysis of rifapentine pharmacokinetics. Of note, the analysis includes only one study in LTBI participants. To-date, these remain the only pharmacokinetic data in this population. Further, there is no evidence to suggest pharmacokinetics would differ by disease state, so we do not expect this to impact the generalizability of our work to LTBI treatment.

In conclusion, rifapentine exhibits autoinduction which is strongly influenced by dosing frequency. Weight was not a clinically relevant predictor of rifapentine clearance; thus, dosing should not be based on an individual’s weight. In fact, weight-based dosing results in substantially lower drug concentrations that could ultimately compromise treatment efficacy. If
stratified dosing is to be implemented, it should be done on the basis of HIV status to ensure that HIV-positive individuals are adequately exposed to drug. Lastly, as rifapentine use becomes more widespread in tuberculosis treatment and prevention, this model can serve as a useful tool in clinical practice and in clinical trial design for dose determination and exposure prediction.
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Figure Legends

Figure 1. PRISMA Flow Diagram.

Figure 2. Final rifapentine pharmacokinetic-enzyme model. The number of transit compartments (NN) was estimated using the relationship of $k_{TR} = (NN + 1)/MTT$, where MTT is the mean transit time and $k_{TR}$ is the transit rate constant. The absorption rate constant ($k_a$) was assumed equal to $k_{TR}$. Rifapentine autoinduction was modeled with an enzyme turnover model, where the effect (EFF) of rifapentine concentration in the central compartment increased the enzyme production rate ($k_{ENZ}$), thereby increasing the enzyme pool (ENZ). Rifapentine clearance (CL) increased as a result of increased ENZ. V is the apparent volume of distribution. The fraction of the drug absorbed (F; relative bioavailability) increased (+) or decreased (-) as indicated.

Figure 3. Rifapentine autoinduction profile. (A) The sigmoid relationship between rifapentine concentration and autoinduction is shown in the black line. Dashed lines represent the average concentration at steady state of daily therapy with 300 mg (yellow), 450 mg (green), and 600 mg (navy) of rifapentine in a typical HIV-negative individual. (B) Rifapentine induction over time following daily administration of 600 mg. Black dashed line represents the time at which the induction process reaches steady state.

Figure 4. Validation of the structural rifapentine population pharmacokinetic model.
Prediction-corrected visual predictive check (VPC) of base model with (A) analysis dataset, (B) validation dataset, and (C) combined dataset. Figures show the model predictions (shaded areas)
compared to observed/raw rifapentine concentrations (dots). Model predictions were based on the base structural model, built from the analysis dataset alone. The 5th (dashed line), 50th (solid line), 95th (dashed line) percentiles of the observed raw data are overlaid onto the 95% confidence intervals of model-predicted concentrations at the 50th (light blue), and 5th and 95th (dark blue) percentiles, obtained from 500 simulations of each respective dataset.

**Figure 5. Relationship between weight and rifapentine clearance.** The relationship was assessed for (A) all subjects and (B) only DS-TB and LTBI patients with final model parameter estimates. Dashed line represents loess regression curve.

**Figure 6. Effect of dose and dosing frequency on rifapentine exposure.** (A) Rifapentine concentration over time, and (B) concentration over time in log-scale, in a typical HIV-uninfected individual following once daily, thrice weekly, twice weekly, and once weekly administration of 600 mg (yellow), 900 mg (green), or 1200 mg (dark blue). Black dashed line = minimum inhibitory concentration (MIC; equal to 0.06 mg/L).

**Figure 7. Pharmacokinetic profiles of rifapentine following (A) 1HP and (B) 3HP regimens.** Concentration-time profiles over 24 hours are shown for the typical adult by HIV status on (A) day 21 of therapy, to reflect steady state concentrations, and (B) after first dose since no accumulation occurs with weekly dosing.

**Figure 8. Predicted rifapentine exposures with different dosing methods for (A) 1HP and (B) 3HP regimens.** Drug exposure over 24 hours (AUC0-24h) profiles are based on 500
simulations. (A) 1HP predictions reflect steady state exposures to account for autoinduction. ‘Weight band’ rifapentine doses were 300 mg for < 35 kg, 450 mg for 35-45 kg, and 600 mg for >45 kg, as currently recommended for 1HP. The ‘Flat’ approach prescribed 600 mg to all individuals, and ‘HIV stratified’ increased dose in HIV-positive to 750 mg. (B) 3HP doses were 750 mg for <50 kg and 900 mg for 50+ kg for the ‘weight band’ approach, as currently recommended. The ‘Flat’ approach prescribed 900 mg to all individuals, and ‘HIV stratified’ increased dose in HIV-positive to 1200 mg. Gray dashed lines represent (B) the median AUC\(_{0-24h}\) (=317 mg*h/L) observed in patients treated with 3HP in the PREVENT-TB trial (i.e., TBTC-26) and (A) the median predicted AUC\(_{0-24h}\) in HIV-positive patients with 600 mg daily (=219 mg*h/L).

**Figure 9. Predictors of month 2 culture conversion.** Data were acquired from two Phase II clinical studies (TBTC29, TBTC29x) where participants received 10 mg/kg rifapentine daily. Odds ratios are from univariate analysis.
### Tables

**Table 1.** Baseline characteristics of the study participants in the pooled datasets.

<table>
<thead>
<tr>
<th>Trial (Ref)</th>
<th>Rifapentine Regimen</th>
<th>N Individuals, (N samples)</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Female sex</th>
<th>HIV-positive</th>
</tr>
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<tr>
<td><strong>Analysis cohort</strong></td>
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<tr>
<td>06-0050 (19)</td>
<td>900 mg thrice weekly with low fat</td>
<td>14, (269)</td>
<td>41 (24-64)</td>
<td>76 (50-97)</td>
<td>3 (21.4)</td>
<td>-</td>
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<tr>
<td>Phase 1 HV PM</td>
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<tr>
<td>Rifquin (12)</td>
<td>900 mg twice weekly or 1200 mg once weekly with high-fat meal</td>
<td>241, (846)</td>
<td>32 (18-80)</td>
<td>56 (38-78)</td>
<td>88 (36.5)</td>
<td>46 (19.1)</td>
</tr>
<tr>
<td>Phase 3 DS-TB PM</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>TBTC-29B (14)</td>
<td>5 - 20 mg/kg once daily with low-fat meal</td>
<td>26, (504)</td>
<td>47 (24-60)</td>
<td>82 (60-99)</td>
<td>5 (19.2)</td>
<td>-</td>
</tr>
<tr>
<td>Phase 1 HV PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBTC-25 (29)</td>
<td>600, 900, or 1200 mg once weekly on empty stomach</td>
<td>35, (357)</td>
<td>44 (18-68)</td>
<td>65 (46-110)</td>
<td>12 (34.3)</td>
<td>-</td>
</tr>
<tr>
<td>Phase 2 DS-TB PH</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ACTG-A5311 (21)</td>
<td>10 mg/kg twice daily or 15 or 20 mg/kg once daily with low- or high-fat meal</td>
<td>44, (1210)</td>
<td>35 (20-59)</td>
<td>82 (60-99)</td>
<td>12 (27.3)</td>
<td>-</td>
</tr>
<tr>
<td>Phase 1 HV PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Validation cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>TBTC-29X (28)</td>
<td>10, 15, or 20 mg/kg once daily with high-fat meal</td>
<td>225, (713)</td>
<td>30 (18-70)</td>
<td>55 (40-83)</td>
<td>66 (29.3)</td>
<td>19 (8.4)</td>
</tr>
<tr>
<td>Phase 2 DS-TB PHZE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBTC-26 (30)</td>
<td>900 mg once weekly with food</td>
<td>77, (77)</td>
<td>40 (19-63)</td>
<td>81 (49-169)</td>
<td>37 (48.1)</td>
<td>-</td>
</tr>
<tr>
<td>Phase 3 LTBI</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>


<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Regimen</th>
<th>Phase</th>
<th>Population</th>
<th>Dosage</th>
<th>Median (Range)</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHBC-29 (22)</td>
<td>10 mg/kg 5 days per week on empty stomach</td>
<td>Phase 2</td>
<td>DS-TB PHZE</td>
<td>158, (158)</td>
<td>36 (18-86)</td>
<td>60 (40-101)</td>
</tr>
<tr>
<td>RioMar (31)</td>
<td>7.5 mg/kg once daily with food</td>
<td>Phase 2</td>
<td>DS-TB PHMZ</td>
<td>43, (167)</td>
<td>58 (45-83)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Data are expressed as median (range) or number (percentage).

A description of each trial is below including study phase, population, and drug regimen.

Definition of abbreviations: NR = not recorded; HV= healthy volunteers; DS-TB = drug-sensitive tuberculosis; LTBI = latent tuberculosis infection; P = rifapentine; H = isoniazid. M = moxifloxacin; [Mdz] = midazolam, only administered in some of the study participants; Z = pyrazinamide; E = ethambutol.
Table 2. Final parameter estimates for the rifapentine population pharmacokinetic model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population Estimate</th>
<th>Inter-individual variability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value [%RSE]</td>
<td>95% CI†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%CV [%RSE]</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>1.11 [1.92]</td>
<td>0.952 - 1.48</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>36.7 [1.99]</td>
<td>28.5 - 40.9</td>
</tr>
<tr>
<td>MTT (h)</td>
<td>1.94 [2.97]</td>
<td>1.83 - 2.04</td>
</tr>
<tr>
<td>NN</td>
<td>2.15 [5.44]</td>
<td>1.66 - 2.70</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>100 fixed</td>
<td>-</td>
</tr>
<tr>
<td>Fixed effects on bioavailability‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>0.0167 [5.30]</td>
<td>0.00343 - 0.0287</td>
</tr>
<tr>
<td>HIV infection</td>
<td>0.729 [6.26]</td>
<td>0.584 - 0.815</td>
</tr>
<tr>
<td>High-fat meal</td>
<td>1.49 [3.05]</td>
<td>1.37 - 1.64</td>
</tr>
<tr>
<td>Fasting</td>
<td>0.731 [5.51]</td>
<td>0.546 - 0.776</td>
</tr>
<tr>
<td>k_{ENZ} (h^{-1})</td>
<td>0.00587 [32.1]</td>
<td>0.00291 - 0.0135</td>
</tr>
<tr>
<td>E_{max} (%)</td>
<td>73.0 [25.2]</td>
<td>51.0 - 116</td>
</tr>
<tr>
<td>E_{50} (mg/L)²</td>
<td>4.27 [39.8]</td>
<td>1.80 - 6.57</td>
</tr>
<tr>
<td>γ</td>
<td>10 fixed</td>
<td>-</td>
</tr>
<tr>
<td>Residual error of rifapentine</td>
<td>0.577 [4.13]</td>
<td>0.573 - 0.699</td>
</tr>
<tr>
<td>CL_{m,fm} (L/h)</td>
<td>3.11 [12.2]</td>
<td>1.89-6.26</td>
</tr>
<tr>
<td>V_{m,fm} (L)</td>
<td>2.15 [7.07]</td>
<td>1.67-3.15</td>
</tr>
<tr>
<td>f_{m,dose} **</td>
<td>0.0185 [3.56]</td>
<td>0.0004 - 0.0266</td>
</tr>
<tr>
<td>HIV effect on CL_{m}</td>
<td>1.36 [9.85]</td>
<td>-</td>
</tr>
<tr>
<td>Residual error of metabolite</td>
<td>0.631 [5.59]</td>
<td>0.560-0.695</td>
</tr>
</tbody>
</table>

¹ Autoinduction parameters were estimated based on the analysis dataset alone.

† Confidence intervals were based on 926 (out of 1000) successful bootstrap runs for rifapentine model and 999 (out of 1000) successful bootstrap runs for metabolite model.

‡ Fixed effects on bioavailability (F) were relative to HIV-negative individuals taking 300 mg of rifapentine with a low-fat meal, where F=1 for each reference condition. Relative bioavailability is calculated as: F=F_{dose}*F_{HIV}*F_{high-fat}*F_{fasting}, where F_{dose} is the relative reduction in bioavailability per 100 mg above 300 mg (equal to 1- estimate*(dose/100 mg)), F_{HIV} is the relative bioavailability in HIV-positive
individuals, $F_{\text{high-fat}}$ is the relative bioavailability with a high-fat meal (vs. low-fat meal), and $F_{\text{fasting}}$ is the relative bioavailability with fasting (vs. low-fat meal).

$^{1}$Translates to an enzyme turnover half-life of 118 hours.

$^{*}$ Fraction metabolized is a function of dose, where $f_m = 1 - f_{m,dose}*(dose/100 \text{ mg})$.

**Definition of abbreviations:** RSE=relative standard error; CI=confidence interval; CV=coefficient of variation; CL/F=apparent clearance; V/F=apparent volume of distribution; MTT=mean transit time; NN=number of transit compartments; $k_{\text{ENZ}}$=enzyme production rate; EC$_{50}$=concentration where effect is 50% of maximum; $E_{\text{max}}$=maximum effect; $\gamma$=steepness for $E_{\text{max}}$ equation; $CL_{m}/f_m$=metabolite clearance; $V_{m}/f_m$=metabolite volume of distribution; $F_{m,dose}$=dose-dependent reduction in fraction metabolized.
Figures

Figure 1. PRISMA Flow Diagram

Figure 2. Final rifapentine pharmacokinetic-enzyme model.
Figure 3. Rifapentine autoinduction profile.

Figure 4. Validation of the structural rifapentine population pharmacokinetic model.
Figure 5. Relationship between weight and rifapentine clearance.

Figure 6. Effect of dose and dosing frequency on rifapentine exposure.
Figure 7. Pharmacokinetic profiles of rifapentine following (A) 1HP and (B) 3HP regimens.
Figure 8. Predicted rifapentine exposures with different dosing methods for (A) 1HP and (B) 3HP regimens.

Figure 9. Predictors of month 2 culture conversion.

<table>
<thead>
<tr>
<th></th>
<th>No. Patients/Total No. Patients (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifapentine AUC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 259 mg*h/L</td>
<td>182/363 (50)</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt; 259 mg*h/L</td>
<td>181/363 (50)</td>
<td>0.49 (0.32–0.75)</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50 kg</td>
<td>267/363 (74)</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt; 50 kg</td>
<td>96/363 (26)</td>
<td>0.60 (0.37–0.96)</td>
</tr>
</tbody>
</table>