A simultaneous population pharmacokinetic analysis of rifampicin in Malawian adults and children

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Rifampicin is a central component of first line therapy against tuberculosis.
- Rifampicin is mainly administered within fixed dose combinations, which confers clear advantages in terms of adherence, but makes dosage modification more difficult when trying to achieve therapeutic peak plasma concentrations (8–24 mg l⁻¹) throughout treatment.
- Low rifampicin plasma concentrations can lead to treatment failure and increased risk of developing drug resistance.

WHAT THIS STUDY ADDS

- Characterization of the population pharmacokinetics of rifampicin in Malawian children and adults with tuberculosis.
- Simulation of the likely population exposures following revised WHO dosing guidelines in Malawian children and adults.
- Comparison of the ability of weight- and age-based dosing bands to achieve target rifampicin exposures.

AIMS

Low rifampicin plasma concentrations can lead to treatment failure and increased risk of developing drug resistant tuberculosis. The objectives of this study were to characterize the population pharmacokinetics (popPK) of rifampicin in Malawian children and adults with tuberculosis, simulate exposures under revised WHO dosing guidelines that aim to reduce the risk of low exposures of rifampicin and examine predicted exposures using weight- and age-based dosing bands under new dosing recommendations.

METHODS

Patients were recruited at least two weeks after initiation of the intensive phase of treatment and received RIF in FDC of anti-TB drugs. A total of 5–6 rich and 1–2 sparse samples were collected. NONMEM (v7.2) was used to build a population-PK model.

RESULTS

A 165 TB patients, 115 adults and 50 children, aged 7 months to 65 years and weighing 4.8 to 87 kg, were included in the one compartment model with first order absorption best described the data. The mean population estimate for CL/F was 23.9 (l h⁻¹ 70 kg⁻¹) with inter-individual variability of 46.6%. Exposure was unaffected by HIV status. Relative bioavailability in children was estimated at 49% lower compared to adults (100% relative bioavailability). Simulations showed significantly lower rifampicin exposure in children vs. adults. In children average AUC was 13.5 mg l⁻¹ h, which was nearly half that was observed in adults (26.3 mg l⁻¹ h). Using age as a surrogate for weight in dosing bands gave similar results compared with the weight bands. Increasing dose to approximately 15 mg kg⁻¹, increased AUC in children to an average of 22 mg l⁻¹ h, bringing expected exposures in children closer to those predicted for adults.

CONCLUSION

The popPK model developed can be used to optimize rifampicin exposures through dosing simulations. WHO dosing recommendations may not be achieved using currently licensed fixed dose combination formulations of TB therapy.

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Keywords

children, dosing bands, NONMEM, population PK, tuberculosis

Received

30 July 2015

Accepted

24 November 2015

Accepted Article

Published Online

27 November 2015

Introduction

More than a million people still die from tuberculosis (TB) worldwide each year despite the availability of effective treatment [1]. During the 1960s, the introduction of the rifamycin class of antibiotics transformed the treatment of TB and, as a component of a three or four drug regimen including isoniazid and pyrazinamide, it was fundamental in reducing the duration of treatment from up to 18 to 6 months, raising rates of cure at 6 months to more than 90%, and reducing relapse to less than 5% [2]. Rifampicin (RIF) remains a central component of first-line therapy [3] since its introduction in 1967. RIF is mainly administered within fixed dose combinations, which confers clear advantages in terms of adherence, but makes dosage modification more difficult when trying to achieve therapeutic peak plasma concentrations ($8\text{--}24\text{ mg l}^{-1}$) throughout treatment [4]. Under exposure could lead to treatment failure and emergence of drug resistance, which is globally increasing in prevalence.

Given that concentration–effect relationships are not likely to differ substantially between children and adults and that RIF-based regimens achieve excellent clinical results, dosing recommendations in children have been targeted to plasma concentrations observed in adults (WHO 2003) [5]. However such recommendations need to account for pharmacokinetic differences between adults and children particularly in bioavailability and maturation of clearance processes, which could affect response to TB drugs. Weight normalized doses for TB drugs in children are typically chosen at the lower end of recommended ranges in order to limit adverse reactions, which would also act to reduce exposure, and it has been highlighted in recent publications that children receiving a particular anti-TB agent are often exposed to lower plasma concentrations of the agent than adults receiving identical mg kg^{-1} dosages [5–8]. Furthermore, plasma exposures lower than those associated with efficacy have also been observed in several studies in adults under current dosing regimens [9–13].

In 2010 the World Health Organization (WHO) revised dosing recommendations for RIF and isoniazid for the treatment of TB in children [14]. The RIF dosage for children was increased from $10\text{ mg kg}^{-1}\text{ day}^{-1}$ ($8\text{--}12\text{ mg kg}^{-1}\text{ day}^{-1}$) to $15\text{ mg kg}^{-1}\text{ day}^{-1}$ ($10\text{--}20\text{ mg kg}^{-1}\text{ day}^{-1}$) [14]. However, the widespread use of paediatric co-formulations containing other components of TB therapy in fixed dosing ratios has constrained widespread implementation of these new dosing recommendations and limited data exist with which to evaluate their likely success in achieving plasma concentrations comparable with adults.

Here, we have applied a population pharmacokinetic (popPK) modelling approach to compare plasma RIF exposures in Malawian adults and children receiving TB

treatment (the latter dosed according to previous recommendations using $8\text{--}12\text{ mg kg}^{-1}\text{ day}^{-1}$ of RIF dosed as part of a fixed dose combination (FDC)). Simulation of likely exposures in children and adults using revised WHO dosing recommendations was undertaken and compared against adult and target RIF concentrations.

Methods

Patients

A total of 165 TB patients, 115 adults and 50 children, were recruited at least 2 weeks after initiation of the intensive phase of treatment and received RIF in FDC of anti-TB drugs approved by the National TB Programme. Children received FDC film coated tablets or dispersible tablets (Macleods pharmaceutical Ltd., India) containing RIF 60 mg, isoniazid (INH) 30 mg and pyrazinamide (PZA) 150 mg, or RIF 60 mg, INH 60 mg, supplemented by single drug 100 mg tablets of ethambutol (ETH). Adults received FDC tablets containing RIF 150 mg, INH 75 mg, PZA 400 mg and 275 mg of ETH (Lupin pharmaceutical Ltd., India) (Table 1). Dosing was administered under observation by ward nursing staff with no restrictions on access to food and water.

Patients were recruited from the Departments of Medicine or Paediatrics at Queen Elizabeth Central Hospital (QECH) in Blantyre. Exclusion criteria included baseline haemoglobin of less than 8 g per 100 ml of blood, vomiting within 72 h preceding proposed study date, diarrhoea more than three times per day during the 3 days preceding the proposed study date and discontinuation of ART (antiretroviral therapy) within 2 weeks prior to the sampling date. All blood sampling was performed after written informed consent had been obtained from the patients or their guardians, and the study was approved by the Research Ethics Committees of the University of Malawi College of Medicine and the Liverpool School of Tropical Medicine. Patient characteristics are shown in Table 2. The following covariates were available, age, gender, body weight and HIV status.

Drug sampling and collection

Rich PK data were collected from 40 adults and 22 children. Blood samples were collected from each patient at sampling times of 0 (pre-dose) and 24 h after observed dosing of their TB treatment, and at three to four randomly allocated sampling times chosen from 0.5, 1, 2, 3, 4, 6, 8 h after observed dosing for a total of five to six blood samples per patient. A maximum total blood volume of 18 ml was sampled from the children. The time of collection of blood samples was optimized for RIF based on its known pharmacokinetic properties following oral administration. Blood was centrifuged and the separated plasma snap-frozen at $-80\text{ }^{\circ}\text{C}$.

Table 1

Adults and children drug amounts per patient body weight FDC formulations in Malawi and WHO recommendations

FDC formulations in Malawi		
Patients' body weight (kg)	Children	
	Initial phase	
	RHZ (mg) [R60/H30/Z150]	
0–6	1	
7–9	1.5	
10–14	2	
15–19	3	
20–24	4	
25–29	5	
Adults		
	RHZE (mg) [R150/H75/Z400/E275]	
30–37	2	
38–54	3	
55–74	4	
75 and over	5	
FDC formulations WHO recommendations		
Patients body weight (kg)	Children	
	[R60/H30/Z150](mg)	[R60/H60](mg)
5–7	1	1
8–14	2	1
15–20	3	2
	[R150/H75] (mg)	[R60/H60](mg)
21–30	2	2
Adults		
	[R150/H75/Z400/E275] (mg)	
30–49	3	
50–70	4	
70 and over	5	

H, hisonizide; E, ethambutol; R, rifampicin (60–150 mg); Z, piazidamyde.

A total of 75 adults and 28 children provided sparse PK. On the study date the patient attended clinic and after observed TB medication ingestion, between one and two samples of 5 ml venous blood from adults and 2 to

Table 2

Summary of patient demographics and baseline clinical characteristics of patients included in the pharmacokinetic modelling

Parameter	Median (range)
Study participants <i>n</i> [M/F]	165 [97/68]
Adults	115
Children	50
Age (years) Children	6.125 (0.58–14)
Weight (kg) Children	15 (4.8–29)
Age (years) Adults	33 (14–65)
Weight (kg) Adults	49 (30–87)
HIV positive Children %	62%
HIV positive Adults %	70%

F, female; M, male; *n*, number of patients.

5 ml from children was collected and promptly centrifuged to allow separation of plasma for storage at –80 °C. The time of sampling was allocated by randomized envelope to be within a window up to 8 h post-dosing.

Quantification of drug concentrations

Plasma concentrations of RIF were determined using validated high-performance liquid chromatography (HPLC) methods. The lower limit of quantification (LLOQ, 0.5 mg l⁻¹) was accepted as the lowest point on the standard curve, with a signal-to-noise ratio of 5:1 and a coefficient of variation (CV) of less than 10% and ranged between 2% CV and 13% CV at all other calibration levels. [15, 16]. Assay analysis was done at the Liverpool School of Tropical Medicine (UK) using appropriate internal standards validated to internationally recognised acceptance criteria [17].

Population PK analysis

The PK model was developed using NONMEM® (ICON, version VII 2.0). The model building strategy was as follows. One and two compartment models with first or zero order absorption without and with lag time were fitted to the data using the first order conditional method of estimation. Proportional, additive and combined proportional and additive error models were explored to describe residual variability. The minimal objective function value (OFV, equal to –2 log likelihood) was used as a goodness-of-fit metric with a decrease of 3.84 corresponding to a statistically significant difference between models ($P = 0.05$, χ^2 distribution, one degree of freedom). Residual plots were also examined. Once the appropriate structural model was established, the following covariates were explored: body weight, age, gender and HIV status. Log-normal distributions were assumed for the description of inter-individual variability in pharmacokinetic parameters, as shown in the following equation:

$$\theta_{xi} = \theta_x * \exp(\eta_{xi}). \quad (1)$$

where θ_{xi} is pharmacokinetic parameter 'x' of the i^{th} individual; θ_x is the fixed effect population parameter estimate; and η_{xi} is the log inter-individual variability for parameter 'x' in individual 'i' drawn from a normal distribution with a mean of zero and variance ω^2 . Dichotomous covariates were introduced as a power model and continuous variables were modelled using a power model with normalized covariate:

$$\theta_x = \theta_x \times \theta_{cov}^{z_i} \quad (2)$$

$$\theta_{xi} = \left(\theta_x \times (\text{COV}_i / \text{COV}_{\text{median}})^{\theta_{\text{cov}}} \right) * \exp(\eta_{xi}) \quad (3)$$

where θ_{xi} is pharmacokinetic parameter 'x' in the i^{th} individual and θ_x is the population parameter estimate

as previously; in equation 2 (dichotomous covariates) θ_{cov} is the ratio value for the typical value of parameter 'x' in individuals according to their dichotomous classification Z_i which is equal to 0 or 1. In equation 3 (for continuous covariates) COV_i is the value of the covariate for the i th individual, COV_{median} is the median value in the population dataset, θ_{cov} is the exponent describing the covariate effect. For weight as a covariate an allometric model [18] was applied to standardize the CL and V pharmacokinetic parameters using a standard weight (WT_{std}) of 70 kg in equation 3 above instead of the median for the dataset, and fixing the exponent to 0.75 for CL and 1 for V .

Dichotomous covariates on clearance were introduced as a power model and continuous variables were modelled using a power model with normalized covariate.

Graphical methods were used to explore the relationship of covariates vs. individual predicted pharmacokinetic parameters. Each covariate was introduced separately into the model and only retained if inclusion in the model produced a statistically significant decrease in OFV of 3.84 ($P \leq 0.05$). A backwards elimination step was then carried out once all relevant covariates were incorporated and covariates were retained if their removal from the model produced a significant increase in OFV (>6.63 points, $P \leq 0.01$, χ^2 distribution, one degree of freedom).

To perform a prediction-corrected visual predictive check (pcVPC) [19] using Perl-speaks-NONMEM (PsN) [20], 1000 datasets were simulated using the parameter estimates defined by the final model with the simulation subproblems option of NONMEM®. Children and adults datasets were simulated separately. From the simulated data, 90% prediction intervals (P5–P95) for each regimen were constructed. Observed data from the original dataset were superimposed for both regimens. At least 90% of data points within the prediction interval (5% above and below) was indicative of an adequate model.

To investigate the different dosing regimen scenarios and to test age as surrogate of weight for a different dosing band strategy, PK simulations were performed. 90% prediction intervals of the simulated RIF concentrations for each category were plotted.

Results

Data from 608 plasma samples were collected. RIF plasma concentrations were in a range of 0.016 to 15.66 mg l⁻¹ with the median C_{max} in children at 2.3 mg l⁻¹, and in adults at 4.3 mg l⁻¹. A one compartment model described the data better than a two compartment model and therefore was retained as the base model. Inter-individual random effects (IIV) were described by an exponential model which was supported for apparent clearance (CL/F) and apparent volume of distribution (V/F), IIV was not estimated for absorption constant (k_a), probably due to the limited data. A proportional model described the residual variability. The introduction of a lag time did not significantly improve the fit and a transit compartment model of absorption did not improve the fitting. In the basic model the mean population estimates for CL/F, apparent (V/F) and k_a were 16.7 l h⁻¹, 63.2 l and 0.47 h⁻¹, respectively. The inclusion of a relative bioavailability factor to allow children to be analyzed as a separate subpopulation within the dataset significantly improved the model fit (Table 3), for the adults this bioavailability factor was fixed at unity. The two sub-populations were identified based on weight. Individuals with a weight between 5 and 29 kg were considered children, which corresponded with age < 15 years. The inter-individual variability in CL/F expressed by the coefficient of variation (CV) was 61% and residual variability was 79%.

A total of four covariates (weight, age, gender and HIV-co-infection) were analyzed using a stepwise forward-backward elimination method. CL significantly ($P < 0.001$) correlated with two covariates: weight and age; HIV status was not found to be a significant covariate. The final models for CL, V and F were described with the following equations:

$$CL_i = \left(\theta_{CL} \times (WT_i/70)^{0.75} \times (AGE_i/AGE_{median})^{\theta^{age}} \right) * \exp(\eta_{CL,i}) \quad (4)$$

$$V_i = (\theta_v \times (WT_i/70)^1) * \exp(\eta_{V,i})$$

$$F_i = 1 \times \theta_F^{Z_i} \quad (\text{where } Z_i = 0 \text{ for an adult, and } 1 \text{ for a child}) \quad (5)$$

Table 3

Summary of the final model selection

Model	ΔOFV	CL/F (IIV)(l h ⁻¹)	V/F (IIV)(liters)	k_a (IIV)(h ⁻¹)	ϵ_{ccv}
Base model	0	16.7 (0.383)	63.2 (0.632)	0.47 (—)	0.219
Relative bioavailability factor (Adults vs. Children)	–81	18.9 (0.315)	77.5 (0.467)	0.24 (—)	0.23
Allometric scaling on CL/F and V/F	–130	27.6 (0.244)	116 (0.312)	0.24 (—)	0.223
Age effect on CL/F	–158	24.1 (0.215)	45.3 (0.81)	0.24 (—)	0.223

ΔOFV= change in NONMEM objective function value; CL/F= apparent clearance; V/F= apparent volume of distribution; k_a = absorption rate constant; ϵ_{ccv} = proportional residual error.

The mean population estimate for CL/F in the adult subpopulation (F fixed to 1) was 23.9 l h^{-1} ; the final model incorporating covariates is detailed in table 4. Inclusion of body weight and age resulted in an improvement of the goodness of the fit ($\Delta\text{OFV} = -158$, $P < 0.001$), a relatively significant decrease in inter-individual variability of 15.5%.

Diagnostic plots and visual predictive checks for the final model showed that predicted and observed data were in adequate agreement (Figures 1 and 2).

Simulation of RIF in FDC formulations in children and adults

In order to illustrate better the differences in plasma exposure between children and adults dosed by weight bands with the FDC formulation, simulations were carried out considering the currently used dosage in Malawi (Table 1) using parameter estimates for the entire popPK model derived from the model fitting exercise i.e. for the PK structural parameters, the covariate model, inter-individual variability and residual random effects. In addition, the WHO growth standard [21, 22] in the Malawian population was used to define the correlation between age vs. weight in order to convert the WHO dosing bands based on subject weight, to an age based system. Two plots were then generated describing the change of the RIF AUC vs. weight and age, incorporating the simulated inter-individual variability as expected from the fitting to the data. Results illustrated a significantly lower RIF exposure in children compared with adults. In children the average AUC was $13.5 \text{ mg l}^{-1} \text{ h}$, which was approximately half that estimated in adults ($26.3 \text{ mg l}^{-1} \text{ h}$). However, due to the high variability in drug exposure some individual children could have an AUC over $30 \text{ mg l}^{-1} \text{ h}$, which is similar to the average in adults (Figure 3). Using age as a surrogate for weight in the dosing bands gave similar results compared with the weight bands.

Table 4

Rifampicin final parameter estimates and standard errors obtained from the final popPK model

Parameter	Estimate	RSE (%)
CL/F (l h^{-1})	23.9	6
V/F (l)	44.6	11
k_a (h^{-1})	0.236	3
F (% relative bioavailability, children)	51.7	18
IIV CL/F (%)	46.6	15
IIV V/F (%)	87.4	30
Residual error		
Proportional (%)	48	8
Factor associated with age on RIF CL/F	0.517	18

BW, body weight; CL/F, apparent oral clearance; IIV, inter-individual variability; k_a , absorption rate constant; RSE (%), relative standard error; RSE defined as $(\text{SE}_{\text{estimate}}/\text{estimate}) \times 100$; V/F, apparent volume of distribution.

Figure 1

Goodness of fit plots for the final pharmacokinetic model illustrating A) population predictions of RIF vs. observed concentrations and B) individual predictions of RIF vs. observed concentrations. The continuous line shows the line of unity and the broken line shows the line of regression

With an increase in dose to approximately 15 mg kg^{-1} as suggested under newer WHO dosing recommendations, the AUC in children increased to an average of $22 \text{ mg l}^{-1} \text{ h}$ (Figure 3), bringing the expected exposures in children closer to those predicted for adults.

Discussion

The study in this paper describes the PK of RIF in a mixed Malawian population of adults and children where the application of a popPK analysis has allowed the differences in exposure between the two sub-groups to be directly compared.

Generally, RIF pharmacokinetics show high variability in patients under the same dosing regimen [23–26]. AUC is the parameter that best correlates with the pharmacological effect of anti-TB drugs [23, 24, 27] and is the most practical representation of exposure, which can be easily compared throughout populations and sub-groups. Using mixed effects modelling it was possible to estimate the individual AUCs, comparing the exposure through

Figure 2

Visual predictive check for the final pharmacokinetic model fitting. 90% prediction interval (broken line) and median population prediction (continuous line) determined from 1000 simulations for RIF (for adults and children) under a 600 mg once daily regimen, with the covariate values of those individuals used in the model building process. Simulations were stratified into the A) adult and B) child subpopulations. Observed data from patients used in the model-building process were superimposed onto the prediction interval. Of 140 and 468 plasma concentrations in children and adults, respectively, 8% were above P95 and none was below P5 for children, 2.7% were above P95 and 5.7% were below P5 for adults. These results suggest that overall the final model performed adequately

the dosing bands and between the adult and child sub-populations.

The model which best described RIF pharmacokinetics was a one compartment model with first order absorption and elimination, this structural model is consistent with those in previously published analyses [23, 28] and in the case of the adult individuals parameter estimates were also consistent [23].

The estimate of the average AUC(0,24 h) in children was 13.5 mg l⁻¹ h, this value is somewhat lower than previous studies [8] which indicated a range between 20.2 to 57 mg l⁻¹ h. However Schaaf *et al.* [29] reported an AUC (0,6 h) of 14.9 mg l⁻¹ h in HIV infected children. The majority of the children involved in this study (61%) were HIV positive. However HIV status was not found to be independently associated with clearance as a categorical covariate either in adults or children, and was thus excluded from the final model. In addition, the observed C_{max} in children (median 2.90 mg l⁻¹), was lower compared with previous studies [29], which is in keeping with the relatively low estimate of AUC. Seth *et al.* [30]

reported a mean C_{max} of 3 mg l⁻¹, and an AUC(0,8 h) of 20.5 mg l⁻¹ h. However the children in that study were malnourished, as opposed to our cohort. Mahajan [31] *et al.* and Tan *et al.* [32] showed a C_{max} of 2.16 and 1.9 mg l⁻¹, respectively. However AUC was not reported.

Median observed C_{max} in adults was 4.3 mg l⁻¹, approximately nearly twice that of children, consistent with estimated AUC (26.3 mg l⁻¹ h adult vs. 13.5 mg l⁻¹ h child). Drug concentrations in adults were low compared against the recommended RIF plasma C_{max} of 8 mg l⁻¹. Exposures in adults were lower than those reported by Tostmann *et al.* [25] in a similar east African population but consistent with several other studies which confirm low RIF exposures [8]. A recent study however reported that an AUC(0,24 h) of RIF ≤ 13 mg l⁻¹ h may be a predictor of poor outcome [24], suggesting that the AUC(0,24 h) seen in this study in adults could still have been adequate for treatment.

In general, low RIF exposures could be related to pharmacogenetic variability [33] or food effects (food intake has been shown to decrease the RIF C_{max} by 36%) [34, 35]. Additionally, the high number of HIV positive patients may have affected the PK analysis [11, 36]. However there was no association between HIV status and clearance. Also, a fundamental aspect in anti-TB therapy, which may be overlooked, is the quality of the drug formulation. Some studies have indicated that bioavailability of RIF in certain FDC formulations could be a great source of variability, frequently resulting in under exposure to the drug [23, 37–43]. Using FDCs with poor RIF bioavailability could lead directly to a poor treatment outcome and may create, not prevent, drug resistance [44]. In our study, the effect of generic formulations may have impacted on RIF PK, particularly in children, where a different generic drug was used compared with adults. However all drug formulations used in the study were WHO approved. In the final model a relative bioavailability factor (*F*) was included, in order to account for the different in exposure between children and adults (while allowing for a similar half-life in the two sub-populations). The relative *F* was significantly lower in children (48.3%), which may be the result of an effectively lower dose given to this sub-group due to differences in the FDC formulation. The lower exposure appears to be consistent in all the dosing bands received by the children (weight bands ranging from <7 kg to 29 kg, based on the dosages of the FDC formulation in Malawi), which may be further evidence for differences in formulation manufacture. Additionally, at the time of the study, the official Malawian guideline divided the dosages of FDC therapy in six weight bands, which may possibly encourage breaking the FDC tablets, in order to follow guidelines dosing. It could be speculated that this may also be a significant source of variability and under exposure [28].

Simulation results of the new WHO dosing instructions for the use of the currently available FDC

Figure 3

Steady-state 90% prediction intervals determined from simulated AUC of RIF administered at different dosing bands. The mean population prediction (continuous thick line) and the 90% prediction interval are represented for each category. (A) Steady-state AUC vs. weight predicted at dosing bands according to the Malawian guides lines. (B) Steady-state AUC vs. age predicted at dosing bands according to the WHO growth standard in the Malawian population using Malawian guide lines dosing bands. (C) Steady-state AUC vs. weight predicted at dosing bands according to the WHO dosing recommendations. (D) Steady-state AUC vs. age predicted at dosing bands according to the WHO growth standard in the Malawian population using WHO dosing bands recommendations

combinations in children, assuming linear pharmacokinetics [45], predict a significant increase in exposure in children under the new regimen, with an average AUC (0,24 h) of 22 mg l⁻¹ h in children vs. 26.3 mg l⁻¹ h predicted in adults. Simulations of exposures under the dosing bands also illustrate the disparity in exposure that can occur for minor changes in weight or age when at the borderline between two dosing bands. This is particularly evident at the border between an adult and child dose at a weight of 30 kg. For example a subject weighing 28 kg can expect approximately two times lower exposure than one weighing 30 kg despite a relatively minor disparity in body weight.

Dosing by age band, as a surrogate of weight was explored. In rural areas of Malawi it might not be possible to weigh a patient. However using a WHO growth reference curve in a Malawian population [21, 22] it was possible to simulate RIF exposure using age bands for the different dosing recommendations. The results from these age band simulations illustrate the same pattern of disparity between adult and child exposures and the large changes in exposure that could occur for minor differences in age at the borderlines of the dosing bands.

We contend that in general, using simulations based on the results from a popPK fitting to data in this manner represents a pragmatic and intuitive approach to assessing the dosing band recommendations and suggest that age-based dosing does not result in an important increase in variability in target PK parameters. These findings however will need to be validated in new PK studies assessing higher doses.

In summary, our popPK study has indicated low RIF exposures in Malawian adults and most particularly in children. Exposure was unaffected by HIV status. The simultaneous analysis of data from adults and children appears a useful and successful approach in that use of the more complete and richly sampled data from adults improved the fitting of the data from children and the precision of predictions of exposure under different alternative dosing schedules. Since RIF is the major drug in TB treatment that drives sterilizing activity, optimizing RIF exposure in all patients may be a key and feasible route to shorter TB treatment. Current WHO proposed dosing strategies for children employing currently marketed paediatric FDCs may not completely eliminate the differences in observed exposure between children and adults and higher paediatric doses need to be explored.

Competing Interests

"All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). SK has received financial support from Merck, Janssen, ViiV Healthcare, BristolMyersSquibb and Gilead Sciences for various investigator-led research in the previous 3 years with no other relationships or activities that could appear to have influenced the submitted work. All other authors declare no support from any organization for the submitted work.

The authors wish to thank Dr Daniel J. Hayes for his contribution to the manuscript.

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