Rifabutin pharmacokinetics and safety among TB/HIV-coinfected children receiving lopinavir/ritonavir-containing second-line ART

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Background: Treatment options are limited for TB/HIV-coinfected children who require PI-based ART. Rifabutin is the preferred rifamycin for adults on PIs, but the one study evaluating rifabutin with PIs among children was stopped early due to severe neutropenia.

Methods: We evaluated rifabutin safety and plasma pharmacokinetics among coinfected children 3–15 years of age receiving rifabutin 2.5 mg/kg daily with standard doses of lopinavir/ritonavir. The AUC0–24 at 2, 4 and 8 weeks after rifabutin initiation was described using intensive sampling and non-compartmental analysis. Clinical and laboratory toxicities were intensively monitored at 12 visits throughout the study.

Results: Among 15 children with median (IQR) age 13.1 (10.9–14.0) years and weight 25.5 (22.3–30.5) kg, the median (IQR) rifabutin AUC0–24 was 5.21 (4.38–6.60) g/Lh/mL. Four participants had AUC0–24 below 3.8 g/Lh/mL (a target for the population average exposure) at week 2 and all had AUC0–24 higher than 3.8 g/Lh/mL at the 4 and 8 week visits. Of 506 laboratory evaluations during rifabutin, grade 3 and grade 4 abnormalities occurred in 16 (3%) and 2 (0.4%) instances, respectively, involving 9 (60%) children. Specifically, grade 3 (n = 4) and grade 4 (n = 1) neutropenia resolved without treatment interruption or clinical sequelae in all patients. One child died at week 4 of HIV-related complications.

Conclusions: In children, rifabutin 2.5 mg/kg daily achieved AUC0–24 comparable to adults and favourable HIV and TB treatment outcomes were observed. Severe neutropenia was relatively uncommon and improved with ongoing rifabutin therapy. These data support the use of rifabutin for TB/HIV-coinfected children who require lopinavir/ritonavir.

Introduction

TB is the leading cause of death among children with HIV.1,2 Compared with those with TB monoinfection, mortality rates are 4-fold higher among coinfected children.1,4 Yet, current co-treatment strategies for children are limited. Many antiretroviral medications have significant drug interactions with rifampicin, a key component of TB treatment, and paediatric formulations for co-treatment are lacking.

The 2016 WHO guidelines recommend lopinavir/ritonavir-based ART for children under 3 years of age as first-line therapy, as well as for older children who have failed first-line ART.5 While the 2019 WHO guidelines promote use of dolutegravir-containing ART as a promising universal treatment strategy for all ages, its use in children remains understudied, particularly among those with TB/HIV coinfection, and dosing guidelines and formulations for young children are not yet available.6 Thus, lopinavir/ritonavir...
remains widely used among children in resource-limited settings. Rifampicin is a potent inducer of cytochrome P450 3A4 and intestinal p-glycoprotein, reducing lopinavir exposure by 90% when given in combination. In children with TB, giving additional ritonavir in combination with lopinavir/ritonavir is recommended to overcome this drug interaction. However, ritonavir is not available in most settings and the oral solution used in young children is unpalatable.

For coinfected adults who require PI-based ART, the WHO recommends rifabutin in place of rifampicin. Rifabutin coadministration has minimal effect on lopinavir concentrations and thus standard PI dosing is recommended. However, all ritonavir-boosted PIs increase serum concentrations of rifabutin, so the concurrent rifabutin dosage is reduced. In adults, rifabutin dosed at 150 mg thrice weekly results in rifabutin exposure below that achieved with the recommended dose of rifabutin (300 mg daily) without ART, while rifabutin 150 mg daily with lopinavir/ritonavir results in higher exposure.

The combination of rifabutin and lopinavir/ritonavir has not been adequately studied in children. US guidelines recommend rifabutin 10–20 mg/kg once daily for treatment of drug-susceptible TB, but no dosing guidelines exist for children receiving lopinavir/ritonavir-containing ART. In the only published study to evaluate rifabutin pharmacokinetics among children receiving lopinavir/ritonavir, two of six children developed treatment-limiting neutropenia. This safety concern contrasts with our programmatic experience in the PEPFAR-supported AIDS Prevention Initiative in Nigeria (APIN) Public Health Initiatives programme that has supported access to rifabutin for coinfected adults and children since 2009. Severe neutropenia was rare in a retrospective analysis of rifabutin safety among 48 coinfected children (median age of 1.7 years) who received concurrent lopinavir/ritonavir-based ART, with only one instance (2%) of grade 3 neutropenia (no grade 4 neutropenia).

Five of six children achieved adequate rifabutin concentrations when dosed 5 mg/kg thrice weekly in the Moultrie et al. study. We evaluated rifabutin 2.5 mg/kg daily along with lopinavir/ritonavir as it provides a similar weekly dosage, while simplifying the treatment regimen by giving all medications once daily.

Methods

Study design and population

We designed a prospective, open-label study to evaluate rifabutin pharmacokinetics and safety among 15 TB/HIV-coinfected children 3–15 years of age receiving lopinavir/ritonavir-based ART. All children were ART experienced, recently diagnosed with active TB infection and required second-line therapy, monthly through completion of TB treatment at 24 weeks, then at 36 and 48 weeks. At each visit, a physical examination was performed, clinical toxicities recorded and blood samples collected for determination of total WBC count, absolute neutrophil count (ANC), haemoglobin, platelet count, ALT and creatinine. Participants were monitored clinically for uveitis, a rare complication of rifabutin, and any child with evidence of eye redness, pain, photophobia or visual changes underwent ophthalmic examination.

Clinical monitoring and toxicity grading

Clinical and laboratory toxicity were monitored at 11 visits over 48 weeks: 1 week after starting TB treatment, every 2 weeks for the first 2 months of therapy, monthly through completion of TB treatment at 24 weeks, then at 36 and 48 weeks. At each visit, plasma concentrations of rifabutin and the primary metabolite, 25-hydroxy-desacetyl rifabutin (des-rifabutin), were quantified simultaneously at the University of Cape Town utilizing a validated LC-MS/MS assay as previously described.

Pharmacokinetic sampling and processing

Steady-state rifabutin pharmacokinetic sampling was performed at three visits: 2, 4 and 8 weeks after starting rifabutin. At each visit, serial rifabutin concentrations were measured pre-dose (0) and at 2, 4, 8, 12 and 24 h after the observed morning dose. Blood samples were processed to separate plasma within 60 min after collection, then stored at −80°C until analysed. Plasma concentrations of rifabutin and the primary metabolite, 25-hydroxy-desacetyl rifabutin (des-rifabutin), were quantified simultaneously at the University of Cape Town utilizing a validated LC-MS/MS assay as previously described.

Statistical analyses

Statistical analyses were performed using Stata version 13.1 (StataCorp). Pharmacokinetic data were analysed using non-compartmental methods, with AUCl0–24 calculated using the linear trapezoidal rule. Concentrations below the LLOQ (BLQ) were given a value of half LLOQ or, in the case of serial BLQ concentrations after maximum drug concentration (Cmax), the first
timepoint was assigned a value half the LOQ and subsequent timepoints were given a value of 0 ng/mL. The $C_{\text{max}}$, and time to $C_{\text{max}}$ ($T_{\text{max}}$) were determined by visual inspection. To account for repeated measures, median (IQR) values were calculated as the population median of each participant’s mean AUC (or other pharmacokinetic parameter) at weeks 2, 4 and 8 (for one participant who had a single pharmacokinetic visit at week 2, these values were used as the mean). Similarly, median laboratory values during rifabutin treatment were calculated as the population median of the mean laboratory value during weeks 1 through 24 for each individual. Mean AUC change (95% CI) was calculated as the population mean change from the week 2 value to week 4 or 8, as indicated, for each participant.

The non-parametric Wilcoxon signed rank test was used to compare paired samples due to non-normal distribution of continuous variables. Mixed-effect longitudinal models were utilized to evaluate clinical or laboratory predictors of rifabutin AUC$_{24}$ (including study week, age, sex, weight (kg), BMI (kg/m²), baseline CD4$^+$ cell count and viral load, and rifabutin dosage (total mg and mg/kg dosage)). Finally, since neutropenia is a potential dose-limiting toxicity of rifabutin use in children, an association between AUC and ANC was explored by Spearman rank based correlation at each of weeks 2, 4 and 8. P values <0.05 were considered significant.

### Results

#### Study population

Fifteen participants were enrolled in this study between January 2017 and March 2018. Baseline patient demographics are summarized in Table 1. The median (range) age of participants was 13.1 (10.2–15.0) years, the median (range) CD4$^+$ cell count was 712 (24–652) cells/mm³ and the median (range) CD4 percentage was 10% (1%–26%). All children were underweight with a median weight (kg), BMI (kg/m²), baseline CD4$^+$ cell count and viral load, and rifabutin dosage (total mg and mg/kg dosage)]. Finally, since neutropenia is a potential dose-limiting toxicity of rifabutin use in children, an association between AUC and ANC was explored by Spearman rank based correlation at each of weeks 2, 4 and 8. P values <0.05 were considered significant.

### Ethics

All patients/caregivers enrolled in the APIN programme provided consent for care and were given the option to allow their de-identified data to be used for future evaluations (Harvard Data Repository protocol 16506). The Partners Institutional Review Board (2014P001768) and Ethics Committees of UCH (UI/EC/15/0072) and JUTH (JUTH/DCS/ADM/127) approved the current study. Since treatment was consistent with standard of care in Nigeria, the primary study intervention involved only sample collection for concentration determination. For study participation, a parent/guardian signed a written consent and children 7 years of age or older signed an assent form. A data safety and monitoring board reviewed results after half of participants were enrolled.

#### Laboratory abnormalities at baseline

Prior to initiating rifabutin, most participants (87%; 13 patients) had one or more laboratory abnormalities and three (20%) had asymptomatic grade 3 or 4 abnormalities (Table 3). Anaemia was present in 12 (80%) children (grade 1, n = 4; grade 2, n = 5; grade 3, n = 2; grade 4, n = 1). Other abnormalities included: three participants (20%) with baseline neutropenia (grade 1, n = 2; grade 2, n = 1), one (grade 1) with thrombocytopenia and two with elevated ALT (grade 1).

#### AE$s$ during rifabutin

Among the 617 individual laboratory evaluations following initiation of rifabutin, compliance with laboratory checks was excellent; excluding the participant who died, all laboratory values were available for 97% (i.e. 150 of 154) of planned visits.

Of the 506 laboratory values obtained during the rifabutin course, there were 56 (11%) AEs (any grade 1–4 events) and 18 (4%) SAEs (grade 3–4 events). After rifabutin initiation, haemoglobin was evaluated 155 times with 83 (54%) meeting criteria for anaemia, but only 16 (13%) instances among seven children were of increased severity from baseline (Table 3). Frequency of severe anaemia decreased over time: seven of eight instances of severe anaemia (six children) occurred at or before the week 6 visit. Two participants exhibited three instances of grade 1 thrombocytopenia and one patient had seven instances of grade 1 ALT elevation (resolved after week 16 despite rifabutin continuation).

During rifabutin therapy, seven (47%) participants had 30 (24%) instances of neutropenia (Table 3). Most (70%; 7 of 10) instances of severe neutropenia fell within the first 8 weeks, during the intensive phase of TB treatment. In all cases, neutropenia resolved or improved despite rifabutin continuation, with no associated adverse clinical events. Of the four participants with grade 3 or 4 neutropenia, it only persisted for two or more consecutive laboratory evaluations once. The proportion of participants experiencing neutropenia by severity grade across study weeks is displayed in Figure 1(a). The intra-participant mean change (95% CI) in ANC from baseline values is notable for a trend toward decreased ANC after treatment initiation that is non-significant with wide inter-participant variability (Figure 1b).

There were no discontinuations of TB or ART medications and no severe clinical toxicities reported. In the one instance of grade 4 neutropenia at the week 4 visit, rifabutin discontinuation was
considered, but continued based on lack of alternative treatment, clinical improvement from baseline, weight gain and repeat ANC improvement and then resolution at week 16 despite rifabutin continuation.

**Table 1.** Patient characteristics prior to rifabutin initiation; \(N = 15\)

| Characteristic | Median (IQR) |
|----------------|--------------|
| Age (years)    | 13.1 (10.9–14.0) |
| Female, \(n (%)\) | 8 (53) |
| Anthropometrics, median (IQR) | 25.5 (22.3–30.5) |
| weight (kg)    | –1.9 (–3 to –1.5) |
| BMI z-score    | 11 (73) |
| WHO clinical stage, \(n (%)\) | 4 (27) |
| 3              | 4 (27) |
| 4              | 73 (10) |
| CD4+ cell count (cells/mm\(^3\)), median (IQR) | 156 (52–294) |
| CD4%age (%), median (IQR) | 10 (4–18) |
| HIV RNA PCR (copies/mL), median (IQR) | 51 530 (22 620–159 241) |
| Duration of first-line ART prior to rifabutin start (years), median (IQR) | 3.8 (2.9–8.1) |
| Patients with lopinavir/ritonavir exposure prior to rifabutin, \(n (%)\) | 1 (7) |
| Rifabutin dosage at start, total (mg), median (IQR) | 75 (58–82) |
| Rifabutin mg/kg dosage at start (mg/kg), median (IQR) | 2.6 (2.5–2.8) |
| ART regimen | 14 (93) |
| NRTI backbone in addition to lopinavir/ritonavir, \(n (%)\) | 1 (7) |
| abacavir + lamivudine | 100 (100) |
| abacavir + lamivudine + tenofovir | 100 (100) |

**Table 2.** TB and HIV treatment outcomes among children who received rifabutin-containing TB treatment in combination with lopinavir/ritonavir-based ART

| TB and HIV treatment outcomes | Six months after rifabutin + lopinavir/ritonavir initiation | Twelve months after rifabutin + lopinavir/ritonavir initiation |
|------------------------------|----------------------------------------------------------|-------------------------------------------------------------|
| TB treatment outcomes, \(n (%)\) | 14 (93) | 14 (93) |
| completed rifabutin course with no TB symptoms | 14 (93) | 14 (93) |
| TB relapse or recurrence | not applicable | 0 |
| died | 1 (7) | 1 (7) |
| lost to follow-up | 0 | 0 |
| HIV treatment outcomes | 71 (–2–155) | 184 (73–316) |
| change in CD4+ cell count (cells/mm\(^3\))^\(a\), median (IQR) | 6.1 (3.6–22.7) | 5.0 (0.6–8.7) |
| change in CD4%a, median (IQR) | 13 (92) | 9 (64) |
| HIV RNA PCR <1000 copies/mL, \(n (%)\) | 4.5 (0–6.5) | 4.5 (3.0–7.6) |
| Clinical outcomes | 4.5 (0–6.5) | 4.5 (3.0–7.6) |

^aDenotes change from baseline to 6 or 12 months after rifabutin + lopinavir/ritonavir initiation.

Pharmacokinetics of rifabutin and 25-hydroxy-desacetyl rifabutin

Based on data from 43 pharmacokinetic visits, the median (IQR) rifabutin AUC\(_{0–24}\) was 5.21 (4.38–6.60) \(\mu\)g·h/mL, above the study target of 3.8 \(\mu\)g·h/mL (Table 4). While the median rifabutin AUC\(_{0–24}\) increased across study weeks (Figure 2), the intra-participant mean changes (95% CI) in rifabutin AUC\(_{0–24}\) from weeks 2 to 4 and 2 to 8 were not statistically significant, with a change of 0.95 (–0.56–2.47) and 1.60 (–0.47–3.67) \(\mu\)g·h/mL, respectively. Four instances of low rifabutin AUC\(_{0–24}\) occurred at week 2; in all cases exposures were >3.8 \(\mu\)g·h/mL at the 4 and 8 week visits. One additional participant had low AUC at both the 4 and 8 week visits, after an AUC of 3.67 \(\mu\)g·h/mL at week 2.

The median (IQR) des-rifabutin metabolite AUC\(_{0–24}\) was 3.12 (2.16–4.28) \(\mu\)g·h/mL (Table 4). Similar to rifabutin, the intra-participant mean changes (95% CI) in des-rifabutin AUC from
Utilizing mixed-effect longitudinal models, only study week and BMI (kg/m²) correlated with rifabutin AUC₀–²₄ in unadjusted models. However, in the adjusted model, the effect estimates were slightly attenuated and thus did not achieve significance. Finally, at weeks 4 and 8 the Spearman rank based correlation coefficients were −0.4 (P = 0.11) and −0.3 (P = 0.25), respectively, suggesting a moderate, not statistically significant, association between higher rifabutin AUC and lower ANC levels.

**Discussion**

Novel co-treatment strategies are urgently needed to expand options for TB/HIV-coinfected children. To the best of our knowledge, this study provides the first pharmacokinetic data...
examining a novel rifabutin dosing strategy among coinfected children receiving lopinavir/ritonavir. We found that rifabutin dosed at 2.5 mg/kg daily among children aged 10–15 years and receiving lopinavir/ritonavir-based ART achieved concentrations comparable to adults receiving standard dosing of rifabutin without a drug–drug interaction.12–14 Severe neutropenia was infrequent and resolved despite rifabutin continuation, which supports our findings in clinical practice, but contrasts with the only other pharmacokinetic study of this combination in children.16,17 Our findings support rifabutin use among children who require concurrent lopinavir/ritonavir-based ART, a crucial addition to the co-treatment armamentarium for this vulnerable population.

In this study, the median rifabutin AUC0–24 was 37% above the mean rifabutin AUC0–24 observed in studies of adults receiving rifabutin 300 mg daily without ART, the current standard of practice.12–14 While the optimal rifabutin exposure is unknown, rifabutin AUC0–24 values less than 3.2 µg·h/mL are associated with acquired rifamycin resistance in one study.22 The median rifabutin Cmax value was also comparable to that among adults receiving rifabutin 300 mg daily (0.30, 0.79 and 0.29 µg/mL, respectively).12–14 By comparison, among adults in two studies conducted in Vietnam and South Africa (rifabutin 150 mg daily versus 150 mg thrice weekly with lopinavir/ritonavir), the target rifabutin concentration was achieved with the daily strategy (AUC0–24 of 7.29 and 4.77 µg·h/mL, respectively), but not the thrice-weekly strategy (AUC0–24 estimated as 3.67 and 2.31 µg·h/mL, respectively)13,14.

Moultrie et al.16 examined concurrent rifabutin+lopinavir/ritonavir in six children utilizing a thrice-weekly dosing strategy at 5 mg/kg, resulting in a median AUC0–24 of 5.36 µg·h/mL (AUC0–48 6.91 µg·h/mL). Their total weekly rifabutin dosage was thus 15 mg/kg, compared with 17.5 mg/kg in our study, yet we observed a total weekly AUC over 1.5 times that observed in their study (weekly AUC 24.2 versus 36.5 µg·h/mL, respectively), which is consistent with adult studies in which increasing from thrice-weekly to daily dosing of rifabutin 150 mg resulted in a > 2-fold increase in AUC0–24.14

Overall, the median rifabutin AUC0–24 increased with time (Figure 2), though this change was not statistically significant given large interparticipant variability. A similar finding was observed among adults receiving combination lopinavir/ritonavir+ritabulin 300 mg thrice weekly.12 A rifabutin half-life of 4.5 h results in an expectation of steady-state rifabutin concentrations by approximately 10 days, so the cause of this finding remains unclear, but the potent inhibitory effect of ritonavir on CYP3A4 activity may be more progressive than previously recognized. Alternately, improved adherence and/or absorption over time could cause a similar finding, though all participants reported perfect adherence through study week 8. Finally, the moderate, but statistically insignificant, association we observed between increasing AUC0–24 and decreasing ANC, also reported in the Moultrie et al.16 study, needs to be evaluated in larger studies.

The primary rifabutin metabolite, des-rifabutin, has antimycobacterial activity equal to rifabutin.26 In two adult studies, receipt of ritonavir-boosted PIs increased metabolite AUC0–24 by approximately 5–10-fold compared with rifabutin 300 mg daily without ART (4.13 versus 0.70 and 4.77 versus 0.27 µg·h/mL, respectively)
that observed in the study by Moultrie et al.29 Currently, lopinavir/ritonavir-based ART remains the standard of care among underweight children in this study, an observed weak association between AUC and BMI (data not shown) indicating additional evaluation among malnourished children is inadequate among underweight children in this study, an observed weak association between AUC and BMI (data not shown) indicating additional evaluation among malnourished children is needed.29 Currently, lopinavir/ritonavir-based ART remains the most widely used second-line ART regimen in children, as well as first-line regimen among children less than 3 years of age. We are currently studying rifabutin pharmacokinetics and safety among coinfected children 12–36 months of age, which will add further data to this practice. Strengths of this study include intensive clinical and laboratory follow-up with few missing data points. Specifically, subjects had near perfect compliance with 11 clinical and laboratory evaluations during 12 months of follow-up with few missing values and three pharmacokinetic visits during treatment, providing robust data for the patient population. Finally, children in this study received a rifabutin suspension that was prepared by pharmacists, which may limit broader implementation, but highlights the importance of developing paediatric formulations.

In conclusion, these data support the use of rifabutin 2.5 mg/kg daily among coinfected children who require lopinavir/ritonavir. This co-treatment strategy achieved AUC0–24 comparable to adults, with favourable HIV and TB outcomes observed and relatively uncommon SAEs. Among adults who require PI-based ART, rifabutin is the rifamycin of choice and is recommended by the WHO.5 To the best of our knowledge, this study provides the first data that support paediatric rifabutin use, a novel addition to current limited co-treatment options for children.

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Transparency declarations

None to declare.
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Disclaimer
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