

## Pharmacokinetics of rifabutin during atazanavir/ritonavir co-administration in HIV-infected TB patients in India

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### SUMMARY

**SETTING:** Rifabutin (RBT) is reported to be as effective as and to have less inducing effect on cytochrome P450 enzymes than rifampicin against tuberculosis (TB). The optimal dose of RBT during ritonavir (RTV) co-administration remains a matter of debate.

**OBJECTIVE:** To study the pharmacokinetics of 150 mg RBT thrice weekly during concomitant atazanavir/RTV administration in human immunodeficiency virus (HIV) infected TB patients.

**METHODS:** This observational study was conducted in 16 adult HIV-infected TB patients being treated for TB with an RBT-containing regimen and an antiretroviral therapy regimen with RTV; the dose of RBT was 150 mg thrice weekly. Serial blood draws were performed at

pre-dosing and at 1, 2, 4, 6, 8, 12 and 24 h after the drug was administered. Plasma RBT was estimated using high-performance liquid chromatography.

**RESULTS AND CONCLUSIONS:** Peak RBT concentration was below the lower therapeutic limit (<0.3 µg/ml) in seven patients, while 10 patients had trough concentrations below the minimal inhibitory concentration against *Mycobacterium tuberculosis* (0.06 µg/ml), suggesting that the RBT dosage may be inadequate. Prospective studies in different settings are required to arrive at the proper therapeutic dose for RBT to be used during co-administration with RTV.

**KEY WORDS:** HIV; TB; pharmacokinetics; rifabutin; ritonavir

TUBERCULOSIS (TB) is the most common opportunistic infection in a significant proportion of human immunodeficiency virus (HIV) infected patients who are eligible for antiretroviral treatment (ART).<sup>1</sup> It is therefore frequently observed that HIV-infected patients on ART also have concomitant TB and require treatment for both conditions.<sup>2</sup> HIV-infected patients with TB merit special consideration, as co-management of both diseases is complicated by shared toxicity, potential pharmacological drug interactions between rifampicin (RMP) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), a large number of medications and adherence issues.

Despite the complexity of these drug interactions, the key role of the rifamycins in the success of anti-tuberculosis treatment mandates that drug-drug interactions between the rifamycins and antiretroviral drugs be addressed and managed appropriately. Current recommendations are to treat patients with HIV-related TB with a regimen including a rifamycin for the full course of anti-tuberculosis treatment. It is thus crucial to fully understand the interactions between

the rifamycins and the various classes of antiretroviral drugs. The rifamycin class of compounds is known to be a potent inducer of the hepatic cytochrome P450 (CYP450) enzyme system, which is responsible for the metabolism of several drugs. The rifamycins vary in their potential as CYP450 inducers, with RMP being the most potent, rifapentine intermediate and rifabutin (RBT) being much less active. RMP markedly lowers the serum levels of PIs and NNRTIs by inducing CYP450 CYP3A4 activity.<sup>3</sup> This could result in suboptimal antiretroviral activity and, subsequently, acquired drug resistance.<sup>4</sup> RBT has been shown to be as effective against TB as RMP,<sup>5,6</sup> and has little, if any, effect on the serum concentrations of PIs, which are metabolised through the CYP3A4 system.<sup>7</sup>

Narita et al. reported that the concomitant use of RBT and ART can lead to the successful treatment of HIV-infected patients with TB without increased side effects.<sup>8</sup> Cohort studies have shown favourable virological and immunological outcomes of PI-based ART in the setting of RBT-based anti-tuberculosis treatment.<sup>9,10</sup> Although no comparative studies have been conducted, the combination of RBT (if available) with

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PI-based ART is the preferred form of treatment for patients unable to take NNRTI-based ART. However, as it is a CYP3A4 inhibitor, ritonavir (RTV) markedly increases serum concentrations and the toxicity of RBT.<sup>8</sup> RTV could enhance RBT bioavailability by reducing either intestinal or hepatic metabolism or both.<sup>11</sup> It therefore becomes necessary to reduce the dosage of RBT when co-administered with RTV. Gallicano et al. have reported that intermittent RBT dosing provided a safe and manageable regimen for concurrent treatment with PIs.<sup>12</sup>

RBT dosage during RTV co-administration remains a matter of debate. There have been conflicting findings from studies conducted in several settings. The RBT dosing recommendations from studies conducted in healthy subjects and in HIV-infected patients differ considerably.<sup>13–19</sup> While some studies conducted among patients have demonstrated that RBT 150 mg thrice weekly is inadequate,<sup>13–15</sup> other studies in healthy subjects suggest that RBT 150 mg on alternate days, thrice weekly or every 4 days is adequate when administered with RTV.<sup>16–19</sup> A study from South Africa suggested that RBT dose should be increased to 150 mg daily.<sup>15</sup> The Revised National TB Control Programme (RNTCP) in India recommends a RBT dose of 150 mg thrice weekly during concomitant RTV administration. No pharmacokinetic data on the adequacy of this dose are available.

The main aim of the present study was to examine RBT pharmacokinetics at the dose of 150 mg thrice weekly during concomitant atazanavir (ATV)/RTV administration in HIV-infected TB patients. The pharmacokinetics of RTV during RBT co-administration was also studied.

## METHODS

### Patients

The study was conducted at the Government Hospital of Thoracic Medicine, Tambaram, Chennai, India. HIV-infected patients with a definitive diagnosis of TB (pulmonary or extra-pulmonary) based on positive smear or culture for *Mycobacterium tuberculosis* and who had received regular standard anti-tuberculosis treatment with RBT-containing regimens for a minimum of 2 weeks were recruited. These patients had failed first-line ART and had been receiving second-line ART containing ATV/RTV for a minimum of 2 weeks. All the patients were adults with body weight  $\geq 30$  kg. Pregnant and breastfeeding women and those with chronic diarrhoea or neutropenia (total neutrophil count  $< 1200$  cells/ $\mu$ l) were not considered for the study.

The ART regimen comprised daily ATV/RTV, zidovudine/tenofovir (zidovudine was replaced by tenofovir if haemoglobin was  $< 9.0$  g/dl) and lamivudine. The doses of ATV and RTV were respectively 330 mg and 100 mg. Anti-tuberculosis treatment was

thrice weekly for 6 or 8 months. The 6-month regimen consisted of RBT 150 mg thrice weekly (Macleods Pharmaceuticals Limited, Mumbai, India), along with isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB) for 2 months, followed by RBT and INH for 4 months. The 8-month regimen consisted of RBT (150 mg thrice weekly), along with INH, PZA, EMB and streptomycin for 2 months, followed by RBT, INH, PZA and EMB for 1 month and RBT, INH and EMB for 5 months. All the patients had received first-line ART, but had an unfavourable response, as evidenced by clinical (new or recurrent World Health Organization Stage 4), immunological (fall of CD4 count to pre-treatment baseline, 50% fall from the on-treatment peak value or persistent CD4 levels of  $< 100$  cells/ $\text{mm}^3$ ) and virological (plasma viral load  $> 10\,000$  copies/ml) failure after at least 6 months of ART.

The study was approved by the Institutional Ethics Committees of the Government Hospital of Thoracic Medicine, and the National Institute for Research in Tuberculosis, Chennai; written informed consent was obtained from all the patients.

### Conduct of the study

Eligible patients were admitted to the hospital at least a day before the pharmacokinetic study. They were asked to fast for 12 h after dinner on the day before the study. On the day of the study, serial blood samples (3 ml) were collected at pre-dosing and at 1, 2, 4, 6, 8, 12 and 24 h after drug administration under direct supervision.

Blood samples were centrifuged immediately and plasma stored at  $-20^\circ\text{C}$  until estimations of RBT and RTV were undertaken. Ascorbic acid 5% solution was added to the plasma to prevent oxidation of RBT; estimations were undertaken within 2 weeks of sample collection.

### Plasma rifabutin estimation

Plasma RBT was estimated using high performance liquid chromatography according to Hemanth Kumar et al.<sup>20</sup> Briefly, plasma samples were de-proteinised with acetonitrile and the supernatant was analysed using a reversed-phase  $\text{C}_{18}$  column (250 mm) and ultraviolet (UV) detection at a wavelength of 265 nm. The assay was specific for RBT and linear from 0.025 to 10.0  $\mu\text{g}/\text{ml}$ . The relative standard deviation of intra- and inter-day assays was below 10%, and average recovery from plasma was 101%.

### Plasma ritonavir estimation

Plasma RTV was estimated per Turner et al., with modifications.<sup>21</sup> Briefly, RTV from plasma was extracted into tertiary butyl methyl ether and analysed using an isocratic mobile phase consisting of sodium acetate buffer and acetonitrile on a reversed-phase  $\text{C}_8$  column (250 mm) and UV detection at a wavelength

of 212 nm; the assay was specific for RTV and linear from 0.25 to 10.0 µg/ml. The relative standard deviation of intra- and inter-day assays was below 10%, and average recovery from plasma was 102%.

#### Calculation of pharmacokinetic variables

Peak concentration ( $C_{max}$ ), trough concentration ( $C_{48h}$ ) and time to attain  $C_{max}$  ( $T_{max}$ ) were determined by visual inspection of data.  $C_{48h}$  was taken as the concentration obtained at pre-dosing, which was 48 h after the last RBT dose. The linear trapezoidal rule was used to compute exposure or area under the time-concentration curve ( $AUC_{0-24}$ ).

#### Statistical analysis

Data analysis was performed using SPSS, version 14.0 (Statistical Product and Service Solutions, Chicago, IL, USA). Peak concentrations  $<0.3$  µg/ml were taken as sub-therapeutic.<sup>13</sup> Groups were compared using the Mann-Whitney test. Correlations were determined using the Pearson's test. Multiple regression analysis was performed to check which of the variables (age, sex, CD4 counts, body mass index) influenced RBT  $C_{max}$ .

## RESULTS

Sixteen HIV-infected patients with TB were admitted to the pharmacokinetic study; 3 were females, and 8 patients were diagnosed with extra-pulmonary TB (TB pleuritis in 3, TB abdomen in 2, TB meningitis in 2, cervical lymphadenitis in 1). The median duration of anti-tuberculosis treatment before this pharmacokinetic study was 0.5 months (Table 1). All patients had virologically failed first-line ART, and were receiving second-line ART containing RTV.

The pharmacokinetic parameters of RBT obtained in the 16 patients are shown in Table 2. Of these, seven had their  $C_{max}$  below the therapeutic range

**Table 1** Patient details ( $n = 16$ )

	<i>n</i>
Age, years, median [IQR]	37.5 [29.8–40.0]
Males	13
Body weight, kg, median [IQR]	54.5 [45.5–59.0]
Pulmonary TB	8
Extra-pulmonary TB	8
Category I*	6
Category II†	10
Duration of anti-tuberculosis treatment, months, median [IQR]	0.50 [0.50–0.50]
CD4 cell counts, cells/mm <sup>3</sup> , median [IQR]	101.5 [30.0–199.3]
Viral load, copies/µl, median [IQR]	66600 [15 650–372 250]

\*6-month regimen recommended by India's RNTCP for newly diagnosed smear-positive, seriously ill smear-negative and seriously ill extra-pulmonary TB patients.

†8-month regimen recommended by India's RNTCP for TB patients who have relapsed, defaulted or failed previous treatment.

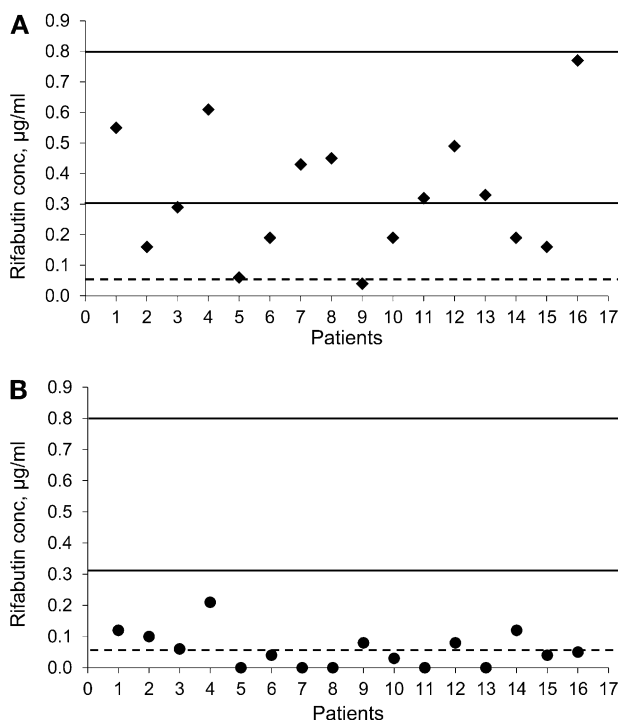
IQR = interquartile range; TB = tuberculosis; RNTCP = Revised National Tuberculosis Control Programme.

**Table 2** Pharmacokinetics of rifabutin in 16 patients

Pharmacokinetic parameters	Median [IQR]
$C_{max}$ , µg/ml	0.33 [0.19–0.48]
$C_{48h}$ , µg/ml	0.045 [0.00–0.095]
$T_{max}$ , h	4.0 [4.0–6.0]
$AUC_{0-24}$ , µg/ml.h	4.61 [2.07–5.34]

IQR = interquartile range;  $C_{max}$  = peak concentration;  $C_{48h}$  = concentration at 48 h;  $T_{max}$  = time to attain  $C_{max}$ ;  $AUC_{0-24}$  = area under the time-concentration curve.

( $<0.3$  µg/ml); there were no patients with  $C_{max}$  above the therapeutic range. Assuming 0.06 µg/ml to be the minimal inhibitory concentration (MIC) of RBT against *M. tuberculosis*,<sup>13</sup> 10 patients had their  $C_{48h} < MIC$ ;  $C_{min}$  was below the limit of quantitation (0.025 µg/ml) in five of these patients. The distribution of  $C_{max}$  and  $C_{48h}$  are shown in the Figure. RBT  $C_{max}$  differed significantly between males and females (0.29 vs. 0.59 µg/ml,  $P = 0.026$ ), while there was no statistically significant difference in male and female  $AUC_{0-24}$  (3.60 vs. 5.68 µg/ml.h,  $P = 0.069$ ) and  $C_{48h}$  (0.06 vs. 0.07 µg/ml,  $P = 0.63$ ). Although patients with CD4 cell counts of  $<200$  cells/mm<sup>3</sup> had lower  $C_{max}$  (0.33 vs. 0.42 µg/ml),  $C_{48h}$  (0.04 vs. 0.11 µg/ml) and  $AUC_{0-24}$  (3.66 vs. 4.95 µg/ml.h) than those with CD4 cell counts of  $>200$  cells/mm<sup>3</sup>, the differences were not significant. Positive significant correlations between CD4 cell counts and  $C_{max}$  ( $r = 0.51$ ,  $P = 0.044$ ,



**Figure** Distribution of peak (A) and trough (B) concentrations of RBT in 16 patients. Solid line = therapeutic range of RBT (0.3–0.8 µg/ml); dashed line = MIC of RBT (0.06 µg/ml) for *M. tuberculosis*. RBT = rifabutin; MIC = minimum inhibitory concentration.

$C_{48h}$  ( $r = 0.71$ ,  $P = 0.002$ ) and  $AUC_{0-24}$  ( $r = 0.55$ ,  $P = 0.028$ ) were observed. A significant positive correlation between RBT and RTV  $C_{max}$  was also observed ( $r = 0.72$ ,  $P = 0.002$ ). Multiple regression analysis by the backward elimination method showed that sex and CD4 cell counts significantly influenced RBT  $C_{max}$  ( $P = 0.008$  and  $0.024$ , respectively,  $R^2 = 0.65$ ).

Anti-tuberculosis treatment outcomes were known in 14 of the 16 patients: one patient could not be traced and treatment was ongoing in one patient. Of the 14 patients, 4 died and the remaining 10 patients had a favourable response as evidenced by end-of-treatment smears negative for TB. RBT  $C_{max}$  in these four patients were 0.06, 0.17, 0.31 and 0.16  $\mu\text{g/ml}$ , while  $C_{48h}$  was below the limit of quantitation ( $<0.025$   $\mu\text{g/ml}$ ) in all patients. The median  $C_{max}$  of the four patients who died was 0.17  $\mu\text{g/ml}$  compared to 0.42  $\mu\text{g/ml}$  in the 10 patients who had a favourable outcome; this difference was statistically significant ( $P = 0.024$ ).

## DISCUSSION

This observational pharmacokinetic study in HIV-infected patients with TB from India has shown that RBT  $C_{max}$  levels were below the therapeutic range ( $<0.3$   $\mu\text{g/ml}$ ) in 44% of the patients; the median  $C_{max}$  was 0.33  $\mu\text{g/ml}$ , which was quite close to the lower end of the therapeutic range. Using a higher cut-off ( $<0.5$   $\mu\text{g/ml}$ ), as reported by Khachi et al.,<sup>14</sup> 13/16 patients (81.2%) would have suboptimal RBT peak levels. None of the patients had a  $C_{max}$  exceeding the therapeutic range, and none had adverse events that required the modification or discontinuation of RBT. Previous reports have documented an increased adverse event profile when RBT and boosted PIs were co-administered.<sup>17,22</sup> Increased RBT dose could produce higher plasma RBT concentrations, potentially increasing the likelihood of toxic events.<sup>22</sup> We observed that 10/16 patients (63%) had  $C_{48h}$  below the MIC of the drug; five patients had undetectable RBT at this time point. As we did not determine the MIC of the *M. tuberculosis* isolates of individual patients, it is not possible to know the exact number of patients who had  $C_{48h}$  below the MIC. Furthermore, it is quite possible that some of the patients had rifamycin resistance at the start of treatment, and hence a different RBT MIC. Nonetheless, the RBT trough concentrations below the MIC in a significant number of patients are a matter of concern. Low RBT levels in all the four patients who died suggest that this may be an important determinant of anti-tuberculosis treatment outcome. An association between low plasma RBT concentrations and acquired rifamycin resistance has been reported.<sup>23</sup> The adequacy of the existing RBT dose of 150 mg thrice weekly during concomitant RTV administration recommended globally and by the RNTCP in India is thus questionable.

Furthermore, RBT is generally prescribed to patients who have failed first-line ART; such patients are most likely to be at an advanced stage of the disease, with low CD4 cell counts. HIV infection has been reported to adversely impact anti-tuberculosis drug levels.<sup>24</sup> In view of the significant correlations observed between  $C_{max}$ ,  $C_{48h}$  and  $AUC_{0-24}$  of RBT and CD4 cell counts, one might consider increasing the RBT dose. A significant positive correlation between RBT and RTV  $C_{max}$ , though unclear, further highlights the need to consider increasing RBT doses.

Reports available on the issue of RBT dosing during RTV co-administration are contradictory. While studies undertaken in healthy subjects suggest that a RBT dose of 150 mg on alternate days, thrice weekly or every 4 days is adequate,<sup>16-19</sup> those conducted in patients have reported that the intermittent dose of 150 mg RBT produced suboptimal drug levels and could be inadequate, and recommend a daily dose of 150 mg.<sup>13-15</sup> However, none of these studies have associated sub-therapeutic RBT levels with anti-tuberculosis treatment outcomes. Relapses with rifamycin-resistant *M. tuberculosis* infection following treatment with RBT 150 mg thrice weekly suggest that the RBT dose should be increased.<sup>25</sup> It is therefore important to plan prospective studies with long-term follow-up that would also periodically monitor RBT concentrations.

Some limitations of the study were the small sample size and the lack of RBT metabolite measurements. Although RTV increases the formation of the primary metabolite, desacetyl RBT,<sup>13</sup> the latter is reported to account for only ~10% of the in vivo antimicrobial activity of RBT.<sup>19</sup> Individual MICs of patient isolates and correlations between blood levels and treatment outcomes were not determined. There is a paucity of pharmacokinetic data on RBT in children. The only available report from six HIV-infected children with TB, in whom a dose of RBT 5 mg/kg thrice weekly was used, observed that two of the children developed grade 4 neutropenia and that the study had to be halted.<sup>26</sup>

In summary, this study has shown that thrice-weekly 150 mg RBT produces trough concentrations below the MIC in a high proportion of patients. This could lead to the development of drug resistance and poor treatment outcomes. More prospective studies in different settings are required to ascertain the optimal dose of RBT for use during RTV co-administration. Pharmacokinetic studies of RBT in the paediatric age group are also required.

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Conflict of interest: none declared.

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## R É S U M É

**CONTEXTE :** On a signalé que la rifabutine (RBT) est un agent aussi efficace que la rifampicine contre la tuberculose et qu'elle induit un effet moindre sur les enzymes cytochromes P450. La dose optimale de RBT au cours d'une co-administration avec le ritonavir (RTV) reste l'objet de débats.

**OBJECTIF :** Etudier la pharmacocinétique de la RBT à raison de 150 mg trois fois par semaine pendant une administration concomitante d'atazanavir/RTV chez des patients TB infectés par le virus de l'immunodéficience humaine (VIH).

**MÉTHODES :** Cette étude observationnelle a été menée chez 16 patients TB adultes infectés par le VIH et traités pour la TB par un régime contenant de la RBT et par un régime de traitement antirétroviral contenant du RTV,

la dose de RBT étant de 150 mg trois fois par semaine. Des prélèvements de sang en série ont été réalisés avant l'administration du médicament et 1, 2, 4, 6, 8, 12 et 24 h après celle-ci. La RBT plasmatique a été estimée par chromatographie liquide à haute performance.

**RÉSULTATS ET CONCLUSIONS :** Chez 7 patients, le pic de concentration du RBT a été inférieur à la limite thérapeutique inférieure ( $<0,3 \mu\text{g/ml}$ ), alors que les concentrations les plus basses en dessous de la concentration minimale inhibitrice contre *M. tuberculosis* ( $0,06 \mu\text{g/ml}$ ) existaient chez 10 patients, ce qui suggère que le dosage de la RBT pourrait avoir été inadéquat. Des études prospectives s'imposent dans différents contextes pour déterminer la dose thérapeutique adéquate de RBT à utiliser au cours d'une co-administration de RTV.

## R E S U M E N

**MARCO DE REFERENCIA:** Se ha comunicado que la rifabutina (RBT) es tan eficaz contra la tuberculosis (TB) como la rifampicina y que induce menos efectos sobre las enzimas de la familia del citocromo P450. La dosis óptima de RBT en su administración asociada con el ritonavir (RTV) sigue siendo fuente de controversia.

**OBJETIVO:** Evaluar las características farmacocinéticas de la RBT en dosis de 150 mg tres veces por semana, durante la administración concomitante de atazanavir o RTV en los pacientes tuberculosos coinfectados por el virus de la inmunodeficiencia humana (VIH).

**MÉTODOS:** El presente estudio observacional se llevó a cabo en 16 pacientes adultos coinfectados por el VIH y la TB, quienes recibían tratamiento antituberculoso con un protocolo que comportaba RBT y tratamiento antirretrovírico con RTV; la dosis de RBT era 150 mg tres

veces por semana. Se obtuvieron muestras seriadas de sangre antes de recibir la dosis de medicamentos y 1, 2, 4, 6, 8, 12 y 24 h después. Se determinó la concentración plasmática de RBT por cromatografía líquida de alta eficiencia.

**RESULTADOS Y CONCLUSIONES:** En siete pacientes, la concentración máxima de RBT estuvo por debajo del límite terapéutico inferior ( $<0,3 \mu\text{g/ml}$ ) y en 10 pacientes las concentraciones valle eran inferiores a la concentración inhibitoria mínima contra *M. tuberculosis* ( $0,06 \mu\text{g/ml}$ ), lo cual indica que la dosis de RBT puede ser inadecuada. Se precisa realizar estudios prospectivos en diferentes entornos, con el fin de definir las dosis terapéuticas apropiadas de RBT cuando se administra concomitantemente con RTV.