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ARTICLE

No implication of HIV coinfection on the plasma exposure to rifampicin, pyrazinamide, and ethambutol in tuberculosis patients

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Abstract

There are contrasting findings regarding the effect of HIV on the pharmacokinetics of first-line anti-tubercular drugs (FLATDs) due to a lack of prospective controlled clinical studies, including patients with tuberculosis (TB) and patients with TB living with HIV. This study aims to assess the effect of HIV coinfection and antiviral therapy on the plasma exposure to FLATDs in patients with TB. HIV negative (TB-HIV− group; $n = 15$) and HIV positive (TB-HIV+ group; $n = 18$) adult patients with TB were enrolled during the second month of FLATDs treatment. All TB-HIV+ patients were on treatment with lamivudine, tenofovir (or zidovudine), and raltegravir (or efavirenz). Serial blood sampling was collected over 24 h and FLATDs pharmacokinetic parameters were evaluated using noncompartmental methods. In the TB-HIV+ patients, dose-normalized plasma exposure area under the curve from zero to 24 h ($nAUC_{0-24}$; geometric mean and 95% confidence interval [CI]) values at steady-state to rifampicin, pyrazinamide, and ethambutol were 18.38 (95% CI 13.74–24.59), 238.21 (95% CI 191.09–296.95), and 18.33 (95% CI 14.56–23.09) μg·h/ml, respectively. Similar plasma exposure was found in the TB-HIV− patients. The geometric mean and 90% CI of the ratios between TB-HIV− and TB-HIV+ groups suggest no significant pharmacokinetic interaction between the selected antivirals and FLATDs. Likewise, HIV coinfection itself does not appear to have any effect on the plasma exposure to FLATDs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

First-line anti-tubercular drugs (FLATDs) plasma exposure is an important variable of tuberculosis (TB) outcome; however, there are contrasting findings regarding the effect of HIV on the pharmacokinetics of FLATDs due to a lack of prospective controlled clinical studies, including HIV positive and HIV negative patients with TB.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluates the effect of HIV coinfection on the pharmacokinetics of rifampicin, pyrazinamide, and ethambutol in patients who are on stable therapy in the second month of FLATDs treatment.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study shows no evidence that the pharmacokinetics of rifampicin, pyrazinamide, and ethambutol in patients with TB are affected by HIV coinfection or by any of the standard of care HIV comedications allowed in the study (lamivudine, zidovudine, tenofovir, efavirenz, or raltegravir).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

HIV coinfection does not require dose adjustment of rifampicin, pyrazinamide, and ethambutol in patients with TB.

INTRODUCTION

Tuberculosis (TB) is a global emergency and is one of the 10 major causes of death in the world. It is the leading cause of death from a single infectious agent. In 2019, 10 million people were diagnosed with TB, a number that has been relatively stable in recent years; 1.41 million people died of TB. Moreover, TB is a leading cause of death in patients coinfected with HIV (0.208 million deaths in 2019).[1]

In 2015, there were 2.1 million new HIV infections worldwide resulting in a total of 36.7 million people living with HIV globally. The risk of developing TB is 17- to 22-fold higher for people living with HIV, making HIV the most important predisposing factor for TB.[2,3] TB and HIV act synergistically on the decline of the host immune response, which is fatal if left untreated.[4,5]

Current TB treatment consists of a 2-month period with four first-line anti-tubercular drugs (FLATDs): rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (ETB) followed by 4 months of RIF and INH.[6,7] This treatment was developed over 40 years ago based on empirical evidence without taking into account the relevance to fluctuations in plasma exposure to FLATDs.[8] In fact, high variability in pharmacokinetics has been reported for FLATDs, with patients who are exposed to lower drug levels being at a potentially higher risk of treatment failure.[9–14] In addition, given the broad spectrum of antiretroviral therapy (ARVT), there is no consensus regarding the need for dose adjustment for FLATDs regimens in HIV coinfected patients.[8,15–21]

It is important to highlight that the chronic or persistent inflammatory status observed in patients with TB and HIV receiving ARVT may result in changes in alpha-1-acid glycoprotein and albumin levels in plasma, as well as increased expression of ABCB1/P-gp or decreased expression of MRP2; ABCC2 and BCRP/ABCG2.[22,23] Such changes can potentially affect the tissue distribution as well as the systemic exposure to FLATDs.

RIF-associated drug interactions should be observed when selecting the ARVT drug regimen.[24] Nucleoside reverse transcriptase inhibitors, such as tenofovir disoproxil fumarate and lamivudine, can be given together with RIF treatment without dose adjustment. Raltegravir plasma concentrations are significantly decreased when co-administered with RIF[25] requiring dose adjustment to 800 mg twice daily. However, conflicting data have been observed in the magnitude of changes in efavirenz plasma concentrations when associated to RIF.[26,27]

Although the treatment of HIV infection has evolved with the approval of novel drugs over the last decade, the consequence of potential pharmacokinetic and/or pharmacodynamic interaction of these new therapies with FLATDs has not been fully characterized or embedded into current guidelines for the treatment of TB. In addition, there has been no specific evaluation of the effect of HIV coinfection on the disposition of FLATDs in patients with TB.[8,15–21] Instead of attempting to further characterize the implications of such interactions, clinical trials exclude patients with HIV who are TB coinfected. Similarly, HIV positive patients with TB are excluded from TB drug trials. These exclusion criteria overlook the prevalence of TB and HIV coinfection.

Even though in vitro techniques are now available and can be used to describe and predict the potential for drug-drug interactions, such data do not allow for an assessment of the potential implications of HIV coinfection on the disposition of FLATDs. In addition, reported data collected from real-life settings are fraught with confounders, such as episodes of vomiting or diarrhea in patients with TB receiving ARVT.

To date, very few controlled studies have been performed to establish the interaction between HIV coinfection and FLATDs pharmacokinetics.[16] In fact, contrasting

reports are available regarding the effect of HIV on FLATDs pharmacokinetics.[28–32] Here, we aim to evaluate the effect of HIV coinfection on the pharmacokinetics of RIF, PZA, and ETB in patients who are on stable therapy in the second month of TB treatment. We focus on standard of care ARVT for patients with TB and HIV, as recommended by local and international guidelines, which includes lamivudine, zidovudine (or tenofovir), and raltegravir (or efavirenz).[6,7]

METHODS

Clinical trial

The study protocol was approved by the local Hospital Research Ethics Committee (CEP/FCFRP no.: 405, Process number: 032398/2016), and all patients signed the informed consent form. This investigation was conducted in accordance with the Declaration of Helsinki and national and institutional standards.

The sample size was calculated using the Power and Sample Calculation program version 3.1.6 (Department of Biostatistics, Vanderbilt University, Nashville, TN). Based on previous FLATDs pharmacokinetics data in patients with TB (area under the plasma concentration–time curve [AUC] mean ± SD = 29.8 ± 13.8 μg·h/ml for RIF, 489.5 ± 126.0 μg·h/ml for PZA, and 19.2 ± 5.6 μg·h/ml for ETB),[33] we estimated that the inclusion of 15 patients with TB and 15 patients with TB and HIV would result in a test power greater than 80% to detect a difference of 50% between groups.

To ensure steady-state conditions, we enrolled patients with TB and diagnosed negative for HIV (TB-HIV− group; $n = 15$) and patients with TB and diagnosed positive for HIV (TB-HIV+ group; $n = 18$) after they had started the second month of therapy with FLATDs. All patients were treated with coated tablets containing RIF 150 mg, INH 75 mg, PZA 400 mg, and ETB 275 mg (Fundação Osvaldo Cruz-Farmanguinhos, Rio de Janeiro, RJ, Brazil) according to their body weight. They received two (20–35 kg), three (36 a 50 kg), or four (> 50 kg) tablets daily according to World Health Organization guidelines[6,7] (Tables 1S1 and 2S1). In addition, the TB-HIV+ patients were receiving lamivudine, tenofovir (or zidovudine), and raltegravir (or efavirenz; see Table 2S1 for further details). All patients were aged between 18 and 60 years, were nonobese, and had no other comorbidities. None of the patients presented diarrhea or vomiting in the previous days and during the study. Serial blood samples were collected over 24 h at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 15, 18, 21, and 24 h after FLATDs administration. The blood samples were centrifuged immediately after collection, and the plasma aliquots were stored at −80°C until analysis.

Liver, kidney, and cardiac functions as well as metabolic markers were assessed by standard hematology and biochemistry tests (Table 3S1). All patients were also diagnosed as sensitive to RIF by MTBDR-plus genotyping (Hain Lifescience, GmbH, Germany) for the screening of RIF-resistant *M. tuberculosis* strains.[34]

Analysis of the antibiotics in plasma

A liquid chromatography-tandem accurate mass spectrometry (LC-MS/MS) method was developed and validated to determine RIF, 25-O-deacetyl-rifampicin (desRIF), PZA, and ETB in plasma with low limits of quantification. Full details of the method development and validation are described in the Supplementary Material S2. The coefficients of variation (CV) and relative standard errors (RSE) for intra- and interassays' precision and accuracy were lower than 15%. The lower limit of quantification values and upper boundary of the linearity range were 1.22–5000, 1.95–1000, 0.61–2500, and 78.12–40000 ng/ml for RIF, desRIF, ETB, and PZA, respectively (Table 3S2).

Pharmacokinetic and statistical evaluation

The pharmacokinetics of RIF, desRIF, PZA, and ETB were derived from the plasma concentrations versus time curves during one dosing interval (0–24 h) using noncompartmental analysis (Phoenix WinNonLin, version 7.0). The following pharmacokinetic parameters were calculated: area under the plasma concentration vs. time curve within a dose interval of 24 h ($AUC_{0–24}$), maximum observed plasma concentration within the dose interval (C_{max}), time corresponding to the maximum observed plasma concentration (T_{max}), average plasma concentration at steady-state ($C_{ss} = AUC_{0–24}$/dose interval of 24 h), apparent clearance ($CL/F = dose/AUC_{0–24}$), apparent volume of distribution ($V/F = dose/AUC_{0–24}·Kel$), where Kel means the constant rate of elimination ($Kel = 0.693/t_{1/2}$) and terminal half-life of elimination ($t_{1/2}$).

The influence of HIV coinfection on plasma exposure to RIF, desRIF, PZA, and ETB was evaluated by comparing the pharmacokinetics parameters by a *t*-test ($p < 0.05$) and by the geometric mean and 90% confidence interval (CI) of the ratios between the TB-HIV− and TB-HIV+ patients.

RESULTS

Patient characteristics

This study included TB-HIV+ ($n = 18$) and TB-HIV− ($n = 15$) patients. All the TB-HIV+ patients were under ARVT

(Tables 1S1 and 2S1). The groups were matched by age and sex, and although the body weight of the TB-HIV+ patients was lower ($p < 0.05$; *t*-test) compared to the TB-HIV− patients, none were considered obese. An overview of the baseline demographic characteristics and clinical laboratory tests is shown in Tables 1S1–3S1. All blood samples were collected at the planned sampling time. In addition, none of the patients presented diarrhea or vomiting during the study.

According to data shown in Table 3S1, all investigated TB-HIV+ patients presented CD4 lymphocytes lower than 460 cells/mm,^{3} and only four presented values higher than 200 cells/mm^3. However, among the 18 TB-HIV+ patients investigated, 11 had undetected viral load, and the other seven had the $\log_{10}$ viral load ranging from 1.60 to 6.26. All investigated TB-HIV+ patients were under ARVT, and had no other comorbidities or complaints of gastrointestinal disorders or opportunistic infection other than TB.

Pharmacokinetics

All blood samples contributed for the pharmacokinetic analysis. No samples were below the lower limit of quantification for any of the analytes. The time course of RIF, PZA, and ETB, and desRIF metabolite concentrations in plasma was described over the period of 24 h. Figure 1 shows the geometric mean and 95% CI for both the TB-HIV− ($n = 15$) and TB-HIV+ ($n = 18$) groups.

The pharmacokinetic parameters of each drug and desRIF are presented in Table 1 as geometric mean and 95% CI. Given the use of different doses based on body weight, dose-normalized estimates were derived to allow direct comparison of pharmacokinetic parameters across the two groups. AUC_{0-24}, C_{max}, and C_{ss} values were dose-normalized to the doses of 600, 1600, and 1100 mg of RIF, PZA, and ETB, respectively.

The difference of AUC_{0-24} geometric means between groups were lower than 20% (1.06 [$p = 0.60$], 1.10 [$p = 0.63$], 1.07 [$p = 0.24$], and 1.09 [$p = 0.72$] of RIF, desRIF, PZA, and ETB). However, considering a difference of 20%, the post-study significance level between the TB-HIV− and TB-HIV+ groups would be 0.023, 0.022, 0.036, and 0.012 with power of 80% to RIF, desRIF, PZA, and ETB, evidencing that the analysis was enough powered.

The pharmacokinetic parameters did not differ between the TB-HIV− and TB-HIV+ groups ($p > 0.05$; Table 1). Besides, the ratios between the TB-HIV+/TB-HIV− groups of each pharmacokinetic parameter ($nAUC_{0-24}$, CL/F, V/F, nC_{max}, and nC_{ss} expressed as geometric mean (Figure 2) were within the range of 0.8–1.25 assumed to be nonclinically relevant, whereas the 90% CI little exceeded this range.

Linear regression between $nAUC_{0-24}$ versus body weight and nC_{max} versus body weight of FLATDs showed no significant correlation, suggesting that the interindividual variability in the plasma exposure to FLATDs is not primarily correlated with differences in body weight (Figure 3).

DISCUSSION

The effect of HIV infection on the pharmacokinetics of FLATDs remains an important issue, as most clinical trials

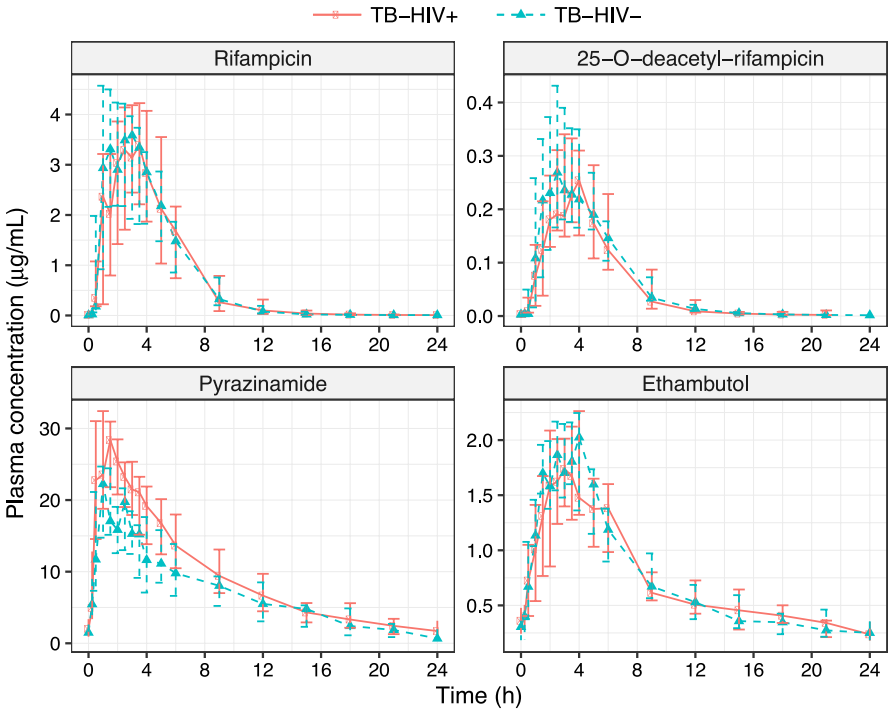

FIGURE 1 Plasma concentrations of the first-line tuberculosis drugs (FLATDs) evaluated in the steady-state during one dose interval (0–24 h) during the second month of tuberculosis (TB) treatment with FLATDs. Data are presented as mean and 95% confidence interval. TB-HIV−, tuberculosis HIV negative patients ($n = 15$) and TB-HIV+, tuberculosis HIV positive patients ($n = 18$).

TABLE 1 Pharmacokinetic parameters of RIF, desRIF, PZA, and ETB in the TB-HIV− ($n = 15$) and TB-HIV+ patients ($n = 18$)

	RIF		desRIF		PZA		ETB	
Parameter	**TB-HIV−**	**TB-HIV+**	**TB-HIV−**	**TB-HIV+**	**TB-HIV−**	**TB-HIV+**	**TB-HIV−**	**TB-HIV+**
nC_{max} (μg/ml)	4.32 (3.47–5.38)	4.13 (3.49–4.88)	0.37 (0.27–0.52)	0.35 (0.28–0.43)	23.43 (17.92–30.65)	30.32 (26.23–35.06)	2.26 (1.75–2.91)	2.03 (1.62–2.55)
T_{max} [a] (h)	1.50 (1.00–2.75)	2.40 (1.50–3.25)	2.50 (2.25–3.25)	3.00 (1.75–3.50)	1.00 (0.50–1.50)	0.75 (0.50–1.50)	3.5 (2.50–4.00)	3.0 (2.00–3.50)
$nAUC_{0-24}$ (μg·h/ml)	19.47 (13.63–27.82)	18.38 (13.74–24.59)	1.74 (1.25–2.44)	1.58 (1.18–2.12)	222.50 (144.46–342.70)	238.21 (191.09–296.95)	18.99 (14.11–25.56)	18.33 (14.56–23.09)
nC_{ss} (μg/ml)	0.81 (0.57–1.16)	0.77 (0.57–1.02)	0.07 (0.05–0.10)	0.07 (0.05–0.09)	6.01 (3.47–10.43)	7.26 (5.73–11.41)	0.79 (0.59–1.07)	0.77 (0.61–0.96)
CL/F (L/h)	30.81 (21.57–44.02)	32.64 (24.40–43.67)	–	–	8.65 (6.43–11.63)	7.20 (5.84–8.88)	57.91 (43.03–77.94)	59.80 (47.54–75.22)
V/F (L)	91.21 (63.18–131.69)	103.06 (77.13–137.71)	–	–	69.04 (55.59–85.75)	57.09 (43.68–74.61)	720.95 (610.28–851.68)	743.80 (518.07–967.88)
t1/2 (h)	2.05 (1.96–2.15)	2.19 (1.99–2.40)	2.26 (2.08–2.46)	2.11 (1.81–2.46)	5.19 (4.20–6.42)	5.25 (4.19–6.44)	9.75 (8.43–11.28)	8.33 (6.84–10.13)

Note:: No $p < 0.05$ differences were found between TB-HIV− and TB-HIV+ groups by *t*-test. The $nAUC_{0-24}$, nC_{max}, and nC_{ss} values were dose-normalized to 600 (RIF), 1600 (PZA), and 1100 (ETB) mg. Data presented as geometric mean and 95% confidence interval.

Abbreviations: CL/F, apparent total clearance; desRIF, 25-O-deacetyl-rifampicin; ETB, ethambutol; $nAUC_{0-24}$, dose-normalized area under the plasma concentration versus time curve during a dose interval (0–24 h); nC_{max}, dose-normalized maximum plasma concentration; nCss, dose-normalized stead-state average concentration; PZA, pyrazinamide; RIF, rifampicin; *t1/2*, terminal half-life; TB-HIV−, tuberculosis HIV negative patients; TB-HIV+, tuberculosis HIV positive patients; T_{max}, time to reach C_{max}; V/F, apparent volume of distribution.

[a]T_{max} are presented as median and 27–75 percentile.

with new antiretrovirals continue to exclude TB-infected patients and trials with novel anti-tubercular drugs exclude TB-HIV+ patients.[35,36] The use of such exclusion criteria persists despite the evidence that both prevalence and incidence of HIV and TB coinfection has increased considerably over the last decade.[1] Previous reports have emphasized the need to evaluate the potential implications of such an interaction in prospective controlled studies.[16] In this study, we have been able to identify a cohort of TB-infected patients, who had no other comorbidities, except for the use of ARVT in the case of patients of the HIV-TB+ group.

PZA is a prodrug that undergoes activation by *M tuberculosis* nicotinamidase/pyrazinamidase, as well as, by liver amidases to generate the active metabolite pyrazinoic acid, which is primarily eliminated by the liver xanthine oxidase to 5-hydroxypyrazinoate.[37] ETB diffuses into actively growing Mycobacterium cells and reaches the highest concentrations in erythrocytes, kidneys, lungs, and saliva. Approximately 20% of ETB is metabolized by alcohol and aldehyde dehydrogenases to the dialdehyde and dicarboxylic acid metabolites, whereas unchanged ETB is excreted in urine (nearly 50%) by glomerular filtration and in feces (nearly 20%).[38] RIF is a strong potent inducer of CYP isoforms (2B6, 2C8, 2C9, 2C19, 2D6, and 3A4), aldehyde dehydrogenases, UDP-glucuronosyltransferases (UGTs), sulfonyl transferases, glutathione-S-transferases (GSTs), P-gp, and MRP2.[39,40] RIF increases intestinal P-gp abundances three to fourfold with minimal impact on renal P-gp and reduces the exposure of the P-gp substrates when administered orally.[40] RIF is metabolized by carboxylesterase 2 (CES2) and is an organic anion transporting polypeptide 1B1 (OATP) substrate.[41,42]

Raltegravir and zidovudine are predominantly metabolized by UGTs.[43] Raltegravir is not a substrate, inducer, or inhibitor of CYP isoforms, P-gp and OATP1B1, whereas zidovudine is a substrate and a possible inhibitor of MRP4, MRP5, and BCRP.[44,45] Tenofovir is a substrate of P-gp and BCRP and possibly an inhibitor of MRP1, MRP2, and MRP3.[43,45] Efavirenz, a CYP3A and BCRP inducer,[39,45] is metabolized mainly by CYP2B6 and to a lesser extent by CYP2A6 and UGT2B7.[43] Lamivudine, a P-gp and an organic cation transport protein (OCT) substrate, is mainly eliminated unchanged by glomerular filtration and tubular secretion dependent on P-gp, and OCT.[43,45,46]

Therefore, it can be noticed that RIF, PZA, and ETB are not mainly metabolized by CYP isoforms and are not known to be important P-gp, MRP, or BCRP substrates.[37–46] Accordingly, the antiretroviral drugs have minimal potential to influence the plasma exposure to FLATDs.[26,32,33,47]

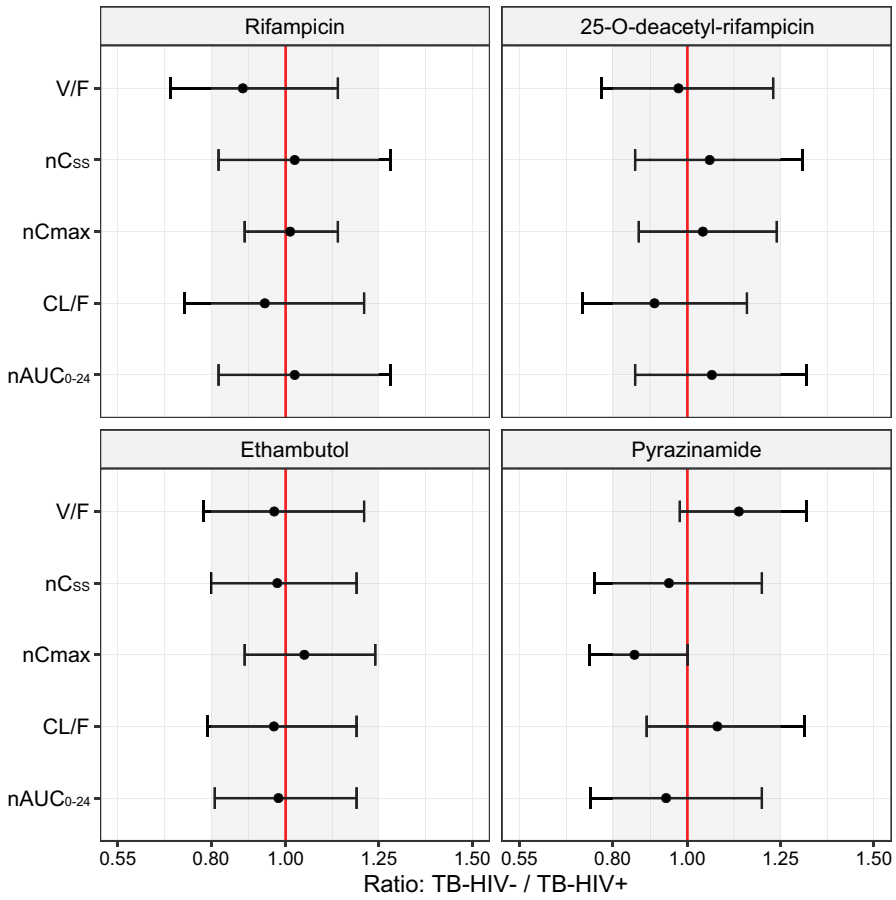

FIGURE 2 Pharmacokinetics parameters ratios between TB-HIV− (tuberculosis HIV negative patients, $n = 15$) and TB-HIV+ (tuberculosis HIV positive patients, $n = 18$) of rifampicin, 25-O-deacetyl-rifampicin, pyrazinamide, and ethambutol. Data are expressed as geometric mean and 90% confidence interval. Grey rectangle indicates a bioequivalence range of 0.8–1.25. CL/F, apparent total clearance; $nAUC_{0-24}$, dose-normalized area under the plasma concentration versus time curve during one dose interval (0–24 h); nC_{max}, dose-normalized maximum plasma concentration; nC_{ss}, dose-normalized stead-state average plasma concentration; V/F, apparent volume of distribution

López-Cortés et al.[26] and Sundell et al.[47] reported, respectively, that the plasma exposure to RIF and PZA did not change when co-administered with efavirenz in TB-HIV+patients, suggesting that rifampicin and PZA could be used with efavirenz without dosage adjustment. Török et al.[33] also showed that the pharmacokinetics of RIF, isoniazid, PZA, and ETB were not changed by the ARVT constituted by zidovudine, lamivudine, and efavirenz in TB-HIV+ patients with tuberculous meningitis.

Given that standard of care drugs for the treatment of HIV are known to have limited potential of influence the plasma exposure to FLATDs[26,32,33,37–47] and no patients had a history of diarrhea or vomiting episodes during and in the days preceding the clinical trial, the main difference between the TB-HIV+ and TB-HIV− patients in our study was HIV coinfection. Besides that, there was no difference in the pharmacokinetics parameters of RIF, desRIF, PZA, and ETB in the TB-HIV+ group between the patients treated with efavirenz or raltegravir (see multivariate analysis of variance [ANOVA] in Supplementary S1).

Our results show that the plasma exposure to RIF, PZA, and ETB is similar between the TB-HIV+ and TB-HIV− groups (Table 1), suggesting that HIV coinfection itself does not affect the kinetic disposition of RIF, PZA, and ETB. Similar findings were described by van Oosterhout et al.[31] in Malawi patients, whereas Rockwood et al.[32] reported higher plasma exposure to RIF in the TB-HIV+ patients from South Africa. On the other hand, Gurumurthy et al.[28] and Sahai et al.[12] reported lower RIF plasma exposure in TB-HIV+ patients that experienced diarrhea compared to the TB-HIV− patients (AUC_{0-24} ratios ≤0.8), although the authors did not provide details about the ARVT used.

Despite such contrasting findings, it is worth mentioning that Chideya et al.[48] found decreased RIF C_{max} values in TB-HIV+ patients who reported diarrhea, but were not receiving ARVT, whereas Requena-Méndez et al.[49] described no change in RIF C_{max} values in TB-HIV+ patients who were not receiving ARVT and did not have diarrhea. A careful review of these results suggests that reported changes in the plasma exposure to RIF in TB-HIV+ patients may be determined by diarrhea or vomiting episodes, rather than by metabolic induction or another mechanism of drug-drug interaction.

In this study, dose-normalized values of RIF $nAUC_{0-24}$ in the TB-HIV− (19.47 μg·h/ml) and TB-HIV+ (18.38 μg·h/ml; Table 1) groups were similar (16.6–36.0 μg·h/ml) to those reported by McIlleron et al.[29] in TB-HIV− and TB-HIV+ patients receiving 10.9 mg RIF/kg and higher than those reported by Pasipanodya et al.[50] in patients with poor long-term outcomes (≤13 μg·h/ml). By contrast, our results are significantly lower than the

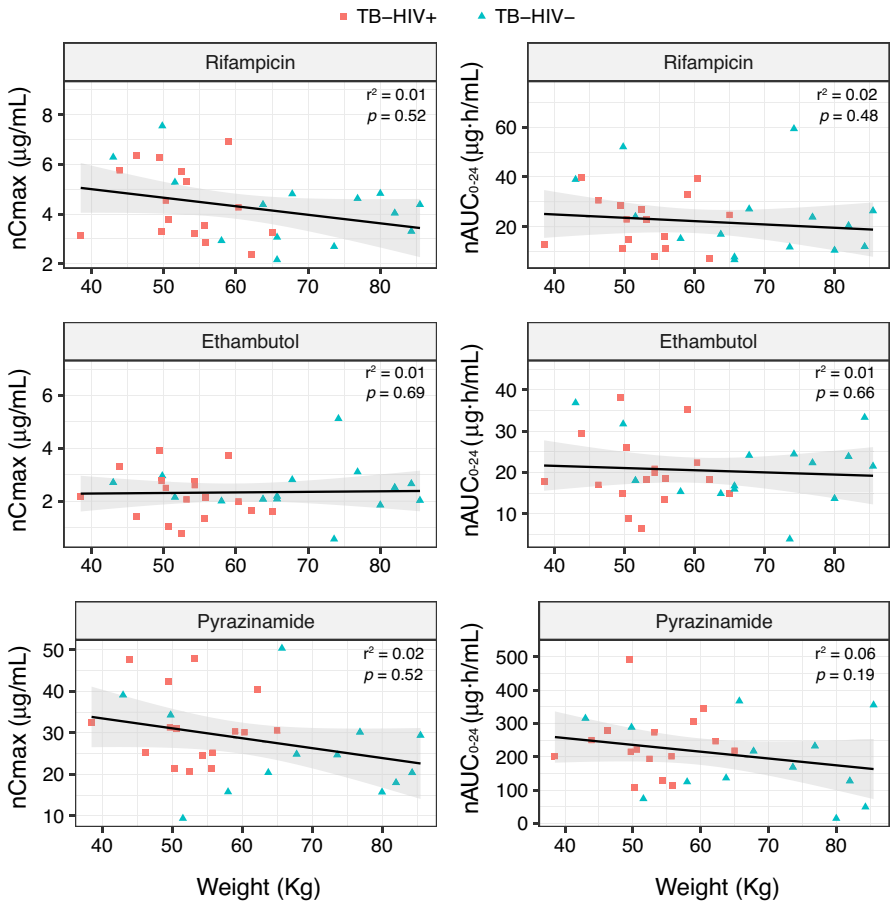

FIGURE 3 Linear regression between nC_{max} and $nAUC_{0–24}$ versus body weight (40–85 kg) for rifampicin, ethambutol, and pyrazinamide including all included patients ($n = 33$). $nAUC_{0–24}$, dose-normalized area under the plasma concentration vs time curve during one dose interval (0–24); nC_{max}, dose-normalized maximum plasma concentration; TB-HIV−, tuberculosis HIV negative patients ($n = 15$); TB-HIV+, tuberculosis HIV positive patients

$AUC_{0–24}$ values reported by Gurumurthy et al.[28] (36.3–52.9 µg·h/ml) in TB-HIV− patients with pulmonary infection receiving 450 mg RIF with no complaints of diarrhea or vomiting or by Muliaditan and Della Pasqua[21] in clinical trial simulations that considers the effect of metabolic autoinduction and body weight ($AUC_{0–24}$ >40 µg·h/ml for patients with weight >50 kg) of TB-HIV− and TB-HIV+ patients with no diarrhea or vomiting treated with 600 mg RIF.[16,21]

Another finding that supports the evidence for a lack of interaction due to HIV coinfection derives from the time course profiles of desRIF. The $AUC_{0–24}$ ratios desRIF/RIF did not differ between the investigated groups (0.089 and 0.086, respectively, for TB-HIV− and TB-HIV+ groups), highlighting that RIF metabolism does not seem to differ between the TB-HIV− and TB-HIV+ patients who do not experience vomiting or diarrhea episodes.

Similar findings were observed for PZA and ETB, providing further evidence for a lack of clinically relevant changes to the plasma exposure to FLATDs due to HIV coinfection.

The plasma exposure to PZA in the TB-HIV+ patients was comparable to that observed in the TB-HIV− patients (238.21 vs. 222.50 µg·h/ml, respectively; Table 1), which is in agreement with previous reports.[29–32] Sundell et al.[47] also reported that PZA plasma exposure did not change between TB-HIV+ patients under ARVT and TB-HIV+ patients who were ARVT naive.

Diverging results have been reported with regard to the effect of HIV coinfection on PZA C_{max}. Sahai et al.[12] reported lower PZA $AUC_{0–24}$ and C_{max} values in TB-HIV+ patients who experienced diarrhea. Similarly, Chideya et al.[48] found a statistically significant reduction of PZA Cmax in TB-HIV+ patients, many of whom were not under ARVT, but experienced diarrhea. In the present study, the nC_{max} values did not differ between TB-HIV+ and TB-HIV− patients, but none experienced diarrhea.

There were no significant differences between $nAUC_{0–24}$ of ETB in TB-HIV+ and TB-HIV− patients (18.33 vs. 18.99 µg·h/ml, respectively; Table 1). These results are in agreement with previous studies,[31,32,48] which have described the pharmacokinetics of ETB in both group of patients. Yet, one study by McIlleron et al.[29] found that the TB-HIV+ patients had slightly lower plasma exposure to ETB (19.2 to 30.8 µg·h/ml), as compared to the control group. Our results are also in agreement with the values reported by Muliaditan and Della Pasqua[21] in clinical trials simulations ($AUC_{0–24}$ = 20–30 µg·h/ml in patients with weight >50 kg receiving 1.1 g ETB).

We acknowledge that our study has some important limitations. First is the lack of data on the pharmacokinetics

of the ARVT administered to the TB-HIV+ patients. We also have not been able to incorporate the potential effect of other covariates that may contribute to the observed interindividual variability, including pharmacogenetic data and larger range of weight as formal covariate on drug disposition parameters. We also realize that the ARVT that were used by the patients included in this study does not allow for wider generalization of the findings and implications for FLATDs dose regimens when other ARVT are used. We have not been able to present the results of INH and its metabolite due to the issues arising with the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) pandemic. Details on the pharmacokinetics of INH and its metabolite will be reported in a future publication.

In summary, our study shows no evidence that the pharmacokinetics of RIF, PZA, and ETB in patients with TB are affected by HIV coinfection or by any of the standard of care HIV comedications allowed in the study (lamivudine, zidovudine, tenofovir, efavirenz, or raltegravir).

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

G.H.B.N., O.D.P., and V.L.L. wrote the manuscript. G.H.B.N., V.R.B., O.D.P., and V.L.L. designed the research. G.H.B.N., A.R., and V.R.B. performed the research. G.H.B.N., O.D.P., and V.L.L. analyzed the data.

DATA AVAILABILITY STATEMENT

Original data are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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