Effect of rifampicin and efavirenz on moxifloxacin concentrations when co-administered in patients with drug-susceptible TB

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Objectives: We compared the pharmacokinetics of moxifloxacin during rifampicin co-treatment or when dosed alone in African patients with drug-susceptible recurrent TB.

Methods: Patients in the intervention arm of the Improving Retreatment Success (IMPRESS) randomized controlled TB trial received 400 mg of moxifloxacin, with rifampicin, isoniazid and pyrazinamide in the treatment regimen. Moxifloxacin concentrations were measured in plasma during rifampicin-based TB treatment and again 4 weeks after treatment completion, when given alone as a single dose. Moxifloxacin concentration–time data were analysed using non-linear mixed-effects models.

Results: We included 58 patients; 42 (72.4%) were HIV co-infected and 40 (95%) of these were on efavirenz-based ART. Moxifloxacin pharmacokinetics was best described using a two-compartment disposition model with first-order lagged absorption and elimination using a semi-mechanistic model describing hepatic extraction. Oral clearance (CL/F) of moxifloxacin during rifampicin-based TB treatment was 24.3 L/h for a typical patient (fat-free mass of 47 kg), resulting in an AUC of 16.5 mg·h/L. This exposure was 7.8% lower than the AUC following the single dose of moxifloxacin given alone after TB treatment completion. In HIV-co-infected patients taking efavirenz-based ART, CL/F of moxifloxacin was increased by 42.4%, resulting in a further 30% reduction in moxifloxacin AUC.

Conclusions: Moxifloxacin clearance was high and plasma concentrations low in our patients overall. Moxifloxacin AUC was further decreased by co-administration of efavirenz-based ART and, to a lesser extent, rifampicin. The clinical relevance of the low moxifloxacin concentrations for TB treatment outcomes and the need for moxifloxacin dose adjustment in the presence of rifampicin and efavirenz co-treatment need further investigation.

Introduction

The WHO recommends moxifloxacin for the treatment of MDR TB1 and it is emerging as a key drug being investigated in shorter, novel drug regimens for the treatment of drug-susceptible and MDR TB.1-3 Moxifloxacin may be used for the treatment of drug-susceptible TB, if intolerance develops to one of the drugs used in standard first-line regimens or in patients with isoniazid monoresistance.4-6

The REMox7 and RIFAQUIN8 studies investigating moxifloxacin-containing regimens for shortening the treatment of drug-susceptible TB to 4 months failed to show non-inferiority for relapse or treatment failure after 18 months of follow up, compared with standard 6 month regimens.7,8 Although there may be several reasons for these results,3,10 given that AUC/MIC is the driver of moxifloxacin efficacy, inadequate moxifloxacin concentrations in plasma and at sites of action against Mycobacterium tuberculosis, using standard 400 mg doses of moxifloxacin, have been...
suggested as a contributing factor. Furthermore, it is unclear whether a known drug interaction with rifampicin results in clinically significant decreases in moxifloxacin plasma concentrations that may have contributed to the outcomes of the REMox clinical trial as no drug concentrations were measured in the REMox study. 

Moxifloxacin is metabolized via glucuronide and sulphate conjugation by the cytosolic enzymes UDP-glucuronosyltransferase (UGT) and sulphotransferase. Moxifloxacin is a substrate of the drug transporter P-glycoprotein, involved in its absorption, distribution and elimination. Previous studies found that rifampicin co-administration decreased moxifloxacin plasma concentrations by up to 31%, 12-15 due to rifampicin induction of glucuronosyltransferase, sulphotransferase and P-glycoprotein. However, rifampicin may also have the paradoxical effect of net inhibition of P-glycoprotein, which may result in higher absorption of co-administered drugs. 16 There are no data in African patients with TB comparing moxifloxacin pharmacokinetics when dosed with or without rifampicin. Variable pharmacokinetics of standard first-line TB drugs have been described in African patients, in whom high levels of host genetic variability in drug-metabolizing and transporter enzymes and co-morbidities, including HIV, may result in suboptimal TB drug concentrations and treatment outcomes. 17-19

In this study, we compared the pharmacokinetics of moxifloxacin when co-administered with rifampicin or dosed alone in African patients with drug-susceptible, recurrent TB, the majority of whom were HIV co-infected and on efavirenz-based ART.

Patients and methods

Study design and setting

We conducted a sequential-design, prospective pharmacokinetic sub-study within the ongoing Improving Retreatment Success (IMPRESS) open-label randomized controlled trial (NCT02114684), from October 2013 in KwaZulu-Natal, Durban, South Africa. The IMPRESS study was designed to determine whether a moxifloxacin-containing regimen, substituting moxifloxacin for ethambutol, of 24 weeks duration is superior to a standard continuation phase of TB treatment. During the intensive phase of treatment, pyrazinamide was used at 1500 and 2000 mg in patients between 38-54 and ≥55 kg, respectively. Patients who remained sputum smear or culture positive continued on pyrazinamide beyond 2 months of treatment, until sputum conversion. After the completion of TB treatment participants were given a single dose of moxifloxacin following a washout period of ~4 weeks. All patients received at least 50 mg of pyridoxine with study drugs. There were no food restrictions in the pharmacokinetic study, although the time of the last meal was recorded in relation to drug dose and pharmacokinetic sample collection.

Follow-up Patients were followed up for 24 months and clinical and safety monitoring was done every 2 months for the first 6 months, or as clinically indicated. Laboratory and safety investigations included haemoglobin as part of a complete blood count, renal and hepatic biochemistry, total protein and albumin determinations, and electrocardiogram monitoring. Sputum smear microscopy and culture were done at predefined timepoints in the study. HIV testing was done monthly in HIV-uninfected patients. HIV RNA viral load [Roche Ampliprep-COBAS Taqman 48 Analyzer platform (Roche Molecular Diagnostics)] and CD4+ T cell count (FACSCalibur flow cytometer, Becton Dickinson Bioscience) were determined annually and viral load at 6 months. Adherence to TB treatment was measured using pill count, based on the number of tablets dispensed, physically returned, reported remaining or lost, as well as participant self-report of missed or incomplete doses in the 4 days prior to the day of study visit or pharmacokinetic sampling. HIV co-infected patients received standard first-line ART containing efavirenz, emtricitabine and tenofovir. Treatment and prophylaxis for opportunistic infections and concomitant treatment used was recorded on case report forms. Patients requiring iron- or zinc-containing supplements or aluminium- and magnesium-containing antacids, known to affect the pharmacokinetics of moxifloxacin, 20,21 were counselled to take these at least 2-4 h before or after moxifloxacin dosing. Information relating to timing of dose for all drugs with known interaction potential with moxifloxacin was recorded on case report forms.

Pharmacokinetic sample collection

Plasma samples were collected prior to drug dose and at 2.5, 6 and 24 h after dose at months 1 and/or 2 during the intensive phase of TB treatment, at month 6 during the continuation phase of TB treatment and ~4 weeks after the completion of TB treatment following a single dose of moxifloxacin. Plasma, collected in EDTA tubes, was centrifuged at 3000 rpm, placed on ice and immediately sent to the CAPRISA laboratory, to be stored in cryovials at −80°C within 1 h of collection. Moxifloxacin concentrations were quantified in clinical plasma samples using validated HPLC-MS/MS at the KwaZulu-Natal Research Institute for Tuberculosis and HIV (KRITH) pharmacology laboratory. The bioanalytical method was developed and validated according to FDA guidelines (2011). 22 Sample preparation included protein precipitation with acetonitrile and subsequent dilution with water. Chromatographic separation was achieved using a Zorbax C18, 3.5 μm, 50 mm × 2.1 mm column and detection with an ABI Sciex 5500 QTrap mass spectrometer operated in positive mode. The following transitions were used; precursor ion → product ion (all in units of m/z): moxifloxacin, 402.1 → 358.2 and 402.1 → 364.1. The internal standard used was ciprofloxacin: 331.6 → 231.0 and 331.6 → 288.1. Moxifloxacin was analysed isocratically with a 22% acetonitrile/water/0.1% formic acid mobile phase. The injection volume was 2 μL and the total analytical run time was 5 min. The method was validated over the concentration range of 50–5000 ng/mL. Overall precision, based on quality control samples evaluated at low, medium and high concentrations, during the validation and analysis of samples ranged from 8.4% to 19.4% and accuracy ranged from 101.9% to 105%. Calculated carry-over at the lower limit of quantification (LLOQ) was 5.4%. The LC-MS/MS system was interfaced with a Dell® Windows® 7 computer running Analyst® software version 1.6.2, used for chromatographic data acquisition, peak integration and quantification of analytes.
Effect of rifampicin and efavirenz on moxifloxacin concentrations

**Ethics**
Ethics approval for the study was provided by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BFC029/13) and the Medicines Control Council of South Africa (MCC Ref:20130510).

**Statistical analysis**
The moxifloxacin concentration–time data were analysed using non-linear mixed-effects (NLME) modelling, implemented with the software NONMEM (version 7.3). Perl-speaks-NONMEM, Xpose and Pirana were used for model diagnostics and to track model development. Additional plots and post-modelling analysis were performed in R software via the RStudio interface.

A stepwise modelling approach was employed by starting with a structural model to describe drug absorption, distribution and elimination processes and then exploring the effect of covariates such as weight, age, sex, rifampicin-based treatment, concurrent ART, adherence to TB treatment, intake of iron and/or magnesium and renal and hepatic function. In particular, for moxifloxacin, the effects of rifampicin co-administration on CL, absorption and bioavailability were investigated.

The tested structural models included one- and two-compartment disposition kinetics with first-order elimination or a semi-mechanistic model describing the effect of the liver both on systemic CL and first-pass extraction. For this latter approach, the moxifloxacin unbound fraction in plasma was assumed to be 50% and a value of 50 L/h was used for hepatic plasma flow in a typical patient. To characterize the absorption process, first-order lagged or transit compartment models were explored. Variability in pharmacokinetic parameters was included, assuming a log-normal distribution to describe changes between patients (between-subject variability (BSV)) and within the same patient but on different dosing occasions (between-occasion variability (BOV)). An adjustment parameter was included in BOV in bioavailability to account for the variability in reported dosing time of the dose administered prior to the pharmacokinetic sampling day. Moxifloxacin concentration data below the nominal LLOQ of the assay were included in the analysis; values <10% of the LLOQ were censored and included by imputing half of the censoring threshold, as suggested by Beal. Combined additive and proportional error model was used to describe the residual unexplained variability, with the additive component bound to be at least 10% of the LLOQ.

Allometric scaling was used to account for the effect of body size on the disposition parameters (the exponent was fixed to 0.75 for clearance and 1 for volume parameters), including hepatic plasma flow in the semi-mechanistic model. Fat-free mass (FFM), and fat mass were calculated based on weight, height and sex as suggested by Janmahasatian et al., and were explored as descriptors of body size along with total body weight, as previously recommended. Covariate effects were evaluated and included if they significantly improved the ability of the model to describe the data. Model improvements were evaluated by inspecting diagnostic plots, including visual predictive checks, and decreases in the objective function value (OFV), which is assumed to have a χ² distribution. Drops of more than 8.4 points for the addition of one parameter were considered significant at P<0.05. Finally, a non-parametric bootstrap with replacement (n = 300) was applied to assess the robustness of the parameter estimates and obtain the 90% CIs.

**Results**

**Baseline characteristics**
Moxifloxacin concentration–time data were available from 58 patients, 209 pharmacokinetic profiles and a total of 822 sampling timepoints. Median weight, FFM and age were 56.9 kg (IQR 51.1–65.2), 46.8 kg (IQR 42.5–50.3) and 37 years (IQR 31–42), respectively. Forty-one (70.7%) patients were male and 42 (72.4%) were HIV co-infected, with 40 (95%) on efavirenz-based ART (Table 1). Of the 209 pharmacokinetic profiles and 822 timepoints available, 204 pharmacokinetic profiles and 739 timepoints were included in the analysis for 58 patients. Reasons for exclusion of pharmacokinetic profiles and time-point data are available in Supplementary data (available at JAC Online).

**Table 1. Baseline characteristics of patients in the IMPRESS intervention arm pharmacokinetic study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result (N = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>37 (31–42)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>41 (70.7)</td>
</tr>
<tr>
<td>Race (black African/Caucasian/coloured), n (%)</td>
<td>56 (96.6)/1 (1.7)/1 (1.7)</td>
</tr>
<tr>
<td>Weight (kg), median (IQR)</td>
<td>56.9 (51.1–65.2)</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>46.8 (42.5–50.3)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR)</td>
<td>19.6 (18.0–23.3)</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L), median (IQR)</td>
<td>74.0 (58.0–97.0)</td>
</tr>
<tr>
<td>Total protein (g/L), median (IQR)</td>
<td>77.0 (73.0–83.0)</td>
</tr>
<tr>
<td>Potassium (mmol/L), median (IQR)</td>
<td>4.5 (4.2–4.9)</td>
</tr>
<tr>
<td>Bilirubin total (mmol/L), median (IQR)</td>
<td>6.0 (5.0–9.0)</td>
</tr>
<tr>
<td>ALT (IU/L), median (IQR)</td>
<td>18.0 (16.0–30.0)</td>
</tr>
<tr>
<td>AST (IU/L), median (IQR)</td>
<td>27.0 (23.0–37.0)</td>
</tr>
<tr>
<td>Haemoglobin (g/dL), median (IQR)</td>
<td>11.8 (10.4–12.7)</td>
</tr>
<tr>
<td>Platelets (10⁹/L), median (IQR)</td>
<td>407.0 (337.0–477.0)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min), median (IQR)</td>
<td>121.0 (97.0–136.0)</td>
</tr>
<tr>
<td>HIV status (positive/negative), n (%)</td>
<td>42 (72.4)/16 (27.6)</td>
</tr>
<tr>
<td>ART, n (%)</td>
<td>40 (95.2)</td>
</tr>
<tr>
<td>Efavirenz + emtricitabine + tenofovir</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Lopinavir/ritonavir + lamivudine + tenofovir</td>
<td>277.0 (139.0–384.0)</td>
</tr>
<tr>
<td>Viral load (log₁₀ copies/mL)</td>
<td>3.3 (1.3–4.2)</td>
</tr>
</tbody>
</table>

aRace (black African/Caucasian/coloured).
bOnly for HIV-positive patients.
cFour missing data.
bdFive missing data.

Moxifloxacin pharmacokinetics
Moxifloxacin pharmacokinetics were best described using a two-compartment disposition model (when compared with one-compartment OFV 45, two additional parameters, P<0.001), with first-order absorption and an absorption lag time, and elimination using the semi-mechanistic liver model describing first-pass extraction (OFV 24 compared with simple first-order elimination from the central compartment, no additional parameters estimated). Since very little information was available in the absorption phase, a prior was added to improve parameter estimation and stabilize the model. Lognormal priors with 30% uncertainty were used, with a typical value of 0.75 h for the absorption lag time and 1.5 h for the absorption rate constant, as previously reported by Zvada et al. in a similar population. A schematic diagram of the final model is depicted in Figure 1 and a detailed description of the semi-mechanistic liver model is provided in the Supplementary data. The model parameter estimates are shown in Table 2; these include parameters of the hepatic model, i.e.
The oral clearance of steady-state moxifloxacin when given as part of TB treatment with rifampicin, isoniazid and pyrazinamide was an estimated 24.3 L/h for a typical patient in the cohort (FFM of 47 kg). When comparing the pharmacokinetic profiles observed during TB treatment with those obtained after a single dose of moxifloxacin, the intrinsic CL (which determines hepatic extraction) and pre-hepatic bioavailability (fraction absorbed and reaching the liver) for moxifloxacin when given at steady-state within rifampicin-based TB treatment and no efavirenz was estimated to be 48.5 L/h (

\[ E_H = \frac{\text{CL}_{\text{int}} \cdot f_u}{\text{CL}_{\text{int}} \cdot f_u + Q_H} \]

where $E_H$ is the hepatic extraction, $\text{CL}_{\text{int}}$ is the (hepatic) clearance intrinsic, $f_u$ is the free (unbound) fraction of drug in plasma, $Q_H$ is the hepatic plasma flow, and $Q$ is the inter-compartmental clearance.

The pre-hepatic bioavailability $F_{\text{pre-H}}$ is the fraction of the drug that is absorbed, crosses the gut wall unchanged, thus entering the portal vein and reaching the liver.

For ease of interpretation, these values have been converted to oral clearance ($\text{CL/F}$) using the formulas in the Supplementary data (Appendix 2) and shown in Table 3.
Effect of rifampicin and efavirenz on moxifloxacin concentrations

Table 3. Typical values of oral clearance and exposure of moxifloxacin when given alone or with rifampicin-based TB treatment, with and without efavirenz-based ART

<table>
<thead>
<tr>
<th>Moxifloxacin scenario</th>
<th>On RIF-based TB treatment?</th>
<th>With EFV-based ART?</th>
<th>Intrinsic CL (CL/F, L/h)</th>
<th>Hepatic extraction (Eh, %)</th>
<th>Pre-hepatic bioavailability (Fpre-H, %)</th>
<th>Oral CL (CL/F, L/h)</th>
<th>Change in CL/F (%)</th>
<th>AUC (mg·h/L)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady-state</td>
<td>yes</td>
<td>no</td>
<td>48.5</td>
<td>33</td>
<td>100 (reference)</td>
<td>24.3</td>
<td>reference</td>
<td>16.5</td>
</tr>
<tr>
<td>Steady-state</td>
<td>yes</td>
<td>yes</td>
<td>69.1</td>
<td>41</td>
<td>100</td>
<td>34.5</td>
<td>+42.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Single doseb</td>
<td>no</td>
<td>no</td>
<td>34.4</td>
<td>26</td>
<td>77</td>
<td>22.4</td>
<td>−7.8</td>
<td>17.9</td>
</tr>
<tr>
<td>Single doseb</td>
<td>no</td>
<td>yes</td>
<td>49.0</td>
<td>33</td>
<td>77</td>
<td>31.8</td>
<td>+31.3</td>
<td>12.6</td>
</tr>
</tbody>
</table>

RIF, rifampicin; EFV, efavirenz.

The typical values reported here refer to an individual with FFM of 47 kg (the median in our cohort).
aAUC for a dose of 400 mg.
bAfter completion of TB treatment.

Discussion

In our cohort of drug-susceptible TB patients, we found low moxifloxacin concentrations (AUC) during concomitant rifampicin-based TB treatment. Higher concentrations (~8%), but still low overall, were observed 1 month after discontinuation of rifampicin, when a single dose of moxifloxacin was administered for comparison. Notably, the increased exposure observed when a single dose of moxifloxacin was given alone after the end of TB treatment was found to be the result of two opposing effects: 30% decreased intrinsic clearance and decreased bioavailability. Moreover, in HIV-co-infected patients on efavirenz-based ART, clearance was increased by 42% when compared with HIV-uninfected patients or those on lopinavir/ritonavir-based ART. The effect of efavirenz, which lowered the AUC by 30%, was present both when moxifloxacin was given alone and when it was given within rifampicin-based TB treatment.

Our findings are in keeping with previous studies investigat- ing the effect of rifampicin co-administration on moxifloxacin drug concentrations in healthy individuals and TB patients, show- ing lower concentrations of moxifloxacin due to rifampicin co-administration. However, these studies reported variable effects of rifampicin co-treatment on moxifloxacin exposure. Bioavailability studies, using cross-over or sequential study designs to limit inter-patient variability, and intensive pharmacokinetic sampling demonstrated much higher differences in steady-state moxifloxacin AUC (27%–31%) without concomitant rifampicin compared with studies in real-world settings, which may be limited by the heterogeneity between the groups compared and the small sample sizes reported. In our study, the model estimated an ~30% decrease in intrinsic CL when moxifloxacin was given alone as opposed to during rifampicin-based TB treatment. On the other hand, the model also estimated a decrease in bioavailability for single-dose moxifloxacin pharmacokinetics when given alone after TB treatment completion. These two phenomena had opposite effects on moxifloxacin concentrations and the reasons are not entirely clear. Several explanations are plausible. Firstly, moxifloxacin AUC at steady-state has been shown to be moderately higher (~30% for 400 mg once daily) than after the first or a single dose of moxifloxacin as used in our study, suggesting that the difference shown in pre-hepatic bioavailability may be a consequence of single-dose versus steady-state dosing. Secondly, it is possible that rifampicin, given concomitantly, increases the absorption of...
moxifloxacin; this may be due to net inhibition of P-glycoprotein by rifampicin during the absorption phase, as has been previously reported with digoxin. This suggests that the true effect of rifampicin co-treatment may be larger and closer to the 30% lower AUC demonstrated by previous studies, compared with moxifloxacin alone.

The higher clearance and lower moxifloxacin concentrations in HIV-co-infected patients on efavirenz-based ART has not been previously described. Efavirenz induces the activity of UGT, involved in moxifloxacin metabolism. There is evidence of efavirenz decreasing concentrations of other antiretroviral drugs metabolized by UGT, such as dolutegravir, by up to 57%. There have been conflicting reports of the effect of HIV co-infection on TB drugs, with some studies reporting decreased drug concentrations while others found non-significant or no changes. It is unclear whether the effect on clearance and AUC seen in those HIV-co-infected patients who are on efavirenz are due to the induction of UGT, HIV co-infection or a combination of these. There were two HIV-co-infected patients who were on lopinavir/ritonavir-based ART, and no decrease in moxifloxacin clearance could be observed in any of the seven pharmacokinetic profiles contributed by these patients, but the small numbers limit our ability to draw reliable conclusions about this observation. These findings are nevertheless concerning, given that this interaction may also impact moxifloxacin exposure in HIV-co-infected patients on efavirenz-based ART taking moxifloxacin-containing MDR TB treatment or in studies using moxifloxacin in novel drug regimens, and need confirmation in other studies.

The plasma concentrations of moxifloxacin achieved in our patients are low regardless of efavirenz or rifampicin co-treatment, when compared with previous reports. Moxifloxacin exhibits extensive inter-individual variability in pharmacokinetic parameters in healthy volunteers and patients with TB, with wide ranges in AUC, $C_{\text{max}}$, and CL/F values. AUC values between 8.5 and 140 mg·h/L and CL/F between 10 and 30.6 L/h have been reported in previous studies using 400 mg moxifloxacin doses. African populations have shown high levels of host genetic diversity and increased variation in drug metabolizing and transport
enzymes, shown to result in lower drug concentrations and variation in drug response to other first-line TB drugs.\textsuperscript{17,18,50} We acknowledge several limitations. Firstly, we used relatively sparse pharmacokinetic sampling methods at each pharmacokinetic visit, a choice that may limit the precision of the individual estimates of exposure. However, we employed NLME modelling for the interpretation of the data; this analysis technique is designed to handle sparse data well, since it pools information across the entire population and is able to robustly identify population parameters, including typical values, variability and covariate effects.\textsuperscript{53} Furthermore, pharmacokinetic sampling around 2 and 6 h after dose has been shown to provide reasonably accurate estimates of moxifloxacin AUC in previous studies.\textsuperscript{29} A second limitation may be due to the fact that moxifloxacin pharmacokinetic parameters (CL/F and AUC) during TB treatment compared with dosing after completion of TB treatment may differ as a result of changes in patient physiology, increased weight and improved disease status. In our model, we have included the effect of body size to account for the effects of rifampicin and efavirenz on moxifloxacin pharmacokinetics. However, several other potential confounding factors, including genetic variability, may limit our model’s ability to robustly quantify the contribution of each separate factor. Thirdly, the study was not designed to determine the impact of the efavirenz interaction on moxifloxacin, hence efavirenz drug concentrations, known to have high variability in exposure,\textsuperscript{53} were not determined. Fourthly, our study used a single dose of moxifloxacin given after completion of TB treatment and compared with moxifloxacin at steady-state given concomitantly with rifampicin. It is possible that changes in the pharmacokinetics of moxifloxacin between single-dose and steady-state treatment may be responsible for the observed increase in pre-hepatic bioavailability. In this case, the actual effect of rifampicin co-administration would only be the \~30\% increase in intrinsic CL, resulting in decreases in moxifloxacin AUC similar to those reported in previous studies.\textsuperscript{12–14} Finally, pharmacokinetic sampling was not ideal, as hospitalization of ambulatory patients overnight, to minimize dosing errors and standardize sampling conditions, was not feasible within our study.

In conclusion, we found high CL and resulting low moxifloxacin concentrations (AUC) in South African patients with drug-susceptible, recurrent TB, further decreased by co-treatment with rifampicin and efavirenz-based ART. The clinical relevance of the low moxifloxacin concentrations is unclear, but the detected interactions, especially the efavirenz effect on moxifloxacin, warrants further investigation in studies to assess the need for dose adjustments and impact on TB treatment outcomes.

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The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to data, commented on drafts, and approved the final report. The corresponding author had final responsibility for the decision to submit for publication.

Transparency declarations

N. P. is the principal study investigator, on the Improving Retreatment Success Trial (IMPRESS) [NCT02114684]. Bayer Pharmaceuticals donated the study drug (moxifloxacin) used during the trial. S. E. is a member of the Global Respiratory Infection Partnership, sponsored by Reckitt and Benckiser. All authors have no other potential conflicts of interest to declare.

Author contributions


The contents of the manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the US government, EDCTP, NRF, Fogarty International Center, National Institutes of Health or the Medical Research Council.

Supplementary data

Descriptions of the reasons for exclusion of data and the moxifloxacin pharmacokinetic model can be found in the Supplementary data at JAC Online (https://academic.oup.com/jac/advance-access).

References

Effect of rifampicin and efavirenz on moxifloxacin concentrations


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