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Anti-TB drug concentrations and drug-associated toxicities among TB/HIV-coinfected patients

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Background: Toxicities due to anti-TB treatment frequently occur among TB/HIV-coinfected patients.

Objectives: To determine the association between anti-TB drug concentrations and the occurrence of hepatotoxicity and peripheral neuropathy among TB/HIV-coinfected patients.

Methods: TB/HIV-coinfected patients were started on standard dose anti-TB treatment according to WHO guidelines. Anti-TB drug concentrations were measured using HPLC 1, 2 and 4 h after drug intake at 2, 8 and 24 weeks following initiation of TB treatment. Participants were assessed for hepatotoxicity using Division of AIDS toxicity tables and for peripheral neuropathy using clinical assessment of tendon reflexes, vibration sensation or symptoms. Cox regression was used to determine the association between toxicities and drug concentrations.

Results: Of the 268 patients enrolled, 58% were male with a median age of 34 years. Participants with no hepatotoxicity or mild, moderate and severe hepatotoxicity had a median C_{max} of 6.57 (IQR 4.83–9.41) μg/mL, 7.39 (IQR 5.10–10.20) μg/mL, 7.00 (IQR 6.05–10.95) μg/mL and 3.86 (IQR 2.81–14.24) μg/mL, respectively. There was no difference in the median C_{max} of rifampicin among those who had hepatotoxicity and those who did not ($P = 0.322$). There was no difference in the isoniazid median C_{max} among those who had peripheral neuropathy 2.34 (1.52–3.23) μg/mL and those who did not 2.21 (1.45–3.11) μg/mL ($P = 0.49$).

Conclusions: There was no association between rifampicin concentrations and hepatotoxicity or isoniazid concentrations and peripheral neuropathy among TB/HIV-coinfected patients.

Introduction

Of the 10.4 million people with TB worldwide, 12% are HIV-coinfected (1.2 million). The risk for TB is up to 30 times higher in HIV-infected patients compared with the HIV-uninfected population. The TB/HIV epidemic is concentrated in sub-Saharan Africa, which bears over 50% of the global burden of TB/HIV-coinfection.[1] Curative treatment for TB is available, though requires adherence to a prolonged duration of drug therapy and may expose patients to drug-induced toxicities. The standard recommended treatment for TB includes rifampicin, isoniazid, ethambutol and pyrazinamide over a 2 month intensive phase followed by a continuation phase with rifampicin and isoniazid for 4 months.

Anti-TB drugs are generally well tolerated though toxicities may occur in up to 80% of patients with TB.[2] One of the most common toxicities of anti-TB drugs is hepatotoxicity associated with isoniazid, rifampicin and pyrazinamide,[3] which occurs in 3%–40% of TB patients.[4–7] Among patients with TB, age over 35 years, female gender, elevated pre-treatment liver function tests, malnutrition and HIV infection increase the increased risk of hepatotoxicity.[8]

Peripheral neuropathy occurs in up to 40% of patients on anti-TB treatment[9] and more frequently among TB/HIV-coinfected patients compared with HIV-uninfected individuals.[10,11] Importantly, neuropathy among HIV-infected patients may have alternative causes including HIV infection itself, particularly among patients

with low CD4 cell counts, and ART, especially nucleoside reverse transcriptase inhibitors.[12] The high burden of toxicities among TB/HIV-coinfected patients[10,11,13,14] may lead to treatment interruption and contribute to morbidity and mortality.[15]

Isoniazid-induced peripheral neuropathy is considered to be concentration dependent and occurs more frequently in slow metabolizers of the drug.[16] Rifampicin-induced hepatotoxicity is also considered to be dose related.[17,18] It is therefore important to optimize TB treatment to enable the attainment of adequate drug concentrations, while minimizing toxicities.

The correlation between blood concentrations of anti-TB drugs and the occurrence of toxicities in TB/HIV-coinfected patients has not been well elucidated. The aim of this study therefore was to determine the association between hepatotoxicity, peripheral neuropathy and serum concentrations of rifampicin and isoniazid given at the standard dose recommended by WHO guidelines.[19]

Patients and methods

Setting

We recruited TB/HIV-coinfected patients at the Infectious Diseases Institute (IDI) in Kampala, Uganda, which runs a large outpatient HIV clinic serving over 8000 persons living with HIV; ~300 patients are diagnosed with TB each year.

Study design and population

This was a prospective observational study enrolling patients aged 18 years and above with new pulmonary TB. Pregnant women, patients with alanine transferase (ALT) >5 times the upper limit of normal (ULN), glomerular filtration rate (GFR) <50 mL/min and those with a history of TB in the past were excluded from the study.

Participants were started on anti-TB medication according to WHO recommendations which require 2 months (intensive phase) of rifampicin, isoniazid, pyrazinamide and ethambutol (RHZE) followed by 4 months (continuation phase) of rifampicin and isoniazid (HR), with dosages according to weight bands: three tablets of RHZE or HR if the patient's weight is <55 kg, four tablets of RHZE or HR for weight ≥55 kg, and five tablets of RHZE or HR for weight ≥70 kg. Participants were on fixed-dose combinations where each tablet contained 150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide and 275 mg ethambutol. Combination antiretroviral treatment (cART) was started at least 2 weeks after initiation of anti-TB treatment and included zidovudine, lamivudine and efavirenz. Patients who were on nevirapine-based cART prior to starting TB treatment were switched to efavirenz.

Assessment of toxicities

Hepatotoxicity was defined as ALT ≥ 40 IU/L. The severity of hepatotoxicity was graded according to the National Institutes of Health Division of AIDS toxicity tables (DAIDS)[20] as follows: ALT 40–119, mild/grade 1; ALT 120–199, moderate/grade 2; ALT >200, severe/grade/grade 3. ALT was measured at the Makerere University Johns Hopkins University (MUJHU) core laboratory, which is a College of American Pathologists (CAP)-certified laboratory. Participants were assessed for hepatotoxicity 2, 8 and 24 weeks after starting TB treatment or when they developed symptoms including vomiting, nausea, anorexia, abdominal pain or jaundice.

Peripheral neuropathy was assessed using a history of symptoms of peripheral neuropathy followed by evaluation for loss of vibration sensation at the malleolus graded from 0 to 3; 0 = vibration felt for >10 s (normal), 1 = vibration felt for 6–10 s (mild loss), 2 = vibration felt for <5 s (moderate loss), 3 = vibration not felt (severe loss). Tendon reflexes were tested and classified as absent, hypoactive, normal, hyperactive and hyperactive with clonus. Peripheral neuropathy was defined using variables from the AIDS Clinical Trial Group Brief Peripheral Neuropathy Screening Tool,[21] as loss of vibration sensation in both limbs and/or abnormal tendon reflexes bilaterally; this was assessed at every study visit (weeks 2, 8 and 24).

All participants were given 25 mg pyridoxine to prevent isoniazid-induced peripheral neuropathy according to WHO TB treatment guidelines.[19] Patients reporting worsening of peripheral neuropathy or new incidence of peripheral neuropathy were given a higher dose of pyridoxine.

Peripheral neuropathy and hepatotoxicity were reported as adverse events if they were not present at baseline or if there was worsening of pre-existing symptoms from baseline assessments.

Pharmacokinetic measurements

Study visits were conducted at weeks 2, 8 and 24 after initiation of anti-TB treatment. On each follow-up visit, blood sampling was performed on participants prior to drug dosing (0 h) and at 1, 2 and 4 h after witnessed dosing of anti-TB drugs and cART where applicable; participants were asked to fast for at least 8 h prior to drug dosing and were allowed to eat after the 2 h blood draw. Adherence counselling was performed at each follow-up visit and adherence was assessed using pill counts, visual analogue scale and by self-report using 7 day recall.

Blood samples were collected in rapid serum vacutainers and the serum separated by centrifuging within 1 h of the blood draw. Serum concentrations of rifampicin, ethambutol and isoniazid were measured in the Translational laboratory of the Infectious Diseases Institute in Kampala using ultraviolet high-performance liquid chromatography (UV-HPLC) (available as Supplementary data at *JAC* Online).

Ethics

Ethics approval was received from the Joint Clinical and Research Centre Institutional Review Board, the Uganda National Council for Science and Technology (reference number HS1303) and the National Drug Authority. Written informed consent was obtained from all study participants prior to enrolment. This study was registered at Clinicaltrials.gov (NCT01782950).

Statistical methods

Participants' baseline characteristics were described as medians with the IQR. Maximum concentrations (C_{max}) of anti-TB drugs were calculated as the highest concentration among the three blood draws (1, 2 and 4 h). The maximum concentrations were established for each visit (weeks 2, 8 and 24). The C_{max} of participants with and without hepatotoxicity and peripheral neuropathy were compared using Wilcoxon rank-sum and Kruskal–Wallis test. Time-updated Cox regression adjusting for age, sex, CD4 cell count and BMI was used to determine the association between serum anti-TB drug concentrations and the occurrence of hepatotoxicity and peripheral neuropathy. The Cox regression was time updated for serum concentrations. The last serum concentration before the occurrence of hepatotoxicity was used in the Cox regression model. Patients with peripheral neuropathy at baseline were excluded from the Cox regression analysis unless there was worsening of the grading of vibration sensation. Patients with elevated ALT at baseline were included in the analysis if ALT levels increased further from the baseline value.

Results

Between May 2013 and November 2015, 268 TB/HIV-coinfected patients were enrolled. Fifty-eight percent were male with a median age of 34 (IQR 29–40) years. Almost half (48.5%) of the participants had peripheral neuropathy prior to starting TB treatment,

Table 1. Baseline characteristics of TB/HIV-coinfected participants with pharmacokinetic data

Characteristics	(*N*=268)
Male gender, *n* (%)	155 (57.8)
Age in years, median (IQR)	33.9 (29–40)
BMI (kg/m^2)	
median (IQR)	19.2 (17.7–21.7)
BMI <18; *n* (%)	74 (27.6)
WHO stage, *n* (%)	
III	233 (86.9)
IV	22 (8.2)
CD4 counts	
all participants (median, IQR)	172 (47–334)
<200 cells/mm^3, *n* (%)	120 (44.8)
<50 cells/mm^3, *n* (%)	55 (20.5)
ART regimen at baseline, *n* (%)	
NNRTI plus 2 NRTIs	56 (20.9)
PI plus 2 NRTIs	3 (1.11)
Baseline symptoms, *n* (%)	
peripheral neuropathy	188 (70.15)
ALT >40–119 U/L (grade 1)	39 (14.6)
ALT >120 U/L (grade 2)	3 (1.1)

Table 2. Proportion of patients with hepatotoxicity at different time points

	Proportion of participants with hepatotoxicity *n* (%)		
	Week 2 (*N*=252)	Week 8 (*N*=227)	Week 24 (*N*=199)
Grade of hepatotoxicity, *n* (%)			
none	205 (81.4)	179 (78.6)	150 (78.38)
mild, grade 1	33 (13.1)	40 (17.6)	39 (19.6)
moderate, grade 2	4 (1.6)	1 (0.44)	2 (1.01)
severe, grade 3	2 (0.79)	1 (0.44)	0
Invalid results	8 (3.17)	6 (2.64)	8 (4.02)

while 15.7% had a grade 1 and grade 2 elevation of ALT (Table 1). One patient had diabetes mellitus. We found 22% of the patients were already on ART before initiation of TB treatment; however, there was no association between baseline ART status and the occurrence of hepatotoxicity (HR 1.32; 95% CI 0.33–5.31; $P = 0.692$) or peripheral neuropathy (HR 1.11; 95% CI 0.70–1.75; $P = 0.651$).

Hepatotoxicity

The median time to developing hepatotoxicity was 16 days (IQR 13–55) after initiation of anti-TB treatment and the proportions of participants with mild, moderate and severe elevation of ALT over time are as shown in Table 2. Excluding patients who had an elevated ALT at baseline, 94 (67%) of 254 patients with a measurement during follow-up developed hepatotoxicity: 84 (33%) mild, 7 (3%) moderate and 3 (1%) severe hepatotoxicity. Although the proportion of participants with mild elevations of ALT increased over time, the proportion of patients with moderate and severe hepatotoxicity remained low.

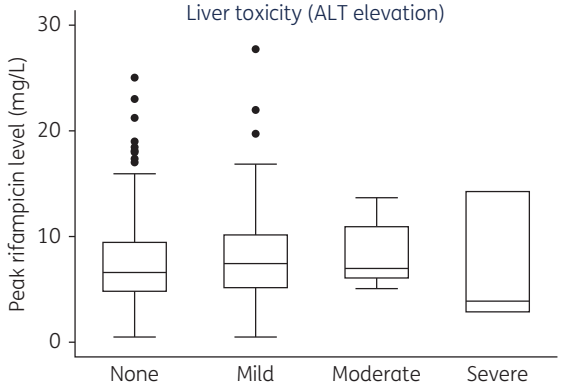

Figure 1. Association between rifampicin concentrations and grade of hepatotoxicity. Box plot showing rifampicin concentrations for each category of hepatotoxicity: the top of each box represents the 75th percentile (Q_3), the bottom the 25th percentile (Q_1), the horizontal line within each box represents the 50th percentile (median) rifampicin concentrations. The top whisker represents $Q_3 + (1.5 \times IQR)$ while the bottom represents $Q_1 - (1.5 \times IQR)$. The dots represent outliers.

Participants with no hepatotoxicity had a rifampicin median C_{max} of 6.57 (IQR 4.83–9.41) μg/mL, while those with mild, moderate and severe hepatotoxicity had a median C_{max} of 7.39 (IQR 5.10–10.20) μg/mL, 7.00 (IQR 6.05–10.95) μg/mL and 3.86 (IQR 2.81–14.24) μg/mL, respectively. These mean C_{max} values were below the recommended lower limit for rifampicin (8 μg/mL). There was no difference in the median C_{max} of rifampicin among those who had hepatotoxicity and those who did not ($P = 0.332$) (Figure 1). Five participants (1.8%) experienced treatment interruption due to hepatotoxicity; only two of these had a median C_{max} of rifampicin above the normal threshold.

We did not find any association between age, sex, BMI, CD4 cell count and rifampicin concentrations (Table 3). Figure 1 shows the maximum rifampicin concentrations among participants with different grades of hepatotoxicity.

There was also no association between the occurrence of hepatotoxicity and the C_{max} of isoniazid (HR 0.65; 95% CI 0.18–2.29; $P = 0.499$).

Peripheral neuropathy

We found 188 (70.15%) patients had baseline peripheral neuropathy, 39 of whom had worsening symptoms during TB treatment. Peripheral neuropathy occurred after a median time of 28 days (IQR 14–58). Of the 79 (83.5%) patients who had no baseline peripheral neuropathy, 66 developed it during the course of TB treatment.

The proportion of participants with new or worsening peripheral neuropathy significantly decreased over time with 127 (58.26%), 84 (45.16%) and 43 (33.1%) of the participants experiencing toxicity at weeks 2, 8 and 24, respectively ($P < 0.001$).

Following Cox regression analysis, we did not find any significant association between the occurrence of new peripheral neuropathy and age, sex, BMI or CD4 count (Table 4). The median C_{max}

Table 3. Hepatotoxicity among TB/HIV-coinfected participants on TB treatment

	Unadjusted hazard ratio (HR)			Adjusted hazard ratio (HR)		
Characteristic	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.00	0.97–1.02	1.00	0.99	0.97–1.03	0.994
BMI	1.04	0.97–1.12	0.238	1.07	0.97–1.14	0.185
Male sex	0.97	0.59–1.61	0.926	1.01	0.65–1.95	0.673
CD4 cell count						
≤250 cells/mm^3	0.84	0.45–1.57	0.579	0.89	0.44–1.59	0.603
>250 cells/mm^3	0.66	0.38–1.21	0.178	0.51	0.35–1.18	0.045
Rifampicin C_{max}	1.85	0.63–5.42	0.264	1.80	0.50–6.48	0.368
Isoniazid C_{max}	1.06	0.37–3.06	0.911	0.65	0.18–2.29	0.499

Table 4. Peripheral neuropathy among patients with TB/HIV coinfection

	Unadjusted hazard ratio (HR)			Adjusted hazard ratio (HR)		
Characteristic	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.00	0.98–1.03	0.619	1.01	0.98–1.04	0.306
BMI	0.99	0.94–1.06	0.949	0.96	0.89–1.03	0.272
Male sex	0.70	0.47–1.05	0.090	0.57	0.33–0.96	0.033
CD4 cell count						
≤250 cells/mm^3	0.85	0.49–1.46	0.117	0.81	0.46–1.44	0.472
>250 cells/mm^3	0.90	0.54–1.52	0.698	0.91	0.53–1.57	0.748
Isoniazid C_{max}	0.98	0.37–2.60	0.972	0.67	0.21–2.09	0.49

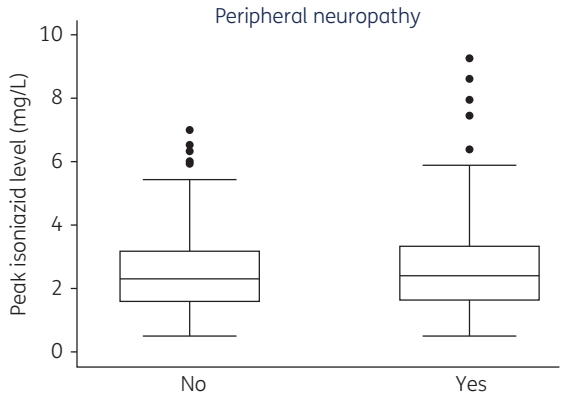

Figure 2. Association between isoniazid concentrations and presence of peripheral neuropathy. Box plot showing isoniazid concentrations for patients with and without peripheral neuropathy. Boxplot conventions are the same as in Figure 1.

of isoniazid among participants with and without peripheral neuropathy were below the recommended lower limit (3 μg/mL); 2.34 (1.52–3.23) μg/mL and 2.21 (1.45–3.11) μg/mL, respectively. There was no association between the occurrence of peripheral neuropathy and isoniazid C_{max} (HR 0.67; 95% CI 0.21–2.09; $P = 0.49$) (Table 4). Figure 2 shows the isoniazid concentrations stratified by the presence or absence of peripheral neuropathy. The dose of pyridoxine was increased up to 50 and 100 mg in 45.7% and 43.4% of the participants, respectively. None of the participants experienced treatment interruption due to peripheral neuropathy.

Discussion

In this study among TB/HIV-coinfected individuals, we documented no correlation between rifampicin and isoniazid concentrations and common toxicities, in particular hepatotoxicity and peripheral neuropathy. Our findings were similar to findings by Jeong *et al.*[6] in HIV-negative patients. In contrast, another study in HIV-negative patients by Satyraddi *et al.*[8] found rifampicin concentrations on the seventh day of anti-TB drug treatment to be correlated with the onset of hepatotoxicity. This may be due to the difference in populations, time points where drug concentrations were measured or possibly because toxicities caused by anti-TB drugs may be due to hypersensitivity or idiosyncratic reactions,[22] which may occur regardless of dose.

Several studies have described low concentrations of anti-TB drugs in patients with TB[23,24] which may be attributed to factors such as malabsorption[25] and drug–drug interactions.[2] In view of the low concentrations of rifampicin in many populations, higher doses of rifampicin are being evaluated to improve treatment outcomes. There is some evidence that high doses of rifampicin are tolerable and not associated with a significant increase

in hepatotoxicity;[5] however, there is insufficient evidence of this among TB/HIV-coinfected populations.

We found a low prevalence (<2%) of moderate and severe hepatotoxicity unlike previous studies in predominantly HIV-infected participants where a higher prevalence of 12%–20%[26,27] was found. This variation could be attributed to difference in study designs; some of these studies were retrospective, and differed in their study populations which included hospitalized patients. Less than 2% of our participants required rifampicin treatment interruption which is consistent with other studies.[5,28] Similar to studies in HIV-infected populations,[27] we observed hepatotoxicity occurring earlier (16 days) than reported in HIV-negative individuals[6] where the median time between initiation of anti-TB treatment and onset of hepatotoxicity was 41 days.

A high proportion (30%–50%) of participants experienced new or worsening peripheral neuropathy even though isoniazid concentrations were similar in patients who developed new or worsening peripheral neuropathy and those who did not. HIV infection itself is a risk factor for peripheral neuropathy regardless of ART status particularly among those with a low CD4 cell count.[12] In our study, the mean CD4 cell count was <200 cells/mm^3 in 44.8% of the participants. We found, however, no association between CD4 cell count and peripheral neuropathy. The proportion of participants with peripheral neuropathy decreased over time. We believe that increasing the dose of pyridoxine, which occurred in over 80% of the participants, may have contributed to this. There was no treatment interruption even while the participants were on isoniazid, implying that isoniazid was generally well tolerated. Isoniazid-induced peripheral neuropathy is thought to be dose dependent; in addition, patients who are slow metabolizers of isoniazid have been found to have higher isoniazid concentrations and are more likely to develop peripheral neuropathy.[29,30] In this TB/HIV-coinfected population, we found no association between isoniazid concentrations and the occurrence of peripheral neuropathy.

The strength of our study is the large sample size, combined with drug concentrations being measured at several time points over the course of TB treatment. We also recognize that our study has some limitations; our participants were on four different anti-TB drugs plus efavirenz, which may also cause hepatotoxicity, making it difficult to ascertain which drug caused the toxicities. There are also other causes of peripheral neuropathy which were difficult to assess, including exposure to neurotoxic agents. Due to the limited number of time points after drug ingestion at which drug concentrations were measured, we were unable to determine whether these toxicities are associated with AUC_{0-12} which is a better measure of drug exposure. Concentrations after 2 h are commonly used to estimate C_{max} for isoniazid and rifampicin but this is an inaccurate estimate due to the variability of absorption (fast versus slow absorbers), and therefore blood samples after 1 and 4 h were also used in this study to obtain a better estimate.

In conclusion, we found no association between drug concentrations and rifampicin- or isoniazid-related toxicities, in particular hepatotoxicity and peripheral neuropathy, among TB/HIV-coinfected patients using the currently recommended doses.

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Transparency declarations

The authors have no conflict of interest to declare. The funders had no role in the study conceptualization, design or writing of this manuscript.

Author contributions

This study was conceptualized by J. F., N. C., A. K., B. C., M. L. and Y. C. M. C. S.-W. wrote this manuscript under the supervision of M. R. K., Y. C. M., B. C. and P. B.-K. A. vB., C. S.-W., A. B., D. M. and U. G. contributed to the data collection. A. U. S. and B. L. performed the data analysis. All authors read and approved the final version of this paper.

Supplementary data

Additional detail of the UV HPLC methods is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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