Tuberculous Drug-induced Liver Injury and Treatment Re-challenge in Human Immunodeficiency Virus Co-infection

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ABSTRACT

Background: Tuberculosis drug-induced liver injury (TB-DILI) is the most common adverse event necessitating therapy interruption. The optimal re-challenge strategy for antituberculous therapy (ATT) remains unclear, especially in human immunodeficiency virus (HIV) co-infected individuals in high-prevalence settings such as South Africa. **Objective:** To determine the incidence of and risk factors for the recurrence of TB-DILI with different ATT re-challenge strategies. **Materials and Methods:** We conducted a retrospective chart review of patients managed for TB-DILI from 2005 to 2013 at King Edward VIII Hospital in Durban, South Africa. Relevant clinical and laboratory data at the presentation of TB-DILI, time to recovery of liver function, method of ATT re-challenge and outcome of re-challenge were documented. **Results:** 1016 charts were reviewed, and 53 individuals with TB-DILI (48 HIV-co-infected) were identified. Following discontinuation of ATT, the median time to alanine aminotransferase normalization was 28 days (interquartile range 13-43). Forty-two subjects were re-challenged (30 regimen re-challenges and 12 step-wise re-challenges). 5 (12%) cases of recurrent TB-DILI were noted. Recurrences were not associated with the method of re-challenge. **Conclusion:** Based on the data available, it appears that full ATT can be safely restarted in the majority of subjects with a recurrence of DILI occurring in about 12% of subjects. The method of re-challenge did not appear to impact on the risk of recurrence. Ideally, a prospective randomized trial is needed to determine the best method of re-challenge.

Key words: Anti-tuberculous treatment re-challenge, drug-induced liver injury, hepatotoxicity, human immunodeficiency virus, tuberculosis

INTRODUCTION

Tuberculosis (TB) remains a major global health threat, and 60-80% of individuals with TB in South Africa are human immunodeficiency virus (HIV) co-infected.[1,2] TB drug-induced liver injury (TB-DILI) occurs in 5-28% of individuals on TB treatment[3] and is the most common reason necessitating treatment interruption.[4] Due to the dearth of potent antituberculous (ATT) agents, re-challenge with first-line agents remains the standard of care. The literature offers little guidance on the best approach to re-introducing ATT following TB-DILI, especially in HIV. Herein, we describe the incidence of, and risk factors for, recurrence of DILI in subjects re-challenged with ATT after presenting with TB-DILI in an HIV-TB-endemic setting.

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MATERIALS AND METHODS

The King Edward VIII Hospital-Infectious Diseases (ID) Department is the referral center for complex ID problems

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for the eastern seaboard of KwaZulu-Natal. This region serves a population of over 10 million people and has one of the highest prevalence of HIV and TB in South Africa.

In- and out-patient charts of patients treated by the Department of ID between 2005 and 2013 were reviewed. Patients fulfilling the following criteria were included:

(1) On ATT, (2) alanine aminotransferase (ALT) >3-fold upper limit of normal (ULN) irrespective of the bilirubin level or presence/absence of symptoms, (3) absence of any other cause for liver injury, (4) temporal relationship between discontinuation of ATT and resolution of DILI and (5) sufficient data for analysis. Relevant clinical and laboratory data at the time of TB-DILI, time to recovery of liver function, method of ATT re-challenge and outcome of re-challenge were documented. Mode of re-challenge was categorized as follows:

1. Regimen challenge: Subjects challenged with a combination of potentially hepatotoxic agents simultaneously (isoniazid [H] + rifampin [R], R + pyrazinamide [Z], H + R + Z)
2. Step-wise challenge: Subjects challenged with one hepatotoxic agent at a time, separated by an interval of 3-8 days, until all drugs were reintroduced or hepatotoxicity recurred. Patients may or may not be on simultaneous liver sparing agents.

Two-tailed Fischer exact test was used to examine associations between categorical variables. Spearman coefficients were calculated to determine correlations between continuous variables. Mann-Whitney U-test was used to compare median values between groups. $P < 0.05$ was considered significant (GraphPad Prism Version 5). Ethical approval for the study was obtained from the University of KwaZulu-Natal Biomedical Ethics Research Committee.

RESULTS

Fifty-three individuals met the inclusion criteria for TB-DILI [Figure 1], of whom 42 (79%) were re-challenged. 11 (21%) subjects were not re-challenged. Five were felt to have had adequate ATT, one had very severe DILI precluding re-challenge, in three re-challenge was deferred with no further records of a re-challenge and in two patients liver function improved with ongoing ATT, so TB treatment was continued.

The baseline clinical and laboratory characteristics at the time of TB diagnosis of all patients re-challenged are tabulated in Table 1. Clinical and laboratory characteristics at the time of presentation with TB-DILI are presented in Table 2. Thirty-nine individuals (93%) were HIV-co-infected. Ten subjects had potential hepatic co-morbidities-one was hepatitis C virus (HCV) positive, one both HCV and hepatitis B virus (HBV) positive and 5 HBV positive. None had hepatitis viral load data. Three individuals (7%) had a history of alcohol abuse as defined by NIH.[5] The

Table 1: Baseline clinical and laboratory characteristics of patients re-challenged with ATT

Parameter	Patients re-challenged (*n* = 42)
Median age, years (IQR)	34 (28-38)
Male sex, *n* (%)	18 (43)
African race, *n* (%)	42 (100)
HIV positive, *n* (%)	39 (93)
Median CD_4 prior to ATT initiation (cells/μl) (IQR)	61 (36-182)
Previous TB, *n* (%)	7 (17)
Previous TB-DILI (%)	0 (0)
Past opportunistic infection (%)	10 (24)
Organs involved with TB, *n* (%)	
Lungs	36 (86)
Disseminated (>1 organ involved)	11 (26)
Pleura	3 (7)
Brain or meninges	2 (5)
Abdomen	2 (5)
TB diagnosis based on, *n* (%)	
Microbiology positive (sputum smear and/or culture)	17 (40)
CXR	6 (14)
Other imaging (US/CT/MRI) suggestive of TB	4 (10)
Clinical signs/symptoms and risk factors	5 (12)
Method of diagnosis unclear from records	10 (24)

Baseline liver enzymes were not available. ATT: Antituberculous therapy, IQR: Interquartile range, CXR: Chest X-ray, US: Ultrasound, MRI: Magnetic resonance imaging, SD: Standard deviation, ARVs: Antiretrovirals, TB-DILI: Tuberculosis drug-induced liver injury, CT: Computed tomography, HIV: Human immunodeficiency virus

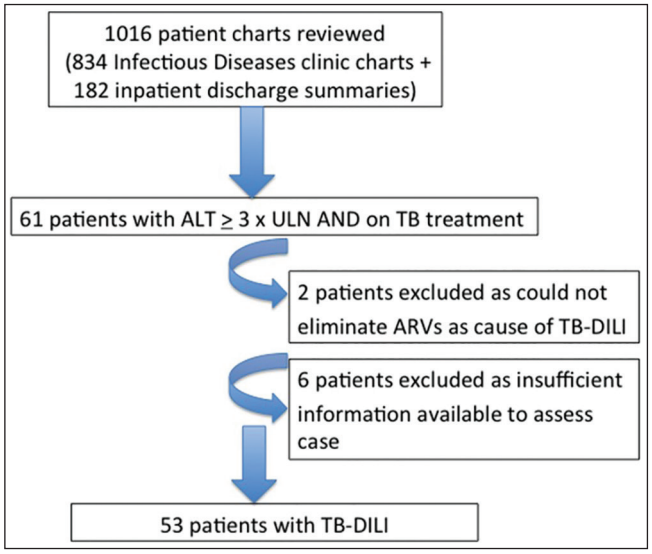

Figure 1: Flow chart depicting the method in which individuals with tuberculosis drug-induced liver injury were identified. Fifty-three individuals were ultimately identified as having tuberculosis drug-induced liver injury

most common noninfectious comorbidity at baseline was peripheral neuropathy, observed in 4 (10%) individuals.

At presentation with TB-DILI, 29 individuals were in the intensive phase of ATT which included pyrazinamide [Table 2]. 27 of 39 (64%) HIV-infected were on antiretrovirals for a median of 1 month (interquartile range [IQR]: 0.25-60 months). All were on efavirenz-based regimens. The median time on ATT prior to TB-DILI was 4 weeks (IQR: 2-8 weeks; range 3 days-32 weeks). The most common presenting feature was jaundice, and the maximum enzyme abnormality seen was an ALT level 43 times upper limit of normal [Table 2]. In those who were HIV-infected, there was no correlation between maximum ALT and CD4 count at baseline (Spearman $r = 0.1362$, 95% confidence interval [CI]: −0.4998 to 0.2682; $P = 0.4982$) or at time of TB-DILI (Spearman $r = -0.08043$, 95% CI: −0.5805 to 0.4637; $P = 0.7757$). Five patients had liver biopsy results available: Two had features of hepatic steatosis; one showed features of granulomatous hepatitis thought to be due to TB, one had features of DILI, and one had nonspecific findings.

Table 2: Patient clinical and laboratory characteristics at time of TB-DILI

Parameter	Patients re-challenged (*n* = 42)
On intensive phase TB treatment (including Z)	29
On continuation phase TB treatment (excluding Z)	13
Concurrent medications in HIV-infected, *n*=39	
ARVs (%)	27 (64)
Efavirenz (%)	27 (64)
Bactrim, *n* (% of HIV-positive patients)	11 (26)
Fluconazole, *n* (% of HIV-positive patients)	1 (2)
Laboratory parameters at admission (22 inpatients only), median (IQR)	
Hg, g/dL (ref: 11.5-13.5 g/dL)	11 (9-11)
MCV, fL (ref: 70-99 fL)	81 (77-88)
White blood cells, ×10⁹/L (ref: 4.0-11×10⁹/L)	6 (4-11)
Platelets, ×10⁹/L (150-450×10⁹/L)	234 (171-412)
Creatinine, µmol/L (ref: 53-115 µmol/L)	67 (61-90)
Total protein, g/L (ref: 59-81 g/L)	70 (60-79)
Albumin, g/L (ref: 32-50 g/L)	24 (19-31)
Total bilirubin, µmol/L (ref: 0-17 µmol/L)	21 (13-73)
ALT, U/L (ref: 10-45 U/L)	153 (52-436)
ALP, U/L (ref: 42-121 U/L)	145 (94-253)
INR (ref: 0.9-1.2)	1.22 (1.04-1.91)
Duration of ATT prior to TB-DILI, weeks; median (IQR) (range)	4 (2-8) 0.40-32
Presenting complaint, *n* (%)	
Jaundice	23 (55)
Nausea and vomiting	6 (14)
Rash/pruritus	3 (7)
Abdominal pain	3 (7)
Confusion	1 (2)
Symptomatic but specific symptom not indicated in records	6 (14)
Asymptomatic	0 (0)
Physical findings, *n* (%)	
Jaundice	23 (55)
Hepatomegaly/tenderness	6 (14)
Ascites	1 (2)
No abnormalities	12 (29)
Maximum liver enzyme derangement (median [IQR]; range)	
Total bilirubin, µmol/L (ref: 0-17 µmol/L)	79 (39-158); 8-511
ALT, U/L (ref: 10-45 U/L)	297 (187-559); 118-1950
ALP, U/L (ref: 42-121 U/L)	241 (147-538); 67-1791
INR (ref: 0.9-1.2)	1.53 (1.12-2.01); 1.07-2.30

TB-DILI: Tuberculosis drug-induced liver injury, Z: Pyrazinamide; ARVs: Antiretrovirals, SD: Standard deviation, ALT: Alanine aminotransferase, INR: International normalized ratio, ALP: Alkaline phosphatase, IQR: Interquartile range, ATT: Antituberculosis therapy, HIV: Human immunodeficiency virus

The time to normalization of liver enzymes could only be determined with some accuracy in inpatients due to the frequency of testing [Table 3]. The time to ATT re-challenge ranged from 2 days to 5 months with a median of 3 weeks. Following normalization of liver enzymes and resolution of clinical symptoms, 42 individuals (79%) were re-challenged. Table 4 for the regimens used for re-challenge. ATT was introduced using the full regimen from the outset (regimen re-challenge) in 30 subjects (57%) or by the stepwise introduction in 12 subjects (23%). 37 (88%) patients did not experience recurrent TB-DILI. Of the five with recurrent DILI, 4 (80%) had a regimen re-challenge and one a stepwise re-challenge (4/30, 13% vs. 1/12, 8%, $P = 0.2063$, Fischer exact test) [Figure 2]. In individuals who experienced recurrent TB-DILI, the median time to the first episode of DILI was no different from that for recurrence (4.40 weeks [IQR: 3.0-8.6] vs. 4.00 weeks [IQR: 0.70-6.0], $P = 0.2904$ by Mann-Whitney U-test) [Figure 3]. Stepwise re-challenge identified an offending agent in two individuals: Rifampin in one individual and pyrazinamide in the other.

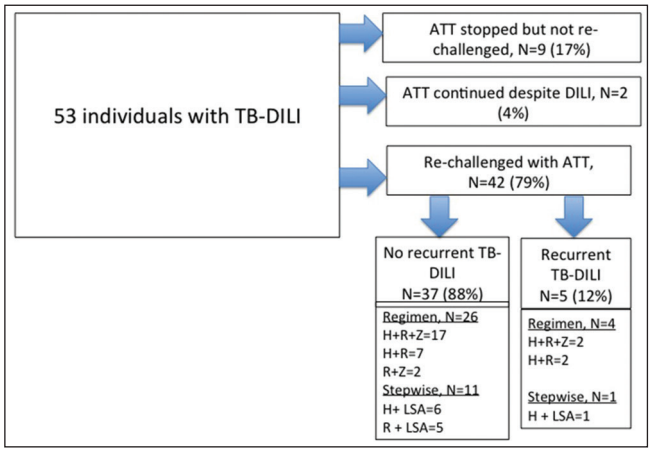

Figure 2: Method of antituberculous treatment (ATT) re-challenge and outcome of patients with tuberculosis drug-induced liver injury. Forty-two patients (79%) were re-challenged with ATT. 38 (88%) did not experience recurrent tuberculosis drug-induced liver injury while 5 (12%) experienced a recurrence. LSA: Liver-sparing agent

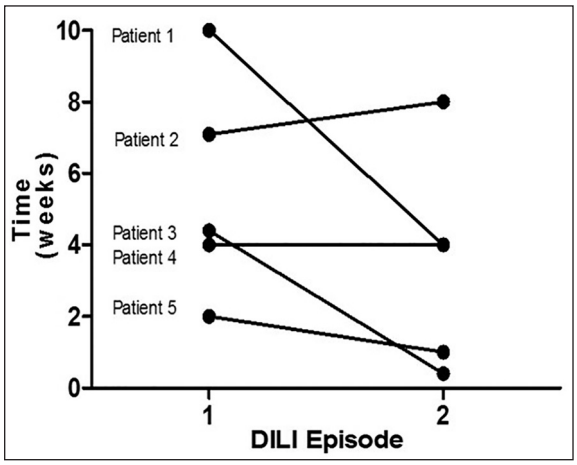

Figure 3: Time to tuberculosis drug-induced liver injury in individuals who experienced recurrence following re-challenge. Median time to the first episode of drug-induced liver injury was no different from the median time to the recurrence (4.40 weeks [interquartile range: 3.0-8.6] vs. 4.00 weeks [interquartile range: 0.70-6.0], $P = 0.2904$ by Mann-Whitney U-test)

The 10 subjects with hepatic co-morbidities (7 with HBV and/or HCV and 3 with alcohol abuse) were no different from those without such co-morbidities in terms of time to TB-DILI (median 4.0 weeks [IQR: 3.5-6.5] vs. 4.0 weeks [IQR: 2.0-10.0], $P = 0.7343$, Mann-Whitney U-test), time to normalization of liver enzymes (median 3.70 weeks [IQR: 2.150-5.0] vs. 3.0 weeks [IQR: 1.10-7.100], $P = 0.7052$, Mann-Whitney U-test), maximum ALT abnormality (median 582 U/L [IQR: 199-620] vs. 390 U/L [IQR: 208-632], $P = 0.6547$, Mann-Whitney U-test) or recurrence of TB-DILI ($P = 0.2773$, Fischer exact test).

Of the factors assessed for association with risk of recurrence, including gender, age, site of TB, CD4 count at initiation of ATT, concomitant use of nonnucleoside reverse transcriptase inhibitor drugs, maximum ALT, maximum bilirubin, clinical jaundice, time to DILI and time to enzyme normalization, only younger age (median 25 years [IQR: 23-30] vs. 34 years [IQR: 28-45], $P = 0.0245$, Mann-Whitney U-test) and higher total bilirubin levels (379 μmol/L [IQR: 246-511] vs. 74 [IQR: 25-137], $P = 0.0256$, Mann-Whitney U-test) were significantly associated with recurrence. Management of the second recurrence was individualized and varied widely in terms of drugs used in the re-challenge and time to re-challenge. On the second re-challenge, all drugs used were tolerated.

DISCUSSION

TB-DILI is thought to be an idiosyncratic reaction leading to hepatocellular injury and/or portal tract inflammation with cholestasis.[6] Although definitions of laboratory parameters that constitute TB-DILI vary in the literature, it is widely accepted that the diagnosis requires exclusion of all other causes of liver injury and a clear temporal relationship between treatment and liver injury.

Individuals with HIV infection are at increased risk of TB-DILI.[6-8] In a study of 198 patients from Brazil, the risk of hepatotoxicity was 7.5-fold greater in HIV-infected subjects compared to HIV-uninfected or those with unknown serostatus.[7] Another study from South Africa demonstrated similar increase risk of hepatotoxicity from ATT among HIV infected.[8] Although multiple factors are likely responsible for this excess risk, some believe a major contributor is that many HIV-infected individuals are on multiple potentially hepatotoxic drugs.[6] In an observational study from Ethiopia, risk factors for initial TB-DILI in HIV-infected individuals included body mass index <18.5 kg/m^2, disseminated TB, CD4 count <50 cells/μl, and WHO stage 4 disease.[9] In our study, we demonstrate that most subjects with HIV and TB co-infection who develop TB-DILI tolerate reintroduction of the anti-TB drugs. Recurrence is seen in a minority of individuals and the method of re-challenge does not impact on the risk of recurrence.

Table 3: Time to LFT normalization following ATT cessation for inpatients ($n = 22$)

Parameter	
Duration of hospital admission for TB-DILI, days (mean±SD)	26±19
Total bilirubin (ref: 0–17 μmol/L)	
Number of inpatients whose total bilirubin normalized during hospitalization (percentage of inpatients)	3 (13)
Time to normalization, days (median [IQR]; range)	32 (2-47); 2-47
ALT (ref: 10-45 U/L)	
Number of inpatients whose ALT normalized during admission (percentage of inpatients)	9 (40)
Time to normalization, days (median [IQR]; range)	28 (13-43); 12-62
ALP (ref: 42-121 U/L)	
Number of inpatients whose ALP normalized during admission (percentage of inpatients)	3 (13)
Time to normalization, days (median [IQR]; range)	26 (4-27); 4-27

Comprehensive LFT data was only available for inpatients during a hospital stay. LFT: Liver function tests, ATT: Antituberculosis therapy, SD: Standard deviation, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, IQR: Interquartile range, TB-DILI: Tuberculosis drug-induced liver injury

Table 4: Regimens used for re-challenge

Regimens	Patients re-challenged ($n = 42$)
Regimen re-challenge (n=30)	
H + R + Z	19
H + R	9
R + Z	2
Stepwise re-challenge (n=12)	
H + LSA	7
R + LSA	5

H: Isoniazid, R: Rifampin, Z: Pyrazinamide, LSA: Liver-sparing agent

The different approaches to re-challenge impact the duration of hospital stay and health care costs. Regimen re-challenge is quicker and more cost effective but, in the event of a recurrence, will not identify the offending drug. On the other hand, stepwise re-challenge may, arguably, facilitate the identification of the causative agent and possibly influence the risk of recurrence through hepatic adaptation.[10,11] With stepwise re-challenge identification of the offending agent assumes that recurrence will occur within the 3-5 day window of starting the next potentially hepatotoxic drug and that the responsible drug is the one most proximal to the recurrence. These assumptions are not necessarily true. In this study, half the recurrences occurred after 4 weeks of re-challenge suggesting that waiting 3-5 days before adding the next drug may not be adequate time to identify the offending agent.

In our study, 5 of the 43 subjects (12%) re-challenged had a recurrence of DILI, with no difference in recurrence irrespective of the method of re-challenge. Only two randomized controlled studies specifically addressed the question of different re-challenge methods on recurrence of DILI.[12,13] None of the studies included patients with HIV infection. Our findings were consistent with the randomized controlled trial by Sharma *et al*. that showed no difference in DILI recurrence with regimen re-challenge (14%) compared with sequential re-challenge with full doses (10%) and sequential re-challenge with incremental doses (9%).[12] However, a second study found that patients randomized to the regimen re-challenge had a significantly higher recurrence (24%) compared to patients with stepwise re-challenge with incremental dosing of each drug (0%).[13] A potential flaw in this study was that the investigators included pyrazinamide in the regimen re-challenge but excluded it from the stepwise re-challenge. They subsequently successfully re-challenged all the recurrences with a regimen excluding PZA, suggesting that PZA was the hepatotoxic agent.[13]

Eight out of 53 subjects with TB-DILI in our study had prior uneventful exposure to ATT suggesting that one cannot exclude the possibility of TB-DILI based on the absence of DILI with prior exposure to TB treatment. In this study, the vast majority of individuals were HIV-infected. Within the limits of our sample size, both re-challenge methods were safe with no statistically significant differences in recurrences of TB-DILI even in HIV-infected individuals.

Consistent with reports by others, we found that 75% of subjects developed TB-DILI within 8 weeks of ATT exposure,[4,9,12-15] highlighting a vulnerable period necessitating high vigilance. However, as demonstrated by one subject in our study, TB-DILI can occur as late as 8 months into treatment. We also found that no patient experienced worsening of their clinical condition while awaiting recovery from DILI off ATT. This suggests that it might be safe to monitor for recovery from DILI as an outpatient provided the patient is not infectious. Furthermore recurrences, if they occur, can be expected to occur within the same timeframe as the first episode making prolonged follow-up for recurrence unnecessary.

The range of ALT abnormalities observed was similar to that observed in other studies.[9,13] The time to normalization of ALT following discontinuation of ATT varied widely (median 28 days and range 12-62 days), and was comparable to that reported for HIV-uninfected individuals. Sharma *et al*. reported a median time to enzyme normalization of 18 days (range 14-28 days) and Tahaoglu *et al*. a mean of 18 days ± 19 days SD (range 6-102 days).[12,13]

Interestingly, we found that individuals who experienced recurrent TB-DILI were younger and had higher maximum bilirubin levels suggesting possible useful markers for risk stratification. It is likely that our small sample size precluded the identification of other risk factors for recurrence.

Some major limitations of our study were the small sample size and the retrospective nature of the study. Although we serve a large catchment area in a TB-endemic region, many cases of TB-DILI are managed by the primary care physicians and typically only complex cases are referred. This data cannot be used to determine the prevalence of TB-DILI in our region. In addition, due to the retrospective nature of the study, drugs used were not uniform for regimen and stepwise re-challenge. Ideally, a prospective randomized trial is needed to definitively determine the best method of re-challenge, but such a study would require large numbers to be adequately powered to answer the question.

In summary, the rate of TB-DILI recurrence in HIV-infected individuals is similar to that observed in HIV-uninfected individuals. Both regimen and step-wise re-challenge methods appear safe with no significant difference in TB-DILI recurrence. High bilirubin secondary to DILI might be a risk factor for recurrence. While awaiting prospective, randomized studies to address this question, this study provides some direction in an area where expert opinion dominates.[16]

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Nil.

Conflicts of interest

There are no conflicts of interest.

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