

Treatment outcomes among patients admitted to hospital with antiretroviral and/or antituberculosis drug-induced liver injury

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Background. South Africa (SA) has among the highest rates of HIV and tuberculosis (TB) in the world. Antituberculosis and antiretroviral treatment (ART) can cause drug-induced liver injury (DILI), consequences of which are disease relapse, treatment failure and drug resistance.

Objectives. To: (i) determine the demographics of patients with DILI and the proportion of patients on antituberculosis drugs v. antiretroviral therapy or both; (ii) determine the median time to DILI after starting medication, and patterns of clinical presentation; (iii) determine the numbers of patients successfully re-challenged to initial therapy as inpatients; and (iv) determine the in-hospital mortality rate and predictors of all-cause mortality.

Methods. This was a retrospective record review of adult patients with DILI admitted to a tertiary hospital in Johannesburg, SA, between October 2015 and February 2017. Data on drug history, biochemical investigations and relevant imaging were collected.

Results. The total sample was 129 records: 79 (61.2%) were males, 46 (35.7%) had TB DILI, 29 (22.5%) had ART DILI, and 54 (41.9%) had mixed TB/ART DILI. Only 7.4% (2/27) of those with ART DILI and 30.6% (11/36) with TB DILI were re-challenged to their original regimen by discharge. Patients were followed from admission until the earlier of death (10 with TB DILI, 2 with ART DILI and 9 with mixed DILI) or discharge (after a median (interquartile range) of 14.0 (9 - 23) days). In adjusted analysis, severe DILI at admission predicted all-cause mortality (adjusted hazard ratio 8.58; 95% confidence interval 1.13 - 65.4).

Conclusions. This study is one of only a few analyses of hospitalised patients with DILI in SA. Among those with severe DILI, outcomes are poor, the majority cannot tolerate standard regimens, and mortality is high.

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South Africa (SA) has one of the highest prevalence rates of HIV in the world.^[1] In 2019, the prevalence of HIV in SA was 19.07% among adults aged 15 - 49 years; 25.8% among females and 15% among males.^[1] Tuberculosis (TB), the most common opportunistic infection affecting HIV-positive individuals, continues to be the leading cause of death in SA.^[1]

Although the benefits of antiretroviral treatment (ART) and anti-TB treatment have been clearly demonstrated, both are associated with adverse drug reactions (ADRs). In general, HIV patients have a higher rate of ADRs to both TB and non-TB medications than the general population, and the risk of ADRs increases with the degree of immunosuppression.^[2] Drug-induced liver injury (DILI) is a well-recognised ADR of TB treatment and ART. It is estimated that DILI affects 5 - 33% of patients on TB treatment, although local data are limited.^[3] Depending on the regimen, 9 - 30% of patients on ART develop DILI.^[4] DILI complicates therapy, and can potentially affect adherence, lead to interruption of treatment and contribute to unfavourable outcomes.^[5,6] TB DILI in HIV co-infection is the most common adverse effect of treatment necessitating drug

interruption,^[5] which can lead to treatment failure, relapse or drug resistance.^[6] Inpatient mortality associated with hepatotoxicity from anti-TB medication is high (27%).^[6]

Concurrent treatment for HIV and TB creates several management challenges.^[7] Because ADRs are among the most important factors resulting in interruption of ART and anti-TB treatment, monitoring and managing adverse reactions is important.

Objectives

Local data on DILI are limited, so this study aimed to describe the characteristics and outcomes of patients with DILI presenting to a tertiary hospital in Johannesburg, SA. The results may help inform guidelines on the management of DILI, thereby improving treatment outcomes among patients on treatment for HIV and/or TB.

Methods

We conducted a retrospective review of an electronic database of HIV-positive adult (≥ 18 years) patients with DILI admitted to Helen Joseph Hospital, a 500-bed tertiary academic hospital in Johannes-

burg, between October 2015 and February 2017. Johannesburg is an area with a high burden of TB-HIV coinfection.

TB DILI is defined by the Southern African HIV Clinicians Society (SAHIVCS) as elevated alanine transaminase (ALT), >120 IU/L in symptomatic patients (nausea, vomiting, malaise, loss of appetite, abdominal pain or jaundice) or >200 IU/L in asymptomatic patients, or total serum bilirubin >40 mmol/L, provided other aetiologies such as acute viral hepatitis, autoimmune hepatitis and other liver diseases are ruled out.^[3] The upper limit of normal for ALT and total bilirubin according to the SA National Health Laboratory Service reference range is 40 IU/L and 21 mmol/L, respectively. Patients are managed according to the SAHIVCS guideline.^[3]

Materials

Patient information on demographics, presenting symptoms, date of onset of drug therapy, drug regimen (including other hepatotoxic drugs) and diagnosis of TB was recorded in an electronic database.

Liver function tests (alkaline phosphatase (ALP), gamma-glutamyl transferase, total bilirubin, ALT, aspartate aminotransferase and international normalised ratio) were monitored on admission and serially as indicated. Results of other tests, including CD4 count, HIV viral load, hepatitis B and hepatitis C status, autoimmune work-up, abdominal ultrasound and liver biopsy (if done to rule out other causes of liver injury), were collected.

Measures

TB patients were classified as bacteriologically confirmed if they were diagnosed through Xpert MTB/RIF (Cepheid, USA), smear microscopy or culture. Patients diagnosed via X-ray were classified as clinically diagnosed, while those with missing diagnostic information who were on anti-TB medication were considered to have presumptive TB.^[8]

TB DILI was defined as DILI in a patient with TB/HIV who was exclusively on anti-TB therapy, ART DILI as DILI occurring in a patient only on ART, and mixed DILI as occurring in a patient on both ART and anti-TB therapy.

The liver function tests were used to derive the R value (patient's ALT/40 divided by ALP/120), which was used to classify the pattern of liver enzyme elevation as hepatocellular ($R \geq 5$), cholestatic ($R \leq 2$) or mixed ($R > 2$ but < 5).

Based on the SAHIVCS definition, the patient's symptoms and liver enzymes were used to categorise the severity of DILI as mild (patient clinically well, with ALT >120 but <200 IU/L, total bilirubin <40 mmol/L), moderate (patient clinically well, with ALT >200 IU/L regardless of bilirubin results) or severe (patient clinically unwell and meets the DILI criteria).

The ART and anti-TB drug regimen on discharge was documented to establish how many patients were successfully re-challenged back to the initial drug regimen.

Statistical analysis

Demographic and clinical characteristics were summarised using frequencies for categorical variables and means with standard deviations for normally distributed data or medians and interquartile ranges (IQRs) for data not normally distributed. To compare demographic and clinical characteristics at baseline between the different types of DILI, we used the Wilcoxon rank-sum or Kruskal-Wallis test for non-parametric data, Student's *t*-test for parametric or normally distributed data, and the χ^2 test (or Fisher's exact test for sparse data) for proportions.

The primary outcome was all-cause mortality, predictors of which were assessed using Cox proportional hazards regression. Patients

were followed from date of admission until the earliest of death or discharge. Variables with a *p*-value <0.25 in the univariate analysis along with *a priori* variables were included in the final multivariate model. The hazard ratio (HR) and corresponding 95% confidence interval (CI) are presented. Because the number with the outcome of interest was limited ($n=21$) and to minimise the risk of overfitting, the final model was restricted by the number of predictors that could be added.

We determined whether use of concomitant medication (e.g. fluconazole, co-trimoxazole, amoxicillin-clavulanic acid, paracetamol or herbal medication) or abnormal ultrasound results (e.g. enlarged liver, echogenic, liver mass, micro-abscesses, intra-abdominal nodes or ascites) were associated with presenting with severe DILI. We used a log-binomial regression model to estimate the crude relative risk (RR) and 95% CI.

Sensitivity analysis considered all-cause mortality within 60 days, and patients were followed from the date of admission until the earliest of death, discharge or 60 days in hospital care. We used Kaplan-Meier survival curves to display survival probabilities from hospital admission within 60 days of follow-up for all-cause mortality. Analyses were conducted in Statistica and SAS version 9.3 (SAS Institute, USA).

Ethical considerations

Ethics approval was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg (ref. no. M170324).

Results

A total of 129 patients were included ($n=79$ (61.2%) males); the median (IQR) age was 35.4 (31.4 - 43.5) years, and 46 (35.7%) had TB DILI, 29 (22.5%) ART DILI and 54 (41.9%) mixed DILI (TB and ART).

Six patients were hepatitis B surface antigen-positive, but no patients were hepatitis C antibody-positive. Sixteen patients had an autoimmune screen; 3 were positive for antinuclear factor, whereas all antimicrobial antibodies and anti-liver-kidney antibodies were negative (Table 1).

The commonest symptom on presentation was nausea and/or vomiting ($n=60$ patients; 46.5%) while 55 (42.6%) had jaundice and 24 (18.6%) abdominal pain. Jaundice was more common in patients with ART DILI (72.4%) than in those with TB DILI (23.9%) and mixed DILI (42.6%) ($p<0.05$).

Patients on ART

On admission, 83 HIV-positive patients were on ART; 89.2% of them were on a fixed-dose combination (FDC) of tenofovir/emtricitabine/efavirenz. Two-thirds ($n=54/83$; 65.1%) presented with a mixed DILI and the remainder with ART DILI, consistent with the co-infection rates for Johannesburg.^[8] The median (IQR) CD4 count was 549 (345 - 741) cells/ μ L in those with ART DILI, and 92.3% of patients had a viral load <1 000 copies/mL. At presentation, most patients with mixed DILI were immunosuppressed (74.1% with a CD4 count <100 cells/ μ L), had a detectable viral load (54.3% had a viral load ≥ 100 copies/mL), and were receiving concomitant hepatotoxic medication (27.8% were on co-trimoxazole). The median time between ART initiation and DILI was 85 days in those with ART DILI v. 168 days in those with mixed DILI.

In two-thirds (62.1%) of patients with ART DILI, DILI was classified as severe, whereas the figure dropped to 55.6% among those with mixed DILI. The median (IQR) ALT, total bilirubin and GGT were highest in the ART DILI group at 626 (292 - 1 293) IU/L,

Table 1. Characteristics of patients admitted for DILI between October 2015 and February 2017

	All (N=129)	TB DILI (N=46) [†]	ART DILI (N=29) [‡]	Mixed DILI (N=54) [§]	p-value
Age (years)					
Median (IQR)	35.4 (31.4 - 43.5)	36.2 (33.2 - 43.8)	35.1 (28.5 - 40.3)	35.4 (31.2 - 43.6)	0.491
<35, n/N (%)	58/129 (45.0)	19/46 (41.3)	14/29 (48.3)	25/54 (46.3)	0.812
≥35, n/N (%)	71/129 (55.0)	27/46 (58.7)	15/29 (51.7)	29/54 (53.7)	
Gender, n/N (%)					
Female	50/129 (38.8)	18/46 (39.1)	8/29 (27.6)	24/54 (44.4)	0.946
Male	79/129 (61.2)	28/46 (60.9)	21/29 (72.4)	30/54 (55.6)	
Concomitant medication, n/N (%)					
Bactrim	25/123 (20.3)	9/40 (22.5)	1/29 (3.5)	15/54 (27.8)	<0.05
Fluconazole	9/123 (7.3)	3/40 (7.5)	1/29 (3.5)	5/54 (9.3)	0.624
Paracetamol	1/123 (0.8)	1/40 (2.5)	0/29 (0)	0/54 (0)	0.351
Amox-clavulanate	12/123 (9.8)	4/40 (10.0)	0/29 (0)	8/54 (14.8)	0.095
Symptoms at presentation, n/N (%)					
Nausea and/or vomiting	60/129 (46.5)	22/46 (47.8)	12/29 (41.4)	26/54 (48.2)	0.820
Abdominal pain	24/129 (18.6)	8/46 (17.4)	7/29 (24.1)	9/54 (16.7)	0.682
Jaundice	55/129 (42.6)	11/46 (23.9)	21/29 (72.4)	23/54 (42.6)	<0.05*
ART regimen at presentation, n/N (%)					
TDF/3TC/EFV	74/83 (89.2)	-	26/29 (89.7)	48/54 (88.9)	0.573
TDF/3TC/NVP	1/83 (1.2)	-	1/29 (3.5)	0/54 (0)	
d4T/3TC/EFV	1/83 (1.2)	-	1/29 (3.5)	0/54 (0)	
AZT/3TC/EFV	1/83 (1.2)	-	0/29 (0)	1/54 (1.9)	
ABC/3TC/EFV	2/83 (2.4)	-	1/29 (3.5)	1/54 (1.9)	
EFV/3TC	1/83 (1.2)	-	0/0 (0)	1/54 (1.9)	
ABC/3TC/LPVr	2/83 (2.4)	-	0/0 (0)	2/54 (3.7)	
TDF/3TC/LPVr	1/83 (1.2)	-	0/0 (0)	1/54 (1.9)	
CD4 count, cells/μL					
Median (IQR)	66 (20 - 228)	37.5 (13.0 - 70.0)	549.0 (345 - 741.0)	56.0 (19.0 - 108.0)	<0.05*
≤50, n/N (%)	56/129 (43.4)	28/46 (60.8)	2/29 (6.9)	26/54 (48.2)	<0.05*
51 - 100, n/N (%)	24/129 (18.6)	9/46 (19.6)	1/29 (3.5)	14/54 (25.9)	
101 - 250, n/N (%)	18/129 (13.9)	7/46 (15.2)	2/29 (6.9)	9/54 (16.7)	
251 - 500, n/N (%)	12/129 (9.3)	2/46 (4.4)	7/29 (24.1)	3/54 (5.5)	
>500, n/N (%)	19/129 (14.7)	0/46 (0)	17/29 (58.6)	2/54 (3.7)	
Viral load (copies/mL)					
Median (IQR)	611 (64 - 332 500)	57 400 (11 300 - 2 180 000)	549 (20 - 245)	1 230 (130 - 143 000)	<0.05*
<1 000, n/N	-	3/19 (15.8)	24/26 (92.3)	16/35 (45.7)	<0.05*
1 000 - 10 000, n/N	-	0/19 (0)	2/26 (7.7)	9/35 (25.7)	
≥10 000, n/N	-	16/19 (84.2)	0/26 (0)	10/35 (28.6)	
Time on ART (days), median (IQR)	-	-	85 (49 - 355)	168 (15 - 354)	0.373
TB regimen at presentation, n/N (%)					
RH	13/100 (13.0)	3/46 (6.5)	-	10/54 (18.5)	0.085
RHZE	73/100 (73.0)	35/46 (76.1)	-	38/54 (70.4)	
MDR	2/100 (2.0)	0/46 (0)	-	2/54 (3.7)	
Other	12/100 (12.0)	8/46 (17.4)	-	4/54 (7.4)	
TB diagnosis, n/N (%)					
Confirmed	76/100 (76.0)	38/46 (82.6)	-	38/54 (70.4)	0.473
Empirical	23/100 (23.0)	8/46 (17.4)	-	15/54 (27.7)	
Presumptive	1/100 (1.0)	0/46 (0)	-	1/54 (1.9)	
Site of TB, n/N (%)					
Pulmonary	55/98 (56.1)	21/45 (46.7)	-	34/53 (64.2)	0.343
Disseminated	35/98 (35.7)	20/45 (44.5)	-	15/53 (28.3)	
Extrapulmonary	4/98 (4.1)	2/45 (4.4)	-	2/53 (3.8)	
Other	4/98 (4.1)	2/45 (4.4)	-	2/53 (3.8)	
Time on TB treatment (days), median (IQR)	19.5 (5.0 - 59.5)	14.0 (0.0 - 35.0)	-	41.0 (15.0 - 92.5)	0.02*

Continued ...

Table 1. (continued) Characteristics of patients admitted for DILI between October 2015 and February 2017

	All (N=129)	TB DILI (N=46) [†]	ART DILI (N=29) [‡]	Mixed DILI (N=54) [§]	p-value
HBsAg, n/N (%)					
Negative	111/129 (86.1)	38/46 (82.6)	26/29 (29.7)	47/54 (87.0)	0.681
Positive	6/129 (4.7)	2/46 (4.4)	2/29 (6.9)	2/54 (3.7)	
Not done	12/129 (9.3)	6/46 (13.0)	1/29 (3.5)	5/54 (9.3)	
Hep C ab, n/N (%)					
Negative	102/129 (79.1)	34/46 (73.9)	26 (89.7)	42/54 (77.8)	0.252
Positive	0/129 (0)	0/46 (0)	0/29 (0)	0/54 (0)	
Not done	27/129 (20.9)	12/46 (26.1)	3/29 (10.3)	12/54 (22.2)	
Liver function, median (IQR)					
ALT (U/L)	193 (79 - 438)	135 (79 - 299)	626 (292 - 1 293)	125 (45 - 291)	<0.05*
Total bilirubin (mmol/L)	75 (25 - 153)	60 (17 - 108)	193 (75 - 286)	64 (21 - 127)	<0.05*
GGT (U/L)	245 (135 - 449)	200 (122 - 304)	322 (131 - 519)	294 (172 - 497)	0.041*
ALP (U/L)	221 (133 - 362)	192 (100 - 342)	272 (177 - 342)	254 (133 - 465)	0.274
Albumin (g/L)	20 (17 - 26)	17 (16 - 22)	30 (25 - 33)	19 (15 - 24)	<0.05*
INR	1.34 (1.2 - 1.8)	1.31 (1.17 - 1.58)	1.39 (1.21 - 2.15)	1.35 (1.20 - 1.81)	0.241
Severity of DILI, n/N (%)					
Mild	21/127 (16.5)	8/44 (18.2)	0/29 (0)	13/54 (24.1)	0.056
Moderate	35/127 (27.6)	13/44 (29.6)	11/29 (37.9)	11/54 (20.4)	
Severe	71/127 (55.9)	23/44 (52.3)	18/29 (62.1)	30/54 (55.6)	
Pattern of liver injury (R value), n/N (%)					
Hepatocellular	40/129 (31.0)	12/46 (26.1)	17/29 (58.6)	11/54 (20.4)	0.0010*
Cholestatic	55/129 (42.6)	20/46 (43.5)	4/29 (13.8)	31/54 (57.4)	
Mixed	34/129 (26.4)	14/46 (30.4)	8/29 (27.6)	12/54 (22.2)	

DILI = drug-induced liver injury; TB = tuberculosis; ART = antiretroviral treatment; IQR = interquartile range; TDF = tenofovir; 3TC = lamivudine; EFV = efavirenz; NVP = nevirapine; d4T = stavudine; AZT = zidovudine; ABC = abacavir; LPVr = lopinavir/ritonavir; R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; MDR = multidrug-resistant TB; HBsAg = hepatitis B surface antigen; Hep C ab = hepatitis C antibody; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase; ALP = alkaline phosphatase; INR = international normalised ratio.

*Significant ($p < 0.05$).

[†]TB treatment alone (HIV-positive not on ART).

[‡]ART alone (no TB treatment).

[§]TB treatment and ART.

193 (75 - 286) mmol/L and 322 (131 - 519) IU/L, respectively. Hepatocellular injury therefore predominated in those with ART DILI (58.6%), while cholestatic injury was noted more in those with mixed DILI (57.4%).

Patients on anti-TB therapy

On admission, 100 patients were on anti-TB therapy. The majority ($n=73$) were on rifampicin, isoniazid, pyrazinamide and ethambutol (RHZE), and 13 patients were on rifampicin and isoniazid only. Among those on anti-TB therapy, 76.0% had a confirmed diagnosis and more than half (56.1%) had pulmonary TB. Of TB patients with DILI, 46 presented with TB DILI and 54 with mixed DILI. For those with TB DILI, the median (IQR) CD4 count was 37.5 (13 - 70) cells/ μ L and 84.2% had a viral load ≥ 10 000 copies/mL. The median time between TB treatment initiation and DILI was 14 days for patients with TB DILI v. 41 days in those with mixed DILI.

The median (IQR) ALT, total bilirubin and GGT in patients with TB DILI was 135 (79 - 299) IU/L, 60 (17 - 108) mmol/L and 200 (122 - 304) IU/L, respectively. Just over half (52.3%) of those with TB DILI were classified as having severe disease, with the main pattern of liver injury being cholestatic (43.5%).

Patient outcomes

Of patients with ART DILI, only 7.4% were discharged on an FDC regimen, whereas 92.6% required a modified regimen (in which efavirenz was substituted with a protease inhibitor such as lopinavir-ritonavir) (Table 2).

Only 6 patients with TB DILI were discharged on the first-line regimen (RHZE) after successful re-challenge, and another 6 patients on a regimen containing rifampicin and isoniazid only. The majority of the patients (66.7%) were discharged on a modified regimen containing only one first-line drug or a bridging therapy regimen (such as moxifloxacin and ethambutol). Of those with mixed DILI, only 6 (13.3%) were discharged on RHZE, and 24 (57.5%) required a modified ART regimen. Patients were followed from admission until the earliest of death ($n=21$; 10 with TB DILI, 2 with ART DILI and 9 with mixed DILI) or discharge (after a median (IQR) of 14.0 (9 - 23) days).

Table 3 shows the results of ultrasound examination and the association with severity of DILI or as predictors of all-cause mortality. Presenting with an enlarged liver (>15 cm) as opposed to a liver of normal size was associated with severe DILI at admission (RR 1.39; 95% CI 0.99 - 1.96; $p=0.057$). In addition, patients who presented with an echogenic liver as opposed to a normal liver were five times more likely to die (HR 4.98; 95% CI 1.39 - 17.85; $p=0.014$). We found no association between use of concomitant hepatotoxic medication (e.g. fluconazole, co-trimoxazole, amoxicillin-clavulanic acid, paracetamol) or herbal medication and the severity of DILI at admission. Concomitant use of herbal or prescription medication did not predict all-cause mortality (Table 3).

Deaths were similar across sexes (male v. female: adjusted hazard ratio (aHR) 0.79; 95% CI 0.32 - 1.93), ages (≥ 35 v. <35 years: aHR 0.94; 95% CI 0.39 - 2.27) and pattern of liver injury (Table 4). Type of DILI (ART, TB or mixed) was not a predictor of all-

Table 2. Outcomes of patients admitted for DILI between October 2015 and February 2017

	All (N=129)	TB DILI (N=46) [†]	ART DILI (N=29) [‡]	Mixed DILI (N=54) [§]	p-value
Outcome, n/N (%)					
Discharge	108/129 (83.7)	36/46 (78.3)	27/29 (93.1)	45/54 (83.3)	0.263
Died	21/129 (16.3)	10/46 (21.7)	2/29 (6.9)	9/54 (16.7)	
Follow-up time (days), median (IQR)	14.0 (9.0 - 23.0)	19.0 (12.0 - 35.0)	9.0 (6.0 - 13.0)	15.0 (10.0 - 23.0)	<0.05*
All (N=108) TB DILI (N=36)[†] ART DILI (N=27)[‡] ART/TB DILI (N=45)[§]					
ART regimen at discharge, n/N (%)					
Same as regimen at presentation	22/72 (30.6)	-	2/27 (7.4)	20/45 (44.4)	0.010*
Modified	50/72 (69.4)	-	25/27 (92.6)	25/45 (55.6)	
TB regimen at discharge, n/N (%)					
Same as regimen at presentation	20/81 (24.7)	11/36 (30.6)	-	9/45 (20.0)	0.274
Modified	61/81 (75.3)	25/36 (69.4)	-	36/45 (80.0)	
TB regimen at discharge, n/N (%)					
RH	19/81 (23.5)	6/36 (16.7)	-	13/45 (28.9)	0.453
RHZE	12/81 (14.8)	6/36 (16.7)	-	6/45 (13.3)	
MDR	32/81 (39.5)	17/36 (47.2)	-	15/45 (33.3)	
Other	18/81 (19.8)	7/36 (19.4)	-	11/45 (24.2)	

DILI = drug-induced liver injury; TB = tuberculosis; ART = antiretroviral treatment; IQR = interquartile range; R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; MDR = multidrug-resistant TB.
 *Significant (p<0.05).
[†]TB treatment alone (HIV-positive not on ART).
[‡]ART alone (no TB treatment).
[§]TB treatment and ART.

cause mortality. In adjusted analysis, only severe DILI at admission predicted all-cause mortality (aHR 8.58; 95% CI 1.13 - 65.4) (Table 4).

To account for differences in follow-up time by severity of DILI (i.e. maximum 83 days for mild, 113 days for moderate and 120 days for severe), we conducted a sensitivity analysis. Fig. 1 shows the probability of retention in care over 60 days by severity of DILI. By 60 days, compared with patients admitted with mild DILI, those with severe DILI had a significantly elevated risk of death (aHR 11.3; 95% CI 1.46 - 87.54).

Discussion

Among HIV-positive patients admitted with DILI, we found that 24.7% and 30.6% of patients could be re-challenged on standard ART or anti-TB regimens, respectively, at discharge. Mortality was high, although similar to what has been described for clinical cohorts in the same setting (9% among HIV-positive patients within the first 6 months of ART, 23% among HIV-positive patients on ART with prevalent TB).^[9,10]

Consistent with other studies, we found that among HIV-positive adults admitted for DILI, most patients had a mixed DILI following combination ART and anti-TB therapy.^[11,12] Those with TB DILI presented a median of 14 days after drug initiation, or 41 days if they were on anti-TB therapy and ART, whereas in another study among outpatients presenting with TB DILI, the average time between TB treatment and time to DILI

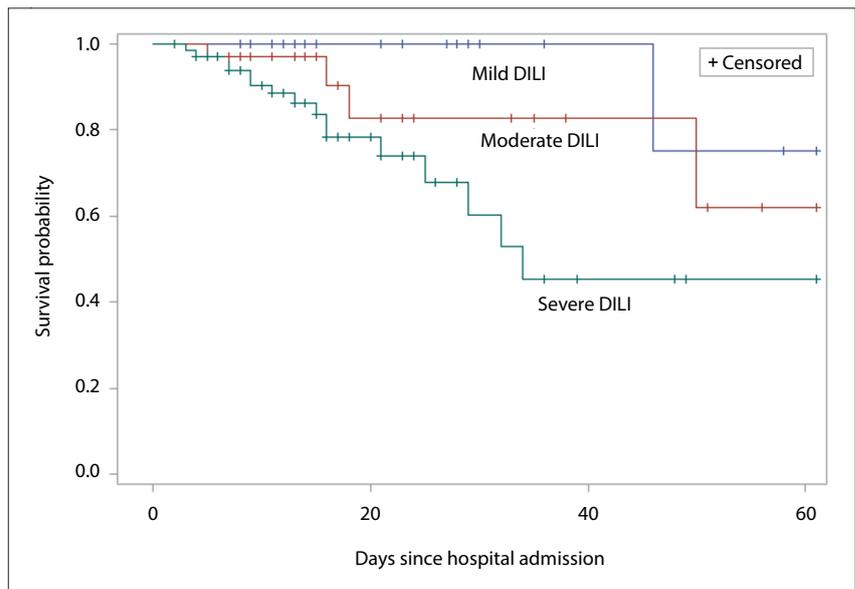


Fig. 1. Kaplan-Meier survival estimates for all-cause mortality following hospital admission (n=21). (DILI = drug-induced liver injury.)

diagnosis was 31 days.^[12] This difference reflects the severity of DILI requiring hospitalisation. The longest time between treatment initiation and presentation with DILI in this group was 92 days.

Patients with ART DILI presented later, with some presenting as late as 355 days after initiation of ART. Even though patients with ART DILI presented later with some immune reconstitution (higher CD4 counts and lower viral loads than those with TB DILI or mixed DILI), this group presented with greater severity of DILI and a predominantly

hepatocellular pattern. Jaundice, seen in nearly three-quarters of our patients, along with elevated liver function tests, despite responding to ART, should alert clinicians to the possibility of ART DILI. Despite the late presentation and greater severity of DILI, patients with ART DILI had the shortest hospital stay and the lowest mortality rate. While an FDC regimen is considered to pose a low risk for development of hepatotoxicity, <10% of patients with ART DILI could be successfully re-challenged back to the original regimen at discharge. Management

Table 3. Association between concomitant medication or ultrasound results and presenting with severe DILI, and concomitant medication or ultrasound results as predictors of all-cause mortality

	Severe DILI (N=71), n/N (%)	Crude RR (95% CI)	Death (N=21), n/N (%)	Crude HR (95% CI)
Concomitant medication				
Bactrim				
No	57/98 (58.2)	1.0	16/98 (16.3)	1.0
Yes	13/25 (52.0)	0.89 (0.59 - 1.35)	4/25 (16.0)	0.95 (0.32 - 2.85)
Fluconazole				
No	66/114 (57.9)	1.0	19/114 (16.7)	1.0
Yes	4/9 (44.4)	0.77 (0.36 - 1.62)	1/9 (11.1)	0.37 (0.05 - 2.98)
Paracetamol				
No	69/122 (56.6)	-	20/122 (16.4)	-
Yes	1/1 (100)	-	0/1 (0)	-
Amox-clavulanate				
No	65/111 (58.6)	1.0	16/111 (14.4)	1.0
Yes	5/12 (41.7)	0.71 (0.36 - 1.41)	4/12 (33.3)	1.88 (0.62 - 5.70)
Herbal medication				
No	70/123 (56.9)	-	20/123 (16.3)	-
Yes		-		-
Ultrasound results				
Enlarged liver (≥15 cm)				
No	31/54 (57.4)	1.0	8/54 (14.8)	1.0
Yes	12/15 (80.0)	1.39 (0.99 - 1.96)*	3/15 (20.0)	1.46 (0.38 - 5.62)
Echogenic				
No	30/52 (57.7)	1.0	4/52 (7.7)	1.0
Yes	13/17 (76.5)	1.33 (0.94 - 1.88)	7/17 (41.2)	4.98 (1.39 - 17.85)*
Liver mass				
No	71/126 (56.4)	-	21/126 (16.7)	-
Yes	0/1 (0)	-	0/1 (0)	-
Micro-abscesses				
No	61/104 (58.7)	1.0	16/104 (15.4)	1.0
Yes	10/23 (43.5)	0.74 (0.45 - 1.21)	5/23 (21.7)	0.90 (0.33 - 2.48)
Intra-abdominal nodes				
No	33/49 (67.4)	1.0	7/49 (14.3)	1.0
Yes	10/20 (50.0)	0.74 (0.46 - 1.20)	4/20 (20.0)	0.80 (0.23 - 2.83)
Ascites				
No	35/56 (62.5)	1.0	6/56 (10.7)	1.0
Yes	8/13 (61.5)	0.98 (0.61 - 1.58)	5/13 (38.5)	2.26 (0.68 - 7.58)
Ultrasound evidence of TB				
No	59/103 (57.3)	1.0	16/103 (15.5)	1.0
Yes	12/24 (50.0)	0.87 (0.57 - 1.35)	5/24 (20.8)	0.87 (0.32 - 2.40)

DILI = drug-induced liver injury; RR = relative risk; CI = confidence interval; HR = hazard ratio; TB = tuberculosis.

requires consideration of other causes of the deranged liver function, including viral hepatitis, other hepatotoxins, sepsis or a chronic liver condition.^[12]

The features of DILI in HIV-positive patients hospitalised for TB DILI or mixed DILI were similar; both groups presented with low CD4 counts and high viral loads, were less likely to present with symptomatic DILI or to have deranged liver function tests than patients with ART DILI, and had a cholestatic liver function pattern. One in four patients with TB DILI or mixed DILI could be successfully re-challenged back to the original TB regimen at discharge, with a higher proportion (44.4%) with mixed DILI re-challenged on their original ART regimen. In contrast to what we observed with ART DILI, while fewer patients with TB DILI or mixed DILI presented with severe DILI, these groups had the longest stay in hospital and a higher mortality rate (21.7% and 16.7% v. 6.9%

for ART DILI). Despite differences in presentation, only the severity of TB DILI at admission was a predictor of all-cause mortality. Age, gender, type of DILI or pattern of liver injury did not predict mortality. Revised monitoring algorithms with more frequent liver function tests (in the first 2 - 3 months of ART or TB treatment) may help to identify symptoms and raised liver enzymes early. Results suggest that patients with severe DILI and, while not significant, those with anti-TB or mixed DILI would probably benefit from early identification to reduce mortality.

Study limitations

The retrospective nature of the study has its limitations, including incomplete data on some patients, which limits interpretation of some results. Also, the study included patients admitted to a large urban tertiary hospital, so results may not be generalisable to other

Table 4. Predictors of death among patients admitted for DILI between October 2015 and February 2017 (N=129)

	Death (N=21), n/N (%)	Crude HR (95% CI)	Adjusted HR (95% CI) (model 2)
Exposure			
TB DILI [†]	10/46 (21.7)	0.92 (0.37 - 2.30)	
ART DILI [‡]	2/29 (6.9)	0.84 (0.18 - 3.97)	
Mixed DILI [§]	9/54 (16.7)	1.0	
Age (years)			
<35	9/58 (15.5)	1.0	1.0
≥35	12/71 (16.9)	0.97 (0.41 - 2.32)	0.94 (0.39 - 2.27)
Gender			
Female	8/50 (38.1)	1.0	1.0
Male	13/79 (61.9)	0.91 (0.38 - 2.21)	0.79 (0.32 - 1.93)
Concomitant medication			
No	14/95 (14.7)	1.0	
Yes, any	7/34 (20.6)	1.18 (0.48 - 2.93)	
CD4 count at presentation (cells/μL)			
≤50	7/56 (12.5)	0.5 (0.18 - 1.45)	
51 - 100	7/24 (29.2)	1.23 (0.43 - 3.54)	
>101	7/49 (14.3)	1.0	
Type of DILI			
Mild	1/21 (4.8)	1.0	1.0
Moderate	4/35 (11.4)	3.38 (0.38 - 30.25)	3.31 (0.37 - 29.72)
Severe	16/71 (22.5)	8.37 (1.10 - 63.65)	8.58 (1.13 - 65.38)*
Pattern of liver injury (R value)			
Hepatocellular	3/40 (7.5)	1.0	
Cholestatic	9/55 (16.4)	1.48 (0.40 - 5.51)	
Mixed	9/34 (26.5)	2.43 (0.66 - 9.03)	

DILI = drug-induced liver injury; HR = hazard ratio; CI = confidence interval; TB = tuberculosis; ART = antiretroviral treatment.

*Significant ($p < 0.05$).

[†]TB treatment alone (HIV-positive not on ART).

[‡]ART alone (no TB treatment).

[§]TB treatment and ART.

settings. We do not have any data on mortality after discharge, and it is possible that DILI could have recurred in some patients after re-challenge in an outpatient setting, potentially underestimating all-cause mortality associated with DILI. Data are not available to determine causes of death and to establish whether it was due to liver failure or sepsis as a result of drug withdrawal. Small numbers and a lack of data on duration or dose of concomitant herbal or prescription medication may have limited our ability to analyse whether these contribute to the severity of DILI, or place patients at increased risk for all-cause mortality. Similarly, only five patients had biopsy results, which limited our ability to consider this in the analysis. Prospective studies of DILI patients with longer follow-up would overcome some of these limitations with more complete data (e.g. including cause of death from mortuary registers). Future studies and/or analyses should also consider biopsy results for patient selection to rule out other causes of liver dysfunction if suspected.

Despite these limitations, we would like to make the following recommendations. Patients should be educated on the symptoms of DILI so that they can identify symptoms, distinguish these from adverse effects caused by drugs, and present earlier while still in the mild stage of illness. Patients should also be provided with a management plan in the event that DILI symptoms arise, and high-risk patients should be targeted for frequent monitoring of liver function (e.g. every 2 weeks in the intensive phase of TB treatment and monthly thereafter, or every month for the first 3 months in patients on ART and then at selected intervals thereafter).

Conclusions

This study is one of the few analyses of hospitalised patients with DILI in SA. Patients with TB DILI presented earlier, in the intensive phase of therapy, whereas those with ART DILI presented up to 1 year after ART initiation, highlighting the importance of maintaining a high index of suspicion and regular surveillance for earlier diagnosis of DILI. Among patients admitted with DILI, those with severe DILI were at increased risk of all-cause mortality. Large cohort studies with longer follow-up are required to predict which patients are at highest risk for DILI, the drugs responsible, and the long-term outcomes.

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Conflicts of interest. None.

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