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Original Article

Antitubercular therapy induced liver function tests abnormalities in human immunodeficiency virus infected individuals

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ARTICLE INFO

Article history:
Received 23 November 2016
Accepted 3 December 2016

Keywords:
Incidence
Drug induced liver injury
Antitubercular therapy
Antiretroviral therapy
HIV positive

ABSTRACT

Background: Both antitubercular therapy (ATT) and antiretroviral therapy (ART) can cause drug induced liver injury (DILI) in tuberculosis (TB) and human immunodeficiency virus (HIV) coinfection. The aim of this research was to study ATT-induced liver function test (LFT) abnormalities in HIV-infected patients.

Methods: HIV-infected patients diagnosed with TB were evaluated with baseline LFT and CD4 counts. ATT regimen was modified if baseline LFT was significantly abnormal. Patients on protease inhibitors were given rifabutin instead of rifampicin. In patients on nevirapine-based ART, efavirenz was substituted for nevirapine. In ART-naive patients, the timing of introduction of ART was according to CD4 cell counts. LFT were repeated fortnightly or as clinically indicated for 10 weeks.

Results: We studied 100 patients with HIV ([M – 67, F – 23], mean age: 40.05 ± 10.75 years, mean CD4 cell count: 239.157 ± 228.49 cells/dL). Sixty-one patients were on ART prior to diagnosis of TB. Baseline LFT abnormalities ($n = 40$) were similar in ART and non-ART group (28/61 vs 12/39, $p = 0.13$). After starting ATT, derangement of LFT was observed in majority of patients (99/100). However, liver sparing ATT was required only in 15 patients. Bilirubin >2.5 mg/dL was seen only in 9 patients. Significant rise in transaminases was commoner in patients on concurrent ART and ATT ($p = 0.044$) and with baseline LFT abnormalities ($p = 0.00016$). There was no case of acute liver failure or mortality.

Conclusion: Mild LFT abnormalities are common in HIV-infected individuals on ATT. Concomitant use of ATT and ART and baseline LFT abnormalities increase the risk of significant DILI. However, with closer follow-up, serious liver injury can be prevented.

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http://dx.doi.org/10.1016/j.mjafi.2016.12.003
0377-1237/

Introduction

Mycobacterium tuberculosis (MTb) is the commonest opportunistic infection in human immunodeficiency virus (HIV) infected persons.[1] We have effective antiretroviral therapy (ART) for HIV infection which has brought a substantial decrease in deaths related to acquired immunodeficiency syndrome (AIDS),[2–4] but it has also increased the drug induced liver injury (DILI) related to ART.[5,6] The reported incidence of ART-related severe DILI is approximately 10%, and life-threatening events occur at a rate of 2.6 per 100 person-years.[7,8] We also have very effective antitubercular therapy (ATT) for MTb infection but again three out of four first-line anti-TB drugs (isoniazid [H], rifampicin [R] and pyrazinamide [Z]) are associated with hepatotoxicity. While concomitant administration of ATT increases the risk of ART related severe DILI[9]; HIV infection and concurrent ART are important predictors of ATT related liver dysfunction.[10,11] The other risk factors associated with ART/ATT related DILI are Hepatitis B/C co-infection, poor nutrition status, low albumin levels, low CD4 cell count, pre-existing chronic liver disease, abnormal liver function tests (LFTs) at baseline, age >35 years, female gender and significant alcohol consumption.[8–12]

This study was carried out with an aim to study the LFT abnormalities in ATT naive HIV positive patients who were started on ATT and to study the pattern of liver dysfunction in these patients.

Materials and methods

This observational study was carried out at an ART Centre of Pune, Maharashtra and was conducted from August 2015 to October 2016. Pregnant and lactating women were excluded. Written informed consent was taken from all patients. The study was approved by the institutional ethics committee. We studied 100 ATT naive adult HIV patients who were diagnosed to have MTb infection and were started on ATT during the study period.

Evaluation included clinical examination, history regarding alcohol consumption and medication including ART, co-trimoxazole and other potentially hepatotoxic drugs. The diagnosis of MTb infection was clinical, radiological and histopathological examination of specimen (when available). Excessive alcohol use was defined as more than 20 g ethanol per day for men and more than 10 g ethanol per day for women. Baseline investigations including complete blood count, CD4 cell count, Hepatitis B surface antigen (HBsAg), antibodies against Hepatitis C virus (anti-HCV antibodies), and LFTs were done in all patients. The LFTs included serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum alkaline phosphatase (SAP), serum albumin and globulin. Grading of LFT abnormalities was done as under.

Grades of transaminitis

- Grade 1: 1–2× upper limit of normal (ULN) (40–80 IU/L)
- Grade 2: >2–3.0× ULN (81–120 IU/L)
- Grade 3: >3–5.0× ULN (121–200 IU/L)
- Grade 4: >5× ULN (>200 IU/L)

Grades of hyperbilirubinemia

- Grade 1: 1–1.5 mg/dL
- Grade 2: 1.6–2.5 mg/dL
- Grade 3: 2.6–5 mg/dL
- Grade 4: >5 mg/dL

Significant LFT abnormalities was defined as AST/ALT > 3 times the ULN, i.e., >120 IU/L and/or serum bilirubin >2.5 mg/dL. For defining the pattern of liver injury in those with significant DILI, we used ratio of serum ALT to SAP levels as multiple of their ULN (R = [ALT/ULN]/[ALP/ULN]).[14]

Pattern of DILI

- R ≤ 2: cholestatic pattern of DILI
- R > 2 and <5: mixed pattern of DILI
- R ≥ 5: hepatocellular pattern of DILI

Introduction of ATT

Patients without significant baseline LFT abnormalities (except those on protease inhibitors) were started on standard ATT (isonazid [H], rifampicin [R], pyrazinamide [Z] and ethambutol [E]). The patients who were on protease inhibitors based therapy were prescribed rifabutin instead of rifampicin. Patients with significant baseline LFT abnormalities were given liver sparing ATT (streptomycin [S], ethambutol [E], levofloxacin [L]).

ART

Details of ART prior to starting ATT were noted. The ART experienced patients who were on nevirapine based ART, were shifted to efavirenz based therapy. ART naïve patients were started on tenofovir, lamivudine and efavirenz (TLE) as per 2015 World Health Organization (WHO) guidelines for treating HIV-tuberculosis (TB) co-infection. Those with CD4 cell count <50 cells/dL were concurrently started on ATT and ART at first visit; patients with CD4 cell count between 50 and 350 cells/dL were given ART after 2 weeks of ATT; and the patients with higher CD4 cell count (>350 cells/dL) were prescribed ART after 8 weeks of ATT.

Follow-up of patients and ATT modification

All patients were followed up fortnightly for 10 weeks. Patients who had significant LFT abnormalities at baseline or who developed significant LFT abnormalities during follow-up were monitored more frequently, i.e., every 3 days as per American Thoracic Society (ATS) guidelines.

ATT was modified to liver sparing ATT if patients became icteric, became symptomatic with AST/ALT > 3× ULN or if transaminases rose to >5× ULN in asymptomatic patients. The standard ATT was re-introduced sequentially as per the ATS guidelines[11] once the ALT was less than 2× ULN.

Table 1 – Baseline characteristics in ART and non-ART group.[a]

	Patients taking ART (61)	Patients not taking ART (39)	p value
Age (years)	37.52 ± 9.61	44 ± 11.36	$p = 0.003$ (95% CI = 2.28–10.68)
BMI (kg/m^2)	19.8 ± 3	19.97 ± 2.97	$p = 0.782$ (95% CI = −1.046–1.39)
Hb (g/dL)	10.15 ± 2.89	10.67 ± 2.67	$p = 1$ (95% CI = −1.142–1.142)
TLC (dL^{-1})	5584.9 ± 2315.8	6387.89 ± 1678.87	$p = 0.064$ (95% CI = −48.15–1654.13)
Platelets (lacs/dL)	2.41 ± 1.01	2.23 ± 0.82	$p = 0.353$ (95% CI = −5.63–0.202)
CD4 count (cells/dL)	205.72 ± 247.94	267.25 ± 184.89	$p = 0.181$ 95% CI = −29.53–154.03
Albumin (g/dL)	3.346 ± 0.677	3.34 ± 0.689	$p = 0.966$ 95% CI = −0.283–0.271

ART, antiretroviral therapy; BMI, body mass index; Hb, haemoglobin; TLC, total leucocyte count; CI, confidence interval.
[a] All values in mean ± SD.

Statistical analysis

Tests for significant difference in means and proportions for various parameters were done. A '*p*' value of less than or equal to 0.05 was considered statistically significant.

Results

We followed up 100 ATT-naive HIV infected patients (mean age: 40.05 years ± 10.75 [M – 67, F – 23]) who were recently detected to have MTb infection. Disseminated TB was diagnosed in 58/100 patients; and the rest had pleuropulmonary infection. The mean body mass index (BMI) was 19.9 ± 2.97 kg/m^2. The mean CD4 cell count was 239.157 ± 228.49 cells/dL and the mean albumin concentration was 3.346 ± 0.677 g/dL. None of the patients was positive for HBsAg or anti-HCV antibody. At the time of diagnosis of TB, 61 patients were already on ART; 51 patients were on non-nucleoside reverse transcriptase inhibitors (efavirenz [*n* = 40] or nevrapine [*n* = 11]), 10 patients were on protease inhibitors (PIs) (ritonavir boosted lopinavir [*n* = 8] or ritonavir boosted atazanavir [*n* = 2]). All 61 patients were on two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) (tenofovir [*n* = 45], zidovudine [*n* = 15] or abacavir [*n* = 1] and either on lamivudine [56] or emtricitabine [5]). A total of 73 patients were on cotrimoxazole at baseline and 60 patients were on fluconazole. Significant alcohol consumption was reported in 38 patients.

Table 2 – Baseline LFT abnormalities in ART and non-ART group.

	Patients taking ART (61)	Patients not taking ART (39)	p value
LFT abnormalities (>ULN)	28	12	$p = 0.13104$
Grade 1	19	10	(z = 1.5066)
Grade 2	4	2	
Grade 3	4	0	
Grade 4	1	0	
Significant LFT abnormalities			
Transaminitis			
3–5 ULN	4	0	
>5 ULN	1	0	
Hyperbilirubinemia			
>2.5 mg/dL	2	0	
Grades of hyperblirubinemia (AIDS Clinical Trials Group)[13]			
Grade 1	0	2	
Grade 2	0	1	
Grade 3	1	0	
Grade 4	1	0	

ART, antiretroviral therapy; LFT, liver function test; ULN, upper limit of normal; AIDS, acquired immunodeficiency syndrome.

LFT abnormalities at baseline

At baseline, 40/100 patients (males – 34, females – 6) had raised transaminases (grade 1–29, grade 2–6, grade 3–4, grade 4–1). The baseline characteristics of these patients were no different from rest of the cohort. The mean age was 40.63 ± 9.77 years which was similar to that of the cohort ($p = 0.77$). The mean BMI (19.32 ± 2.6 kg/m^2) and mean albumin (3.357 ± 0.825 g/dL) was comparable to whole cohort (95% confidence interval (CI): −1.16 to 0.48, $p = 0.28$, 95% CI: −0.2560 to 0.2780, $p = 0.94$). The mean CD4 cell count of this group was 182.68 ± 161.23 cells/dL which was no different from rest of cohort (95% CI: −21.82 to 134.77, $p = 0.16$). There is a negative correlation between CD4 cell count and ALT values; however the relationship is very weak (r: −0.1634, r^2: 0.0267).

Table 1 summarizes the baseline characteristics of patients on ART and not on ART. The patients on ART had a lower mean age. There was no difference between the prevalence of baseline LFT abnormalities in ART and non-ART group ($p = 0.13$, Table 2) nor did significant alcohol consumption made any difference in baseline LFT abnormalities (15/40 vs 23/60, $p = 0.93$). Concurrent use of co-trimoxazole (31/40 vs 46/60, $p = 0.92$) and fluconazole (26/40 vs 34/60, $p = 0.41$) also made no difference in baseline LFT abnormalities.

There were 5 patients who had significant LFT abnormalities. All 5 patients were on ART (tenofovir = 4, zidovudine = 1, effavirenz = 3, nevirapine = 1, ritonovir boosted lopinavir = 1) and cotrimoxazole prophylaxis, while 4 patients were also on fluconazole in addition. Three patients had history of

Table 3 – Follow-up of LFT abnormalities in ATT alone and concurrent ATT and ART groups.

	1st visit (n)	02 weeks (n)	04 weeks (n)	06 weeks (n)	08 weeks (n)	10 weeks (n)
LFT abnormalities (on ATT alone)	12 (39)	23 (38)	28 (32)	31(32)	32(32)	NIL
• Mild (Grade 1 and 2)	12	23	28	31	31	
• Significant (Grade 3 and 4)	0	0	0	0	01	
LFT abnormalities (on ATT and ART group)	28 (61)	42 (62)	61 (68)	68 (68)	67 (68)	99 (100)
• Mild (Grade 1 and 2)	23	35	54	56	45	85
• Significant (Grade 3 and 4)	05	7	7	12	12	14
Grades of hyperbilirubinema (on ATT alone)	03 (39)	10 (38)	15(32)	17(32)	18 (32)	NIL
• Mild (Grade 1 and 2)	03	08	15	15	16	
• Significant (Grade 3 and 4)	00	02	0	02	02	
Grades of hyperbilirubinema (on ATT and ART)	2 (61)	15 (62)	21 (68)	31 (68)	25 (68)	48 (100)
• Mild (Grade 1 and 2)	0	12	15	24	18	39
• Significant (Grade 3 and 4)	2	3	6	7	7	9

n, total number of patients; LFT, liver function test; ATT, antitubercular therapy; ART, antiretroviral therapy; ULN, upper limit of normal; AIDS, acquired immunodeficiency syndrome; G, grade.

significant alcohol consumption; however none had features of chronic liver disease. Significant hyperbilirubinemia was found in two patients.

All 100 patients were started on ATT, ART and co-trimoxazole prophylaxis (73/100 were already on cotrimoxazole; 27 were started afresh). While standard ATT (isoniazid, rifampicin, pyrazinamide and ethambutol [HRZE]) was started in 86 patients; 5 patients with significantly abnormal LFT abnormalities were started on liver sparing ATT. Nine patients on protease inhibitors based ART were given rifabutin instead of rifampicin. One patient with CD4 cell count of 37 cells/dL was started on ART at first visit and 6 patients with CD4 cell count between 50 and 350 cells/dL were started on ART after 2 weeks of ATT and the rest 32 patients were started on ART by end of 8 weeks. Eleven patients on nevirapine were shifted to efavirenz-based therapy.

Follow-up of cohort

Almost all patients (99/100) developed transaminitis on follow-up. However majority of patients (85/99) had mild rise in transaminases. At 8 weeks, 32 patients were started on ART. Out of these, at week 8, only 1/32 patient had significant transaminases whereas 12/68 patients receiving ART had developed significant derangement of LFT ($z = 2.0143$, $p = 0.044$) (Table 3).

Hyperbilirubinemia was found in 48/100 patients; however significant rise in bilirubin (>2.5 mg/dL) was seen only in 9 patients at 8 weeks (combined ATT and ART = 7, only ATT = 2). There was no statistically significant difference in incidence of new LFT abnormalities in patients with normal (37/60) and abnormal LFTs at baseline (22/40, $z = 1.75$, $p = 0.08$). However the new onset significant LFT abnormalities (transaminases >3× ULN) were commoner in group with baseline LFT abnormalities (12/40 vs 2/60, $z = 3.77$, $p = 0.00016$).

Significant LFT abnormalities

At end of 10 weeks, 14 patients (males = 11/67, females = 03/23, $z = -0.038$, $p = 0.69$) had significant transaminitis. Eight patients had in addition significant hyperbilirubinemia. There was no difference in mean age (43.04 ± 11.34 years), mean BMI (20.26 ± 3.28 kg/m^2), mean albumin (3.27 ± 0.74 g/dL) and the mean CD4 cell count (156.54 ± 153.94 cells/dL) of this group from rest of the cohort, nor did concurrent co-trimoxazole and fluconazole made any statistical difference ($p > 0.05$). However significantly more number of patients were on ART in this group at week 8 ($p = 0.044$).

At the start of study, 5 patients were on modified ATT; during follow-up 10 more patients required liver sparing ATT. The standard ATT was reintroduced in 6 patients as per ATS guidelines by the end of the study period. None of our patients developed features of acute liver failure (ALF) and there was no mortality.

Pattern of LFT abnormalities

Of the patients with significant LFT abnormalities at baseline, 3/5 patients had mixed pattern of liver injury (R: 2–5). At the end of the study, 14 patients had significant LFT abnormalities, of which 11 patients had mixed pattern of liver injury (R: 2–5), 2 patients had hepatocellular pattern of liver injury ($R > 5$) while 1 patient had cholestatic pattern ($R \leq 2$).

Discussion

HIV and MTb co-infection is amongst the greatest killers of this century. Irrespective of the CD4 cell count and ART therapy, the risk of death in co-infected individuals is twice that of HIV positive patients without TB.[15] While HIV infection speeds up the progression from latent to active TB almost 12–20 times,[1,16] TB bacteria accelerates the progress of HIV infection to full blown AIDS.[17] In 2013, an estimated 1.1/9 million (13%) people who developed TB, were HIV positive. In the same year, 25% of all TB deaths (360,000), and 25% of all deaths in HIV positive people (1.5 million) were in co-infected HIV-TB patients.[12]

Today we have effective multi drug therapy in form of ART and ATT for HIV and MTb infections respectively. But both ART and ATT are potentially hepatotoxic. Almost 5–33% patients on first line ATT[18] and around 9–30% patients on ART (depending on regimen) develop DILI.[19] Even in the absence of ART, there

is twofold higher risk of ATT related DILI in HIV positive individuals.[20,21]

The basic principles of management of HIV-TB coinfection include timing of institution of ART and ATT depending on CD4 cell count, avoidance of nevirapine due to hepatotoxicity and use of rifabutin instead of rifampcin in patients on PIs. As per WHO guidelines for treating HIV infection, all patients with HIV-TB co-infection should be started on ART irrespective of the CD4 cell count. The timing of introduction of ART depends on the CD4 cell count and the risk of dying from HIV infection if ART is delayed. For patients with CD4 cell count <50 cells/dL, ART should be introduced within 2 weeks of starting ATT; in rest the initiation of ART may be delayed till the completion of intensive phase of ATT (8 weeks). This time gap is kept to prevent Immune Reconstitution Inflammatory Syndrome (IRIS) which is known to occur in 11–45% of patients co-infected with HIV-TB.[22] However at lower CD4 cell count, the risk of dying from untreated HIV infection due to various opportunistic infections is more than the risk of morbidity and mortality from IRIS.[23] The HIV positive patients who are on nevirapine based ART should be shifted to efavirenz based therapy to prevent enhanced hepatotoxicity when ATT is co-administered with nevirapine based ART.[20] Also the patients on PIs should be given rifabutin instead of rifampicin to prevent potential drug interactions; or else the dose of PIs is to be increased.[24] To prevent drug induced ALF, all patients who become symptomatic with transaminases >3× ULN or those with transaminases >5× ULN irrespective of symptoms; standard four drug ATT should be substituted with liver sparing ATT.[9,10] Apart from this; any other potentially hepatotoxic drug should be discontinued.[18]

We studied 100 ATT naive HIV patients who were recently started on ATT. 40% of our patients had LFT abnormalities at baseline which is comparable to other studies[25,26] but only 5 patients had significant LFT abnormalities at baseline (all in ART group, Table 2) standard four drug ATT was started in 95 patients and 5 were given liver sparing ATT. Eleven patients on nevirapine based ART were shifted to efavirenz based therapy and nine patients on PIs were given rifabutin instead of rifampicin. All 39 ART naive patients were started on ART during the study period. In patients with higher CD4 cell count (32/39), ART was introduced only after intensive phase of ATT (at 8 weeks). During follow-up, most of the patients developed mild transaminitis (99/100); however LFT abnormalities requiring modification of ATT was seen only in 15 patients. As per ATS guidelines, we followed all patients fortnightly, however the patients with significant LFT abnormalities were followed every 3 days till the time ALT decreased to less than 2× ULN. We could reintroduce standard ATT in 6 of our patients during the study period.

At 8 weeks, significant LFT abnormalities were lower in patients who were yet not exhibited ART emphasizing the dual hepatotoxicity of ART and ATT.[27–29] Also the patients who had abnormal baseline LFT abnormalities were more likely to have new significant LFT abnormalities when started on ATT as has been documented in earlier studies.[30] The most common pattern of liver injury found in HIV-TB co-infected patients is mixed type[18] as documented in our study as well. Three of the four standard ATT drugs and almost all ART drugs are associated with DILI.[19,31,32] Rifampicin can interfere with bilirubin uptake, resulting in unconjugated hyperbilirubinaemia.[11] Pyrazinamide may cause both hepatocellular injury and granulomatous hepatitis. Mono-acetyl hydrazine, one of the main metabolites of isoniazid is toxic to hepatocytes. Co-trimoxazole prescribed as preventive therapy or treatment for *Pneumocystis jirovecii* or toxoplasmosis is associated with cholestatic jaundice and hepatic necrosis both.[33] It is very difficult to differentiate hepatic TB-IRIS from DILI attributed to ATT, ART or co-trimoxazole. Tender hepatomegaly, maintained synthetic liver function, increased levels of SAP, absence of jaundice, and the presence of IRIS features in other organs may suggest IRIS rather than DILI; however definite diagnosis can be established only by a liver biopsy which is invasive and not always feasible.[34] When in doubt, it is safer to manage LFT abnormalities as DILI rather than IRIS.

The other documented predictors of severe liver injury like older age, low CD4 cell count, low BMI, low albumin levels and female gender, drugs like fluconazole and cotrimoxazole[7,9,10] were not associated with higher or severe LFT abnormalities in our cohort. This may be due to comparable baseline characteristics of our cohort. We could continue ART and co-trimoxazole in all our patients; 15 patients required modified ATT owing to significant LFT abnormalities. Standard ATT could be successfully re-introduced in six patients. None of our patients had life threatening DILI; none had drug induced ALF which has been documented to be as high as 27–35% in patients with significant DILI.[35] This highlights the importance of regular follow-up of these patients and timely change in therapy as per the existing guidelines to prevent drug induced ALF.

Conclusion

Mild LFT abnormalities are extremely common in HIV-TB co-infected patients on ATT. However significant LFT abnormalities requiring change in therapy are common in concurrent ATT-ART group and the ones who had baseline LFT abnormalities. A meticulous follow-up and timely change of therapy may prevent serious adverse events like drug induced ALF in these patients.

Conflicts of interest

The authors have none to declare.

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