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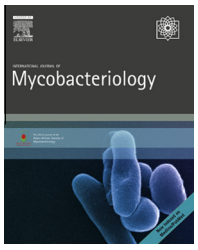

Antituberculosis drugs and hepatotoxicity among hospitalized patients in Jos, Nigeria

Samson E. Isa [a,b,*], *Augustine O. Ebonyi* [b,c], *Nathan Y. Shehu* [a,b], *Patrick Idoko* [a], *Joseph A. Anejo-Okopi* [b,d], *Gomerep Simji* [a], *Rachael U. Odesanya* [e], *Isaac O. Abah* [e], *Hafsat O. Jimoh* [e]

[a] *Department of Medicine, University of Jos/Jos University Teaching Hospital, Jos, Nigeria*
[b] *AIDS Prevention Initiative in Nigeria (APIN), Jos University Teaching Hospital, Jos, Nigeria*
[c] *Department of Pediatrics, University of Jos/Jos University Teaching Hospital, Jos, Nigeria*
[d] *Department of Microbiology, University of Jos, Jos, Nigeria*
[e] *Department of Pharmacy, Jos University Teaching Hospital, Jos, Nigeria*

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ABSTRACT

Background: Tuberculosis (TB) could be fatal if left untreated, however, adverse effects of anti-TB medications (anti-TBs) themselves may limit treatment. We determined the incidence and clinical characteristics of hepatotoxicity in hospitalized patients receiving first-line anti-TB treatment.

Methods: A retrospective cohort study of patients aged ⩾18 years seen at the medical wards of the Jos University Teaching Hospital from January 2013 to June 2013 was carried out. Data were retrieved for 110 patients who were prescribed anti-TBs. Their demographic and clinical characteristics were described, and the incidence of symptomatic hepatotoxicity determined. The incidence of hepatotoxicity by strict American Thoracic Society criteria (symptomatic hepatotoxicity plus alanine transaminase in IU/L levels >3 × upper limit of normal) was also determined.

Results: Twenty patients developed symptomatic hepatotoxicity, giving an incidence of 18.2%. Furthermore, 18 (16.4%) patients had hepatotoxicity according to the American Thoracic Society criteria. Those with symptomatic hepatotoxicity unexpectedly had lower baseline alanine transaminase interquartile range (IQR) (35 [16–63] vs. 67 [4–226]; $p = .04$) and bilirubin (μmol/L): total IQR (15.3 [10.2–74.8] vs. 20.4 [20.4–20.4]; $p = .01$) and conjugated IQR (7.6 [5.1–34.8] vs. 10.2 [10.2–10.2]; $p = .004$). However, there were no significant differences in age, sex, body mass index, and duration of anti-TB treatment, human immunodeficiency virus infection status, antiretroviral therapy status, alcohol consumption, and the presence of hepatitis B surface antigen or hepatitis C virus antibody.

Conclusion: Hepatotoxicity due to first-line anti-TBs, whether based on clinical features alone or backed by liver chemistry, is common among hospitalized patients in our environment. Studies to determine the predictors of hepatotoxicity to guide clinical interventions aimed at the prevention or timely identification of cases are needed.

* Corresponding author at: Department of Medicine, Jos University Teaching Hospital, PMB 2076, Jos, Nigeria.
E-mail address: ejijisa@yahoo.com (S.E. Isa).

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Introduction

Tuberculosis (TB) is one of the most common infectious diseases and there were an estimated 9 million incident cases worldwide according to the global tuberculosis report of 2014 [1]. Since the scale-up of nationwide directly observed treatment (DOTS) in 2002 in Nigeria, a total of 640,113 of all forms of TB have been registered, with 90,447 notifications (400/100,000 population) in 2008 alone [2]. The first line regimen which requires administration of a combination of anti-TB medications (anti-TBs) for 6–9 months achieved a treatment success rate of about 84%, a death rate of 5%, and a defaulter rate of 8% in Nigeria [2]. The DOTS program, which has established or strengthened linkages with tertiary hospitals in recent years, is the major provider of TB treatment using the standard short course chemotherapy [2].

Adverse drug reactions to anti-TBs could lead to treatment interruptions with resultant poor outcomes, including the risk of drug resistance [3]. Hepatotoxicity is one of the most important adverse drug reactions associated with anti-TBs [4], and depending on the definition of hepatotoxicity, the incidence range is from 2% to 28% [5]. Although it may be challenging to predict when hepatotoxicity will occur, it is known that certain patient characteristics put them at higher risk. These include hepatic abnormalities, like chronic hepatitis B virus and hepatitis C virus (HCV), disseminated TB, Asian ethnicity, female sex, significant alcohol use, concurrent administration of other hepatotoxic medications, being elderly, and being malnourished [6–9]. Although human immunodeficiency virus (HIV)/AIDS is significantly associated with development of hepatotoxicity [10], the reason for this association is obscure. However, this may be as a result of excessive immune activation leading to less efficient handling of oxidative stress and detoxification of drug metabolites [11].

The advantage of regular monitoring of liver function test (LFT) in patients receiving anti-TBs, especially in countries where health budgets are meagre, has not been clearly established. However, the prevention or early detection of hepatotoxicity is important as morbidity and mortality can be substantial among those with symptomatic hepatotoxicity. Some guidelines only emphasize clinical monitoring while others additionally recommend routine biochemical monitoring at varying frequencies among the high risk groups [12,13]. Although there are attempts to improve the quality of patient care under DOTS, data on anti-TB hepatotoxicity in Nigeria, whether clinical or biochemical, are scarce. We describe the incidence and the clinical and laboratory characteristics of hospitalized patients receiving anti-TBs who developed hepatotoxicity at the Jos University Teaching Hospital (JUTH), Jos, Nigeria.

Materials and methods

This was a retrospective cohort study of new TB cases aged ⩾18 years seen at the infectious diseases wards of JUTH from January 2013 to June 2013 who were receiving first line anti-TBs. Data were retrieved from the case notes of all of the 110 patients seen in that period who met the inclusion criteria. Usually, all patients starting anti-TBs have baseline LFT done, however, it is only repeated in those who developed hepatotoxicity or if there are other indications. The data collected included: socio-demographic data (age, sex, and alcohol consumption), features of symptomatic hepatotoxicity (including fatigue, loss of appetite, nausea, vomiting, right hypochondrial pain/tenderness, fever, and jaundice), pulmonary or extrapulmonary TB, HIV status, combination antiretroviral therapy (cART) status, and body mass index (BMI; kg/m^2). Laboratory data included alanine transaminase (ALT; IU/L), aspartate transaminase (IU/L), total and conjugated bilirubin (μmol/L), total serum protein and albumin (g/L), hepatitis B surface antigen (HBsAg), and HCV antibody (anti-HCV).

Diagnosis of TB was based on Ziehl–Neelsen sputum smear microscopy, GeneXpert assay, or any combination of clinical and radiological/pathological evidence. Hepatotoxicity was defined as: (1) any combination of newly developing or worsening features of symptomatic hepatitis with a temporal relationship to anti-TB initiation without an apparent alternative explanation; (2) a stricter increase in serum ALT >3 times upper limit of normal (ULN) together with features of symptomatic hepatitis according to the American Thoracic Society (ATS) [13]. This is a part of the ATS definition which also considers ALT >5 times ULN in the absence of symptoms as hepatotoxicity. Our laboratory normal reference for both ALT and aspartate transaminase was <40 IU/L, and <17 μmol/L for total bilirubin. All admitted patients are routinely reviewed and the diagnosis of hepatotoxicity was made by at least a specialty registrar.

We also excluded those who were not prescribed a standard anti-TB regimen or who were already on anti-TBs before hospital admission. Standard anti-TB regimen is: isoniazid, rifampicin, ethambutol, and pyrazinamide with dosages decided according to the weight of the patient [2]. Ethical approval was obtained from the JUTH Ethics Committee.

Statistical analyses

Analyses were carried out using Stata software version 10.0 (Stata Corporation, College Station, TX, USA). The main outcome variable was hepatotoxicity (symptomatic hepatitis ± ALT >3 × ULN).

Baseline characteristics of the 110 patients were described and the characteristics of patients with symptomatic hepatitis were compared with those without. Continuous variables were presented as mean (standard deviation [SD]) or as median (interquartile range [IQR]) while the categorical variables were presented as proportions. Chi-square test or Fisher's exact test was used to determine the association between each categorical variable and the outcome. Comparisons between two means or between two medians were done using unpaired *t* test or Mann–Whitney test. A p value <.05 was considered significant for all tests.

Results

The baseline characteristics of all 110 patients are shown in Table 1. There were 20 (18.2%) patients who developed symptomatic hepatotoxicity, in which 10 (50%) manifested with jaundice as part of the features of hepatotoxicity. Furthermore, 18 (16.4%) of the 20 patients met the stricter criteria for hepatotoxicity. Therefore, the cumulative incidence of hepatotoxicity based on clinical features alone was 18.2%, whereas it was 16.4% according to the ATS criteria.

The characteristics of the 20 (18.2%) patients who developed symptomatic hepatotoxicity are compared with those who did not in Table 2. The median age of patients with hepatotoxicity was slightly lower than that of those without hepatotoxicity, although this difference was not significant, 35 (IQR 27–43) years vs. 37 (IQR 30–45) years; $p = .34$. Although the proportion of females (10, 50%) was higher among those with hepatotoxicity versus those without (40, 44%), the difference was not significant; $p = .65$. Similarly, the higher mean BMI of those with hepatotoxicity (18.8 kg/m^2, SD 3.4) was not significantly different from those without hepatotoxicity (18.4 kg/m^2, SD 3.8), $p = .70$. The median duration of anti-TB treatment was the same for those with hepatotoxicity compared with those without, 14.0 days (IQR 9–36) vs. 14 days (IQR 9–39), $p = .60$. Similarly, there was no significant difference between those with/without hepatotoxicity in HIV positive status (65% vs. 70.8%; $p = .61$), those on cART (55% vs. 52.8%; $p = .86$), alcohol consumption (35% vs. 32.6%; $p = .84$), HBsAg positivity (7.2% vs. 11.4%; $p = .35$), and HCV antibody positivity (0% vs. 2.9%; $p = > .99$). Counterintuitively, those who did not have hepatotoxicity in the course of treatment had significantly higher baseline median ALT IQR (67 [4–226] vs. 35 [16–63]; $p = .04$) and bilirubin: median total IQR (20.4 [20.4–20.4] vs. 15.3 [10.2–74.8]; $p = 0.01$) and median conjugated IQR (10.2 [10.2–10.2] vs. 7.6 [5.1–34.8]; $p = .004$).

Table 1 – Baseline characteristics of 110 patients before start of antituberculosis treatment.

Characteristics	N (%)	Mean (SD)/median (IQR)
Age (years), median (IQR)	110 (100)	37 (30–45)
Sex		
Male	60 (54.6)	
Female	50 (45.4)	
BMI (kg/m^2), mean (SD)	105 (95.5)	18.5 (3.7)
Pulmonary TB		
Present	89 (81.0)	
Absent	21 (19.0)	
Extra-pulmonary TB		
Present	67 (61.0)	
Absent	43 (39.0)	
HIV status		
Positive	76 (69.7)	
Negative	33 (30.3)	
cART		
Yes	58 (53.2)	
No	51 (46.8)	
Alcohol consumption		
Yes	36 (33.0)	
No	73 (67.0)	
HBsAg status		
Positive	9 (10.7)	
Negative	75 (90.4)	
HCV antibody status		
Positive	2 (2.4)	
Negative	81 (97.6)	
Liver function tests		
ALT (IU/L), median (IQR)	91 (82.7)	33 (18–64)
AST (IU/L), median (IQR)	88 (80)	66.5 (35.0–109.5)
Total bilirubin (μmol/L), median (IQR)	66 (60)	10.2 (10.2–10.2)
Conjugated bilirubin (μmol/L), median (IQR)	66 (60)	5.1 (5.1–5.1)
Total protein (g/L), median (IQR)	72 (65.5)	72.5 (63.0–78.0)
Albumin (g/L), median (IQR)	70 (63.6)	31 (25–36)

Note: ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; cART = combination antiretroviral therapy; HBsAG = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquartile range; SD = standard deviation; TB = tuberculosis.

Table 2 – Characteristics of the 20 patients with or without antituberculosis hepatotoxicity.

Characteristics	Hepatotoxicity		
	Yes N (%)[a]	No N (%)[a]	p[b]
Age (years), median (IQR)	35 (25–77)	37 (19–78)	.34
Sex			.65
Male	10 (50.0)	50 (55.6)	
Female	10 (50.0)	40 (44.4)	
BMI (kg/m^2), mean	18.8 (3.4)	18.4 (3.8)	.70
Pulmonary TB			.99
Present	16 (80)	73 (81.1)	
Absent	4 (20.0)	17 (18.9)	
Extrapulmonary TB			.23
Present	10 (50.0)	57 (63.3)	
Absent	10 (50.0)	33 (36.7)	
Duration of anti-TB treatment (d), median (IQR)	14 (9–36)[c]	14 (9–39)[d]	.60
HIV status			.61
Positive	13 (65.0)	63 (70.8)	
Negative	7 (35.0)	26 (29.2)	
cART			.86
Yes	11 (55.0)	47 (52.8)	
No	9 (45.0)	42 (47.2)	
Alcohol consumption			.84
Yes	7 (35.0)	29 (32.6)	
No	13 (65.0)	60 (67.4)	
HBsAg status			.35
Positive	1 (7.2)	8 (11.4)	
Negative	13 (92.8)	62 (88.6)	
HCV antibody status			.99
Positive	0 (00.0)	2 (2.9)	
Negative	13 (100)	68 (97.1)	
Baseline liver function tests			
ALT (IU/L), median (IQR)	35 (16.0–63.0)	67(4–226)	.04
AST (IU/L), median (IQR)	66 (28–117)	81(6–293)	.09
Total bilirubin (μmol/L), median (IQR)	15.3 (10.2–74.8)	20.4 (20.4–20.4)	.01
Conjugated bilirubin (μmol/L), median (IQR)	7.6 (5.1–34.8)	10.2 (10.2–10.2)	.004
Total protein (g/L), median (IQR)	66.5 (58.5–74.5)	56 (52–60)	.42
Albumin (g/L), median (IQR)	30.5 (24–33.5)	16 (16–16)	.19

Note: ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; cART = combination antiretroviral therapy; HBsAG = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquartile range; TB = tuberculosis.

[a] This refers to the number (%) for categorical variables or the mean (standard deviation) or median (interquartile range) for continuous variables.

[b] p value for chi-square test or Fisher's exact test for the difference between categorical variables; or t-test or Mann–Whitney for the difference between two means.

[c] Days on anti-TB until hepatotoxicity developed.

[d] Days on anti-TB until the last day of in-patient stay.

Discussion

We found an incidence of symptomatic hepatotoxicity of 18% and a 16% incidence according to the ATS [13]. Makhlouf et al. [14] similarly reported an incidence of 15%, but among outpatients in Egypt. However, some investigators in Africa and Asia found comparatively lower incidence of between 4% and 11.5% [15–18]. By contrast, Yimer et al. [19] found a higher prevalence of 30%, probably because the majority of patients in their study were likely to have experienced the combined hepatotoxic effects of anti-TBs and cART, compared with only about 50% of patients receiving cART in the current study. Variations in the reported rates of hepatotoxicity are also likely as a result of differences in study design, patient characteristics, diagnostic criteria for hepatotoxicity, and concurrent use of hepato-protective therapy with anti-TBs. Although the mean BMI of patients with hepatotoxicity of 18.8 kg/m^2 was not significantly different from 18.4 kg/m^2 in

those without hepatotoxicity, low BMI is generally a recognized risk factor for hepatotoxicity [8]. Problems with drug absorption in wasted patients with advanced HIV/AIDS and the imprecise, but practical, anti-TB dosing based on weight bands might have confounded our findings. The median time to the development of hepatotoxicity was 14 days (IQR 9–36 days). This finding differs from those of other studies, although with some overlap, which reported a median of 28 days and a range between 14 and 60 days [16,17]. The observed difference could have arisen because we followed our patients only while in hospital, a generally shorter period of follow up compared with the 14–60 days it took for most cases of hepatotoxicity to occur [16,17].

Some studies found older age as a risk factor for hepatotoxicity [8,20,21]. However, our study, like some others [7,20,21], did not find an association. The probable reason is that our cohort is predominantly young where the median age is <40 years. We did not find sex and BMI to be associated with hepatotoxicity. Similar findings were previously reported [13,14,22]. Nonetheless, females were thought to be at an increased risk due to their lower BMI and slow acetylator status [23,24].

Coinfection with hepatitis B virus, HCV, or HIV was not found to be associated with hepatotoxicity in the current study. Several other studies had clearly indicated that they were risk factors for anti-TB hepatotoxicity [13,22,23]. However, there was only one patient with HBsAg and none with anti-HCV antibody among those with hepatotoxicity in the current study. Our study also did not find concomitant antiretroviral therapy or alcohol consumption to be associated with hepatotoxicity. Hussain et al. [24] also did not find alcohol as a significant risk factor. This is at variance with studies that found them to be important risk factors for hepatotoxicity [23,25–27]. Surprisingly also, ALT and bilirubin were significantly higher in those without hepatotoxicity. Although abnormal baseline LFT is predictive of anti-TB hepatotoxicity [28], differences in abilities of individuals to activate adaptive liver-protective mechanisms aimed at ameliorating effects of exposure to hepatotoxic agents [29] may partly explain our finding. In addition, data on concurrent use of other hepatotoxic medications or pre-existing liver disease were not assessed in the present cohort.

The present study has important limitations. Our findings may not be widely generalizable as the data emanated from a relatively few patients who were hospitalized in a single tertiary hospital. The estimation of incidence was based on symptomatic hepatotoxicity. Because LFT is not routinely repeated following initiation of anti-TBs, patients with asymptomatic hepatotoxicity [13] might have been missed. It was therefore also not possible to determine if this group of patients were at increased risk of progressing to the more clinically relevant overt hepatotoxicity.

Conclusions

The incidence of symptomatic hepatotoxicity among our hospitalized patients is high and ALT levels were mostly in excess of 3 times ULN among cases. While doubts about the utility of LFT in preventing or detecting hepatotoxicity may exist, close clinical and laboratory monitoring are important in hospitalized patients. Appropriately designed studies to determine the rates of both symptomatic and asymptomatic anti-TB induced hepatotoxicity and their predictors are needed in our environment.

Conflicts of interest

All authors have no conflicts of interest to declare.

REFERENCES

[1] WHO, Global tuberculosis report 2014, from <http://www.who.int/tb/publications/global_report/en/> (accessed 15.07.2015).
[2] National Tuberculosis and Leprosy Control Program—Workers Manual, fifth ed., Federal Ministry of Health, Nigeria, 2010.
[3] L.P. Ormerod, Chemotherapy and management of tuberculosis in the United Kingdom: recommendations of the Joint Committee of the British Thoracic Society, Thorax 45 (1990) 403–408.
[4] E.B. Bassey, M.A. Momoh, S.O. Imadiyi, et al, The trend of pulmonary tuberculosis in patients seen at DOTS clinics in the Federal Capital Territory, Abuja, Nigeria, Public Health 119 (2005) 405–408.
[5] A. Tostmann, M.J. Boeree, R.E. Aarnoutse, et al, Antituberculosis drug-induced hepatotoxicity: concise up-to-date review, J. Gastroenterol. Hepatol. 23 (2008) 192–202.
[6] W.M. Wong, P.C. Wu, M.F. Yuen, et al, Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection, Hepatology 31 (2000) 201–206.
[7] J.R. Ungo, D. Jones, D. Askin, et al, Anti-TB drug-induced hepatotoxicity. The role of hepatitis C and the HIV, Am. J. Respir. Crit. Care Med. 157 (1998) 1871–1876.
[8] J.N. Pande, S.P.N. Singh, G.C. Khilnani, et al, Risk factors for hepatotoxicity from anti-TB drugs: a case-control study, Thorax 51 (1996) 132–136.
[9] Y.S. Huang, H.D. Chern, W.J. Su, et al, Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis, Hepatology 37 (2003) 924–930.
[10] L.A. Ozick, L. Jacob, G.M. Comer, et al, Hepatotoxicity from isoniazid and rifampin in inner-city AIDS patients, Am. J. Gastroenterol. 90 (1995) 1978–1980.
[11] M. Gross, T. Kruisselbrink, K. Anderson, et al, Distribution and concordance of N-acetyltransferase genotype and phenotype in an American population, Cancer Epidemiol. Biomarkers Prev. 8 (1999) 683–692.
[12] C. Tam, W. Yew, C. Leung, et al., Monitoring for hepatotoxicity during antituberculosis treatment. General recommendations. A consensus statement of the Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority. Hong Kong, April, 2002, from <http://www.info.gov.hk/tb_chest/doc/Drughep.pdf> (accessed 02.08.2015).
[13] J. Jussi, D.L. Saukkonen, M.J. Robert, et al, An official ATS statement: hepatotoxicity of antituberculosis therapy, Am. J. Respir. Crit. Care Med. 174 (2006) 935–952.
[14] H.A. Makhlouf, A. Helmy, E. Fawzy, et al, Prospective study of antituberculous drug-induced hepatotoxicity in an area endemic for liver diseases, Hepatol. Int. 2 (2008) 353–360.

[15] A.A. Hassen, T. Belachew, A. Yami, et al, Anti-tuberculosis drug induced hepatotoxicity among TB/HIV co-infected patients at Jimma University Hospital, Ethiopia: nested case-control study, PLoS One 3 (2008) e1809.
[16] H. An, X. Wu, Z. Wang, et al, The clinical characteristics of anti-tuberculosis drug induced liver injury in 2457 hospitalized patients with tuberculosis in China, Afr. J. Pharm. Pharmacol. 7 (2013) 710–714.
[17] R. Shakya, B.S. Rao, B. Shrestha, Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors, Ann. Pharmacother. 38 (2004) 1074–1079.
[18] Y. Xiang, L. Ma, W. Wu, et al, The incidence of liver injury in Uyghur patients treated for TB in Xinjiang Uyghur autonomous region, China, and its association with hepatic enzyme polymorphisms nat2, cyp2e1, gstm1 and gstt1, PLoS One 9 (2014) e85905.
[19] G. Yimer, N. Ueda, A. Habtewold, et al, Pharmacogenetic and pharmacokinetic biomarker for efavirenz based ARV and rifampicin based anti-TB drug induced liver injury in TB-HIV infected patients, PLoS One 6 (2011) e27810.
[20] V.W. Senaratne, M.J. Pinidiyapathirage, G.A. Perera, et al, Anti-tuberculosis drug induced hepatitis – a Sri Lankan experience, Ceylon Med. J. 51 (2006) 9–14.
[21] M. Sharifzadeh, M. Rasoulinejad, F. Valipour, et al, Evaluation of patient-related factors associated with causality, preventability, predictability and severity of hepatotoxicity during anti-TB treatment, Pharmacol. Res. 51 (2005) 353–358.
[22] K. Tahaoglu, G. Atac, T. Sevim, et al, The management of anti-tuberculosis drug-induced hepatotoxicity, Int. J. Tuberc. Lung Dis. 5 (2001) 65–69.
[23] A. Fernandez-Villar, B. Sopena, J. Fernandez-Villar, et al, The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity, Int. J. Tuberc. Lung Dis. 8 (2004) 1499–1505.
[24] Z. Hussain, P. Kar, S.A. Hussain, Antituberculosis drug-induced hepatitis: risk factors, prevention and management, Indian J. Exp. Biol. 41 (2003) 1226–1232.
[25] H. Khalili, S. Dashti-Khavidaki, M. Rasoolinejad, et al, Anti-tuberculosis drugs related hepatotoxicity; incidence, risk factors, pattern of changes in liver enzymes and outcome, DARU 17 (2009) 163–167.
[26] D. Marks, K. Dheda, R. Dawson, et al, Adverse events to anti-TB therapy: influence of HIV and antiretroviral drugs, Int. J. STD AIDS 20 (2009) 339–345.
[27] E. Pukenyte, F.X. Lescure, D. Rey, et al, Incidence of and risk factors for severe liver toxicity in HIV-infected patients on anti-TB treatment, Int. J. Tuberc. Lung Dis. 11 (2007) 78–84.
[28] M.D. Teleman, C.B. Chee, A. Earnest, et al, Hepatotoxicity of tuberculosis chemotherapy under general program conditions in Singapore, Int. J. Tuberc. Lung Dis. 6 (2002) 699–705.
[29] G.M. Williams, M.J. Iatropoulos, Alteration of liver cell function and proliferation: differentiation between adaptation and toxicity, Toxicol. Pathol. 30 (2002) 41–53.