

Prospective Study

Viral hepatitis prevalence in patients with active and latent tuberculosis

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Abstract

AIM: To assess the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and association with drug induced liver injury (DILI) in patients undergoing anti-tuberculosis (TB) therapy.

METHODS: Four hundred and twenty nine patients with newly diagnosed TB - either active disease or latent infection - who were due to commence anti-TB therapy between September 2008 and May 2011 were included. These patients were prospectively tested for serological markers of HBV, HCV and human immunodeficiency virus (HIV) infections - hepatitis B core antigen (HBcAg), hepatitis B surface antigen (HBsAg), hepatitis B e antigen, IgG and IgM antibody to HBcAg (anti-HBc), HCV IgG antibody and HIV antibody using a combination of enzyme-linked immunosorbent assay, Western blot assay and polymerase chain reaction techniques. Patients were reviewed at least monthly during the TB treatment initiation phase. Liver function tests were measured prior to commencement of anti-TB therapy and 2-4 wk later. Liver function tests were also performed at any time the patient had significant nausea, vomiting, rash, or felt non-specifically unwell. Fisher's exact test was used to measure significance in comparisons of proportions between groups. A *P* value of less than 0.05 was considered statistically significant.

RESULTS: Of the 429 patients, 270 (62.9%) had active TB disease and 159 (37.1%) had latent TB infection. 61 (14.2%) patients had isolated anti-HBc positivity, 11 (2.6%) were also HBsAg positive and 7

(1.6%) were HCV-antibody positive. 16/270 patients with active TB disease compared to 2/159 patients with latent TB infection had markers of chronic viral hepatitis (HBsAg or HCV antibody positive; $P = 0.023$). Similarly the proportion of HBsAg positive patients were significantly greater in the active *vs* latent TB infection group (10/43 *vs* 1/29, $P = 0.04$). The prevalence of chronic HBV or HCV was significantly higher than the estimated United Kingdom prevalence of 0.3% for each. We found no association between DILI and presence of serological markers of HBV or HCV. Three (5.3%) patients with serological markers of HBV or HCV infection had DILI compared to 25 (9.5%) patients without; $P = 0.04$.

CONCLUSION: Viral hepatitis screening should be considered in TB patients. DILI risk was not increased in patients with HBV/HCV.

Key words: Epidemiology; Hepatitis B; Hepatitis C; Tuberculosis; Drug induced liver injury

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Core tip: Tuberculosis (TB) patients are not routinely tested for viral hepatitis in the United Kingdom. This is the first study from a European centre investigating the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) in patients with TB. We found that chronic HBV and HCV prevalence in TB patients were 9 and 5 times greater than the estimated United Kingdom prevalence respectively. We also found that a significantly greater proportion of patients with active TB had chronic Hepatitis B compared with patients with latent TB infection. In our study there was no association between drug induced liver injury risk and presence of serological markers of HBV/HCV.

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INTRODUCTION

Tuberculosis (TB) is the leading cause of death from a curable infectious disease; in 2010, 1.45 million people died from TB and there were 8.8 million incident cases^[1]. In the United Kingdom, the incidence of TB has steadily increased over the past two decades^[2]. 7892 cases were reported in 2013, the majority in urban areas, with London accounting for 38% of those cases^[2]. Over 80% of cases are non-United Kingdom born, and rates of TB in the non-United Kingdom born

are approximately twenty-fold higher (86/100000) than those born in United Kingdom (4/100000)^[2].

Standard four-drug anti-TB therapy for active disease (isoniazid, rifampicin, pyrazinamide and ethambutol) is associated with a range of significant side effects, the most serious of which is drug induced liver injury (DILI), which carries a mortality rate of up to 5%^[3,4]. All anti-TB medications are potential causes of DILI^[5]. The incidence of DILI from anti-TB treatment has been variably reported - between 2% and 28% - with a number of factors, including HLA phenotype and ethnicity, having been found to alter an individual's risk for a hepatotoxic drug reaction^[5,6]. The clinical presentation of DILI ranges from transient mild elevation of liver enzymes to fulminant liver failure, and a commonly used definition of DILI is an increase in serum alanine transaminase (ALT) greater than 3 or 5 times the upper limit of normal (ULN) with or without symptoms of acute hepatitis respectively^[4].

The World Health Organization (WHO) estimates approximately 240 million people worldwide are chronically infected with hepatitis B virus (HBV)^[7]. Areas of high prevalence are similar to the global TB epidemiological "hotspots" and include sub-Saharan Africa and South Asia, where the prevalence is estimated to be between 8 and 20%^[8]. The WHO estimate 3% of the World's population are infected with hepatitis C virus (HCV), with 170 million being chronic carriers^[9]. European countries report a prevalence of HCV in the general population of between 0.5%-2% and global areas of high prevalence again include Africa, particularly Egypt, and Asia^[9]. In 2011 it was estimated that around 216000 individuals were the United Kingdom are chronically infected with HCV^[10], and the HPA and WHO estimate the United Kingdom prevalence of chronic HBV infection to be similar to this, at 0.3%. Chronic infection with HBV and/or HCV can cause progressive liver fibrosis and cirrhosis, liver failure and liver cancer. Effective therapies exist for both these viruses if they are diagnosed before advanced liver disease occurs, and early detection and treatment is important in minimising the health burden associated with chronic HBV and HCV. However, both these viruses are relatively asymptomatic and hence international liver associations recommend screening for HBV and HCV in high risk groups^[11,12].

Several studies report an increased prevalence of viral hepatitis infection in TB patients^[14-17] (Table 1). However, none of these studies have been performed in a European setting, so their applicability to the United Kingdom is not known. Although results are not universal, a number of international studies suggest that co-existing viral hepatitis may be a significant risk factor for DILI^[13,18-22]. No studies on the prevalence of viral hepatitis in patients undergoing anti-TB therapy and the risk they add to DILI have been carried out in the United Kingdom or Europe, which have seen an increase in TB cases over recent years.

Table 1 Prevalence of hepatitis B virus and hepatitis C virus infection in tuberculosis patients in other studies *n* (%)

Study (country)	Study population	Number of patients	HBsAg	HBsAg or anti-HBc	Anti-HCV
Kuniholm <i>et al</i> ^[14] (Georgia)	All active TB patients	300	13 (4.3)	27 (9)	36 (12)
Blal <i>et al</i> ^[15] (Brazil)	All active TB patients	209	6 (2.8)	56 (26.8)	-
Sirinak <i>et al</i> ^[16] (Thailand)	HIV infected active TB patients	849	70 (9)	-	237 (31)
Aires <i>et al</i> ^[17] (Brazil)	All active TB patients	402	13 (3.2)	103 (25.6)	-

HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HBc: Hepatitis B core; TB: Tuberculosis.

United Kingdom patients infected with TB are offered human immunodeficiency virus (HIV) screening^[23] due to an increased prevalence of co-infection, but viral hepatitis screening is not routinely offered and might be of value if the background prevalence of viral hepatitis is significant in patients with TB infection. London is a multicultural city with a significant number of immigrants from high endemic TB countries, suggesting that the prevalence of viral hepatitis infection may be higher than suspected.

MATERIALS AND METHODS

Recruitment

We recruited patients with newly diagnosed TB - either active disease or latent infection - at St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, who were due to commence standard anti-TB therapy for either stages of the infection between September 2008 and May 2011. The inclusion criteria were: newly diagnosed TB (active or latent); 18 years of age or above; ability to give informed consent; and no known history of chronic liver disease, viral hepatitis or HIV. No patients were immunosuppressed. Research ethics approval was obtained (No. 10/H0709/44).

Clinical phenotyping

TB infection was confirmed using the standard protocols in our clinic. Active TB infection was defined by clinical and radiological characteristics of symptomatic TB infection, with or without confirmatory culture information. If culture negative, then the patient was deemed to have had active TB if they made a satisfactory response to anti-tuberculosis therapy.

Latent TB infection was defined as an asymptomatic patient without radiographic evidence of active TB disease, and with a positive tuberculin skin test read at 48-72 h by an experienced nurse (defined as > 5 mm induration if not BCG vaccinated or ≥ 15 mm if BCG vaccinated), subsequently confirmed with a positive interferon gamma release assay [either T.Spot. TB (Oxford Immunotec, Oxford, United Kingdom), or Quantiferon Gold-in-Tube (Cellestis Ltd, Victoria, Australia)].

Drug treatment

For active disease, standard anti-tuberculous therapy in our clinic was rifampicin 600 mg/d (R), Isoniazid

300 mg/d (H), Pyrazinamide 25 mg/kg per day (Z) (these three jointly given as Rifater with the number of tablets dependent on weight; if the weight was sufficiently low, then the drugs were given separately as per guidelines^[23]), and Ethambutol 15 mg/kg per day (E) for 2 mo; followed by continuation rifampicin and isoniazid for a further 4 mo [8 mo if central nervous system (CNS) involvement]. Treating clinicians had the option to extend the initiation phase to 3 mo if the patient was persistently smear positive after one month of therapy and could extend the total duration of therapy if they felt the initial burden disease was high, on a case by case basis. Adjuvant steroid therapy was used in patients with pericardial or CNS disease, as per national guidelines^[23] and weekly pyridoxine 50mg orally was administered to all cases. Drug resistant cases were treated according to culture results as per national guidelines^[23].

For latent infection, patients were treated with 3 mo of Rifampicin 600mg daily (R) and Isoniazid 300 mg daily (H) (jointly given as Rifinah-300, two tablets daily), in keeping with standard United Kingdom practice.

Data collection

Patients' demographic, serological and clinical data were collected following informed consent, from the London TB register, hospital clinical databases and clinical notes. Demographic information collected included age, gender and ethnicity. In addition to biochemical liver function tests, the following serological results were also collected: HIV antibody, hepatitis B core antigen (HBcAg), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), IgG and IgM antibody to HBcAg (anti-HBc) and HCV IgG antibody (anti-HCV).

As per standard clinical protocol, patients were reviewed at least monthly during the TB treatment initiation phase. Liver function tests, including alanine transaminase (ALT) levels, were measured prior to commencement of anti-TB therapy and again 2-4 wk later. An ALT level of 40 IU/mL was taken as the upper limit of normal (ULN). DILI was defined as an ALT of greater than 80IU/ml (2 × ULN), as defined by the Council for International Organisation of Medical Sciences (CIOM) DILI diagnostic scale^[24] with no other apparent cause for abnormal liver biochemistry. Severe DILI was defined at an ALT of 5 × ULN. Liver

Table 2 Demographic and Serological data of patients *n* (%)

Characteristic	Patients				
	Total	HBV/HCV Negative	HBsAg	Isolated Anti-HBc (IgG)	HCV (IgG)
Female	209 (48.7)	173 (40.3)	4 (0.9)	31 (7.2)	1 (0.2)
Male	220 (51.3)	177 (41.3)	7 (1.6)	30 (7.0)	6 (1.4)
Age (yr)					
18-35	155 (36.1)	132 (30.8)	0 (0.0)	21 (4.9)	2 (0.5)
36-53	133 (31.0)	106 (24.7)	7 (1.6)	16 (3.7)	4 (0.9)
54-71	88 (20.5)	67 (15.6)	3 (0.7)	17 (4.0)	1 (0.2)
72-90	51 (11.9)	43 (10.0)	1 (0.2)	7 (1.6)	0 (0.0)
> 90	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity					
Indian Subcontinent	152 (35.4)	132 (30.8)	1 (0.2)	18 (4.2)	1 (0.2)
Black African (Sub Saharan)	104 (24.2)	73 (17.0)	6 (1.4)	23 (5.4)	2 (0.5)
Black Caribbean	21 (4.9)	17 (4.0)	0 (0.0)	4 (0.9)	0 (0.0)
North African	25 (5.8)	20 (4.7)	0 (0.0)	5 (1.2)	0 (0.0)
South East Asia	34 (7.9)	26 (6.1)	3 (0.7)	5 (1.2)	0 (0.0)
White all other (European/American/Australian)	46 (10.7)	38 (8.9)	1 (0.02)	5 (1.2)	2 (0.5)
White South American	15 (3.5)	15 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
White UK	32 (7.5)	29 (6.8)	0 (0.0)	1 (0.02)	2 (0.5)
Total	429	350 (81.6)	11 (2.6)	61 (14.2)	7 (1.6)

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HBc: Hepatitis B core.

function tests (LFTs) were performed at any time the patient had significant nausea, vomiting, rash, or felt non-specifically unwell.

HIV, HBV and HCV serological tests were performed at St Mary's hospital pathology department. Enzyme-linked immunosorbent assay (ELISA) was used for detection of anti-HIV antibodies and confirmed by Western blot assay. Screening for HBV and HCV was conducted using second generation ELISA and confirmatory tests for HBsAg or HCV positive results included polymerase chain reaction techniques. Data were analysed using Prism 5 (GraphPad Software Inc.). Fisher's exact test was used to measure significance in comparisons of proportions between groups. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Demographics

A total of 487 patients were recruited. 58 patients were excluded due to absent results or loss to follow up. Of the remaining 429 patients, 270 (62.9%) patients had active TB disease and 159 (37.1%) had latent TB infection. The mean age was 46.4 years and 51.3% of patients were male. The majority of patients were from the Indian Subcontinent and Sub Saharan Africa, together accounting for 59.7% of patients. 7.5% of patients were White British (Table 2).

Prevalence of HCV/HBV markers

Of 429 patients screened, 79 (18.4%) had positive serological markers for HBV or HCV infection. 61 (14.2%) had isolated anti-HBc antibody only; 11 (2.6%) were also HBsAg positive and 7 (1.6%) were positive for HCV IgG antibody. No patients had HBV/

HCV co-infection (Table 2). All patients positive for HBsAg and HCV Antibody were previously unknown to have a history of viral hepatitis.

Active TB disease vs latent TB infection

A similar proportion of patients in both groups had serological markers for HBV or HCV infection (49/270 active TB disease patients vs 30/159 latent TB infection patients; *P* = 0.9, Fisher's exact test) (Table 3).

However, there was a significant difference between these groups with respect to chronic viral hepatitis: 16/270 patients with active TB disease compared to 2/159 patients with latent TB infection had markers of chronic viral hepatitis (HBsAg or HCV antibody positive; *P* = 0.023, Fisher's exact test). Similarly, while there was no difference between the groups with respect to anti-HBc antibody positivity (43/270 in active TB disease group vs 29/159 in latent TB infection group; *P* = 0.59, Fisher's exact test), the proportion of this group whose HBsAg was positive was significantly greater in the active TB patient group (10/43 in active TB patients vs 1/29 in latent TB infection group; *P* = 0.04, Fisher's exact test).

A greater proportion of active TB disease patients were HCV seropositive compared to latent TB infection patients although this difference was not significant (6/270 active TB disease patients vs 1/159 latent TB infection patients; *P* = 0.27, Fisher's exact test).

Viral hepatitis and HIV co-infection

Fifteen patients were already known to be HIV positive and a further 260 patients consented to HIV screening (245 active TB disease, 30 latent TB infection). Eleven patients were newly diagnosed with HIV meaning that, of the 275 patients, 26 (9.5%) were infected with HIV. Six (23.1%) of the HIV positive patients were co-

Table 3 Prevalence of hepatitis B virus and hepatitis C virus infection in active TB disease vs latent tuberculosis infection patients *n* (%)

HBV/HCV infection	Patients		<i>P</i> value (Fisher's exact test)
	Active	Latent	
HBsAg/HCV Ab both negative	221 (81.9)	129 (81.1)	0.9
HBsAg or HCV Ab positive	49 (18.1)	30 (18.9)	
HCV (IgG) positive	6 (2.2)	1 (0.6)	0.27
Anti-HBc (IgG) positive	43 (12.2)	29 (17.6)	0.59
Of these: HBsAg positive	> 10 (23.2)	> 1 (3.4)	> 0.04

HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HBc: Hepatitis B core.

infected with HBV or HCV ($P = 0.26$, Fisher's exact test).

Pre-treatment ALT Levels

Pre-treatment ALT levels were available in 399 patients, 71 of whom were HCV or anti-HBc positive (including those also positive for HBsAg). Fourteen (19.7%) of these patients had ALT levels of greater than 40 IU/mL compared to 61 (18.6%) patients negative for markers of HBV or HCV ($P = 0.87$, Fisher's exact test). 13 (3.3%) patients had ALTs of greater than $2 \times$ ULN (> 80 IU/mL), 3 of whom had ALTs of greater than $5 \times$ ULN (> 200 IU/mL). All of these patients were negative for all markers for HBV and HCV.

Post-treatment ALT Levels

Post-treatment ALTs were documented in 396 patients, 72 of whom were HCV or anti-HBc positive (including those also positive for HBsAg). 16 (22.2%) of these patients had ALT elevation > 40 IU/mL compared to 89 (27.5%) patients negative for markers of HBV or HCV ($P = 0.31$, Fisher's exact test). Six (8.3%) anti-HBc or HCV positive patients had ALT > 80 IU/mL compared to 33 (10.2%) patients without serological evidence of HBV or HCV ($P = 0.83$, Fisher's exact test). Of the 13 patients with ALT > 200 IU/mL, only one was positive for HBV or HCV serological markers ($P = 0.48$, Fisher's exact test).

ALT levels post-treatment following normal pre-treatment levels

Three hundred and twenty patients had normal (< 40 IU/mL) pre-treatment ALTs and also had follow-up LFTs; of these, 57 were positive for serological markers HBV or HCV. ALT elevation of greater than 80 IU/mL was seen in 3 (5.3%) patients with positive HBV or HCV serological markers, compared to 25 (9.5%) patients negative for serological markers HBV/HCV ($P = 0.44$, Fisher's exact test). Twelve patients had ALT > 200 IU/mL of whom only one had serological evidence of HBV/HCV ($P = 0.70$, Fisher's exact test). Five patients required interruption of treatment due to significantly elevated LFTs, none of whom had

serological evidence of HBV/HCV. Overall, 13 (46.4%) of the 28 patients with DILI were above the age of 50 and 14 (50%) were male.

DISCUSSION

This is the first study from a European centre to investigate the prevalence of HBV and HCV in patients with TB. We found that 18.4% of newly diagnosed TB patients at a central London teaching hospital had markers of HBV or HCV; 2.6% of patients were HBsAg positive and 1.6% were anti-HCV Ab positive. All these diagnoses were new, and led to specialist referral with the aim of preventing long-term complications of chronic viral hepatitis.

Our study found that chronic HBV prevalence in TB patients was almost 9 times greater than the estimated overall United Kingdom prevalence. Similarly, the prevalence of HCV amongst TB patients in our study was over 5 times greater than the estimated United Kingdom prevalence of HCV. The majority of infected patients were of Indian Subcontinent or Black African origin, and our distribution of ethnicities was representative of London's multi-racial TB population^[25].

A recent study by Uddin and colleagues looked at the prevalence of HBV and HCV in South Asian immigrants in England attending community centres^[26]. 4998 individuals were screened and HBsAg or anti-HCV Ab was present in 1.2% and 1.6% of patients respectively, again higher than the national estimated prevalence. This may be partially explained by the older demographic screened in this study - attending mosques and temples - who are more likely to have been born and raised in South Asia and hence would be at a greater risk of acquiring infection with HBV/HCV at younger ages. The prevalence of chronic hepatitis B in our study was more than twice that found in the study by Uddin *et al.*^[26], reflecting the wider ethnic background to our population, and suggesting that screening for HBV and HCV may be more effective in health care settings which might capture a wider range of infected individuals.

Although HIV and HBV/HCV have similar risk factors, we found no significant association between these infections in our cohort of TB patients, suggesting that HIV seropositivity alone would not identify patients with unknown HBV/HCV.

Of note, a significantly greater proportion of patients with active TB had chronic Hepatitis B compared with patients with latent TB infection. The proportion of patients in the latent and active groups positive for anti-HBc did not differ, suggesting that whilst both groups had equal exposure to the virus, the group with active TB were more likely to fail to clear virus and remain sAg positive. This could be attributable to the relatively small number of latent TB patients in the study; alternatively, there may be shared pa-

thways of immune control, perhaps involving MHC I-restricted CD8 T cells important in both viral^[27] and mycobacterial^[28] control, which could link immune dysregulation in both Hepatitis B viral infection and *M. tuberculosis* infection.

It is relevant to note that, on further follow-up, none of the patients with HBsAg and/or Anti HCV positivity had cirrhosis, as chronic liver disease itself is a potential risk factor for acquiring TB.

Different studies have used varying definitions of hepatotoxicity; our study employed a range of thresholds, including one which is lower than the ATS guidelines on hepatotoxicity^[29], with the aim of providing a more comprehensive analysis of the derangement in liver function that might occur in this population. Our study followed a standard protocol whereby LFTs were measured pre-treatment and 2-4 wk after treatment. Further LFTs were only measured if the patient had abnormal levels at week 2-4 or developed symptoms; it is therefore possible that patients developing asymptomatic DILI after 2-4 wk of treatment may have been missed, although this is not common^[29]. As with a number of other studies, we found no association between HBV/HCV seropositivity and DILI at both a lower and a higher threshold for diagnosis^[5,16,30]; suggesting that anti-TB medication can generally be safely administered to those infected with HBV/HCV in settings similar to ours, provided liver function is regularly monitored. Although DILI tends to occur early in the course of anti-TB therapy, the prevalence of DILI in our study may potentially be underestimated as follow-up liver function tests were only checked once, unless clinically indicated.

It is also important to note that over 14% of patients undergoing anti-TB treatment were positive for anti-HBc. Without prophylactic anti-viral therapy, these patients are at risk of HBV reactivation and liver failure if they are immunosuppressed or undergo immunomodulatory therapy or chemotherapy in the future.

Without early detection and appropriate management, chronic infection with HBV or HCV can lead to cirrhosis, liver failure and liver cancer. The Health Protection Agency (United Kingdom) advises HCV screening in intravenous drug users (IVDU) and men who have sex with men^[10] and the ATS recommends viral hepatitis screening in TB patients with risk factors such as IVDU, those born in endemic areas and in HIV positive individuals^[29]. As the majority of TB patients in the United Kingdom are immigrants from areas of the world where viral hepatitis is endemic, this strengthens the clinical utility of screening TB patients for viral hepatitis.

The high prevalence of HBV and HCV in our cohort likely reflects the relatively high prevalence of these viruses in their countries of origin. The relevance of our findings is that screening recommendations for HBV for individuals born in high prevalence areas, such as the American Association for the Study of Liver

Diseases guidelines on chronic HBV, should be carried out in TB patients and extended to HCV screening.

We propose that screening for hepatitis B and C be considered in TB patients (particularly those with active TB) in multicultural cities of the United Kingdom with high rates of patients originating from areas of the world where HBV and HCV are relatively more highly prevalent. Further studies to identify TB patients at highest risk of HBV/HCV co-infection, to investigate links between active TB and Hepatitis B, and to investigate the health economics of screening are warranted.

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COMMENTS

Background

Tuberculosis (TB) is the leading cause of death from a curable infectious disease. Standard four-drug anti-TB therapy for active disease (isoniazid, rifampicin, pyrazinamide and ethambutol) is associated with a range of significant side effects. London is a multicultural city with a significant number of immigrants from high endemic TB countries, suggesting that the prevalence of viral hepatitis infection may be higher than suspected.

Innovations and breakthroughs

This study aims to assess the prevalence of hepatitis B virus and hepatitis C virus (HCV) infection and association with drug induced liver injury in patients undergoing anti-TB therapy.

Applications

This is the first study from a European centre investigating the prevalence of hepatitis B virus (HBV) and HCV in patients with TB. Chronic HBV and HCV prevalence in TB patients were 9 and 5 times greater than the estimated United Kingdom prevalence respectively, and a significantly greater proportion of patients with active TB had chronic Hepatitis B compared with patients with latent TB infection. In this study there was no association between drug induced liver injury risk and presence of serological markers of HBV/HCV.

Peer-review

This manuscript is a full, complete and very well-written review. There are some minor errors to be amended and some points that could be better addressed to improve its quality.

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