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4<sup>th</sup> February 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Viral Hep and TB\_WJG\_Nooredinvand et al\_030215).

Title: *Viral Hepatitis Prevalence in Patients with Active and Latent Tuberculosis*

Authors: *Hesam Ahmadi Nooredinvand, David W Connell, Mahmoud Asgheddi, Mohammed Abdullah, Marie O'Donoghue, Louise Campbell, Melissa I Wickremasinghe, Ajit Lalvani, Onn Min Kon & Shahid A Khan*

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript No.: *16036*

We thank the Editor for the opportunity to resubmit our manuscript following improvements made in response to the Reviewers' comments. We also thank the Reviewers for taking the time to read our paper and offer useful insights. As a result, our manuscript has been amended and improved, and every one of the points from both Reviewers has been addressed, as detailed below. Changes made to modified, attached manuscript are in **bold**:

#### **Reviewer 1**

We thank the Reviewer for commenting that our study was "*well conducted*" and "*the purpose... relevant*". Below are Reviewer 1's specific comments (in *italics*) and our response to each one in **bold**.

#### Comments: Major points

1. *Manuscript - Material and Methods: Which were the inclusion and exclusion criteria? Was it only: newly diagnosed TB; 18 years of age or above; no known chronic liver disease?*

**The Reviewer has raised an important point. The inclusion criteria were: newly diagnosed TB (active or latent); 18 years of age or above and able to give informed consent; and no known history of chronic liver disease, viral hepatitis or HIV. This has been added to the manuscript (page 6, para1).**

2. *Manuscript – Discussion: The population with TB in this study was a high risk population for HBV and HCV infection. I believe that the conclusions drawn by the authors namely the increased prevalence of HBV and HCV markers on TB diagnosed patients in the UK (that is stated to be 9 and*

5 times greater than the estimated UK prevalence, respectively) are not a big novelty. In fact, it is mentioned in the introduction that, in the UK, 84% of TB cases are non-UK born and that the rates of TB in the non-UK born are 20-fold higher. So, this high prevalence of HBV and HCV in this group of TB patients reflects the prevalence of these diseases in their countries of origin (as we can see in table 1) and not the prevalence in a European country per se. Probably the emphasis should lay on the relevance of following screening suggestions for HBV for individuals born in areas of high prevalence rates of infection (such as the American Association for the Study of Liver Diseases guidelines on Chronic Hepatitis B) and extending it to HCV.

**We agree with these comments but perhaps did not make this clearer in the original text. Hence we have added a further paragraph (p13, para 2) to our Discussion in line with these comments.**

3. *Manuscript – Discussion: Another point is the proposal that screening for viral hepatitis be considered in TB patients in the UK. Considering that the high prevalence of HBV and HCV reflects the prevalence of the infection in their countries of origin (as explained above), that London is a multicultural city with a significant number of immigrants (affirmed in the introduction) and that London (where this study took place) accounts for 38% of TB cases in the UK, extending screening programs to the whole country isn't, perhaps, supported by strong data.*

**We accept these comments and have amended the concluding paragraph of our manuscript accordingly (p13, para 3).**

#### Minor points

4. *Abstract - Methods: There are some discrepancies regarding the use of abbreviations. For example in the subtitle methods, Human Immunodeficiency Virus is not abbreviated while HBV and HCV are.*

**This has been rectified and Human Immunodeficiency Virus is now abbreviated (Abstract/ Methods, p2, lines 5-6).**

5. *Abstract - Results: In the sentence: "... had latent B infection", there is a missing B.*

**This has been corrected from "latent B" to "latent TB" (Abstract/ Results, p2, 2<sup>nd</sup> line).**

6. *Manuscript - Material and Methods: A positive tuberculin skin test was defined as >5mm induration if not BCG vaccinated or ≥15mm if BCG vaccinated. Was the immune status of the patients taken in consideration? Were there any immunosuppressed patients?*

**No patients were immunosuppressed. This has now been stated in the updated manuscript (p6, para 1, penultimate sentence).**

7. *Manuscript - Material and Methods: Were patients with a positive interferon gamma release assay considered to have latent tuberculosis if they had a negative tuberculin skin test?*

**Our protocol for Latent TB Infection routinely checks with a repeat interferon gamma release assay in discordant results but if a repeat IGRA is again positive, this is regarded as LTBI.**

8. *Manuscript - Material and Methods: Latent TB was treated with 3 months of Rifampicin 600mg daily and Isoniazid 300mg daily. Why this regimen and not any other (for example Isoniazid 9 months)?*

**The standard UK practice is to offer 3 months of rifampicin and isoniazid in keeping with national guidance – most clinicians use this shorter regime as this has been proven to have the**

highest uptake. Recognised UK alternatives are isoniazid for 6 months (not 9 months) or rifampicin for 6 months (referenced in UK NICE CG117 2011). The phrase “in keeping with standard UK practice” has been added to the Materials and methods section (on p7, para 2).

## **Reviewer 2**

We thank the Reviewer for stating that our study was “*well written*” and contained “*a well-researched review of the literature*”. Below are Reviewer 2’s specific points (in *italics*) and our response to each one in **bold**.

*1. In the introduction section it has been mentioned that Over 9040 cases were reported in 2009, the majority in urban areas, with London accounting for 38% of those cases. It would have been good if data from recent years could have been presented if available.*

**This has been replaced by data from 2013, when there were 7,892 cases in the UK, of which 2,985, or 37.8%, were in London – please see p4, para 1.**

*2. The result of this study states that chronic HBV prevalence in TB patients was almost 9 times greater than the estimated overall UK prevalence and the prevalence of HCV amongst TB patients in the study was over 5 times greater than the estimated UK prevalence of HCV which is slightly misleading since the patient population of the TB patient is vastly different from the general UK population. If we take the country of origin of the TB patients then the prevalence of HBV and HCV may not be very different from their country of origin. The message could be that TB patients have a higher incidence of HBV/HCV in addition to that attributable to ethnicity and country of origin.*

**Similar comments were made by Reviewer 1. We accept these points and the amendments/additions we have made to page 13 (paras 2 and 3) of our manuscript reflect this.**

*3. There is no mention of what proportion of patients with HBsAg and Anti HCV positive patients had cirrhosis or CLD because CLD is itself a risk factor for TB and whether the increased risk of TB is because of Chronic hepatitis or cirrhosis needs to be differentiated.*

**The Reviewer has raised an important point. None of the patients with HBsAg and/or Anti HCV positivity had cirrhosis or chronic liver disease (CLD). This has now been specified by the addition of an additional sentence on p12, para 2 of the revised manuscript.**

*4. Some grammatical mistakes like latent B infection instead of latent TB infection in the results section of abstract.*

**The grammatical errors in the abstract have been corrected (p2).**

We hope these improvements to our manuscript are satisfactory. Thank you again for considering publishing our manuscript in the World Journal of Gastroenterology.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Shahid A Khan', with a horizontal line underneath.

**Dr Shahid A Khan**  
Consultant Physician and Adjunct Reader