

June 2, 2018

Dear Editor and Reviewers:

Please find enclosed the edited manuscript in Word format (file name: 38950-Revised Manuscript.docx).

Title: Hepatitis B reactivation in patients receiving direct-acting antiviral therapy or interferon-based therapy for hepatitis C: A systematic review and meta-analysis

Author: Xian-Wan Jiang, Jian-Zhong Ye, Ya-Ting Li, Lan-Juan Li

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 38950

Thank you for your letter and for the reviewers' constructive comments and suggestions on our manuscript. We sincerely appreciate the time and effort you have spent in reviewing our manuscript as well as the opportunity to revise our manuscript. The concerns of the reviewers and their suggestions for improving the manuscript have been carefully studied and addressed. Revised portions of the text are highlighted in yellow in the paper. Below, we provide a point-by-point responses to the comments that we hope will meet with approval.

We look forward to hearing from you soon.

Sincerely,

Lanjuan Li

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Response to editorial comments:

- 1.All of the suggested editorial changes have been made.
- 2.The “Non-Native Speakers of English Editing Certificate” has been uploaded.
- 3.The requested audio core tip has been uploaded.
- 4.The “Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)” has been provided.
- 5.The “Article Highlights” section has been added in the revised manuscript.

Reviewer #1 (Reviewer's code: 00503536):

The review written by Jiang X-W et al. summarizes the HBV reactivation in patients receiving anti-HCV treatment. It is a serious problem during the anti-HCV treatment and the review gives the readers important information. There is a concern that needs to be addressed. It is not surprising that preemptive anti-HBV therapy could completely suppress HBV reactivation rate with NUCs. However, there might be a problem in cost effectiveness if all patients with HCV patients receiving DAAs concomitantly receive antiviral prophylaxis. A close monitoring of HBV DNA might be sufficient in some patients. Therefore, it is more practical if the patients who should receive preemptive anti-HBV therapy could be limited and selected. The authors should discuss more on that point.

Classification: Grade B (Very good)

Language Evaluation: Grade B: minor language polishing

Conclusion: Minor revision

Response:

We thank the reviewer very much for the positive comments on our manuscript and for pointing out this highly important aspect. As the EASL guideline suggested^[1], the risk of HBV reactivation in patients with previous HBV infection is low, close monitoring of ALT and HBV DNA is sufficient for those patients. Preemptive anti-HBV therapy with NUCs is recommended in HBsAg-positive patients because of the high risk of HBV reactivation and reactivation related-hepatitis, especially those with detectable serum HBV DNA. However, HBV/HCV-coinfected patients receiving DAAs to receive antiviral prophylaxis is expensive especially in developing countries. Further studies are needed to evaluate the use and cost-effectiveness of preemptive anti-HBV therapy with NUCs in HBsAg-positive patients.

Reviewer #2 (Reviewer's code: 03262379):

Hello, I reviewed the manuscript entitled "Hepatitis B reactivation in patients receiving direct-acting antiviral therapy or interferon-based therapy for hepatitis C: a systematic review and meta-analysis". This is a well-designed and well-organized meta-analysis for evaluation of HBV reactivation in HCV patients undergoing treatment with DAAs. The study showed the importance of HBV reactivation and the need for therapeutic prevention of HBV reactivation in HBV-HCV coinfecting patients treated with HCV DAAs. I have few comments to improve the scientific presentation of the manuscript: 1. In introduction, authors stated "The global prevalence of HBV/HCV dual infection is approximately 5-10%, and the prevalence is reported to be 8.4% in China and 12-14% in East Asia". It is vague the frequency included for HBV infection in patients with HCV or vice versa. 2. There are few included studies with small number of patients even 1 patient. I recommend authors to exclude studies with less than 5 patients. 3. I recommend authors to exclude the subheading "Efficacy of anti-HCV treatment" and the related sentences from discussion and conclusion. Since the treatment of HCV with DAA is impacted by different treatment regimens and also the condition of the disease and patient pooling the data of efficacy from different studies makes no sense. Moreover, the "Efficacy of anti-HCV treatment" is not in

line with the main objective of study as "Hepatitis B reactivation in patients receiving direct-acting antiviral therapy or interferon-based therapy for hepatitis C" Regards.

Classification: Grade A (Excellent)

Language Evaluation: Grade A: priority publishing

Conclusion: Minor revision

Response:

We are grateful for the reviewer's constructive comments regarding our study.

1.We appreciate the reviewer's comments and apologize that the prevalence of HBV/HCV dual infection was not clearly defined in the introduction. This deficiency has been corrected with the following statement: "The global prevalence of HBV/HCV dual infection is approximately 5-10% in patients with chronic HCV infection, and the prevalence is reported to be as high as 8.4% in China and 12-14% in East Asia."

2.As suggested, the studies with fewer than 5 patients have been excluded from the evaluation of the incidence of HBV reactivation and reactivation-related hepatitis. The results were similar after removing the studies with a small number of patients and the related data and information have been updated.

3.We agree with the reviewer. The efficacy of anti-HCV treatment is not comparable because of the different treatment regimens and various other factors. The subheading "Efficacy of anti-HCV treatment" and the related sentences in the discussion and conclusion have been removed.

REFERENCE

- 1 **European Association for the Study of the Liver.**EASL Recommendations on treatment of hepatitis C 2016.*J Hepatol* 2017; **66**: 153–94.[DOI: <https://doi.org/10.1016/j.jhep.2016.09.001>]