Response to reviewer

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Manuscript Type: Invited Review

Manuscript Title: Advances in Treatment and Prevention of Hepatitis B

Dear Editor,
We appreciate the thorough review of our original submission and appreciate the insightful comments from the reviewer and the science editor.
We have responded to the comments and revised our manuscript accordingly.
We sincerely hope that you will find our revised manuscript suitable for publication in your esteemed journal.

Sincerely,
Kumar Pallav

1. In the present manuscript, the authors summarized the new progress of HBV research after the publication of the AASLD 2018 Hepatitis B Guidance by searched the HBV related literatures within the last three years. I have several comments list below. 1. For the title "Advances in treatment and prevention of Hepatitis B", the new progress in present manuscript was mainly focused on the advances for the AASLD 2018 Hepatitis B Guidance. However, there are some other HBV-related guides, such as EASL 2017 Guidelines and APASL 2019 Guidelines. The contents of these guides are not exactly the same, thus the topic does not fully reflect the main subject of the manuscript.

   Response: We have modified our abstract, introduction, and core tip in response to this comment to clarify that we are not presenting an update to any particular guideline. We have clarified that the overwhelming majority of data cited in most recent guidelines, including AASLD, EASL, TASL, and APASL, were published before 2018. As such, we decided to review data published in 2018 onward to identify newer developments and existing challenges.

   Our reasoning for using 2018 as an arbitrary cutoff to decide what we consider "recent literature" is as follows. This explanation is for reviewer response only and not included in the manuscript.

   - The most recent EASL guidelines on hepatitis B were published in 2017
   - The most recent APASL guidelines on hepatitis B were published in 2016 http://apasl.info/guidelines/. While our search did not reveal newer APASL guidelines on Hepatitis B, we did come across the TASL guidelines. The experts of the Taiwan Association for the study of the liver (TASL) have helped formulate APASL guidelines in the past and released a consensus statement in 2018(published finally 2019), to "publish the guidelines on HBV management of Taiwan." For due diligence, we reviewed the statement and found that only eight citations (out of 312 total citations) were from 2018, the rest being older than 2018. https://pubmed.ncbi.nlm.nih.gov/30527436/
   - The most recent AASLD guidelines update were published in 2018 and only included four publications from 2018 https://pubmed.ncbi.nlm.nih.gov/29405329/

2. For the markers HBV testing, such as cccDNA, HBcrAg and HBV RNA, which have been studied for a long time, but they were not mentioned in the AASLD 2018 Hepatitis B Guidance. This is because these biomarkers have their limitations which have not been completely resolved, thus authors should fully discuss.

Response: We have added the following to our manuscript with appropriate references.

- Multiple challenges must be met before these biomarkers can be fully utilized in clinical practice. The specific methods and technical details of serum RNA detection vary widely between different studies, and standardization is urgently needed. To exclude interference from viral DNA, methods for measuring pgRNA usually require a selective DNA degradation step, which is complicated and time-consuming and compromises detection accuracy. Further research is needed to determine specific cutoff values of HBcrAg to determine clinical outcomes and determine the role of HBV RNA in occult hepatitis B infection, HbsAg seroclearance, HBV reactivation, and development of HCC. Additionally, the biomarkers will need to be validated in different racial and ethnic populations. Studies correlating novel biomarkers with hepatic fibrosis and cccDNA will require serial liver biopsies, which would likely result in reduced sample sizes. In a recent trial, Brakenhoff et al. showed that Hepatitis B virus RNA decline without concomitant viral antigen decrease is associated with a low probability of sustained response and hepatitis B surface antigen loss and highlighted the need for future trials that consider the kinetics of combined biomarkers to assess antiviral efficacy.

3. For Hepatitis B vaccination strategies, the prevention of mother-to-child transmission (MTCT) for HBV is key to reducing the global burden of chronic hepatitis B. Concurrent use of hepatitis B immunoglobulin and hepatitis B vaccine has substantially reduced the MTCT of HBV, nearly zero infection in children of carrier mother with negative HBeAg and 5-10% infection in children of HBeAg-positive mothers. Through improved immune strategies and antiviral treatment in HBeAg-positive mothers, the infection rate of MTCT of HBV can be reduced to less than 1%. The authors should highlight the efficacy and barriers of the currently validated measures for the prevention of HBV MTCT.

Response: We have created a subsection of Mother to Child Transmission of Hepatitis B under Special Populations.

- In this section, we present the current recommendations from AASLD and MWWMR and the most recent guidelines from WHO addressing the addition of perinatal antiviral regimen to reduce the risk of MTCT in those with high HBV load/HBeAg positivity.
- We additionally present the recent studies addressing the utilization of antivirals in this population.
- We had previously addressed general public health challenges that hinder our ability to prevent and treat hepatitis B. Per the reviewer's recommendation, we have added a paragraph in the 'future direction' section to address the barriers specific to measures aimed at reduction of MTCT, including birth immunization, Neonatal HBIG administration and testing and treatment of those with high perinatal HBV DNA levels.

4. In the AASLD 2018 Hepatitis B Guidance, immune-Tolerant CHB do not be recommended for treatment. However, in the present manuscript immune-tolerant (HBeAg positive) CHB patients were also received TDF and/or Emtricitabine, does this mean a change in the antiviral therapy?

Response: We **<u>are not</u>** recommending a change in antiviral therapy based on the limited data presented in our manuscript. We do believe that this knowledge may contribute to future developments directly or indirectly.

- Per our review, the AASLD recommendation against antiviral treatment for adults with immune tolerant CHB stems from a lack of solid evidence/long-term experience with these patients. The AASLD guidelines highlight the need for such studies by making the following statements.
- Natural history studies have found a strong association between serum HBV DNA levels and the development of HCC and cirrhosis, independent of serum ALT level, HBV genotype, and HBeAg status in

adults, which raises the issue of whether adults in the immune-tolerant phase of infection would benefit from antiviral therapy.

- There are no data to inform a recommendation for earlier treatment initiation of immune-tolerant persons with a family history of HCC.
- Additional studies of longer-term therapy and follow-up are needed to better assess the safety and benefits of antiviral therapy in adults in the immune-tolerant phase of CHB, particularly in persons with a family history of HCC.

5. Language polishing

Response: All our authors are native speakers of the English language. To further improve the language quality, we have reviewed and improved our manuscript and used a language processing tool.