Dear Editor,

Thanks for the kind and thoughtful suggestions from the review of our manuscript entitled "Antiviral Treatment for Chronic Hepatitis B: Safety, Effectiveness, and Prognosis".

We have carefully considered the editor and reviewer's comments. According to the suggestions, the manuscript has been fully revised. Please find below our point-by-point responses to the comments. The revisions in the manuscript was highlighted in yellow for easy identification.

Sincerely,

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Point-by-point responses

Response to the editors:

1.For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Article'.

R: The language certificate by professional English language editing company has been provided.

2. Please provide the decomposable figure of Figures, whose parts are movable and editable. So you can put the original pictures in PPT and submit it in the system.

R: Yes, it has been provided.

3. Your manuscript should be prepared with word-processing software, using 12 pt Book Antiqua font and 1.5 line spacing with ample margins.

R: Modifications have been made as required.

4. Please revise and perfect your manuscript according to peer-reviewers' comments. Please upload the required files on the system.

Please revise the manuscript according to the review report and my comments.
And answer all of the reviewers' comments carefully (point-to-point).

R: The article has been revised, the comments of peer-reviewers' have been answered point-to-point, and the required documents have been uploaded.

5. Please add pictures and tables in your article

R: Pictures and tables have been added in the article.

6. Running title. A short running title of no more than 6 words should be provided. It should state the topic of the paper. For example, Losurdo G et al. Two-year follow-up of duodenal lymphocytosis. (no more than 6 words)

R: Yes, it has been provided. (line: 7)

7. ORCID number should be provided.

R: Yes, ORCID numbers have been provided. (line: 15-16)

8. you need to provide the grant application form(s) or certificate of funding agency for every grant, or we will delete the part of "Supported by..."

R: The certificate of funding agency for every grant has been provided.

9. Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

R: Yes, the core tip has been added. (line: 73-82)

10. In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information.

R: Yes, an audio core tip has been provided.

11. Please provide all authors abbreviation names and manuscript title here. The abbeviation names should be the same as the copyright. World J Clin Cases 2019; In press

R: All authors abbreviation names and manuscript title have been added in the required places. (line:85-86)

12. Please check and confirm that there are no repeated references!

R: The references have been checked and the PubMed citation numbers have been added.

Reviewer 1:

1. *Add the unique of this study compared to other studies discuss the same issue.*

R: Thank you for your suggestion. In this study, different antiviral treatment endpoints for chronic hepatitis B and the safety and prognosis of drug withdrawal were discussed. It was concluded that patients with HBsAg clearance had the safest drug withdrawal and the best prognosis improvement. HBsAg clearance is not just a slogan, it should be pursued in clinical practice as much as possible. The unique point of this paper is that we put forward the concept of "advantageous population" and suggest to pursue HBsAg clearance as far as possible on the basis of safety and effectiveness through "optimized antiviral treatment strategy". (line:52-63, 73-82, 449-459)

2. *Add more on the basic of this disease in the introduction*

R: Thank you for your suggestion. We have added the basic knowledge of chronic hepatitis B in the introduction. (line:96-101)

3. *Discuss role of imaging using these ref*
   Razek AA, Khashaba M, Abdalla A, et al. Apparent diffusion coefficient value of hepatic fibrosis and inflammation in children with chronic hepatitis. Radiol Med 2014;119:903-9.
   Razek AA, Abdalla A, Omran E, Fathy A, Zalata K. Diagnosis and quantification of hepatic fibrosis in children with diffusion weighted MR imaging. Eur J Radiol 2011;78:129-34.

R: Thank you very much for your suggestion. We have read the references you mentioned, which are very meaningful. It is suggested that diffusion weighted MR imaging plays an important role in the diagnosis of chronic hepatitis B in children. However, in this article, we discuss the safety and prognosis of discontinuation of antiviral therapy for chronic hepatitis B, which does not involve the imaging diagnosis of cirrhosis and hepatocellular carcinoma. In addition, this study mainly explores that adult chronic hepatitis B does not involve the diagnosis and treatment of children chronic hepatitis B. Children chronic hepatitis B is different from adult hepatitis B and has its unique characteristics. Therefore, we do not think this article is suitable to cite the above references at present. Of course, your research is very meaningful, and we will definitely consider the application in future research.

4. *English language correction through the manuscript*

R: Thank you for your suggestion. We have corrected the language.

5. *Update of references as most of references are old using these ref*
   Besheer T, Elalfy H, Abd El-Maksoud M, et al. Diffusion-weighted magnetic resonance imaging and micro-RNA in the diagnosis of hepatic fibrosis in chronic hepatitis C virus. World J Gastroenterol. 2019 Mar 21;25(11):1366-1377.
   Besheer T, Arafa M, El-Maksoud MA, et al. Diagnosis of cirrhosis in patients with chronic hepatitis C genotype 4: Role of ABCB11 genotype polymorphism and plasma bile acid levels. Turk J Gastroenterol 2018;29:299-307.

R: Thank you for your suggestion. We have updated the references. And we have read the references you mentioned. Diffusion-weighted magnetic resonance imaging, micro-RNA, ABCB11 genotype polymorphism and plasma bile acid levels play an important role in the diagnosis of hepatitis C fibrosis and cirrhosis. However, this article mainly discusses the relationship between the different end points of antiviral therapy for chronic hepatitis B and the

safety of drug withdrawal and the improvement of prognosis, and does not involve the diagnosis of hepatitis C fibrosis and cirrhosis. Your research is very meaningful. We will cite the references you provide in future studies.

Reviewer 2:

The authors reviewed the different antiviral treatment endpoints in terms of the safety of drug withdrawal, improvements in prognosis and relevant advances. It is well written and is useful for readers. I have a few minor comments.

Minor comments

#1. P5, line 33. What does 4006 mean?

R: Sorry for the confusion. 4006 is the trial number. This study confirms that long-term LAM therapy can reduce disease progression and hepatocellular carcinoma. It is the only global multi-center prospective study in the field of hepatitis B compared with placebo. Since this study, the importance of antiviral treatment in improving patient prognosis has been established. This has been explained in the article. (line:248-255)

#2. P6, line 6. It must be "total", but not "average".

R: Thank you for your reminding. We have modified it in the article.(line:266)

#3. P7, line 16. It must be "total", but not "median".

R: Thank you for your reminding. We have modified it in the article.(line: 324)

Reviewer 3:

1. *Although the safety of antiviral therapy in the title of the article, the side effects and safety of antiviral therapy are not adequately discussed in this article.*

R: Thank you very much for your suggestion. In this paper, we only focus on the possible harm caused by different drug withdrawal endpoints, but ignore the side effects and safety of long-term antiviral therapy . We supplement this in the article. (line:160-172)

2. *Some studies should be included in this article:*
   "Hepatitis B surface antigen reduction by switching from longterm nucleoside/nucleotideanalogue administration to pegylated interferon."

R: Thank you very much for your question. In fact, the article has already included this aspect. The two studies (OSST study, New Switch study)

mentioned in this paper are both prospective, multi-center studies of long-term NA treatment followed by Peg-IFN treatment. The above studies showed that patients undergoing NA treatment can achieve high HBsAg clearance rates by switching to Peg-IFN treatment, and the lower the HBsAg level, the higher the possibility of HBsAg clearance. (line:393-410)

"Hepatitis B surface antigen reduction by administration nucleoside/nucleotide analogue after 48 week pegylated interferon treatment."

R: The effect of NA is mainly limited to virus suppression, and the decrease of HBsAg level mainly depends on the effect of Peg-IFN. After 48 weeks of treatment with Peg-IFN and then NA treatment, although the post-effects of Peg-IFN may lead to the continued decline of HBsAg levels and even HBsAg clearance, we have not yet seen the literature reports of the research schemes involved for this purpose.