

Dear Editor,

We have recently submitted an invited manuscript (ID 63543 – “Current impact of viral hepatitis on liver cancer development – the challenge remains”) in order to be appreciated for publication in your prestigious journal. Now, we would like to resubmit it after answering to the reviewer’s comments (see below).

We would like to thank the reviewer for his/her thorough evaluation of our work and for his/her relevant suggestions. We hope that, after considering our answers to his/her comments and the changes in the manuscript, you will find it suitable for publication in its present form.

We would also like to inform that there are only five self-cited references in the manuscript, which is under 10% of the references.

Thank you for your attention.

Sincerely yours,

Angelo Z. Mattos

Response to reviewer’s comments:

Dear Reviewer,

Thank you very much for your comments on our paper. Your suggestions were highly relevant and certainly allowed us to greatly improve our manuscript.

The following are the responses to each of your comments:

**Comment 1:** First, the formation of liver cancer involves many factors, including host factors, viral factors or therapeutic factors. In this paper, viral factors in the occurrence and progression of liver cancer are not described in detail.

**Answer Comment 1** – Thank you very much for your comment. We have never intended to cover every aspect of hepatocarcinogenesis in a single article, but we agree that we could have described some of the associated factors in more detail, especially regarding hepatitis C virus. Therefore, aside from the sections

on “Immune aspects of viral hepatitis in hepatocarcinogenesis” and “Implications on hepatocellular carcinoma”, we have further discussed the role of viral factors on hepatocarcinogenesis in page 12, lines 6-14.

**Comment 2:** Second, this paper does not clearly state what are the challenges we are facing now and how to deal with these challenges. Besides regular monitoring, are there other ways to reduce the risk of liver cancer? such as different regimen for antiviral therapy.

**Answer Comment 2** – Thank you for your comment. In order to clearly identify the most important challenges regarding viral hepatitis-related hepatocellular carcinoma and how to deal with them, we have added two subsections to the paper: “Major challenges” on hepatitis B (from page 11, line 20, to page 12, line 2) and “Major challenges” on hepatitis C (page 14, lines 13 to 24).

**Comment 3:** Third, the meaning of this sentence "Co-infection of HBV and HIV in addition to HDV is rather uncommon" in this paper is not clear.

**Answer Comment 3** – Thank you for your comment. Now the text reads “Triple co-infection of HIV, HBV and HDV is rather uncommon...” (page 16, line 13) and we hope it is clearer.

Once more, we would like to deeply thank you for reviewing our paper. We hope that you will now consider our manuscript suitable for publication in the World Journal of Gastroenterology.