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Dear Prof. Ghosh and Prof. Tarnawski:

Thank you for your decision letter regarding our manuscript, entitled “Microbiomic and metabolomic analysis of hepatitis B virus-infected patients in the immune-tolerant phase” (Manuscript Number ID: 77025). We also thank the reviewers for the recognition of the scientific merits of our study and their valuable comments. We have revised the manuscript according to the reviewers’ suggestions. The revised portions are marked in red color in the revised manuscript, and the point-by-point responses to the reviewers’ comments are listed as follows.

Best Regards,

Da-Wu Zeng, MD

The First Affiliated Hospital, Fujian Medical University,

No. 20 Chazhong Road, Taijiang District,

Fuzhou, Fujian, China, 350005

**Reviewer #1:**

1. Congratulations ! This is very interesting study. Regarding the title, I suggest including "... in the immune-tolerant and immune-active phases."

**Response:** Thanks for your comment and suggestion. We have added “... in the immune-tolerant and immune-active phases” in the revised title. The new title of the revised manuscript is “Gut microbiota of hepatitis B virus-infected patients in the immune-tolerant and immune-active phases and their implications in metabolite

changes.” The running title is “Omics analysis of CHB patients.”

**Reviewer #2:**

1. The title need to be more specific with respect to abstract.

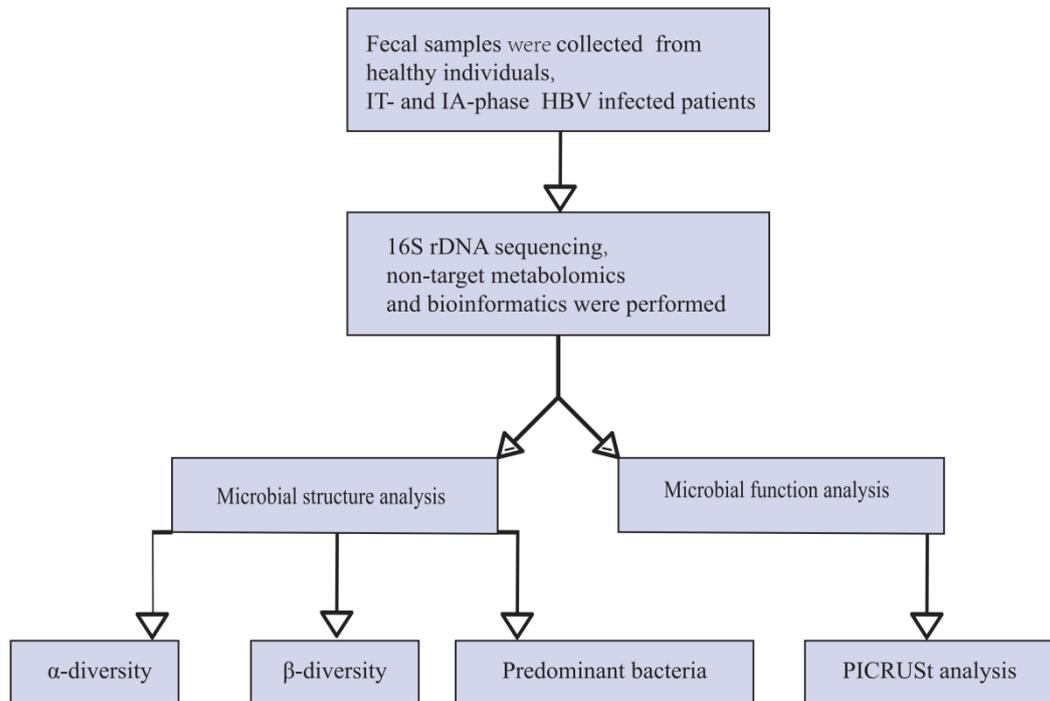
**Response:** Thanks very much for your suggestion. We have revised the title. The new title of the revised manuscript is “Gut microbiota of hepatitis B virus-infected patients in the immune-tolerant and immune-active phases and their implications in metabolite changes. Running title: Omics analysis of CHB patients.”

2. The results shall be in a more meaningful descriptive manner.

**Response:** Thanks a lot for your comment and suggestion. In the revised manuscript, meaningful descriptive sentences have been added to the results section. (Pages 2, Lines 34–37, 39–43).

3. Graphical abstract can be included.

**Response:** Thanks for your comment. We have drawn a flow chart for the graphical abstract. See bellow.



4. Some sentences are repeating ..egRepeating sentence in line number 95-100(. The criteria for IT patients were as follows(11):at least 18 years old;H··).

**Response:** Thanks very much for your careful review of this paper. We apologize for this error. We have deleted the repeated sentences and reorganized the text. The revised sentences are as follows: “All HBV-infected patients were at least 18 years old, HBsAg positive for  $\geq 6$  months, and HbeAg positive; moreover, the IT patients had a normal ALT level ( $< 40$  IU/L), HBV DNA  $> 1$  million IU/mL, and no fibrosis found by FibroScan analysis (17); the IA patients had an HBV DNA serum concentration of  $> 20,000$  IU/mL as well as elevated alanine aminotransferase and/or aspartate aminotransferase levels (17).”

5. Relevance of alpha fetoprotein need to be mentioned ... usually it is a preferred marker in HCC condition.

**Response:** This is a very good suggestion, thank you very much. The present study focused on the dynamic profiles of the gut microbiota in IT-phase and IA-phase HBV-infected patients without liver fibrosis by 16S rDNA sequencing and analysis. We measured the liver stiffness and alpha-fetoprotein level of every patient in our study. All of the alpha-fetoprotein values were in the normal range. We have excluded liver cancer in our study.

6. More supporting articles need to be mentioned in the discussion and introduction part.

**Response:** Thanks for your kind suggestion. We have read some papers about Omics analysis of CHB patients. In the revised manuscript, related supporting publications have been cited (Page 4, Lines 61, 63,72; Page 5, Lines 75; Page 15, Line 312; Page 16, Line 320; Page 17, Line 352; Page 19, Line 382).

7. The article need to be in a crisp mode, so the readers will not get tired. A proper rearrangement is needed.

**Response:** Thank you for a very good suggestion. We have rearranged the article in the revised manuscript, and some subtitles have been changed into simpler and clearer ones.

8. Graphs and tables can be with more clarity. figure legends needed. all the diagrams label are not clear.

**Response:** We would like to thank the respected reviewer 2 for their useful comments. We have tried to consider all comments in the revised manuscript to improve this paper. Figure legends have been added, and the diagram labels have been made clearer in the revised manuscript.