

Dear Editor,

Please find the enclosed revised manuscript in Word format (HDV Review WJG Final.R2.Marked.docx).

Title: Chronic Hepatitis Delta: A State-of-the-Art Review and New Therapies

Authors: Christy Gilman MD, Theo Heller MD, Christopher Koh MD MHSc

Name of Journal: World Journal of Gastroenterology

Manuscript Number: 49302

Manuscript Type: Review

We are greatly appreciative of the time and effort taken to review our manuscript. The comments and suggestions provided by the reviewers have improved the quality of our manuscript. We are now submitting a revised manuscript that takes into account the recommendations provided by the reviewers. It is our hope that this revision will be suitable for publication in your journal.

Each comment has been answered accordingly in the manuscript and the modifications can be found in the highlighted areas of the revised manuscript. The specific point-by-point responses can be found below.

Thank you for your consideration.
Sincerely,

Christopher Koh, MD MHSc

Response to reviewer's comments:

We thank the reviewers and editor for their time and feedback. We have provided our point-by-point response below.

REVIEWER #1

Christy Gilman et al. reported a systematic review and new therapies for chronic hepatitis delta. The topic is interesting, but the form of the manuscript did not follow the guidelines at all. Also, this is not a systematic review. PRISMA checklist and flow diagram should include in the manuscript. In the management and investigational therapies section, some tables for summarizing protocol and outcome would help readers to understand easily.

We thank the reviewer for these comments and apologize for the confusion. This was meant to be a state-of-the-art review and agree with the reviewer that this is not a systematic review. The title has been changed to reflect this.

We appreciate the suggestion for the addition of tables in the management and investigational therapies section and completely agree. Two new tables have been added to this manuscript; one which describes previous interferon clinical trials and one which describes current clinical trials with novel therapies.

REVIEWER #2

1. On one hand, the authors state that Delta Hepatitis (HDV) is the most severe form of viral hepatitis. On the other hand, the authors state that clinical course of HDV infection is typically benign. Only when superinfected with chronic HBV, HDV infection is more severe than HBV monoinfection. So, it should be that chronic HDV infection is the most severe form of chronic viral hepatitis. 2. I think that it is better to use systematic evaluation and meta analysis to evaluate the efficacy of HDV therapy.

We thank the reviewer for these comments and apologize for this error. We agree with the reviewer, chronic HDV infection is the most severe form of chronic viral hepatitis and the change has been made in the manuscript. This manuscript was meant to be a state-of-the-art review rather than a systematic review and the change is reflected in the manuscript.

REVIEWER #3

This reviewer does not have further comment for this review paper.

We thank the reviewer for their time and consideration.

REVIEWER #4

This is a well write, interesting and comprehensive review on Hepatitis Delta virus infection. I think that the review is of great interest for the readers considering the new treatment options that probably will be available in the next future. There are some point to be reviewed: • Figure 1 is missing • Page numbering is missing • Please re-evaluate the definition of acronyms • In the EPIDEMIOLOGY chapter in the second paragraph the retrospective study of northern California should be better characterized and the last sentence "Fourteen (67%) HDV patients ..." is unclear • In the CLINICAL PRESENTATION AND DIAGNOSIS the last sentence should be rewritten because unclear • In the INVESTIGATIONAL THERAPIES chapter, section Inhibiting assembly of viral particles, at the end of the second paragraph, penultimate line, there is a mistake: deceased instead of decreased. In the same paragraph, in the subsequent sentence, please specify the trend of HBV-DNA. In the same chapter, section Preventing export of viral particles, the molecule REP 2055 should be better characterized.

We thank the reviewer for these suggestions and will address each separately.

• Figure 1 is missing:

We apologize if Figure 1 was missing. Figure 1 is currently present in the manuscript.

- **Page numbering is missing:**

We apologize for this. Page numbers have been added to the manuscript.

- **Please re-evaluate the definition of acronyms:**

We apologize for the confusion. The manuscript was proofread again and the acronyms have been adjusted.

- **In the EPIDEMIOLOGY chapter in the second paragraph the retrospective study of northern California should be better characterized and the last sentence “Fourteen (67%) HDV patients ...” is unclear:**

We apologize for the confusion. We have now improved the characterization of this study and have clarified the last sentence. It now reads: “In a retrospective study of 1191 patients in northern California from 1989-2007, only 499 (42%) patients were tested for HDV (HDV ab or HDAg or both) [4]. Of those tested, 42 (8%) patients were confirmed to be HDV infected (HDV ab (n=29), HDAg (n=6), both (n=7)). Interestingly, 67% of the HDV patients were diagnosed with cirrhosis compared to only 17% of HBV monoinfected patients tested for HDV and 22% of the total HBV monoinfected cohort (including patients not tested for HDV).”

- **In the CLINICAL PRESENTATION AND DIAGNOSIS the last sentence should be rewritten because unclear:**

We apologize for the confusion. As recommended, this sentence has been rewritten. “Current therapy for chronic HDV infection is limited to interferon alpha. Identifying patients who warrant treatment highlights the need for specific HDV scoring systems and fibrosis markers.”

- **In the INVESTIGATIONAL THERAPIES chapter, section Inhibiting assembly of viral particles, at the end of the second paragraph, penultimate line, there is a mistake: deceased instead of decreased. In the same paragraph, in the subsequent sentence, please specify the trend of HBV-DNA. In the same chapter, section Preventing export of viral particles, the molecule REP 2055 should be better characterized:**

We apologize for the grammatical error of “deceased” and the change has been made to “decreased.”

We also apologize for not specifying the trend of HBV DNA and this change has been made. “There were no significant changes noted in ALT, HBsAg or HBV DNA levels but a trend towards increased HBV DNA levels was noted in Group 2.”

We also apologize for not better characterizing REP 2055. As recommended, this change has been made. “Studies of NAPs (REP 2006, 2031, 2055) in the duck hepatitis B virus model of HBV infection also showed exhibition of antiviral activity [116-118].”