

**Reviewer #1 (05848252)**

*In this paper, the author made a detailed review of HDV, introduced the virology, epidemiology and clinical diagnosis and treatment of HDV. From more attention to HBV infection, we have turned our attention to HDV infection and realize the severity of HDV-related infections. Overall, the article is well organized and its presentation is good. However, on one point, I suggest that CHD should be commented to avoid ambiguity when it first appears in the text.*

We thank the Reviewer for suggesting to accept our paper for publication.

As suggested, we have added a brief comment to CHD when it first appears in the text in order to avoid ambiguity (changes highlighted in green).

**Reviewer #2 (03664122)**

*Since the discovery of HDV, it has remained an important pathogen influencing the course of hepatitis B virus disease. The continuing need for increased attention to routine HDV screening and the search for new treatments is a prerequisite for the publication of such a review. I do not have any specific comments on the review, it is well written and includes an analysis of interesting treatment options, even though there were no alternative points of view or hypotheses. Just, the mentioned role of integrated HBV DNA in maintaining high HBsAg levels even after Myrcludex treatment seems rather questionable, but not impossible.*

We thank the Reviewer for suggesting to accept our paper for publication.

We agree with the Reviewer that the mention of integrated HBV-DNA in maintaining high HBsAg levels in patients treated with Myrcludex could be confounding. So, we have decided to remove the sentence in the conclusions (changes highlighted in red)

**Reviewer #3 (00070897)**

*This review focuses on new advances in HDV infection and treatment. The knowledge is helpful for further understanding of life cycle and new therapeutic strategies of hepatitis delta virus.*

We thank the Reviewer for his/her comments and for suggesting to accept our paper for publication.

**Reviewer #3 (00863327)**

*It is an interesting review article explores hepatitis delta virus (HDV), a RNA virus requiring the hepatitis B virus (HBV)-encoded hepatitis B surface antigen (HBsAg) for its assembly and transmission, either in co-infection or super-infection status. The main option of conventional*

*treatment is interferon administered as mono-therapy, while only a minority of patients achieve a sustained response. Nevertheless, this article puts an emphasis on new therapeutic strategies that target specific steps in the HDV life cycle. The most promising drugs are myrcludex B and lonafarnib, which inhibit virus entry into hepatocytes and farnesylation of the viral-encoded large hepatitis D antigen, respectively. The manuscript is well written in English and directly relevant to clinical application. There are some suggestions as follows.*

*1. Since this article emphasizes the novel therapies of HDV infection, the authors should summarize the current knowledge including both established and undergoing treatments into a Table.*

We thank the Reviewer for his/her suggestion. We have provided to add a table (Table 1) summarizing both established and undergoing drugs used in the management of HDV chronic hepatitis (changes highlighted in light-blue)

*2. Some typographical errors needed to be corrected as follows. In page 3 Key words, the authors should remove "Hepatitis D". In page 11, there were no references for "Delta-4 fibrosis score" and "Delta Fibrosis Score". In page 15 New therapeutic targets in HDV, --- these represent inhibitors of the NTCP receptor and farnesyltransferase and "to" the group of nucleic acid polymers. The authors should remove "to". In page 31 Figure 1, L-HDAg - "HBsAG". The author should use HBsAg.*

We apologise for our spelling and grammar mistakes that have been amended in the revised version of the manuscript (changes highlighted in yellow).

1. In page 3 "Hepatitis D" has been removed (page 3 key words).
2. In page 11 references for "Delta-4 fibrosis score" and "Delta Fibrosis Score" has been added (page 11 lines 27-28, ref n 46-47).
3. In page 15 the word "to" has been removed (page 16 line 29).
4. In Figure 1 the word "HBsAG" has been replaced with "HBsAg" (page 32 Figure 1).

## **Response to the Editor:**

The text of manuscript has been revised according to Reviewers' suggestions: the requested Table summarizing both established and undergoing treatments has been added and typographical errors have been corrected.

Original figure documents have been uploaded both in PowerPoint and Word format.

Required certificates/documents (Conflict-of-Interest Disclosure Form and Copyright License Agreement) were provided.