

October 9, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4665-review.doc).

**Title:** *Human Immunodeficiency Virus and Nodular regenerative hyperplasia of liver – a systematic review*

**Authors:** Archita Sood, Mariana Castrejón, and Sammy Saab

**Name of Journal:** *World Journal of Hepatology*

**ESPS Manuscript NO:** 4665

The manuscript has been improved according to the suggestions of reviewers:

- 1 Format has been updated
- 2 Revision has been made according to the suggestions of reviewer 13180
  - (1) *A major omission in the article is the absence of a histopathology figure. NRH is a hisopathological diagnosis and the value of the article will be enhanced by the addition of a figure of NRH.*  
We have included a histology figure.
  - (2) *Page 6, first paragraph, 2nd to 4th sentence, In one series....liver dysfunction noted by normal INR". This requires reference which likely was missed by oversight.*  
We have added a reference
  - (3) *Table 1. Adding reference number after authors name in the first column will aid in easily identifying the article.*  
Reference number after authors name has been added.
  - (4) *Table 1. Under Mallet et al. The figure 16 patients is incorrect. It is 13.*  
We corrected the number.
  - (5) *Figure 1. Also under Mallet et al. under clinical presentation, "unknown" is incorrect and should be replaced by portal hypertension.*  
We corrected the clinical presentation.
  - (6) *Under references: Reference 27, the tile is placed within parenthesis. Does it need to be deleted?*  
Parentheses were deleted.
  - (7) *Reference 52. After Saito K "&" needs to be deleted*  
We deleted the symbol "&"
- 3 Revision has been made according to the suggestions of reviewer 38981
  - (1) *English grammar needs improvement across the text and in particular in the abstract. E.g. "The appropriate management of HIV-infected persons with suspected NRH is yet to be outlined, however it is an important concept as it can be a clinically subtle condition that is difficult to diagnose". This sentence should be changed, for example, as follows: "The appropriate*

*management of HIV-infected persons with suspected NRH is yet to be outlined. However, NRH is a clinically subtle condition that is difficult to diagnose, and it is important to be able to manage it according to the best available evidence".*

The Abstract was changed. We sought assistance from a medical writer to review the manuscript in its entirety.

- (2) *References for the pathophysiological mechanisms suggested in the introduction should be given. Similarly, references for the sentence "On ultrasound, findings may include widespread nodularity of the liver can mimic cirrhosis" should be given.*

References were added.

- (3) *Paragraph focusing on causes of NCPH other than NRH in HIV patients should be added; I am referring in particular to idiopathic portal hypertension, since this has been also linked to antiretroviral therapy sharing the same pathophysiological mechanisms as NRH, and it has been hypothesised that IPH can lead both to NRH and portal vein thrombosis in this population (see Chang PE et al. Am J Gastroenterol 2009 and the references in this paper).*

We included an additional paragraph in the Discussion on the differences between other causes of NCPH and NRH in patients infected with HIV. We made reference to the manuscript by Chang et al, and others.

#### 4 Revision has been made according to the suggestions of reviewer 45831

- (1) *Title: Existing "The approach to the patient with HIV and nodular regenerative hyperplasia" Suggested: HIV and Nodular regenerative hyperplasia of liver – a systematic review.*

Title changed

- (2) *Abstract: The abstract emphasizes the need for information in this field but doesn't summarize the concept and some guidelines to follow. Material and Methods: In view of complexities and variability nomenclature of NRH the material methods needs to mention the exact inclusion and exclusion that were applied in the final analysis. A flow diagram would have been appropriate.*

Search strategy detailed in Methods

- (3) *It is appropriate that only biopsy proven cases were included. Since the entire applicability of this review depends on biopsy proof, has any pathologist experienced in liver pathology has been involved in the analysis of reports before inclusion?*

No. Reinterpreting the diagnosis may be beyond the scope of the review. We relied on the authors' interpretation.

- (4) *The authors mention that "Liver associated test abnormalities were most often consistent with a cholestatic picture, with findings of some combinations of elevated bilirubin, alkaline phosphate or gamma glutamyl transpeltidase(GGT)" Page 5 Para 3 lines 2,3 and 4. Comment: Cholestatic picture is unusual with pure non HIV related NRH. How what are the histopathological findings in such cases? A reference to this aspect is necessary. Are these cases of some kind of overlap clinical entities with NRH.*

The cholestatic picture was seen in only a few case studies. Reference to this was deleted given its rarity. The reader is referred to Table 3 for complete description of the published literature.

- (5) *Needs revision in discussion, the flow of contents and order. 1. Some discussion on pathogenesis in terms of differences between HIV specific and HIV non specific NRH, especially occurrence of*



Ascites (32%), hepatocellular dysfunction and the need for liver transplantation on the basis of dysfunction rather than uncontrolled portal hypertension. Could be thought provoking.

We added a paragraph in our discussion.

- (6) Discussion of liver biopsy (Page 11, para 4) is non specific and inappropriate to the topic under consideration. The discussion should evolve around complexities in diagnosing NRH in patient with HIV rather than too well know facts of liver biopsy in any situation.

We updated our Discussion with inclusion of complexities of the NCPH.

- (7) Page 12 para 3, Could be summarized in further in three or four sentences.

Paragraph simplified

- (8) Suggested flow: Relative rarity of the entity; discussion on pathogenesis relevant to HIV; high index of suspicion in patient of HIV presenting with portal hypertension or incidental finding in imaging; ruling out other causes of similar clinical picture; the need and specific difficulties in biopsy assessment; and suggested management.

Flow was altered in the manuscript to improve readability.

- (9) Some references are of general nature not particularly relevant to the topic under consideration; like those on liver biopsy; could be deleted for want of being specific. Supporting reference to cholestatic presentation and reference to HIV cholangiopathy can be incorporated.

References were reviewed for appropriateness. References to the cholestatic presentation were removed.

5 Revision has been made according to the suggestions of the Editor

- (1) Title should not include acronym

HIV was spelled out in the title.

- (2) Affiliations should follow format

Affiliations updated according to form

- (3) Author contributions should be provided.

Author contributions were detailed in the title page

- (4) Abstract needs to be formatted

Abstract reformatted according to Editor's recommendations

- (5) Key words should be included

We included key words: Nodular regenerative hyperplasia; portal hypertension; human immunodeficiency virus

- (6) Summary

Summary is included

- (7) Headings should be revised according to the example

All headings were revised

- (8) References need to be bracketed and no blank space needed before words.

References were reformatted

- (9) Columns should have headings in Table 1

Columns and headings were included

- (10) References should be cited as recommended in the example in Table 1

References were corrected

- (11) Please provide "Highlighted contents"

Highlighted contents included

- (12) Add PubMed citation DOI citations to the reference list, and list all authors

We included PubMed and DOI reference numbers, and included all authors

6 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*

Sincerely yours,



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