

ANSWERING REVIEWERS

Name of journal: World Journal of Hepatology

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Column: Review

Title: Genetic diversity of hepatitis viruses in West-African countries from 1996 to 2018

Reviewer #1: In this manuscript, the authors searched and analyzed literature from three databases to get information of hepatitis virus endemic in West-African. Findings of genetic diversity and genotype prevalence of common hepatitis viruses were reported. Although this manuscript provided information of about the clinical endemic of hepatitis viruses in West-African, some issues were raised for the improvement.

1. The severity of hepatic pathology and the responses to treatment depended on the hepatitis virus genotypes. Therefore, the difference in disease severity and treatment responses between hepatitis virus genotypes should be mentioned.

Information on response to treatments according to hepatitis virus genotypes has been included in the introduction on page 6. « The response to interferon treatments is more effective against HBV genotypes A and B compared to genotypes C, D and I. HBV genotype E seem to have the worst response to treatment.^[1] Rapid progression of hepatic disease and hepatocellular carcinoma has also been associated with HBV genotype A1.^[2] HCV subtype 1b is associated with a high risk of developing hepatocellular carcinoma compared to other genotypes.^[3] First generations of developing vaccines protect against subtype 1b while the genotype 3, which accounts for 30.1% of HCV global infections, is less likely to first and second generation of direct-acting antivirals currently used for HCV treatment.^[4, 5] »

2. Page 4. The authors cited a reference about the description of HGV as recent study. In fact, this reference was published at 1999.

The sentence has been redrafted [Introduction page 1]: Another human lymphotropic virus belonging to the Flaviviridae family and closely related to HCV, was identified as hepatitis G virus (HGV) or GB virus C (GBV-C). However, several studies have shown that GBV-C/HGV infection is not clearly associated with any disease and may play a role in modulating HIV disease.

3. Page 6. 1.1. A statement of double-stranded was duplicated and the core antigen was abbreviated as HBcAg.

The sentence has been corrected [Introduction page 7]: It is a double-stranded circular DNA enveloped virus of small.... the core antigen (HBcAg).

4. The prevalence genotypes varied among East, West, and other regions of African. A discussion was of importance.

Discussion page 17: Africa has a high diversity of HBV genotypes and subgenotypes displaying distinct geographical distributions. Genotype A is found mainly in south-eastern Africa, genotype E in western and central Africa and genotype D prevails in northern Africa. Genotype E is rarely found outside Africa, except in individuals of African descent.

5. The enrolled periods were 1996 to 2018. Whether a trend change of hepatitis virus genotypes can be found? If there was a change, the information would be more practical.

A slight decrease in the overall frequency of HBV genotype E in West African countries has been found between 2003-2010 (94.4%) compared to 2011-2018 (90.0%) with emergence of genotypes A and D.

Reviewer #2: The article of Assih et al is a quite interesting article describing prevalence of different genotypes of 5 Hepatitis viruses (especially B, C) in west African countries included in the WAEMU area. Anyway, I have some recommendations:

1) The introduction section should better describe the global diffusion and prevalence of hepatitis viruses and their correlation with HCC development. I suggest the following articles to include in reference list: a) Hepatitis Delta Virus and Hepatocellular Carcinoma: an update. *Epidemiology and Infection* 2018 Jul 11;117:1-7. DOI: 10.1017/S0950268818001942. b) Epidemiology of Hepatitis B virus (HBV) and Hepatitis C virus (HCV) related Hepatocellular carcinoma. *The Open Virology Journal*, 2018; 12 (Suppl.-1, M3) 26-32. c) HCV and Hepatocellular Carcinoma: pathogenetic mechanisms and impact of DAA's. *The Open Virology Journal*, 2018; 12 (Suppl.-1, M3) 16-25. d) HCV genotypes distribution among hepatocellular carcinoma patients in Southern Italy: a three-year retrospective study. *Infectious Agents and Cancer* 2017; 12:52. DOI 10.1186/s13027-017-0162-5. e) Global epidemiology of Hepatitis C Virus (HCV) infection: an up-date of the circulation of HCV genotypes. *World J. Gastroenterol.* 2016; 22(34): 7824-7840. IF. 3,365

The introduction has been rewritten considering the remarks and suggestions and in light of all manuscript suggested by the reviewers. Inserted references are highlighted in green in the References section.

2) Concerning the methodology, authors should better describe:

a) exclusion criteria:

Eligible studies had to report genotype of viral hepatitis in populations from included countries regardless of method used for viremia detection. Both risk groups or general population were eligible for inclusion. HBV and HCV viremia detection were based on DNA/RNA amplification. Genotypes detection was performed using PCR or direct sequencing. HCV genotype classification was considered because in many studies, HCV

cases were classified at the genotype level but not at the subtype level. Journal articles, publisher correspondence, news, letters, book chapters and studies whose data were ambiguous or could not be extracted were systematically excluded.

b) selected population included in the study (risk groups or not) Both risk groups or general population were eligible for inclusion.

3) Methods:

a) please, specify methods used in the selected studies for detection of viremia (especially for HBV and HCV): HBV and HCV viremia detection were based on DNA/RNA amplification

b) please, specify methods used for genotyping (HCV): Genotypes detection was performed using PCR or direct sequencing.

4) Why authors decided to use an HCV genotype classification and not subtype? HCV genotype classification was considered because in many studies, HCV cases were classified at the genotype level but not at the subtype level.

Reviewer #3: This is an interesting manuscript were the authors, using available bibliographic data, analyze the different genetic variants of hepatitis viruses present in west African countries. The authors explain well the methodology used in their analysis to compares the strains, but never explain what are the main differences among those strains, this is important for readers that are unfamiliar with Hepatitis viruses. Also, it is important since they state this difference can lead to different courses in the disease or the response to antivirals. Along the texts there are several language issues, maybe words incorrectly translated or typos, along with weird grammar and some HIV that maybe should be HCV or HBV? All these little errors are marked in yellow in the attached file.

All the remarks and suggestions of the reviewer have been considered in the introduction which has been rewritten and language issues have also been corrected in the manuscript. [Introduction page 6]:

The severity of hepatic pathology and the response to treatment depend on the virus genotype in the infected host. For example, HBV genotype A infection tends to chronicity whereas genotype D has a high frequency of mutation influencing response to treatment. Liver cirrhosis and progression to hepatocellular carcinoma are strongly associated with HBV genotypes C and D compared to other genotypes.^[1, 6] Furthermore, superinfection of chronic HBV patients by HDV leads to increased liver damage and more rapid progression of cirrhosis in 90% of cases.^[7] HDV genotype III is thought to be associated with severe forms of liver disease, while a more moderate clinical evolution and a wide variety of clinical conditions are observed with genotypes II and I, respectively. The response to interferon treatments is more effective against HBV genotypes A and B compared to genotypes C, D and I. HBV genotype E seem to have the worst response to treatment.^[1] Rapid progression of hepatic disease and hepatocellular carcinoma has also been associated with HBV genotype A1.^[2] HCV subtype 1b is associated with a high risk of developing hepatocellular carcinoma compared to other genotypes.^[3] First generations of developing vaccines protect against subtype 1b while the genotype 3, which accounts for 30.1% of HCV global infections, is less likely to first and second generation of direct-acting antivirals currently used for HCV treatment.^[4, 5]