Title: Virological pattern of HBV infection in an HIV Positive Patient with a Fatal HBV-related fulminant hepatitis (FHB): a case report.

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To Colette Homan

Journal of Medical Case Reports Editorial Team

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Dear Colette Homan,

herein, included the revised version of the manuscript entitled: “VIROLOGICAL PATTERN OF HBV INFECTION IN AN HIV-POSITIVE PATIENT WITH FATAL HBV-RELATED FULMINANT HEPATITIS (FHB): A CASE REPORT”, by Bagaglio et al. in accordance with the Reviewer’s comments. These comments required additional sentences. So, the word count of the manuscript exceeded 2,200 words. We now have modified the manuscript conforming to the Journal style. To do this, necessarily we have revised the Cover letter too and the Figure 2. We re-submit a revised version of the manuscript (text), cover letter and Figure 2.

Reviewer 1.

Point by point revision.

We tried to better explain the bio-molecular characteristics of HBV genome in some regions that are involved in a severe course of acute hepatitis B, while the complex interaction between HBV and HIV needs functional analyses of the immune response, that is not the primary objective of the present study. However, we have interpreted the important suggestions of the Reviewer by adding more precise information on the mutational pattern of HBV in the section “Introduction”, page 2, lines 4-6 from the top and 1 important reference (now, reference [2] in the text) in the section
“Reference”, page 10, lines 4, 5 from the top. Additionally, we have separated the contents of the section “Virological assays” in two different subsections that could be more explicative for the readers of JMCR. In these 2 subsections, we have specified why we used a specific molecular assay and the expected results by employing this assay.

In detail:

Section “Virological assays”, page 3, line 1 from the bottom, we have included a subsection: **HBV-DNA and HIV-RNA quantitation** that now includes the methods and the results referred to HIV and HCV viral load. However, the methods and the results are the same of those included in the original version of the manuscript.

Similarly, we have included an other subsection referred to HBV genotyping and analysis of sequences in different compartments entitled: **HBV genotyping and pre-core mutational analysis in liver tissue, PBMCs and plasma**, see page 4, line 10 from the top.

The description of virological assays was simplified, while, it was better defined for each experiment why we used a specific virological approach, see page 4, lines 15-18 from the top, lines 19-21 from the top. Each HBV region investigated was referred to the specific compartment explored beginning from the Pre-S domain in plasma, than pre-core region in liver, PBMCs and plasma. Additionally, the description of aa mutations within the specific epitopes of the pre-S domain, that was previously located in the section “Virological assays” has now been included in the legend of the Figure 1. We added in Figure 2 (B) a schematic representation of the lower stem of the epsilon region, that includes the pre-core domain, where the most important point mutations associated with the stability of this secondary structure are indicated.

We hope that these changes in the section “Virological assays” have contributed to better understand the objective of the study and the consequent results by using a bio-molecular approach.

Reviewer 2

1. A sentence with appropriate references [12,13] concerning the clinical impact of HBV replication in the hepatic and extra-hepatic compartments have been included in the section “Discussion”, page 7, lines 1-5 from the top, and section “References”, page 11, lines 4-9 from the top.
2. Data supporting the early treatment of severe acute hepatitis B with antiviral drugs have been added in the section “Discussion”, page 7, lines 13-16 from the top. The related reference [14] was added in the section “References” page 11, lines 10-11 from the top.

Finally, as suggested from both the Reviewers, the manuscript has been extensively edited.