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Reply to: "Hepatocyte expression of hepatitis B surface and core antigens across phases of chronic hepatitis B infection"

To the Editor:

We would like to thank Drs. Chu and Liaw[1] for their interest in our work and we appreciate their comments on the findings described in our manuscript.[2]

The classification of chronic HBV patients in clinical phases is based on the serum levels of HBV DNA, alanine aminotransferase (ALT) and HBeAg, and strict thresholds have been defined for their classification, which were originally meant to guide clinical decision making. For our transcriptomic and immunohistochemical study, we designated 4 patients with ALT levels ~50 IU/ml as immunotolerant patients, since their ALT levels were slightly elevated but stable over time, along with minimal immune infiltrate as observed by histology.

The intrahepatic viral antigen expression data generated using state of the art digital pathology techniques allowed us to profile the intrahepatic HBsAg and HBcAg burden across the different phases of chronic HBV infection. Seminal work performed by Drs. Chu and Liaw[3,4] has previously shown differential expression patterns of HBsAg and HBcAg in chronic HBV-infected livers using fresh frozen tissue. While there are some discrepancies in the data obtained between the studies, it is important to note that differences in technologies and primary antibody clone epitopes used makes comparison between the studies difficult. Fresh frozen tissue has traditionally been considered more sensitive than FFPE tissue; however, recent advances in technologies allowing amplification of signal, such as the InSituPlex technology used in our study, and the use of well characterized antibodies has greatly improved the sensitivity and specificity of FFPE assays.[5,6] Finally, in addition to technological differences, intra- and inter-patient heterogeneity in viral burden makes it challenging to reliably interpret a small number of regions of interest from each biopsy.[7] The ability to scan and analyze the entire biopsy using whole slide images increases our confidence by enabling consistent and unbiased analysis of our data.

We appreciate the opportunity to clarify these important points.

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Conflict of interest

NRM, and AB declare no conflict of interest related to the content of this letter. At the time this study was conducted, AA, RR, LD, LL and BF were employees and stockholders of Gilead Sciences, Inc.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors were involved and approved the final version of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.033.

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