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Understanding virologic heterogeneity in chronic hepatitis B treatment

To the Editor:

Wang *et al.*'s recent study on the virologic trajectories in patients with chronic hepatitis B (CHB) treated with nucleos(t)ide analogue (NA) therapy is a commendable piece of work, utilizing a large dataset and advanced analytical methods to address a critical issue in HBV management.[1] The latent class mixed modeling (LCMM) approach applied in the study reveals the diversity in treatment response, offering a fresh perspective on the heterogeneity of virologic suppression. However, upon closer analysis, several important points merit further discussion and consideration.

First, while the study provides crucial insights into virologic suppression, it predominantly focuses on viral load (VL) as the main outcome measure, potentially overlooking other key clinical markers. While VL suppression is undeniably important, especially given its association with reduced transmission and liver disease progression, the exclusive emphasis on VL may oversimplify the complexities of chronic HBV treatment. Recent studies have increasingly highlighted the importance of additional biomarkers, such as quantitative HBsAg levels, liver stiffness measurements, and inflammatory markers, which are critical in assessing the broader implications of HBV therapy beyond virologic control.[2] By integrating these markers, future research could offer a more holistic view of patient outcomes, particularly as we aim for long-term management strategies that balance viral suppression with overall liver health.

Second, the study's findings on the five distinct VL trajectories, particularly the "slow virologic suppression" group (Class 5), deserve deeper reflection on their clinical implications. The observation that this group had a twofold increased risk of fibrosis or cirrhosis compared to those with long-term suppression raises important questions regarding current treatment protocols. While Wang *et al.* correctly point out the potential risks associated with suboptimal suppression, the absence of data on treatment escalation – such as the use of combination therapy – limits the applicability of their conclusions. Given that guidelines do suggest adding additional antiviral agents for patients with persistent viraemia, it would have been highly valuable to explore how clinical interventions, such as switching or intensifying therapy, impacted these subgroups. Moreover, the potential of novel agents like tenofovir alafenamide (TAF) to accelerate suppression in these challenging cases should not be overlooked.[3] Their omission reduces the practical utility of the findings, especially in light of emerging therapies that offer more potent and targeted suppression strategies.

Third, while the LCMM model provides a robust and innovative method for classifying VL trajectories, it also introduces potential limitations. The model assumes that patients remain in fixed trajectory classes throughout treatment, which may not fully capture the dynamic nature of CHB and its management. In reality, patients' virologic responses can shift over time due to various factors, including adherence, lifestyle changes, and therapeutic adjustments.[4] This dynamic variability suggests the need for more flexible modeling techniques that allow for transitions between trajectory classes, especially as treatment evolves. Furthermore, given the study's emphasis on long-term data, it would be insightful to examine whether some patients initially classified as slow suppressors eventually achieve full suppression with prolonged treatment. By addressing this, future research could offer more nuanced guidance on how to adapt treatment for patients whose suppression trajectories shift over time.

Despite these considerations, it is important to acknowledge the significant contributions of Wang *et al.*'s study. The size of the cohort, the innovative use of health informatics, and the application of LCMM to uncover previously unrecognized virologic patterns are clear strengths. The authors' ability to capture real-world data over a substantial follow-up period adds a degree of practical relevance often absent in clinical trial-based studies. Their work paves the way for future investigations into more personalized treatment strategies for patients with CHB, particularly as treatment guidelines expand to include a broader population. As such, this study provides a solid foundation upon which more detailed investigations into virologic trajectories and therapeutic outcomes can be built.

In conclusion, Wang *et al.*'s study brings valuable insights into the heterogeneity of virologic responses in patients with CHB treated with NAs. While there are areas where deeper exploration would enhance the practical application of the findings, particularly regarding treatment adjustments and alternative biomarkers, the study remains a crucial step toward understanding the complexities of CHB treatment. Its innovative methodology and use of large-scale real-world data are commendable, and it sets the stage for more refined, personalized approaches to managing chronic hepatitis B.

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Supplementary data

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References

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[1] Wang T, Campbell C, Stockdale AJ, et al. Distinct virologic trajectories in chronic hepatitis B identify heterogeneity in response to nucleos/tide analogue therapy. JHEP Rep 2024. https://doi.org/10.1016/j.jhepr.2024.101229.

[2] **Jiang B**, **Wang L**, Liu H, et al. Association of HBV serological markers with host antiviral immune response relevant hepatic inflammatory damage in chronic HBV infection. J Med Virol 2024;96:e29569. https://doi.org/10.1002/jmv.29569.

[3] Yamashige D, Hosaka T, Suzuki F, et al. Effectiveness of tenofovir alafenamide for chronic hepatitis B patients with a poor response to the previously used nucleos (t) ide analogs. J Gastroenterol 2021;56:1008–1021. https://doi.org/10.1007/s00535-021-01826-8.

[4] **Lieveld FI**, **van Vlerken LG**, Siersema PD, et al. Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review. Ann Hepatol 2013;12:380–391. https://doi.org/10.1016/S1665-2681(19)31000-2.