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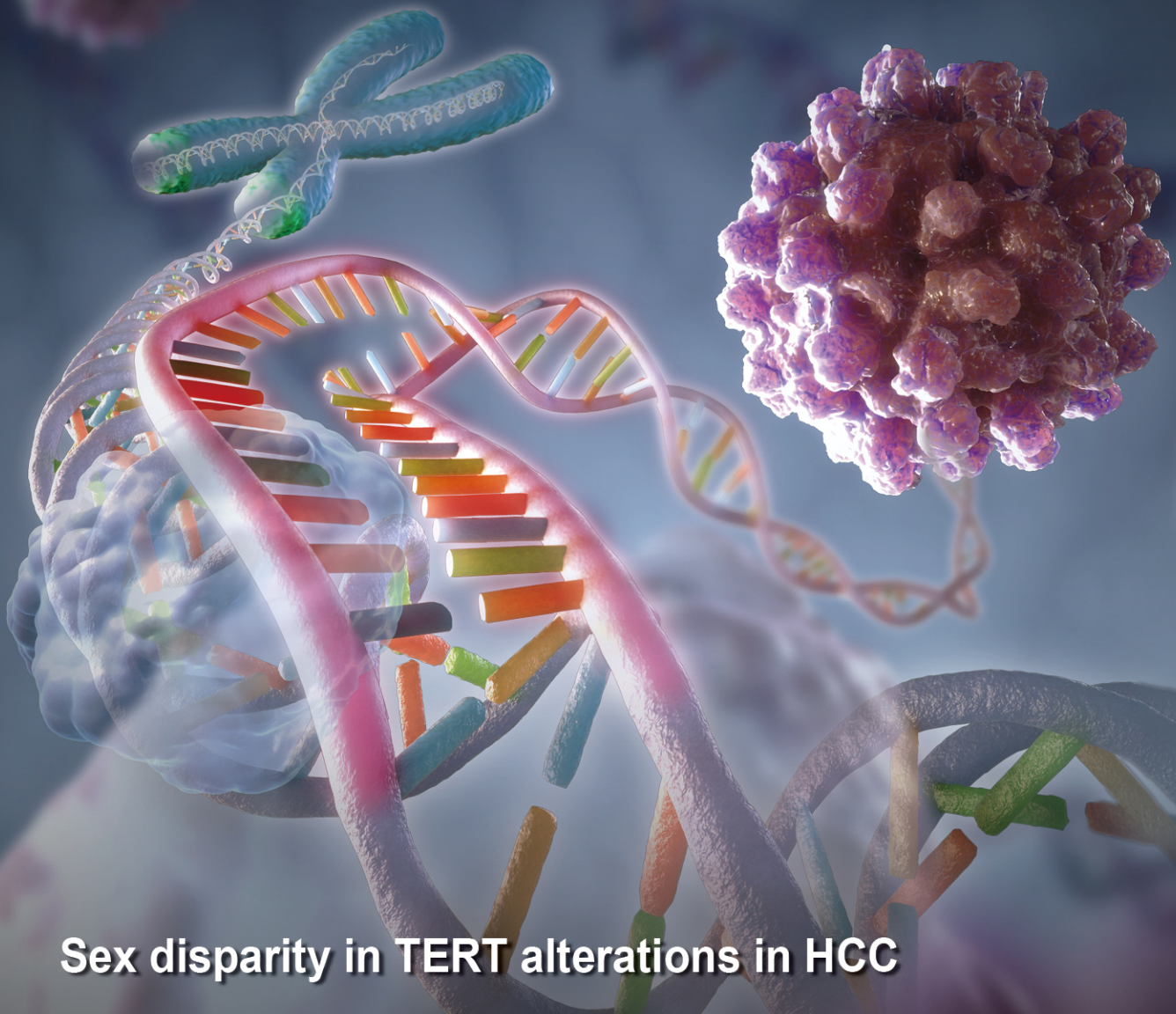

Sex disparity in TERT alterations in HCC

Economic evaluation of hepatitis C elimination
GOLM1 promotes MASH-related gallstone formation
Molecular characterization of sarcomatoid HCC

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Editorial

Reconsidering treatment indications for chronic hepatitis B: Insights from the TORCH-B roll-over study: Editorial on "Antiviral therapy for chronic hepatitis B with mildly elev\ated aminotransferase: A rollover study from the TORCH-B trial"

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Hsu and colleagues have contributed a significant study to *Clinical and Molecular Hepatology*, presenting extended data from the TORCH-B trial.[1] This roll-over study offers valuable insights into the treatment efficacy of tenofovir disoproxil fumarate (TDF) in patients with chronic hepatitis B (CHB) who have mild elevations in alanine aminotransferase (ALT)—a group often overlooked in current treatment guidelines due to lack of substantial evidence demonstrating clear clinical benefits.[2-4] Their findings suggest that TDF has therapeutic potential for the "gray-zone" patients, indicating that a reassessment of treatment guideline may be warranted. However, the study also highlights unresolved issues relevant to the expansion of treatment indications for CHB.

The study is an open-label extension of the TORCH-B trial,[5] in which participants previously on a placebo were transitioned to TDF, while those already on TDF continued their therapy. The design allowed researchers to evaluate the histological, biochemical, and virological effects of prolonged TDF treatment over a six-year period. The study is noteworthy for its rigor, incorporating paired liver biopsies for histopathological assessment and achieving high patient retention, thereby strengthening the robustness of its findings.

During the three-year extension period, 60.2% of participants experienced decreases in the Ishak fibrosis scores, while 26.0% remained stable. Additionally, 47.2% showed improvement and 23.6% had no change in the Knodell inflammatory scores. Since liver histopathology, particularly

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fibrosis severity, is strongly correlated to liver-related morbidity/mortality,[6] these findings support the potential beneficial role of antiviral therapy in patients who fall below the traditional ALT thresholds for treatment. Importantly, improvements in fibrosis were observed regardless of initial treatments in the TORCH-B trial, suggesting benefits of long-term antiviral therapy for patients in the gray-zone.

Despite demonstrating benefits in virological, biochemical and histopathological endpoints, the study also exposed current limitations of antiviral therapy for CHB. Notably, none of the participants achieved clearance of hepatitis B surface antigen (HBsAg), highlighting a well-recognized limitation of nucleos(t)ide analogue (NUC) therapy in achieving a functional cure.[7] The persistence of HBsAg underscores the challenge of indefinite therapy duration, which remains a concern when initiating NUC therapy in young patients without advanced liver fibrosis or overt clinical hepatitis.[8] These findings are consistent with previous studies reporting that HBsAg clearance remains elusive with currently available antiviral agents,[9] emphasizing the need for novel therapeutic approaches.

Moreover, the study demonstrated that NUC therapy may not halt disease progression in a subgroup of CHB patients. Specifically, 13.8% of participants exhibited increases in fibrosis scores, and 29.3% experienced higher inflammation scores after three years of TDF therapy. These findings remind us that antiviral treatment is no panacea for managing CHB in gray-zone patients and that a multifactorial approach is essential. Although the study was not specifically designed to identify factors influencing disease progression despite NUC treatment, *post hoc* analyses indicated that incomplete viral suppression and concurrent metabolic liver conditions, such as hepatic steatosis,[10] may continue to damage the liver in patients receiving TDF. These exploratory findings underscore the need for an integrated treatment approach that addresses medical adherence and modifiable lifestyle factors,[11,12] such as obesity, cigarette smoking, and alcohol consumption.

The evidence provided by this study is supportive but not yet conclusive for the effectiveness of NUC therapy in improving clinical outcomes of patients in the gray-zone. The study relies on surrogate endpoints, instead of "hard" clinical outcomes, such as hepatocellular carcinoma (HCC), liver failure, or mortality. Furthermore, the study design did not address the optimal timing of treatment initiation and the potential of treatment discontinuation. The roll-over data appears to show that patients initially receiving placebo achieved comparable histological, virological, and biochemical outcomes after 3 years of TDF therapy to those treated continuously for 6 years, provided they could be closely monitored and promptly treated for acute hepatitis flares. Although the comparison is not prespecified and requires cautious interpretation, it points out that the TORCH-B trial and the roll-over study do not directly ascertain that immediate initiation of NUC therapy for gray-zone patients effectively reduces their risks of developing HCC, experiencing complications of liver failure, or dying from liver-related diseases.

There is a growing body of literature suggesting that antiviral treatment is associated with improved clinical outcomes in patients whose treatment eligibility is conventionally controversial.[13,14] However, these studies are observational in design and can be subject to potential bias or confounding. The debate may not be easily resolved without compelling evidence from randomized controlled trials that use clinically important events as study endpoints. This critical gap in knowledge is being addressed in an ongoing trial targeting a patient population similar to the TORCH-B study but employing a composite primary endpoint including HCC, hepatic decompensation, liver transplantation, and death. The prespecified interim report is encouraging,[15] and more definitive evidence is eagerly awaited to support the expansion of treatment guidelines.

Expanding treatment criteria could improve clinical outcomes but also raises considerations regarding resource allocation. Increasing the eligible patient pool for long-term, essentially indefinite, antiviral therapy would entail substantial implications for investments in healthcare infrastructure. Notably, CHB is disproportionately prevalent in low- and middle-income countries.[16] Therefore, policy adaptations, such as improving access to generic medications, decentralizing healthcare delivery, and securing sustainable

Abbreviations:

ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; NUC, nucleos(t)ide analogue; TDF, tenofovir disoproxil fumarate

funding for patient care, would be crucial in supporting broader treatment implementation.

This study highlights several research priorities to further refine treatment strategies for CHB. First, future research should focus on prospective follow-up of long-term clinical outcomes, such as HCC incidence, liver-related mortality, and liver failure, in gray-zone CHB patients. These "hard" clinical outcomes would provide more direct evidence to support expanded treatment guidelines. Second, the risks of clinical complications are not shared among patients within gray-zone. Stratifying patients at distinct risks of disease progression or treatment response could help tailor therapy to individual needs in such a heterogeneous patient population. Risk assessment tools based on readily available information or novel biomarkers could be useful to better guide treatment decisions for gray-zone patients.[17] Third, studies assessing the cost-effectiveness of expanded treatment criteria, along with feasibility studies in diverse healthcare contexts, would provide crucial data for policymakers considering guideline revisions. Fourth, the persistence of HBsAg in CHB patients on TDF underscores the need for novel therapies targeting HBsAg clearance. Developing combination regimens that integrate direct antiviral agents with immune modulators may hold promise for achieving a functional cure, in order to reduce the burden of lifelong therapy.[18] Lastly, accumulating data showed greatly increased HBsAg loss rate (~39% over 5-year) after stopping NUC therapy in a subset of CHB patients,[19] suggesting a need to find optimal subpopulation benefits from finite NUC therapy in gray-zone CHB patients.

In conclusion, Hsu and colleagues' roll-over study from the TORCH-B trial provides empirical data supporting the reconsideration of treatment eligibility criteria for CHB patients with mild ALT elevation. While TDF therapy demonstrates clear benefits in histopathological and virological endpoints, certain caveats—such as the lack of HBsAg clearance and fibrosis progression in a minority of patients—highlight the complexities of treating CHB in the gray-zone populations. As CHB management continues to evolve, future guidelines should balance these clinical insights with practical considerations to ensure that expanded eligibility translates into improved health outcomes across diverse patient populations. This study represents a step forward toward more inclusive and data-driven approaches in CHB management, opening doors for broader treatment access and, ultimately, improved care for millions of patients worldwide.

Authors' contribution

Chih-Wen Wang: Validation. Ming-Lung Yu: Conceptualization, Writing draft, Critical revision of the manuscript and Supervision.

Conflicts of Interest

Research support from Abbvie, Abbott, BMS, Gilead, Merck, Novo Nordisc and Roche. Consultant for Abbvie, Abbott, BMS, Gilead, Merck, Novartis, Pharmaessential and Roche. Speaker for Abbvie, Abbott, BMS, Gilead, Merck and Roche.

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