

## CORRESPONDENCE

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# Letter to the Editor: Optimizing MASLD treatment—A “lead-in phase” before resmetirom

To the editor,

We read with great interest the recent practical guideline by Chen VL et al. on resmetirom,<sup>[1]</sup> the first drug approved for patients with metabolic dysfunction-associated steatotic liver disease (MASLD). While the histological benefits of resmetirom are promising, they are modest, highlighting the need for a comprehensive treatment strategy that includes lifestyle changes (LSC) and comorbidity management, as noted in the guideline.<sup>[1]</sup>

LSC, through diet and exercise, remain the cornerstone of MASLD treatment. Indeed, weight loss through LSC significantly reduces steatosis, inflammation, and fibrosis.<sup>[2]</sup> Even with the advent of pharmacological treatments like Resmetirom, LSC will remain essential for optimizing outcomes and reducing the risk of comorbidities. Additionally, alcohol consumption, even in small amounts, contributes to liver fibrosis progression,<sup>[3]</sup> emphasizing the need for complete abstinence. Addressing comorbidities, particularly obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia, is also critical, as these conditions contribute to disease progression. Some antidiabetic drugs, such as semaglutide and tirzepatide, have demonstrated efficacy in reducing steatohepatitis.<sup>[4,5]</sup> Managing obesity, improving glycemic control, and normalizing the lipid profile not only benefit these conditions but also significantly improve MASLD outcomes and slow disease progression.



We propose incorporating a preliminary or “lead-in phase” in MASLD treatment, focusing on LSC, alcohol cessation, and optimization of cardiometabolic factors before initiating MASLD-specific drugs. Similar approaches in chronic conditions like arterial hypertension and T2DM have shown significant benefits. This phase could improve insulin sensitivity, reduce hepatic steatosis, and enhance the patient's cardiovascular profile ultimately boosting the effectiveness of subsequent drug therapy. It may also reduce the need for medication in patients who respond favorably to LSC. Each patient's unique profile -including age, comorbidities, and adherence potential- should guide the design

of their “lead-in phase”. Furthermore, this approach could yield public health benefits by reducing reliance on costly medications like resmetirom, reserving their use for those who do not achieve adequate improvements through LSC. The method for evaluating the regression or progression of the disease would be the same as that suggested by the authors of this guide.

In conclusion, we believe a “lead-in phase” could enhance MASLD treatment outcomes, and reduce the need for pharmacological interventions. Further research is needed to evaluate the long-term impact of this approach on disease progression and clinical outcomes.

## CONFLICTS OF INTEREST

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## REFERENCES

1. Chen VL, Morgan TR, Rotman Y, Patton HM, Cusi K, Kanwal F, et al. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. *Hepatology*. 2025;81:312–20.
2. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology*. 2015;149:367–378.e5.
3. Marti-Aguado D, Calleja JL, Vilar-Gomez E, Iruzubieta P, Rodríguez-Duque JC, Del Barrio M, et al. Low-to-moderate alcohol consumption is associated with increased fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease. *J Hepatol*. 2024;81:930–40.
4. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, et al. Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. *N Engl J Med*. 2024;391:299–310.
5. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med*. 2020;384:1113–24.