HBV infection in the era of T-cell engagers in multiple myeloma: unresolved challenges and unmet needs. Comment on: "Hepatitis B virus reactivation following T-cell engager therapy in multiple myeloma despite negative hepatitis B core antibody serology: implications for screening in patients with hematological malignancies"

We read with interest the recent case report by Rees *et al.*,[1] which describes the clinical case of a 72-year-old patient with triple-refractory multiple myeloma (MM) who had received multiple lines of treatment, including autologous stem cell transplantation (ASCT) and bispecific antibodies or T-cell engager therapies, such as talquetamab and teclistamab. Despite having tested negative for hepatitis B in screenings prior to each line of therapy and having been vaccinated against hepatitis B (HBV), the patient developed active hepatitis with positive HBsAg and an HBV-DNA level of 3.28×10^7 IU/mL in August 2025 after the fourth relapse, treated with the SVD regimen (selinexor, bortezomib, and dexamethasone).

In Figure 1 of the case report, HBV-DNA (365 IU/mL) is shown as detectable in June 2024, before treatment with teclistamab. At that time, despite negative HBV serologic screening (HBsAg, HBcAb, and HBsAb all negative), the patient tested positive for HBV-DNA. This raises the question of whether liver function tests were altered to the extent that prompted HBV-DNA testing.

This case report presents several critical issues. Firstly, it does not appear to represent a case of HBV reactivation.

The initial serological profile showed only a non-protective positivity for HBsAb, for which the patient subsequently received vaccination. A particularly unusual scenario then emerged, with the detection of HBV DNA positivity (365 IU/mL). At that point, the initiation of antiviral therapy would likely have been warranted.

Potential explanations for the events described may be attributed to the patient's profound immunosuppression, which could have led to *de novo* HBV infection due to failure of vaccine-induced protection, or HBV reactivation, in the event the patient had received a vaccine containing attenuated virus.

Based on the available data, and considering the HBV-DNA positivity in June 2024, the patient would have merited prophylactic treatment with entecavir at that time, prior to initiation of teclistamab therapy.

The topic of HBV prophylaxis in hematologic patients undergoing immunosuppressive therapies has been of significant clinical interest for years. The European Association for the Study of the Liver (EASL) guidelines[2] have consistently addressed this issue in detail.

The development of newer, more effective drug classes has contributed to improved overall survival in MM, but has also introduced increased immunosuppression due to a higher number of therapeutic lines, thus requiring a more comprehensive approach to the management of patients with occult HBV infection.

MM accounts for approximately 10% of hematologic malignancies, and all patients with active MM requiring therapy should undergo full HBV screening.

Despite the introduction of innovative agents such as proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies, MM remains an incurable disease.[3] More recently, the availability of bispecific antibodies or T-cell engager therapies has further improved survival outcomes. However, these agents are also associated with an increased risk of infectious complications, including Cytomegalovirus reactivation and progressive multifocal leukoencephalopathy. We agree with the authors that the risk of HBV reactivation remains uncertain, as patients positive for anti-HBc were excluded from pivotal registration trials, leaving the real-world risk of reactivation unknown.[4-5] In particular, patients with occult HBV infection (anti-HBcAb positive, HBV-DNA negative) require close monitoring of liver function and HBV-DNA levels to detect potential viral reactivation.

The most recent EASL guidelines, published in August 2025, revisit the topic of HBV screening in immunocompromised patients undergoing various forms of immunosuppressive therapy (e.g., stem cell transplantation, chimeric antigen receptor T-cell therapy, Bruton's tyrosine kinase inhibitors, etc.). The guidelines emphasize the need to assess HBsAg, HBcAb, HBsAb, and HBV-DNA levels prior to the initiation of treatment. They also provide detailed recommendations on monitoring and prophylaxis tailored to the patient's serologic status.

In conclusion, further clinical studies, close collaboration with hepatologists, more accurate screening protocols,

and widespread HBV vaccination will be essential in redefining the screening and prophylactic strategies for immuno-hematologic patients receiving immunosuppressive treatments.

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Contributions

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