Infection and Drug Resistance

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RESPONSE TO LETTER

The HIV/HBV Co-infection Paradox: Immune Modulation Amid Persistent Risk [Response To Letter]

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Dear editor

We thank Peppa et al for their thoughtful response to our review and for contributing important emerging data on immune phenotypes in HIV/HBV co-infection. Their observations add valuable mechanistic insight, particularly by highlighting distinctions in immune remodeling between treated and untreated states of HIV/HBV co-infection in individuals receiving long-term HBV-active antiretroviral therapy. Such data are important for refining our understanding of host–virus interactions in the modern treatment era.

We agree that the immunologic landscape of treated HIV/HBV co-infection is more complex than a uniformly detrimental model would imply. The reported findings of enhanced adaptive NK-cell activity and preserved HBV-specific $CD8^+$ T-cell responses in well-characterized cohorts of individuals with HIV/HBV co-infection receiving long-term suppressive therapy are significant[1,2] and may help explain clinical observations such as higher rates of HBsAg clearance reported in people with co-infection following initiation of HBV-active ART.[3,4] These findings appropriately emphasize that effective treatment can partially reshape immune dysfunction associated with chronic dual infection. However, extrapolation of these observations to imply a protective or advantageous state would be premature. Rather, they highlight context-dependent immune adaptation under conditions of sustained viral suppression, which does not negate the broader evidence of increased clinical risk. A substantial body of evidence continues to demonstrate that untreated or incompletely treated HIV/HBV co-infection is associated with greater immune dysregulation, accelerated liver disease, and worse long-term outcomes than either infection alone.[5–7] Importantly, our use of the term "synergistic reinforcement" was intended to reflect the overall biological and clinical trajectory across disease states, rather than a uniform immunologic phenotype under all treatment conditions. As Peppa et al note, co-infection is not benign.

Comparable examples have been described in other chronic viral infections. In patients with HBV and HCV coinfection, the introduction of direct acting antivirals for hepatitis C led to reports of HBV reactivation, including severe and occasionally fatal cases, following rapid HCV clearance.[8] This phenomenon likely reflects the removal of suppressive antiviral pathways induced during chronic HCV infection. Similarly, cytomegalovirus can enhance specific immune modulatory responses while simultaneously driving chronic inflammation, immune senescence, and end-organ disease, particularly in older adults and immunocompromised individuals.[9,10] These examples demonstrate that measurable immune effects during co-infection do not necessarily translate into reduced clinical risk.

The same principle applies to HIV/HBV co-infection in the tenofovir era. Although HBV-active antiretroviral therapy has markedly improved prognosis,[11] it is premature to conclude that fibrosis progression, hepatic decompensation, or liver-related mortality have normalized. Several longitudinal studies continue to show progression to advanced fibrosis or persistent cirrhosis in a subset of treated individuals, and fibrosis regression appears less pronounced than that reported in

https://doi.org/10.2147/IDR.S621913
Received: 4 May 2026
Accepted: 8 May 2026
Published: 14 May 2026

HBV monoinfection.[3,12,13] Residual risk likely reflects multiple factors beyond HBV replication alone, including metabolic comorbidity, prior immunosuppression, delayed diagnosis, and ongoing immune activation. Likewise, reductions in hepatic events and mortality should be interpreted cautiously. While outcomes have improved substantially in well-resourced cohorts with broad access to therapy,[11] population-level studies remain heterogeneous, and excess mortality persists in some settings, particularly where treatment access is delayed or incomplete.[5,6] Contemporary data from resource-limited regions continue to demonstrate higher mortality among persons with HIV/HBV co-infection than among those with HBV monoinfection.[6,14] Thus, current therapies have transformed prognosis, but have not fully eliminated disparities in outcome.

Viewed in this context, the findings presented by Peppa et al add a useful clarification to the field but do not alter the central conclusion that HIV/HBV co-infection remains a clinically important state of aggregated risk, particularly when untreated or treated suboptimally. Recognizing both the benefits of modern therapy and the persistence of residual risk is essential for accurate interpretation of emerging immunologic data.

As emphasized in our initial work, and as Peppa et al concur, individuals with HIV/HBV co-infection, regardless of current or past treatment status, should be included in cure-directed and immune-based therapeutic studies. Their historical exclusion has limited progress in a population with a substantial unmet need. Inclusion of diverse cohorts, longitudinal sampling, and tissue-based investigation will be critical to determining how these immunologic observations relate to meaningful clinical outcomes. Finally, we appreciate the authors' contribution and welcome continued investigation in this area. We agree that our framework may not fully capture the biology of individuals receiving long-term suppressive therapy, and we value insights provided by Peppa et al in helping to refine this distinction. At the same time, interpretation of these findings should remain balanced, recognizing important mechanistic advances while staying grounded in the broader clinical evidence base, which continues to support co-infection as a state of increased risk.

Funding

This work was supported by the Translational Virology Core at the San Diego Center for AIDS Research (P30 AI036214), the HOPE T32 Training program (AI007384), the National Institute of General Medical Sciences of the National Institutes of Health under award T32GM154642 (University of California San Diego Medical Scientist Training Program) and The James B. Pendleton Charitable Trust. Additional support was provided through the ACTG (AI068636, UM1).

Disclosure

The authors report no conflicts of interest in this communication.

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