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Hepatic Viral Reservoirs in Concurrent HIV and HBV: From Mechanistic Insight to Integrated Cure Strategies

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Purpose of Review: Concurrent HIV and hepatitis B virus (HBV) affect an estimated 4–5 million people worldwide and remain a major driver of liver-related morbidity and mortality, even among individuals receiving tenofovir-containing antiretroviral therapy (ART). Both viruses establish long-lived reservoirs that are not eliminated by current antiviral therapies. This review summarizes current mechanistic and clinical frameworks for understanding concurrent HIV and HBV, highlights the interplay between their viral reservoirs, and discusses the implications of these interactions for cure strategies.

Recent Findings: The liver functions as a multicellular reservoir. HBV persists within hepatocytes as nuclear covalently closed circular DNA (cccDNA) and integrated viral sequences. HIV persists as integrated provirus in tissue-resident CD4⁺ T cells and liver macrophages, with evidence supporting viral transfer or cell-to-cell spread involving stellate cells and hepatocytes. Concurrent HIV and HBV accelerate fibrosis and immune dysfunction through shared pathogenic pathways, including epigenetic silencing, cytokine- and checkpoint-mediated T-cell exhaustion, metabolic stress, and inflammation driven by the gut–liver axis. HBV-associated liver injury promotes recruitment of HIV target cells, while HIV-associated immune dysregulation impairs HBV control. Despite these interlinked biological mechanisms, individuals living with HIV and HBV are frequently excluded from clinical trials, slowing therapeutic progress and exacerbating health inequities.

Summary: Concurrent HIV and HBV represent a synergistic disease model that demands integrated therapeutic approaches and inclusive research frameworks. Priority needs include robust tissue-based reservoir measurements, validated biomarkers that distinguish latent from transcriptionally active viral states, combination strategies incorporating antiviral, antifibrotic, and immunomodulatory agents, and community-engaged clinical trial designs that are inclusive of individuals living with HIV and HBV and safe in the context of HBV. Advancing these areas will be essential to achieving durable remission—and ultimately functional cure—for both viruses.

Plain Language Summary: HIV and hepatitis B virus (HBV) often occur together and affect millions of people worldwide. Both viruses can persist in the liver, forming “viral reservoirs” that current treatments cannot eliminate. These hidden viral reservoirs contribute to long-term liver damage, including scarring (fibrosis) and liver cancer.

This review explains how HIV and HBV interact and reinforce each other’s persistence. We describe how different liver cells—including immune cells and hepatocytes—create an environment that allows both viruses to survive. We also highlight emerging scientific tools and treatment strategies designed to better target viral reservoirs. Importantly, people living with HIV and HBV are often excluded from research studies. Including these individuals in future clinical trials will be essential to develop fair and effective cures for both viruses.

Keywords: HIV, hepatitis B virus, liver, viral reservoirs, persistence, cure strategies

Introduction

HIV and hepatitis B virus (HBV) remain two of the most prevalent chronic viral infections worldwide, contributing substantially to global morbidity and mortality.^{1,2} Both viruses can be effectively suppressed with long-term antiviral therapy; yet, neither can be eradicated with current drugs, as each establishes long-lived reservoirs resistant to immune clearance and pharmacologic intervention.^{3,4} The co-occurrence of HIV and HBV is common, affecting an estimated 7–11% of people with HIV (PWH), up to 4.4 million individuals globally,^{1,2} and is associated with accelerated liver disease, increased risk of hepatocellular carcinoma (HCC), worsened treatment outcomes, and increased mortality.^{1,5–7} This substantial disease burden underscores the need to move beyond virological suppression toward a mechanistic understanding of viral persistence and immune dysfunction within the liver.

The liver is central to the biology of both pathogens. HBV directly infects hepatocytes, where it persists as covalently closed circular DNA (cccDNA) and as integrated viral DNA within the host genome.^{8–10} This establishes a durable nuclear reservoir that resists clearance and underlies lifelong persistence. In parallel, HIV targets CD4⁺ T cells and liver-resident immune cells, including Kupffer cells, with evidence of low-level infection or cell-to-cell transfer involving stellate cells and hepatocytes.¹¹ Recent studies reveal that the liver serves as a multicellular reservoir for HIV, where viral persistence is linked to immune exhaustion, fibrogenesis, and inflammatory remodeling. Although the contribution of hepatocytes to replication-competent HIV reservoirs remains debated,^{11,12} accumulating evidence indicates that the liver is a key site of viral persistence,^{13–17} even in individuals on suppressive antiretroviral therapy (ART).

Historically, most insights into HIV and HBV reservoirs have been derived from blood-based studies, which do not capture the complexity of intrahepatic viral–immune interactions.^{8,18–20} The liver's unique vascular architecture, constant exposure to gut-derived antigens, and abundance of specialized immune and stromal cells create an environment in which immune tolerance and activation coexist. This balance limits excessive inflammation while facilitating chronic viral persistence. Emerging tissue-based approaches—including liver biopsies, single-cell analyses, and rapid autopsy studies—are now elucidating the cellular and molecular determinants of persistence within the hepatic microenvironment.^{12,16,21}

The presence of both HIV and HBV introduces additional layers of biological complexity. HIV-associated CD4⁺ T cell depletion impairs HBV-specific immune responses, lowering the likelihood of spontaneous clearance and functional cure.^{5,7,22} At the same time, HBV-driven inflammation, hepatocyte apoptosis, and stellate cell activation create an environment that favors HIV persistence.^{23–25} Shared mechanisms, including IL-10–mediated immunoregulation, epigenetic silencing of viral transcription, and checkpoint-driven T-cell exhaustion, establish a state of synergistic reinforcement, that contributes to accelerated liver disease in individuals living with both viruses.

This review integrates mechanistic, clinical, and community perspectives to provide a unified framework for understanding concurrent HIV and HBV. We summarize the epidemiology and immunological consequences of dual viral exposure, examine the liver as a unique multicellular reservoir, and discuss overlapping mechanisms of persistence. Finally, we emphasize the importance of community engagement and the inclusion of individuals living with HIV and HBV in clinical trials, given their disproportionate risk of morbidity and mortality, and outline key research gaps and future directions toward achieving functional cure.

Methods

Search Strategy

A targeted narrative literature search was conducted to identify studies examining concurrent HIV and HBV, hepatic reservoirs, mechanisms of persistence, and therapeutic implications. Searches were performed in PubMed/MEDLINE, Embase, Web of Science, and Google Scholar from January 1990 through October 2025. Search terms combined controlled vocabulary and free-text keywords related to HIV, HBV, epidemiology, hepatic reservoirs, viral persistence, immune exhaustion, and cure strategies. Reference lists of key articles and reviews were manually screened to identify additional relevant work.

Scope and Approach

Because the goal was to synthesize mechanistic insights across diverse types of evidence, a narrative review methodology was utilized rather than a systematic or quantitative approach. This approach enabled integration of basic, translational, and clinical evidence to describe current understanding and highlight knowledge gaps relevant to mechanisms of persistence and cure strategies in the setting of concurrent HIV and HBV.

Epidemiology and Clinical Implications in the Setting of Concurrent HIV and HBV

In 2023, an estimated 39.9 million people were living with HIV worldwide, with 1.3 million new diagnoses and 630,000 deaths annually.² HBV is even more widespread. In 2022, an estimated 257.5 million people had chronic HBV, with marked regional variations.²⁶ The prevalence of chronic HBV is the highest in the African Region (5.8%) and in Western Pacific Region (5%), compared to 0.5% in the Region of the Americas. Each year, HBV causes approximately 1.1 million deaths, mostly due to cirrhosis and HCC.²⁷

Because HIV and HBV share routes of transmission, including sexual contact, parenteral exposure, and perinatal transmission, their co-occurrence is common.⁷ Concurrent HIV and HBV affect an estimated 7–11% of people with HIV (PWH), representing approximately 4.4 million individuals globally – with the greatest burden in sub-Saharan Africa, Southeast Asia, and the Western Pacific.² Sub-Saharan Africa alone accounts for approximately 70% of individuals living with both viruses (~1.9 million people). In these endemic regions, HBV is often acquired in early childhood through vertical or horizontal transmission, leading to lifelong persistence before subsequent HIV acquisition in adulthood.²⁶ High-risk populations include men who have sex with men, people who inject drugs, and infants born in high-prevalence regions.

Vaccination is a cornerstone of HBV prevention; yet, global coverage remains suboptimal. In 2021, only 42% of infants worldwide received a timely birth dose, with coverage as low as 17% in the African Region.² Among adults with HIV, vaccine uptake and seroconversion rates are also low. In a US cohort, more than one-third of PWH remained eligible for HBV vaccination after one year of care, and fewer than 10% initiated the vaccine series.²⁸ Reduced vaccine immunogenicity among PWH further limits protection, underscoring the need for optimized vaccine formulations and booster strategies.

Clinically, the presence of both HIV and HBV is associated with substantially worse outcomes compared with either virus alone. Individuals with both viruses develop fibrosis, cirrhosis, and HCC more rapidly and experience higher rates of liver-related and all-cause mortality.¹ Moreover, people living with HBV and HIV have an increased risk of acquiring hepatitis D virus (HDV), which is associated with more rapid liver disease progression and higher mortality than HBV and HIV in the absence of HDV.²⁹

Mechanistically, HIV-induced CD4⁺ T-cell depletion impairs HBV-specific immune responses, while HBV-induced inflammation and hepatocyte apoptosis promote HIV persistence in the liver.^{25,30–32} This bidirectional interaction highlights how immune dysregulation links clinical severity to molecular persistence.

Current treatment relies on antiretroviral regimens that suppress both viruses, typically tenofovir combined with lamivudine or emtricitabine.^{8,33,34} As ART simplification strategies and long-acting HIV regimens without HBV activity (eg, cabotegravir/rilpivirine) are increasingly adopted, individuals with HIV and HBV may face heightened risks of HBV reactivation and potentially fatal hepatitis flares.³⁵ Additionally, although long-term therapy is effective in controlling viremia, functional cure remains rare for both viruses due to persistent cccDNA (for HBV) and integrated provirus (for HIV).³⁶ These therapeutic constraints highlight the need to address underlying mechanisms of persistence, as explored in the next sections.

A comparative overview of key virological features, persistence mechanisms, and therapeutic responses for HIV and HBV is summarized in [Table 1](#), which provides a reference framework for the sections that follow.

Liver Anatomy and Immune Cells

The liver is the largest internal organ, receiving ~25% of cardiac output and filtering an estimated 1.5 liters of blood per minute—equivalent to ~2000 liters daily—primarily through the portal vein. This continuous exposure to gut- and

Table 1 Comparative Features of Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV)^{1,5,37–40}

Feature	Hepatitis B Virus	Human Immunodeficiency Virus
Viral genome	Partially double-stranded DNA; reverse transcription via RNA intermediate	Single-stranded RNA; reverse transcription and integration
Primary target cells	Hepatocytes	CD4 ⁺ T cells, macrophages
Nuclear persistence mechanism	Stable cccDNA minichromosome and integrated HBV DNA in hepatocytes	Integrated proviral DNA in long-lived immune cells and tissue reservoirs
Transmission	Blood, sexual, perinatal; highly infectious	Blood, sexual, perinatal; less infectious per exposure than HBV
Natural history	Adults often clear acute HBV; chronicity rare in adults but common in neonates; chronic disease can progress to cirrhosis/HCC	Progressive CD4 decline leading to AIDS and opportunistic complications if untreated
Effect of coinfection	Higher HBV DNA levels, more HBeAg positivity, faster fibrosis and liver-related mortality	HBV coinfection worsens HIV outcomes and increases risk of hepatotoxicity with ART
Vaccination	Effective recombinant vaccines; reduced response in people with HIV	No vaccine available
Therapy goals	HBV DNA suppression; rare HBeAg loss (functional cure)	Durable HIV RNA suppression to undetectable levels; immune reconstitution
Complications	Cirrhosis, hepatocellular carcinoma, hepatic decompensation, extrahepatic immune-complex disease (eg, glomerulonephritis, cryoglobulinemia), and non-Hodgkin lymphoma	AIDS-defining illnesses and non-AIDS comorbidities (eg, cardiovascular, renal, malignancy)

Abbreviations: cccDNA, Covalently Closed Circular DNA; HCC, Hepatocellular carcinoma; HBeAg, Hepatitis B e-Antigen; ART, antiretroviral therapy; HBsAg, Hepatitis B surface antigen.

blood-derived antigens requires finely tuned immune regulation to balance pathogen defense with tolerance to harmless dietary and microbial products.⁴¹ Structural cells such as liver sinusoidal endothelial cells (LSECs), Kupffer cells, hepatic stellate cells (HSCs), and hepatocytes interact with infiltrating lymphocytes (CD4⁺ and CD8⁺ T cells, NK cells, and NKT cells), dendritic cells, and monocytes to maintain this balance.⁴² Many of these cell types are either directly permissive to HIV and/or HBV or functionally modulated by viral proteins, reinforcing the liver's role as a long-term viral reservoir.

Structural Cells with Immune Functions

Liver Sinusoidal Endothelial Cells (LSECs)

LSECs line the hepatic sinusoids and regulate the exchange of molecules between blood and hepatocytes. Beyond this structural role, they actively internalize circulating proteins and express MHC I, MHC II, and costimulatory molecules,^{43–46} enabling antigen presentation. Through adhesion molecules such as ICAM-1, VCAM-1, and VAP-1, LSECs promote lymphocytes retention and facilitate cell–cell interactions.^{47–49} Functionally, they can stimulate T and NK cells while also promoting tolerogenic programs,⁵⁰ and driving activated T cells toward a regulatory phenotype.^{51,52} In the setting of concurrent HIV and HBV, this dual capacity—immune activation coupled with tolerance—creates an environment that permits viral persistence despite ongoing immune surveillance.

Kupffer Cells

As liver-resident macrophages, Kupffer cells clear pathogens, toxins, apoptotic cells, and debris.^{53–56} They produce proinflammatory mediators (TNF- α , IL-12, and IL-18),^{57–59} yet also suppress responses via IL-10⁶⁰ and PD-L1.⁶¹ This functional plasticity makes Kupffer cells pivotal regulators in the presence of both HIV and HBV. They can mount antiviral defenses but also create an immunoregulatory environment that sustains HIV and HBV persistence.

Hepatic Stellate Cells (HSCs)

Traditionally known for vitamin A storage,⁶² HSCs also have important immune functions. They act as non-classical antigen-presenting cells, expressing MHC I, MHC II, and CD1d⁶³ as well as innate receptors such as TLR4, CD14,

and MD2, which allow them to sense microbial products.^{64,65} Through these pathways, they activate or suppress T and NK cells via PD-L1 signaling.^{24,66} HSCs are highly responsive to bacterial LPS, linking gut-derived antigens to hepatic immunity.⁶⁵ When chronically activated, HSCs drive hepatic fibrosis through upregulation of α -smooth muscle actin and increased extracellular matrix deposition, a process that is accelerated in the presence of both HIV and HBV. Multiple intracellular signaling pathways contribute to this process, including TGF- β , PD-L1, IFN- γ , IL-4 and TLRs.^{62,66}

Hepatocytes

Hepatocytes are the predominant parenchymal cells of the liver and the main target of HBV. They detect pathogen-associated and damage-associated molecular patterns (PAMPs/DAMPs) through multiple pattern recognition receptors (PRRs), including RIG-I and MDA5 (RIG-like receptor family), NLR1–3 (NOD-like receptor family), and multiple Toll-like receptors. Engagement of these receptors induces interferon production and interferon-stimulated genes (ISGs), thereby restricting viral replication.^{67,68} They express MHC I and II but have limited costimulatory capacity and high PD-L1 expression,¹⁷ biasing local immune responses toward tolerance. While this reduces immune-mediated injury, it also facilitates HBV cccDNA persistence and may permit low-level HIV replication or cell-to-cell transfer.

Together, structural cells of the liver, including LSECs, Kupffer cells, HSCs, and hepatocytes, maintain the delicate balance between activation and tolerance. By simultaneously sensing pathogens, presenting antigen, and shaping immune responses, they create a microenvironment that protects against excessive injury but also provides a niche that HBV and HIV exploit for long-term persistence.

Infiltrating and Resident Immune Cells

In addition to structural components, the liver harbors specialized immune populations that mediate antiviral defense yet can be dysregulated during chronic viral persistence.

NK Cells

NK cells are unusually abundant in the liver, comprising up to 50% of hepatic lymphocytes compared with ~10% in peripheral blood.⁶⁹ Unlike blood NK cells, which are predominantly cytotoxic CD56^{dim} cells, liver NK cells include large proportions of CD56^{bright} subsets,^{70–73} enabling both regulatory and cytotoxic activity. These cells secrete IFN- γ and TNF- α to restrict viral replication, while responding to and producing IL-10 and TGF- β .^{74,75} In the setting of concurrent HIV and HBV, HBeAg-mediated NK suppression,⁷⁶ and HIV-driven NK exhaustion weaken early antiviral responses and contribute to persistence.⁷⁷

Liver Tissue-Resident Memory T Cells (L-TRMs)

L-TRMs patrol the hepatic sinusoids and provide rapid, localized immune responses to microbial and viral antigens.⁷⁸ Constant exposure to microbial and viral antigens drives their expression of CD69 and CD103, promoting tissue retention.^{79–82} Functionally, L-TRMs act as “sensing and alarm” cells, rapidly producing cytokines and mobilizing other immune subsets. However, their constant activation also predisposes them to bystander-driven inflammation and fibrosis.⁸³ In the presence of both HIV and HBV, chronic antigen exposure and high checkpoint signaling render L-TRMs both hyperactivated and exhausted, amplifying inflammation without achieving viral clearance.

Dendritic Cells (DC)

Hepatic DCs continuously sample antigens from portal blood and shape the balance between tolerance and immunity. At steady state, they promote regulatory pathways through IL-10, TGF- β , and PD-L1 expression.^{84,85} Upon inflammation, they shift toward immunogenicity, activating NK and T cells. Both viruses exploit this plasticity: HIV impairs type I IFN production and antigen presentation by DCs,⁸⁶ while HBV skews them toward a tolerogenic phenotype.⁸⁷ When both viruses are present, this dual impairment blunts adaptive immune priming and undermines durable immune control.

Natural Killer T (NKT) Cells

NKT cells co-express TCRs and NK markers and recognize lipid antigens presented by CD1d. They are enriched in the liver relative to blood and act as rapid cytokine producers (IFN- γ , IL-4, IL-17) with potent cytotoxic capacity.^{88,89} HBV

proteins can suppress NKT activation,⁹⁰ while HIV causes their selective depletion and dramatically reduce their activation by APCs.⁹¹ In the setting of concurrent HIV and HBV, these defects weaken early antiviral control and contribute to chronic inflammation and fibrogenesis.⁹²

Conventional T Lymphocytes and Monocytes

The liver also recruits circulating monocytes and harbors conventional CD4⁺ and CD8⁺ T cells. These cells provide essential antiviral effector functions but are also major targets of HIV replication. They also become exhausted or functionally impaired during chronic HBV infection (upregulation of inhibitory receptors, reduced proliferation and diminished cytokine production).

In summary, multiple hepatic parenchymal and immune cell populations coordinate antigen sensing, immune tolerance, inflammation, and antiviral defense. In the setting of concurrent HIV and HBV, these functions become dysregulated—shifting toward impaired antiviral activity, heightened immune tolerance, chronic activation, and fibrogenesis—thereby facilitating persistent viral replication and progressive liver injury. This convergence of immune activation, dysfunction, and viral persistence reinforces the liver as a sanctuary site for both viruses. Key cell types and their roles are summarized in Table 2.

Table 2 Structural and Infiltrating Immune Cells in the Liver and Their Role in the Setting of Concurrent HIV HBV

Cell Type	Main Functions	Impact in HIV/HBV Coinfection	Affected by HIV and/or HBV
Liver sinusoidal endothelial cells	Antigen uptake and presentation; regulate lymphocyte retention; dual role in activation and tolerance via IL-10.	Promote tolerance that allows viral persistence despite immune surveillance.	Indirectly modulated; not primary targets.
Kupffer cells	Phagocytosis of pathogens and debris; secrete TNF- α , IL-12, IL-18; suppress via IL-10 and PD-L1.	Plasticity sustains chronic infection; antiviral potential countered by immunoregulation that promotes persistence.	Can be infected by HIV; sense HBV products but not directly infected.
Hepatic stellate cells	Non-classical APC; sense microbial products via TLR4/CD14/MD2; activate or suppress T/NK cells via PD-L1; drive fibrosis when chronically activated.	Accelerated fibrosis under coinfection due to chronic activation and viral modulation.	Can be infected by HIV; activated by HBV-induced inflammation.
Hepatocytes	Primary HBV target; sense PAMPs/DAMPs via PRRs; induce interferons and ISGs; bias toward tolerance via PD-L1 expression.	Support HBV cccDNA persistence and may permit low-level HIV replication.	Primary HBV target (cccDNA, integration); low-level HIV DNA detected.
Natural killer Cells	Abundant (up to 50% of hepatic lymphocytes); regulatory and cytotoxic subsets; secrete IFN- γ , TNF- α , IL-10, TGF- β ; impaired by HBV and HIV.	Weakened antiviral responses due to HBV suppression (HBeAg) and HIV-driven exhaustion.	Function altered by both; HIV causes exhaustion, HBV proteins suppress activity.
Liver tissue-resident memory T cells	Patrol sinusoids; rapid cytokine production (CD69 ⁺ , CD103 ⁺ retention); hyperactivated yet exhausted in chronic coinfection.	Amplify inflammation yet fail to clear virus due to chronic activation and checkpoint signaling.	Impaired by both; exhaustion and checkpoint expression heightened in coinfection.
Dendritic cells	Sample antigens from portal blood; promote tolerance (IL-10, TGF- β , PD-L1) or immunity; impaired by HIV (IFN-I) and HBV (tolerogenic skewing).	Dual impairment (HIV blunts IFN-I, HBV induces tolerance) undermines adaptive priming.	Low-level infection by HIV is possible, but their main role is in capturing and transferring HIV to CD4 ⁺ T cells ("trans-infection"); also strongly modulated by both viruses
Natural killer T cells	Recognize lipid antigens via CD1d; rapid cytokine producers (IFN- γ , IL-4, IL-17); reduced frequency and skewed function in HBV/HIV.	Impaired responses reduce early antiviral control and contribute to chronic inflammation/fibrosis.	Reduced frequency/function by both viruses.

(Continued)

Table 2 (Continued).

Cell Type	Main Functions	Impact in HIV/HBV Coinfection	Affected by HIV and/or HBV
Monocytes	Recruited from blood; differentiate into macrophages/DC-like cells; produce pro-inflammatory cytokines (TNF- α , IL-1 β) and IL-10.	Sustain hepatic inflammation and serve as HIV reservoirs, reinforcing persistence.	HIV-infected monocytes/macrophages act as reservoirs; respond to HBV-driven inflammation.
Conventional CD4 ⁺ and CD8 ⁺ T lymphocytes	CD8 ⁺ T cells mediate cytotoxicity; CD4 ⁺ T cells provide help; both impaired/exhausted in chronic HBV and depleted by HIV.	Loss of CD4 ⁺ help and exhaustion of CD8 ⁺ effectors amplify viral persistence and fibrosis.	CD4 ⁺ T cells are HIV targets; CD8 ⁺ T cells impaired in HBV.

Abbreviations: IL, Interleukin; TNF- α , Tumor Necrosis Factor alpha; PD-L1, Programmed Death-Ligand 1; APC, Antigen-Presenting Cell TLR, CD, cluster of differentiation; Toll-like Receptor; NK, Natural Killer cell; MD-2, Myeloid Differentiation factor 2; PAMPs, Pathogen-Associated Molecular Patterns; DAMPs, Damage-Associated Molecular Patterns; PRRs, Pattern Recognition Receptors; ISG, Interferon-Stimulated Genes; cccDNA, Covalently Closed Circular DNA; IFN- γ , Interferon-gamma; TGF- β , Transforming Growth Factor-beta; IFN-I, Type I Interferon; DC, Dendritic cell.

Mechanisms of Viral Persistence and Synergy in the Setting of Concurrent HIV and HBV

The liver's immunologic landscape—characterized by its dual capacity for activation and tolerance—creates a microenvironment uniquely permissive for viral persistence. Within this setting, HIV and HBV exploit overlapping molecular and cellular mechanisms to establish chronic reservoirs, evade immune surveillance, and drive progressive injury. These processes operate across multiple biological layers, including nuclear persistence, multicellular reservoirs, cellular proliferation, epigenetic regulation, cytokine tolerance, immune exhaustion, innate–adaptive immune disruption, hepatocyte injury, metabolic remodeling, and viral crosstalk (Figure 1). Understanding how these mechanisms converge is essential to identify actionable therapeutic targets and design integrated cure strategies.

Nuclear Reservoirs

HBV persistence is anchored by cccDNA, a stable episomal form within hepatocyte nuclei that serves as the transcriptional template for viral proteins. The infectious virion contains an outer lipid envelope (HBsAg) surrounding a nucleocapsid composed of hepatitis B core antigen (HBcAg), polymerase, and relaxed circular DNA (rcDNA).⁹³ Once rcDNA enters the nucleus, it is converted to cccDNA, which resists immune clearance and underlies life-long viral persistence.^{9,94} Integrated HBV DNA – while not required for replication – contributes to pathogenesis and sustained HBsAg expression.

HIV persists through integrated proviral DNA within long-lived immune cells, especially memory CD4⁺ T cells, macrophages, and, at lower levels, hepatocytes.^{9,95,96} The presence of both HIV and HBV expands these reservoirs: HIV impairs HBV clearance, leading to larger intrahepatic cccDNA pools,⁹² while HBV-driven inflammation recruits and activates HIV target cells.²⁵ Clonal expansion of HIV-infected CD4⁺ T cells within the hepatic microenvironment adds to reservoir stability.⁹⁷

Key Point

Nuclear reservoirs anchor chronicity for both viruses, interact with cellular proliferation pathways, and represent a primary barrier to functional cure.

Multicellular Reservoirs in the Liver

Despite long-term suppressive ART, HIV DNA and RNA are detectable in liver tissue, confirming a hepatic reservoir.^{98,99} While tissue-resident CD4⁺ T cells constitute the best-defined component, additional hepatic cell types sustain or facilitate local persistence.

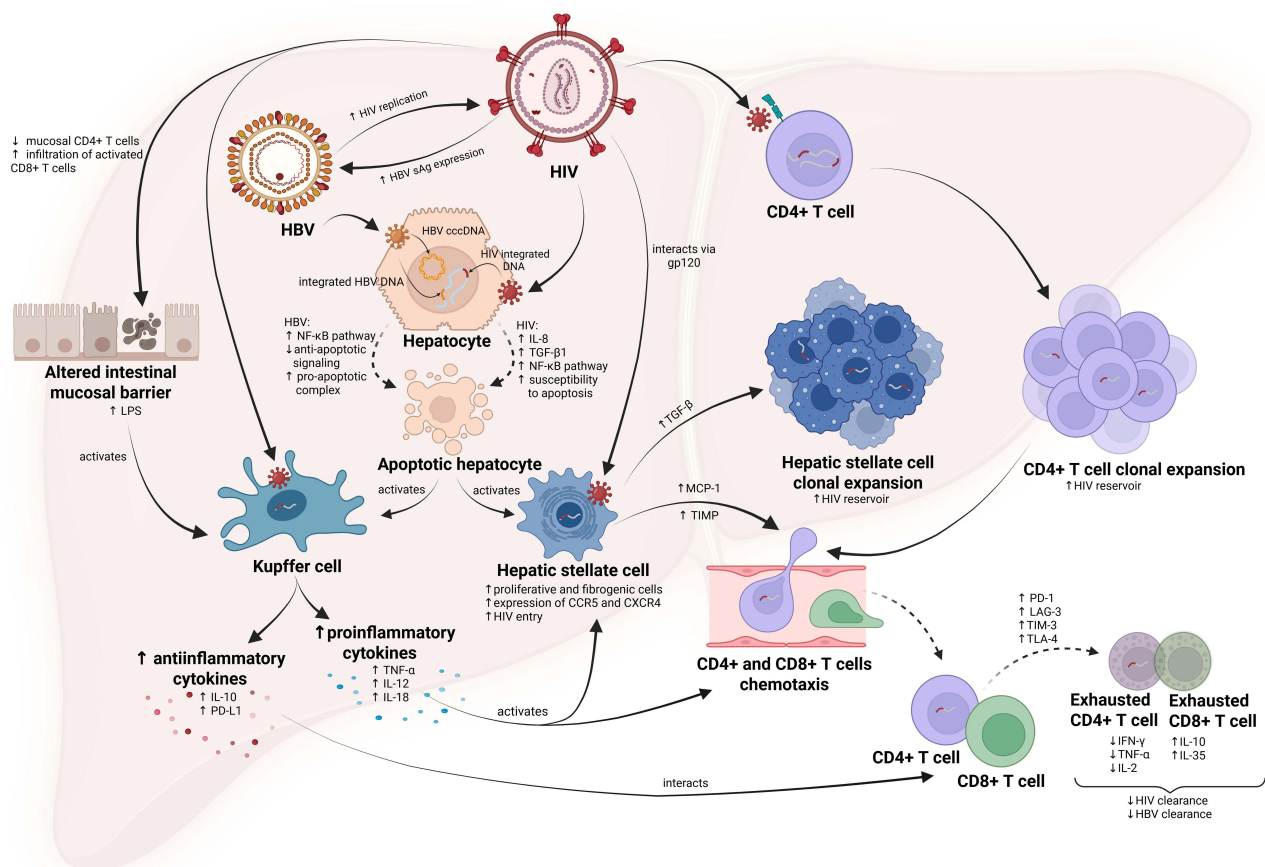


Figure 1 Conceptual schematic: Mechanisms of viral persistence and immune dysregulation in the setting of concurrent HIV HBV. The liver provides a permissive environment for HIV and HBV persistence through complementary and synergistic mechanisms. HBV persists within hepatocytes as nuclear covalently closed circular DNA (cccDNA) and integrated viral DNA, promoting antigen expression, impairing NF-κB-mediated anti-apoptotic signaling, and sensitizing hepatocytes to apoptosis. HIV persists as integrated proviral DNA in CD4⁺ T cells and, at lower levels, is detectable in hepatic stellate cells (HSCs), hepatocytes, and Kupffer cells. HIV gp120 activates HSCs, inducing TGF-β, MCP-1, and TIMP production, which promote fibrogenesis, immune cell recruitment, and local viral persistence. Both viruses contribute to hepatocyte injury and apoptosis, further activating Kupffer cells and HSCs. Kupffer cells generate proinflammatory cytokines (TNF-α, IL-12, IL-18) alongside immunoregulatory signals (IL-10, PD-L1), sustaining chronic inflammation and immune tolerance. CD4⁺ and CD8⁺ T cells are recruited to the liver, undergo clonal expansion, and progressively develop exhaustion characterized by checkpoint receptor expression (PD-1, TIM-3, LAG-3, CTLA-4). Exhausted CD4⁺ T cells lose helper function, while exhausted CD8⁺ T cells exhibit diminished cytotoxicity and increased production of tolerogenic cytokines (eg, IL-10, IL-35), impairing clearance of both viruses. HIV-associated gut barrier disruption increases microbial translocation and lipopolysaccharide (LPS) exposure, further fueling Kupffer cell activation and inflammatory signaling. Together, these processes establish a self-reinforcing cycle of immune dysregulation, reservoir expansion—including clonal proliferation of HIV-containing CD4⁺ T cells and activated HSCs—and fibrogenesis that accelerates liver disease progression in individuals living with concurrent HIV and HBV. Solid arrows indicate direct interactions and signaling pathways; dotted arrows denote indirect or secondary effects. Small arrows (↑, ↓) indicate relative increases or decreases in cellular processes, signaling pathways, or biological outcomes. Created in BioRender. Bobadilla, (R) (2026) <https://BioRender.com/491a84e>.

Kupffer Cells

Kupffer cells express both CCR5 and CXCR4 and can be infected by HIV.^{23,100,101} Infected Kupffer cells display heightened proinflammatory responses to secondary stimuli such as LPS,¹⁰¹ potentially reinforcing inflammatory loops. Some studies suggest Kupffer cells may not harbor replication-competent virus,¹⁰² while others report depletion in PWH,¹⁰³ highlighting context-dependent outcomes.

Hepatic Stellate Cells (HSCs)

Activated HSCs express CCR5 and CXCR4 and are susceptible to HIV entry.¹⁰⁴ Gp120 triggers monocyte chemoattractant protein (MCP-1) and tissue inhibitor of metalloproteinase (TIMP) production, promoting leukocyte recruitment and fibrogenesis. Infected HSCs may undergo clonal expansion, linking fibrosis, and reservoir maintenance.¹⁰⁵

Hepatocytes

HIV DNA is detectable at low levels in hepatocytes in individuals on ART.¹² Although lack of CD4 limits productive replication, hepatocytes can transmit surface-bound virus to CD4⁺ T cells via cell–cell contact, supporting local spread^{106,107} and may permit very low-level replication.¹¹

Key Point

Together, these findings support a multicellular hepatic reservoir in which CD4⁺ T cells remain central, while Kupffer cells, HSCs, and hepatocytes modulate the inflammatory and structural context that stabilizes persistence.

Reservoir Expansion Through Cellular Proliferation

The presence of both HIV and HBV amplifies reservoirs through combined viral and host-driven mechanisms. HIV reduces HBV clearance and enlarges cccDNA pools, while HBV-driven inflammation recruits HIV target cells. In parallel, HIV-infected CD4⁺ T cells expand clonally within the liver reinforcing reservoir size.⁹⁷ Chronically activated HSCs proliferate in parallel, contributing to both fibrosis and viral persistence.^{104,108} In HBV, hepatocyte turnover during chronic injury replenishes cccDNA reservoirs and propagates integrated HBV DNA. Concurrent HIV and HBV accelerate this turnover, linking hepatocyte regeneration with reservoir amplification.

Key Point

Proliferation of infected immune and stromal cells and turnover of hepatocytes create a self-sustaining loop of inflammation, fibrosis, and persistence.

Epigenetic and Transcriptional Regulation

Both viruses regulate transcription through epigenetic mechanisms that toggle between latency and replication. HBV cccDNA transcription is controlled by histone acetylation, methylation, and DNA methylation, with HBx and HBc proteins serving as key regulators.^{109,110} This allows HBV to alternate between functional silencing and active replication. Similarly, HIV latency is governed by chromatin remodeling and histone modifications at proviral integration sites, maintaining replication-competent but transcriptionally silent genomes.^{10,37} These epigenetic strategies enable both viruses to evade immune detection while retaining the potential for reactivation.

Key Point

Epigenetic control represents a shared and druggable mechanism of persistence.

Cytokine-Mediated Tolerance and Checkpoint Exhaustion

Cytokine-Mediated Tolerance

Elevated IL-10 levels during chronic HBV dampen antigen presentation and CD8⁺ T-cell cytotoxicity, limiting hepatic injury, but promoting viral survival and progression to chronic infection.^{32,111,112} At the same time, HIV amplifies this pathway, with Tat protein directly inducing IL-10 and suppressing HIV-specific T-cell responses.^{113–115} The paradoxical role of IL-10 – limiting liver immunopathology while undermining antiviral immunity – highlights a shared vulnerability. Additional cytokines such as TGF- β and IL-35 contribute to this tolerogenic milieu.^{87,112,116}

T-Cell Exhaustion and Checkpoint Pathways

Persistent antigen exposure and suppressive cytokines drive T cell exhaustion, marked by upregulation of PD-1, TIM-3, LAG-3, and CTLA-4.^{117–119} PD-1 is a key biomarker across HBV disease phases.^{31,120,121}

In HIV, PD-1 expression correlates with higher virus levels and impaired control.^{122,123} Importantly, exhausted HIV-infected CD4⁺ T cells are not simply terminally dysfunctional but can undergo clonal proliferation, linking dysfunction and persistence.⁹⁷

In the setting of concurrent HIV and HBV, HBV can exploit this exhausted and proliferative state, as reflected by higher HBV DNA levels, larger intrahepatic reservoirs, and more advanced fibrosis compared to HBV alone.^{124–126} These effects lead to impaired viral control and greater risk of progressive liver disease.

Key Point

Tolerance and exhaustion act synergistically to blunt antiviral immunity while stabilizing viral reservoirs.

Synergistic Disruption of Innate and Adaptive Immunity

CD4⁺ T-cell depletion, a hallmark of HIV, correlates with higher HBV replication and increased HCC risk.¹²⁷ HIV promotes inhibitory receptor expression on HBV-specific T cells,¹²⁸ and disrupts Kupffer cell antigen presentation.²⁵ In parallel, gp120-mediated activation of HSCs induces TGF- β and fibrosis.^{108,116} Together, HIV and HBV increase profibrogenic cytokines such as CXCL10 and TNF- α , accelerating fibrogenesis, precipitating hepatic flares, and worsening disease severity compared with either virus alone.^{116,129} HBV further impairs NK cytotoxicity¹³⁰ and skews dendritic cells toward a regulatory phenotype,¹³¹ suppressing HBV-specific adaptive immunity.^{132,133} Chronic antigenic stimulation progressively erodes effector function and fuels bystander inflammation and fibrosis.¹³ Effector T cells decline in polyfunctionality, while newly recruited naïve T cells adopt an inflammatory yet less specific phenotype. HIV mirrors and amplifies this process, with PD-1 and other checkpoint pathways tightly linked to higher virus levels and impaired clearance.^{122,134} In both infections, exhausted T cells exhibit diminished production of IFN- γ , TNF- α , and IL-2¹²⁷, enabling viral reservoirs to persist unchecked.¹⁴

Key Point

HIV and HBV jointly remodel innate and adaptive immunity, creating an immunologic environment favorable to both viruses.

Hepatocyte Injury and Apoptosis

The cumulative effects of immune dysregulation converge on hepatocytes. HBV surface antigen (HBsAg) sensitizes hepatocytes to TNF α -mediated apoptosis by inhibiting NF- κ B-dependent survival pathways and promoting pro-apoptotic complex II assembly. HIV exacerbates this injury by inducing IL-8, HIF-1 α , and TGF- β 1 signaling,^{14,116} and by enhancing hepatocyte susceptibility to TRAIL-mediated apoptosis.^{30,135} These interactions accelerate fibrotic remodeling, impair clearance, and expand infected cell pools.

Key Point

Recurrent hepatocyte injury closes the loop between immune dysregulation, inflammation, and reservoir persistence.

Metabolic and Mitochondrial Dysregulation

Metabolic reprogramming represents an emerging mechanism. Chronic viral infection drives mitochondrial stress,^{38,136} reactive oxygen species (ROS) accumulation,^{137,138} and impaired β -oxidation in hepatocytes and HSCs.¹³⁹ Viral proteins – including Tat and HBx – disrupt mitochondrial respiration and transcription factors (PPAR α , SREBP-1c).^{21,140–142} In Kupffer cells and T lymphocytes, metabolic exhaustion mirrors immune exhaustion with persistent antigenic stimulation that promotes a shift toward glycolysis at the expense of oxidative phosphorylation¹⁴³ and limits antiviral effector capacity. Older ART regimens (particularly NRTIs and tenofovir) may exacerbate mitochondrial injury.¹⁴⁰ These metabolic shifts sustain inflammation and fibrosis, thereby reinforcing persistence.

Key Point

Metabolic remodeling represents a potentially targetable axis of persistence and disease progression.

Viral Crosstalk and Gut–Liver Axis Effects

The bidirectional interaction between HIV and HBV confers significant advantages to both viruses. Mechanistically, the HBV X protein (HBx) can activate the HIV long terminal repeat (LTR) promoter, enhancing HIV replication,¹⁴⁴ while HIV Tat protein directly upregulates HBV surface antigen expression, further promoting HBV replication.²¹

Another mechanism by which HIV promotes HBV chronicity is through gut-associated dysbiosis. HIV-induced gut barrier disruption leads to microbial translocation, introducing LPS into the portal circulation and activating hepatic TLRs. This proinflammatory milieu enhances HBV replication and chronicity.^{38,39} Together, these mechanisms form a self-reinforcing cycle of viral persistence and pathology.

Key Point

Viral crosstalk and gut–liver axis effects amplify both persistence and liver disease.

Translational and Therapeutic Integration

As illustrated in [Figure 1](#), overlapping mechanisms represent convergent therapeutic targets, including nuclear persistence, clonal expansion, cytokine-mediated tolerance, and checkpoint-driven exhaustion (Summarized in [Table 3](#)). Translational strategies combining antivirals, immunomodulators, and antifibrotic interventions should be prioritized in future trials. Addressing shared pathways provides a conceptual foundation for integrated HIV and HBV cure strategies.

Key Point

Mechanistic convergence offers practical therapeutic entry points for integrated HIV/HBV cure efforts.

Therapeutic Implications in the Setting of Concurrent HIV and HBV

The management of HBV differs fundamentally from that of HIV. While HIV treatment follows a “treat all” approach, HBV therapy remains phase-specific, guided by viral replication level, serum aminotransferases, and stage of liver

Table 3 Mechanisms of Viral Persistence and Synergistic Pathogenesis in the Setting of Concurrent HIV HBV

Mechanism	Primary Cell Targets	Key Molecular/Cellular Processes	Impact on Persistence and Disease	Representative References
Nuclear reservoirs	Hepatocytes (HBV), CD4 ⁺ T cells, macrophages (HIV)	HBV cccDNA and integrated DNA resist immune clearance; HIV integrates into host genome of long-lived cells	Establishes durable nuclear reservoirs; sustains antigen production and reactivation risk	[69–72,117,118]
Multicellular hepatic reservoirs	CD4 ⁺ T cells, Kupffer cells, HSCs, hepatocytes	HIV and HBV infect multiple hepatic cell types via CCR5/CXCR4 and NTCP receptors; HSCs and KCs amplify inflammation	Links viral persistence to chronic inflammation and fibrosis	[105–116]
Reservoir expansion via proliferation	Infected CD4 ⁺ T cells, HSCs, hepatocytes	Clonal expansion of HIV-infected T cells; proliferation of HSCs during HBV/HIV injury spreads integrated DNA	Maintains or increases reservoir size even under ART/NA therapy	[37,119]
Epigenetic regulation of latency	Hepatocytes, CD4 ⁺ T cells	Histone modifications (acetylation/methylation), DNA methylation, and HBx/HBc-mediated chromatin remodeling	Silences transcription without eliminating replication-competent DNA; enables reactivation	[71–73]
Cytokine-mediated tolerance	Kupffer cells, HSCs, T cells	IL-10, TGF- β , and IL-35 create immunosuppressive milieu; HIV Tat induces IL-10 production	Dampens cytotoxic responses; promotes chronic infection and fibrosis	[74–79]
Checkpoint exhaustion	CD4 ⁺ and CD8 ⁺ T cells, DCs	Overexpression of PD-1/TIM-3/LAG-3/CTLA-4 in both infections; impaired TCR signaling	Loss of effector function and viral clearance; promotes clonal expansion of infected T cells	[80–85,91,92]
Synergistic disruption of innate and adaptive immunity	CD4 ⁺ T cells, KCs, HSCs, NK/DC cells	CD4 loss, NK/DC dysfunction, PD-1 upregulation, gp120-induced TGF- β production	Accelerates fibrosis, immune exhaustion, and reservoir maintenance	[86–98]
Hepatocyte injury and apoptosis	Hepatocytes	HBsAg sensitizes cells to TNF- α and TRAIL; HIV gp120 triggers HIF-1 α , IL-8, TGF- β I	Promotes apoptosis, ROS production, and fibrotic remodeling	[93–100]
Gut–liver axis disruption	LSECs, KCs, hepatocytes	Microbial translocation and LPS activate TLR pathways and inflammation	Enhances HBV replication and hepatic immune activation	[122,123]
Metabolic and mitochondrial dysregulation	Hepatocytes, HSCs, KCs, T cells	Viral proteins (Tat, HBx) impair oxidative phosphorylation, increase ROS, and alter lipid/glucose metabolism	Promotes immune exhaustion, fibrosis, and hepatotoxicity; potential target for metabolic therapy	[133–139]

Abbreviations: cccDNA, Covalently Closed Circular DNA; CD, Cluster of differentiation; CCR5, C-C Chemokine Receptor Type 5; CXCR4, C-X-C Chemokine Receptor type 4; NTCP, Na⁺-taurocholate cotransporting polypeptide; HSC, Hepatic stellate cells; KC, Kupffer cells; ART, antiretroviral therapy; NA, Nucleotide/nucleoside analogs; IL, Interleukin; TGF- β , Transforming Growth Factor-beta; NK, Natural killer; DCs, Dendritic cells; PD-1, Programmed Cell Death Protein 1; TIM-3, T-cell Immunoglobulin and Mucin-Domain Containing-3; LAG-3, Lymphocyte Activation Gene-3; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; TCR, T Cell Receptor; TRAIL, Tumor necrosis factor Related Apoptosis-Inducing Ligand; Gp120, Glycoprotein 120; HIF-1 α , Hypoxia-Inducible Factor 1-alpha; LPS, lipopolysaccharide; TLR, Toll-like Receptor; LSEC, Liver sinusoidal endothelial cells; ROS, Reactive Oxygen Species.

disease. In both settings, long-term nucleos(t)ide analogues (NAs) therapy—including agents such as tenofovir, lamivudine, or emtricitabine—are safe and effective for suppressing viremia.⁹⁶ However, neither virus is curable with current regimens: HIV persists as integrated proviral DNA, while HBV is maintained as nuclear covalently closed circular DNA (cccDNA) and integrated viral sequences. Consequently, therapy remains lifelong for most individuals.⁸

HIV fundamentally alters the natural history of HBV disease. Beyond the established excess liver-related morbidity, discontinuation of HBV-active agents carries a substantial risk of HBV reactivation.^{35,145,146} Accordingly, optimization of HBV antiviral strategies is a critical component of care in the setting of concurrent HIV and HBV.

Current guidelines recommend entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) as first-line agents for HBV due to their potent antiviral activity and high barrier to resistance.^{96,147} Among these, TAF provides reduced systemic exposure and a more favorable safety profile with respect to renal function and bone mineral density.^{40,147} The primary goals of HBV antiviral therapy are to suppress HBV DNA to undetectable levels, stabilize serum aminotransferases, and limit hepatic inflammation and fibrosis. Lowering HBV DNA reduces antigen burden and chronic immune stimulation that drives T-cell exhaustion.^{148,149} Although this approach can partially restore HBV-specific immune responses, the extent and durability of immune recovery remain variable.

In individuals living with both HIV and HBV, management is further complicated by several interrelated factors.

First, individuals experience accelerated liver disease progression, with earlier development of cirrhosis and HCC, necessitating intensified monitoring of liver function, fibrosis stage, and cancer surveillance compared with HBV alone.^{5–7}

Second, antiviral selection is critical to prevent resistance: historical use of lamivudine or emtricitabine without additional HBV-active therapy led to high rates of HBV resistance.^{150,151} As a result, contemporary guidelines recommend regimens containing at least two HBV-active agents—typically tenofovir combined with lamivudine or emtricitabine—to ensure durable viral suppression.⁹⁶

Third, discontinuation of HBV-active NAs within ART regimens can precipitate severe hepatitis flares due to HBV reactivation.^{35,152} Maintaining continuous HBV suppression is essential, and any ART modification or interruption must carefully account for continued HBV-active coverage.

Finally, although tenofovir-associated nephrotoxicity is not consistently higher than in people with HIV alone, observational studies suggest increased overall rates of renal complications in people with both viruses,¹⁵³ underscoring the need for careful renal monitoring.

In sum, management of concurrent HIV and HBV requires a careful balance between sustained viral suppression, prevention of antiviral resistance, and minimization of drug-related toxicity. While current NA-based regimens are highly effective at controlling viral replication, they do not eliminate latent viral reservoirs, rendering lifelong therapy the norm. The persistent challenges of accelerated liver disease, HBV reactivation risk, and cumulative toxicity highlight both the progress achieved and the substantial gaps that remain, underscoring the need for innovative therapeutic strategies and more inclusive clinical trials.

Future Directions and Research Gaps

Exclusion of Individuals with Concurrent HIV and HBV from Cure Trials

Despite their high prevalence and disproportionate morbidity, individuals living with concurrent HIV and HBV are routinely excluded from both HIV and HBV cure studies,³³ due to the concern of serious hepatocellular injury from HBV reactivation during trials that require ART interruption.³⁵ Additional concerns include drug–drug interactions, and confounding endpoints.^{8,92,154} This practice widens health inequities, limits generalizability of findings, and creates gaps in the available evidence. Individuals with advanced fibrosis, metabolic comorbidities, or substance-use disorders are often omitted, despite representing most patients in clinical care. These exclusionary practices disproportionately affect women, older adults, and populations in low-resource settings.

Path Forward

Safely include individuals with concurrent HIV and HBV with HBV-active ART backbones, dual virological endpoints, and vigilant flare monitoring. Sustain community partnerships to ensure cultural competence, responsiveness to local priorities, and long-term trust.

Lack of Reliable Biomarkers to Distinguish Latent versus Active Infection

Accurate discrimination between latent and active infection is a major barrier for both viruses. In HIV, proviral DNA may be transcriptionally active yet translationally silent, complicating reservoir quantification.^{155,156} Plasma viral load is practical for quantifying viremia but not reservoir size. For HBV, differentiating between active and latent infection relies on a constellation of serological markers—HBsAg, anti-HBs, HBeAg, anti-HBe, and HBV DNA—that can yield ambiguous results depending on dynamics and host immune responses.^{96,145} Occult HBV, characterized by detectable intrahepatic HBV DNA despite absent HBsAg, highlights the challenges of monitoring persistence.^{152,157} Occult HBV can be categorized into two forms: seropositive (anti-HBc and/or anti-HBs positive) and seronegative (anti-HBc and anti-HBs negative).¹⁴⁶ In occult disease, clinical history and conventional serologic markers are insufficient to reliably exclude HBV.¹⁵⁸ Although emerging biomarkers such as hepatitis B core-related antigen (HBcrAg) and HBV RNA offer improved detection, diagnostic uncertainty remains particularly problematic in individuals living with concurrent HIV and HBV, where immunosuppression increases the risk of viral reactivation.^{157,159}

Path Forward

Develop and validate biomarkers that reflect transcriptional activity, replication competence, and tissue reservoir burden in the setting of concurrent HIV and HBV.

Limited Access to Liver Tissue for Reservoir Studies

The liver is central to persistence, yet tissue access is scarce¹⁵ due to the decline in biopsy procedures and limited global infrastructure for specimen storage and sharing. Liver biopsies are invasive and increasingly rare in clinical practice, while autopsy studies remain underutilized. This lack of access hampers investigation into intrahepatic reservoirs, including nuclear persistence, clonal expansion, and immune exhaustion.

Path Forward

Expanding ethically governed liver biorepositories and rapid research autopsy programs—such as *The Last Gift*—will enable direct study of intrahepatic persistence, immune exhaustion, and epigenetic regulation, which are critical for advancing cure strategies. Community participation is central to these efforts, ensuring transparency, informed consent, and cultural sensitivity around tissue donation and post-mortem research.

Limited Tools for Intrahepatic Reservoir Assessment

Even when tissue is available, current diagnostics rely heavily on systemic measures that do not fully reflect intrahepatic infection dynamics. No FDA-approved assays exist to directly quantify reservoir activity in liver tissue.⁴

Path Forward

Standardize and scale liver-focused approaches, biopsy studies, rapid autopsy, single-cell/spatial multi-omics, to assess cccDNA, integrated HBV DNA, HIV provirus, epigenetic states, and exhaustion in situ.

Incomplete Understanding of Mechanisms Driving HBsAg Clearance in Individuals with Concurrent HIV and HBV

HBV functional cure, defined as sustained HBsAg loss, remains rare during HBV alone but may occur more frequently in individuals living with concurrent HIV and HBV following initiation of HBV-active ART—reported in up to ~20% within two years—potentially through immune reconstitution.^{36,160} The mechanisms underlying this phenomenon remain poorly understood, and most HBV cure trials exclude individuals with concurrent HIV and HBV, limiting mechanistic insight.

For HIV, latency is established through integrated proviral DNA, which is stable despite long-term ART. Experimental strategies for HIV cure – including latency reversal, immune modulation, and therapeutic vaccination^{3,18–20} – carry specific risks for coinfecting individuals, particularly HBV reactivation.

Path Forward

Trial designs must plan explicitly for HBV safety, while studying drivers of HBsAg loss in the context of concurrent HIV and HBV.

Translational and Therapeutic Integration for Dual-Cure Strategies

Future research must bridge mechanistic understanding with therapeutic innovation. The overlapping pathways of persistence—epigenetic silencing, immune exhaustion, cytokine-mediated tolerance, and fibrosis-driven clonal expansion—provide tangible targets for intervention. Notably, an oral TLR8 agonist (selgantolimod) is being tested for HBsAg loss in individuals living with concurrent HIV and HBV, while also assessing effects on the HIV reservoir.¹⁶⁰ TLR8 agonists bind to TLR8 on APCs and activate them to produce IL-12 and other immunomodulatory mediators, triggering innate and adaptive immune responses that simultaneously target both HIV and HBV through distinct downstream cytokines.^{161–164} Yet most strategies remain siloed, targeting either HIV or HBV alone.

Path Forward

Build a translational framework to evaluate combination interventions that disrupt both reservoirs. Leverage spatial transcriptomics, single-cell multi-omics, and precision imaging to map intrahepatic niches and quantify on-target effects and embed these tools into biomarker-driven trials with dual virologic and hepatic endpoints. Equitable inclusion of individuals living with concurrent HIV and HBV and sustained community partnership are essential to ensure biologically sound and socially responsive trial designs. Given emerging evidence that metabolic and mitochondrial dysfunction fuel persistence and fibrosis in the setting of concurrent HIV and HBV, metabolic modulators and antioxidant strategies should also be explored.

Community Engagement as a Cornerstone of Research

Community advisory boards (CABs), patient advocates, and civil-society organizations have long been essential to the success of HIV research, ensuring that clinical trials reflect participant priorities and ethical standards.^{165,166} Similar models are increasingly being adopted in HBV research, particularly in high-burden settings such as sub-Saharan Africa and the Western Pacific.¹⁶⁷ This approach ensures that possible research guided interventions are responsive to the experiences and needs of those most affected, thereby reducing disparities and improving outcomes.

Path Forward

Sustained community participation improves recruitment, retention, and adherence while fostering trust and ensuring that study outcomes translate into local health benefits. For studies involving concurrent HIV and HBV, engagement must also emphasize cross-virus literacy, bridging communities that have historically operated in parallel rather than in partnership.

Equity, Sex Differences, and Comorbidities

Sex and gender differences remain underexplored in the setting of concurrent HIV and HBV. Hormonal and immunologic factors—such as estrogen-mediated immune modulation and differences in hepatic metabolism—may influence reservoir dynamics, vaccine responses, and disease progression; yet, most studies continue to overrepresent cisgender men.^{168,169}

Path Forward

Future research must intentionally include women, transgender, and gender-diverse participants and analyze outcomes by sex and hormonal status. Coinfected individuals also face a high burden of comorbidities, such as alcohol-related liver disease, non-alcoholic fatty liver disease (NAFLD), diabetes, and cardiovascular complications^{5,7,39,140} that can modify liver inflammation and fibrosis. Integrating comorbidity screening and management within research protocols is essential to disentangle virus-driven from host-driven mechanisms of injury.

As summarized in Table 4, these research gaps span trial design, diagnostics, tissue access, and mechanistic understanding. Addressing them is essential to advance equitable and effective cure strategies for concurrent HIV and HBV.

Table 4 Priority Research Gaps in the Setting of Concurrent HIV HBV

Domain	Knowledge Gap	Underlying Challenge	Potential Path Forward
Clinical research inclusion	Exclusion of HIV/HBV-coinfected individuals from cure and immunotherapy trials	Safety concerns (HBV reactivation during ART interruption), drug–drug interactions, confounding of endpoints	Design inclusive trials with HBV-active ART backbones, dual virological endpoints (HIV and HBV), and robust flare monitoring; strengthen community engagement to promote ethical inclusion
Viral dynamics	Inability to distinguish latent vs active infection for both viruses	Lack of biomarkers that accurately reflect transcriptional vs translational activity (HIV) or replicative vs occult infection (HBV)	Develop molecular assays measuring transcriptional activity, cccDNA transcription rate, and HIV proviral reactivation potential; validate composite biomarker panels
Tissue-based reservoirs	Limited access to and analysis of liver tissue	Invasive nature of biopsies, underutilization of rapid autopsy programs, and limited tissue biorepositories	Expand ethically governed liver biopsy and rapid autopsy networks (eg, <i>Last Gift</i> model); standardize tissue collection and sharing protocols
Reservoir quantification tools	Lack of reliable assays to measure intrahepatic reservoirs	No FDA-approved methods to quantify cccDNA, integrated HBV DNA, or HIV provirus in tissue; variability across labs	Develop and validate standardized ddPCR, Intact Proviral DNA Assay, and single-cell/spatial omics assays for liver tissue; create multi-site assay harmonization consortia
Mechanistic understanding	Incomplete understanding of mechanisms underlying HBsAg loss in coinfecting individuals	Limited data from excluded populations; unclear contribution of immune reconstitution vs direct viral interaction	Conduct longitudinal studies of immune restoration on ART; include coinfecting cohorts in HBV functional cure trials
Gender-based and hormonal differences	Understudied impact of sex hormones and gender differences on viral persistence and immune regulation	Most studies focus on cisgender men; few examine effects of estrogen, progesterone, or menopause	Integrate sex-based analyses into cure trials; assess hormonal modulation of immune exhaustion and viral reservoir dynamics
Comorbidities and confounding factors	Metabolic, cardiovascular, and microbial comorbidities alter liver inflammation and fibrosis progression	Coinfecting populations often face coexisting conditions (alcohol use, NAFLD, diabetes) confounding outcomes	Use multi-omic and systems biology approaches to disentangle comorbidity-driven vs virus-driven inflammation
Immunologic profiling	Incomplete understanding of intrahepatic immune exhaustion and checkpoint regulation	Limited availability of fresh tissue for flow cytometry/single-cell analysis	Apply high-dimensional single-cell and spatial technologies to define exhaustion pathways and therapeutic targets
Implementation science	Persistent disparities in HBV vaccination and screening in PWH	Suboptimal vaccine response, health system fragmentation, and stigma-related barriers	Evaluate novel HBV vaccine adjuvants and delivery models in PWH; expand global implementation research in high-burden settings

Abbreviations: ART, Antiretroviral therapy; cccDNA, Covalently Closed Circular DNA; FDA, Food and Drug Administration; ddPCR, Droplet Digital Polymerase Chain Reaction; HBsAg, Hepatitis B surface antigen; NAFLD, Nonalcoholic Fatty Liver Disease; PWH, People with HIV.

The Ethical Imperative of Inclusion and Path Forward

Excluding coinfecting or high-risk populations from research exacerbates existing disparities and slows progress toward global elimination goals. Ethically, inclusion is essential for justice and equity. Scientifically, it is vital for understanding how therapies perform across biological and social contexts.

Path Forward

Future clinical trial designs should:

- Deliberately include participants with concurrent HIV and HBV with appropriate safeguards (HBV-active ART backbones, flare monitoring, dual virological endpoints)
- Incorporate sex- and gender-based analyses and stratified recruitment targets
- Address comorbidities and social determinants of health that influence outcomes
- Invest in sustainable community partnerships that ensure trials are culturally competent, transparent, and responsive to participant needs

Together, these principles lay the foundation for a truly inclusive research agenda that bridges bench, bedside, and community, paving the way for equitable cure strategies.

Discussion

Despite sustained viral suppression with current antiretroviral and nucleos(t)ide analogue regimens, cure or durable remission of HIV and HBV without ongoing drug exposure remains out of reach. Shared, reinforcing reservoir mechanisms within the liver, largely unaffected by existing approaches, stabilize viral persistence, including nuclear viral reservoirs, epigenetic silencing, immune tolerance and exhaustion, fibrogenic remodeling, and metabolic stress. This review advances the field by reframing concurrent HIV and HBV as a unified, liver-centric reservoir disorder rather than two parallel infections with overlapping epidemiology.

For cure efforts, the liver must be recognized as a primary reservoir and regulatory site rather than a downstream target of injury. Accordingly, cure approaches must move beyond single-modality interventions. Viral suppression should be combined with strategies that ameliorate immune exhaustion, fibrotic remodeling, and metabolic dysfunction within the liver. Integrated approaches pairing antivirals with immunomodulatory, antifibrotic, or metabolic interventions are more likely to disrupt hepatic reservoirs than strategies targeting either virus in isolation, and cure trials should incorporate intrahepatic, not solely peripheral, endpoints.

Progress toward cure is constrained by limited tools to quantify intrahepatic reservoirs and distinguish latent from transcriptionally active viral states. Systemic markers incompletely capture liver biology, particularly in the context of occult HBV or immune reconstitution. Expanded access to liver tissue through ethically governed biopsy and rapid-autopsy programs, together with single-cell and spatial multi-omic technologies, will be essential to define meaningful cure endpoints and validate biomarkers of reservoir disruption.

Finally, the routine exclusion of individuals with HIV/HBV coinfection from cure trials remains a major scientific and ethical barrier. This population bears disproportionate disease burden; yet, is frequently omitted due to safety concerns, particularly HBV reactivation. Trial designs that maintain HBV-active antiretroviral backbones, incorporate dual virologic and hepatic endpoints, and include proactive flare monitoring can enable safe inclusion while accelerating discovery.

In summary, HIV/HBV coinfection underscores that cure will require integrated, liver-centric strategies targeting viral reservoirs, immune dysfunction, and tissue remodeling. Aligning mechanistic insight with tissue-informed endpoints and inclusive trial design is essential to move beyond lifelong suppression toward durable functional cure.

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