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Artificial intelligence for mechanistic understanding of hepatitis B virus

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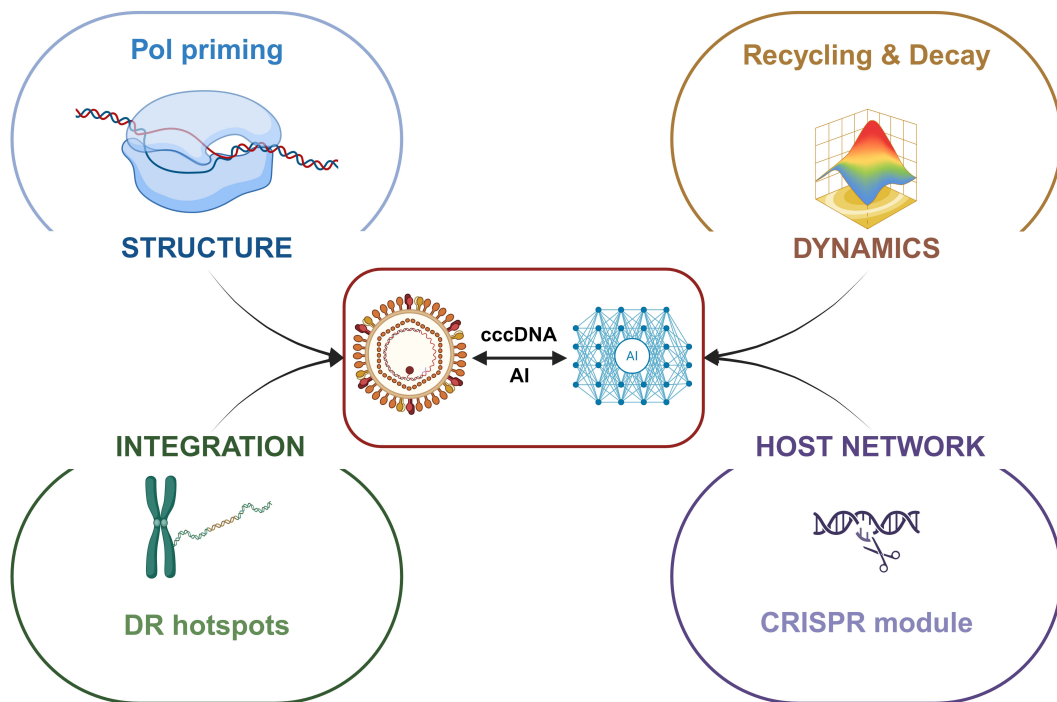
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Chronic hepatitis B virus (HBV) persists through a compact proteome, deep reliance on host pathways, and a nuclear covalently closed circular DNA (cccDNA) reservoir that current antivirals rarely extinguish. This Mini Review synthesizes advances from 2020–2025 in which artificial intelligence (AI) augments mechanistic understanding of HBV rather than serving only predictive ends. We summarize (i) AI-enabled structural modeling that clarifies polymerase priming and HBx architecture; (ii) physics-informed and multiscale inference that links sparse measurements to replication and cccDNA kinetics; (iii) sequence-based learners that expose non-random host-genome integration contexts and mutational constellations associated with immune tolerance or escape; (iv) network-aware analyses that prioritize host dependencies and connect CRISPR perturbations to virus–host modules governing cccDNA transcriptional control; and (v) AI-assisted antiviral discovery that couples virtual screening with mechanism-anchored interpretation (e.g., capsid assembly modulators). Across these domains, AI sharpens hypotheses by mapping viral mutations and host factors to discrete steps of the life cycle, quantitatively elevating high-leverage processes such as nucleocapsid recycling and cccDNA silencing, and guiding structure- or phenotype-guided intervention design. We also outline practical constraints—data sparsity, cross-cohort heterogeneity, and interpretability—and propose priorities that couple computation and experiment: mechanism-aware gray-box models, causal and spatially resolved analyses, calibrated uncertainty and benchmarking across genotypes, and active-learning loops that maximize information gained per experiment. Framed this way, AI emerges as a mechanism-aware partner to experimental virology, accelerating routes toward durable functional cure through eradication or stable transcriptional silencing of cccDNA.

KEYWORDS

hepatitis B virus, artificial intelligence, machine learning, cccDNA, viral replication

Mechanism-Aware AI Reveals



GRAPHICAL ABSTRACT

Mechanism-aware artificial intelligence (AI) links key mechanistic domains in hepatitis B virus (HBV) research (1). A central cccDNA–AI module is connected to four surrounding modules: structural modeling of polymerase priming (“STRUCTURE”), replication and cccDNA recycling/decay (“DYNAMICS”), sequence-based discovery of integration DR hotspots (“INTEGRATION”), and host-network modules including CRISPR-based perturbations (“HOST NETWORK”), summarizing how AI maps onto discrete steps of the HBV life cycle.

Introduction

Hepatitis B virus (HBV) chronically infects over 250 million people worldwide and causes significant morbidity and mortality due to liver cirrhosis and hepatocellular carcinoma (2, 3). The persistence of HBV is primarily driven by the formation of covalently closed circular DNA (cccDNA) in the nuclei of infected hepatocytes (4), which serves as a stable episomal mini-chromosome that continuously produces viral RNAs and progeny virions (5). This nuclear cccDNA reservoir is not eliminated by current antiviral therapies and is a key obstacle to curing

Abbreviations: AI, artificial intelligence; CAM, capsid assembly modulator; cccDNA, covalently closed circular DNA; CRISPR, clustered regularly interspaced short palindromic repeats; CTL, cytotoxic T lymphocyte; DDB1, damage-specific DNA-binding protein 1; HBcAg, hepatitis B core antigen; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBx, hepatitis B virus X protein; HCV, hepatitis C virus; HLA, human leukocyte antigen; MD, molecular dynamics; ML, machine learning; NTCP, sodium taurocholate cotransporting polypeptide; ODE, ordinary differential equation; PPI, protein–protein interaction; QSAR, quantitative structure–activity relationship; rcDNA, relaxed circular DNA; RNase H, ribonuclease H; RT, reverse transcriptase; SHAP, SHapley Additive exPlanations; VINN, virology-informed neural network.

chronic HBV infection. Additionally, integration of HBV DNA into the host genome can contribute to oncogenesis and HBsAg production, further complicating disease persistence (6, 7). HBV’s life cycle relies on intricate interactions between viral proteins and host cell factors: for example, the HBx protein modulates epigenetic and signaling pathways to favor viral persistence, and the viral polymerase (Pol) carries unique domains for genome replication that have proven challenging to characterize structurally (8, 9). These and other mechanistic complexities – including immune evasion via exhausted T cell responses and decoy viral antigens – underscore the need for new approaches to dissect HBV biology (10).

In parallel, the past decade has seen rapid growth in the application of artificial intelligence (AI) and machine learning (ML) in biomedical research (11, 12). AI methods excel at finding patterns in high-dimensional data and have already revolutionized fields like protein structure prediction and image analysis. In virology, AI approaches have been employed to study virus–host interactions, predict viral evolution, and improve antiviral drug discovery (13–15). For HBV, which generates diverse data from genomic sequences to patient biomarkers, AI offers a powerful toolkit to uncover hidden relationships and generate predictive models that complement experimental findings. Crucially, AI techniques can help bridge gaps where traditional virological methods face limitations: for instance,

TABLE 1 AI approaches mapped to HBV mechanistic questions.

Mechanistic domain	AI approach (primary)	Key inputs	Mechanistic readout/insight	Representative refs	Validation evidence
Viral protein structure (Pol, HBx)	Deep learning structure prediction \pm MD/docking	Viral protein sequences; cross-species alignments; partial constraints	TP-RT geometry for protein priming; HBx fold hypotheses; mapping mutational effects onto 3D	(16–19)	Mutational mapping aligns with model; cross-species conservation; docking/geometry consistency
Replication & cccDNA dynamics	Physics-informed/VINN; multiscale inference	Time series (virus/capsids/serology); life-cycle ODE priors	Rates for infection/production; cccDNA replenishment via capsid recycling; cccDNA decay; scenario testing	(20–23)	External multiscale fits and serology-cccDNA correlation; parameters biologically plausible
Genomics & integration	Attention/transformer sequence learners	Host genome \pm repeats/epigenomic tracks; viral genomes/quasispecies	Non-random integration hotspots; short-motif/microhomology cues; mutational constellations linked to immune phase	(24, 25)	Independent test sets; cancer epi-enrichment; attention motif attribution
Host-virus networks & immunity	Network integration (PPI + CRISPR); epitope/immune ML	PPI maps; KO/GOF screens; transcriptomes; HLA/epitope data	Core host modules (SMC5/6, UPS, Ca ²⁺ , chromatin) controlling cccDNA transcription; candidate T/B cell epitopes & escape	(26–29)	CRISPR/KO confirmation of SMC5/6 restriction; HBx-mediated degradation validated
Antiviral discovery & MoA	Transformer-QSAR + virtual screening; ML on MD ensembles	SMILES libraries; capsid tetramer trajectories	Prioritized capsid-engaging hits; CAM class-specific “hotspots” explaining acceleration <i>vs</i> misdirection	(30, 31)	Prospective hit nomination and <i>in-vitro</i> validation for core inhibitors; ML-based MoA for CAM classes

Concise overview aligning major AI/computational paradigms with specific HBV endpoints. For each domain—viral protein structure (polymerase, HBx), replication and cccDNA kinetics, genomics and integration, host-virus networks and immunity, and antiviral discovery & mechanism of action—the table lists the primary approach, key inputs, and the principal mechanistic readout/insight, together with representative references and a “Validation evidence” column summarizing the strongest orthogonal or external support. Abbreviations: AI, artificial intelligence; CAM, capsid assembly modulator; cccDNA, covalently closed circular DNA; CRISPR, clustered regularly interspaced short palindromic repeats; HLA, human leukocyte antigen; MD, molecular dynamics; PPI, protein-protein interaction; QSAR, quantitative structure-activity relationship; UPS, ubiquitin-proteasome system; VINN, virology-informed neural network.

predicting viral behavior without invasive biopsies, or simulating molecular processes that are difficult to capture experimentally.

Here, we delineate how AI has advanced mechanistic understanding of HBV, emphasizing applications from roughly 2020 to 2025 that interrogate replication and cccDNA kinetics, resolve viral protein structure-function (polymerase, HBx), map host-virus dependency networks, and parse immune modulation relevant to persistence. Our synthesis privileges studies in which AI yields explanatory insight—pinpointing viral or host determinants that govern cccDNA maintenance, polymerase activity, capsid dynamics, or immune escape—rather than purely prognostic models unless they illuminate underlying biology. We further identify methodological and data constraints and outline where computation and experiment should be coupled to address HBV-specific bottlenecks. Framed this way, AI emerges not as an adjunct but as a mechanism-aware partner to experimental virology, sharpening hypotheses, prioritizing interventions, and accelerating routes toward durable functional cure.

To orient readers across methods and mechanistic endpoints, Table 1 maps representative AI approaches to core HBV questions—structure/function, replication and cccDNA kinetics, genomics/integration, host-virus networks, and antiviral discovery.

Selecting an AI framework should reflect inductive bias, data regime, and validation. Physics-informed networks embed governing Ordinary Differential Equation/Partial Differential Equations (ODE/PDEs) into the loss (32), constraining fits to biologically plausible trajectories and enabling parameter identification under sparse time-series (e.g., latent cccDNA kinetics); they differ from neural ODEs by enforcing explicit mechanistic residuals rather than learning unconstrained latent dynamics. PINNs thus excel when priors are

strong and labels are limited, but require credible process models and careful scaling of data-physics terms. In contrast, attention-based sequence learners/Transformers capture long-range dependencies in genomes and epigenomic context (33), well-suited for HBV integration hotspot discovery and motif attribution (24), but need larger labeled sets and rigorous interpretability checks. Structure predictors (e.g., AlphaFold-class models) leverage evolutionary and geometric priors to generate atomistic hypotheses for Pol/HBx that can be tested by mutagenesis or docking (16). Across paradigms, validation should include internal resampling plus external validation on independent cohorts/systems, and whenever possible orthogonal experimental tests (e.g., cryo-EM comparison, CRISPR perturbation, targeted biochemistry). This pragmatic rubric—mechanistic bias *vs.* data scale, with tiered validation—helps match models to HBV questions spanning replication kinetics, integration, and host-dependency mapping.

AI-driven structural insights into HBV proteins

A central barrier in HBV biology has been the lack of high-confidence structures for key viral proteins (34, 35). Deep learning-based folding (e.g., AlphaFold2) recently produced the first full-length model of HBV polymerase (Pol), resolving a decades-long impasse (17). The model reveals an unexpected arrangement in which the terminal protein (TP) wraps around the reverse transcriptase (RT), positioning the priming tyrosine directly above the RT active site—providing a structural rationale for

protein-primed DNA synthesis. RT and RNase H adopt a retrovirus-like orientation despite limited sequence homology, and the overall fold, including TP placement, appears conserved across mammalian and avian hepadnaviruses. These insights rationalize prior mutant phenotypes, enable *in silico* docking, and open structure-guided avenues beyond the active site (e.g., allosteric pockets), advancing mechanistic studies of replication and cccDNA generation.

AI modeling has likewise suggested HBx, a small, partially disordered regulator essential for replication and implicated in oncogenesis (36). AlphaFold yields a coherent HBx fold with similarity to palmitoleoyl transferases, suggesting membrane-proximal functions or functional mimicry (18). Comparison with alternative threading models and integration with partial experimental data and molecular dynamics favor the AlphaFold solution. Conservation analysis highlights residues critical for transcriptional activity (e.g., Cys61, Cys69, Cys137, His139) across hepadnaviruses, alongside human-HBV-specific sites linked to subcellular targeting, implying a conserved core with host-adapted features. These predictions generate testable hypotheses for HBx–host interactions (e.g., DDB1 engagement, membrane association) (37).

Beyond Pol and HBx, AI-enabled structural virology supports hypothesis-driven work on other proteins. For HBcAg and HBsAg—already characterized by crystallography/cryo-EM (38)—AI can assess mutation impacts, heterogeneity, and conformational preferences, refining genotype–phenotype mapping and antigenicity models. Notably, the Pol structure is already informing interpretation of deep mutational scanning by mapping functional effects onto a 3D framework. More broadly, coupling AI-predicted structures with molecular dynamics should illuminate functionally relevant conformational changes during reverse transcription and capsid assembly (19, 39). Collectively, these advances move previously “undruggable” targets into view and provide a structural foundation for mechanistic experimentation and antiviral design.

AI in modeling HBV replication and cccDNA dynamics

AI is extending classical ODE-based frameworks of HBV dynamics to enable data-efficient inference for hard-to-observe compartments such as cccDNA and intracellular capsids (40, 41). Physics-informed neural networks embed established virological equations into the loss function so that fitted solutions respect known kinetics while accommodating sparse, noisy time series. A recent virology-informed neural network (VINN) instantiated a four-compartment model (susceptible hepatocytes, infected hepatocytes, rcDNA-containing capsids, and free virus) with explicit capsid recycling to replenish cccDNA, and recovered infection, production, and cccDNA replenishment rates even when only capsid measurements were available (20). The resulting parameter sets were biologically plausible and supported

in silico counterfactuals (e.g., varying cccDNA degradation) for mechanism-guided scenario testing.

Physics-informed neural networks (PINNs) differ from neural ODEs in how they encode mechanism and handle sparse data (21, 22). PINNs train the network while penalizing violations of known life-cycle equations and initial/boundary conditions, so the learned trajectories stay close to biologically plausible HBV dynamics; this tends to improve parameter identifiability under limited, noisy time-series and helps recover latent compartments such as cccDNA or intracellular capsids—provided the process equations are credible and the data/physics terms are balanced appropriately. By contrast, neural ODEs learn a flexible latent vector field from data with minimal mechanistic constraints (23); they are useful when prior knowledge is weak or measurements are rich, but may require extra regularization if one needs properties like mass balance or saturation to hold. In practice, many HBV use-cases benefit from a “gray-box” compromise: embed the trusted parts of the replication model (e.g., infection, production, recycling) and let a small learnable residual capture unmodeled effects, then validate with held-out time windows/genotypes and orthogonal assays in addition to predictive metrics. This rubric—mechanistic bias vs. data regime, with tiered validation—helps non-specialists choose an appropriate framework for replication and cccDNA kinetics.

Complementary multiscale models connect intrahepatic HBV DNA/ccDNA kinetics to serum biomarkers (HBsAg, HBV DNA, HBcAg), with machine learning optimizing fits across large clinical datasets (42, 43). These frameworks can noninvasively estimate intrahepatic cccDNA trajectories, recapitulate the slow decline observed under nucleos(t)ide analog therapy, and reveal substantial inter-patient heterogeneity in cccDNA turnover—implicating host or viral determinants that AI can help identify through feature discovery (44).

Model-based sensitivity analyses converge on two dominant levers—cccDNA replenishment via capsid recycling and cccDNA decay—thereby defining tractable intervention points. By capturing high-order coupling, AI models convert these rankings into mechanism-driven experiments rather than purely descriptive fits.

Machine learning for HBV genomics and integration

The 3.2-kb HBV genome is highly diverse across 9–10 genotypes and myriad variants, with specific mutations shaping replication efficiency, immune escape, and oncogenic risk (25, 45–47). AI has been leveraged to extract mechanistic signals from these sequences. A leading example is deep learning for host-genome integration: an attention-based model (DeepHBV) trained on curated integration loci discriminates true sites from genomic background by local sequence context and auxiliary features (24). Incorporating repetitive elements and cancer epigenomic signals markedly boosts performance (AUC rising from ~0.64 with sequence alone to ~0.94 with full features), indicating that integration strongly favors particular chromatin states and repeat

architectures. Genome-wide deployment of the trained model nominates previously unreported hotspots, while attention weights highlight candidate sequence motifs (e.g., short direct repeats) that plausibly scaffold microhomology-mediated integration—mechanistic clues with direct relevance to HCC pathogenesis and surveillance.

Machine learning has likewise linked viral genomic variation to immune phase and control. Classifiers trained on whole-genome sequences from chronic infection cohorts separate immune-tolerant from immune-active HBeAg-positive cases with ~0.88 AUC, outperforming conventional markers by exploiting mutational and diversity features (48). These models “rediscover” canonical determinants—such as the precore stop codon (G1896A) and basal core promoter substitutions associated with HBeAg loss—while suggesting additional combinatorial signatures that modulate whether replication proceeds quietly or provokes immune attack, thereby framing testable hypotheses on epitope presentation, RNA structure, and transcriptional regulation.

Together, these approaches tighten genotype–phenotype links in HBV by exposing DNA-level determinants of integration and by associating specific mutational constellations with immunological state and treatment responsiveness.

AI and HBV host–virus interactions

HBV commandeers host processes throughout its cycle—NTCP-mediated entry, cccDNA maintenance, host-driven transcription, assembly, and egress—while regulators such as HBx remodel DDB1-dependent proteostasis, epigenetic control, and innate sensing (26, 27). AI now systematizes this landscape. Deep learning on omic datasets resolves host-response states and prioritizes dependency factors (28); integrative network models that fuse PPI maps with CRISPR screens consistently surface SMC5/6, proteasome function, calcium signaling, and chromatin modifiers governing cccDNA (29, 49, 50). Features extracted from infection transcriptomes implicate RNA modification machinery (e.g., m⁶A writers/readers) as pro-/antiviral regulators, subsequently validated by perturbation of HBV transcripts (51).

Immune interplay is similarly tractable. Neural models for T- and B-cell epitope prediction scan HBV proteins across genotypes to nominate peptides with high HLA class I/II presentation or antibody accessibility and to flag escape-associated substitutions in core or polymerase, complementing experimental evidence of CTL evasion and informing therapeutic immunogen design tuned to population HLA diversity (52). Single-cell and repertoire analyses aided by ML further delineate exhaustion phenotypes and cytokine programs associated with viral control versus persistence (30, 53).

Phenotypic readouts add orthogonal evidence. High-content microscopy combined with convolutional classifiers distinguishes infection stages from fluorescence signatures of viral markers, enabling automated assessment of entry, replication, nuclear core trafficking, assembly, and release; detected phenotypes (e.g., nuclear core accumulation) direct targeted biochemical studies (31, 54). Emerging computational pathology quantifies spatial relationships

between infected hepatocytes and immune infiltrates, linking microenvironmental architecture to immune containment or escape. Collectively, these AI-enabled approaches compress high-dimensional host–virus data into testable mechanisms and convergent pathways that HBV exploits, providing a rational basis for host-targeted antivirals and combination strategies that both restrict replication and restore antiviral immunity.

AI in antiviral discovery and therapeutics for HBV

AI is accelerating HBV therapeutic discovery by compressing hit identification and illuminating mechanisms of action. Ligand-based deep learning now predicts antiviral activity directly from molecular structure: a transformer–NN framework (HBCVTr) trained on curated HBV/HCV datasets outperformed traditional QSAR (55), enabled virtual screening of ~10⁷ compounds within days, and prioritized novel candidates with docking/MD consistent with core (capsid) protein engagement—thereby shifting brute-force screening toward mechanism-guided triage. Beyond triage, AI helps explain how small molecules perturb viral assemblies. Machine-learning analyses of molecular-dynamics ensembles of HBV core tetramers classify apo versus capsid assembly modulators (CAMs) and separate Class I (accelerating) from Class II (misdirecting) agents with high accuracy, while feature attribution localizes drug-specific “hotspots” on the capsid interface (56). These maps suggest Class I CAMs stabilize early inter-dimer geometries, whereas Class II CAMs induce non-native contacts—actionable insight for designing next-generation modulators and extensible to other targets (e.g., polymerase allostery).

Methodologically, reinforcement learning and knowledge-graph inference are being explored to optimize combination schedules and repurpose compounds that hit HBV dependencies (viral or host). Together, these approaches shorten the path from chemical space to validated leads and, crucially, couple predictive screening with mechanistic interpretability—a prerequisite for rational, multi-pronged regimens that target entry, capsid/replication, cccDNA control, secretion, and immune restoration.

Several AI-guided pipelines have progressed beyond *in silico* triage toward pre-clinical evaluation. A transformer-QSAR framework (HBCVTr) prioritized core-engaging chemotypes at multi-million-scale and proposed testable hits (e.g., “IJN-04”), establishing a tractable route from sequence-to-activity learning to wet-lab follow-up (55). Complementarily, recent virtual-screening campaigns against HBV core, augmented by ML-assisted docking/MD consensus, yielded novel capsid inhibitors that advanced to *in vitro* validation, demonstrating HBV replication suppression and acceptable drug-likeness/tox profiles in cell systems (57). While many capsid assembly modulators (CAMs) now in clinical trials were not originally discovered by AI, machine-learning analysis of MD ensembles has clarified their mechanisms—separating Class I (accelerating) from Class II (misdirecting) effects and localizing drug-specific inter-dimer “hotspots”—thereby informing next-generation scaffold design and resistance-risk

assessment (56, 58). In parallel, knowledge-graph and QSAR-driven repurposing workflows are maturing, with external validations reported in other viral settings and growing adoption in HBV pipelines to shortlist host/viral targets for bench testing (59, 60). Together, these examples illustrate a practical translation path: AI narrows chemical/target space, MoA-aware models de-risk leads, and cellular assays close the loop en route to animal studies and early clinical evaluation.

Discussion

Recent applications of AI to HBV research illustrate not merely algorithmic novelty but a changing epistemology for mechanistic virology. Where data are scarce, latent, or ethically difficult to obtain, AI has supplied principled surrogates: structural predictions that stand in for recalcitrant crystallography; physics-informed inference that exposes hidden state variables such as cccDNA; and representation learning that compresses high-dimensional host–virus measurements into tractable hypotheses (61–63). The value of these contributions is twofold. First, they expand the space of askable questions—e.g., what domain geometries of polymerase are compatible with protein priming, which genomic contexts are permissive for integration, or which host modules gate transitions between immune tolerance and activity. Second, they translate diffuse signals into experimentally testable statements, enabling a tighter discovery loop between computation and bench work.

A unifying theme is inductive bias: models that encode known virology or physics produce more credible inferences under limited data (64, 65). Physics-informed networks regularize learning with life-cycle constraints (e.g., mass balance, initial/boundary conditions), whereas neural ODEs learn flexible latent dynamics with minimal mechanistic priors; the former is preferable when trusted equations exist, the latter when trajectories are rich but priors are weak (66, 67). Practically, hybrid (“gray-box”) pipelines work well: couple sequence/structure priors with mutational or MD readouts, and augment ODE life-cycle models with a small learnable residual to capture unmodeled effects. This design supports counterfactual tests *in silico*, and keeps estimates aligned with biology. Applied to HBV, such constrained models consistently elevate the same high-leverage levers—nucleocapsid-mediated cccDNA replenishment and cccDNA loss/silencing—thereby focusing experimental prioritization.

A second practical theme is data governance and benchmarking. HBV datasets are fragmented across platforms (bulk and single-cell transcriptomics, proteomics, imaging, CRISPR perturbations), genotypes, and clinical contexts. Without harmonization, model generalizability and causal interpretability remain uncertain (68, 69). We recommend establishing: (i) genotype-stratified reference corpora with shared metadata and controlled vocabularies (infection system, MOI, time post-infection, readouts); (ii) multi-site challenge tasks with predefined splits for out-of-distribution testing (e.g., training on genotypes B/C, testing on A/D) to quantify portability; (iii) gold-standard targets for

cccDNA (paired biopsy/serology time series where available) to calibrate latent-state estimators; and (iv) standardized performance/uncertainty reporting (confidence intervals, calibration curves, decision-relevant metrics such as Net Benefit for triage use-cases).

Causality and perturbation should be foregrounded. Many current studies are associational—useful for hypothesis generation but limited for mechanism (70). HBV is unusually amenable to controlled perturbations (siRNA/CRISPR screens, inducible HBx, CAMs with well-defined MoAs). Embedding such interventional data within causal graphical frameworks and counterfactual learners would sharpen claims about necessity and sufficiency of host factors or viral processes. In practice, marrying pooled-CRISPR readouts with graph neural networks over protein–protein and chromatin contact maps can identify bottleneck nodes whose modulation produces large effects on replication or cccDNA transcription. Importantly, these models should propagate experimental interventions as exogenous “do” operators rather than observational covariates, enabling proper estimation of causal effects.

The spatial dimension of HBV pathobiology is underexploited and well matched to modern AI (71, 72). Spatial transcriptomics/pathology and high-content imaging can map the mesoscale organization of infected hepatocytes, stromal cells, and immune infiltrates. Learning on such data (e.g., attention-based multiple-instance models) can quantify how micro-anatomical niches modulate viral production, antigen presentation, and immune surveillance. Coupling spatial features to VINN-like latent-state models would connect tissue architecture to cccDNA kinetics—potentially explaining patient-to-patient variability in functional cure despite similar systemic exposures.

To be clinically consequential, uncertainty and interpretability must be first-class citizens. For structural models, confidence measures should guide experimental validation (e.g., targeted mutagenesis at low-confidence loops versus high-confidence catalytic motifs) (73). For kinetics and integration predictors, Bayesian or conformal methods can flag low-confidence regimes (rare genotypes, extreme biomarker values), preventing overconfident extrapolation (74, 75). Local attribution (e.g., attention maps in DeepHBV) should be complemented by global analyses (e.g., SHAP interaction values) to uncover non-linear epistasis or motif–chromatin interactions that drive integration. These practices convert “black-box” outputs into actionable priors for the lab.

A forward-leaning agenda should also embrace closed-loop, active learning. In HBV drug discovery, propose–test–update cycles can be formalized so that each experimental batch maximizes expected information gain about a mechanistic objective (e.g., capsid inter-dimer angle distributions, cccDNA transcriptional burst frequency). In host-factor discovery, adaptive CRISPR libraries can refine around emergent network bottlenecks. For immunology, generative models conditioned on HLA distributions and escape landscapes can design peptide sets that are prospectively screened in T-cell assays, with immunogenicity results feeding back into the generator. Across use-cases, this experiment-aware AI can make small datasets perform like large ones by choosing the right measurements (76).

Finally, ethics and dual-use considerations warrant explicit handling, particularly for generative models and high-resolution life-cycle simulators (77, 78). Mechanistic fidelity that empowers cure research could, in principle, be misapplied (79). Governance should include access controls for sensitive models/datasets, transparent model cards documenting training data and intended use, and pre-publication risk assessment. In parallel, privacy-preserving analytics (federated learning, secure aggregation) would allow multi-center HBV cohorts to contribute to robust models without exposing identifiable data—critical for assembling the scale necessary to answer genotype- and ancestry-specific questions. For biosecurity vetting, we align with DURC/P3CO oversight by incorporating pre-publication risk review and institutional vetting of models/datasets most likely to enable misuse, alongside access-controlled release, with model cards that document training data, intended use, and prohibited applications (80, 81). In parallel, upstream controls such as DNA/RNA synthesis customer and sequence screening (e.g., International Gene Synthesis Consortium harmonized protocol) and national measures that strengthen nucleic-acid synthesis procurement screening further reduce misuse pathways for sequence-generating or sequence-editing tools. For data governance, we recommend multi-center collaboration via privacy-preserving analytics—notably federated learning with secure aggregation—to train across institutions without centralized transfer of sensitive data (82), and adoption of GA4GH frameworks/standards (e.g., data-use governance and htsgat APIs) to enable auditable access, fine-grained consent, and interoperable sharing of virology datasets. Together, these measures allow the field to scale mechanism-aware AI for HBV while meeting contemporary expectations for biosecurity, privacy, and accountability.

Conclusions and future directions

Artificial intelligence is reshaping HBV mechanistic research by turning scarce, heterogeneous measurements into testable hypotheses about replication, cccDNA persistence, host dependencies, and immune escape. The most durable gains arise when models embed virological structure—physical constraints for proteins, life-cycle kinetics for within-host dynamics, and network priors for host–virus interactions—so that predictions remain biologically interpretable and experimentally actionable.

Future work should prioritize six directions. (i) Mechanism-aware modeling. Advance gray-box approaches that couple ODE/PDE life-cycle models and structural constraints with learnable residuals, enabling counterfactual *in silico* perturbations on processes such as capsid recycling and cccDNA silencing. (ii) Causal and interventional inference. Integrate CRISPR/perturb-seq and pharmacologic interventions into causal graphs and counterfactual learners to identify necessary and sufficient host dependencies, moving beyond association. (iii) Spatially resolved HBV biology. Fuse spatial transcriptomics/pathology and high-content imaging with latent-state models to connect microanatomy to cccDNA kinetics and immune containment. (iv) Uncertainty and interpretability. Pair Bayesian or conformal

calibration with global/local attribution (e.g., interaction-aware feature importance) to delineate confidence regimes, nominate mutation/epitope targets, and guide experimental validation. (v) Benchmarking and data governance. Establish genotype-stratified reference corpora, out-of-distribution challenges across cohorts and genotypes, and shared cccDNA “gold standards,” with standardized reporting of calibration and decision-relevant metrics. (vi) Closed-loop discovery. Use active learning in drug and target discovery—propose, test, and update—to maximize information gain per experiment; extend to immunogen design conditioned on HLA landscapes and escape pathways.

Attention to ethics and dual-use is essential. Access-controlled sharing, transparent model cards, and privacy-preserving analytics (e.g., federated learning) will enable multi-center models without compromising participant data. With these safeguards and priorities, AI can accelerate a shift from descriptive virology to predictive, intervention-ready mechanisms, bringing durable functional cure within closer reach.

Author contributions

YH: Conceptualization, Data curation, Formal Analysis, Methodology, Resources, Software, Validation, Visualization, Writing – original draft. WJ: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

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