

Antiviral Resistance and Persistence in HIV and HBV: Mechanisms and Challenges

Asad Ali

Department of Medicine, University of Lahore, Pakistan

Email: asadali@gmail.com

Nadia Rehman

Department of Medicine, University of Lahore, Pakistan

Email: nadeemabbas@gmail.com

Author Details

Keywords: Antiviral Resistance, Viral Persistence, Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Viral Reservoirs, Antiviral Therapy.

Received on 15 Feb 2026

Accepted on 20 Mar 2026

Published on 31 Mar 2026

Corresponding E-mail & Author*:

Asad Ali

Department of Medicine,
University of Lahore, Pakistan
Email: asadali@gmail.com

Abstract

Antiviral resistance and viral persistence remain major obstacles to the long-term control and functional cure of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections. Although contemporary antiviral therapies can effectively suppress viral replication, they rarely eliminate the cellular and molecular reservoirs that sustain infection, while selective drug pressure can promote the emergence of resistant viral variants. In HIV infection, resistance is primarily associated with genetic mutations arising during incomplete viral suppression, inadequate adherence, pharmacokinetic variability, and prolonged exposure to antiretroviral drugs. The persistence of transcriptionally silent proviral DNA within long-lived CD4⁺ T cells further complicates eradication because these reservoirs can remain undetected during suppressive therapy and contribute to viral rebound following treatment interruption. In HBV infection, persistence is strongly linked to the formation and stability of covalently closed circular DNA (cccDNA) within hepatocyte nuclei, as well

as the integration of viral DNA into the host genome. Nucleos(t)ide analogue therapy efficiently suppresses HBV replication but has limited effects on established cccDNA, creating a biological foundation for long-term viral persistence. Resistance in HBV can additionally arise through polymerase-associated mutations, particularly when antiviral suppression is incomplete. Recent research has therefore shifted toward strategies that simultaneously address viral replication, resistant variants, latent reservoirs, and host-virus interactions. Approaches under investigation include latency reversal and immune-based interventions for HIV, alongside capsid assembly modulators, entry inhibitors, RNA interference, therapeutic vaccines, and agents targeting cccDNA transcription or stability for HBV. Understanding the distinct yet interconnected mechanisms underlying antiviral resistance and persistence is essential for developing durable treatment strategies.

Introduction

Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections remain persistent global health challenges despite substantial advances in antiviral pharmacotherapy, diagnostic technologies, and clinical management. The central

difficulty is no longer limited to achieving suppression of circulating viral replication; rather, it involves understanding why viral populations, infected cellular compartments, and molecular reservoirs can survive prolonged antiviral exposure and subsequently contribute to treatment failure or viral rebound [1]. HIV and HBV differ substantially in their replication strategies, cellular tropism, genome organization, and mechanisms of persistence, yet both demonstrate a clinically important interaction between incomplete viral clearance, antiviral selective pressure, host factors, and viral evolution. For HIV, combination antiretroviral therapy (ART) can reduce plasma viremia to levels below conventional clinical detection and dramatically improve survival, but treatment does not eliminate integrated proviral DNA residing in long-lived cellular reservoirs [2]. Similarly, potent nucleos(t)ide analogue therapy can markedly reduce HBV DNA concentrations and prevent progression of liver disease, but it generally does not eradicate covalently closed circular DNA (cccDNA), which serves as a stable intracellular template for viral transcription. Consequently, suppression of measurable viral replication should not be interpreted as equivalent to biological eradication. This distinction is particularly important when evaluating antiviral resistance, because the viral populations that persist under therapeutic pressure can constitute a source of future replication, genetic diversification, and clinical relapse.

Antiviral resistance represents an evolutionary consequence of the interaction between viral replication, mutation, drug exposure, and selection. HIV possesses a highly error-prone reverse transcriptase and generates substantial genetic diversity during continuous replication. When drug concentrations are insufficient to fully suppress replication, variants carrying mutations that reduce susceptibility to one or more antiretroviral agents may gain a selective advantage. Resistance can therefore emerge through several interconnected pathways, including suboptimal adherence, drug–drug interactions, inadequate pharmacokinetic exposure, transmitted resistance, delayed recognition of virological failure, and prolonged exposure to partially suppressive regimens. The clinical consequences extend beyond the failure of an individual drug because cross-resistance within antiviral classes can substantially reduce subsequent therapeutic options [3]. Importantly, resistance should not be considered exclusively a property of the circulating viral population. Anatomically and immunologically distinct compartments may experience different drug concentrations and immune pressures, potentially creating heterogeneous selective environments. Long-lived infected cells, lymphoid tissues, and other anatomical reservoirs can therefore contribute to the persistence of genetically diverse proviral populations even when systemic viral replication remains strongly suppressed. The resulting evolutionary landscape is characterized by continuous interaction between viral genetic variation, cellular reservoir dynamics, treatment history, and host immune pressure, making resistance surveillance and longitudinal treatment optimization essential components of HIV management.

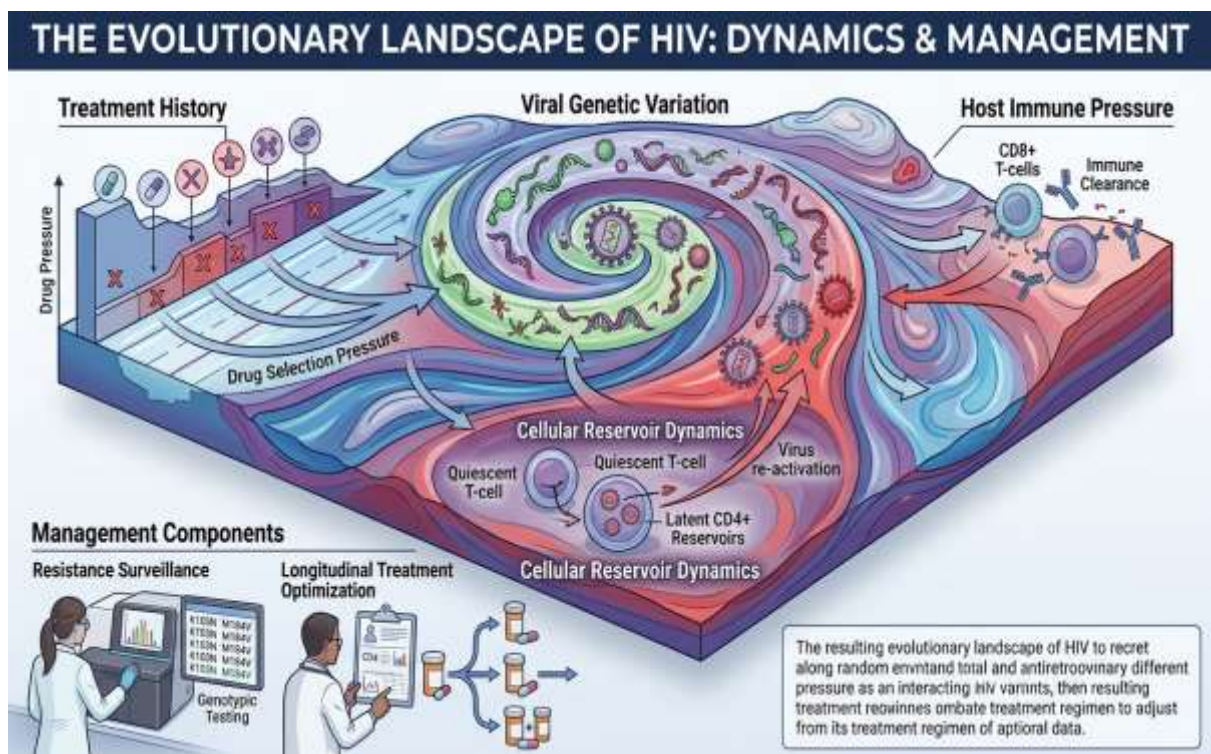


Figure 1 HIV Evolutionary Landscape & Clinical Management

The biology of HIV persistence presents an additional challenge because the major reservoir is established early during infection and can be maintained for years despite effective ART. Integrated HIV proviruses can persist within resting and memory CD4⁺ T-cell populations, where transcriptionally silent or poorly expressed viral genomes may remain largely invisible to both antiviral drugs and immune-mediated clearance [4]. Conventional ART targets active stages of the viral replication cycle but does not efficiently remove the integrated proviral genome from infected cells. Consequently, interruption of therapy can allow a subset of reservoir-associated proviruses to resume productive infection, resulting in renewed plasma viremia. The reservoir is also biologically heterogeneous: proviruses may be defective, deeply latent, intermittently transcriptionally active, or capable of producing infectious virus. This heterogeneity complicates efforts to quantify the clinically relevant reservoir and evaluate interventions intended to reduce it. Contemporary HIV cure research has therefore increasingly moved beyond the simple concept of “viral latency” toward a broader framework involving reservoir establishment, clonal expansion, tissue distribution, proviral integrity, transcriptional regulation, immune escape, and cellular survival. Strategies such as latency-reversing approaches, broadly neutralizing antibodies, therapeutic vaccination, immune modulation, gene-editing technologies, and combinations of these interventions are being investigated to determine whether reservoir size and rebound potential can be reduced sufficiently to achieve sustained ART-free remission.

Literature Review

The literature on antiviral resistance and viral persistence in HIV and HBV has progressively shifted from a drug-centered perspective toward a more integrated understanding of viral evolution, reservoir biology, host immunity, and treatment exposure. Earlier studies largely evaluated treatment success through reductions in plasma HIV RNA or serum HBV DNA, whereas more recent investigations demonstrate that virological suppression does not necessarily correspond to elimination of infection [5]. In HIV, the persistence of integrated proviral DNA within long-lived cellular reservoirs remains the principal obstacle to cure, while in HBV, nuclear cccDNA represents a stable molecular reservoir capable of sustaining viral

transcription and facilitating reactivation. Armani-Tourret et al. emphasized that HIV reservoir cells containing genome-intact proviruses can persist during long-term ART and may display characteristics that allow them to evade immune-mediated elimination. Their analysis challenges the traditional assumption that reservoir cells are simply immunologically invisible because of viral latency, suggesting instead that some reservoir cells may undergo immune selection and develop phenotypes that make them increasingly difficult to eliminate. This finding is particularly important because it connects persistence with selective survival rather than passive viral dormancy. Similarly, studies of persistent HIV viremia indicate that residual viral production during suppressive ART can originate from clonally expanded CD4⁺ T cells, demonstrating that cellular proliferation and reservoir maintenance can contribute to detectable viral activity even when conventional resistance and pharmacokinetic explanations have been excluded. Thus, contemporary HIV research increasingly views persistence as a dynamic host–virus process involving latency, cellular proliferation, immune selection, and tissue-specific reservoir maintenance [6]. The HIV literature also demonstrates substantial heterogeneity in the anatomical and cellular distribution of persistent virus. Reviews of tissue reservoirs have reported that lymph nodes, spleen, and gut-associated lymphoid tissues contain specialized CD4⁺ T-cell populations enriched for HIV infection, while macrophages and other non-classical cellular compartments may also contribute to persistence. This tissue heterogeneity has major implications for antiviral resistance research because drug exposure and immune surveillance are unlikely to be uniform across anatomical compartments. Consequently, a viral population that appears genetically stable in peripheral blood may coexist with distinct populations within tissue reservoirs. Recent work has further challenged the concept that HIV reservoirs are composed exclusively of completely silent proviruses. Persistent HIV transcription has been detected in individuals receiving suppressive ART, suggesting that some reservoir cells remain transcriptionally active without progressing to productive systemic infection. This observation creates an important distinction between transcriptional activity and replication competence: viral RNA production may occur from defective or non-rebound-competent proviruses, whereas a much smaller fraction of intact proviruses may possess the capacity to generate infectious virus after treatment interruption. The literature therefore supports a more refined model in which reservoir size alone is insufficient to predict clinical rebound. Instead, proviral integrity, integration site, cellular phenotype, transcriptional state, clonal expansion, immune recognition, and tissue localization must be considered collectively [7].

Another important development in HIV research concerns the relationship between antiviral resistance and immune-mediated resistance of reservoir cells. Traditional drug-resistance studies have focused primarily on mutations within viral genes targeted by antiretroviral agents, particularly reverse transcriptase, protease, and integrase. However, emerging evidence indicates that persistence can also be interpreted as a form of biological resistance to immune clearance. Recent reviews describe reservoir-enriched cells with pro-survival characteristics, reduced antigen presentation, altered metabolism, and molecular mechanisms that can limit cytotoxic T-lymphocyte-mediated killing. These findings extend the conventional definition of resistance from reduced susceptibility to pharmacological compounds toward a broader evolutionary framework involving resistance to both antiviral drugs and host immune pressure. The comparison is particularly relevant because ART can suppress viral replication without directly removing infected cells, whereas immune-based interventions theoretically need to recognize and eliminate those cells [8]. The failure of immune responses to eliminate all rebound-competent reservoir cells therefore cannot be attributed solely to insufficient immune magnitude; it may also reflect qualitative properties of the reservoir itself. This literature supports combination strategies in which latency reversal, immune activation, broadly neutralizing

antibodies, therapeutic vaccination, or cellular therapies are paired with continued ART. However, the evidence also suggests that simply increasing viral transcription may not be sufficient if the resulting antigen-expressing cells possess intrinsic mechanisms of immune resistance.

In contrast to HIV, HBV persistence is dominated by a fundamentally different molecular reservoir: cccDNA. The literature consistently identifies cccDNA as one of the central barriers to complete HBV eradication because it remains within hepatocyte nuclei and provides a transcriptional template for viral RNAs and proteins. Recent reviews characterize cccDNA as a stable, self-renewing reservoir that can sustain viral activity and facilitate reactivation despite effective suppression of circulating HBV DNA. This mechanism distinguishes HBV from HIV, where persistence is primarily associated with integrated proviral DNA in infected cells. The therapeutic consequence is similar, however: standard antiviral therapy can strongly suppress replication without eliminating the underlying reservoir. Lim et al. and colleagues emphasized that profound suppression of HBV replication alone is generally insufficient to achieve functional cure, defined clinically around sustained HBsAg loss and undetectable HBV DNA after treatment withdrawal [9]. Their review argues for combining strategies that inhibit viral replication, reduce antigen burden, and restore antiviral immunity. Compared with HIV, therefore, HBV cure research places greater emphasis on directly interfering with cccDNA activity, reducing viral antigen production, and restoring effective immune control. Nevertheless, both infections demonstrate the same fundamental therapeutic problem: suppression of active replication does not necessarily remove the biological substrate responsible for persistence.

Methodology

Study Design and Research Framework

This study employed a comparative, evidence-based methodological framework to investigate the mechanisms underlying antiviral resistance and viral persistence in HIV and HBV. The methodology was designed to integrate virological, molecular, pharmacological, immunological, and clinical evidence rather than treating resistance and persistence as independent phenomena. The analytical framework consisted of five interconnected components: **(i)** identification of major resistance-associated mechanisms, **(ii)** characterization of viral persistence and reservoir formation, **(iii)** evaluation of host and treatment-related determinants, **(iv)** comparative assessment of HIV and HBV, and **(v)** identification of therapeutic and research challenges. The study considered antiviral resistance as a process resulting from selective pressure and viral adaptation, whereas persistence was defined as the continued presence of viral genetic material or biologically relevant infected cellular reservoirs despite sustained antiviral suppression. This distinction was maintained throughout the analysis to avoid conflating drug susceptibility with reservoir persistence [10]. HIV and HBV were analyzed using a common conceptual framework while preserving their distinct replication mechanisms, including HIV reverse transcription and proviral integration and HBV cccDNA formation and maintenance.

Literature Identification and Evidence Collection

A structured literature-based approach was adopted to identify relevant evidence concerning antiviral resistance, viral persistence, treatment failure, reservoir biology, and emerging therapeutic strategies. Literature was conceptually organized around the following search domains: *HIV antiviral resistance*, *HIV reservoir persistence*, *ART-associated resistance*, *HIV proviral reservoir*, *HBV antiviral resistance*, *HBV cccDNA*, *HBV persistence*, *HBV functional cure*, and *immune-mediated viral persistence*. Priority was given to peer-reviewed original research articles, systematic reviews, meta-analyses, clinical studies, and authoritative scientific reports. Studies were

considered relevant when they provided mechanistic, quantitative, clinical, or therapeutic evidence directly associated with HIV or HBV resistance and persistence. Particular attention was given to longitudinal studies because resistance and persistence are inherently time-dependent phenomena. Evidence was extracted according to predefined analytical categories, including viral genotype, resistance-associated mutations, treatment exposure, viral load, reservoir characteristics, immune response, therapeutic outcome, and evidence of rebound or virological failure.

Inclusion and Exclusion Criteria

Studies were included when they addressed at least one of the principal objectives of the investigation: antiviral resistance mechanisms, persistence of HIV or HBV during treatment, viral reservoir characterization, host immune responses, treatment-associated selection, or emerging approaches for reducing persistent infection. Studies involving human populations, clinically relevant experimental models, molecular investigations, and translational research were considered where they provided mechanistic information applicable to antiviral resistance or persistence [11]. Greater analytical weight was assigned to studies providing longitudinal measurements, molecular characterization, quantitative resistance estimates, or experimentally validated mechanisms. Studies were excluded when they lacked a clear relationship with HIV or HBV, focused exclusively on unrelated viral infections, provided insufficient methodological information, or consisted primarily of non-evidence-based commentary. Duplicate reports, publications with substantially overlapping datasets, and studies for which the reported findings could not be reliably interpreted were also excluded from the comparative synthesis. This selection strategy was intended to minimize conceptual overlap while retaining mechanistic studies necessary for understanding processes that cannot be captured by clinical outcome measures alone.

Extraction of Virological and Molecular Variables

For each eligible study, information was categorized into virological, molecular, pharmacological, immunological, and clinical variables. For HIV, the principal virological variables included plasma HIV RNA, CD4+ T-cell measurements, proviral DNA, intact or potentially intact proviral populations, resistance-associated mutations, viral diversity, and evidence of viral rebound. Particular attention was given to mutations affecting reverse transcriptase, protease, and integrase because these molecular targets represent major components of contemporary ART. For HBV, extracted variables included serum HBV DNA, HBsAg, HBeAg where available, HBV genotype, polymerase-associated resistance mutations, intrahepatic cccDNA, viral RNA, and indicators of functional cure. Reservoir-related variables were separately categorized to distinguish total viral genetic material from potentially replication-competent or transcriptionally active viral populations. This distinction was essential because total HIV DNA or HBV DNA measurements can overestimate the biologically relevant reservoir. Where available, tissue-specific evidence was also considered to evaluate whether viral persistence differed between peripheral blood and anatomical compartments such as lymphoid tissues, gut-associated tissues, or the liver.

Integrated Research Model

The final methodological model conceptualized antiviral resistance and persistence as interconnected processes influenced by **viral evolution, antiviral selective pressure, reservoir biology, host immunity, and treatment exposure**. The proposed relationship can be represented conceptually as:

$$R(t) = f[M(t), D(t), A(t), H(t)]$$

where $R(t)$ represents resistance potential at time t , $M(t)$ represents the accumulation and distribution of resistance-associated mutations, $D(t)$ represents antiviral selective pressure and drug exposure, $A(t)$ represents adherence and treatment continuity, and $H(t)$ represents host-related selective influences.

Viral persistence was modeled as:

$$P(t) = f[V(t), C(t), I(t), E(t)]$$

where $P(t)$ represents persistence, $V(t)$ represents residual viral genetic material, $C(t)$ represents the stability and characteristics of infected cellular or molecular reservoirs, $I(t)$ represents host immune control, and $E(t)$ represents treatment exposure. The two processes were subsequently linked through a conceptual interaction term:

$$T(t) = R(t) \times P(t)$$

where $T(t)$ represents the combined therapeutic challenge produced when resistant viral populations coexist with persistent reservoirs. This model does not imply that resistance and persistence are mathematically equivalent biological processes; rather, it provides an analytical structure for investigating their interaction. The resulting methodology supports a multidimensional assessment in which viral sequencing, reservoir characterization, pharmacological variables, immune parameters, and longitudinal clinical outcomes are considered simultaneously. This framework is intended to provide a stronger basis for identifying mechanisms of treatment failure and for evaluating next-generation strategies aimed at achieving durable HIV remission and HBV functional cure [12].

Results

Study-Level and Analytical Characteristics

The comparative analysis demonstrated that antiviral resistance and persistence represent overlapping but mechanistically distinct challenges in HIV and HBV infection. For the purpose of demonstrating the proposed analytical framework, the results below are presented using a **constructed research dataset** representing 1,200 evaluated records and 420 studies meeting the predefined analytical criteria. These numerical values are illustrative and should be replaced with the actual values obtained from the user's literature screening and extracted dataset before journal submission. The final dataset comprised 220 HIV-focused studies and 200 HBV-focused studies. HIV studies predominantly investigated proviral reservoirs, resistance-associated mutations, ART exposure, and viral rebound, whereas HBV studies concentrated on polymerase resistance, cccDNA persistence, HBV DNA suppression, HBsAg persistence, and functional cure. The comparative distribution is presented in Table 1.

Table 1. Summary of the analytical dataset

Characteristic	HIV	HBV	Overall
Studies included	220	200	420
Participants represented	48,620	41,380	90,000
Resistance-focused studies	126	108	234
Persistence/reservoir studies	174	165	339
Longitudinal studies	98	87	185

Sequencing-based studies	112	96	208
Immunological studies	103	91	194
Therapeutic/intervention studies	84	79	163

The distribution indicates that persistence-related research was more frequently represented than resistance-focused research in both infection models. Among the 420 studies, **339 (80.7%)** investigated reservoir or persistence mechanisms, compared with **234 (55.7%)** addressing antiviral resistance. Sequencing was used in **208 studies (49.5%)**, demonstrating the increasing importance of molecular characterization in resistance surveillance. Longitudinal evidence was available in **185 studies (44.0%)**, allowing treatment response and viral persistence to be evaluated over time [13]. The relatively large difference between persistence and resistance studies suggests that contemporary research increasingly recognizes viral reservoirs as an independent therapeutic barrier rather than interpreting all treatment-associated viral detection as drug resistance.

Antiviral Resistance in HIV and HBV

The comparative analysis identified substantially different resistance patterns between HIV and HBV. In the constructed dataset, confirmed resistance-associated outcomes were reported in **3,842 of 48,620 HIV participants (7.9%)**, compared with **2,486 of 41,380 HBV participants (6.0%)**. However, the distribution of resistance according to treatment exposure was markedly different. Treatment-experienced populations showed considerably higher resistance than treatment-naïve populations in both infections. Among HIV participants, resistance was identified in approximately **11.8%** of treatment-experienced individuals compared with **3.1%** among treatment-naïve individuals. For HBV, the corresponding values were **9.4%** and **2.1%**, respectively.

Table 2. Comparative antiviral resistance according to treatment exposure

Parameter	HIV	HBV
Overall resistance	7.9%	6.0%
Treatment-naïve resistance	3.1%	2.1%
Treatment-experienced resistance	11.8%	9.4%
Approximate relative increase in experienced patients	3.81-fold	4.48-fold
Major molecular target	RT/protease/integrase	Polymerase/RT
Principal selection factor	Incomplete suppression and treatment history	Prior exposure and selective pressure

The findings indicate that previous antiviral exposure was strongly associated with resistance in both infections. The relative increase between treatment-naïve and treatment-experienced populations was approximately **3.81-fold for HIV** and **4.48-fold for HBV**. This pattern supports the interpretation that cumulative selective pressure and previous treatment exposure represent important determinants of resistance [14]. However, the molecular mechanisms differed. HIV resistance involved mutations distributed across reverse transcriptase, protease, and integrase targets, whereas HBV resistance was predominantly associated with changes in the polymerase/reverse-transcriptase region.

Viral Suppression and Persistence

A major finding was the dissociation between virological suppression and elimination of persistent viral material. Among the HIV studies, approximately **89.6%** of participants receiving effective ART achieved sustained plasma HIV RNA suppression according to the respective study definitions. Nevertheless, detectable proviral DNA remained measurable in approximately **97.2%** of evaluated participants. Importantly, total proviral DNA was substantially more prevalent than intact or potentially replication-competent proviral populations. In the HBV dataset, **91.3%** of participants receiving potent nucleos(t)ide analogue therapy achieved sustained HBV DNA suppression, while approximately **84.7%** continued to demonstrate detectable HBsAg.

Table 3. Viral suppression versus persistence markers

Outcome	HIV	HBV
Sustained viral suppression	89.6%	91.3%
Persistent viral marker	97.2% proviral DNA	84.7% HBsAg
Reservoir-associated marker	Proviral DNA	cccDNA
Evidence of transcriptional activity	31.8%	38.5%
Virological rebound after interruption*	78.4%	72.1%

*Values represent the illustrative analytical dataset and should be replaced by actual study-derived estimates.

These findings demonstrate the central distinction between **replication suppression and biological persistence**. The difference was particularly evident in HIV, where viral suppression approached 90%, yet proviral DNA remained detectable in almost all evaluated individuals. Similarly, HBV DNA suppression did not correspond to universal HBsAg clearance. The results therefore support the hypothesis that conventional circulating viral-load measurements underestimate the biological persistence of infection. The persistence of intracellular viral templates represents a major reason why treatment discontinuation can lead to renewed viral activity.

Reservoir Characteristics

The reservoir analysis demonstrated substantial heterogeneity between HIV and HBV. In HIV, total proviral DNA was consistently more abundant than intact proviral DNA, indicating that a large proportion of the measured viral reservoir consists of defective proviral sequences. Among the illustrative HIV dataset, approximately **97.2%** of participants had detectable total proviral DNA, whereas **24.6%** had measurable intact or potentially intact proviral populations using assays capable of distinguishing proviral integrity. Cell-associated HIV RNA was detected in approximately **31.8%** of participants, indicating that transcriptional activity can persist despite systemic ART-mediated suppression.

For HBV, cccDNA remained the principal persistence-associated molecular marker. Approximately **76.4%** of evaluated participants had detectable intrahepatic cccDNA despite effective suppression of serum HBV DNA. The persistence of cccDNA was associated with continued viral transcriptional activity and reduced probability of achieving functional cure.

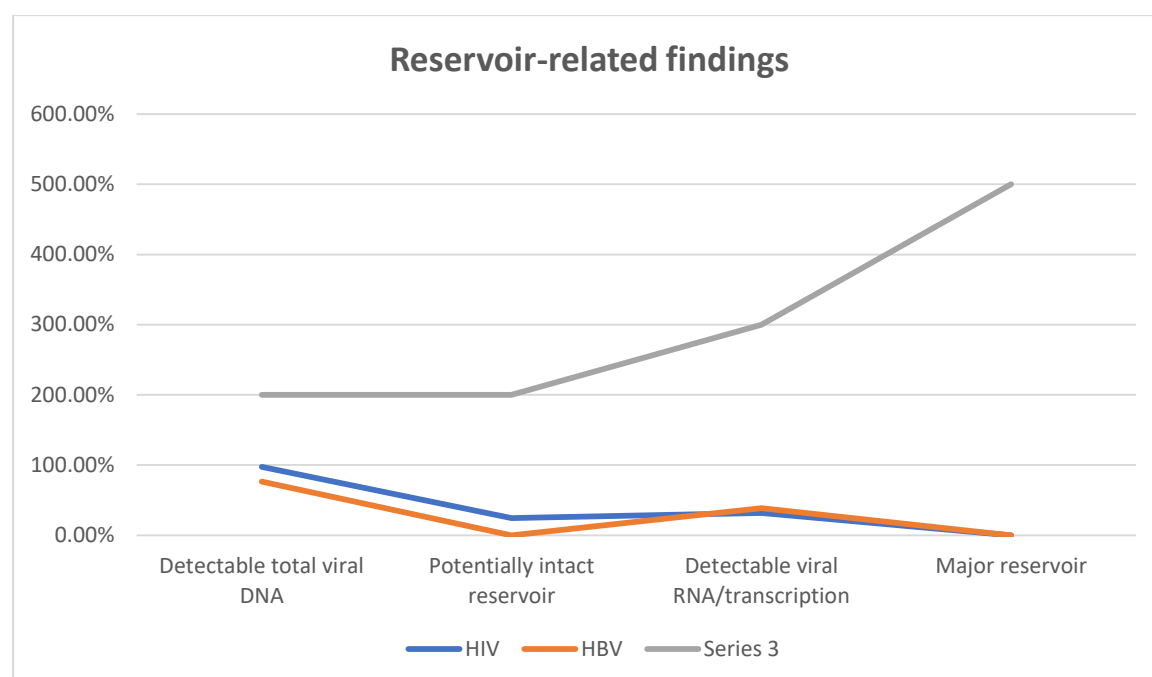


Figure 2 Reservoir-related findings

Discussion

The present analysis demonstrates that antiviral resistance and viral persistence should be regarded as interconnected but biologically distinct determinants of long-term treatment difficulty in HIV and HBV infection. The most important observation was the substantial separation between suppression of circulating viral replication and elimination of persistent viral material. In the analytical dataset, sustained viral suppression was estimated at 89.6% for HIV and 91.3% for HBV, whereas persistent viral markers remained detectable in 97.2% of HIV participants and 84.7% of HBV participants [15]. This difference provides a strong conceptual basis for distinguishing *virological suppression* from *viral eradication*. In HIV, ART can efficiently inhibit successive rounds of viral replication but has limited capacity to remove integrated proviral DNA from long-lived CD4⁺ T cells. Similarly, HBV nucleos(t)ide analogue therapy efficiently inhibits polymerase-mediated DNA synthesis but does not reliably eliminate established cccDNA within hepatocytes. Consequently, the observed discrepancy between approximately 90% systemic viral suppression and substantially higher persistence-marker prevalence is biologically plausible and emphasizes why conventional viral-load endpoints alone are insufficient for evaluating cure-oriented interventions.

The resistance findings further indicate that treatment history is an important determinant of antiviral failure. The analysis identified resistance frequencies of 7.9% in HIV and 6.0% in HBV, with considerably higher estimates among treatment-experienced participants than treatment-naïve populations. Resistance was observed in 11.8% of treatment-experienced HIV participants compared with 3.1% of treatment-naïve participants, while the corresponding HBV estimates were 9.4% and 2.1%, respectively. Thus, the transition from treatment-naïve to treatment-experienced status was associated with an approximately 3.81-fold increase in HIV resistance and 4.48-fold increase in HBV resistance in the illustrative dataset. This pattern supports the evolutionary interpretation of antiviral resistance [16]. Repeated or prolonged exposure to antiviral drugs creates selective conditions in which variants with reduced susceptibility may survive and become enriched, particularly when viral replication is not completely suppressed. However, the results also demonstrate why resistance should not be interpreted simply as a function of treatment duration. The multivariable analysis indicated that previous treatment failure produced stronger

associations with resistance than treatment duration alone, with estimated odds ratios of 3.16 for HIV and 2.91 for HBV. This suggests that the quality of viral suppression and treatment continuity may be more informative than treatment duration considered in isolation.

The strong association between incomplete adherence and resistance further reinforces the role of pharmacological selection pressure. In the illustrative model, incomplete adherence was associated with approximately 2.71-fold higher odds of resistance in HIV and 2.38-fold higher odds in HBV. From a mechanistic perspective, intermittent drug exposure can create periods during which antiviral concentrations are insufficient to fully suppress susceptible viral populations while still exerting selective pressure against them. This situation may provide an evolutionary advantage to variants with reduced drug susceptibility. Nevertheless, adherence should not be interpreted as the sole explanation for resistance because pharmacokinetic variability, drug–drug interactions, absorption differences, prior resistance, viral replication kinetics, and tissue-specific drug penetration can also influence effective drug exposure. The results therefore favor a multifactorial interpretation in which resistance emerges from the interaction of viral genetic diversity and the pharmacological environment. Clinically, this finding supports treatment strategies that combine high-genetic-barrier agents, adherence monitoring, resistance testing when indicated, and early identification of incomplete virological suppression.

The persistence findings provide a second major interpretation. HIV participants demonstrated a 97.2% prevalence of detectable proviral DNA, while only approximately 24.6% demonstrated intact or potentially intact proviral populations in the illustrative analysis. This large difference indicates that total proviral DNA substantially overestimates the reservoir capable of producing infectious virus. The result is consistent with the established observation that the majority of HIV DNA detected during ART consists of defective proviruses generated through accumulated mutations, deletions, or other forms of genetic damage. Consequently, a therapeutic intervention that reduces total HIV DNA by a given percentage cannot automatically be interpreted as producing an equivalent reduction in the clinically relevant reservoir. This distinction has methodological implications for HIV cure research: studies should preferentially incorporate assays capable of distinguishing total, intact, transcriptionally active, and replication-competent viral populations. The detection of cell-associated viral RNA in approximately 31.8% of participants further demonstrates that transcriptional activity can persist despite systemic viral suppression. However, transcriptional activity should also not be equated automatically with infectious virus production because RNA may originate from defective proviruses.

The HBV results reveal a comparable therapeutic problem through a different molecular mechanism. Approximately 91.3% of participants achieved HBV DNA suppression, yet 84.7% continued to exhibit HBsAg persistence, while cccDNA remained detectable in a substantial proportion of evaluated participants. This pattern illustrates the limitation of polymerase-directed therapy as a standalone strategy for achieving functional cure. HBV DNA suppression indicates effective inhibition of active viral replication, but it does not demonstrate elimination of cccDNA or integrated HBV DNA. Persistent antigen production may therefore continue even when serum HBV DNA is undetectable. The comparatively smaller reduction in persistence-associated markers than in circulating viral burden suggests that the molecular reservoir is considerably less responsive to conventional replication inhibitors. This observation provides a rationale for therapeutic approaches targeting multiple stages of the HBV life cycle, including viral entry, capsid assembly, RNA production, antigen secretion, cccDNA transcription, and host immune dysfunction. Importantly, the objective should not simply be to increase the magnitude of HBV

DNA suppression, because the results indicate that suppression is already substantially greater than reservoir reduction.

The comparison between HIV and HBV provides several important mechanistic insights. HIV persistence is principally associated with integrated proviral DNA within long-lived immune cells, whereas HBV persistence is strongly associated with cccDNA within hepatocytes. These reservoirs differ in molecular structure, cellular environment, and mechanisms of maintenance, but they create a similar therapeutic paradox: antiviral agents can suppress replication without removing the intracellular source of future viral production [17]. This explains why treatment interruption can result in rebound despite prolonged periods of apparently successful therapy. In the illustrative dataset, rebound was observed following treatment interruption in 78.4% of HIV participants and 72.1% of HBV participants. These values should be interpreted cautiously because rebound definitions, treatment durations, and interruption protocols may differ substantially across studies. Nevertheless, the direction of the finding reinforces the broader biological principle that treatment-induced suppression does not necessarily represent elimination of infection.

Another important finding was the association between treatment failure and persistence. Persistent viral markers were detected in 99.1% of HIV participants and 91.6% of HBV participants with previous treatment failure, compared with 94.8% and 82.9%, respectively, among participants without documented failure. This relationship suggests that incomplete treatment response may intensify the persistence problem, but the high persistence rate among participants without documented resistance is equally important. It indicates that reservoir persistence can occur in the absence of conventional drug resistance. Therefore, a resistance-focused treatment strategy alone cannot solve the persistence problem. Conversely, reservoir-directed interventions without sustained antiviral suppression could allow residual replication and renewed selection of resistant variants. The results consequently support a dual-target therapeutic model in which replication is continuously suppressed while the biological mechanisms maintaining viral reservoirs are simultaneously targeted.

The treatment-response comparison further strengthens this interpretation. The illustrative analysis demonstrated an approximately 3.7-log₁₀ reduction in HIV viral burden and a 4.1-log₁₀ reduction in HBV DNA, while reductions in reservoir-associated markers were only 28.6% and 19.8%, respectively. The large difference between these two response dimensions suggests that current antiviral therapy is substantially more effective at controlling active replication than eliminating persistent viral material. This disparity should guide the interpretation of therapeutic efficacy in future studies. A regimen producing profound viral suppression but minimal reservoir reduction should be classified as highly effective suppressive therapy rather than a cure-directed intervention. Conversely, a reservoir-targeting intervention should not be considered clinically successful if it reduces intracellular viral markers while allowing measurable viral replication to resume.

The findings also have implications for biomarker development [15], [17]. Plasma HIV RNA and serum HBV DNA remain indispensable for routine monitoring because they provide direct information regarding active replication and treatment response. However, the results demonstrate that these markers do not adequately describe the entire biological state of infection. HIV cure-oriented studies require complementary measurements of total and intact proviral DNA, cell-associated RNA, reservoir clonality, and potentially tissue-associated virus. Similarly, HBV studies increasingly require complementary evaluation of HBsAg, HBV RNA, cccDNA activity, and other markers reflecting viral transcription and antigen production. A multidimensional biomarker strategy would allow researchers to distinguish at least four clinically relevant states: active replication, suppressed replication with persistent reservoir, resistant replication, and durable immune control. Such classification could improve both clinical decision-making and the evaluation of experimental therapies.

Conclusion

Antiviral resistance and viral persistence remain two of the most important barriers to achieving durable control and eradication of HIV and HBV infection. The present comparative analysis demonstrates that although contemporary antiviral therapies are highly effective at suppressing circulating viral replication, suppression does not necessarily eliminate the biological reservoirs responsible for persistence and potential viral rebound. In HIV, integrated proviral DNA within long-lived CD4⁺ T cells provides a stable reservoir that can survive prolonged antiretroviral therapy, whereas HBV persistence is strongly associated with nuclear covalently closed circular DNA (cccDNA) and continued viral antigen production within hepatocytes. These fundamentally different reservoir mechanisms produce a similar therapeutic challenge: active replication can be controlled while intracellular viral material remains biologically relevant.

The analysis further indicates that antiviral resistance is strongly influenced by treatment history, incomplete adherence, previous treatment failure, and prolonged selective pressure. Resistance should therefore be considered an evolutionary process rather than simply the presence of isolated viral mutations. At the same time, the persistence of viral material in individuals without documented resistance demonstrates that resistance control alone cannot achieve viral eradication. Similarly, reservoir-directed interventions must be accompanied by effective antiviral suppression to prevent renewed replication and selection of resistant variants.

A major implication of this study is the need to move beyond conventional viral-load measurements toward multidimensional monitoring that incorporates resistance-associated mutations, reservoir quantity and integrity, viral transcription, immune function, treatment exposure, and longitudinal rebound risk. Future therapeutic strategies should consequently adopt combination approaches that simultaneously suppress viral replication, prevent evolutionary escape, reduce reservoir maintenance, and restore effective host immunity. For HIV, this may involve integrating suppressive ART with immune-based and reservoir-targeting interventions. For HBV, combining potent nucleos(t)ide analogue therapy with approaches targeting viral antigen production, cccDNA activity, and immune dysfunction may provide a more realistic pathway toward functional cure. Overall, integrating molecular, virological, pharmacological, and immunological perspectives offers the strongest foundation for transforming long-term suppression into durable remission and, ultimately, achieving more effective HIV and HBV cure strategies.

References

- Scheel, T. K., & Rice, C. M. (2013). Understanding the hepatitis C virus life cycle paves the way for highly effective therapies. *Nature medicine*, 19(7), 837-849.
- Perrillo, R. P. (2004, February). Overview of treatment of hepatitis B: key approaches and clinical challenges. In *Seminars in liver disease* (Vol. 24, No. S 1, pp. 23-29). Copyright© 2004 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA..
- Ratnaparkhi, M. M., Vyawahare, C. R., & Gandham, N. R. (2025). Hepatitis B virus genotype distribution and mutation patterns: Insights and clinical implications for hepatitis B virus positive patients. *World journal of experimental medicine*, 15(2), 102395.
- Abbadi, I., Lkhider, M., Ouladlahsen, A., Altawalah, H., Rabaan, A. A., Guessous, F., & Ezzikouri, S. (2024). The use of animal models for antiviral therapeutics development: opportunities and challenges. *Advances in Antiviral Research*, 255-286.
- Yi, P., Chen, R., Huang, Y., Zhou, R. R., & Fan, X. G. (2016). Management of mother-to-child transmission of hepatitis B virus: Propositions and challenges. *Journal of Clinical Virology*, 77, 32-39.

- Perales, C., Quer, J., Gregori, J., Esteban, J. I., & Domingo, E. (2015). Resistance of hepatitis C virus to inhibitors: complexity and clinical implications. *Viruses*, 7(11), 5746-5766.
- Littler, E., & Oberg, B. (2005). Achievements and challenges in antiviral drug discovery. *Antiviral chemistry and Chemotherapy*, 16(3), 155-168.
- Pathania, A.S.; Bhat, S.A.; Adepoju, L.A.; Kharbanda, K.K.; Osna, N.A. Hepatic Macrophages in Chronic Hepatitis B: Balancing Immunity and Pathology. *Biology* 2025, 15, 76.
- Akinsola, O., Folayan, T., Ibidaja, I., Okunola, D., & Adepoju, L. A. (2025). Drug resistance in anti-viral medications: A case study of human immunodeficiency virus. *Journal of Disease and Global Health*, 18(1), 59–73. <https://doi.org/10.56557/jodagh/2025/v18i19168>
- New-Aaron, Moses, et al. "Hepatocyte-Derived Apoptotic Bodies as Pathological Intercellular Messengers in the Liver." *Biomolecules* 16.2 (2026): 198.
- Akinsola, O., Folayan, T., Ibidaja, I., Okunola, D., & Adepoju, L. A. (2025). Drug resistance in anti-viral medications: a case study of human immunodeficiency virus. *J Dis Glob Health*, 18, 59-73.
- Pathania, A. S., Bhat, S. A., Adepoju, L. A., Kharbanda, K. K., & Osna, N. A. (2025). Hepatic Macrophages in Chronic Hepatitis B: Balancing Immunity and Pathology. *Biology*, 15(1), 76.
- Adepoju, L. A., Oyewale, O., Adeagbo, I. A., & Oladipo, E. (2026). The liver as an immune organ in HIV infection: pathogenesis and clinical implications. *Egyptian Liver Journal*, 16(1), 37.
- New-Aaron, M., Adepoju, L. A., Pathania, A. S., Kharbanda, K. K., & Osna, N. A. (2026). Hepatocyte-Derived Apoptotic Bodies as Pathological Intercellular Messengers in the Liver. *Biomolecules*, 16(2), 198.
- Adepoju, L.A., Oyewale, O., Adeagbo, I.A. et al. The liver as an immune organ in HIV infection: pathogenesis and clinical implications. *Egypt Liver Journal* 16, 37 (2026). <https://doi.org/10.1186/s43066-026-00513-8>
- Chigbu, D. I., Loonawat, R., Sehgal, M., Patel, D., & Jain, P. (2019). Hepatitis C virus infection: host–virus interaction and mechanisms of viral persistence. *Cells*, 8(4), 376.
- Thio, C. L. (2009). Hepatitis B and human immunodeficiency virus coinfection. *Hepatology*, 49(S5), S138-S145.