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Review article

Evolution of HBV antiviral resistance: A threat to current therapeutic strategies

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ABSTRACT

Background: Hepatitis B virus (HBV) continues to be a significant global health issue, impacting millions of people around the globe. Although antiviral medications have greatly enhanced the treatment of chronic HBV infection, the development of antiviral resistance presents a difficult obstacle to current therapeutic approaches. This review analyses the progression of antiviral resistance in HBV, providing insight into the underlying mechanisms and consequences for clinical treatment. The use of nucleos(t)ide analogues (NAs) and interferon-based therapy represented important achievements in the management of chronic HBV infection. Nevertheless, the extended utilization of nucleoside analogues (NAs), such as lamivudine, entecavir, and tenofovir, has been linked to the emergence of resistance mutations in the gene responsible for viral polymerase. These modifications provide the virus with a specific benefit, which reduces the effectiveness of antiviral drugs and requires changes in treatment. Moreover, the presence of both wild-type and drug-resistant strains inside the same patient exacerbates the complexity of treatment outcomes. The emergence of HBV antiviral resistance highlights the significance of diligent surveillance and prompt intervention to enhance treatment results and presents a substantial risk to current therapeutic approaches. Continued research endeavours to comprehend the genetic and molecular foundation of resistance, together with the creation of innovative antiviral substances, are crucial to tackle this problem and improve the long-term control of chronic HBV infection.

Introduction

Hepatitis B Virus (HBV) infection is a significant worldwide health problem, affecting millions of people and causing a significant amount of illness and death [1].

Hepatitis B is a viral infection that can lead to chronic disease, including serious complications such as cirrhosis, hepatocellular cancer, and liver failure. The significant extent of its occurrence and the seriousness of its related sequelae emphasize the utmost significance of understanding the complex aspects of HBV infection for efficient disease control [2].

HBV, classified as a bloodborne pathogen, primarily spreads through percutaneous or mucosal exposure to contaminated blood or other bodily fluids [2]. The virus exhibits a unique ability to persist within the host, establishing chronic infections that may last for years, if not a lifetime. This proclivity for persistence contributes to the development of long-term complications and significantly elevates the global disease burden [1].

Chronic HBV infection manifests in distinct phases, each characterized by intricate interactions between the virus and the host immune system [3]. The chronicity of the infection is a key

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factor contributing to the progression of liver diseases, necessitating a nuanced understanding of the dynamic interplay between the virus and the host [3,4]. Considering its profound impact on public health, initiatives aimed at effective disease management necessitate a comprehensive grasp of the underlying pathophysiology and the complexities involved in HBV infection [5].

Therapeutic interventions are crucial in reducing the effects of chronic HBV infection [6]. These interventions, such as nucleos(t)ide analogues (NAs) and interferons, are used to suppress viral replication, reduce liver inflammation, and slow down the progression of the disease [6,7]. The evolution of these therapeutic approaches mirrors the ongoing effort to combat the global health challenge posed by HBV [8].

Understanding the complexities of HBV infection, how it spreads, and the potential consequences for affected individuals is crucial for developing effective strategies to prevent the disease, diagnose it early, and manage it optimally [9]. This basic knowledge forms the foundation for a thorough examination of different aspects of HBV infection, ranging from the significance of antiviral therapies to the emerging challenges posed by antiviral resistance [10]. Such insights are fundamental to the pursuit of improved public health outcomes and the development of innovative approaches in the ongoing battle against the global impact of HBV.

The aim of this study is to present the evolution of HBV antiviral resistance and its implication treatments of HBV and its associated complications.

Literature search and data collection

Three electronic databases (Google Scholar, Scopus, and PubMed) were carefully searched for literatures relating to the subject matter, key search terms such as “hepatitis B” “resistance” “mutation” “drugs” “treatment” where search in singular units and in combinations using Boolean parameters (AND/OR) as deemed appropriate. The summary of the literature search process is represented in figure 1.

Overview of hepatitis B Virus (HBV) Infection as a global health concern

Hepatitis B is a major public health issue with approximately 296 million people living with chronic HBV infection globally [11]. The World Health Organization (WHO) estimates that HBV-related complications result in nearly 887,000 deaths annually, making it a leading cause of liver-related mortality [12]. The virus exhibits a diverse geographic distribution, with varying prevalence rates across different regions. While some areas, such as sub-Saharan Africa and parts of Asia, experience high endemicity, others, including North America and Western Europe, exhibit lower prevalence [12].

HBV infection poses a complex and multifaceted challenge due to its ability to establish persistent infections, leading to long-term complications. The virus primarily targets hepatocytes, where it undergoes replication, and its persistence is associated with complex interactions between the virus and the host immune system [13]. The natural history of HBV infection involves distinct phases, including acute infection, chronic infection, immune tolerance, immune clearance, and, in some cases, reactivation [14].

Significance of antiviral therapies in managing chronic HBV infection

Antiviral medications are crucial in the treatment of chronic HBV infection, with the goal of inhibiting viral replication, decreasing liver inflammation, and halting the advancement of the disease. The prognosis for persons with chronic HBV has greatly improved over time due to the advancement of antiviral medications [15–17]. Two main classes of antiviral drugs are commonly used: nucleos(t)ide analogs (NAs) and interferons [18].

Nucleos(t)ide analogs, such as lamivudine, entecavir, and tenofovir, target the viral polymerase and inhibit reverse transcription, thereby impeding viral replication [19]. Interferons, on the other hand, exert their antiviral effects through modulation of the host immune response [19]. These therapies aim to achieve sustained virological suppression, leading to improved clinical outcomes, prevention of liver-related complications, and, ideally, a functional cure [20].

Emerging challenge of antiviral resistance

Antiviral therapies, while effective, have led to a significant problem: antiviral resistance [21]. This occurs when the virus mutates and becomes less susceptible or completely resistant to the effects of antiviral drugs [10]. This phenomenon poses a formidable obstacle to the long-term success of chronic HBV management.

The occurrence of resistance is specifically linked to the utilisation of nucleoside analogues

(NAs), with extensively recorded instances of resistance to medications like lamivudine, adefovir, and entecavir. Resistance mutations frequently occur in the YMDD motif of the viral polymerase gene, which is highly conserved [22]. This compromises the effectiveness of treatment. The presence of drug-resistant strains in patients is concerning because it can lead to treatment failure, disease progression, and the possibility of transmitting resistant variants [23].

Therefore, the management of chronic HBV infection necessitates ongoing surveillance for the establishment of antiviral resistance [24]. Clinicians must navigate the delicate balance between achieving virological suppression and avoiding the emergence of drug resistance. This challenge underscores the need for ongoing research efforts to understand the genetic and molecular basis of resistance, along with the development of novel antiviral agents to address this evolving threat.

Historical perspective on antiviral therapies

Introduction of nucleos(t)ide analogs (NAs) and interferon-based therapies

The progression of antiviral treatments for Hepatitis B Virus (HBV) has experienced notable advancements, particularly with the implementation of nucleos(t)ide analogues (NAs) and interferon-based therapies, which have played pivotal roles in the control of chronic HBV infection [19].

1. Nucleos(t)ide analogues (NAs):

The advent of NAs revolutionized the treatment landscape for chronic HBV. Lamivudine, adefovir, entecavir, telbivudine, and tenofovir are among the key NAs employed in the management of HBV [25]. Lamivudine, the first oral antiviral approved for HBV in 1998, demonstrated efficacy in suppressing viral replication. However, the emergence of resistance prompted the development of newer generations of NAs, including entecavir and tenofovir, which exhibited improved resistance profiles and enhanced antiviral potency [25]. These drugs function by inhibiting the viral polymerase, impeding the reverse transcription process critical for viral replication [26]. The structure of the nucleos(t)ide analogues and the dosage is represented in figure 2 and table 1 respectively.

2. Interferon-based therapies:

Interferons, which are a component of the innate immune system, have also had a crucial impact on HBV therapy. Interferon-alpha, the primary interferon used in HBV management, elicits antiviral effects by modulating host immune responses [27]. Its approval in the 1980s marked a significant milestone, offering an alternative to the oral antiviral agents [28]. Interferon-based therapies, while effective, have limitations such as variable response rates, side effects, and the need for parenteral administration .

Milestones and limitations in the advancement of antiviral agents for hepatitis B virus (HBV)

1. Milestones:

Entecavir and tenofovir: Entecavir, introduced in the early 2000s, exhibited strong antiviral effects and a high level of resistance to genetic changes. Tenofovir, available in oral formulations, further expanded the therapeutic arsenal against HBV[29]. These drugs, belonging to the class of nucleotide analogs, have been essential in the management of chronic HBV due to their effectiveness and resistance profiles.

Secondly, the development of antivirals with improved resistance profiles addressed a longstanding challenge [30]. Specifically, drugs like entecavir and tenofovir have shown a decreased likelihood of resistance compared to previous medications, hence improving their long-term efficacy.

Interferon lambda, a type III interferon, is being investigated as a potential therapy for HBV [31]. Recent breakthroughs in this field have shown promising results, indicating a more favourable side effect profile and increased tolerance.

2. Limitations:

a.Antiviral resistance: Despite advancements, the emergence of resistance remains a significant concern. Prolonged use of NAs, especially older agents like lamivudine, can result in the emergence of resistance mutations. This highlights the need for vigilant surveillance and modifications in treatment approaches [32].

b. Side effects and tolerability: Interferon-based therapies are linked to adverse effects such as flu-like symptoms, depression, and hematological abnormalities [33]. These limitations impact patient adherence and overall treatment outcomes.

c. Challenges in achieving a cure: Achieving a functional cure, which is maintaining virological suppression without therapy, is still a difficult problem [34]. While current therapies can control viral replication, a complete eradication of the virus is elusive.

The historical evolution of antiviral therapies for HBV reflects a trajectory from interferon-based treatments to the development of NAs with improved efficacy and resistance profiles. While significant progress has been made, challenges such as antiviral resistance and the quest for a cure underscore the ongoing need for research and innovation in the field of HBV therapeutics.

Mechanisms of HBV antiviral resistance

Dynamics of HBV replication and reverse transcriptase activity

Hepatitis B virus (HBV) replication is a complicated process that is closely connected to the function of its reverse transcriptase enzyme [35]. HBV is a virus with partially double-stranded DNA that undergoes reverse transcription inside the liver cells of the host [36]. The reverse transcriptase enzyme, which is produced by the viral polymerase gene, is essential in converting the viral pregenomic RNA into viral DNA. This conversion takes place within the nucleocapsid, resulting in the formation of the viral DNA genome, which is then integrated into the genome of the host cell [37–39]. Figure 3 illustrates the replicative cascade of the HBV virus.

The replication of HBV is affected by the error-prone characteristics of the reverse transcriptase enzyme, which does not possess proofreading skills. The natural tendency of viruses to have low accuracy during replication leads to the creation of a wide range of viral quasispecies within the host. The virus's high mutation rate enables it to quickly adjust to selection pressures, such as the existence of antiviral medications, resulting in the development of resistant forms.

Key mutations within the viral polymerase gene, with focus on the YMDD motif

The development of resistance to antiviral drugs in individuals with chronic HBV infection is frequently associated with mutations in the viral polymerase gene. Of particular interest is the YMDD motif found in the catalytic domain of the reverse transcriptase enzyme [40]. The YMDD motif plays a crucial role in the interaction with nucleos(t)ide analogues (NAs), which are a type of medicines frequently employed to hinder HBV replication. Antiviral drugs, such as lamivudine, entecavir, and telbivudine, specifically act on the YMDD motif to interfere with the replication of viral DNA. This disruption inhibits the production of viral DNA [23]. The region of the YMDD motif is illustrated in figure 4.

The occurrence of mutations linked with resistance in the YMDD motif is extensively described. Frequent instances of lamivudine resistance involve the substitution of methionine (M) with either leucine (L) or isoleucine (I) in the YMDD sequence. This leads to the well-known mutations YMDD-to-YIDD or YMDD-to-YVDD [40]. These mutations compromise the binding efficacy of NAs, rendering them less effective in inhibiting HBV replication.

Factors influencing the choice and long-term existence of resistant variants

Several factors contribute to the selection and persistence of HBV variants with resistance to antiviral drugs. Prolonged exposure to antiviral therapy is a major factor, providing a selective pressure that favors the survival of mutants with reduced drug susceptibility. Non-compliance with medication regimens or suboptimal drug concentrations in the bloodstream can also contribute to the emergence of resistance [41].

The rapid rate at which HBV replicates and the quick turnover of viral particles generate an environment that is favourable for the emergence and selection of resistant genotypes. Moreover, the simultaneous presence of both wild-type and drug-resistant strains inside individual patients is a frequent occurrence, which makes treatment options more complex [42]. This phenomenon is particularly pronounced in chronic HBV infections, where long-term therapy is often required.

Host factors, such as the individual's immune condition, may also influence the persistence of resistant variants [43]. Immune selection pressure may further drive the evolution of drug-resistant strains, as the immune system exerts selective forces on the viral population.

The mechanisms of HBV antiviral resistance involve the dynamic interplay between the error-prone replication of the virus, specific mutations within the viral polymerase gene, and various factors influencing the selection and persistence of resistant variants. Gaining a comprehensive understanding of these mechanisms is essential for the development of efficient therapeutic methods and addressing the difficulties presented by the rise of drug-resistant HBV strains [44].

Progression of resistance to nucleos(t)ide analogue therapies

Lamivudine and the emergence of resistance

Lamivudine, a nucleoside analogue, was one of the initial antiviral treatments used for chronic hepatitis B (CHB). Although lamivudine is initially effective, prolonged use of this antiviral drug has been linked to the development of resistance mutations in the HBV polymerase gene, specifically in the YMDD motif [40]. This emergence of lamivudine-resistant strains presents a significant clinical obstacle, as it undermines the long-term effectiveness of the drug.

Lamivudine resistance is mainly caused by the replacement of leucine (L) or isoleucine (I) with methionine (M) at position 204 in the YMDD motif [23]. This mutation prevents lamivudine from binding to the viral polymerase, leading to a decrease in its antiviral effectiveness [23]. Research has demonstrated that the likelihood of developing lamivudine resistance rises as the duration of treatment extends, reaching a maximum of 70% after five years of therapy [40].

Entecavir and Tenofovir: Resistance patterns and implications

Entecavir and tenofovir, both nucleos(t)ide analogs, represent advancements in HBV antiviral therapy. However, their use is not without challenges, as prolonged treatment may lead to the emergence of resistance. Resistance to entecavir typically arises through mutations in the viral polymerase gene, including substitutions at positions T184, S202, and M204 [45]. Studies have reported that entecavir resistance is less common than that observed with lamivudine, occurring in approximately 1-2% of patients after five years of treatment [46].

Tenofovir, particularly tenofovir disoproxil fumarate (TDF), has shown a strong ability to prevent the development of resistance. However, long-term administration may still result in resistance, albeit at lower frequencies compared to lamivudine [47]. Resistance to tenofovir is often associated with amino acid substitutions at positions A194T and N236T in the HBV polymerase [48].

Coexistence of wild-type and drug-resistant strains in patients

One notable challenge in the evolution of antiviral resistance is the coexistence of wild-type and drug-resistant strains within the same patient [49]. This phenomenon can complicate treatment decisions and contribute to treatment failure. In patients undergoing prolonged antiviral therapy, viral replication may persist despite the emergence of drug-resistant variants [10,50].

The presence of both wild-type and drug-resistant strains is extensively described in the context of lamivudine therapy. Research has indicated that even after the emergence of resistance to lamivudine, the original form of the virus may still exist in different amounts within the patient's viral population [51]. This coexistence raises questions about the optimal management strategies, including potential treatment modifications and the implications for long-term clinical outcomes.

Understanding the dynamics of coexisting wild-type and drug-resistant strains is essential for tailoring therapeutic interventions. Regular monitoring of viral populations, utilizing sensitive molecular assays, is crucial for identifying changes in the viral quasispecies and guiding clinical decisions [52].

Interferon-based therapies and resistance

Overview of interferon-based treatments for HBV

Interferon-based medicines have played a crucial role in the treatment of chronic Hepatitis B virus (HBV) infection. Interferons, particularly pegylated interferon-alpha (peg-IFN-α), have proven effective in suppressing HBV replication and stimulating immunomodulatory responses, making them a viable alternative to nucleos(t)ide analogues (NAs) [53]. Peg-IFN-α is administered over a finite duration, typically ranging from 48 to 96 weeks, offering a distinct advantage over the continuous, long-term administration required with NAs [54]. The therapeutic goal of interferon-based treatments is to achieve sustained virological response (SVR), characterized by undetectable HBV DNA levels and normalization of liver enzymes.

Challenges and limitations in interferon therapy

Despite the promising features of interferon-based therapies, several challenges and limitations hinder their widespread use. One significant challenge is the adverse effects associated with interferon treatment, including flu-like symptoms, depression, and hematological abnormalities [55]. These side effects can lead to treatment discontinuation, compromising patient adherence and overall efficacy.

Moreover, the variable response rates observed with interferon therapy pose a limitation.

Response rates are impacted by factors such as HBV genotype, baseline viral load, and host factors, which complicates the prediction of treatment outcomes [56]. This variability underscores the need for personalized treatment approaches and highlights the importance of identifying predictive factors for treatment response.

Lesser propensity for resistance compared to NAs

One notable advantage of interferon-based therapies is their lesser propensity for inducing antiviral resistance compared to NAs. Unlike NAs, which directly target the viral polymerase, interferons exert their antiviral effects through immunomodulation and direct inhibition of viral replication [48,57,58]. This multifaceted mechanism makes it more challenging for the virus to develop resistance.

The resistance observed with interferon therapy is typically associated with host factors and viral evasion mechanisms rather than the emergence of specific resistance mutations [59,60]. This reduced likelihood of resistance is a crucial factor in considering interferon-based treatments, especially in cases where long-term viral suppression is desirable.

Interferon-based therapies provide a distinct method for managing chronic HBV infection. They have the benefit of a limited treatment period and a reduced chance of causing antiviral resistance compared to NAs. Nevertheless, the difficulties presented by adverse reactions and inconsistent reaction rates require thoughtful examination and personalised treatment approaches. Current research is continuously improving our comprehension of the mechanisms that underlie interferon therapy and its promise in achieving long-term virological responses [61,62].

Clinical implications and management strategies

Impact of antiviral resistance on treatment outcomes

The occurrence of antiviral resistance in the setting of Hepatitis B Virus (HBV) infection has a substantial impact on treatment results, presenting obstacles to the effectiveness of antiviral therapy. Antiviral resistance can undermine the virological response, causing ongoing viral replication, heightened likelihood of liver disease advancement, and reduced rates of sustained virological response [63]. This has significant consequences for the long-term treatment of chronic HBV infection and can lead to clinical complications like liver cirrhosis and hepatocellular carcinoma [64].

Antiviral-resistant strains exhibit reduced susceptibility to the effects of nucleos(t)ide analogs (NAs) and interferon-based therapies, limiting the effectiveness of these treatment modalities [47]. For instance, lamivudine, one of the initial NAs employed for HBV treatment, has been hindered in its effectiveness due to the emergence of resistant variants. This has resulted in virological breakthroughs and disease progression in certain patients [65].

Monitoring strategies for early detection of resistance

Timely detection of antiviral resistance is crucial for informing treatment decisions and optimizing clinical outcomes. Regular monitoring of viral load and genotypic analysis are essential components of monitoring strategies. Quantitative polymerase chain reaction (PCR) techniques provide the quantification of viral load, which helps in the early detection of virological breakthroughs and the possible emergence of resistant strains [66].

Genotypic analysis involves sequencing the viral genome to identify specific mutations associated with antiviral resistance. This method provides insights into the genetic changes within the HBV polymerase gene, especially in the YMDD motif, which is critical for detecting resistance to NAs [67]. High-throughput sequencing technologies have enhanced the sensitivity and accuracy of genotypic analysis, enabling the identification of low-frequency resistant variants that may go undetected with conventional sequencing methods [68].

Therapeutic adjustments and optimization of treatment regimens

Therapeutic modifications are necessary to preserve the effectiveness of treatment considering the identification of antiviral resistance [69]. Clinicians frequently require adjustments to the current treatment plan, either by transitioning to alternative antiviral agents that have a greater resistance threshold or by combining multiple agents with complementary resistance profiles [69]. For example, tenofovir, a powerful nucleoside analogue with a high resistance threshold, is often utilised as a rescue therapy for individuals who have developed resistance to other nucleoside analogues [70].

Therapeutic optimization may also involve the consideration of alternative treatment modalities, such as interferon-based therapies. Interferon-based treatments, although associated with lower rates of resistance, are characterized by challenges such as variable response rates and limited tolerability [30]. The choice of therapeutic adjustments is guided by a comprehensive understanding of the patient's virological and clinical profile, as well as the genetic characteristics of the resistant strains.

The impact of antiviral resistance on treatment outcomes in chronic HBV infection necessitates vigilant monitoring and proactive therapeutic adjustments. Regular viral load monitoring and genotypic analysis are integral components of monitoring strategies, enabling the early detection of resistance [71]. Therapeutic adjustments involve the optimization of treatment regimens, considering alternative antiviral agents and treatment modalities to overcome the challenges posed by resistance. These management strategies aim to achieve sustained virological response, mitigate disease progression, and improve long-term clinical outcomes in individuals with chronic HBV infection [72].

Ongoing research and future directions

Present knowledge regarding the genetic and molecular factors that contribute to resistance

Molecular virology and genomics studies have greatly enhanced our knowledge of the genetic and molecular mechanisms underlying resistance to Hepatitis B virus (HBV). Studies have revealed important mutations in the viral polymerase gene, specifically in the YMDD motif, that make the virus resistant to nucleos(t)ide analogues (NAs) like lamivudine, entecavir, and tenofovir [73]. The HBV genome's ability to change over time, along with the error-prone behaviour of its reverse transcriptase, leads to the survival and prevalence of these resistant forms [74,75].

Genomic studies have identified specific resistance-associated mutations, such as rtM204V/I, rtL180M, and rtA181T/V, which are crucial in understanding the molecular basis of resistance to NAs [76]. Furthermore, advancements in next-generation sequencing technologies have enabled a more comprehensive analysis of the entire HBV genome, shedding light on additional regions that may play a role in antiviral resistance [77].

Advancement of innovative antiviral compounds and therapeutic strategies.

Exploring new antiviral medicines and therapeutic strategies is a viable way to tackle the problem of HBV antiviral resistance. Scientists are investigating novel drug targets in the life cycle of the HBV virus, including viral entry, replication, and assembly. Their goal is to discover compounds that are more effective and less likely to develop resistance [78]. For instance, compounds targeting viral entry receptors or interfering with viral assembly may provide alternative strategies to combat HBV.

The findings of Bello et al (2023) reveal that there are variation in the treatment patterns of HBV in relation to the varying genotypes [79]. The severity of HBV is dependent on the HBV genotypes.

Progress in the field of medicinal chemistry and drug design has made it possible to develop new antiviral drugs that have better characteristics in terms of how they are absorbed, distributed, metabolised, and excreted in the body, as well as how they interact with their target. Preclinical and clinical evaluations are currently being conducted on small molecules and peptides that target different stages of the HBV life cycle [80]. Additionally, host-targeted therapies are being explored to manipulate cellular factors involved in HBV replication, which opens further possibilities for therapeutic advancements [81,82].

Challenges and opportunities in the pursuit of an HBV cure

Developing a treatment for HBV is hindered by various obstacles, mainly because of the distinctive characteristics of the HBV life cycle and the presence of covalently closed circular DNA (cccDNA) in infected liver cells. Although there are powerful antiviral drugs available, it is still difficult to achieve a functional cure, which is defined as a sustained virological response without medication [83]. A significant obstacle lies in the elimination of cccDNA, which acts as the blueprint for viral transcription and replication. Efforts to eliminate cccDNA are currently in the initial phases of development, focusing on the investigation of gene-editing techniques like CRISPR/Cas9 to directly target and disrupt cccDNA [84,85]. However, off-target effects and delivery challenges need to be

addressed before these approaches can progress to clinical applications.

Opportunities for a cure lie in the continued advancement of immunotherapeutic approaches. Therapeutic vaccines and immune modulators that enhance the host's immune response against HBV-infected cells are actively under investigation. Additionally, combination therapies incorporating antiviral agents, immune modulators, and direct-acting antivirals are being explored to achieve more robust and sustained responses [86].

To summarize, the continuous investigation into the genetic and molecular foundation of resistance, the creation of innovative antiviral substances, and the quest for a cure for HBV offer both difficulties and possibilities. Understanding resistance mechanisms is important for informing treatment methods. However, the development of novel therapies and combination treatments shows potential for obtaining better and longer-lasting outcomes in managing chronic HBV infection.

Table1. Oral nucleos(t)ide analogues for the treatment of chronic hepatitis B

Drugs	Dosage	Antiviral activity	Drug resistance	Specific side effects	Pregnancy category
Lamivudine	100 mg daily	Low	70% in 5 y	Negligible	C
Adefovir dipivoxil	10 mg daily	Low	29% in 5 y	Nephrotoxicity, hypophosphatemia	C
Entecavir	0.5 mg daily	High	1.2% in 5 y	Negligible	C
Telbivudine	600 mg daily	High	30% in 3 y	Myopathy	B
Tenofovir disoproxilfumarate	300 mg daily	High	0% in 5 y	Nephrotoxicity, hypophosphatemia, bone loss	B

Figure 1. Summary of the data retrieval process

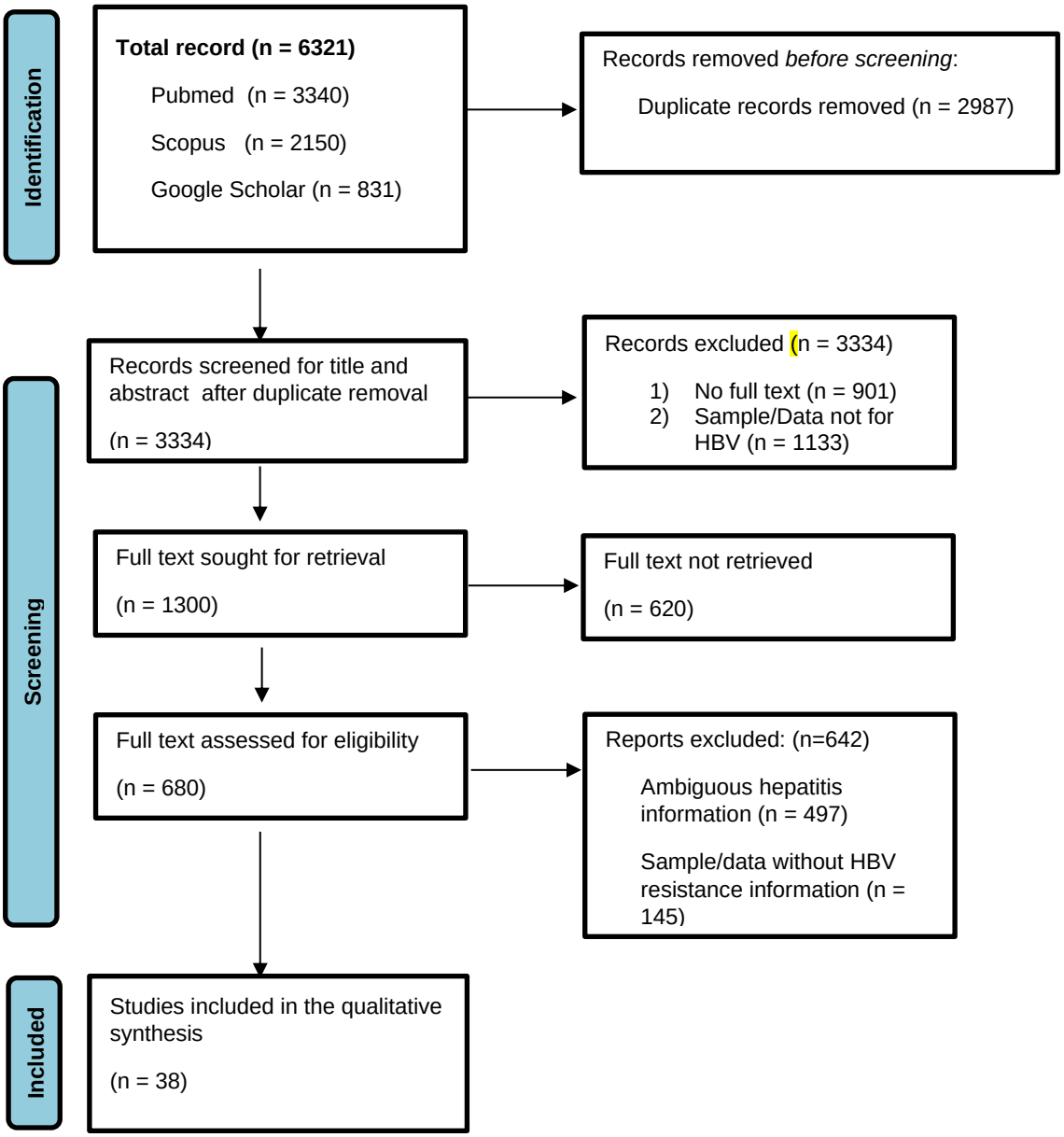


Figure 2. Structures of nucleos(t)ide-based drugs for the treatment of HBV infections.

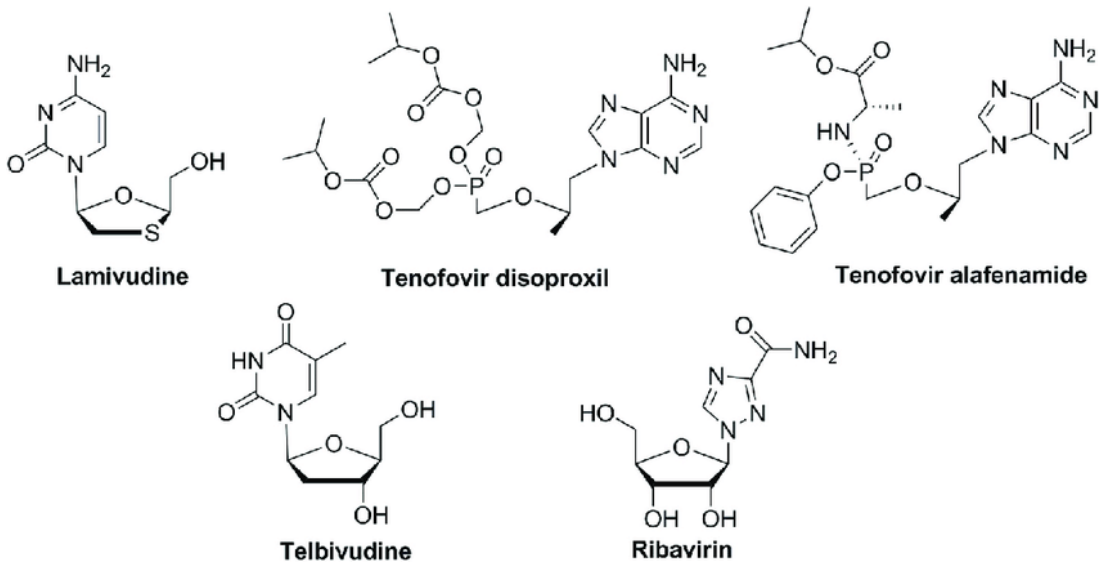


Figure 3. The HBV replication cycle. HBV replicates by reverse transcription in the cytoplasm of infected hepatocytes.

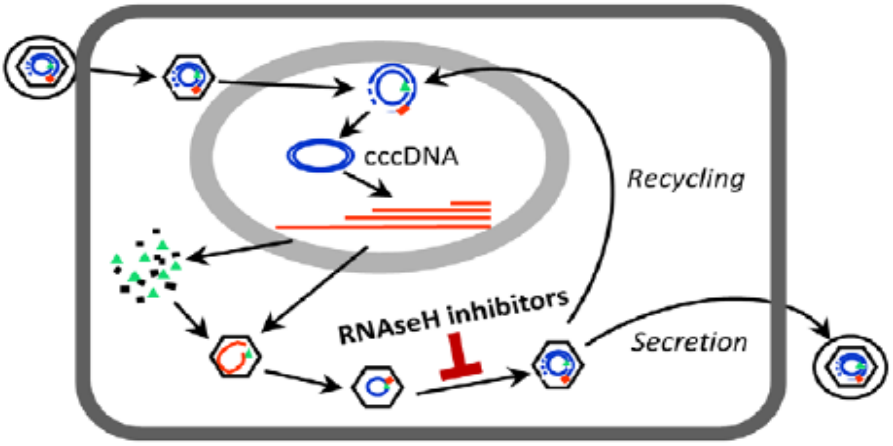
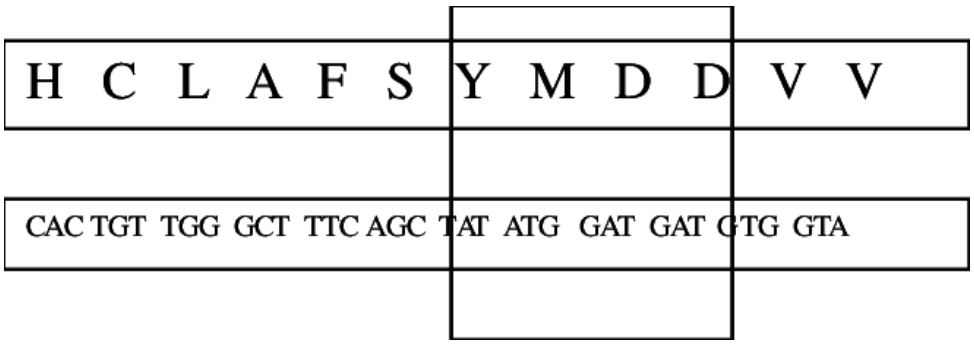


Figure 4. Reverse Transcriptase of hepatitis B virus with YMDD motif demonstrated.



Conclusion

The development of resistance to antiviral treatments for Hepatitis B Virus (HBV) is a result of a complicated interaction between the dynamics of the virus, elements within the host, and the specific pressure applied by the antiviral medicines. The recapitulation of the evolution of HBV antiviral resistance emphasizes the intricate challenges posed by the virus. Ongoing research and vigilant clinical management are crucial to staying ahead of emerging resistance patterns. Prospects hold promises for transformative advancements, paving the way for more effective and personalized strategies in the fight against HBV antiviral resistance.

Ethical declarations

There is no ethical issue.

Authors contributions

ASAM and KEB conceived and designed and the flow of the study, YAN, ASAM and KEB drafted the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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