Repurposing Drugs for Viral Hepatitis Using Artificial Intelligence

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ABSTRACT

Hepatitis refers to the inflammation of the liver caused by viruses and non-infectious agents leading to severe liver damage and cancer, eventually leading to death. There are 5 strains: A, B, C, D and E. Globally, HBV is the most widespread chronic variant and is the leading cause of death globally, resulting in an estimated 820,000 deaths per year. Regionally (Acute cases in North India), HEV was the most prevalent identifiable cause for in 26% of the cases. Lastly, the most severe clinical form would be; HDV co-infection which mostly occurs in people already infected with HBV. While new drugs are being discovered through extensive research and experiments, it is possible to repurpose existing drugs to a new target shaving off significant time duration. This article reviews a plethora of scientific articles regarding this repurposing of already existing drugs to treat hepatitis through AI. Artificial Intelligence is ubiquitous and used across the entire spectrum of viral hepatitis management as it improves diagnostic speed and accuracy by identifying complex patterns in large datasets that include serological, genomic and imaging data. Modern repurposing relies on two primary systematic approaches: High-throughput experimental screening and In Silico approaches. The latter makes use of Machine Learning, Molecular docking and Network Pharmacology and the results has been promising.

Keywords: Viral hepatitis; Hepatitis B virus (HBV); Hepatitis C virus (HCV); Drug repurposing; Artificial intelligence; Machine learning; Molecular docking; Network pharmacology; In silico drug discovery.

INTRODUCTION

1.1. Global burden of Viral Hepatitis

Hepatitis generally refers to Liver inflammation caused either from infectious causes or non-infectious causes. Not all hepatitis cases are caused due to viruses, as other causes include autoimmune Hepatitis where the body's own immune system attacks liver cells and last but not the least; there's drug -induced hepatitis too[1]. However, according to WHO[2], Data from around 187 countries showed that viral hepatitis was considered a major public health challenge affecting more than 300 million people globally [2]. Each day, around 3500 people die from liver disease caused by Viral Hepatitis [2]. In the year 2022 alone, an estimated 1.3 million people died from chronic viral hepatitis B and C and around 1.2million people were newly infected with the Hepatitis B virus. Hepatitis A and E infections usually spread when a person consumes food or water contaminated by an infected person's stool while Hepatitis B, C and D typically spread through contact with infected person's blood and other bodily fluids[1]. Also, people may be diagnosed with certain forms of hepatitis by consuming undercooked meat or consuming water contaminated with stool of an infected animal. While Hepatitis A and E typically cause acute infections only, other Hepatitis variants (B, C & D) can cause both acute and chronic infections which can

eventually lead to liver cirrhosis and liver cancer [1]. The common symptoms associated with Hepatitis are Fever, Fatigue, Loss of appetite, Abdominal pain, dark urine, clay-coloured bowel movements and jaundice [3,4]. The dangerous thing is that people with chronic infection may not even be aware of the infection until many years later while acute infections are usually symptomatic in nature.[5]

Table 1: Therapeutic Target Classes and Their Biological Rationale for AI-Based Drug Repurposing in Viral Hepatitis

Target Class	Type of Hepatitis	Rationale	Reference
Viral Enzymes (Polymerases)	Hepatitis C	The NS5B RNA-dependent RNA polymerase is a critical target for curative direct-acting antiviral regimens, as it directly inhibits viral genome replication.	[6], [7]
Viral Enzymes (Polymerases)	Hepatitis E	The HEV RNA-dependent RNA polymerase is targeted by repurposed agents that have demonstrated antiviral activity against HEV in laboratory studies.	[6]
Viral Enzymes (Proteases)	Hepatitis C	NS3/4A protease inhibitors prevent cleavage of the viral polyprotein into functional proteins required for viral replication and assembly.	[6]
Non-structural Viral Proteins	Hepatitis C	NS5A inhibitors target the viral replication complex, inducing structural changes that block viral RNA replication and virion assembly.	[6], [7]
Viral Entry Receptors	Hepatitis D	Entry inhibitors block the sodium taurocholate co-transporting polypeptide (NTCP) receptor on hepatocytes, preventing HDV entry and infection of new liver cells.	[6], [8], [9]

Diagnosis and Tests [4]

- ALT Blood Test
  ALT stands for Alanine transaminase, an enzyme that speeds up certain chemical reactions and is usually found in liver. Normally, ALT levels are low in bloodstream, but when liver cells are damaged/inflamed, ALT leaks into the bloodstream. This test helps diagnose certain liver diseases early.
- Antibody Serology Test
  Infections cause antibodies to get produced which is what Antibody-Serology tests look for. However, the tests can't show whether the antibodies are from a current or past infection or even due to vaccination. They simply reveal how the body reacts to a pathogen.
- AST Test
  AST stands for Aspartate aminotransferase, an enzyme like the ALT and is responsible for catalysing chemical reactions. High levels of AST in Blood shows that liver cells are damaged.
- Smooth Muscle Antibody Test
  This test primarily diagnoses autoimmune hepatitis more than viral hepatitis as they are antibodies produced by our own body regardless of presence of any pathogens. This test is primarily used to determine the primary cause for the supposed symptoms resembling Hepatitis.

1.2. Current antiviral therapies and their limitations

Antiviral therapies for Viral hepatitis can vary based on the virus type and its strain ranging from supportive care to curative regimens for chronic situations.

Hepatitis A and Hepatitis E

- Hepatitis A is caused by the Hepatitis A virus, a ribonucleic picornavirus. To date, there are no specific antiviral drugs for Hepatitis A and treatment is simply supportive care, but most patients do make a full recovery.[6],[9]
- Like HAV, HEV causes acute infections and therefore self-limiting and does not require antiviral therapy. However, studies have suggested Ribavirin; a synthetic guanosine analogue with a broad spectrum of antiviral activity as an effective therapy for immunocompromised patients presenting with severe cases. One other drug called Sofosbuvir previously known as PS-7977 showed promising results in vitro against HEV but exhibited low clinical efficacy against. However, paired with other antiviral drugs against chronic HCV infections showed otherwise.[6]

Hepatitis B (HBV)

- HBV is a small deoxyribonucleic acid virus and infects hepatocytes through its replication cycle via an RNA intermediate and can integrate into the host genome.[6]
- Current HBV therapies focus on long-term viral suppression rather than a complete cure.
    1. Immunomodulators: Pegylated Interferon-alpha is the first-line therapy that offers a finite treatment duration and a higher chance of sustained anti-viral response, though they are less tolerated compared to Nucleos(t)ide Analogues (Nas)[6]
    2. Nucleos(t)ide Analogues: These are oral medications that effectively suppress viral replication and reduce the risk of liver cirrhosis and liver cancer. First-line drugs include Entecavir and Tenofovir. HIV drug Lamivudine is also still being used but in very specific co-infection cases.[5],[6]
    3. Investigational therapies: Current research suggested functional cures through SiRNA-based therapies, capsid/core protein inhibitors and entry inhibitors like Bulevirtide.[5],[6]

Hepatitis C (HCV)

Hepatitis C is a spherical, enveloped, positive-strand ribonucleic acid virus approximately 55nm in diameter. It is a silent systemic disease like a hepatotropic and lymphotropic virus with a high chronicity rate. It is characterized by increased levels of pro-inflammatory cytokines and chemokines. In the last decade, significant advances have been made about treating Hepatitis C infection. IFN therapy dominated for more than 20 years then, Pegylated-IFN came about which reduced frequency of SC injections from 3 to once a week. PEG-IFN Ribavirin combination showed significant effectiveness but was poorly tolerated. Same case was with the first protease inhibitors introduced in the year 2011, Telaprevir and Boceprevir exhibited great benefits but was still poorly tolerated and eventually resulted in suboptimal cure rate. The first polymerase inhibitor sofosbuvir changed hepatitis C history due to excellent tolerance and high cure rate. Later, the treatment of HCV was revolutionized by combination curate oral regimens[6]

- Direct acting Antivirals (DAAs): These agents are highly effective regardless of genotypes and contain strong barrier to resistance.[5]
- Pan-genotypic Regimens: WHO recommends drugs like Sofosbuvir/Velpatasvir which are effective against all viral genotypes and requires a short treatment course.[6],[9]
- Genotype-Specific Regimens: These combinations are used for specific viral genotypes and include Ledipasvir/Sofosbuvir (Genotypes 1,4,5,6) and Elbasvir/Grazoprevir (Genotypes 1,4).[6]

Hepatitis D (HDV)

Hepatitis D virus is a single-stranded circular RNA virus first reported in 1977. However, HDV is considered a defective virus so, does not produce viral envelope or capsid and therefore HBV infection is required for HDV infection in humans. Due to the dependence of HBV envelope, the presence of HBSAg is necessary to diagnose HDV infection. Treatments for HDV are classified as follows:[9]

- Standard Therapy: Pegylated Interferon-alpha is currently recommended though it is limited by poor tolerance and low response rates[6],[9]
- Novel agents: Bulvirtide is a novel therapeutic agent that blocks the virus from entering hepatocytes and is a recently authorized by the European Medicines Agency under the trade name "Hepcludex".[5],[6]
- Investigational agents: Other drugs targeting different stages of the HDV life cycle such as Lonafarnib (prenylation inhibitor) and REP 2139 (HBsAg release inhibitor) which is still under clinical investigation.[6]

1.3. Limitations to current antiviral therapies

Current antiviral therapies for viral hepatitis have made significant strides, particularly with the introduction of curative regimens for HCV, but they face several critical limitations across different virus types.

- Inability to achieve a complete cure: Primarily, current anti-HBV drugs such as nucleos(t)ide analogues only achieve viral suppression than a complete cure[6]. The root cause of viral persistence is due the incorporation of cccDNA reservoir or the viral genome into the host genome which these drugs won't be able to eliminate.[6],[10],[11]
- Need for lifelong therapy: Because drugs like Nucleos(t)ide analogues achieve a functional cure, patients often require long-term and even lifetime treatment which eventually leads to challenges such as patient adherence and long-term monitoring.[6],[9]
- Drug Resistance: More use of antivirals leads to viral mutations which creates viral resistance particularly with older medications like Lamivudine which will start to make these medications obsolete and will create high demand for innovative drugs.[5],[11]
- Systemic toxicity: Older formulations of first-like drugs like Tenofovir are associated with side effects like proximal renal tubular dysfunction and low bone mineral density.[6]
- Clinical Vs Real-World Effectiveness: While direct-acting antivirals (DAAs) have cure rates of up to 95%, real-world effectiveness is often hampered due to low disease awareness and lack of modern screening technologies.[6],[9]
- Risk of Reinfection: Although sometimes a successful cure is observed, certain high-risk populations still face reinfection situations demanding constant surveillance.[6]
- Poor Tolerability of certain drugs: Drugs like Interferon and pegylated-Interferon alpha are standard therapy for HDV. However, they are limited by their low tolerability and high risk of adverse events.[6]
- Diagnostic Gaps: In general, Major limitation to any therapy is the lack of fast and efficient diagnostic tools. Millions of people remain undiagnosed, which hinders the expansion of new knowledge against these viral diseases.[5],[12]
- Access & Equity: Another significant challenge lies within the country itself. Low and middle-income countries are restricted to advanced therapies due to their limited affordability of high-cost medications and poor healthcare infrastructure. [5],[10],[13].

1.4. Drug repurposing as a cost and time-effective strategy

Drug repurposing-also known as drug repositioning, reprofiling, or re-tasking – is a discovery strategy that identifies new therapeutic applications for existing pharmaceutical drugs that are either approved or has clinically failed in trials.[7],[13]

Traditional, de novo drug discovery is a laborious and exhaustive process that takes up to 15 years and costs billions to bring a single therapeutic drug into the market. Roughly, 9/10 medications fail during FDA assessments therefore, repurposing them offers a more efficient alternative to building a molecule from scratch.[7],[14]

- Reduced Timeline: The development period for repurposed drugs is shortened to about 3-12 years depending on the drug itself, the global distribution of the illness, amount of tangible data available etc.[14]

- Lowered risk and cost: Since safety, pharmacokinetic properties and human toxicity data are already established, scientists can bypass these time-consuming stages unless there's a need for an update.[7],[14]
- Clinical drugs: Physicians and other scientists already have long-term experience with these drugs, their mechanisms, adverse events which makes it convenient to test for new indications.[14]

The effectiveness of this strategy has been demonstrated in the management of Viral Hepatitis:

- HIV to HBV adaption: Since HBV and HIV share similar host replication pathways, drugs originally developed as anti-HIV medication were successfully repurposed for HBV treatment saving decades of research.[10]
- Natural formulations: Polyherbal formulations like Nkabinde were originally developed for HIV but through the usage of Network pharmacology to identify multi-target pathways that can be repurposed to combat HBV persistence than developing new single-target antivirals.[10],
- Ai-driven repositioning: Computational workflows can screen virtual compound libraries containing billions of molecules in a few days to find an anti-hepatitis drug candidates among existing drugs, a process that would take decades.[15]

1.5. Evolution of AI in Pharmaceutical research

The evolution of artificial intelligence in pharmaceutical research marks a profound shift from empirical, high-throughput screening to predictive discovery methodologies. [15]

Historically, pharmaceutical research followed "Eroom's law" which elucidates that costs increase exponentially while new drug approvals decline[15]. Traditional research relief on the slow, manual "Design-Synthesis-Test-Analysis" cycle[14],[15]. But now with Ai, generative models such as Variational Autoencoders and Generative Adversarial Networks can generate thousands of chemically plausible candidates within hours and predict their pharmacokinetic profiles with high efficiency. Breakthroughs like Google AlphaFold have evolved away research understand viral proteins, allowing them to predict complex morphologies of proteins.[15]

The role of Ai in managing Viral hepatitis has explained from basic data analysis to advanced clinical decision support[16]. Radiology and imaging tools now utilize deep learning models primarily Convolutional Neural Networks, having evolved to detect HCV-related Liver lesions and cirrhosis from CT scans more accurately surpassing traditional radiological assessments[12],[16]. Ai tools also can evaluate histological slides with accuracy comparable to expert pathologists, being able to identify microscopic markers and predicting early stages of supposed chronic diseases.[12],[16]

Moreover, AI has advanced more towards "precision Hepatology" tailoring treatments based on the individual patient's biological profile.[5],[16]

- Predicting responses: Machine learning models like XGBoost and Bayesian networks are used to predict the likelihood of HBsAg Sero-clearance or possible treatment failures in HCV patients.[15],[16]
- Public Health Surveillance: On a broader scale, AI models help forecast hepatitis outbreaks and identify high-risk populations by analyzing demographic trends, real-time health records and environmental factors.[16]

Currently, the technological tools used in hepatitis research have become increasingly sophisticated from basic ML to Deep learning [16], Quantum Machine Learning and last but not the least; Closed -Loop Discovery. The latter marks an evolution beyond simple AI models [12],[15],[16]. In this system, AI makes predictions that are immediately validated by automated robotics, with the results fed back to retrain the model in real-time[15]. Another significant milestone refers to the rise of Digital Twins- virtual representations of patients created from longitudinal data is allowing researchers to simulate clinical trials and reduce the need for actual humans [15]. Last but not the least, public health has evolved to use big data and NLP to scan electronic health records and unstructured clinical notes to find "hidden" carriers who might have been missed by traditional screening.[12],[16]

2. BIOLOGY OF VIRAL HEPATITIS AND THERAPEUTIC RATIONALE

2.1. Overview of Viral Hepatitis

The term viral hepatitis encompasses the group of five distinct hepatotropic viruses, namely, hepatitis A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV) [17], [18], [22]. Notably, the causative agents differ substantially, both in terms of their genome architecture and transmission routes. Indeed, whereas HBV is a partially double-stranded DNA virus, HCV, HDV, and HEV are RNA viruses [27], [36], [37]. The key characteristic feature of viral hepatitis is its substantial burden at the global level. For example, the number of people chronically infected with HBV and HCV is estimated at 257 million and 71 million, respectively. Particularly HBV and HCV are widespread in Asia and sub-Saharan Africa [21], [27], and Central, East Asia, Eastern Europe [35]. In 2016, viral hepatitis was the direct cause of 1.4 million deaths worldwide, of which 48% were attributable to HBV and 47% to HCV [35]. In turn, HDV is reported to infect 4.5% of HBsAg-positive people, as HDV replication depends on the assistance of the HBV genome [21]. Finally, HEV is estimated to cause 20 million infections per year, primarily in developing countries, with a fecal-oral route of transmission [21].

A special property of HBV and HCV is that they possess exceptionally high risks of chronicity and the development of cirrhosis and hepatocellular carcinoma **[31], [33], [36], [37]**. At the same time, it is noteworthy that despite the fact that therapeutic drugs capable of eliminating the virus from the body (DAA) have been developed for HCV, for HBV, the only available treatment is the suppression of the viral load **[21], [24], [32]**. Given the complexity of the processes of viral replication, the interaction of viruses with the host, and the appearance of mutations leading to chronic hepatitis, the application of computer drug discovery methods is relevant to find new treatments for these diseases **[20], [22]**.

2.2 Viral Life Cycle

Each of the viruses that cause hepatitis has a complex life cycle that includes several stages, during which candidate drugs can inhibit their replication. For example, the life cycle of HBV includes several stages, such as attachment and entry of the virus into hepatocytes via the sodium-taurocholate cotransporting polypeptide (NTCP) receptor, penetration, uncoating, and relaxation of the viral genome into the cell nucleus **[27], [36], [38]**. Subsequently, the viral genome is converted into covalently closed circular DNA (cccDNA) which encodes hepatitis B virus (HBV) RNA; this RNA is further transported to the cytoplasm, where it is packaged into the pregenomic form of RNA (pgRNA), which encodes the polymerase (Pol). After that, pgRNA is subject to reverse transcription (RT) by Pol, resulting in the formation of a relaxed circular DNA (rcDNA) molecule **[27], [29]**. Finally, the immature nucleocapsids are formed and secreted out of the cell **[27]**.

Meanwhile, the HCV life cycle differs from that of HBV in several aspects. In particular, HCV gains entry into hepatocytes by interacting with a number of receptor molecules **[30]**. Next, the positive-sense RNA genome of the virus is translated directly into a polyprotein, which is subject to proteolytic cleavage catalyzed by NS3/4A protease, resulting in the formation of structural and non-structural (NS) proteins **[19], [37]**. The newly formed viral genome is further replicated by NS5B RNA-dependent RNA polymerase (RdRp) in a membrane-associated replication complex **[18], [19]**. The p7 viroporin is involved in the budding process of the virus, which ultimately leaves the infected cell **[25], [27], [40]**.

In turn, the mechanisms of replication of HDV and HEV are less studied. In particular, HDV is a defective virus that relies on the presence of HBV to achieve infectivity and replication. In other words, to gain entry into hepatocytes and replicate, HDV uses the envelope proteins of HBV and the NTCP receptor **[25], [27], [34]**. Similarly, the HEV life cycle involves the replication of the viral RNA genome and its entry into the bile ducts and the systemic circulation **[25], [27], [39]**.

Thus, all the described stages of viral replication can be targeted by drug molecules. For example, the study [19] identified a number of promising antiviral drugs that target the entry of HCV into hepatocytes and inhibit its replication, while [9] suggests that HDV can be inhibited by blocking the NTCP by the drug compounds.

2.3 Viral and Host Therapeutic Targets

A large number of proteins can serve as targets for the treatment of viral hepatitis. In particular, for HBV, the following proteins can be targeted: Pol, which catalyzes RT and viral DNA synthesis, and HBx protein, which

plays a critical role in viral transcription, replication, and immune modulation **[21], [27], [29], [36]**. In addition, one of the challenges in combating HBV is the persistence of cccDNA, which encodes viral RNAs and serves as a template for DNA synthesis; this feature makes it a promising target for research **[21], [23], [27], [38]**. Another interesting target is the Core protein, which is part of the viral capsid and regulates the process of HBV DNA packaging **[21], [23], [27], [38]**. Last but not least, the surface antigen (HBsAg) is also a promising target for drug development **[21], [27]**.

For HCV, the main targets are the NS3/4A serine protease, which is responsible for processing the viral polyprotein **[19], [25], [26], [37]**, NS5A protein **[25], [26], [41]**, and NS5B RNA polymerase **[18], [19], [25]**. In addition, researchers have noted the potential of the p7 viroporin as a target for the development of new antiviral drugs **[25]**.

As for HDV and HEV, the study **[21]** indicates that the most promising target for HDV is the large hepatitis delta antigen (L-HDAg) and prenylation, a post-translational modification process necessary for the assembly of HDV particles **[25], [30]**. At the same time, the study **[25]** argues that for HEV, the most promising target is the viral RdRp and helicase.

One of the most promising host targets for combating HBV and HCV is the NTCP receptor, which is a portal of entry of these viruses into hepatocytes **[28]**. Other host factors that can serve as drug targets are cyclophilin A, which is involved in the replication of HCV **[28]**. According to **[24], [32]**, liver-specific transcription factors, such as Retinoic Acid Receptor (RAR), control the expression of many genes, including viral ones, and may be promising therapeutic targets. The study **[18]** notes that the application of FDA-approved “lipid-lowering” drugs, such as fluvastatin, can potentially improve the treatment of HCV infection in patients with fatty liver disease by regulating lipid metabolism.

Finally, the study **[32]** highlights the role of innate immunity, particularly the JAK-STAT signaling pathway, in the body’s defense against HBV and HCV infections; however, the researchers do not provide specific information on cell signaling drugs that could be used to combat these diseases.

2.4 Mechanisms of Viral Persistence

An important feature of viral persistence is that, in most cases, the viruses are unable to be completely eliminated from the body. In particular, for HBV, the main challenge in treatment is the persistence of cccDNA, which is a stable episomal maintenance element within the cell nucleus **[27], [32], [36]**. According to **[36]**, the formation of this molecule is achieved by the conversion of rcDNA into an approximately 3.5-kb cccDNA. However, as noted in **[27], [36]**, nucleoside analogues are unable to completely suppress the synthesis of cccDNA, which leads to a viral rebound after finishing the course of treatment.

Meanwhile, for HCV, the key challenge in eliminating this virus is the formation of quasi-species that differ in genome sequences due to the high variability of this virus **[19], [20], [37]**. As a result, it becomes difficult for the immune system to recognize these variants, leading to the establishment of chronic infection with this virus **[37]**.

Moreover, chronic HBV and HCV infections are often accompanied by the development of liver cirrhosis and hepatocellular carcinoma **[31], [33], [37]**. Another obstacle to curing these diseases is the fact that mutations of viral proteins can lead to a decrease in the effectiveness of targeted therapy **[23]**. Indeed, the study **[23]** argues that the development of resistance to treatment is facilitated by the fact that the binding site for therapeutic molecules is altered due to mutations.

2.5 Why these Targets are Suitable for Drug Repurposing

By applying AI to the task of drug identification, it is possible to select, among thousands of drugs, the most promising molecules whose mechanism of action may have a positive effect on the disease of interest. In particular, it is especially relevant to apply computer technologies to the fight against viral hepatitis, since there are a limited number of effective drugs for this disease, despite its burden at the global level. In addition, the complexity of the life cycle of viruses and the multiplicity of mechanisms that maintain their persistence make it difficult to find effective treatments for these diseases.

Most of the proteins listed above are integral parts of the viral life cycle, which means that their inhibition can prevent the replication of pathogens. Some of the proteins described above, such as HBV Pol or NS5B of HCV, are enzymes that catalyze irreversible reactions; this feature makes these proteins attractive therapeutic targets **[18], [19], [22], [27]**. At the same time, viral proteins are often similar in amino acid sequences, so AI can be used to find analogues of previously known drugs **[22]**.

Another advantage of the described proteins is that they can interact with a variety of drugs, both viral and endogenous. For example, since the entrance of viruses into hepatocytes through the NTCP receptor is critical for their replication, this protein can be a target for both viral and host drugs **[28], [35]**. This approach has already borne fruit in research **[40]**, which has revealed the possibility of using the antihistamine drug cimetidine to inhibit the entry of HCV into hepatocytes and block its replication. In addition, **[25]** suggests that small interfering RNAs (siRNAs) can be used to target NTCP and reduce the level of HBV.

Furthermore, the study **[21]** sheds light on the key role of host factors in viral replication, which means that their inhibition by FDA-approved drugs can be a way to combat these viruses. Indeed, many researchers have noted the high degree of conservation of most of the described proteins, making them attractive therapeutic targets **[18], [19], [22], [27]**.

The study **[23]** provides evidence of the potential of AI-driven drug repurposing for combating viral hepatitis. In particular, the researchers identified several FDA-approved drugs that could potentially be used to treat HBV. Voriconazole, an antifungal agent, was found to interact with the protein core of HBV; simultaneously, tazarotene, a topical retinoid, was found to affect the transcription of HBV by interacting with RAR transcription factors **[23]**. The study **[24]** also highlights the potential of such an approach by exploring new molecular mechanisms of action of drugs. In particular, the researchers identified several compounds that modulate nuclear receptors and have a positive effect on the biological processes of drug metabolism and bile acid signaling. These proteins are involved in the regulation of liver function and can be promising therapeutic targets for various liver diseases, including viral hepatitis. By analyzing the interactions between drugs and disease targets, AI can identify potential candidates for further investigation.

The study **[32]** illustrates the potential application of machine learning methods to explore new treatment opportunities for HBV. Researchers have developed an approach that has helped identify a number of promising molecular targets for the development of new antiviral drugs. The study **[18]** demonstrates the potential of computational screening of small molecules with high therapeutic efficacy. Such drugs are likely to be discovered in the context of the search for treatments for other diseases, which underscores the attractiveness of the drug repurposing concept. Moreover, the authors of **[21]** have identified several potential targets for HDV by analyzing the protein structures of this virus and their similarities with the proteins of other viruses. This finding may help in selecting drugs that inhibit HDV replication by targeting conserved viral factors.

3. DRUG REPURPOSING: PRINCIPLES AND CURRENT LANDSCAPE

3.1. Traditional versus AI-Driven Drug Repurposing

Drug repurposing traditionally has relied on serendipity, clinical observations, and patient data mining [41,47,48].

For example, the drug sildenafil was initially designed for use in patients with angina but was later discovered to have utility in the treatment of erectile dysfunction after observing side effects in patients [48]. Other traditional approaches to drug repurposing include phenotype-based screening and binding assays, which test a drug's effect on biological targets in vitro or in vivo [43,53]. These conventional approaches are characterized as "laborious and costly" [53] and primarily depend on "chance findings" [41,47]. For example, clinicians may observe a favorable effect of an untargeted drug on a specific condition [41,47]. Although traditional methods have contributed to the identification of therapeutics with clinical utility, they are limited by the lack of systematic exploration of a drug's potential [41,44].

2.2. AI-Driven and Computational Approaches

In contrast to traditional methods, contemporary drug repurposing increasingly relies on artificial intelligence (AI) and computational biology [44,49]. Specifically, machine learning (ML) algorithms and deep learning (DL) approaches, including generative models, have been utilized [49,50]. These approaches enable the mining of genomics, proteomics, and electronic health record (EHR) data to identify "novel drug-disease relationships" that are not apparent from clinical observations or traditional screening methods [50,51,54].

Some of the specific AI-driven techniques utilized in drug repurposing include:

- Machine learning: These algorithms have been used for *in silico* drug discovery and target identification by analyzing large-scale chemical libraries and biological data sets [43,44,53].
- Deep learning: Computational methods such as convolutional neural networks, recurrent neural networks, and long short-term memory networks enable the identification of pattern recognition in FDA-approved drugs and the prediction of pharmacological network interactions [46,52,56,60].
- Knowledge graphs: Knowledge graphs can represent biological data in graphical formats and have been used to predict multi-target relationships for diseases with complex etiologies [43,57,62,63].
- Bioinformatics and human genetics: Phenome-wide association studies (PheWAS) leverage de-identified genetic and EHR data to inform decision-making in drug repurposing in a more systematic and rapid manner compared to observational studies [47].

2.3. Target Identification and Technological Innovations

Computational approaches to drug repurposing enable structure-guided research and rapid screening, which can facilitate more accurate predictive drug repurposing compared to traditional approaches [41]. For example, network-based methods and molecular docking can leverage multi-omics data to identify repurposable therapeutics for use in oncology [61]. Additionally, AI-driven approaches to drug repurposing can optimize combinations of drugs and identify novel targets more rapidly than traditional approaches or expert-driven discovery [53,57]. Furthermore, AI can enable "exploration of vast chemical and biological spaces," which increases the likelihood of clinical success by improving the efficacy and safety profiles of therapeutics [49]. Notably, recent advances in large language models have enabled the representation of biomedical concepts for use in drug repurposing [66].

3. Advantages and Challenges of Drug Repurposing

3.1. Cost and Time Savings

The most significant advantage of drug repurposing is the substantial reduction in the time and cost associated with developing a new therapeutic [61]. Traditional drug discovery and development are characterized by high costs and lengthy timelines [61]. In contrast, repurposing an existing drug can result in regulatory approval "within half the time and at a fraction of the cost" [43]. Specifically, time and cost savings are achieved because the pharmacological, toxicological, and clinical properties of the therapeutics are already established [43,48,53].

The specific advantages of drug repurposing include:

- Cost: The cost of developing a new drug can be reduced from over $1 billion to tens of millions of dollars for a repurposed therapeutic [47].
- Time: The timeline for Food and Drug Administration (FDA) approval can be reduced to less than three years for a repurposed drug compared to over ten years for a novel therapeutic [47].
- Lower risks: The "lower risks" of repurposed therapeutics stem from the fact that the safety profile of the drug is already established, which reduces the likelihood of discontinuation due to adverse events [42,47,60].

3.2. Technical and Data-Related Challenges

A major challenge of AI-driven drug repurposing is the dependence on the quality of data utilized in training the algorithms [45,49]. With increasing "OMICs data complexity," it has become necessary to develop standardized approaches for accurate and reproducible results [45,49].

Additional technical and data-related challenges of AI-driven drug repurposing include:

- Heterogeneity: Traditional methods of drug repurposing have been limited by the heterogeneity of biological data, which leads to a loss of information during data conversion [57,62].
- Interpretability: The lack of interpretability of many ML and DL algorithms is a major limitation of AI-driven drug repurposing [49,50,63].
- Need for validation: Although AI-driven approaches to drug repurposing enable rapid identification of therapeutics, these candidates still require extensive "experimental validation (*in vitro* and *in vivo*)" and "human and expert intervention" prior to clinical use [45,48,49,55].

3.3. Financial and Intellectual Property Challenges

Financial and intellectual property (IP) challenges represent major obstacles to drug repurposing [41,58]. Specifically, the "weak or fragmented IP protection" of therapeutics limits the financial incentive to identify new indications for a drug [41,58].

The specific financial and IP challenges of drug repurposing include:

- Limited financial incentive: There is "limited financial incentive" to repurpose generic drugs because these therapeutics do not offer "value" to the pharmaceutical company [48,53].
- IP challenges: There are complex legal and regulatory challenges in drug repurposing, including navigating "purpose-limited patents" and "data/market exclusivity" regulations [58]. For example, companies need to develop "new composition of matter patents" to ensure that they can profit from the additional indication [48].
- Market exclusivity: Variations in health technology assessment and legal regulations across jurisdictions can reduce the commercial viability of a repurposed therapeutic [58].

4. REGULATORY CONSIDERATIONS AND ROADMAPS

4.1. FDA 505(b)(2) Pathway and Requirements

The US Food and Drug Administration (FDA) has a specific regulatory pathway for repurposed therapeutics, including those that have been identified through AI-driven approaches. Specifically, the FDA 505(b)(2) pathway enables the submission of a New Drug Application (NDA) that relies on "existing safety and efficacy information" of an approved drug or published literature [48,59].

The advantages of the FDA 505(b)(2) pathway include:

- Reduced testing: This pathway reduces the need for extensive preclinical and clinical testing, which accelerates the time to market [47,71].
- Market exclusivity: Therapeutics approved via the 505(b)(2) pathway can receive "legal exclusivity," which provides a financial incentive to developers [47,59,74].
- Commercialization bridge: The FDA 505(b)(2) pathway helps bridge the gap between scientific discovery and commercialization by enabling the use of the FDA's multi-payer system for reimbursement [59].

Recent reviews of FDA-approved drugs identified through the 505(b)(2) pathway highlight the trends in advanced formulation approaches as well as the regulatory requirements for leveraging existing information [71,77].

4.2. Comparative Analysis of EU, UK, and US Approaches

Regulatory pathways for drug repurposing differ between the US, the EU, and the UK. Comparative studies suggest that although the US FDA 505(b)(2) pathway is well-established, the EU and the UK also have specific mechanisms to facilitate the clinical development of repurposed therapeutics [67,68]. For example, Article 10 of Directive 2001/83/EC enables the use of "hybrid" approaches to drug development in the EU, similar to the FDA pathway [48]. However, the EU framework is considered to be "ill-suited to the current innovative landscape" because of the complexity of the IP system [58].

4.3. Market Exclusivity and Legal Incentives

IP considerations and the provision of legal incentives play an integral role in drug repurposing [69,78]. Legal exclusivity and reimbursement are critical for ensuring that scientific innovation can be translated into commercially viable therapeutics [59]. In the US, the Hatch-Waxman Act, the Orange Book, and various "orphan exclusivity" regulations provide a complex but comprehensive framework for the protection of repurposed therapeutics [58]. Similarly, the EU's 8+2(+1) data/market exclusivity and Supplementary Protection Certificates (SPCs) provide legal incentives, although the clinical translation of repurposed therapeutics remains challenging due to the complexity of the regulatory framework [58].

5.AI-PREDICTED REPURPOSED DRUGS FOR VIRAL HEPATITIS

The global burden of viral hepatitis, encompassing Hepatitis B, C, D, and E, remains a significant public health challenge, necessitating the rapid development of effective therapeutic interventions. Drug repurposing, the process of identifying new therapeutic uses for existing, approved drugs, offers an accelerated and cost-effective alternative to de novo drug discovery. Artificial intelligence (AI) and machine learning (ML) have emerged as pivotal tools in this endeavor, enabling the systematic screening of large chemical libraries and the prediction of drug-virus interactions with high precision.

- This report synthesizes evidence from current scholarly literature and computational studies regarding AI-predicted repurposed drugs for viral hepatitis. Key findings highlight several promising candidates:
- Hepatitis B Virus (HBV): KX2-391 has been identified as a dual inhibitor through multi-omics analysis. Retinoic acid receptor (RAR) agonists, such as tazarotene, show potential in repressing viral transcription. Computational models have also prioritized voriconazole, enasidenib, and lovastatin as potential capsid assembly disruptors.
- Hepatitis C Virus (HCV): AI-driven platforms have predicted a wide array of candidates targeting non-structural (NS) proteins, including naftifine and butalbital (NS3), vinorelbine and epicriptine (NS3/4A), pipecuronium and trimethaphan (NS5A), and olodaterol and vemurafenib (NS5B). Other notable candidates include candesartan cilexetil and fluvastatin.
- Hepatitis D (HDV) and E (HEV): While research is less extensive, AI models and computational screenings have identified entry inhibitors and host-pathway modulators as potential therapies.

The integration of network pharmacology, quantitative structure-activity relationship (QSAR) modeling, and deep learning architectures is transforming the landscape of hepatitis therapy. However, the translation of these in silico predictions into clinical practice requires rigorous experimental validation and consideration of viral mutations and host heterogeneity. This comprehensive analysis details the methodologies, candidate drugs, and mechanistic insights derived from AI-enabled drug repurposing efforts across all major viral hepatitis types, providing a roadmap for future research and clinical development.

Viral hepatitis represents a diverse group of infectious diseases that primarily affect the liver, characterized by inflammation and potentially progressing to life-threatening conditions. Chronic infections with Hepatitis B (HBV) and Hepatitis C (HCV) are leading causes of cirrhosis and hepatocellular carcinoma (HCC) worldwide. Despite the availability of vaccines for HBV and highly effective direct-acting antivirals (DAAs) for HCV, significant gaps remain in treatment accessibility, the management of drug-resistant variants, and the development of curative therapies for HBV and HDV [79], [84], [96].

The traditional drug discovery pipeline is notoriously long, expensive, and prone to high failure rates. Drug repurposing has become an essential strategy in the modern pharmaceutical toolkit, particularly for infectious diseases where rapid response is critical [82], [88]. By leveraging existing safety and pharmacokinetic data of FDA-approved drugs, researchers can significantly reduce the developmental timeline [90], [104], [107]. Artificial intelligence (AI) and machine learning (ML) enhance this process by providing sophisticated frameworks for predicting drug-disease associations, identifying novel biological targets, and optimizing lead compounds with unprecedented speed [95], [100], [103], [106].

In the context of viral hepatitis, AI applications span from initial diagnosis and genotype analysis to the prediction of treatment outcomes and the discovery of new therapeutic agents [98], [109], [115], [116]. This report focuses on the predictive power of AI and machine learning in identifying repurposed drugs that can inhibit viral replication, disrupt the viral life cycle, or modulate host responses to clear the infection. The subsequent sections detail the computational methods used to screen thousands of compounds and the specific drugs identified for each hepatitis virus type.

5.1. Methodological Deep-Dive: AI and Machine Learning in Drug Discovery

The identification of repurposed drugs for viral hepatitis relies on several advanced computational methodologies that integrate complex biological data with algorithmic modeling. These methods allow researchers to explore the "off-target" effects of existing drugs and their potential to interact with viral proteins or essential host factors [90], [137].

5.2. Systems Biology and Network Pharmacology

Systems biology approaches analyze the core signaling pathways of viral pathogenesis to identify biomarkers and drug targets. For HBV, deep learning and systems biology have been used to investigate these pathways, providing a foundation for both biomarker identification and drug discovery [80]. Network pharmacology further expands this by constructing comprehensive compound-disease target networks. This method was used to study the mechanism of Yi Gan Tang in HBV treatment, identifying active components like quercetin and their stable associations with central genes such as ERBB2 and JUN through machine learning and molecular docking [94]. Similarly, network pharmacology and AI-based approaches are recommended as promising alternatives for screening natural compounds for HBV therapy, allowing for the exploration of multi-target effects [81].

5.3. QSAR and Chemoinformatics-Based Models

- Quantitative Structure-Activity Relationship (QSAR) modeling remains a cornerstone of computational drug discovery. By correlating chemical structures with biological activity, machine learning models can predict the potency of thousands of compounds against specific viral proteins.
- HCV NS Proteins: In HCV research, QSAR-ML and molecular docking have been used to identify inhibitors targeting the non-structural proteins NS3, NS3/4A, NS5A, and NS5B. The "Anti-HCV" platform, for instance, predicts repurposed drugs targeting these proteins with high binding affinities [119].
- Sequence-Specific Prediction: Specialized models like Pred-AHCP use robust feature selection and machine learning to predict anti-Hepatitis C peptides based on sequence and physicochemical properties, focusing on features like hydrophobicity and dipeptide motifs [122], [123].
- Statistical and ML Algorithms: Various algorithms, including Support Vector Machines (SVM), Random Forest, Genetic Algorithm-Multiple Linear Regression (GA-MLR), and LightGBM, have been employed to classify and identify inhibitors of the HCV NS3 protease and NS5B polymerase with high accuracy [124], [130], [135], [136].

5.4. Deep Learning and Transformer Architectures

Recent advancements have seen the introduction of deep neural networks (DNN) and transformer-based models in hepatitis drug research, which are capable of learning complex representations from molecular data.

- HBCVTr: This end-to-end transformer hybrid model has been developed to predict anti-HBV and anti-HCV activity directly from SMILES (Simplified Molecular Input Line Entry System) strings, representing a significant shift toward chemical-language-based prediction [101].
- DeepHBV: This model predicts HBV integration sites, which is crucial for understanding how the virus contributes to cancer development and identifying potential therapeutic targets within the human genome [99].
- S2DV: A programmatic tool that converts SMILES to drug vectors to predict the activity of anti-HBV small molecules, leveraging deep learning for feature extraction [111].
- StackHCV: An integrative machine-learning framework designed for the large-scale identification of HCV NS5B inhibitors, offering a web-based tool for fast and precise drug screening [126], [131].

5.5. Virtual Screening and Molecular Dynamics

Virtual screening involves the automated searching of large chemical databases to find molecules that fit into the binding pocket of a target protein.

- Molecular Docking: This technique predicts the preferred orientation of a drug when bound to a protein and is used extensively in the discovery of HCV protease inhibitors and HBV capsid modulators [86], [94], [119], [134].
- Molecular Dynamics (MD): MD simulations provide insights into the stability and flexibility of drug-target complexes over time, ensuring that the predicted interactions are biologically plausible [125], [132], [133].

5.6. AI-Predicted Candidate Drugs for Hepatitis B (HBV)

HBV research has shifted toward achieving a "functional cure," defined as the persistent loss of HBsAg with or without seroconversion. AI and drug repurposing have identified several molecules that target various stages of the HBV life cycle, from entry to HBsAg release [84], [110].

5.7. Transcriptional Inhibitors: The Role of RAR Agonists

A significant discovery through drug repurposing screens is the potential of Retinoic Acid Receptor (RAR) agonists as potent HBV inhibitors. Tazarotene, an FDA-approved RAR agonist, was found to inhibit HBV by repressing the transcription of cccDNA (covalently closed circular DNA) and activating viral promoters [87]. This mechanism involves the modulation of genes associated with RAR and metabolic pathways, specifically involving RARβ. Notably, tazarotene does not induce a typical interferon response, suggesting a novel pathway for viral suppression that could complement existing therapies [87].

5.8. Capsid Assembly Modulators (CAMs)

Targeting the HBV core protein (HBcAg) to disrupt capsid assembly is a critical antiviral strategy, as the capsid is essential for viral genome protection and delivery. Computational-aided drug repurposing identified several promising candidates that target the core protein:

- Voriconazole, Enasidenib, and Lovastatin: These drugs, traditionally used for fungal infections, leukemia, and high cholesterol respectively, have shown potential in disrupting capsid assembly in computational models [86].
- Ciclopirox olamine: A fragment-based drug discovery study highlighted this antifungal agent as a potential inhibitor of the HBV core protein [86], [112].

- Novel Hits: Computational studies have identified compounds like ZINC86859997 and ZINC63280172 as potential leads for further development [86].

5.9. Dual-Action Inhibitors and HCC Management

Multi-omics analysis of HBV-associated hepatocellular carcinoma identified KX2-391 (Tirbanibulin) as a dual inhibitor through a drug repurposing strategy [83]. KX2-391 targets pathways involved in tumor growth and viral pathogenesis, acting as a tumor suppressor by interacting with factors that inhibit the Wnt/β-catenin signaling pathway [83]. This highlights the potential for repurposed drugs to address both the viral infection and its long-term complications, such as liver cancer.

5.10. Natural Compound Screening and TCM Integration

The integration of Traditional Chinese Medicine (TCM) with modern AI has provided new leads. The study of Yi Gan Tang used machine learning to establish ERBB2 and JUN as central genes in the treatment of HBV. Quercetin, a common flavonoid, was identified as a component that shows stable associations with these pivotal targets through molecular docking, suggesting its potential as a repurposed natural compound [94].

6. AI-PREDICTED CANDIDATE DRUGS FOR HEPATITIS C (HCV)

HCV drug discovery has been highly successful with the development of DAAs, but AI continues to play a role in identifying novel scaffolds and repurposed drugs to combat resistance and manage complications.

6.1. Targeting the NS3/4A Protease Complex

The NS3 protease and its cofactor NS4A are vital for the biogenesis of the viral replication complex. AI-driven platforms have predicted several repurposed candidates:

- Naftifine and Butalbital: Predicted by the "Anti-HCV" platform to target the NS3 protein with high binding affinity [119].
- Vinorelbine and Epicriptine: Identified as inhibitors of the NS3/4A protease complex through QSAR and machine learning [119].
- Novel Potent Ligands: Computer-aided design has identified novel molecules with higher binding affinity than standard inhibitors like simeprevir, voxilaprevir, and telaprevir [128].

NS5A and NS5B Polymerase Inhibition Strategies

- The NS5B RNA-dependent RNA polymerase (RdRp) is a primary target for inhibiting HCV replication.
- NS5A Inhibitors: Pipecuronium and trimethaphan have been predicted as promising repurposed drugs targeting NS5A [119].
- NS5B Inhibitors: Olodaterol and vemurafenib were identified as candidates targeting NS5B [119].
- Candesartan cilexetil: A neural-network-based SAR study suggested this heart failure prodrug as a potential inhibitor of the HCV RNA polymerase [120].
- Fluvastatin and Olopatadine: Computational chemistry analysis revealed good binding affinity to the NS5B Thumb I allosteric site [127]. Fluvastatin is particularly noted for potential benefits in patients with non-alcoholic fatty liver disease (NAFLD), aligning with its mechanism of action and the characteristics of chronic HCV infection [127].
- Isothiazole Derivatives: AI-guided design has focused on isothiazole derivatives as new and selective inhibitors of HCV polymerase NS5B, interacting with the active site 221 binding pocket [132].

6.2. Entry, Assembly, and Host-Factor Inhibitors

- Dasatinib: An AI-predicted candidate that inhibits viral entry into hepatocytes, potentially preventing the initial stages of infection [121].
- Celgosivir: This drug interferes with viral assembly by altering host-directed glycosylation, a process essential for the proper folding of viral envelope proteins [121].
- Sorafenib: Traditionally used for HCC, sorafenib has been found to block HCV replication by inhibiting the host factor c-raf [121].

6.3. Large-Scale Network Analysis of Candidate Drugs

A study analyzing chemical-protein and chemical-chemical interactions identified 20 significant candidate compounds for HCV treatment after extensive clustering [121]. This network-based approach highlighted drugs such as acyclovir, ganciclovir, atorvastatin, and zidovudine as having potential anti-HCV activity based on their interactions with HCV target genes [121]. This multi-target perspective is crucial for developing robust therapeutic strategies.

6.4. AI-Predicted Candidate Drugs for Hepatitis D and E

Research into AI-predicted repurposed drugs for Hepatitis D and E is less abundant but shows emerging potential through cross-virus screening and host-factor targeting.

- Hepatitis D (HDV): Entry and Receptor Targeting. HDV is a satellite virus that requires HBV for its life cycle, specifically requiring the HBsAg for virion assembly.
- Myrcludex B (Bulevirtide): While well-established, AI and computational models are used to study its binding to the NTCP receptor. It prevents both HBV and HDV infection by competing for NTCP binding, effectively blocking viral entry [96].
- Bile Acid Reabsorption Inhibitors (BARIs): Repurposed BARIs have been identified as entry inhibitors for HDV. These compounds interact with the NTCP-homologous ASBT receptor, showing certain selectivity and the potential for oral administration [82].
- Zafirlukast: AI drug discovery screenings have highlighted zafirlukast as a potential repurposing candidate for other viral infections including HDV [79], [92].
- Hepatitis E (HEV): Pyrimidine Synthesis and Host Factors. HEV research has benefited from the application of AI to identify inhibitors of its unique replication machinery and host dependencies.
- Vidofludimus Calcium and Pyrazofurin: Identified as novel chemical entities for HEV interventions through drug repurposing libraries. Vidofludimus calcium inhibits dihydroorotate dehydrogenase (DHODH), while pyrazofurin selectively targets uridine monophosphate synthetase (UMPS), both disrupting the pyrimidine synthesis pathway essential for viral RNA production [85].
- Etravirine: An in silico network controllability analysis predicted etravirine as a potent inhibitor of CK1ε, a host factor essential for HEV infection [92].
- Amodiaquine and Lumefantrine: Biocomputational analysis identified these antimalarial drugs as candidates that target the HEV RdRp and capsid proteins [93].
- Ivermectin: Predicted and validated to inhibit HEV replication by targeting the host nuclear transport protein importin α1 [88].
- Zinc Salts: Computational and experimental evidence suggests zinc inhibits HEV replication by blocking the activity of the viral RdRp [91].

The following table provides a high-level comparison of the primary AI-predicted repurposed drugs across the different hepatitis viruses.

Emerging AI Frameworks and Drug Discovery Platforms

Table 2: Comparative Summary of Candidate Drugs and Mechanisms

Virus	Candidate Drug(s)	Primary Target / Mechanism	AI / Computational Method	Reference
HBV	KX2-391	Dual inhibitor; Wnt/β-catenin modulation	Multi-omics, Drug Repurposing	[83]
HBV	Tazarotene	Retinoic Acid Receptor (RAR) agonist; cccDNA repression	AI-based Drug Repurposing Screen	[87]
HBV	Voriconazole, Lovastatin	Capsid assembly modulation	Capsid Targeting Model	[86]
HBV	Quercetin	ERBB2 and JUN interaction	Network Pharmacology, Machine Learning	[94]
HCV	Naftifine, Butalbital	NS3 protein inhibition	QSAR, Machine Learning	[119]
HCV	Vinorelbine, Epicriptine	NS3/4A protease inhibition	QSAR, Machine Learning	[119]
HCV	Pipecuronium, Trimethaphan	NS5A protein inhibition	QSAR, Machine Learning	[119]
HCV	Olodaterol, Vemurafenib	NS5B RNA-dependent RNA polymerase inhibition	QSAR, Machine Learning	[119]
HCV	Candesartan cilexetil	RNA polymerase inhibition	Structure–Activity Relationship (SAR), Machine Learning	[120]
HCV	Fluvastatin, Olopatadine	NS5B Thumb I allosteric site inhibition	Computational Chemistry	[127]
HCV	Sorafenib	c-Raf inhibition (viral replication)	Interaction Network Analysis	[121]
HDV	Myrcludex B (Bulevirtide)	NTCP receptor-mediated viral entry inhibition	Entry Inhibition Screening	[96]
HEV	Vidofludimus calcium	Dihydroorotate dehydrogenase (DHODH); pyrimidine synthesis inhibition	Drug Repurposing Library Screening	[85]
HEV	Etravirine	Casein kinase 1 epsilon (CK1ε) inhibition	Network Controllability Analysis	[92]

The development of specialized AI frameworks is crucial for the ongoing success of drug repurposing in hepatitis research. Platforms like StackHCV provide web-based interfaces for identifying NS5B inhibitors specifically for liver cancer therapy [126]. The Anti-HCV platform utilizes QSAR and machine learning to predict inhibitors for all non-structural proteins of HCV [119]. For HBV, models like HBCVTr offer end-to-end prediction from molecular structures, facilitating the rapid screening of newly synthesized or existing chemical libraries [101]. These platforms often integrate molecular docking and molecular dynamics (MD) simulations to provide a comprehensive evaluation of drug-target interactions [125], [132], [133].

7. LIMITATIONS AND CHALLENGES IN COMPUTATIONAL REPURPOSING

Despite the significant promise of AI-driven drug repurposing, several critical limitations must be addressed to ensure the clinical success of these candidates:

- Data Quality and Scarcity: AI models are highly dependent on the quality and volume of training data. For emerging variants of hepatitis viruses or rare genotypes, data may be insufficient, leading to poor model generalizability [89], [118].
- Experimental Validation: All AI-predicted candidates are essentially hypotheses that require rigorous *in vitro* and *in vivo* validation. Discrepancy between *in silico* binding affinities and actual biological activity is common [94], [97].
- Viral Mutation and Resistance: The high mutation rate of viruses like HCV and HEV means that drugs identified today may become ineffective against future variants [122], [129].
- Clinical Translation: Legal, ethical, and regulatory barriers often slow the transition from computational prediction to clinical trials. There is also a need for better internal and external validation of AI models to gain the trust of clinicians and regulatory bodies [88], [118].
- Off-Target Effects: While repurposing leverages existing safety data, new therapeutic uses may involve different dosing regimens or interact with previously unrecognized targets, potentially leading to unforeseen side effects [90], [117].

8. FUTURE DIRECTIONS: TOWARDS PRECISION HEPATOLOGY

Future research should focus on developing more robust and explainable AI models.

- Explainable AI (XAI): Understanding the "reasoning paths" of AI models is essential for gaining mechanistic insights into how a drug works [113].
- Multi-Modal Integration: Combining chemical, genetic, clinical, and multi-omics data will provide a more holistic view of drug-virus interactions [108].
- Real-Time Surveillance: AI can be used to monitor viral mutations in real time and predict which repurposed drugs will remain effective against emerging variants [102], [118].
- Personalized Medicine: Leveraging host genetic variants to predict which patients will benefit most from specific repurposed therapies is a key research frontier [105], [114].

Artificial intelligence and machine learning have significantly accelerated the identification of repurposed drugs for viral hepatitis. By systematically analyzing the complex interactions between viral proteins, host pathways, and existing chemical libraries, AI has identified diverse candidates targeting almost every stage of the viral life cycle. From the repression of HBV cccDNA by RAR agonists to the multi-target inhibition of HCV non-structural proteins and the targeting of host factors in HEV, these computational predictions provide a wealth of opportunities for developing new therapies. While challenges in data quality and clinical translation remain, the integration of human and machine intelligence represents the most promising strategy for combating the ongoing global epidemic of viral hepatitis and achieving the goal of viral elimination.

9. ARTIFICIAL INTELLIGENCE TECHNOLOGIES EMPLOYED FOR DRUG REPURPOSE

AI technologies are transforming drug repurposing by enabling a systematic identification of new therapeutic uses for existing medications through leveraging vast biological datasets to predict how established drugs might interact with novel disease targets.

A. Machine learning and Deep learning Architectures

Machine learning serves as a basic predictive engine for identifying drug-disease associations through analyzing chemical structure, pathways and clinical outcomes.

- Algorithms like Support Vector Machines, Random Forest and K-nearest neighbors are used to classify drugs based on their potential to suppress a virus or to predict inhibitory concentrations through supervised learning.
- Deep learning tools such as Deep Neural Networks and Convolutional Neural Networks has the capability to process multidimensional data, chemical imagery, and biological sequences to provide more depth into drug's therapeutic action.
- Generative AI models such as Variational Autoencoders and Generative Adversarial Networks can generate chemically plausible molecular variations or predict ADMET profiles to ensure repurposed candidates are safe for new indications.

B. Network Pharmacology and Molecular Docking
   - These methods work in tandem with AI to simulate physical interactions at a molecular level.
   - This approach incorporates systems biology and bioinformatics to map complex drug-target-disease interaction networks.

C. Molecular Docking
   - This technology simulates and predicts 3-dimensional binding affinity between drug molecules and target protein. This gives an idea to the researchers of how well the existing drug fits to the new target is.

D. Signature-based and Knowledge-based Approaches
   - Signature-based approach relies on the logic that if a drug can reverse the gene expression pattern of a disease back to a healthy state. It relies on comparing two distinct molecular profiles:
     - Disease Signature: The specific set of genes that are upregulated/downregulated after a healthy tissue gets infected.
     - Drug signature: The specific set of genes that are upregulated/downregulated after a healthy/infected tissue is treated with that drug.

E. Knowledge-based Association: These systems consolidate large amounts of data regarding drug profiles, chemical structures, side effects, adverse effects to predict possible unexplored mechanisms.

F. Natural Language processing: NLPs are primarily employed to do literature mining, going through millions of scientific papers, patents, patient reports, clinical data reports to possibly find hidden relationships between drugs and diseases that human researchers might have missed. For e.g., electronic health records are one possible evidence that serve useful for drugs off label uses.

10. AI BASED DRUG DISCOVERY WORKFLOW

The AI based drug discovery workflow represents a paradigm shift from traditional empirical methods toward predictive discovery methodologies, aiming to reduce the historical 10-15 years' timeline and billions of cost associated with bringing a drug into the market. Traditional workflow typically follows a tiered structure: Target discovery, lead discovery, lead optimization and clinical development. These stages are made more efficient and faster with the incorporation of Artificial intelligence.

A. Target Identification and Validation
   - This initial phase uses AI to process vast amounts of multi-omics data (genomics, proteomics and metabolomics) to identify new targets with high precision.
   - Utilizes Deep Learning and Network analysis to predict protein-protein interactions and identify disease relevant nodes.
   - Popular tools like Google AlphaFold accurately predicts protein structures which is considered critical to designing drugs against previously undruggable or uncharacterized proteins.

B. Lead Discovery and Chemical Space Navigation

Once a target is validated, the workflow shifts to identifying molecules that can interact with it.

- Generate AI: Models such as Generative Adversarial Networks and Variational Autoencoders perform de novo drug design, generating novel drug-like molecules that satisfy multiple optimization criteria simultaneously.
- Virtual Screening and Retrieval-Augmented Docking: The latter uses molecular embeddings to retrieve chemically plausible subsets for high-throughput docking, making large-scale computationally tractable.
- Drugs repurpose: AI scans existing drug databases to find new therapeutic applications for already approved pharmaceuticals, a strategy that is particularly effective urgent health threats like viral epidemics.

C. Lead Optimization

In this stage, candidate molecules are refined to enhance their therapeutic profile while minimizing risks.

- ADMET Prediction: AI models predict ADMET profiles of candidates with significantly higher efficiency than traditional methods.
- Reinforcement Learning: This is used to optimize structure-activity relationships allowing for 2-3x faster lead optimization and a 45% reduction in candidate selection time.
- Multi-Objective Optimization: Algorithms rank candidates based on a combined score of binding affinity, solubility and synthesizability.

D. Clinical Trial Optimization

AI-driven workflows extend into the design and execution of clinical trials to reduce the high rate of clinical failure.

- Patient Selection: AI analyses electronic health records and genetic data for precise patient stratification, identifying suitable participants and predicting potential dropout rates.
- Protocol Design: Predictive analytics optimize trial protocols and suggest modifications to improve success probability, potentially reducing trial duration by 25-30%.
- Synthetic Clinical Trials: The use of Digital Twins-Virtual patient replicas derived from longitudinal data-allows for in silico simulations that can support regulatory evidence and reduce reliance on large concurrent control arms.

11. CASE STUDIES

There are several case studies of drug repurposing for the management of Viral hepatitis, primarily focusing on Hepatitis B and Hepatitis C.

A. HBV research focuses heavily on targeting the cccDNA reservoir and achieving a functional cure:

- Nitazoxanide: Originally an antiparasitic and antiprotozoal agent, NTZ was repurposed because it inhibits the interaction between the HBV regulatory protein X and the host protein DDB1. This action restores the host's Smc5/6 restriction complex, which suppresses viral transcription from cccDNA. Pilot clinical trials have shown it can reduce HBV RNA and HBsAg levels.
- Ciclopirox: This antifungal agent was identified through fragment-based discovery and computational docking to bind to the HBC core protein. It disrupts the assembly of the viral capsid, thereby blocking replication.
- Imatinib: Made for treating cancer, it is being repurposed to target HBV entry into liver cells. Graph convolutional networks screened roughly 10,000 FDA-approved drugs and identified imatinib as a candidate that can prevent HBV replication and HCC metastasis in vitro.

B. Repurposing Antiretrovirals

Due to the biological similarity between HBV and HIV-specifically their shared use of reverse transcription-several HIV drugs have been successfully adapted for HBV.

- Tenofovir and Lamivudine: These were originally developed for HIV/AIDS but are now first-line therapies for HBV because they inhibit the HBV reverse transcriptase.
- TDF for resistance: TDF has been successfully repurposed for patients with lamivudine-resistant HBV where it has shown superior efficacy in suppressing viral levels over 240 weeks.

C. Repurposing Hepatitis C

- Ferroquine: Originally developed as a synthetic antimalarial compound for chloroquine-resistant strains, FQ has been identified as an effective inhibitor of HCV RNA replication by affecting early steps in the viral life cycle.
- Remdesivir: While widely used against COVID-19, it was developed for Hepatitis C before being repurposed Ebola and later the SARS-CoV-2 pandemic.

D. Natural Product and Polyherbal formulation repurposing

- Product Nkabinde: A patented African polyherbal formulation originally developed for HIV; it is currently being evaluated as multi-target therapy for HBV. Network pharmacology and molecular docking identified that its phytochemicals, such as beta-sitosterol, oleanolic acid and quercetin, bind strongly to 10 host proteins that HBV hijacks for survival including PIK3CB and STAT1.

12. CHALLENGES

Despite these tremendous milestones, the evolution of AI faces "New Productivity Paradox" wherein the speed of digital iteration outpaces the capacity for real-world validation, challenges like algorithmic bias, black box dilemma and data privacy remains as critical drawbacks to obtain regulatory approval and clinical adoption of AI completely. While AI can generate thousands of drug candidates in hours, the downstream physical validation-synthesis, experimental testing and clinical trials remain constrained by physical throughput. High performance deep learning models often lack transparency in how they reach decisions (Black-Box). This makes it difficult for regulators to validate model credibility and ensure the absence of hidden bias, contradicting the pharmaceutical principle of transparency in causality. Furthermore, often there's a misalignment between in-silico outputs and biological reality – known as "Translational Gap". This is because models are trained on homogenous datasets and memorize patterns. While this can be useful in certain situations, without understanding fundamental chemical or biological principles, leading to failure when applied to dynamic human systems.

Furthermore, Accountability and liability become a major issue because if an AI predicted repurposed molecule causes unforeseen harm in patients, currently it is unclear as how the liability should be distributed. While standardized audits can be performed, on what criteria the AI should be evaluated and audited remains as a matter of question and discussion. Nonetheless, the major problems revolve around maintenance, regulation and data privacy concerns.

13. FUTURE PERSPECTIVES

Future perspectives on drug repurposing for viral hepatitis focus on transitioning from discovery to a systematic, AI-driven and patient-centric paradigm aimed at achieving functional cures. This evolution is characterized by the integration of emerging computational power with novel biological targets and global data-sharing frameworks.

The future of drug discovery is increasingly reliant on hybrid AI frameworks that combine multi-omics data with longitudinal clinical records to optimize drug selection.

- Quantum-enhanced simulations: Next-generation virtual screening pipelines are expected to integrate with quantum computing, allowing for ultra-large-scale docking against conformationally dynamic targets – HBV capsid in seconds than weeks.
- Predictive Transformers and GCNs: Models like the HBCVTr transformer and Graph Convolutional Networks will become standard for predicting drug-virus interactions with higher accuracy, potentially identifying high-affinity novel agents for viruses like HBV at faster rates than traditional docking.

- Research is shifting from mere viral suppression toward the elimination of viral reservoirs which is the goal of hepatitis therapy.
- cccDNA inactivation: A major future focus is repurposing drugs that can specifically target and inactivate or eliminate the HBV cccDNA reservoir in the hepatocyte nucleus.
- Host-directed Multi-targeting: Rather than inhibiting a single viral enzyme, future therapies like product Nkabinde aim to modulate host signaling nodes that viruses hijack for survival. This approach may restore antiviral immunity and prevent progression more effectively than traditional antivirals.

Regulatory acceptance of Real-world evidence: Agencies are expected to increasingly accept well-designed observational studies and post-marketing data as supportive evidence accelerating the implementation of AI-identified repurpose opportunities.

CONCLUSION

The integration of Artificial Intelligence and systematic drug repurposing represents a paradigm shift in the management of Viral hepatitis, transitioning the field from empirical, slow-moving research toward a more predictive, precise and cost-effective discovery engine.

- AI as a Disruptive Diagnostic and Prognostic force

AI technologies have evolved beyond simple data analysis to become critical tools for early detection and non-invasive staging of liver disease. By utilizing machine learning algorithms like KNN, SVM and Random forests, clinicians can identify HBV and HCV cases with accuracy rates nearing 100%

- Efficiency through Drug repurposing

Drug repurposing has emergied as an essential strategy for addressing the “Eroom law” of declining pharmaceutical productivity. By leveraging existing safety and pharmacokinetic data, repurposing can reduce drug development timelines from 15 years to 3-12 years and lower costs by up to 70%. This is particularly vital for achieving a functional cure for Hepatitis.

- The Shift to Host-directed and Personalised therapy:

The future of Hepatitis management lies in precision hepatology. Research is moving away from single-target antivirals toward host-directed therapies such as polyherbal formulation Product Nkabinde which uses multi-target mechanisms to reverse immune exhaustion and impede viral persistence

Despite these digital advancements, a significant gap remains between rapid computational predictions and the slower pace of real-world clinical validation. Moving forward, the field must address critical ethical issues including black-box dilemma of opaque algorithms and the need for robust data privacy frameworks to maintain patient trust. To meet the WHO 2030 elimination targets, advancements in AI and drug discovery must be integrated into broader public health strategies. Furthermore, while biological persistence (cccDNA) and regulatory lag remain as formidable challenges, the convergence of AI, drug repurposing provide a clear roadmap for transforming viral hepatitis into a manageable and ultimately curable condition on a global scale.

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