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HIV/HBV coinfection: understanding the complex interactions and their impact on spontaneous HBV clearance, chronic liver damage, cirrhosis, and hepatocellular carcinoma

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Abstract

Compared to either HIV or hepatitis B virus (HBV) monoinfected individuals, HIV/HBV-coinfected individuals have a decreased probability of spontaneous HBV clearance and a greater risk of developing chronic liver damage and a faster progression to cirrhosis and hepatocellular carcinoma. This manuscript attempts to provide a comprehensive review of the landscape of current HIV/HBV coinfection research with a focus on the intricate interactions between these two viruses. Our review will help understand the disease dynamics of HIV/HBV coinfection and has important implications for designing public health strategies.

Keywords

HIV. HBV. Coinfection. Hepatocellular carcinoma. Pathogenesis. Prevalence. Liver disease.

Introduction

According to the data from the World Health Organization, about 39.0 million people worldwide are infected with HIV at the end of 2022, and about 296 million people (Fig. 1) worldwide are infected with the hepatitis B virus (HBV) at the end of 2019. About 350,000 to 700,000 people worldwide have HIV/HBV/HDV triple infections[1]. Since HIV and HBV share similar transmission routes, they have a high coinfection rate. Overall, 7.7% of HIV-infected individuals also have an HBV infection[2,3]. In China, HIV/HBV coinfection accounts for about 10% of HIV-infected patients, and the prevalence rate varies from 5% to 15% in different regions[4]. On the other hand, the infection rate of HBV among HIV-infected patients in China is 11.29%, with higher coinfection rates in the western (10.73%) and southern regions (14.18%) and the lowest in the northern region (6.36%)[5].

In China, the annual number of deaths from liver fibrosis and liver cancer due to HBV infection alone is about 620,000[6]. It has been reported that HIV/HBV-coinfected individuals are 8 times more likely to die from liver diseases than HIV-monoinfected individuals and 19 times more likely than HBV-monoinfected individuals[7]. Therefore, how liver diseases progress in HIV/HBV coinfection and what mechanisms are involved is an active area of current research. In this

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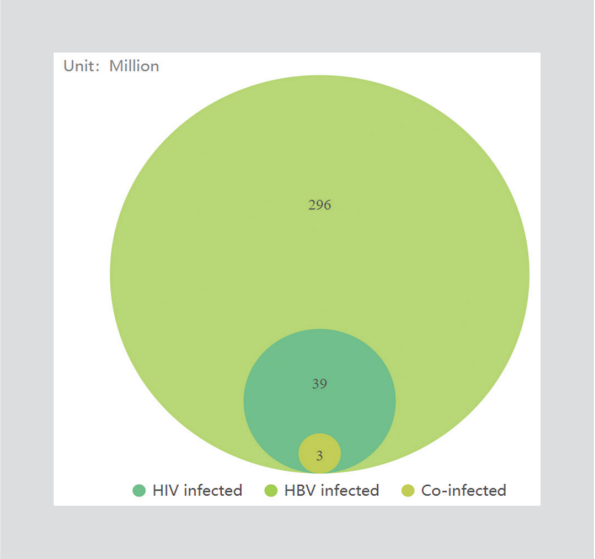

Figure 1. *Global status of HIV/HBV coinfection. The smallest circle represents the estimated number of people coinfected with HIV/HBV worldwide. The largest circle represents the number of people in the world infected with HBV, which is approximately 39 million. The medium-sized circle represents the number of people in the world infected with HIV, which is approximately 296 million. Data from the WHO.*

review, we present an overview of existing research on HIV/HBV coinfection with a highlight on the interactions between HIV and HBV that govern disease pathogenesis and progression.

Impact of HIV/HBV coinfection on disease outcomes

HIV/HBV coinfection hastens HIV disease progression. Even with antiretroviral therapy (ART), peripheral CD4+ T cells rise slowly, suggesting that HBV impairs CD4+ T cell reconstitution[8]. It is reported that the mortality rate of AIDS-related diseases in HIV/HBV-coinfected individuals was nearly twice as higher than that in HIV-monoinfected individuals.

Immune reconstitution is important for HBV clearance in HIV-HBV-coinfected individuals. The rapid decrease of HBsAg and HBeAg levels after ART in HIV/HBV-coinfected individuals may be attributed to the immune responses against viral antigens and a decrease in the levels of HBV antigens. This process is often accompanied by hepatocyte damage and hepatitis, suggesting the presence of HBV-associated immune reconstitution inflammatory syndrome (IRIS)[9]. Indeed, a study from Thailand showed that when ART was administered to HIV-HBV-coinfected individuals at an advanced stage of HIV disease with low CD4+ T cell counts, 22% of patients developed HBV flares and IRIS-related liver injury[10]. In summary, a low CD4+T cell count is an important factor in triggering IRIS in HIV/HBV-coinfected individuals.

HIV accelerates HBV-associated liver disease progression

The mechanisms by which HIV accelerates HBV-associated liver disease progression are complicated, which include elevated viral replication and liver inflammation (Fig. 2), accelerated fibrosis progression, and increased susceptibility to hepatocellular carcinoma (HCC). HIV can infect tissue macrophages present in the liver to accelerate disease progression[11].

- HIV can also infect hepatic stellate cells (HSC)[11] and speed up liver fibrosis. Through gp120, HIV interacts with CXCR4 on activated HSCs to promote fibrosis, suggesting that CXCR4 inhibitors may become potential anti-fibrotic medications for coinfected individuals[12].
- HIV causes microbial translocation and increases the level of lipopolysaccharide (LPS) in both the portal vein and systemic circulation. As the main toxic component of endotoxin, LPS can mount an inflammatory response to disrupt the integrity of the vascular endothelium and cause liver damage and hemorrhage[13]. In a study conducted in simian immunodeficiency virus-infected rhesus monkeys, heightened microbial translocation in the livers of experimental animals instigated chemokine production and amplified the population of CXCR6-activated natural killer cells (NKs), which in turn started liver fibrosis[14]. In addition, binding of CXCL-10 to CXCR3 expressed on activated T cells induces the migration of these activated T lymphocytes to the liver and triggers liver inflammation. Finally, HIV infection may also lead to depletion of HBV-specific T cells[15], which ultimately impairs the immune response against HBV and hinders its clearance.

HIV/HBV coinfection increases the risk of developing HCC

HIV/HBV coinfection increases the risk of HCC[16,17], which might be attributed to HIV-induced defects in immune surveillance against tumorigenesis[18]. While there is clear epidemiological evidence implicating HBV as the primary cause of HCC[18,19], in the context of HIV infection, HBV infection has been shown to have

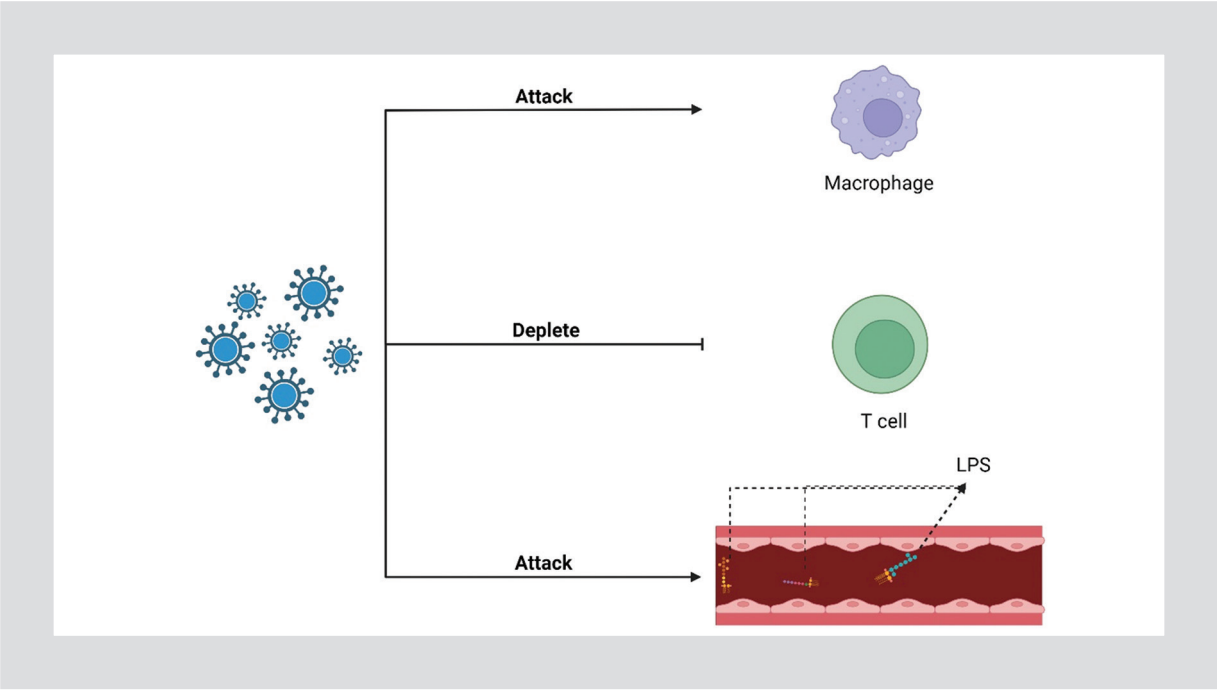

Figure 2. *HIV influences the disease process of chronic HBV infection. HIV compromises immune responses at least by 3 methods: attacking macrophage, depleting T cells, and increasing the level of circulatory lipopolysaccharide. Created with BioRender.com.*

a greater risk of chronicity, as seen by a higher HBV DNA level, a lesser likelihood of spontaneous viral clearance and a faster progression to end-stage liver diseases[20]. Recent studies demonstrated that HBV, which was typically non-cytopathic, could become cytopathic through unchecked replication in the presence of severe immunodeficiency[21].

In HIV/HBV-coinfected individuals, certain cancer-associated gene mutations more frequently occurred; this may be related to both viruses having reverse transcriptase and being able to partially share these reverse transcriptase enzymes[22]. Although the majority of scholars believe that HIV does not infect hepatocytes, the HIV trans-activating protein TAT can be detected in hepatocytes, and TAT in hepatocytes contributes to the development of HCC (Fig. 3)[23].

Influence of HBV on HIV disease progression

An active immune response in HBV chronically infected individuals may promote HIV replication (Fig. 4). In addition, HBV may accelerate the apoptosis of $CD4^+$ T lymphocytes and delay immune reconstitution after ART. Compromised $CD4^+$T cell recovery in coinfected individuals[24] may be due to the following three reasons:

- Immunological recovery may be negatively impacted by HBV replication. In both untreated and treated HIV/HBV coinfection, apoptotic pathways are activated, which accelerates $CD4^+$ T cell depletion.
- Chronic HBV infection may trigger certain levels of systemic immunological activation and heighten T-cell depletion.
- HBV-associated liver fibrosis may lead to increased splenic damage to lymphocytes and impaired T-cell recovery.

A cohort study showed that recovery of $CD4^+$ T lymphocytes was significantly slower in coinfected individuals than in those with HIV infection alone during the first 3 years of ART. In addition, HBV X protein was shown to be capable of inducing HIV replication, suggesting that HBV promotes disease progression in HIV-infected individuals[25].

Other possible mechanisms in the pathogenesis of HIV/HBV coinfection

- CXC motif chemokine 10 (CXCL-10).

CXCL10, also known as interferon γ-inducible protein 10 (IP-10), binds to chemokine receptor 3 (CXCR3) and recruits CXCR3-expressing cells such as B cells, activated T cells, and NK cells to the sites of inflammation[26].

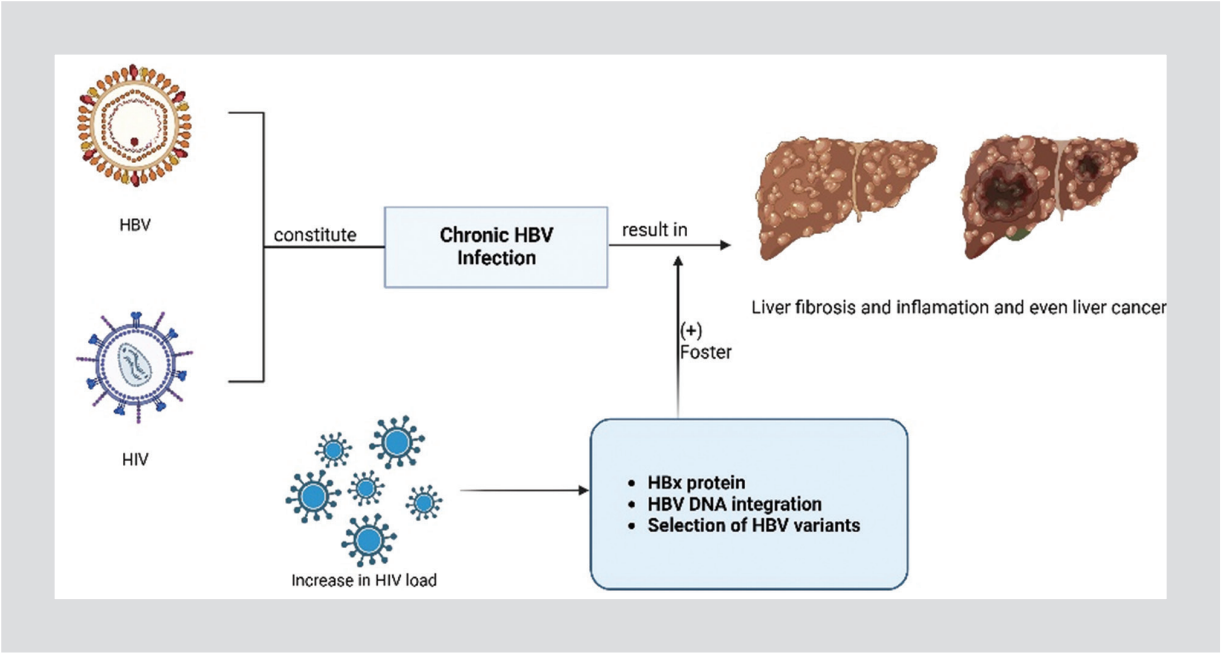

Figure 3. *HBV/HIV coinfection increases the risk of hepatocellular carcinoma (HCC). Interaction between HBV and HIV finally causes cirrhosis and HCC in individuals. Created with BioRender.com.*

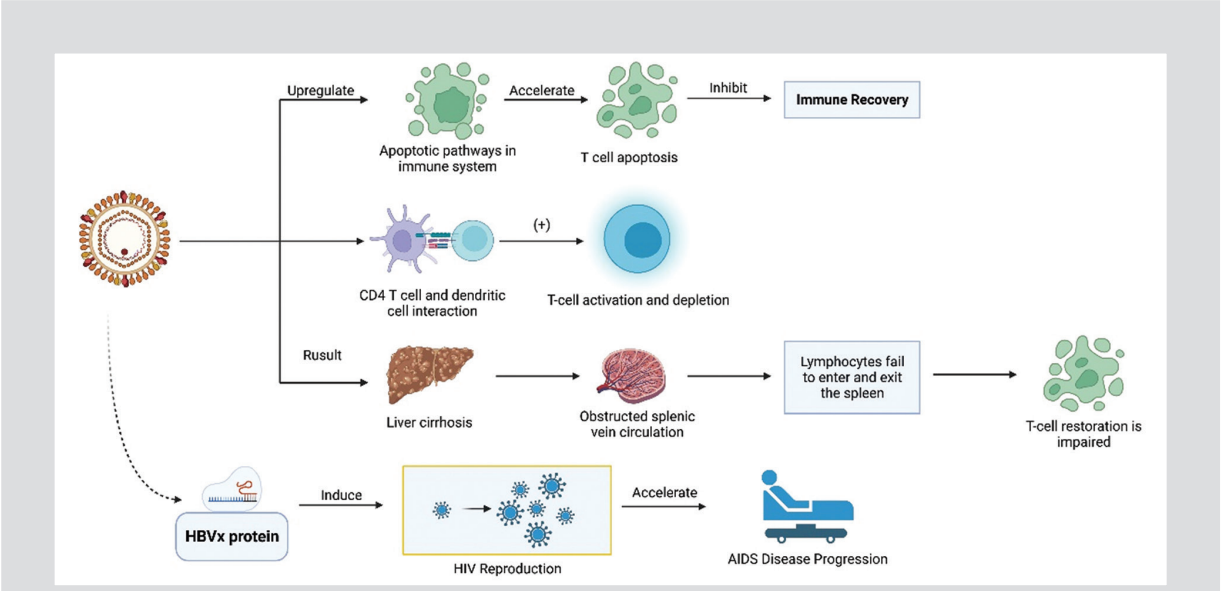

Figure 4. *Influence of HBV infection on HIV disease progression. The virus on the left is HBV. HBV can affect the progression of AIDS in a number of ways, and it is noteworthy that the HBV X protein may be able to accelerate HIV replication, which we guess may be related to the fact that the two viruses partially share the reverse transcriptase enzyme. Created with BioRender.com.*

Increased CXCL10 expression in HIV/HBV coinfection is associated with accelerated liver damage, as demonstrated by immunohistochemical staining of CXCL-10 in liver tissues[27]. HIV gp120 can bind to CXCL10 on HSCs and cause pro-fibrotic gene expression and inflammation in the liver[28]. There is strong evidence that HIV can infect human hepatocytes[29-31]. In parental and HBV-transfected hepatocyte cell lines, in the pres-

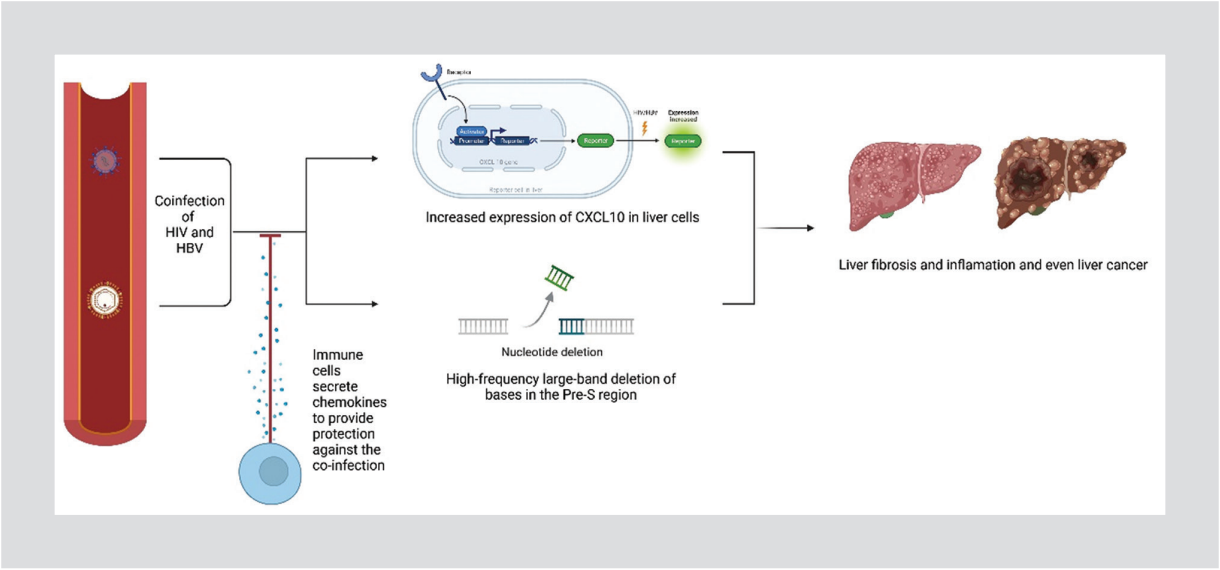

Figure 5. *HIV/HBV infection-related molecules. HBV/HIV accelerates the progression of liver-associated disease by increased expression of CXCL10 in liver cells and increased loss of Pre-S proteins, but human immune cells can inhibit this process by secreting CXCL10 and other factors that antagonize viral. Created with BioRender.com.*

ence of IFN-γ/P3CSK4, HIV infection of hepatocytes led to a notable rise in CXCL10 synthesis, indicating that CXCL10 production was dependent on viral integration or subsequent viral replication. Studies show that IFN-γ, CXCL10, CXCR3, and HIV DNA and RNA have significant and complicated interactions.

The conclusion is that individuals coinfected with HIV and HBV exhibit liver disorders characterized by an elevated presence of intrahepatic mRNA for CXCL10 and CXCR3. Furthermore, there is a pronounced association between CXCL10 and intrahepatic HIV DNA and RNA but not with HBV replication. In this study, investigations have established that the coinfection of hepatocytes with HIV and HBV *in vitro* significantly amplifies the production of CXCL10. Hepatic CXCL10 and CXCR3 mRNAs are associated with liver fibrosis and inflammation after hepatocyte coinfection with HIV. HBV may also expedite liver damage in individuals who are coinfected with HIV.

- High-frequency deletion of the HBV Pre-S region in coinfection may be associated with accelerated liver disease progression. A study from Taiwan reported that the HBV Pre-S gene encodes large, medium, and small surface proteins and that deletion of the Pre-S gene produced a large number of truncated large HBsAg. These truncated large HBsAg were retained inside cells, forming ground-glass hepatocytes, which led to endoplasmic reticulum stress and increased oxidative production. Oxidatives damage DNA and stimulate the expression of aberrant tumor-associated genes[32]. In addition, the truncated large HBsAg may function as a trans-activator, upregulate cyclin A expression and suppress cyclin D1 expression, eventually causing the formation of hepatic nodules in transgenic mice[33]. Research found that a high-frequency deletion of the Pre-S region predominated in HIV/HBV-coinfected individuals[34]. These results may partly explain why hepatic diseases progress faster in HIV/HBV-coinfected individuals[34].
- CCR5Δ32 provides protection against HIV infection, but it is yet unknown whether it also offers protection against HBV infection. CCR5 is one of the HIV co-receptors, and CCR5Δ32 refers to a 32-base deletion in the coding region of the CCR5 gene. Expression of heterozygous CCR5Δ32 on the cell surface is decreased, and individuals with the homozygous CCR5Δ32 gene are fully protected from HIV infection[35]. Studies have demonstrated that CCR5Δ32 nearly halves the risk of developing persistent HBV infection and exhibits nearly identical levels of protection against HBV infection in both HIV-negative and positive pairings, which raises questions regarding its potential effects on the pathogenesis and prognosis of HBV infection[36]. It has been proposed that CCR5Δ32 deficit or haploinsufficiency may modify the susceptibility to HBV infection and interfere with the immune system's

ability to respond to HBV infection[37]. However, a study in southern Brazil failed to find any protective effects of CCR5Δ32 in both HBV monoinfection and HBV/HIV coinfection.

Impact of early diagnosis and intervention on the prognosis of patients with HBV/HIV coinfection

- For HIV, the early start of ART reduces the damage to the immune system and the size of the HIV reservoir.
- For HBV, the morbidity of cirrhosis and HCC is reduced.
- For both viruses, their transmission can be prevented.

In 3625 individuals with HBV/HIV coinfection, the incidence of HCC was unchanged in those getting TDF or TAF treatment but rose in those receiving regimens without TDF or TAF[38]. In a study of antiretroviral-treated HBV monoinfected individuals (n = 53,974 cases) and HBV/HIV-coinfected individuals (n = 822 cases), the incidence of HCC was lower in the latter group than in the former[39]. Similar to this, a study using claims data found that individuals with HBV/HIV coinfection (n = 7764) had a lower risk of HCC than those with HBV monoinfection (n = 13964)[40]. These findings imply that universal antiretroviral treatment for CHB individuals may lower the risk of HCC if HIV coinfection serves as a surrogate for early HBV antiviral therapy.

Research on the evolution study of HBV in individuals coinfected with HIV undergoing ART

At least eight HBV genotypes named A-H have been identified[41]. The distribution of HBV genotypes is geographically specific with genotypes B and C predominating in China[42,43]. Different genotypes not only affect the course and outcome of HBV disease but also the efficacy of antiviral drugs.

Some studies indicated[44] that HBV genotypes changed with the use of lamivudine, adefovir, and entecavir (ETV), but the reason behind this finding was not clear. It is possible that viral mutations occur under the pressure of antiviral drugs and that new dominant strains are selected to adapt to the changing environment. The time of genotypic change emergence varies in different individuals after ETV treatment. Some individuals undergo genotype switching within a short period of time after ETV starts, while others do so over a long period of time[44].

Increased HBV replication affects viral genetic variation, and deletions in the Pre-S1/S2 region are frequently seen in HIV/HBV-coinfected individuals[45], suggesting that variability in the Pre-S/S region may be related to the selective pressure on this region. This study also indicated that the contribution to HBsAg false negativity may be due to the presence of several mutations that may have the potential to alter protein secretion from hepatocytes or to change protein structure, inhibit antibody binding in the detection assay, and/or reduce the overall replication efficiency of the virus.

The natural course of HBV infection is adversely affected by HIV. Viral persistence is related to chronic course, liver disease, and mortality[46,47].

The clearance rate of HBeAg is 5-fold lower in coinfected individuals compared to HBV-monoinfected individuals in the absence of antiviral treatment[47,48].

HBV evolutionary rates are estimated based on the nucleotide sequences of the S or pre-C/C region and expressed as the number of nucleotide substitutions per site and per year. In the case of coinfection, the estimated rates in HBV-monoinfected individuals in the S and pre-C/C regions were 5-fold and 2-fold higher than those in coinfected individuals, respectively[41]. Moreover, when the intra-host analysis of the genetic distance was performed, there was no significant difference in the mean distance between clones calculated from the S gene in HBV-infected individuals and HBV- and HIV-coinfected patients. Since individuals with coinfection appeared to have weaker immunological pressure and significantly lower CD4-T cell numbers, these data point to a possible consequence of stronger immune pressure in HBV-infected individuals. This reasoning is reinforced by earlier research showing that in individuals coinfected with HIV and HBV, lower CD4-T cell numbers were associated with decreased HBV-specific T cell responses in terms of size, frequency, and quality[49]. Even so, in individuals coinfected with HIV and HBV, the prevalence of mutations under positive selection was lower. This is in line with the weakened HBV-specific T-cell response seen in coinfections of HIV and HBV[45].

Interestingly, the identification of these mutants in the baseline sera highlights the circulation of HBV lamivudine resistance mutants（S135Y、V173L、T128I、V142A 和 L229M） in this geographical area and clinical setting[50], which is characterized by a high proportion of drug addicts. The increasing circulation of these resistant mutants is significant for public health and may impact the currently applied antiviral therapies. The determination of HBV variants is crucial in the management of HIV-1/HBV-coinfected individuals undergoing treatment, emphasizing its importance in clinical practice.

Furthermore, the high number of Pre-S/S mutants found in HBsAg-negative individuals at baseline and the persistence of these mutants in other genomic regions throughout the long observation period undergoing ART, extending up to 9 years, is noteworthy. To our knowledge, this is the longest HBV whole-genome analysis conducted on HIV-1/HBV-coinfected individuals[50].

Hepatitis delta superinfection in HIV/HBV coinfection

A recent study conducted in Europe revealed that approximately 15% of individuals with serum HBsAg positivity are also positive for anti-HDV[51]. A number of systematic reviews have shown that the prevalence of anti-HDV positivity in HBsAg+ individuals in China ranges from 2.1% to 5.57%[52-54], which is significantly increased compared with that a decade ago. However, these findings across different studies exhibit considerable variation, with positivity rates being lower relative to those reported in Europe. This could be attributed to the lower HDV screening rate and the larger population of HBsAg-positive individuals in China.

Notably, the demographic profile of individuals with HDV infection has undergone significant changes in the last few decades[51]. While injection drug users in Europe were predominant in the 80s, there has been a shift toward immigrants and refugees from HDV-endemic regions in later years[55]. However, in regions where any of these viruses are endemic and access to mother-to-child preventive measures is limited, perinatal transmission of HIV, HBV, and HDV occurs. At present, hepatitis delta is frequently diagnosed in individuals engaged in high-risk behaviors such as drug-involved sexual activities ("slamming"). This hints at the possibility of triple infections in endemic regions, and thus, further attention is warranted[55].

Chronic hepatitis delta has the potential to progress to liver cirrhosis in approximately half of the individuals within an average of 5 years, which is faster compared to chronic hepatitis B or C. The progression to HCC in individuals coinfected with HIV and HDV may be accelerated due to a convergence of distinct pathogenic insults. HDV's intrinsically harmful effects result in more inflammation, fibrosis, and cirrhosis than other hepatitis viruses[56]. In addition, for HIV/HBV/HDV-coinfected individuals, the persistent direct carcinogenic effects of HBV, the liver damage associated with HIV immunodeficiency, and the specific carcinogenic impact of high HIV-RNA all contribute to this accelerated path[1]. Comorbidities, such as the toxic and metabolic effects of antiretroviral drugs and high rates of alcohol and tobacco consumption, further heighten the risk of HCC among PLWH with hepatitis delta infection[57]. According to new research, hepatitis delta has become a leading cause of liver transplantation in Europe[58].

In summary, hepatitis D is associated with a higher incidence of decompensated liver diseases, HCC, and liver-related mortality. We should not ignore the possibility of simultaneous superinfection with HDV in HBV/HIV-coinfected individuals. Moreover, this can be seen as a consensus that all HBsAg-positive individuals with HIV should be routinely screened for HDV infection with anti-HDV Ab. Serum HDV RNA should be checked to confirm an active infection if anti-HDV Ab is positive.

Conclusion

It is widely accepted that the major cause of damage to hepatocytes is not direct HBV replication in hepatocytes but instead the immunopathological harm brought on by the interactions between HBV and the hosts. Certain factors have been demonstrated to be involved in the increased likelihood of HBV insertional mutagenesis, the high frequency of Pre-S gene deletion, and elevated chemokine levels in HIV/HBV coinfection. These factors include suppressed immune reconstitution, increased circulatory LPS levels, and an abnormal immune attack against HIV/HBV antigens in the liver. Without effective ART, the speedy development of cirrhosis and hepatocellular cancer is expected. At present, animal models or *in vitro* cell culture systems to study HIV/HBV coinfection are lacking. Chimpanzees that are susceptible to both HIV and HBV infection are feasible as an animal model. Chimpanzees are the only animals known to be fully susceptible to human HBV infection and have a very similar host response to HBV infection as humans but with the obvious disadvantage that chimpanzees are expensive and not readily available[18,59].

The risk of IRIS and potential liver failure can be prevented in individuals with a low CD4 count with a regimen containing two active agents against HBV.

Screening for HIV, HBV, and HDV infection is essential for the early diagnosis of coinfections. It is imperative to avoid misdiagnosing individuals with monoinfections of either HIV or HBV or HDV, as such misdiagnosis may subsequently lead to inappropriate treatment regimens. The potential concurrent superinfection of HDV in individuals coinfected with HBV and HIV should not be overlooked. HIV/HBV coinfection presents a multifaceted challenge necessitating comprehensive research efforts to elucidate the intricate

interactions between these two viruses. It is hoped that HBV and HIV infections could be cured in the future with ongoing research in the HIV/HBV field.

Author contributions

JX: writing, reviewing, and editing; conceptualization; methodology; visualization; project administration; YZ: writing, reviewing, and editing; conceptualization; methodology; JW: writing, reviewing, and editing; conceptualization; methodology; XC: writing, reviewing, and editing; supervision; funding acquisition; WZ: writing, reviewing, and editing; supervision; funding acquisition.

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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