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HIV-Hepatitis B virus co-infection: epidemiology, pathogenesis and treatment

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Abstract

HIV infection has a significant impact on the natural history of chronic HBV infection, with increased levels of HBV DNA, accelerated progression of liver disease and increased liver-associated mortality compared to HBV mono-infection. Widespread uptake and early initiation of HBV-active antiretroviral therapy (ART) has substantially improved the natural history of HIV-HBV co-infection but the prevalence of liver disease remains elevated in this population. In this paper, we review recent studies examining the natural history and pathogenesis of liver disease and seroconversion in HIV-HBV co-infection in the era of HBV-active ART and the effects of HIV directly on liver disease. We also review novel therapeutics for the management of HBV with a particular emphasis on clinical strategies being developed for an HBV cure and an HIV cure and their impact on HIV-HBV co-infected individuals.

Keywords

Liver / hepatitis; Antiretroviral therapy; antiviral therapy; Pathogenesis; Reverse Transcriptase inhibitors

1. Introduction

Combination antiretroviral therapy (ART) has dramatically reduced HIV-related mortality and morbidity and increased life expectancy amongst those living with HIV. In the setting of co-infection with Hepatitis B Virus (HBV), the availability of ART, with activity against both HIV and HBV, particularly tenofovir, has led to significant improvements in outcomes. However even with effective suppression of both HIV and HBV replication, morbidity and mortality are significantly higher in those with HIV-HBV coinfection than with HIV alone [1–7] (Table 1). End stage liver disease, cirrhosis and hepatocellular carcinoma (HCC) account for an increasing proportion of deaths amongst HIV-infected individuals[8–10]. One of the main challenges in the management of both HIV and HBV is that antiviral treatment must be continued lifelong as both viruses have long lived forms that persist on antiviral therapy. Research to find a cure for both HIV and HBV is being actively pursued and will have significant implications for coinfected individuals. In this review, we will focus on the major issues related to pathogenesis and management of HIV-HBV co-infection in the setting of optimal treatment with tenofovir-based ART.

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2. Epidemiology

Approximately 37 million people are infected with HIV globally and 5–20% are also co-infected with HBV[11]. Rates of chronic HBV in HIV-infected individuals vary significantly between regions and risk based groups, reflecting different patterns of transmission (Figure 1)[5, 12–81]. For example in Vietnam, the prevalence of chronic HBV in HIV-infected individuals who inject drugs or who are sex workers (SW), is 28% and 15% respectively [50]. The prevalence of HIV-HBV co-infection overall in China has been estimated at 10% but varies between regions from 5 to 15% [25]. Accurate data are still lacking for coinfection in many parts of the world, however rates appear to be highest in parts of West and South Africa (Figure 1).

3. The HBV life cycle and effects of antiviral therapy

HBV replicates in hepatocytes[82–85]. Following entry and uncoating, the HBV genome-containing nucleocapsid is transported into the nucleus where the genome is released as relaxed circular (rc) DNA. In the nucleus, the rcDNA is converted by host cell repair mechanisms into an episomal covalently closed circular (ccc) DNA minichromosome. cccDNA is very stable, persisting indefinitely and is the main barrier to cure[85].

cccDNA is the template for all HBV RNA transcripts, leading to the production of DNA polymerase; the structural HBV 'core' or capsid protein (HBcAg); HBeAg (a secreted, soluble form of the core protein); the multifunctional X protein, involved in control of cccDNA transcriptional activity, and the envelope or surface protein (HBsAg).

The polymerase encodes the large pregenomic RNA (pgRNA) which is the RNA template for HBcAg and the polymerase protein. The polymerase and pgRNA is co-packaged into nucleocapsids with assembly of core protein subunits, triggering reverse transcription of the pgRNA to form HBV rcDNA. This is then enveloped with HBsAg and released from the cell as a mature infectious virion, or alternatively is 'recycled' to the nucleus to replenish/amplify cccDNA.

Reverse transcription of pgRNA can also lead to the formation of double stranded linear HBV DNA, which can become integrated into the host genome, similar to HIV.

Two classes of antiviral medications are approved for the treatment of hepatitis B. Pegylated interferon-alpha (peg-IFN) is infrequently used due to side effects and low rates of treatment success. Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) inhibit reverse transcription and therefore inhibit HBV DNA production (Figure 1), but do not eradicate cccDNA from infected cells, meaning that ongoing treatment is required to suppress viremia (Figure 2). Furthermore, as HBsAg is produced from separate RNA transcripts to pgRNA, production continues in the presence of HBV active NRTIs [85, 86] (Figure 2). An HBV cure has been described as 'functional' (HBsAg loss with undetectable serum DNA, allowing treatment cessation without rebound), or complete (physical elimination of cccDNA) [87–89].

4. Natural history of HIV-HBV co-infection in the era of HBV-active anti-retroviral therapy

a) Liver disease progression

Early studies of the natural history of HIV-HBV coinfection demonstrated that liver-related mortality in this population was nineteen times that in HBV infection without HBV, and 8 times higher than in individuals with HIV mono-infection. Mortality rates increased in individuals with lower CD4+ T-cell counts [90]. The NRTIs lamivudine (LMV), emtricitabine (FTC) and tenofovir (disoproxil fumurate (TDF) and alafenamide (TAF)) all have dual activity against both HIV and HBV, with TDF and TAF a pivotal therapeutic agent in this setting due to a very high barrier to HBV drug resistance. The inclusion of tenofovir for management of HBV has led to significant improvements in HBV viral control and liver fibrosis and decreased HBV drug resistance [64, 91–94]. However, recent studies continue to report that overall mortality, liver related mortality and hospital utilization rates and risk of hepatocellular carcinoma (HCC) remain elevated in HIV-HBV co-infected individuals compared to HIV mono- or HBV mono-infected individuals [2, 3, 5, 6, 8, 70, 95–99]. Furthermore, liver disease progression continues to occur in 10–20% of individuals on tenofovir-containing HBV-active ART [5, 100, 101] (summarized in Table 1).

b) Virological suppression

The vast majority of HBV-infected individuals treated with TDF have undetectable HBV DNA (lower limit of detection, LLOD<20 IU/ml). In a large prospective multi-centre international cohort of HIV-HBV co-infected individuals, we recently demonstrated that detectable HBV DNA persisted in close to 10% of co-infected individuals on TDF [92]. We observed several patterns of detectable HBV DNA. Interestingly, we and others have been unable to identify any signature drug resistant mutations in the HBV polymerase even when TDF had been administered for over five years and in the presence of detectable HBV viremia [102–105]. Furthermore, using deep sequencing of virus in plasma, we recently demonstrated that residual viremia on HBV-active ART was associated with evolution of virus sequences over time consistent with active viral replication rather than passive release from long lived reservoirs such as cccDNA [102]. Improved tools to measure low level viremia and deep sequencing are needed to better understand the clinical implications of residual HBV viremia in HIV-HBV co-infection.

c) HBsAg and HBeAg seroconversion

The formation of stable episomal cccDNA and integrated HBV DNA to a lesser extent, leads to sustained production of HBsAg even on NRTI [85, 86]. HBsAg is produced in large quantities in HBV infection and is generally considered to inhibit adaptive immunity and effective production of anti-HBV surface antibodies (HBsAb), which is required for long term HBV control [106]. Persistent high levels of HBsAg have been associated with elevated risk of HCC in untreated HBV mono-infection [107, 108]. Following antiviral treatment of HBV mono-infection, HBsAg loss is uncommon, and after 12 months treatment with NRTI or pegylated interferon (IFN), HBsAg loss occurs in of 0–3% and 3–7% of individuals respectively [109].

Various studies have shown rates of HBsAg loss and/or seroconversion might be higher in co-infection compared to mono-infection. In studies of HIV-HBV co-infection up to 22% of participants lost HBsAg, depending on duration of follow up [36, 110–118]. A higher frequency of HBsAg loss has been associated with lower CD4+ T cell count prior to initiation of HBV-active ART [114, 115, 117] and a greater increase in CD4+ T-cells following ART [115, 118] but many of these studies were retrospective or didn't include individuals with low CD4+ T-cells prior to ART. The relationship between low CD4+ T-cell count and enhanced HBsAg loss and seroconversion may potentially be secondary to brisk immune reconstitution that has been associated with high levels of IL18 production which could enhance dendritic cell function, adaptive immunity and antibody production [119].

HBsAg loss following treatment of HIV-HBV co-infection has also been associated with low HBsAg levels at baseline or with a larger decline post treatment [110, 114, 116, 117, 120] although this has largely been described in HBeAg-positive disease [114, 116] and paradoxically associated with higher baseline HBV DNA [114, 115]. In HIV-HBV HBeAg negative disease, pretreatment HBsAg level of ≤100 IU/ mm^3 was predictive of HBsAg loss. Other studies report no statistically significant associations between HBsAg titre and HBsAg seroconversion [113]. Understanding predictors of HBsAg loss is an important research priority in identifying novel strategies to achieve HBV remission and HIV-HBV co-infected individuals may represent a unique group to interrogate these associations.

HBeAg is a secreted protein that contributes to immune tolerance and viral persistence[83]. HBeAg has been shown to attenuate T cell responses to the intracellular nucleocapsid protein, with which it shares T cell epitopes, precluding elimination of HBV infected cells by T-cell mediated pathways[121].

Production of anti-HBe antibodies are considered to be indicative of virological control and precede the production of antibodies to HBsAg in the setting of acute cleared infection [82]. Mutations in the precore region that occur over time in chronic untreated HBV infection lead to viral mutants that don't produce HBeAg, and therefore HBeAg negative disease, which is associated with periods of high viral replication and necro-inflammatory activity in the liver [82]).

Following treatment of HIV-HBV co-infection with NRTIs, rates of HBeAg seroconversion range from 15–57% [111, 112, 114, 116–118, 122]. Lower baseline quantitative (q)HBeAg level and a larger decline in qHBeAg levels have been associated with increased HBeAg seroconversion [110, 114, 122]. qsAg levels at baseline has been found to predict HBeAg seroconversion in HIV-HBV[92, 110]. Studies are needed to further investigate the relationship between HBeAg seroconversion and HBsAg loss/seroconversion in HIV-HBV.

d) Hepatocellular carcinoma (HCC)

There is an approximately five- to six-fold risk increase in HCC incidence amongst HIV-infected individuals compared with the general population and this increased risk has persisted with ART [95, 123, 124].

HCC amongst individuals with HIV infection has been associated with lower CD4 T cell counts, and high HBV DNA [125, 126], however the increased risk of HCC in coinfection in the era of TDF containing HBV active ART suggests that other factors are also important. In patients with HBV monoinfection, HBV DNA suppression with NRTI has been demonstrated to lower but not eliminate the risk of HCC[127, 128]. Similar large, long-term natural history studies of HCC risk in HIV-HBV coinfection are still needed.

HIV is not sufficient to cause HCC in itself, and the exact role of HIV in promoting HCC is not well understood[125]. A significant component of the increased risk of HCC is attributable to the increased prevalence of viral hepatitis amongst HIV infected populations. The main predisposing factor for the development of HCC is the presence of cirrhosis, development of which is accelerated in the presence of HIV as discussed above. Other co-factors that may drive HCC amongst HIV infected individuals include a higher prevalence of other known risk factors including alcohol, and non-alcoholic steatohepatitis[129]. In HBV infection, HCC may also arise in the absence of cirrhosis, which may be related to intracellular persistent forms including integrated DNA. It is not known whether there is an increased risk in HCC in HIV-HBV in the absence of cirrhosis.

There is increasing evidence that certain mutations in the HBV viral genome are associated with a significantly increased risk of progression to HCC in individuals with HBV monoinfection. The double mutation T1762/A1764 in the HBV basal core promotor in HBV genotypes B and C, may be detected in plasma up to 8 years prior to HCC diagnosis and is a risk factor for developing HCC [130]. This same double mutation T1762/A1764 was found more commonly amongst those with HIV-HBV in some studies [131] but not others [132–134].

PreS deletion mutants have also been significantly associated with increased risk of HCC in prospective studies of HBV mono-infected individuals[135] , and were found to be more common in HIV-HBV coinfected individuals[131, 133]. Mutations in the HBsAg can lead to accumulation of HBsAg in hepatocytes and consequent cytotoxicity of the endoplasmic reticulum, the generation of reaction oxygen species, DNA damage and genomic instability[136]. Further long term follow-up of HIV-HBV co-infected individuals with specific mutations in HBV is still needed to fully understand the risk for increased progression to HCC.

e) Drug resistance

TDF has been demonstrated in a wide range of studies to retain anti-HBV activity in individuals who have failed LMV [113, 137, 138]. In a recent study from India of TDF treatment in HBV mono infected individuals with long durations of preceding LMV exposure, 40% of individuals had treatment failure[139]. A longer time to viral suppression in individuals with preceding LMV exposure has been demonstrated in other studies, in contrast to the antiviral response seen in treatment naïve individuals[140].

The persistence of detectable HBV DNA in plasma in HIV-HBV coinfected individuals taking tenofovir has been investigated by a number of groups. In most cases, TDF-associated mutations have not been detected and adverse clinical outcomes have not been observed, with most individuals achieving an undetectable DNA with time [103, 104, 141]. Previous

exposure to LMV as well as higher HBV DNA have been associated with a longer time to an undetectable HBV DNA on TDF [104]. The HBV polymerase mutations rtA282T/V and/or NS236T were reported as being associated with reduced potency of TDF [142], but this was not confirmed in subsequent studies [92, 104] or in cases of virological failure, which is more commonly related to poor adherence [92].

f) Immune Reconstitution Disease (IRD)

IRD or Immune reconstitution Inflammatory Syndrome (IRIS) is defined as worsening symptoms related to an opportunistic infection or malignancy in an HIV-infected individuals following initiation of ART [143]. In HIV-HBV co-infection, IRD is defined as a hepatic flare or a significant increase in hepatic transaminases following initiation of ART. We previously showed that in a cohort of HIV-HBV co-infected individuals initiating ART with advanced disease (median CD4+ T-cell count being 50 cells/μl) in Bangkok Thailand, 22% had a hepatic flare consistent with IRD. Our study confirmed the findings of others that a high pathogen load (as measured by HBV DNA prior to ART), high baseline alanine transaminase (ALT) and a low CD4+ T-cell count were the biggest risk factors for developing HBV-related IRD [144, 145]. The immunological drivers of IRD are still unknown although may potentially be secondary to persistent elevation of the interferon stimulated gene CXCL10 leading to enhance T-cell recruitment to the liver following ART initiation [145, 146]. (summarized in Figure 2)

The occurrence of hepatic flares has been linked to seroconversion in Hepatitis B monoinfection. In HIV-HBV coinfection, IRD may be reflecting a similar process and this may be the basis for the increased levels of HBsAg loss and seroconversion seen in HIV-HBV co-infecion. In three HIV-HBV infected individuals with hepatic flare following commencement of TDF-containing ART, a significant decline in qsAg levels was observed [146].

5. Pathogenesis

The mechanism of how HIV infection accelerates the progression of HBV-related liver disease, particularly in the presence of HBV-active ART, is multifactorial. Potential factors include the direct interaction of HIV and HBV in target cells such as the hepatocyte, direct infection by HIV of multiple cells in the liver, increased microbial translocation and elevated lipopolysaccharide (LPS) in the portal and systemic circulations activating Kupffer cell and hepatic stellate cell (HSC) activation, and exhaustion of HBV-specific T-cells (Figure 3).

a. HIV replication in the liver

A number of studies have shown various cell types in the liver are permissive to HIV infection *in vitro* including HSC[147], Kupffer cells [148, 149] and hepatocytes [150, 151]. HIV infection of these cells has also been demonstrated *in vivo* in individuals naïve to ART [152, 153] and HIV sequences from the liver in individuals off ART have distinct compartmentalised sequences when compared to other tissue sites [154]. There have been few studies to determine whether HIV persists in the liver on ART but studies of animal models, including SIV-infected macaques and HIV-infected humanized mouse models both suggest

that HIV can persist in the liver on ART, primarily in Kupffer cells [155, 156]. Recently, infectious replication competent HIV was isolated from Kupffer cells obtained from liver at autopsy from three HIV-infected individuals who died on ART [148].

In the absence of virus replication on ART, HIV may also contribute to liver inflammation and fibrosis by binding of gp120 to CXCR4 which is expressed on hepatocytes and HSC [157]. The effect of HIV infection and or HIV proteins in the liver has primarily been studied in the context of HIV-HCV co-infection *in vitro* but not in HIV-HBV co-infection. HIV infection alone, or in the presence of HCV, induced profibrotic processes in hepatocyte and HSC cell lines including increased chemokine production, HSC migration, hepatocyte apoptosis and expression of profibrotic genes [158, 159].

c) HIV, microbial translocation and immune activation

In untreated HIV infection, depletion of $CD4^+$ T-cells in the gastrointestinal (GI) tract leads to increased microbial translocation [160], resulting in elevated levels of circulating LPS. LPS binds to toll like receptor (TLR)4 and activates nuclear factor kappa B (NF-kB) and other pathways leading to the production of pro-inflammatory cytokines. In HIV-infected individuals, there is dysregulation of the TLR4 response to LPS *ex-vivo* [161]. As the liver is the first organ to filter blood from the GI tract, the concentrations of LPS in the portal veins is elevated and Kupffer cells have a "tolerised" or reduced response to LPS [162]. We have demonstrated persistently elevated levels of circulating LPS in HIV-HBV co-infected individuals compared to uninfected controls and HBV mono-infected individuals [163], however, we did not find a direct correlation between elevated circulating LPS and liver fibrosis consistent with similar studies in HIV-HCV co-infection [164–166]. It is possible that the concentration of LPS in the portal vein and/or in the liver, which are both difficult to measure, may be more important than LPS levels in blood in driving liver disease.

Recent studies in SIV-infected rhesus macaques suggest that increased microbial load in the liver can also trigger chemokine production and an increased infiltrate of CXCR6+ activated NK cells, which may contribute to liver fibrosis [167]. We have also demonstrated that the chemokine CXCL-10, ligand for CXCR3 which is expressed on activated T-cells, is associated with elevations in liver enzymes in HIV-HBV co-infection and may contribute to liver disease via migration of activated T-cells to the liver [163]. Inhibition of these chemokines may potentially play a role in reducing liver disease in HIV-HBV co-infection and should be further explored.

d) Immune exhaustion and tolerance

PD-1 is upregulated on total and HBV-specific CD8+ T-cells in treated and untreated chronic HBV infection but this has not been examined in HIV –HBV co-infection [168]. We have previously shown that HBV-specific T cells are infrequently detected in chronic HIV- HBV co-infection and do not increase in frequency following ART [169]. Immune checkpoint blockade with anti-PD1 and anti-CTLA4 have recently been licensed for the treatment of malignancy [170] and may potentially have effects on both HIV-specific and HBV-specific T-cells and clearance of persistent virus. The safety of these antibodies in the setting of HIV or

HBV mono-infection for the treatment of malignancy and as strategies for cure are currently being explored (Table 2).

6. Treatment

The most common treatment for HIV-HBV co-infection is HBV-active ART, which includes two NRTI, usually either lamivudine or emtricitabine together with tenofovir [171]. Limited studies of interferon have been performed in HIV-HBV co-infected individuals since the widespread availability of HBV-active ART, but recent studies have shown that the addition of pegylated interferon to HBV-active ART in HBeAg positive co-infected individuals did not lead to increased rates of HBeAg or HBsAg clearance, despite faster declines of antigen levels during treatment [172, 173].

a) New antivirals for HBV

i) Tenofovir alafenamide—Tenofovir alafenamide (TAF) is a prodrug of tenofovir that has activity against HIV-1, HIV-2 and HBV [174] with higher intracellular concentrations in PBMCs and hepatocytes relative to plasma compared with TDF, thereby allowing for lower dosing and reduced toxicity [174]. TAF has reduced adverse effects on renal function and bone mineral density seen while maintaining high rates of viral suppression in both HIV and HBV [138, 174].

In HIV-HBV co-infection, switching from a TDF to a TAF-containing regimen demonstrated similar high levels of HBV virological control (ClinicalTrials.gov number NCT02071082) [175, 176].

ii) HBV entry inhibitors and others—New antiviral agents currently in development for HBV include inhibitors of HBV entry, conversion of relaxed circular (rc)DNA to cccDNA and capsid assembly, but none of these agents are licensed nor have they been evaluated in HIV-HBV co-infection (Table 2). The synthetic lipopeptide, Myrcludex-B™ (Universitatsklinikum Heidelberg, Heidelberg, Germany) which is derived from the HBV L-protein competes with the viral pre-S1 motif for binding of the NTCP receptor, blocking *de novo* HBV infection [177]. A large randomised phase 1b/2 clinical trial comparing Myrcludex-B™ to entecavir in chronic HBV is in progress (Clinicaltrials.gov NCT02637999). Other drugs already in use that block the *in vitro* interactions of HBV with NTCP include the immunomodulatory agent CyclosporinA, anti-retroviral ritonavir, ezetimibe (cholesterol lowering) and irbesarten (anti-hypertensive angiotensin II receptor antagonist) [178]. Recent studies have identified new small molecules (derivatives of CyclosporinA) which are able to inhibit HBV viral attachment, without impairing the NTCP-dependent uptake of bile acids, suggesting that these functions may be separated [179].

b) New antivirals/strategies for HIV and their impact in HIV-HBV co-infection

i) Integrase inhibitors—In the 2016 updated WHO adult HIV treatment guidelines, first line recommended regimens have been updated to include integrase strand transfer inhibitors (INSTI) [171], consistent with guidelines from high income countries . Three INSTI

dolutegravir (DTG), raltegravir (RAL) and elvitegravir/cobicistat (EVG/c) are now in widespread use.

In phase 3 randomised studies of DTG, individuals coinfected with HIV and HBV or HCV (n=324, 11% of total) were more likely to experience liver enzyme flares which was attributed to IRID [180]. In ART naïve individuals less liver enzyme elevations were seen in those with HIV and HBV/HCV who were on DTG in comparison to RAL. In combined analysis of three double blind, randomized controlled studies of RAL in HIV, 6% of individuals (34 of 563) had hepatitis B or C coinfection [181]. Liver enzyme elevations were again more common in coinfected individuals, however clinical sequelae were not seen, and there was no difference in efficacy in terms of HIV suppression between RAL and control groups. Similar results were seen in subsequent observational studies including over 150 individuals commenced on RAL, coinfected with either HCV or HBV [182].

EVG/c is of particular interest in new strategies to manage HIV-HBV co-infection as this was the first INSTI coformulated with TAF (in addition to cobicistat and emtricitabine) as a single table regimen for treatment of HIV. The 48 week outcomes from an open-label, non-comparative study evaluating the efficacy and safety of switching to this combination in HIV-HBV coinfected adults without cirrhosis and with CD4 count>200 cells per μL (n=72) were recently published [176]. All individuals with suppressed HBV DNA at the time of switch (n=62, 86%) continued to remain suppressed, with seven of the remaining 10 participants becoming undetectable by week 48. Creatinine clearance improved and statistically significant decreases in markers of bone turnover were observed[176]. Drug interactions are important considerations in the use of cobicistat as with ritonavir and need to be considered when treating an individuals with HIV-HBV co-infection [183].

iii) NRTI sparing regimens—Recent studies have looked at the feasibility of NRTI sparing ART regimens in HIV mono-infection to decrease toxicity and avoid drug resistance [184] . Cessation of HBV-active NRTI, including TDF, TAF, FTC or 3TC. would have significant implications for the treatment of HIV-HBV coinfected individuals and whether this is a safe option, even after HBsAg seroconversion, remains unknown.

7. Impact of HBV and HIV cure strategies

As in HIV, there has been recent increased interest in strategies that may lead to a cure for HBV. In contrast to HIV infection, there is a clear biomarker for HBV remission which is the development of antibodies to HBsAg [reviewed by Revill et al [185]]. The main barriers to cure include the persistence of cccDNA and HBsAg [88] (Figure 2). The use of currently available NRTIs can successfully suppress replication of HBV DNA and reduce but not eliminate HBsAg production but have little impact on cccDNA. Hence, in most individuals in the absence of HBsAg seroconversion, HBV DNA rebounds following cessation of NRTI [186]. Furthermore, although suppression of plasma HBV DNA leads to decreased levels of fibrosis, cirrhosis and HCC, levels of HBsAg still remain elevated which may be related to the persistence of cccDNA.

Eradication of cccDNA is the ultimate goal of cure strategies for HBV, however other interim goals including the clearance of HBsAg or seroconversion persisting off treatment which may also be beneficial in terms of clinical outcomes and is sometimes described as a 'functional cure'. Current strategies to eliminate cccDNA include pro-apoptosis, gene editing and immunomodulatory strategies as summarised in [88, 177] and their potential effects on HIV infection are summarized in Table 3a. Similarly, some of the current strategies being developed for HIV cure, such as latency reversal using histone deacetylase inhibitors or reversal of immune exhaustion with immune checkpoint blockade –have the potential to have adverse effects on HBV replication and/or hepatic inflammation [145] (Table 3b). HIV-HBV co-infected individuals have often been excluded from clinical trials of agents aimed at curing either HIV or HBV but in the future, it will be important for this population to have the opportunity to participate in these clinical trials

Conclusion

Despite highly effective HBV-active ART, liver related mortality remains elevated in HIV-HBV co-infected individuals and fibrosis is still accelerated in some individuals. There are multiple mechanisms through which HIV can adversely affect HBV pathogenesis, even on suppressive HBV-active ART. New treatment strategies should be explored to reduce fibrosis, which still occurs in a subset of HIV-HBV co-infected individuals on ART. In the future, specific consideration of HIV-HBV co-infected individuals will be required when assessing the role of new antivirals for HBV, nucleotide sparing regimens and any HIV or HBV cure interventions.

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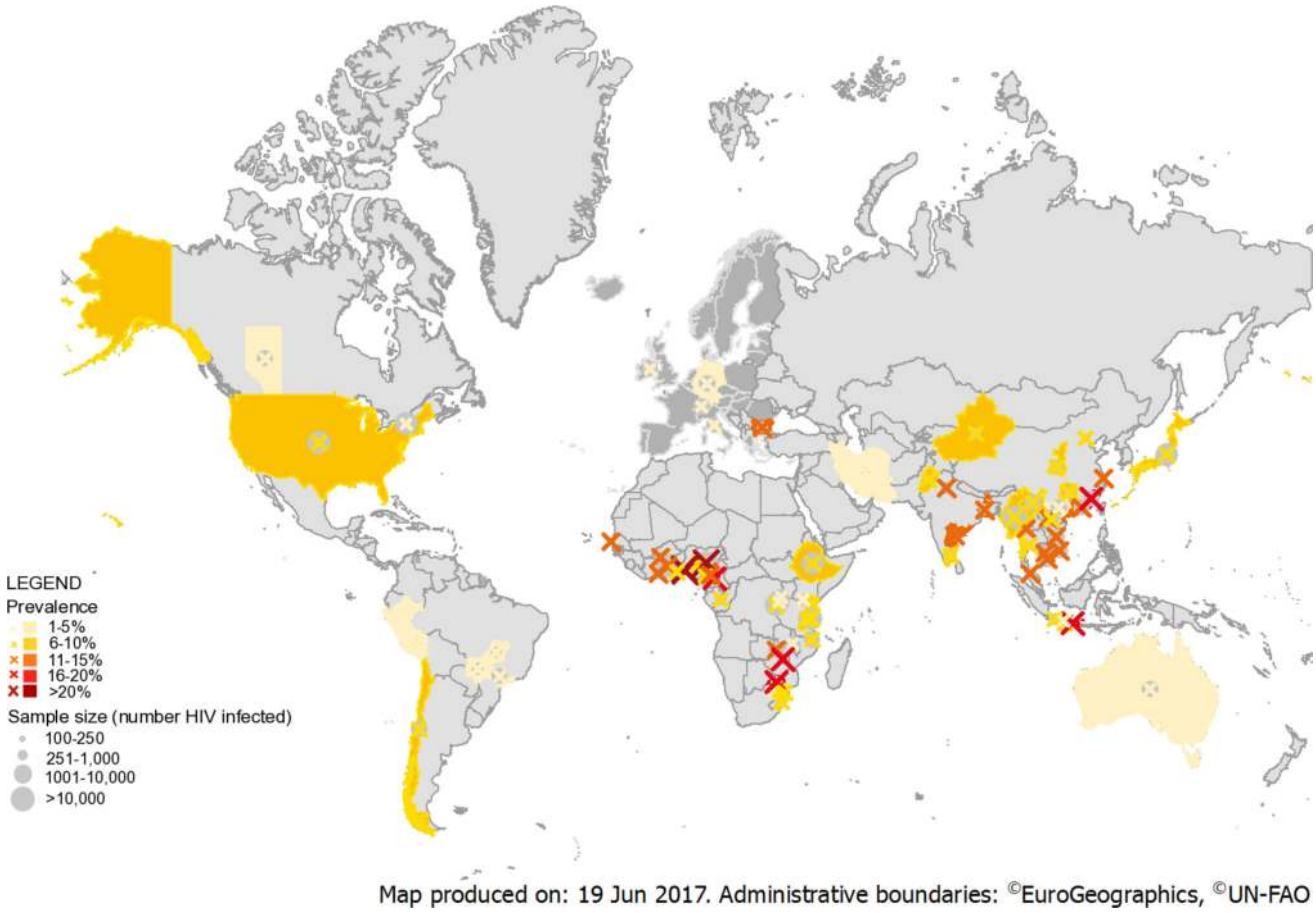

Figure 1. Prevalence of chronic hepatitis B amongst HIV infected individuals

Prevalence rates reported in the last 5 years from studies that included a minimum of 100 HIV-infected individuals are shown in graduated colours (filled and crosses). The number of HIV infected individuals surveyed in each study is represented by the size of the grey circles. Many regions have not formally evaluated prevalence and these regions are represented in white. Created using EMMa ECDC map maker[237].

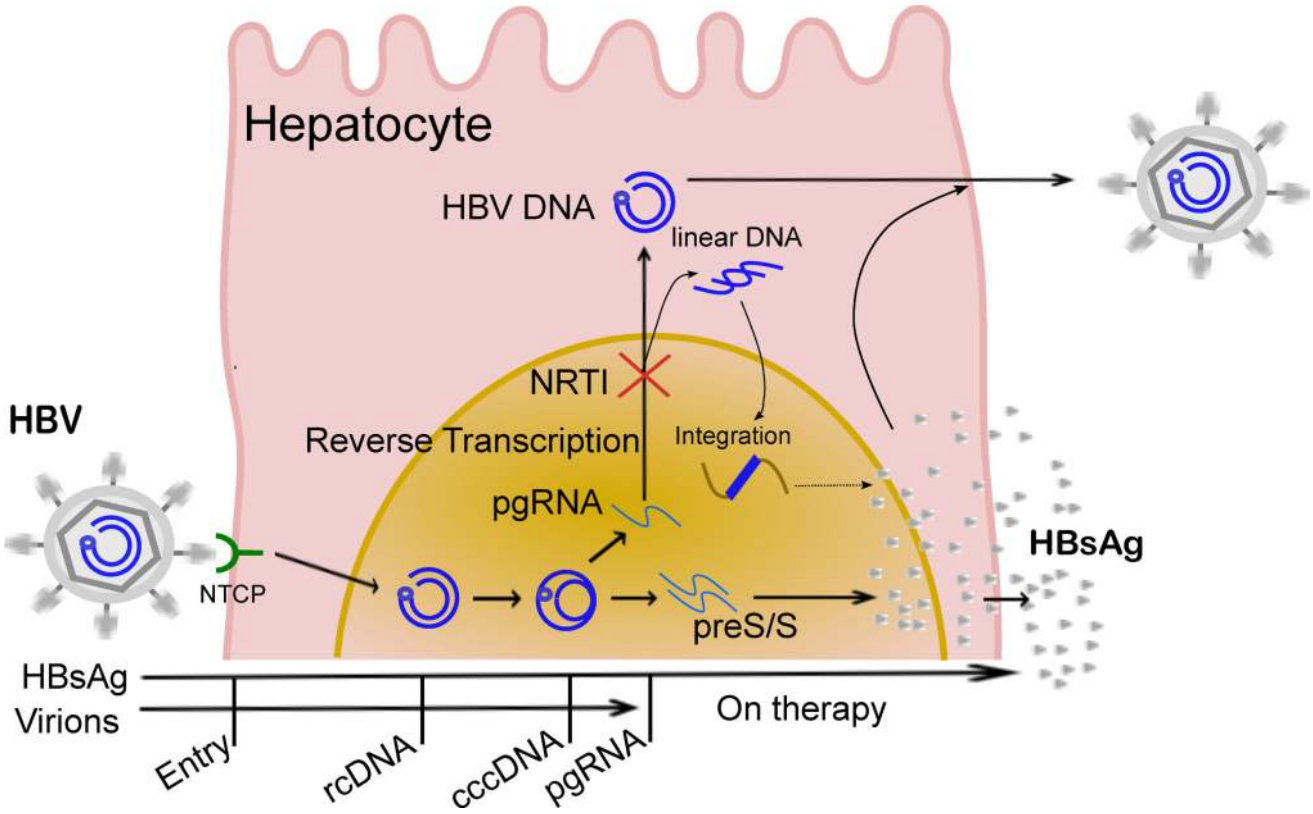

Figure 2. Hepatitis B (HBV) replication

HBV enters the hepatocyte upon binding to the putative sodium taurocholate co-transporting polypeptide (NTCP) receptor. Following entry and uncoating, relaxed circular (rc) DNA and then covalently closed circular (ccc) DNA minichromosome is formed. cccDNA is then transcribed into pregenomic RNA (pgRNA) and ultimately HBV DNA (following reverse transcription) which can be blocked by nucleos(t)ide reverses transcriptase inhibitors (NRTIs). HBsAg is coded for by preS1 and preS2/S from separate RNA transcripts and is produced even in the presence of NRTIs. HBV can also become integrated into the host genome and produce HBsAg.

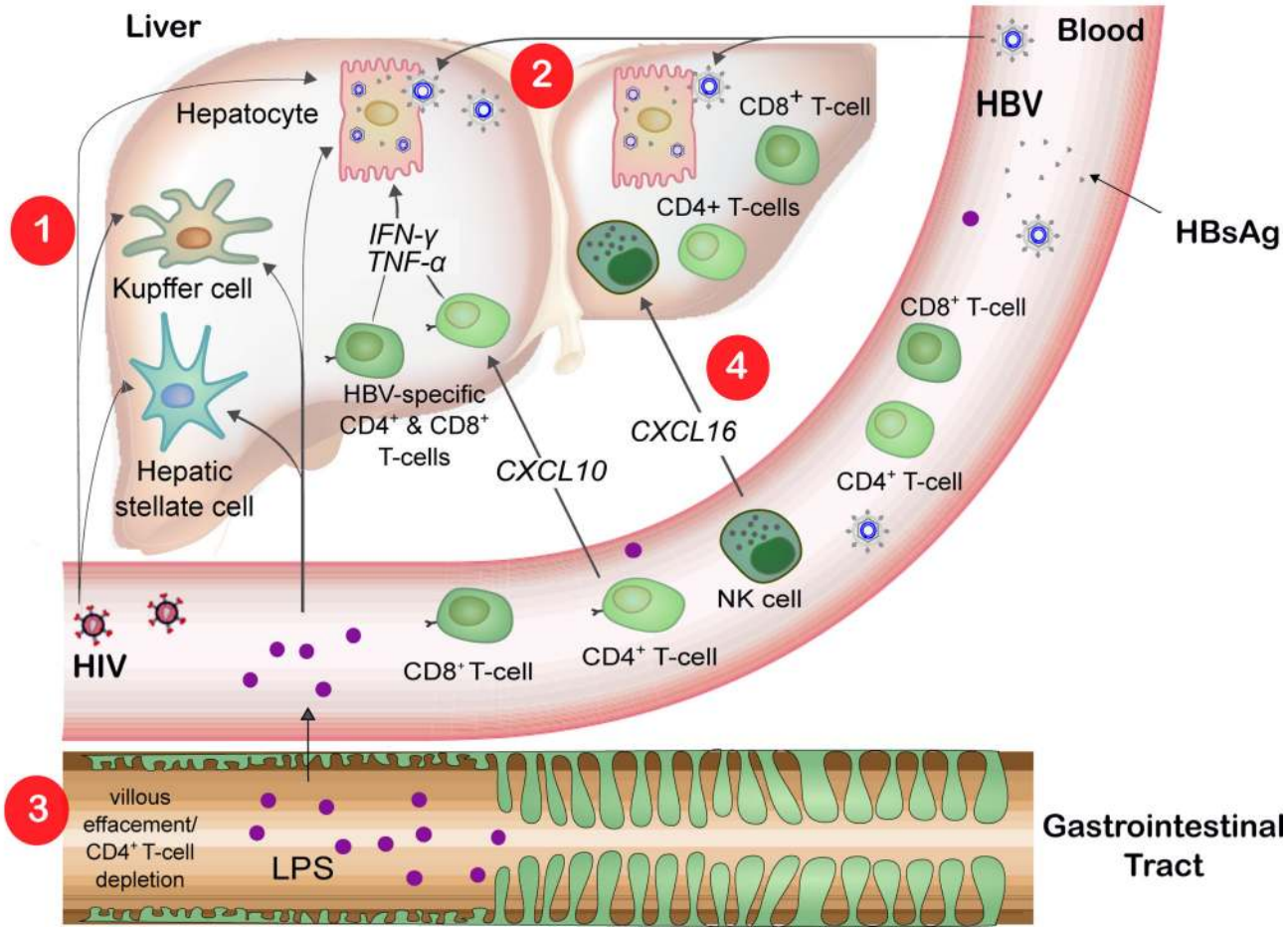

Figure 3. Effects of HIV and HBV on the liver and circulating HBV-specific immune cells

1. HIV has been shown to directly infected hepatocytes, hepatic stellate cells (HSC) or Kupffer cells while 2. HBV only infects hepatocytes. 3. HIV can also significantly impair the integrity of the gastrointestinal tract leading to elevated levels of lipopolysaccharide (LPS). LPS can directly activate Kupffer cells and HSC leading to increased intrahepatic inflammation and fibrosis. 4. In HBV infection, liver disease can also be mediated by migration from the blood to the liver of HBV specific and non-HBV specific T cells, CXCR6+ NK cells (by chemokines CXCL10 and CXCL16 respectively) and monocytes (by chemokine CCL2). (adapted with permission from Chang et al[238])

Table 1

Impact of HIV-HBV co-infection in the era of HBV-active ART containing TDF

Author, year	Location	number HIV participants	HBsAg, %	Deaths, n	Duration Follow-up, years	HBV-active ART, %	HBV-active agents	Outcomes
Weber *et al*, HIV Med 2012 [7]	Switzerland	9,053	11	459	4	68	N/A	• Increased risk of death (any cause) associated with 'active' HBV (HBsAg +/eAg+ or HBV DNA+) IRR 1.60 (1.12–2.27)
Chun *et al*, JAIDS 2012 [1]	US	2352	3	NR	9	93	LMV, TDF or FTC	• Increased risk of AIDS or death (combined) in chronic HBV
Coffin *et al* 2013, J Clin Virol [5]	US	1,400	3	NR	6	94	TDF+FTC/LMV	• Significant liver disease in ~11%
Ladep *et al* J AIDS Clin Res. 2013 [187]	Nigeria	3,833	20	38	4	100	TDF/FTC.	• HBsAg+ not a predictor of mortality (in the TDF era)
Van Griensven *et al*, PLOS One 2014 [57]	Cambodia	3,089	11	240	4	100	22.6% on tenofovir after 2 years	In HIV-HBV: • Smaller increase CD4 count at 1, 3 and 5 years in co-infected • 60% higher mortality • Increased risk liver toxicity.
Morlat *et al*, AIDS 2014 [6]	France	82,000	13	728	5	73	N/A	• 13% deceased had HIV-HBV compared with 8% non-deceased • Liver disease cause of death in 1% HIV only compared with 27% HIV-HBV
Crowell *et al* 2015, JAIDS [4]	US	15,927	13		5	70	TDF, LMV or FTC	• Higher hospitalisation rates in HIV-HBV than HIV alone
Rajbhandari *et al*, J Viral Hep 2016 [3]	US	214,620 discharges; 72,584 HBV mono-infection, 133,880 HIV mono-infection, 8,156 HIV-HBV co-infection	6		N/A	N/A		• Higher length of stay and total hospitalisation rates in HIV-HBV than either HBV or HIV alone. • Higher in-hospital mortality (11%) associated with HIV/HBV compared with HBV alone (regardless of liver disease severity)

Author, year	Location	number HIV participants	HBsAg, %	Deaths, n	Duration Follow-up, years	HBV-active ART, %	HBV-active agents	Outcomes
Chen *et al* 2016, PLOS One [188]	Asia-Pacific	5,656	11		3	100%, 90% on HBV-active ART	87% on LMV, 7% on ART containing FTC,	• Risk factors affecting mortality included HCV but not HBV co-infection.
Grant 2016, CROI[189]								•
Vinikoor 2017, CID[100]	Zambia	463	13		1	98%	TDF/FTC	• Median change in liver stiffness measurement was −0.7kPa (IQR, −1.5 to +0.3) similar with and without HBV;

*Analysis was limited to those with HBsAg test result (37.3%). NR = not reported. N/A = not applicable

Table 2

Novel strategies for the cure of (a) HBV and (b) HIV and their potential impact in coinfected individuals.

Strategy	Target	Mechanism	Class/agent (example)	Clinical development phase[a]	Ref (studies in HBV)	Potential HIV activity
(a) HBV						
↓ HBsAg production	Unknown	HBsAg release inhibitor	Rep2139 (replicor)	2	[174] NCT02565719	Unlikely (unknown)
	SiRNA	Inhibit viral protein production, enhance HBV-specific T-cell responses	ARC-520/ARC-521 (Arrowhead)	2	[175]	Unlikely (unknown)
↓ HBV replication	RNAseH	RNAseH inhibitor	Hydroxylated tropolones	Preclinical	[176]	Possible inhibition of HIV RNAseH/ Integrase [177]
	Nucleocapsid	CpAM	HAP	Preclinical	[178]	Unlikely (unknown)
		Prevent encapsidation of pregenomic RNA	Phenylpropenamide/sulphamoylbenzamide derivatives	Preclinical	[179]	Unknown
	NTCP receptor (viral entry)	Blockade/inteference	HBV pre-S1-derived lipopeptide (MyrcludexB™)	2	[180]	Unlikely (unknown)
		↓ NTCP expression	Ro41–5253 (selective RAR-antagonist)	Preclinical	[181]	Possible via RIG (activate HIV transcription/apoptosis [182, 183]
↓cccDNA	cccDNA	Inhibit rcDNA to cccDNA conversion	Disubstituted sulphonamides	Preclinical	[184]	Possible (unknown)
		Epigenetic control of cccDNA transcription	Interleukin 6	Preclinical	[185, 186]	Possible (increased in chronic inflammation [187])
		DNA cleavage enzymes	CRISPR/Cas protein endonuclease	Preclinical	[188]	Unlikely (unknown)
Apoptosis promoting	APOBEC3A/3B	Induce expression, catalysing cytidine deamination of cccDNA → degradation	Lymphotoxinβ receptor agonists	Preclinical	[189]	Restrict HIV expression [190]
Immune modulation	TLR/PRR	TLR7 agonist	GS9620 (Gilead)	Phase 2 (+ tenofovir)	[191]	LRA [192, 193]
					NCT02166047 NCT02579382	Inhibits HIV replication [194]
		TLR9 agonist	Heplisav-B (Dynavax) = TLR9 agonist (1018 ISS) and HBsAG	Phase 3	NCT02117934 [195]	LRA and increases anti HIV responses [196]
		TLR3 activation	Poly(I:C)	Phase 4 (+ entecavir)	[197] NCT02532413	TLR3 activation may reverse HIV latency [198]
	T-cell function	Reverse immune exhaustion (block negative immunoregulatory pathways)	PD-1/CTLA4 inhibitors, for example, Nivolumab/ipilimumab	Animal studies (Licensed in cancer; Phase 2 HCC including HBsAg +)	[199] NCT01658878	Likely [182]
		Therapeutic vaccination (Augment HBV-specific immune response)	Nasvac (vaccine containing HBsAg and HBcAg) and peg-IFN	Phase 3	NCT01374308	Unlikely (unknown)
		Anti-PD-1 and therapeutic vaccination	Nivolumab and GS-4774	Phase 1	[200]	Likely [182]
Strategy	Target	Mechanism	Class/Agent	Clinical development phase[b]	Ref (Studies in HIV)	Activity against HBV
(b) HIV						

Strategy	Target	Mechanism	Class/agent (example)	Clinical development phase[a]	Ref (studies in HBV)	Potential HIV activity
↓ Virus entry	CCR5 gene	Genome editing ($CD4^+$ T cells) (autologous)	Zinc Finger Nuclease	Phase 1/2	[201]	Possible – CCR5 has been implicated in immune responses to HBV [202]

Table 3

Novel strategies for the treatment/cure of (a) HBV and (b) HIV and their potential impact in co-infected individuals

(a) HBV						
Strategy	**Target**	**Mechanism**	**Class/Agent (example)**	**Clinical Development Phase***	**Refs (Studies in HBV)**	**Potential HIV activity**
↓HBsAg production	Unknown	HBsAg release inhibitor	Rep2139 (Replicor)	2	[190] NCT02565719	Unlikely (unknown)
	SiRNA	Inhibit viral protein production, enhance HBV-specific T cell responses	ARC-520/ARC-521 (Arrowhead)	2	[191]	Unlikely (unknown)
↓HBV replication	RNAseH	RNAseH inhibitor	Hydroxylated tropolones	Preclinical	[192]	Possible inhibition of HIV RNAseH/ Integrase [193]
	Nucleocapsid	Core protein allosteric modifiers (CpAM)	Heteroaryldihydropyrimidines (HAP)	Preclinical	[194]	Unlikely (unknown)
		Prevent encapsidation of pregenomic RNA	Phenylpropenamide / sulphamoylbenzamide derivatives	Preclinical	[195]	Unknown
	NTCP receptor (viral entry)	Blockade/ interference	HBV preS1-derived lipopeptide (MyrcludexB™)	2	[196]	Unlikely (unknown)
		↓NTCP expression	Ro41-5253 (selective RAR- antagonist)	Preclinical	[197]	Possible via RIG (activate HIV transcription/ apoptosis[198, 199])
↓cccDNA	cccDNA	Inhibit rcDNA to cccDNA conversion	Disubstituted sulphonamides	Preclinical	[200]	Possible (unknown)
		Epigenetic control of cccDNA transcription	IL6	Preclinical	[201, 202]	Possible (increased in chronic inflammation[203])
		DNA cleavage enzymes	CRISPR/Cas protein endonucleases	Pre-clinical	[204]	Unlikely (unknown)
Apoptosis promoting	APOBEC3A/3B	Induce expression, catalysing cytidine deamination of cccDNA → degradation	Lymphotoxinβ receptor agonists	Preclinical	[205]	Restrict HIV expression[206]
Immune modulation	TLR/PRR	TLR7 agonist	GS9620 (Gilead)	Phase 2 (+ tenofovir)	[207] NCT02166047 NCT02579382	LRA [208, 209]Inhibits HIV replication[210]
		TLR9 agonist	Heplisav-B (Dynavax)=TLR9 agonist (1018 ISS) + HBsAg	Phase 3	NCT02117934[211]	LRA and increases anti HIV responses [212]
		TLR3 activation	Poly(I:C)	Phase 4 (+ entecavir)	[213] NCT02532413	TLR3 activation may reverse HIV latency[214]
	T cell function	Reverse immune exhaustion (block negative immunoregulatory pathways)	PD-1/CTLA4 inhibitors e.g. Nivolumab/ipilimumab	Animal studies (Licensed in cancer; Phase 2 HCC incl HBsAg +)	[215] NCT 01658878	Likely [198]
		Therapeutic vaccination (Augment HBV-specific immune response)	Nasvac (vaccine containing HBsAg and HBcAg) +peg-IFN	Phase 3	NCT01374308	Unlikely (unknown)
		Anti-PD1 + therapeutic vaccination	Nivolumab + GS-4774	Phase 1	[216]	Likely [198]

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(b) HIV						
Strategy	**Target**	**Mechanism**	**Class/Agent**	**Clinical Development Phase**	**Refs (Studies in HIV)**	**Activity against HBV**
↓ Virus entry	Gp120 envelope protein	HIV attachment inhibition by binding to gp120 preventing conformational change	BMS-663068 (Fostemsavir) an oral prodrug of HIV attachment inhibitor BMS-626529	Phase 2b	[217, 218]	Unlikely (unknown)
	CCR5 gene	Genome editing (CD4+ T cells) (autologous)	Zinc Finger Nuclease	Phase 1/2	[219]	Possible - CCR5 has been implicated in immune responses to HBV[220]
	CCR5 co-receptor	Humanized IgG4 monoclonal antibody	PRO140	Phase 2b	[221]	
Reverse viral latency	Chromatin acetylation (Epigenetic silencing)	Inhibit chromatin deacetylation, thereby inducing HIV LTR promoter expression	HDAC inhibitors	Licensed (CTCL, MM)	[222, 223]	May suppress pro-oncogenic effects of HBV [224, 225]; and enhance HBV replication [226]
	Transcription activation	PKC agonists AKT agonists	Bryostatin-1, prostratin disulfiram	Phase 1/ 2	[227]	May enhance HBV replication
Inactivate integrated provirus	Integrated HIV DNA	Cleave/mutate integrated HIV directly	CRISPR/Cas9	Pre-clinical	[228, 229]	Unlikely (unknown)
Apoptosis promoting	RIG-1	Inducers of RIG-1 (detects intracellular viral RNA, inducing interferon-mediated apoptosis)	Acitretin	Licensed in psoriasis	[199]	May enhance HBV-specific immunity
immune modulation	TLR agonists	APC activation, T cell priming augmentation and NK cell activation induction; May activate HIV from latency	Pam3CSK4 (TLR1-2 agonist)	Pre-clinical	[230]	May enhance HBV-specific immunity [231]
			GS-9620, GS-986 (TLR7 agonist)	Phase 1	[209] NCT02858401	See above
			MGN1703 (TLR9 agonist)	Phase 1b/2a (phase 3 CRC)	[232] NCT02443935	See above
	Enhance immune response	T cell vaccination	various	Animal studies	[233]	
		Broadly neutralising antibodies	3BNC117 VRC01	Phase 1	[234, 235]	Unlikely (unknown)
		Reverse immune exhaustion (block negative immunoregulatory pathways)	Anti-PD-1/CTLA4	Phase 1 (HIV associated tumours)	[236] NCT02408861, NCT02595866	hepatic flare

*Refers to HBV clinical development unless otherwise stated

Abbreviations: *APOBEC, apolipoprotein B mRNA editing enzyme, catalytic polypeptide;* Crispr/cas9, *Clustered regularly interspaced short palindromic repeats/Crispr associated protein-9 nuclease; HCC, hepatocellular carcinoma;* HDACi, Histone DeAcetylase Inhibitor; IAP, inhibitors of apoptosis proteins; *LRA, latency reversing agent; NCT, national clinical trials reference number* (at ClinicalTrials.gov); PRR, pattern-recognition receptors; PD-1/CTLA4, Programmed cell Death-1/Cytotoxic T lymphocyte Associated protein 4; *RAR, retinoic acid receptor; SiRNA, small interfering RNA;* TLR7, Toll Like Receptor 7;

Abbreviations: APC, antigen-presenting cells; CRC, colorectal cancer; CTCL, cutaneous T cell lymphoma; HDACi, Histone DeAcetylase Inhibitor; MM multiple myeloma; NK cells, natural killer cells; NSCLC, non-small cell lung cancer; RIG, retinoic acid-inducible gene I inducers; SMAC, second mitochondria-derived activator of caspase mimetics; TLR, toll-like receptors