Published in final edited form as:

AIDS. 2017 September 24; 31(15): 2035–2052. doi:10.1097/QAD.0000000000001574.

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

Kasha P Singh, Megan Crane, Jennifer Audsley, and Sharon R Lewin

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 coinfecting 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.

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 HIV, 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 fumarate (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/ mm³ 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 coinfecting 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 reactive 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 coinfecting 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-infection. In three HIV-HBV infected individuals with hepatic flare following commencement of TDF-containing ART, a significant decline in qAg 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- κ B) 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](https://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™ (Universitätsklinikum 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](https://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 coinfecting 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 coinfecting 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, coinfecting 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 coinfecting 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 coinfecting 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.

Acknowledgments

The article was conceived by S.R.L. K.P.S, M.C. and J.A. reviewed the literature and drafted the manuscript. S.R.L. supervised the drafting and edited the manuscript. All authors provided comment on the manuscript and approved the final version.

S.R.L was supported by National Health and Medical Research Council of Australia (NHMRC) grants (1101836 and 1024406), NHMRC Practitioner Research Fellowship (1042654) and United States National Institutes of Health (U19 AI096109). K.P.S was supported by an NHMRC post-graduate fellowship (1039055).

References

1. Chun HM, Mesner O, Thio CL, Bebu I, Macalino G, Agan BK, et al. HIV outcomes in Hepatitis B virus coinfecting individuals on HAART. *Journal of acquired immune deficiency syndromes*. 2014; 66(2):197–205. [PubMed: 24694929]
2. Pinchoff J, Tran OC, Chen L, Bornschlegel K, Drobnik A, Kersanske L, et al. Impact of hepatitis B on mortality and specific causes of death in adults with and without HIV co-infection in NYC, 2000–2011. *Epidemiol Infect*. 2016:1–11.
3. Rajbhandari R, Jun T, Khalili H, Chung RT, Ananthakrishnan AN. HBV/HIV coinfection is associated with poorer outcomes in hospitalized patients with HBV or HIV. *Journal of viral hepatitis*. 2016; 23(10):820–829. [PubMed: 27291562]
4. Crowell TA, Berry SA, Fleishman JA, LaRue RW, Korthuis PT, Nijhawan AE, et al. Impact of hepatitis coinfection on healthcare utilization among persons living with HIV. *Journal of acquired immune deficiency syndromes*. 2015; 68(4):425–431. [PubMed: 25559601]
5. Coffin CS, Osowy C, Myers RP, Gill MJ. Virology and clinical sequelae of long-term antiviral therapy in a North American cohort of hepatitis B virus (HBV)/human immunodeficiency virus type

- 1 (HIV-1) co-infected patients. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*. 2013; 57(2):103–108. [PubMed: 23465393]
6. Morlat P, Roussillon C, Henard S, Salmon D, Bonnet F, Cacoub P, et al. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. *Aids*. 2014; 28(8): 1181–1191. [PubMed: 24901259]
7. Weber R, Ruppik M, Rickenbach M, Spoerri A, Furrer H, Battegay M, et al. Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. *HIV Medicine*. 2012
8. Rosenthal E, Roussillon C, Salmon-Ceron D, Georget A, Henard S, Huleux T, et al. Liver-related deaths in HIV-infected patients between 1995 and 2010 in France: the Mortavic 2010 study in collaboration with the Agence Nationale de Recherche sur le SIDA (ANRS) EN 20 Mortalite 2010 survey. *HIV Med*. 2015; 16(4):230–239. [PubMed: 25522874]
9. Ioannou GN, Bryson CL, Weiss NS, Miller R, Scott JD, Boyko EJ. The prevalence of cirrhosis and hepatocellular carcinoma in patients with human immunodeficiency virus infection. *Hepatology* (Baltimore, Md). 2013; 57(1):249–257.
10. Goehringer F, Bonnet F, Salmon D, Cacoub P, Paye A, Chene G, et al. Causes of Death in HIV-Infected Individuals with Immunovirologic Success in a National Prospective Survey. *AIDS Res Hum Retroviruses*. 2017; 33(2):187–193. [PubMed: 27981873]
11. HIV/AIDS JUNPo. , editor. UNAIDS. Global AIDS Update. Geneva: United Nations; 2016.
12. Yanagimoto S, Yotsuyanagi H, Kikuchi Y, Tsukada K, Kato M, Takamatsu J, et al. Chronic hepatitis B in patients coinfecting with human immunodeficiency virus in Japan: a retrospective multicenter analysis. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. 2012; 18(6):883–890. [PubMed: 22760340]
13. Thio CL, Smeaton L, Saulynas M, Hwang H, Saravanan S, Kulkarni S, et al. Characterization of HIV-HBV coinfection in a multinational HIV-infected cohort. *Aids*. 2013; 27(2):191–201. [PubMed: 23032418]
14. Zoufaly A, Onyoh EF, Tih PM, Awasom CN, Feldt T. High prevalence of hepatitis B and syphilis co-infections among HIV patients initiating antiretroviral therapy in the north-west region of Cameroon. *Int J STD AIDS*. 2012; 23(6):435–438. [PubMed: 22807539]
15. Huang SM, Cai WP, Hu FY, Lan Y, Liao BL, Chen YP, et al. Epidemiological and clinical characteristics of hepatitis B virus in HIV-infected patients in Guangdong, China. *Int J STD AIDS*. 2016; 27(10):890–897. [PubMed: 26384940]
16. Saha D, Pal A, Biswas A, Panigrahi R, Sarkar N, Sarkar J, et al. Characterization of treatment-naïve HIV/HBV co-infected patients attending ART clinic of a tertiary healthcare centre in eastern India. *PLoS One*. 2013; 8(8):e73613. [PubMed: 24023688]
17. Templeton DJ, Wright ST, McManus H, Lawrence C, Russell DB, Law MG, et al. Antiretroviral treatment use, co-morbidities and clinical outcomes among Aboriginal participants in the Australian HIV Observational Database (AHOD). *BMC Infect Dis*. 2015; 15:326. [PubMed: 26265164]
18. Bivigou-Mboumba B, Francois-Souquiere S, Deleplancque L, Sica J, Mouinga-Ondeme A, Amougou-Atsama M, et al. Broad Range of Hepatitis B Virus (HBV) Patterns, Dual Circulation of Quasi-Subgenotype A3 and HBV/E and Heterogeneous HBV Mutations in HIV-Positive Patients in Gabon. *PLoS One*. 2016; 11(1):e0143869. [PubMed: 26764909]
19. Akhtar A, Khan AH, Sulaiman SA, Soo CT, Khan K. HBV and HIV co-infection: Prevalence and clinical outcomes in tertiary care hospital Malaysia. *J Med Virol*. 2016; 88(3):455–460. [PubMed: 26255632]
20. Wandeler G, Musukuma K, Zurcher S, Vinikoor MJ, Llenas-Garcia J, Aly MM, et al. Hepatitis B Infection, Viral Load and Resistance in HIV-Infected Patients in Mozambique and Zambia. *PLoS One*. 2016; 11(3):e0152043. [PubMed: 27032097]
21. Agyeman AA, Ofori-Asenso R. Prevalence of HIV and hepatitis B coinfection in Ghana: a systematic review and meta-analysis. *AIDS research and therapy*. 2016; 13:23. [PubMed: 27190544]
22. Oliveira MP, Lemes PS, Matos MA, Del-Rios NH, Carneiro MA, Silva AM, et al. Overt and occult hepatitis B virus infection among treatment-naïve HIV-infected patients in Brazil. *J Med Virol*. 2016; 88(7):1222–1229. [PubMed: 27061406]

23. Puglia M, Stasi C, Da Fre M, Voller F. Prevalence and characteristics of HIV/HBV and HIV/HCV coinfections in Tuscany. *Braz J Infect Dis.* 2016; 20(4):330–334. [PubMed: 26748234]
24. Ramirez-Mena A, Glass TR, Winter A, Kimera N, Ntamatungiro A, Hatz C, et al. Prevalence and Outcomes of Hepatitis B Coinfection and Associated Liver Disease Among Antiretroviral Therapy-Naïve Individuals in a Rural Tanzanian Human Immunodeficiency Virus Cohort. *Open Forum Infect Dis.* 2016; 3(3) ofw162.
25. Xie J, Han Y, Qiu Z, Li Y, Li Y, Song X, et al. Prevalence of hepatitis B and C viruses in HIV-positive patients in China: a cross-sectional study. *Journal of the International AIDS Society.* 2016; 19(1):20659. [PubMed: 26979535]
26. Bagheri Amiri F, Mostafavi E, Mirzazadeh A. HIV, HBV and HCV Coinfection Prevalence in Iran--A Systematic Review and Meta-Analysis. *PLoS One.* 2016; 11(3):e0151946. [PubMed: 27031352]
27. Noubiap JJ, Aka PV, Nanfack AJ, Agyingi LA, Ngai JN, Nyambi PN. Hepatitis B and C Co-Infections in Some HIV-Positive Populations in Cameroon, West Central Africa: Analysis of Samples Collected Over More Than a Decade. *PLoS One.* 2015; 10(9):e0137375. [PubMed: 26371878]
28. Mehta SH, McFall AM, Srikrishnan AK, Kumar MS, Nandagopal P, Cepeda J, et al. Morbidity and Mortality Among Community-Based People Who Inject Drugs With a High Hepatitis C and Human Immunodeficiency Virus Burden in Chennai, India. *Open Forum Infect Dis.* 2016; 3(3) ofw121.
29. Zhang C, Li X, Liu Y, Qiao S, Chen Y, Zhou Y, et al. Co-infections of tuberculosis, hepatitis B or C viruses in a cohort of people living with HIV/AIDS in China: predictors and sequelae. *AIDS Care.* 2016:1–4.
30. Wu S, Yan P, Yang T, Wang Z, Yan Y. Epidemiological profile and risk factors of HIV and HBV/HCV co-infection in Fujian Province, southeastern China. *J Med Virol.* 2017; 89(3):443–449. [PubMed: 27552721]
31. Alexiev I, Alexandrova M, Golkocheva-Markova E, Teoharov P, Gancheva A, Kostadinova A, et al. High Rate of Hepatitis B and C Coinfections Among People Living with HIV-1 in Bulgaria: 2010–2014. *AIDS Res Hum Retroviruses.* 2017; 33(3):228–229. [PubMed: 27841662]
32. Sadlier C, O'Rourke A, Carr A, Bergin C. Seroepidemiology of hepatitis A, hepatitis B and varicella virus in people living with HIV in Ireland. *J Infect Public Health.* 2017
33. Mansha S, Imran M, Shah A, Jamal M, Ahmed F, Atif M, et al. Hepatitis B and C Virus Infections Among Human Immunodeficiency Virus-Infected People Who Inject Drugs in Lahore, Pakistan. *Viral immunology.* 2017
34. Price H, Dunn D, Zachary T, Vudriko T, Chirara M, Kityo C, et al. Hepatitis B serological markers and plasma DNA concentrations. *Aids.* 2017; 31(8):1109–1117. [PubMed: 28328795]
35. Umutesi J, Simmons B, Makuza JD, Dushimiyimana D, Mbituyumuremyi A, Uwimana JM, et al. Prevalence of hepatitis B and C infection in persons living with HIV enrolled in care in Rwanda. *BMC Infect Dis.* 2017; 17(1):315. [PubMed: 28464899]
36. Toscano AL, Correa MC. Evolution of hepatitis B serological markers in HIV coinfecting patients: a case study. *Rev Saude Publica.* 2017; 51(0):24. [PubMed: 28380208]
37. Jaquet A, Wandeler G, Nouaman M, Ekouevi DK, Tine J, Patassi A, et al. Alcohol use, viral hepatitis and liver fibrosis among HIV-positive persons in West Africa: a cross-sectional study. *Journal of the International AIDS Society.* 2017; 19(1):1–10.
38. Ogwu-Richard SO, Ojo DA, Akingbade OA, Okonko IO. Triple positivity of HBsAg, anti-HCV antibody, and HIV and their influence on CD4+ lymphocyte levels in the highly HIV infected population of Abeokuta, Nigeria. *Afr Health Sci.* 2015; 15(3):719–727. [PubMed: 26957958]
39. Jansen K, Thamm M, Bock CT, Scheufele R, Kucherer C, Muenstermann D, et al. High Prevalence and High Incidence of Coinfection with Hepatitis B, Hepatitis C, and Syphilis and Low Rate of Effective Vaccination against Hepatitis B in HIV-Positive Men Who Have Sex with Men with Known Date of HIV Seroconversion in Germany. *PLoS One.* 2015; 10(11):e0142515. [PubMed: 26555244]

40. Matthews PC, Beloukas A, Malik A, Carlson JM, Jooste P, Ogwu A, et al. Prevalence and Characteristics of Hepatitis B Virus (HBV) Coinfection among HIV-Positive Women in South Africa and Botswana. *PLoS One*. 2015; 10(7):e0134037. [PubMed: 26218239]
41. Vinikoor MJ, Musukuma K, Munamunungu V, Masaninga M, Sikazwe I, Chi BH, et al. Implementation of routine screening for chronic hepatitis B virus co-infection by HIV clinics in Lusaka, Zambia. *Journal of viral hepatitis*. 2015; 22(10):858–860. [PubMed: 25781348]
42. Calisti G, Muhindo R, Boum Y 2, Wilson LA, Foster GM, Geretti AM, et al. Epidemiology of HBV infection in a cohort of Ugandan HIV-infected patients and rate and pattern of lamivudine-resistant HBV infection in patients receiving antiretroviral therapy. *Trans R Soc Trop Med Hyg*. 2015; 109(11):723–729. [PubMed: 26386408]
43. Hoffmann CJ, Dayal D, Cheyip M, McIntyre JA, Gray GE, Conway S, et al. Prevalence and associations with hepatitis B and hepatitis C infection among HIV-infected adults in South Africa. *Int J STD AIDS*. 2012; 23(10):e10–13. [PubMed: 23104758]
44. Funk A, Kanfers S, Nansubuga M, Mwehire D, Featherstone A, Druyts E, et al. Cohort profile: the MUg Observational Cohort. *Int J Epidemiol*. 2012; 41(6):1594–1594f. [PubMed: 23171870]
45. Attia KA, Eholie S, Messou E, Danel C, Polneau S, Chenal H, et al. Prevalence and virological profiles of hepatitis B infection in human immunodeficiency virus patients. *World J Hepatol*. 2012; 4(7):218–223. [PubMed: 22855697]
46. Balogun TM, Emmanuel S, Ojerinde EF. HIV, Hepatitis B and C viruses' coinfection among patients in a Nigerian tertiary hospital. *Pan Afr Med J*. 2012; 12:100. [PubMed: 23133700]
47. Tremeau-Bravard A, Ogbukagu IC, Ticao CJ, Abubakar JJ. Seroprevalence of hepatitis B and C infection among the HIV-positive population in Abuja, Nigeria. *Afr Health Sci*. 2012; 12(3):312–317. [PubMed: 23382745]
48. Bell TG, Makondo E, Martinson NA, Kramvis A. Hepatitis B virus infection in human immunodeficiency virus infected southern African adults: occult or overt—that is the question. *PLoS One*. 2012; 7(10):e45750. [PubMed: 23049685]
49. Anggorowati N, Yano Y, Heriyanto DS, Rinonce HT, Utsumi T, Mulya DP, et al. Clinical and virological characteristics of hepatitis B or C virus co-infection with HIV in Indonesian patients. *J Med Virol*. 2012; 84(6):857–865. [PubMed: 22499006]
50. Dunford L, Carr MJ, Dean J, Nguyen LT, Ta Thi TH, Nguyen BT, et al. A multicentre molecular analysis of hepatitis B and blood-borne virus coinfections in Viet Nam. *PLoS One*. 2012; 7(6):e39027. [PubMed: 22720022]
51. Maimaiti R, Zhang Y, Pan K, Wubuli M, Andersson R. Frequent coinfection with hepatitis among HIV-positive patients in Urumqi, China. *J Int Assoc Provid AIDS Care*. 2013; 12(1):58–61. [PubMed: 23087203]
52. Phuangchoei P, Chotiayaputta W, Chayakulkeeree M. Clinical characteristics of hepatitis B and C virus infections in HIV-infected patients. *J Med Assoc Thai*. 2015; 98(3):226–231. [PubMed: 25920291]
53. Kerubo G, Khamadi S, Okoth V, Madise N, Ezech A, Ziraba A, et al. Hepatitis B, Hepatitis C and HIV-1 Coinfection in Two Informal Urban Settlements in Nairobi, Kenya. *PLoS One*. 2015; 10(6):e0129247. [PubMed: 26068212]
54. Prasetyo AA, Sariyatun R, Reviono Sari Y, Hudiyo Haryati S, et al. The APOBEC3B deletion polymorphism is associated with prevalence of hepatitis B virus, hepatitis C virus, Torque Teno virus, and *Toxoplasma gondii* co-infection among HIV-infected individuals. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*. 2015; 70:67–71. [PubMed: 26305823]
55. Khamduang W, Gaudy-Graffin C, Ngo-Giang-Huong N, Jourdain G, Moreau A, Luekamlung N, et al. Long-Term Hepatitis B Virus (HBV) Response to Lamivudine-Containing Highly Active Antiretroviral Therapy in HIV-HBV Co-Infected Patients in Thailand. *PLoS ONE*. 2012; 7(7):e42184. [PubMed: 22860080]
56. Ladep NG, Agaba PA, Agbaji O, Muazu A, Ugoagwu P, Imade G, et al. Rates and impact of hepatitis on human immunodeficiency virus infection in a large African cohort. *World J Gastroenterol*. 2013; 19(10):1602–1610. [PubMed: 23538773]

57. van Griensven J, Phirum L, Choun K, Thai S, De Weggheleire A, Lynen L. Hepatitis B and C co-infection among HIV-infected adults while on antiretroviral treatment: long-term survival, CD4 cell count recovery and antiretroviral toxicity in Cambodia. *PLoS One*. 2014; 9(2):e88552. [PubMed: 24533106]
58. Ayuk J, Mphahlele J, Bessong P. Hepatitis B virus in HIV-infected patients in northeastern South Africa: prevalence, exposure, protection and response to HAART. *S Afr Med J*. 2013; 103(5):330–333. [PubMed: 23971125]
59. Bado G, Penot P, N'Diaye MD, Amiel C, Hema A, Kamboule EB, et al. Hepatitis B seroprevalence in HIV-infected patients consulting in a public day care unit in Bobo Dioulasso, Burkina Faso. *Med Mal Infect*. 2013; 43(5):202–207. [PubMed: 23701923]
60. Belyhun Y, Maier M, Mulu A, Diro E, Liebert UG. Hepatitis viruses in Ethiopia: a systematic review and meta-analysis. *BMC Infect Dis*. 2016; 16(1):761. [PubMed: 27993129]
61. Brandao NA, Pfrimer IA, Martelli CM, Turchi MD. Prevalence of hepatitis B and C infection and associated factors in people living with HIV in Midwestern Brazil. *Braz J Infect Dis*. 2015; 19(4): 426–430. [PubMed: 25766773]
62. Chandra N, Joshi N, Raju YS, Kumar A, Teja VD. Hepatitis B and/or C co-infection in HIV infected patients: a study in a tertiary care centre from South India. *Indian J Med Res*. 2013; 138(6):950–954. [PubMed: 24521641]
63. Chasela CS, Kourtis AP, Wall P, Drobeniuc J, King CC, Thai H, et al. Hepatitis B virus infection among HIV-infected pregnant women in Malawi and transmission to infants. *Journal of hepatology*. 2014; 60(3):508–514. [PubMed: 24211737]
64. Ding Y, Duan S, Ye R, Yang Y, Yao S, Wang J, et al. More improvement than progression of liver fibrosis following antiretroviral therapy in a longitudinal cohort of HIV-infected patients with or without HBV and HCV co-infections. *Journal of viral hepatitis*. 2017; 24(5):412–420. [PubMed: 27925409]
65. Dziuban EJ, Marton SA, Hughey AB, Mbingo TL, Draper HR, Schutze GE. Seroprevalence of hepatitis B in a cohort of HIV-infected children and adults in Swaziland. *Int J STD AIDS*. 2013; 24(7):561–565. [PubMed: 23970772]
66. Fibriani A, Wisaksana R, Alisjahbana B, Indrati A, Schutten M, van Crevel R, et al. Hepatitis B virus prevalence, risk factors and genotype distribution in HIV infected patients from West Java, Indonesia. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*. 2014; 59(4):235–241. [PubMed: 24529845]
67. Freitas SZ, Soares CC, Tanaka TS, Lindenberg AS, Teles SA, Torres MS, et al. Prevalence, risk factors and genotypes of hepatitis B infection among HIV-infected patients in the State of MS, Central Brazil. *Braz J Infect Dis*. 2014; 18(5):473–480. [PubMed: 24662138]
68. Hawkins C, Christian B, Ye J, Nagu T, Aris E, Chalamilla G, et al. Prevalence of hepatitis B co-infection and response to antiretroviral therapy among HIV-infected patients in Tanzania. *Aids*. 2013; 27(6):919–927. [PubMed: 23196935]
69. Khamduang W, Gaudy-Graffin C, Ngo-Giang-Huong N, Jourdain G, Moreau A, Luekamlung N, et al. Long-term hepatitis B virus (HBV) response to lamivudine-containing highly active antiretroviral therapy in HIV-HBV co-infected patients in Thailand. *PLoS One*. 2012; 7(7):e42184. [PubMed: 22860080]
70. Klein MB, Althoff KN, Jing Y, Lau B, Kitahata M, Lo Re V 3, et al. Risk of End-Stage Liver Disease in HIV-Viral Hepatitis Coinfected Persons in North America From the Early to Modern Antiretroviral Therapy Eras. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2016; 63(9):1160–1167. [PubMed: 27506682]
71. Luma HN, Eloumou SA, Ekaney DS, Lekpa FK, Donfack-Sontsa O, Ngahane BH, et al. Sero-prevalence and Correlates of Hepatitis B and C Co-infection Among HIV-infected Individuals in Two Regional Hospitals in Cameroon. *Open AIDS J*. 2016; 10:199–208. [PubMed: 27867437]
72. Otto-Knapp R, Cortes CP, Saavedra F, Wolff M, Weitzel T. Hepatitis B prevalence and influence on HIV treatment outcome and mortality in the Chilean AIDS Cohort. *Int J Infect Dis*. 2013; 17(10):e919–924. [PubMed: 23849398]

73. Patassi A, Benaboud S, Landoh DE, Salou M, Dagnra AC, Saka B, et al. Hepatitis B infection in HIV-1-infected patients receiving highly active antiretroviral therapy in Lome, Togo: Prevalence and molecular consequences. *S Afr Med J*. 2016; 106(6)
74. Prussing C, Chan C, Pinchoff J, Kersanske L, Bornschlegel K, Balter S, et al. HIV and viral hepatitis co-infection in New York City, 2000–2010: prevalence and case characteristics. *Epidemiol Infect*. 2015; 143(7):1408–1416. [PubMed: 25170631]
75. Puri P, Sharma PK, Lolusare A, Sashindran VK, Shrivastava S, Nagpal AK. Liver Function Tests Abnormalities and Hepatitis B Virus & Hepatitis C Virus Co-infection in Human Immunodeficiency Virus (HIV)-infected Patients in India. *J Clin Exp Hepatol*. 2017; 7(1):1–8. [PubMed: 28348464]
76. Salpini R, Colagrossi L, Bellocchi MC, Surdo M, Becker C, Alteri C, et al. Hepatitis B surface antigen genetic elements critical for immune escape correlate with hepatitis B virus reactivation upon immunosuppression. *Hepatology (Baltimore, Md)*. 2015; 61(3):823–833.
77. Tsuchiya N, Pathipvanich P, Rojanawiwat A, Wichukchinda N, Koga I, Koga M, et al. Chronic hepatitis B and C co-infection increased all-cause mortality in HAART-naïve HIV patients in Northern Thailand. *Epidemiol Infect*. 2013; 141(9):1840–1848. [PubMed: 23114262]
78. Wandeler G, Mulenga L, Vinikoor MJ, Kovari H, Battegay M, Calmy A, et al. Liver fibrosis in treatment-naïve HIV-infected and HIV/HBV co-infected patients: Zambia and Switzerland compared. *Int J Infect Dis*. 2016; 51:97–102. [PubMed: 27596685]
79. Webale MK, Budambula V, Lihana R, Musumba FO, Nyamache AK, Budambula NL, et al. Hepatitis B virus sero-profiles and genotypes in HIV-1 infected and uninfected injection and Non-injection drug users from coastal Kenya. *BMC Infect Dis*. 2015; 15:299. [PubMed: 26223795]
80. Xie DD, Li J, Chen JT, Eyi UM, Matesa RA, Obono MM, et al. Seroprevalence of Human Immunodeficiency Virus, Hepatitis B Virus, Hepatitis C Virus, and *Treponema pallidum* Infections among Blood Donors on Bioko Island, Equatorial Guinea. *PLoS One*. 2015; 10(10):e0139947. [PubMed: 26448460]
81. Zaw SK, Tun ST, Thida A, Aung TK, Maung W, Shwe M, et al. Prevalence of hepatitis C and B virus among patients infected with HIV: a cross-sectional analysis of a large HIV care programme in Myanmar. *Trop Doct*. 2013; 43(3):113–115. [PubMed: 23800421]
82. Gish RG, Given BD, Lai CL, Locarnini SA, Lau JY, Lewis DL, et al. Chronic hepatitis B: Virology, natural history, current management and a glimpse at future opportunities. *Antiviral research*. 2015; 121:47–58. [PubMed: 26092643]
83. Tong S, Revill P. Overview of hepatitis B viral replication and genetic variability. *Journal of hepatology*. 2016; 64(1 Suppl):S4–16. [PubMed: 27084035]
84. Revill PA, Locarnini SA. New perspectives on the hepatitis B virus life cycle in the human liver. *The Journal of clinical investigation*. 2016; 126(3):833–836. [PubMed: 26901815]
85. Nassal M. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. *Gut*. 2015; 64(12):1972–1984. [PubMed: 26048673]
86. Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HL, Chan HL. The role of quantitative hepatitis B surface antigen revisited. *Journal of hepatology*. 2017; 66(2):398–411. [PubMed: 27575311]
87. Zoulim F, Durantel D. Antiviral therapies and prospects for a cure of chronic hepatitis B. *Cold Spring Harb Perspect Med*. 2015; 5(4)
88. Zeisel MB, Lucifora J, Mason WS, Sureau C, Beck J, Levrero M, et al. Towards an HBV cure: state-of-the-art and unresolved questions--report of the ANRS workshop on HBV cure. *Gut*. 2015; 64(8):1314–1326. [PubMed: 25670809]
89. Lucifora J, Protzer U. Attacking hepatitis B virus cccDNA--The holy grail to hepatitis B cure. *Journal of hepatology*. 2016; 64(1 Suppl):S41–48. [PubMed: 27084036]
90. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002; 360(9349):1921–1926. [PubMed: 12493258]
91. Stockdale AJ, Phillips RO, Beloukas A, Appiah LT, Chadwick D, Bhagani S, et al. Liver Fibrosis by Transient Elastography and Virologic Outcomes After Introduction of Tenofovir in Lamivudine-Experienced Adults With HIV and Hepatitis B Virus Coinfection in Ghana. *Clinical*

- infectious diseases : an official publication of the Infectious Diseases Society of America. 2015; 61(6):883–891. [PubMed: 26021992]
92. Matthews GV, Seaberg EC, Avihingsanon A, Bowden S, Dore GJ, Lewin SR, et al. Patterns and causes of suboptimal response to tenofovir-based therapy in individuals coinfecting with HIV and hepatitis B virus. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2013; 56(9):e87–94. [PubMed: 23315316]
 93. Matthews GV, Seaberg E, Dore GJ, Bowden S, Lewin SR, Sasadeusz J, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfecting individuals. *Aids*. 2009; 23(13):1707–1715. [PubMed: 19584701]
 94. Audsley J, Robson C, Aitchison S, Matthews GV, Iser D, Sasadeusz J, et al. Liver Fibrosis Regression Measured by Transient Elastography in Human Immunodeficiency Virus (HIV)-Hepatitis B Virus (HBV)-Coinfected Individuals on Long-Term HBV-Active Combination Antiretroviral Therapy. *Open Forum Infect Dis*. 2016; 3(1) ofw035.
 95. Shiels MS, Engels EA. Evolving epidemiology of HIV-associated malignancies. *Curr Opin HIV AIDS*. 2017; 12(1):6–11. [PubMed: 27749369]
 96. Ryom L, Lundgren JD, De Wit S, Kovari H, Reiss P, Law M, et al. Use of antiretroviral therapy and risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons. *Aids*. 2016; 30(11):1731–1743. [PubMed: 26752282]
 97. Crowell TA, Gebo KA, Balagopal A, Fleishman JA, Agwu AL, Berry SA, et al. Impact of hepatitis coinfection on hospitalization rates and causes in a multicenter cohort of persons living with HIV. *Journal of acquired immune deficiency syndromes*. 2014; 65(4):429–437. [PubMed: 24256631]
 98. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet*. 2014; 384(9939):241–248. [PubMed: 25042234]
 99. Chun HM, Roediger MP, Hullsiek KH, Thio CL, Agan BK, Bradley WP, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. *J Infect Dis*. 2012; 205(2): 185–193. [PubMed: 22147794]
 100. Vinikoor MJ, Sinkala E, Chilengi R, Mulenga LB, Chi BH, Zyambo Z, et al. Impact of Antiretroviral Therapy on Liver Fibrosis Among Human Immunodeficiency Virus-Infected Adults With and Without HBV Coinfection in Zambia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2017; 64(10):1343–1349. [PubMed: 28158504]
 101. Ruiz-Artacho P, Tellez-Molina MJ, Vergas-Garcia J, Altali-Alhames K, Estrada-Perez V, Fernandez-Cruz-Perez A. HIV/HBV coinfection: Serological control and therapeutic strategies. *Revista clinica espanola*. 2013; 213(6):285–290.
 102. Audsley J, Bent SJ, Littlejohn M, Avihingsanon A, Matthews G, Bowden S, et al. Effects of long-term tenofovir-based cART in HIV-HBV co-infection on persistent HBV viremia and the role of HBV quasispecies diversity. *Aids*. 2016
 103. Boyd A, Gozlan J, Maylin S, Delaugerre C, Peytavin G, Girard PM, et al. Persistent viremia in human immunodeficiency virus/hepatitis B coinfecting patients undergoing long-term tenofovir: Virological and clinical implications. *Hepatology (Baltimore, Md)*. 2014; 60(2):497–507.
 104. Childs K, Joshi D, Byrne R, Bruce M, Carey I, Agarwal K, et al. Tenofovir-based combination therapy for HIV/HBV co-infection: factors associated with a partial HBV virological response in patients with undetectable HIV viraemia. *Aids*. 2013; 27(9):1443–1448. [PubMed: 23435302]
 105. Audsley J, Arrifin N, Yuen LK, Ayres A, Crowe SM, Bartholomeusz A, et al. Prolonged use of tenofovir in HIV/hepatitis B virus (HBV)-coinfecting individuals does not lead to HBV polymerase mutations and is associated with persistence of lamivudine HBV polymerase mutations. *HIV Med*. 2009; 10(4):229–235. [PubMed: 19178592]
 106. Seto WK, Wong DK, Fung J, Huang FY, Lai CL, Yuen MF. Reduction of hepatitis B surface antigen levels and hepatitis B surface antigen seroclearance in chronic hepatitis B patients receiving 10 years of nucleoside analogue therapy. *Hepatology (Baltimore, Md)*. 2013; 58(3): 923–931.

107. Yang Y, Gao J, Li HL, Zheng W, Yang G, Zhang W, et al. Dose-response association between hepatitis B surface antigen levels and liver cancer risk in Chinese men and women. *Int J Cancer*. 2016; 139(2):355–362. [PubMed: 26990915]
108. Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. *Gastroenterology*. 2012; 142(5):1140–1149. e1143. quiz e1113–1144. [PubMed: 22333950]
109. Liver EAftSot. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of hepatology*. 2017
110. Boyd A, Maylin S, Moh R, Mahjoub N, Gabillard D, Eholié SP, et al. Hepatitis B surface antigen quantification as a predictor of seroclearance during treatment in HIV-hepatitis B virus coinfecting patients from Sub-Saharan Africa. *Journal of gastroenterology and hepatology*. 2016; 31(3):634–644. [PubMed: 26313291]
111. Boyd A, Gozlan J, Mialhes P, Lascoux-Combe C, Cam MS, Rougier H, et al. Rates and determinants of hepatitis B 'e' antigen and hepatitis B surface antigen seroclearance during long-term follow-up of patients coinfecting with HIV and hepatitis B virus. *Aids*. 2015; 29(15):1963–1973. [PubMed: 26153669]
112. Huang AJ, Núñez M. Outcomes in HIV/HBV-Coinfected Patients in the Tenofovir Era Are Greatly Affected by Immune Suppression. *J Internat Assoc Prov AIDS Care (JIAPAC)*. 2015; 14(4):360–368.
113. Hamers RL, Zaaijer HL, Wallis CL, Siwale M, Ive P, Botes ME, et al. HIV-HBV coinfection in Southern Africa and the effect of lamivudine- versus tenofovir-containing cART on HBV outcomes. *Journal of acquired immune deficiency syndromes*. 2013; 64(2):174–182. [PubMed: 23892239]
114. Matthews GV, Ali RJ, Avihingsanon A, Amin J, Hammond R, Bowden S, et al. Quantitative HBsAg and HBeAg predict hepatitis B seroconversion after initiation of HAART in HIV-HBV coinfecting individuals. *PLoS One*. 2013; 8(4):e61297. [PubMed: 23593455]
115. Jaroszewicz J, Reiberger T, Meyer-Olson D, Mauss S, Vogel M, Ingiliz P, et al. Hepatitis B Surface Antigen Concentrations in Patients with HIV/HBV Co-Infection. *PLoS ONE*. 2012; 7(8):e43143. [PubMed: 22905219]
116. Kosi L, Reiberger T, Payer BA, Grabmeier-Pfistershammer K, Strassl R, Rieger A, et al. Five-year on-treatment efficacy of lamivudine-, tenofovir- and tenofovir + emtricitabine-based HAART in HBV-HIV-coinfecting patients. *Journal of viral hepatitis*. 2012; 19(11):801–810. [PubMed: 23043387]
117. Maylin S, Boyd A, Lavocat F, Gozlan J, Lascoux-Combe C, Mialhes P, et al. Kinetics of hepatitis B surface and envelope antigen and prediction of treatment response to tenofovir in antiretroviral-experienced HIV-hepatitis B virus-infected patients. *Aids*. 2012; 26(8):939–949. [PubMed: 22333748]
118. Zoutendijk R, Zaaijer HL, de Vries-Sluijs TE, Reijnders JG, Mulder JW, Kroon FP, et al. Hepatitis B surface antigen declines and clearance during long-term tenofovir therapy in patients coinfecting with HBV and HIV. *J Infect Dis*. 2012; 206(6):974–980. [PubMed: 22782950]
119. Tan HY, Yong YK, Shankar EM, Paukovics G, Ellegard R, Larsson M, et al. Aberrant Inflammasome Activation Characterizes Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. *J Immunol*. 2016; 196(10):4052–4063. [PubMed: 27076678]
120. Strassl R, Reiberger T, Honsig C, Payer BA, Mandorfer M, Grabmeier-Pfistershammer K, et al. Viral determinants predicting hepatitis B surface antigen (HBsAg) seroclearance in HIV-/HBV-coinfecting patients. *Journal of viral hepatitis*. 2014; 21(7):508–516. [PubMed: 24112778]
121. Walsh R, Locarnini S. Hepatitis B precore protein: pathogenic potential and therapeutic promise. *Yonsei Med J*. 2012; 53(5):875–885. [PubMed: 22869468]
122. Boyd A, Maylin S, Gozlan J, Delaugerre C, Simon F, Girard PM, et al. Use of hepatitis B surface and "e" antigen quantification during extensive treatment with tenofovir in patients co-infected with HIV-HBV. *Liver Int*. 2015; 35(3):795–804. [PubMed: 24606220]
123. Hleyhel M, Hleyhel M, Bouvier AM, Belot A, Tattevin P, Pacanowski J, et al. Risk of non-AIDS-defining cancers among HIV-1-infected individuals in France between 1997 and 2009: results from a French cohort. *Aids*. 2014; 28(14):2109–2118. [PubMed: 25265077]

124. Robbins HA, Shiels MS, Pfeiffer RM, Engels EA. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. *Aids*. 2014; 28(6):881–890. [PubMed: 24300545]
125. Pinato DJ, Dalla Pria A, Sharma R, Bower M. Hepatocellular carcinoma: an evolving challenge in viral hepatitis and HIV coinfection. *Aids*. 2017; 31(5):603–611. [PubMed: 28121711]
126. Gjaerde LI, Shepherd L, Jablonowska E, Lazzarin A, Rougemont M, Darling K, et al. Trends in Incidences and Risk Factors for Hepatocellular Carcinoma and Other Liver Events in HIV and Hepatitis C Virus-coinfected Individuals From 2001 to 2014: A Multicohort Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2016; 63(6):821–829. [PubMed: 27307505]
127. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *Journal of hepatology*. 2010; 53(2):348–356. [PubMed: 20483498]
128. Li ZQ, Hu CL, Yu P, Gu XY, Zhang JJ, Li H, et al. The development of hepatocarcinoma after long-term antiviral treatment of Chinese patients with chronic hepatitis B virus infection: Incidence, long-term outcomes and predictive factors. *Clin Res Hepatol Gastroenterol*. 2017; 41(3):311–318. [PubMed: 28237828]
129. Vallet-Pichard A, Mallet V, Pol S. Nonalcoholic fatty liver disease and HIV infection. *Semin Liver Dis*. 2012; 32(2):158–166. [PubMed: 22760655]
130. Levvero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *Journal of hepatology*. 2016; 64(1 Suppl):S84–101. [PubMed: 27084040]
131. Li KW, Kramvis A, Liang S, He X, Chen QY, Wang C, et al. Higher prevalence of cancer related mutations 1762T/1764A and PreS deletions in hepatitis B virus (HBV) isolated from HBV/HIV co-infected compared to HBV-mono-infected Chinese adults. *Virus Res*. 2016; 227:88–95. [PubMed: 27720823]
132. Liao H, Li X, Liu Y, Xu Z, Huang P, Nian X, et al. Intergenotype recombinant analysis of full-length hepatitis B virus genomes from 516 Chinese patients with different illness categories. *J Med Virol*. 2017; 89(1):139–145. [PubMed: 27328656]
133. Audsley J, Littlejohn M, Yuen L, Sasadeusz J, Ayres A, Desmond C, et al. HBV mutations in untreated HIV-HBV co-infection using genomic length sequencing. *Virology*. 2010; 405(2):539–547. [PubMed: 20655563]
134. Revill PA, Littlejohn M, Ayres A, Yuen L, Colledge D, Bartholomeusz A, et al. Identification of a novel hepatitis B virus precore/core deletion mutant in HIV/hepatitis B virus co-infected individuals. *Aids*. 2007; 21(13):1701–1710. [PubMed: 17690567]
135. Yu L, Zhang BF, Cheng ML, Zhao XK, Zhang Q, Hu YX, et al. Quantitative assessment of mutations in hepatitis B virus genome with liver cirrhosis and hepatocellular carcinoma development. *Oncotarget*. 2016
136. Pollicino T, Cacciola I, Saffioti F, Raimondo G. Hepatitis B virus PreS/S gene variants: pathobiology and clinical implications. *Journal of hepatology*. 2014; 61(2):408–417. [PubMed: 24801416]
137. Lim YS, Lee YS, Gwak GY, Byun KS, Kim YJ, Choi J, et al. Monotherapy with Tenofovir Disoproxil Fumarate for Multiple Drug-Resistant Chronic Hepatitis B: 3-Year Trial. *Hepatology (Baltimore, Md)*. 2017
138. Chan, HL. EASL. Amsterdam: 2017. Improved Bone and Renal Safety of Switching from Tenofovir Disoproxil Fumarate (TDF) to Tenofovir Alafenamide (TAF): Preliminary Results From 2 Phase 3 Studies in HBeAg-positive and HBeAg-negative Patients with Chronic Hepatitis B.
139. Banerjee P, Chakraborty A, Mondal RK, Khatun M, Datta S, Das K, et al. HBV quasispecies composition in Lamivudine-failed chronic hepatitis B patients and its influence on virological response to Tenofovir-based rescue therapy. *Sci Rep*. 2017; 7:44742. [PubMed: 28303969]
140. Kim HN, Rodriguez CV, Van Rompaey S, Eron JJ, Thio CL, Crane HM, et al. Factors associated with delayed hepatitis B viral suppression on tenofovir among patients coinfecting with HBV-HIV in the CNICS cohort. *Journal of acquired immune deficiency syndromes*. 2014; 66(1):96–101. [PubMed: 24500175]

141. Audsley J, Bent SJ, Littlejohn M, Avihingsanon A, Matthews G, Bowden S, et al. Effects of long-term tenofovir-based combination antiretroviral therapy in HIV-hepatitis B virus coinfection on persistent hepatitis B virus viremia and the role of hepatitis B virus quasispecies diversity. *Aids*. 2016; 30(10):1597–1606. [PubMed: 26950313]
142. Sheldon J, Camino N, Rodes B, Bartholomeusz A, Kuiper M, Tacke F, et al. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. *Antiviral therapy*. 2005; 10(6):727–734. [PubMed: 16218172]
143. Shahani L, Hamill RJ. Therapeutics targeting inflammation in the immune reconstitution inflammatory syndrome. *Transl Res*. 2016; 167(1):88–103. [PubMed: 26303886]
144. Avihingsanon A, Matthews GV, Lewin SR, Marks P, Sasadeusz J, Cooper DA, et al. Assessment of HBV flare in a randomized clinical trial in HIV/HBV coinfecting subjects initiating HBV-active antiretroviral therapy in Thailand. *AIDS research and therapy*. 2012; 9(1):6. [PubMed: 22405335]
145. Crane M, Oliver B, Matthews G, Avihingsanon A, Ubolyam S, Markovska V, et al. Immunopathogenesis of hepatic flare in HIV/hepatitis B virus (HBV)-coinfected individuals after the initiation of HBV-active antiretroviral therapy. *J Infect Dis*. 2009; 199(7):974–981. [PubMed: 19231993]
146. Mitsumoto F, Murata M, Ura K, Takayama K, Hiramane S, Shimizu M, et al. The kinetics of the hepatitis B surface antigen level after the initiation of antiretroviral therapy for hepatitis B virus and human immunodeficiency virus coinfecting patients. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. 2015; 21(4):264–271. [PubMed: 25596071]
147. Tuyama AC, Hong F, Saiman Y, Wang C, Ozkok D, Mosoian A, et al. Human immunodeficiency virus (HIV)-1 infects human hepatic stellate cells and promotes collagen I and monocyte chemoattractant protein-1 expression: implications for the pathogenesis of HIV/hepatitis C virus-induced liver fibrosis. *Hepatology (Baltimore, Md)*. 2010; 52(2):612–622.
148. Kandathil, AJ., Durand, CM., Quinn, J., Cameron, A., Thomas, DL., Balagopal, A. Liver Macrophages and HIV-1 Persistence. *CROI; Seattle*. 2015.
149. Kandathil AJ, Sugawara S, Balagopal A. Are T cells the only HIV-1 reservoir? *Retrovirology*. 2016; 13(1):86. [PubMed: 27998285]
150. Kong L, Cardona Maya W, Moreno-Fernandez ME, Ma G, Shata MT, Sherman KE, et al. Low-level HIV infection of hepatocytes. *Virology journal*. 2012; 9:157. [PubMed: 22877244]
151. Iser DM, Warner N, Revill PA, Solomon A, Wightman F, Saleh S, et al. Coinfection of hepatic cell lines with human immunodeficiency virus and hepatitis B virus leads to an increase in intracellular hepatitis B surface antigen. *Journal of virology*. 2010; 84(12):5860–5867. [PubMed: 20357083]
152. Housset C, Lamas E, Courgnaud V, Boucher O, Girard PM, Marche C, et al. Presence of HIV-1 in human parenchymal and non-parenchymal liver cells in vivo. *Journal of hepatology*. 1993; 19(2): 252–258. [PubMed: 8301058]
153. Cao YZ, Dieterich D, Thomas PA, Huang YX, Mirabile M, Ho DD. Identification and quantitation of HIV-1 in the liver of patients with AIDS. *Aids*. 1992; 6(1):65–70. [PubMed: 1543567]
154. Penton PK, Blackard JT. Analysis of HIV quasispecies suggests compartmentalization in the liver. *AIDS Res Hum Retroviruses*. 2014; 30(4):394–402. [PubMed: 24074301]
155. Denton PW, Long JM, Wietgreffe SW, Sykes C, Spagnuolo RA, Snyder OD, et al. Targeted cytotoxic therapy kills persisting HIV infected cells during ART. *PLoS pathogens*. 2014; 10(1):e1003872. [PubMed: 24415939]
156. North TW, Higgins J, Deere JD, Hayes TL, Villalobos A, Adamson L, et al. Viral sanctuaries during highly active antiretroviral therapy in a nonhuman primate model for AIDS. *Journal of virology*. 2010; 84(6):2913–2922. [PubMed: 20032180]
157. Hong F, Saiman Y, Si C, Mosoian A, Bansal MB. X4 Human immunodeficiency virus type 1 gp120 promotes human hepatic stellate cell activation and collagen I expression through interactions with CXCR4. *PLoS One*. 2012; 7(3):e33659. [PubMed: 22479424]

158. Salloum S, Holmes JA, Jindal R, Bale SS, Brisac C, Alatrakchi N, et al. Exposure to human immunodeficiency virus/hepatitis C virus in hepatic and stellate cell lines reveals cooperative profibrotic transcriptional activation between viruses and cell types. *Hepatology* (Baltimore, Md). 2016
159. Shi L, Qin E, Zhou J, Zhao J, Nie W, Jiang T, et al. HIV and HCV Co-Culture Promotes Profibrogenic Gene Expression through an Epimorphin-Mediated ERK Signaling Pathway in Hepatic Stellate Cells. *PLoS One*. 2016; 11(6):e0158386. [PubMed: 27362846]
160. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nature medicine*. 2006; 12(12):1365–1371.
161. Lester RT, Yao XD, Ball TB, McKinnon LR, Omenge WR, Kaul R, et al. HIV-1 RNA dysregulates the natural TLR response to subclinical endotoxemia in Kenyan female sex-workers. *PLoS One*. 2009; 4(5):e5644. [PubMed: 19461969]
162. Debes JD, Bohjanen PR, Boonstra A. Mechanisms of Accelerated Liver Fibrosis Progression during HIV Infection. *J Clin Transl Hepatol*. 2016; 4(4):328–335. [PubMed: 28097102]
163. Crane M, Avihingsanon A, Rajasuriar R, Velayudham P, Iser D, Solomon A, et al. Lipopolysaccharide, immune activation, and liver abnormalities in HIV/hepatitis B virus (HBV)-coinfected individuals receiving HBV-active combination antiretroviral therapy. *J Infect Dis*. 2014; 210(5):745–751. [PubMed: 24585898]
164. Kooij KW, Wit FW, van Zoest RA, Schouten J, Kootstra NA, van Vugt M, et al. Liver fibrosis in HIV-infected individuals on long-term antiretroviral therapy: associated with immune activation, immunodeficiency and prior use of didanosine. *Aids*. 2016; 30(11):1771–1780. [PubMed: 27088320]
165. Marquez M, Romero-Cores P, Montes-Oca M, Martin-Aspas A, Soto-Cardenas MJ, Guerrero F, et al. Immune activation response in chronic HIV-infected patients: influence of Hepatitis C virus coinfection. *PLoS One*. 2015; 10(3):e0119568. [PubMed: 25775475]
166. Peters L, Neuhaus J, Duprez D, Neaton JD, Tracy R, Klein MB, et al. Biomarkers of inflammation, coagulation and microbial translocation in HIV/HCV co-infected patients in the SMART study. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*. 2014; 60(3):295–300. [PubMed: 24793968]
167. Evans TI, Li H, Schafer JL, Klatt NR, Hao XP, Traslavina RP, et al. SIV-induced Translocation of Bacterial Products in the Liver Mobilizes Myeloid Dendritic and Natural Killer Cells Associated With Liver Damage. *J Infect Dis*. 2016; 213(3):361–369. [PubMed: 26238685]
168. Ye B, Liu X, Li X, Kong H, Tian L, Chen Y. T-cell exhaustion in chronic hepatitis B infection: current knowledge and clinical significance. *Cell Death Dis*. 2015; 6:e1694. [PubMed: 25789969]
169. Crane M, Sirivichayakul S, Chang JJ, Avihingsanon A, Ubolyam S, Buranapraditkun S, et al. No increase in hepatitis B virus (HBV)-specific CD8+ T cells in patients with HIV-1-HBV coinfections following HBV-active highly active antiretroviral therapy. *Journal of virology*. 2010; 84(6):2657–2665. [PubMed: 20053751]
170. Gubin MM, Zhang X, Schuster H, Caron E, Ward JP, Noguchi T, et al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. *Nature*. 2014; 515(7528):577–581. [PubMed: 25428507]
171. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2016.
172. Boyd A, Piroth L, Maylin S, Maynard-Muet M, Lebosse F, Bouix C, et al. Intensification with pegylated interferon during treatment with tenofovir in HIV-hepatitis B virus co-infected patients. *Journal of viral hepatitis*. 2016; 23(12):1017–1026. [PubMed: 27486094]
173. Mialhes P, Maynard-Muet M, Lebosse F, Carrat F, Bouix C, Lascoux-Combe C, et al. Role of a 48-week pegylated interferon therapy in hepatitis B e antigen positive HIV-co-infected patients on cART including tenofovir: EMVIEG study. *Journal of hepatology*. 2014; 61(4):761–769. [PubMed: 24882048]
174. Callebaut C, Stepan G, Tian Y, Miller MD. In Vitro Virology Profile of Tenofovir Alafenamide, a Novel Oral Prodrug of Tenofovir with Improved Antiviral Activity Compared to That of

- Tenofovir Disoproxil Fumarate. Antimicrobial agents and chemotherapy. 2015; 59(10):5909–5916. [PubMed: 26149992]
175. Gallant J, Brunetta J, Crofoot G, Benson P, Mills A, Brinson C, et al. Brief Report: Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1/Hepatitis B-Coinfected Adults. *Journal of acquired immune deficiency syndromes*. 2016; 73(3):294–298. [PubMed: 27171740]
 176. Gallant JE, Daar ES, Raffi F, Brinson C, Ruane P, DeJesus E, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV*. 2016; 3(4):e158–165. [PubMed: 27036991]
 177. Liang TJ, Block TM, McMahon BJ, Ghany MG, Urban S, Guo JT, et al. Present and future therapies of hepatitis B: From discovery to cure. *Hepatology (Baltimore, Md)*. 2015; 62(6):1893–1908.
 178. Nkongolo S, Ni Y, Lempp FA, Kaufman C, Lindner T, Esser-Nobis K, et al. Cyclosporin A inhibits hepatitis B and hepatitis D virus entry by cyclophilin-independent interference with the NTCP receptor. *Journal of hepatology*. 2014; 60(4):723–731. [PubMed: 24295872]
 179. Shimura S, Watashi K, Fukano K, Peel M, Sluder A, Kawai F, et al. Cyclosporin derivatives inhibit hepatitis B virus entry without interfering the NTCP transporter. *Journal of hepatology*. 2016
 180. Curtis L, Nichols G, Stainsby C, Lim J, Aylott A, Wynne B, et al. Dolutegravir: clinical and laboratory safety in integrase inhibitor-naïve patients. *HIV Clin Trials*. 2014; 15(5):199–208. [PubMed: 25350958]
 181. Rockstroh J, Teppler H, Zhao J, Sklar P, Harvey C, Strohmaier K, et al. Safety and efficacy of raltegravir in patients with HIV-1 and hepatitis B and/or C virus coinfection. *HIV Med*. 2012; 13(2):127–131. [PubMed: 21599819]
 182. Hurt CB, Napravnik S, Moore RD, Eron JJ Jr. Hepatic safety and tolerability of raltegravir among HIV patients coinfecting with hepatitis B and/or C. *Antiviral therapy*. 2014; 19(4):415–422. [PubMed: 24458137]
 183. Liverpool HIV Drug Interactions. In.
 184. Baril JG, Angel JB, Gill MJ, Gathe J, Cahn P, van Wyk J, et al. Dual Therapy Treatment Strategies for the Management of Patients Infected with HIV: A Systematic Review of Current Evidence in ARV-Naïve or ARV-Experienced, Virologically Suppressed Patients. *PLoS One*. 2016; 11(2):e0148231. [PubMed: 26849060]
 185. Revill P, Testoni B, Locarnini S, Zoulim F. Global strategies are required to cure and eliminate HBV infection. *Nat Rev Gastroenterol Hepatol*. 2016; 13(4):239–248. [PubMed: 26907881]
 186. Petersen J, Heyne R, Mauss S, Schlaak J, Schiffelholz W, Eisenbach C, et al. Effectiveness and Safety of Tenofovir Disoproxil Fumarate in Chronic Hepatitis B: A 3-Year Prospective Field Practice Study in Germany. *Digestive diseases and sciences*. 2015
 187. Ladep NG, Agbaji OO, Agaba PA, Muazu A, Ugoagwu P, Imade G, et al. Hepatitis B Co-Infection is Associated with Poorer Survival of HIV-Infected Patients on Highly Active Antiretroviral Therapy in West Africa. *J AIDS Clin Res*. 2013; (Suppl 3)
 188. Chen M, Wong WW, Law MG, Kiertiburanakul S, Yuniastuti E, Merati TP, et al. Hepatitis B and C Co-Infection in HIV Patients from the TREAT Asia HIV Observational Database: Analysis of Risk Factors and Survival. *PLoS One*. 2016; 11(3):e0150512. [PubMed: 26933963]
 189. Hawkins JLGOAMMPUMSCTAPRMC. Long-term changes in liver fibrosis in HIV and HIV/HBV infected Nigerians on ART. CROI; Boston. 2016.
 190. Al-Mahtab M, Bazinet M, Vaillant A. Safety and Efficacy of Nucleic Acid Polymers in Monotherapy and Combined with Immunotherapy in Treatment-Naïve Bangladeshi Patients with HBsAg+ Chronic Hepatitis B Infection. *PLoS One*. 2016; 11(6):e0156667. [PubMed: 27257978]
 191. Schluep T, Lickliter J, Hamilton J, Lewis DL, Lai CL, Lau JY, et al. Safety, Tolerability, and Pharmacokinetics of ARC-520 Injection, an RNA Interference-Based Therapeutic for the Treatment of Chronic Hepatitis B Virus Infection, in Healthy Volunteers. *Clin Pharmacol Drug Dev*. 2016

192. Lu G, Lomonosova E, Cheng X, Moran EA, Meyers MJ, Le Grice SF, et al. Hydroxylated tropolones inhibit hepatitis B virus replication by blocking viral ribonuclease H activity. *Antimicrobial agents and chemotherapy*. 2015; 59(2):1070–1079. [PubMed: 25451058]
193. Didierjean J, Isel C, Querre F, Mouscadet JF, Aubertin AM, Valnot JY, et al. Inhibition of human immunodeficiency virus type 1 reverse transcriptase, RNase H, and integrase activities by hydroxytropolones. *Antimicrobial agents and chemotherapy*. 2005; 49(12):4884–4894. [PubMed: 16304149]
194. Stray SJ, Bourne CR, Punna S, Lewis WG, Finn MG, Zlotnick A. A heteroaryldihydropyrimidine activates and can misdirect hepatitis B virus capsid assembly. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102(23):8138–8143. [PubMed: 15928089]
195. Yang J, Ma M, Wang XD, Jiang XJ, Zhang YY, Yang WQ, et al. Synthesis and quantitative structure-activity relationships study for phenylpropenamide derivatives as inhibitors of hepatitis B virus replication. *Eur J Med Chem*. 2015; 99:82–91. [PubMed: 26057705]
196. Blank A, Markert C, Hohmann N, Carls A, Mikus G, Lehr T, et al. First-in-human application of the novel hepatitis B and hepatitis D virus entry inhibitor myrcludex B. *Journal of hepatology*. 2016; 65(3):483–489. [PubMed: 27132172]
197. Kaneko M, Watashi K, Kamisuki S, Matsunaga H, Iwamoto M, Kawai F, et al. A Novel Tricyclic Polyketide, Vanitaracin A, Specifically Inhibits the Entry of Hepatitis B and D Viruses by Targeting Sodium Taurocholate Cotransporting Polypeptide. *Journal of virology*. 2015; 89(23):11945–11953. [PubMed: 26378168]
198. Rasmussen TA, Anderson JL, Wightman F, Lewin SR. Cancer therapies in HIV cure research. *Curr Opin HIV AIDS*. 2017; 12(1):96–104. [PubMed: 27607592]
199. Li P, Kaiser P, Lampiris HW, Kim P, Yukl SA, Havlir DV, et al. Stimulating the RIG-I pathway to kill cells in the latent HIV reservoir following viral reactivation. *Nature medicine*. 2016; 22(7):807–811.
200. Cai D, Mills C, Yu W, Yan R, Aldrich CE, Saputelli JR, et al. Identification of disubstituted sulfonamide compounds as specific inhibitors of hepatitis B virus covalently closed circular DNA formation. *Antimicrobial agents and chemotherapy*. 2012; 56(8):4277–4288. [PubMed: 22644022]
201. Palumbo GA, Scisciani C, Pediconi N, Lupacchini L, Alfalate D, Guerrieri F, et al. IL6 Inhibits HBV Transcription by Targeting the Epigenetic Control of the Nuclear cccDNA Minichromosome. *PLoS One*. 2015; 10(11):e0142599. [PubMed: 26580974]
202. Bouezzedine F, Fardel O, Gripon P. Interleukin 6 inhibits HBV entry through NTCP down regulation. *Virology*. 2015; 481:34–42. [PubMed: 25765005]
203. Bastard JP, Soulie C, Fellahi S, Haim-Boukobza S, Simon A, Katlama C, et al. Circulating interleukin-6 levels correlate with residual HIV viraemia and markers of immune dysfunction in treatment-controlled HIV-infected patients. *Antiviral therapy*. 2012; 17(5):915–919. [PubMed: 22436412]
204. Kennedy EM, Kornepati AV, Cullen BR. Targeting hepatitis B virus cccDNA using CRISPR/Cas9. *Antiviral research*. 2015; 123:188–192. [PubMed: 26476375]
205. Lucifora J, Xia Y, Reisinger F, Zhang K, Stadler D, Cheng X, et al. Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA. *Science*. 2014; 343(6176):1221–1228. [PubMed: 24557838]
206. Malim MH. APOBEC proteins and intrinsic resistance to HIV-1 infection. *Philos Trans R Soc Lond B Biol Sci*. 2009; 364(1517):675–687. [PubMed: 19038776]
207. Gane EJ, Lim YS, Gordon SC, Visvanathan K, Sicard E, Fedorak RN, et al. The oral toll-like receptor-7 agonist GS-9620 in patients with chronic hepatitis B virus infection. *Journal of hepatology*. 2015; 63(2):320–328. [PubMed: 25733157]
208. Sloan, DDIA., Tsai, A., Kaur, J., Lalezari, J., Murry, J., Cihlar, T. TLR7 agonist GS-9620 activates HIV-1 in PBMCs from HIV-infected patients on cART. *Annual Conference on Retroviruses and Opportunistic Infections*; Seattle, WA. 2015.
209. Whitney, JBL.S., Osuna, CE., Sanisetty, S., Barnes, TL., Hrabec, P., Cihlar, T., Geleziunas, R., Hesselgesser, J. Treatment with a TLR7 agonist induces transient viremia in SIV-infected ART-

- suppressed monkeys. 22nd Annual Conference on Retroviruses and Opportunistic Infections; Seattle, WA. 2015.
210. Bam RA, Hansen D, Irrinki A, Mulato A, Jones GS, Hesselgesser J, et al. TLR7 Agonist GS-9620 Is a Potent Inhibitor of Acute HIV-1 Infection in Human Peripheral Blood Mononuclear Cells. *Antimicrobial agents and chemotherapy*. 2016
 211. Huang LR, Wohlleber D, Reisinger F, Jenne CN, Cheng RL, Abdullah Z, et al. Intrahepatic myeloid-cell aggregates enable local proliferation of CD8(+) T cells and successful immunotherapy against chronic viral liver infection. *Nat Immunol*. 2013; 14(6):574–583. [PubMed: 23584070]
 212. Offersen R, Nissen SK, Rasmussen TA, Ostergaard L, Denton PW, Sogaard OS, et al. A Novel Toll-Like Receptor 9 Agonist, MGN1703, Enhances HIV-1 Transcription and NK Cell-Mediated Inhibition of HIV-1-Infected Autologous CD4+ T Cells. *Journal of virology*. 2016; 90(9):4441–4453. [PubMed: 26889036]
 213. Wu J, Huang S, Zhao X, Chen M, Lin Y, Xia Y, et al. Poly(I:C) treatment leads to interferon-dependent clearance of hepatitis B virus in a hydrodynamic injection mouse model. *Journal of virology*. 2014; 88(18):10421–10431. [PubMed: 24920792]
 214. Alvarez-Carbonell D, Garcia-Mesa Y, Milne S, Das B, Dobrowolski C, Rojas R, et al. Toll-like receptor 3 activation selectively reverses HIV latency in microglial cells. *Retrovirology*. 2017; 14(1):9. [PubMed: 28166799]
 215. Tzeng HT, Tsai HF, Liao HJ, Lin YJ, Chen L, Chen PJ, et al. PD-1 blockage reverses immune dysfunction and hepatitis B viral persistence in a mouse animal model. *PLoS One*. 2012; 7(6):e39179. [PubMed: 22761734]
 216. Gane, E., Gaggar, A., Nguyen, AH., Subramanian, GM., McHutchison, JG., Schwabe, C., Dunbar, R. EASL. Amsterdam, Netherlands: *Journal of Hepatology*; 2017. A phase1 study evaluating anti-PD-1 treatment with or without GS-4774 in HBeAg negative chronic hepatitis B patients; p. S26-S27.
 217. al TMe. Abstract 545. CROI; Seattle, WA. 2015.
 218. Nowicka-Sans BGY, McAuliffe B, Dicker I, Ho HT, Zhou N, Eggers B, lin PF, Ray N, Wind-Rotolo M, et al. In vitro antiviral characteristics of HIV-1 attachment inhibitor BMS-626529, the active component of the prodrug BMS-663068. *Antimicrobial agents and chemotherapy*. 2012; 56:9.
 219. Tebas P, Stein D, Tang WW, Frank I, Wang SQ, Lee G, et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. *The New England journal of medicine*. 2014; 370(10):901–910. [PubMed: 24597865]
 220. Sanchooli J, Sanadgol N, Kazemi Arababadi M, Kennedy D. CCR5 plays important roles in hepatitis B infection. *Viral immunology*. 2014; 27(1):2–6. [PubMed: 24405101]
 221. Cytodyn. Cytodyn reports full virologic suppression in eleven HIV. In.
 222. Rasmussen TA, Tolstrup M, Brinkmann CR, Olesen R, Erikstrup C, Solomon A, et al. Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial. *Lancet HIV*. 2014; 1(1):e13–21. [PubMed: 26423811]
 223. Elliott JH, Wightman F, Solomon A, Ghneim K, Ahlers J, Cameron MJ, et al. Activation of HIV transcription with short-course vorinostat in HIV-infected patients on suppressive antiretroviral therapy. *PLoS pathogens*. 2014; 10(10):e1004473. [PubMed: 25393648]
 224. Hsieh YH, Su JJ, Yen CJ, Tsai TF, Tsai HW, Tsai HN, et al. Histone deacetylase inhibitor suberoylanilide hydroxamic acid suppresses the pro-oncogenic effects induced by hepatitis B virus pre-S2 mutant oncoprotein and represents a potential chemopreventive agent in high-risk chronic HBV patients. *Carcinogenesis*. 2013; 34(2):475–485. [PubMed: 23172669]
 225. Lachenmayer A, Toffanin S, Cabellos L, Alsinet C, Hoshida Y, Villanueva A, et al. Combination therapy for hepatocellular carcinoma: additive preclinical efficacy of the HDAC inhibitor panobinostat with sorafenib. *Journal of hepatology*. 2012; 56(6):1343–1350. [PubMed: 22322234]

226. Ritchie D, Piekarz RL, Blombery P, Karai LJ, Pittaluga S, Jaffe ES, et al. Reactivation of DNA viruses in association with histone deacetylase inhibitor therapy: a case series report. *Haematologica*. 2009; 94(11):1618–1622. [PubMed: 19608677]
227. Gutierrez C, Serrano-Villar S, Madrid-Elena N, Perez-Elias MJ, Martin ME, Barbas C, et al. Bryostatins for latent virus reactivation in HIV-infected patients on antiretroviral therapy. *Aids*. 2016; 30(9):1385–1392. [PubMed: 26891037]
228. Zhu W, Lei R, Le Duff Y, Li J, Guo F, Wainberg MA, et al. The CRISPR/Cas9 system inactivates latent HIV-1 proviral DNA. *Retrovirology*. 2015; 12:22. [PubMed: 25808449]
229. Hu W, Kaminski R, Yang F, Zhang Y, Cosentino L, Li F, et al. RNA-directed gene editing specifically eradicates latent and prevents new HIV-1 infection. *Proceedings of the National Academy of Sciences of the United States of America*. 2014; 111(31):11461–11466. [PubMed: 25049410]
230. Novis CLAN, Buzon MJ, Verdin E, Round JL, Lichterfeld M, Margolis DM, Planellas V, Bosque A. Reactivation of latent HIV-1 in central memory CD4+ T cells through TLR-1/2 stimulation. *Retrovirology*. 2013; 10(1)
231. Wang S, Chen Z, Hu C, Qian F, Cheng Y, Wu M, et al. Hepatitis B virus surface antigen selectively inhibits TLR2 ligand-induced IL-12 production in monocytes/macrophages by interfering with JNK activation. *Journal of immunology*. 2013; 190(10):5142–5151.
232. Vibholm, LSM., Offersen, R., et al. TLR9 agonist MGN1703 treatment enhances cellular immune responses in HIV-infected individuals on ART. *HIV Persistence: Pathogenesis and Eradication (Keystone Symposium X7)*; Olympic Valley, CA. 2016.
233. Hansen SG, Ford JC, Lewis MS, Ventura AB, Hughes CM, Coyne-Johnson L, et al. Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. *Nature*. 2011; 473(7348):523–527. [PubMed: 21562493]
234. Caskey MKF, Lorenzi JC, Seaman MS, West AP Jr, Buckley N, Kremer G, Nogueira L, Braunschweig M, Scheid JF, et al. Viremia suppressed in HIV-1 infected humans by broadly neutralizing antibody 3BNC117. *Nature*. 2015; 522(7557):4.
235. Lynch RMBE, Coates EE, DeZure A, Madden P, Costner P, Enama ME, Plummer S, Holman L, Hendel CS, et al. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. *Sci Transl Med*. 2015; 7
236. Eron, JGC., Bosch, R., et al. Safety, immunologic and virologic activity of anti-PD-L1 in HIV-1 participants on ART. *CROI*; Boston MA. 2016.
237. EMMa, ECDC Map Maker. ECDC network;
238. Chang, CC., Crane, M., Jaworowski, A., Lloyd, A., French, MA., Lewin, SR. Immunopathogenesis of HIV Coinfections. In: Hope, TJ, Stevenson, M., Richman, D., editors. *Encyclopedia of AIDS*. New York, NY: Springer New York; 2014. p. 1-15.

Map produced on: 19 Jun 2017. Administrative boundaries: ©EuroGeographics, ©UN-FAO

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 reverse 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 <i>et al</i> , HIV Med 2012 [7]	Switzerland	9,053	11	459	4	68	N/A	<ul style="list-style-type: none"> Increased risk of death (any cause) associated with 'active' HBV (HBsAg +eAg+ or HBV DNA+) IRR 1.60 (1.12–2.27)
Chun <i>et al</i> , JAIDS 2012 [1]	US	2352	3	NR	9	93	LMV, TDF or FTC	<ul style="list-style-type: none"> Increased risk of AIDS or death (combined) in chronic HBV
Coffin <i>et al</i> 2013, J Clin Virol [5]	US	1,400	3	NR	6	94	TDF+FTC/LMV	<ul style="list-style-type: none"> Significant liver disease in ~11%
Ladep <i>et al</i> J AIDS Clin Res. 2013 [187]	Nigeria	3,833	20	38	4	100	TDF/FTC.	<ul style="list-style-type: none"> HBsAg+ not a predictor of mortality (in the TDF era)
Van Griensven <i>et al</i> , PLOS One 2014 [57]	Cambodia	3,089	11	240	4	100	22.6% on tenofovir after 2 years	<p>In HIV-HBV:</p> <ul style="list-style-type: none"> Smaller increase CD4 count at 1, 3 and 5 years in co-infected 60% higher mortality Increased risk liver toxicity.
Morlat <i>et al</i> , AIDS 2014 [6]	France	82,000	13	728	5	73	N/A	<ul style="list-style-type: none"> 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 <i>et al</i> 2015, JAIDS [4]	US	15,927	13		5	70	TDF, LMV or FTC	<ul style="list-style-type: none"> Higher hospitalisation rates in HIV-HBV than HIV alone
Rajbhandari <i>et al</i> , 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		<ul style="list-style-type: none"> 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 <i>et al</i> 2016, PLOS One ^[188]	Asia-Pacific	5,656	11		3	100%, 90% on HBV-active ART	87% on LMV, 7% on ART containing FTC,	<ul style="list-style-type: none">Risk factors affecting mortality included HCV but not HBV co-infection.
Grant 2016, CRO ^[189]								<ul style="list-style-type: none">
Vinikoor 2017, CID ^[100]	Zambia	463	13		1	98%	TDF/FTC	<ul style="list-style-type: none">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 coinfectd 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/sulphanoylbenzamide derivatives	Preclinical	[179]	Unknown
	NTCP receptor (viral entry)	Blockade/inteference	HBV pre-S1-derived lipopeptide (MycludexB™)	2	[180]	Unlikely (unknown)
↓cccDNA	cccDNA	↓ NTCP expression	Ro41–5253 (selective RAR-antagonist)	Preclinical	[181]	Possible via RIG (activate HIV transcription/apoptosis [182, 183])
		Inhibit reDNA 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])
Apoptosis promoting	APOBEC3A/3B	DNA cleavage enzymes	CRISPR/Cas protein endonuclease	Preclinical	[188]	Unlikely (unknown)
		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]
		TLR9 agonist	Heplisav-B (Dynavax) = TLR9 agonist (1018 ISS) and HBsAg	Phase 3	NCT02166047 NCT02579382	Inhibits HIV replication [194]
		TLR3 activation	Poly(I:C)	Phase 4 (+ entecavir)	NCT02117934 [195]	LRA and increases anti HIV responses [196]
	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 +)	[197] NCT02532413	TLR3 activation may reverse HIV latency [198]
		Therapeutic vaccination (Augment HBV-specific immune response)	Nasvac (vaccine containing HBsAg and HBcAg) and peg-IFN	Phase 3	[199] NCT01658878	Likely [182]
		Anti-PD-1 and therapeutic vaccination	Nivolumab and GS-4774	Phase 1	NCT01374308	Unlikely (unknown)
Strategy	Target	Mechanism	Class/Agent	Clinical development phase ^b	Ref (Studies in HIV)	Activity against HBV
(b) HIV						
					[200]	Likely [182]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

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]

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

Table 3

(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 (MyrceludexB™)	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]
		TLR7 agonist	GS9620 (Gilead)	Phase 2 (+ tenofovir)	[207] NCT02166047 NCT02579382	LRA [208, 209]Inhibits HIV replication[210]
Immune modulation	TLR/PRR	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]
		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]
	T cell function	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]

(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 prodrg 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	Bryostatins-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 1 inducers; *SMAC*, second mitochondria-derived activator of caspase mimetics; *TLR*, toll-like receptors