Hepatitis B virus coinfection in human immunodeficiency virus-infected patients: A review

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Abstract

Hepatitis B virus (HBV) infection is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma worldwide. Due to the shared modes of transmission, coinfection with HBV and human immunodeficiency virus (HIV) is not uncommon. It is estimated that 10% of HIV-infected patients worldwide are coinfected with HBV. In areas where an HBV vaccination program is implemented, the HBV seroprevalence has declined significantly. In HIV/HBV-coinfected patients, HBV coinfection accelerates immunologic and clinical progression of HIV infection and increases the risk of hepatotoxicity when combination antiretroviral therapy (cART) is initiated, while HIV infection increases the risk of hepatitis events, cirrhosis, and end-stage liver disease related to chronic HBV infection. With the advances in antiviral therapy, concurrent, successful long-term suppression of HIV and HBV replication can be achieved in the cART era. To reduce the disease burden of HBV infection among HIV-infected patients, adoption of safe sex practices, avoidance of sharing needles and diluent, HBV vaccination and use of cART containing tenofovir disoproxil fumarate plus emtricitabine or lamivudine are the most effective approaches. However, due to HIV-related immunosuppression, using increased doses of HBV vaccine and novel approaches to HBV vaccination are needed to improve the immunogenicity of HBV vaccine among HIV-infected patients.

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Key words: Viral hepatitis; Seroepidemiology; Sexually transmitted diseases; Nucleoside reverse-transcriptase inhibitor; Vaccination

Core tip: We provide an updated review of hepatitis B virus (HBV) coinfection among human immunodeficiency virus (HIV)-infected patients, focusing on the epidemiology, management and prevention of HBV infection. The mutually detrimental interactions between HBV and HIV are discussed. Three updated treatment guidelines for the management of patients with HIV/HBV coinfection are summarized. We also review the published data on the effectiveness or efficacy of HBV vaccination studies, with emphasis on the different approaches to improvement of the serologic responses to HBV.
conventional HBV vaccine among HIV-infected patients.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) worldwide[1]. Due to the shared modes of transmission, coinfection with HBV and human immunodeficiency virus (HIV) is not uncommon. It is estimated by the Joint United Nations Program on HIV/AIDS that 10% of 33 million HIV-infected patients has concurrent chronic HBV infection[2]. The prevalence or incidence of HBV infection among HIV-infected patients may vary widely with risks for HIV and HBV transmission, implementation of HBV vaccination programs, and the geographic regions with different levels of endemicity of HBV infection in the general population[2]. HBV and HIV have a mutually detrimental impact in that HIV infection accelerates HBV-related liver damage, leading to earlier cirrhosis and end-stage liver disease[3,4], and the presence of HBV infection complicates the management of HIV infection, impairs CD4 recovery, accelerates immunologic progression, and increases the morbidity and mortality of HIV-infected patients[4-8]. In this article we review the epidemiology, interactions between HIV and HBV, and management and prevention of HBV infection in HIV-infected patients in the era of combination antiretroviral therapy (cART) that often contains 1 or 2 nucleos(t)ide reverse-transcriptase inhibitors (NRTIs) that are active against HBV as well as HIV.

Epidemiology of hepatitis B virus coinfection in HIV-infected patients

Epidemiology of hepatitis B virus in HIV-infected populations

According to the World Health Organization[9], the world can be divided into 3 areas based on the levels of endemicity of HBV infection that are defined by the prevalence of chronic HBV infection: low endemicity, < 2%; intermediate endemicity, 2%-8%; and high endemicity, > 8%. In areas of high endemicity of chronic HBV infection, the transmission of HBV mainly occurs through perinatal transmission (predominantly in East and Southeast Asia) or in young children through close household contact or through medical or traditional scarification procedures (predominantly in Africa)[2,9]. Given the shared transmission routes of HIV and HBV, coinfection with HBV and HIV is common. Approximately 10% of the HIV-infected population in Asia and Africa has concurrent chronic HBV infection with coinfection more common in areas of high prevalence for both viruses[2,10]. The rate can be as high as 25% in countries where the viruses are highly endemic[10]. In areas where HBV is less endemic (North America, Europe, and Australia), HBV and HIV are most often acquired during adolescence or adulthood through sexual transmission or injection drug use[10]. In Western Europe and the United States, the overall prevalence of chronic HBV infection among HIV-infected persons is estimated to be 6%-14%[11-13], including 4%-6% of HIV-infected heterosexuals[11,12], 9%-17% of HIV-infected men who have sex with men (MSM)[13,15], and 7%-10% of injecting drug users[13,14]. Previous studies have shown that seropositivity for syphilis and HIV infection, the number of lifetime sexual partners, and receptive anal intercourse are associated with increased risk of HBV infection in MSM[14-16].

Seroprevalence of hepatitis B virus before and after implementation of vaccination

In a recent review of global epidemiology of HBV infection[17], the prevalence of HBV infection has been shown to be decreasing, particularly evident in central sub-Saharan Africa, tropical and central Latin America, southeast Asia and central Europe. Expanded programs of immunization against HBV have been proposed to significantly contribute to such an observation[17]. In areas that implemented universal neonatal HBV vaccination program such as Taiwan and Alaska, the incidence of acute HBV infection[18,19], prevalence of chronic HBV infection[19,20] and incidence of HCC in children have significantly declined[19,20], so has mortality due to chronic liver disease as well as HCC in persons aged 5-29 years[20].

Recent studies that evaluated the long-term impact of universal neonatal HBV vaccination on HBV seroprevalence among HIV-infected populations and persons at high risk for HIV transmission in Taiwan also demonstrated decreasing trends in chronic HBV infection in those persons born after implementation of neonatal HBV vaccination and catch-up vaccination programs (Figure 1)[21,22]. The prevalence of hepatitis B surface antigen (HBsAg) positivity in HIV-infected patients born after July 1984, when the nationwide HBV vaccination program in Taiwan was initially implemented to vaccinate newborns of HBsAg-positive mothers, has declined to 3.3% vs 20.3% in those born before July 1984 (P < 0.05)[20]. Furthermore, the prevalence of HBsAg positivity was similar between HIV-infected MSM and HIV-uninfected MSM (3.7% vs 2.4%) who were born in the era of universal HBV vaccination (in or after 1986), despite the fact that HIV-infected MSM were more likely to have syphilis (21.2% vs 2.8%) and had a higher prevalence of HBV core antibody (anti-HBc) positivity (26.3% vs 19.6%), while HIV-infected MSM born in 1984-1985 had a significantly higher prevalence of HBsAg positivity than HIV-
infected MSM born in or after 1986 (7.8% vs 3.7%)\(^6\). Additionally, syphilis and positive anti-HCV were significantly associated with HBsAg positivity in HIV-infected patients born in the era of universal HBV vaccination.

**Genotype distribution of HBV and its impact**

Based on the extent of genetic diversity in HBV sequences, HBV can be divided into 10 genotypes (A to J) and several subtypes\(^{25,28}\). Genotypes A to D are more prevalent, with genotype A in sub-Saharan Africa, Northern Europe, and West Africa; genotypes B and C in Asia; and genotype D in Africa, eastern Europe, the Mediterranean region, and India. Other HBV genotypes are less prevalent with genotype E in West Africa; genotype F in Central and South America; genotype G in France, Germany, and the United States; and genotype H in Central America. Unlike other genotypes, the 2 newly identified genotypes, I and J, have yet to establish characteristic geographic and ethnic distribution. Genotype I is known as a recombinant of genotypes A, C, and G, and was found in Vietnam and Laos\(^{27}\). Genotype J was first identified in Ryukyu Island, Japan\(^{29}\).

Many retrospective and prospective studies have been conducted to determine the impact of HBV genotypes on disease outcomes among the general population. Although some controversial results were observed likely due to the transmission route and age when HBV infection occurs, which are closely correlated with seroprevalence of HBV in the geographic areas studied, several studies suggested that patients infected with genotypes C and D had lower rates of seroconversion than patients infected with genotypes A and B, which is likely correlated with the relatively delayed onset of spontaneous HBV envelope antigen (HBeAg) seroconversion and HBsAg seroclearance\(^{29,31}\), infection with genotype C was associated with an increased risk of HCC than with genotype B in retrospective, prospective, and case-control studies\(^{32-36}\), and patients infected with genotype C tended to have higher HBV viral load and higher frequency of basal core promoter A1762T/G1764A mutation than those with genotype B\(^{34,35,37}\). In addition, although HBV genotyping before antiviral therapy is not recommended by current guidelines\(^{38}\), the impact of HBV genotypes on clinical responses to interferon (IFN) have been described. First, in HBeAg-positive patients receiving standard IFN-α, the sustained virologic response rate was higher in patients infected with genotypes A and B than those with genotypes C and D\(^{39,41}\). Even among HBeAg-negative patients treated with IFN-α, HBSAg clearance was significantly higher in patients with genotype A (20%) than those with genotypes B (6%), C (9%), and D (6%)\(^{42}\). While Chien et al\(^{43}\) first reported that the sustained response rate to lamivudine (LAM) was much higher in patients with genotype B than those with genotype C, subsequent studies demonstrated similar therapeutic responses or risk of emergence of LAM resistance among patients infected with different HBV genotypes\(^{44,45}\). No statistically significant difference was observed in response to adefovir dipivoxil (ADV)\(^{47}\) and telbivudine (LdT)\(^{48}\), either.

In HIV/HBV-coinfected patients, HBV genotype A is the most prevalent in Western countries\(^{49}\), although the distribution of HBV genotypes might also vary according to the risk factors, geographic origin, and coinfection with other hepatitis viruses\(^{30,33}\). The impact of HBV genotypes on the course of HBV infection observed included more advanced fibrosis in patients infected with non-A genotypes\(^{49}\), especially with genotype \(G\)^{50}, although a recent study with more than 5 years of follow-up demonstrated that infection with HBV genotype \(G\) was not significantly associated with severe liver disease and had no impact on fibrosis progression\(^{51}\). In another study in HIV/HBV-coinfected patients receiving long-term LAM-containing ART by Sheng et al\(^{44}\), patients coinfected with genotype B were more likely to experience acute exacerbations of hepatitis, HBeAg seroconversion, LAM resistance, and liver disease-related death than those coinfected with genotype C.

**INTERACTIONS BETWEEN HBV AND HIV IN THE ERA OF COMBINATION ANTIRETROVIRAL THERAPY**

**Impact of HBV coinfection on HIV infection**

It is suggested that a persistent state of immune activation in patients with chronic HBV infection could upregulate HIV replication\(^{45}\), and an in vitro study showed that HBV X protein could induce ongoing HIV replication and long-term repeated transcription of HIV by synergizing with kappa B-like enhancer and T-cell activation signals\(^{52,57}\). Early prospective cohort studies of HIV/HBV-coinfected patients revealed a 3.6 to 6.8-fold relative risk of progression to AIDS compared to those without coinfection\(^{46,49}\). However, other reports failed to confirm
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The goal of antiviral therapy for HBV is to suppress HBV DNA replication, reduce necroinflammatory activity, and prevent progression to cirrhosis and HCC. At present, seven therapeutic agents, including IFN, pegylated-interferon (peg-IFN), LAM, emtricitabine (FTC), ADV, entecavir (ETV), LdT and tenofovir disoproxil fumarate (TDF) are approved by the US Food and Drug Administration (FDA) for the treatment of chronic HBV infection[89]. The characteristics of anti-HBV therapeutic agents are shown in Table 1[70-81]. LAM, FTC and TDF have both anti-HBV and anti-HIV activities. According to current treatment guidelines for HIV-infected adult patients, when patients meet the criteria to start cART, 2 agents active against HBV should be included and the most commonly chosen agent is TDF in combination with either FTC or LAM[89,82]. If TDF is not available or not well tolerated, either ADV or ETV in combination with either FTC or LAM are recommended (Table 2)[82-84]. CART regimens containing LAM as the only agent with anti-HBV activity should be avoided due to the high risk of emergence of HBV with LAM resistance during therapy[85-90].

IFN
Peg-IFN is superior to conventional IFN in the treatment of chronic HBV infection because of its long-acting characteristics and weekly administration[91]. The response rate of HBeAg serocconversion and suppression of HBV replication to peg-IFN with or without LAM among HBV-monoinfected patients ranges from 24% to 32%[91,92], compared with 0% to 20% among HBV/HIV-coinfected patients[71]. Nevertheless, IFN should be avoided in patients with low CD4 counts due to significant lymphocytopenia related to IFN[93]. As IFN has potential anti-HIV effects[94] without resulting in emergence of IFN-resistant HIV[93], IFN can be used in those who may need anti-HBV therapy but not anti-HIV therapy (e.g., CD4 count > 500 cells/μL). However, IFN is contraindicated in patients with decompensated liver disease because of concerns about hepatic failure and deaths during IFN treatment[93].

Lamivudine and emtricitabine
LAM has activity against both HIV and HBV at the daily dose of 300 mg and 100 mg, respectively. This agent is well tolerated with few adverse effects[98]. The rates of HBeAg serocconversion and HBV viral suppression (HBV DNA < 400 copies/mL) among HBV/HIV-coinfected patients receiving LAM 300 mg daily for 1 year ranged from 22% to 35% and 40% to 84%, respectively[85,88]. However, the genetic barrier to LAM resistance is low and LAM resistance rates may be as high as 50% after 2 years and 90% after 4 years of LAM therapy in HIV/HBV-coinfected patients[85,99].

FTC is a cytosine analogue that is structurally similar to LAM, and the daily dose for both HBV and HIV is 200 mg. The resistance profile and efficacy of FTC against HIV and HBV are also similar to LAM[85,99]. After 2 years of treatment with FTC, 53% of HBV-monoinfected individuals had significantly impaired CD4 recovery during the first 3 years of cART despite similar virologic effectiveness of antiretroviral therapy compared to patients without HBV infection[504 cells/μL (95%CI: 496-511) vs 449 cells/μL (95%CI: 428-469)].

Impact of HIV infection on HBV infection
Compared to HIV-uninfected subjects, patients with HIV infection have a higher risk of chronicity after acute HBV infection[84]. A higher proportion of chronic HBs antigenemia has been found in HIV-infected patients because HIV destroys CD4 cells which compromises host immunity against HBV[85]. A previous study on pregnant women with chronic HBV infection in Zambia showed that those with HIV coinfection had a 3-fold higher HBeAg-positive rate than HIV-uninfected pregnant women (25% vs 8.5%, P < 0.05)[85]. Another similar study showed that HBV DNA was detected in 26.7% of pregnant women with HIV/HBV coinfection vs 9.4% of those with HBV infection alone (P = 0.06)[86]. Clinical observational studies have demonstrated that HIV/HBV-coinfected patients may have faster progression of hepatic fibrosis and a higher risk of cirrhosis, end-stage liver disease, and HCC than HBV-monoinfected patients[4,63]. Similarly, compared with HIV-monoinfected patients, those with HIV/HBV coinfection, especially HBV genotype B, had a higher risk of acute hepatitis, hepatic decompensation, and liver-related mortality[4,34,64]. Superinfection or coinfection with hepatitis D virus may further exacerbate the complications in patients with HIV/HBV coinfection, which has recently been observed to increase in incidence in an area which was used to be hyperendemic for HBV infection[87].

MANAGEMENT OF HBV COINFECTION IN HIV-INFECTED PATIENTS

Interferon and nucleos(t)ide reverse-transcriptase inhibitors
The goal of antiviral therapy for HBV is to suppress HBV infection in an area which was used to be hyperendemic for HBV which has recently been observed to increase in incidence and liver-related mortality[4,54,66]. Superinfection or coinfection with hepatitis D virus may further exacerbate the complications in patients with HIV/HBV coinfection, which has recently been observed to increase in incidence in an area which was used to be hyperendemic for HBV infection[87].

these results[4,64]. To minimize the influence of duration of HIV infection, a prospective observational cohort of adult patients with primary HIV infection (seroconversion window ≤ 6 mo)[1] has shown that HBV coinfection (adjusted hazards ratio, 3.46; 95%CI: 1.16-10.32) was an independent predictor of immunologic progression that was defined as the occurrence of a CD4 cell count < 350 cells/μL 3 mo or more after diagnosis of primary HIV infection[7]. Chun et al[8] examined the interactions of HBV and HIV using the composite endpoint of AIDS-defining illnesses and death among HIV-infected individuals who had a seroconversion window of ≤ 3 years in a large cohort, which revealed that the hazards ratio for an AIDS or death event was almost constant (adjusted hazards ratio, 1.80; 95%CI: 1.20-2.69) for those with HBV coinfection. The adverse impact of HBV on HIV was also recently demonstrated by the Swiss HIV Cohort Study[85], in which patients who tested positive for HBsAg had significantly impaired CD4 recovery during the first 3 years of cART despite similar virologic effectiveness of antiretroviral therapy compared to patients without HBV infection [504 cells/μL (95%CI: 496-511) vs 449 cells/μL (95%CI: 428-469)].
**Table 1: Characteristics of antiviral drugs for chronic hepatitis B in human immunodeficiency virus-infected patients**

| Characteristics | Interferon alfa-2b | Pegylated interferon alfa-2a | Lamivudine | Emtricitabine | Adefovir | Entecavir | Telbivudine | Tenofovir disoproxil fumarate |
|-----------------|---------------------|-------------------------------|------------|--------------|----------|-----------|------------|-----------------------------|
| **Antiviral effect** | Immune modulation | Immune modulation | Interference of HBV DNA synthesis | Interference of HBV DNA synthesis | Interference of HBV DNA synthesis | Interference of HBV DNA synthesis | Interference of HBV DNA synthesis | Interference of HBV DNA synthesis |
| **HIV-1 activity** | No | No | Yes | Yes | No, at low dose | Yes | No | Yes |
| **Dosage and administration** | 10 million IU SC or IM 3 times a week | 180 mg SC once a week | 300 mg/d oral | 200 mg/d oral | 10 mg/d oral | 0.5 mg/d oral | 600 mg/d oral | 300 mg/d oral |
| **Defined treatment duration** | 48 wk | 48 wk | Indefinite | Indefinite | Indefinite | Indefinite | Indefinite | Indefinite |
| **Undetectable HBV DNA** | - | - | 40%-84% at 1 yr | 53% at 2 yr | 8.6% and 5.7% at 36 and 48, respectively | 38% by the end of study (mean follow-up, 74 wk) | - | Up to 91% at 5 yr |
| **HBeAg seroconversion** | 0%-20% | 0%-20% | 22%-35% at 1 yr | 14% at 48 wk | 9% at 144 wk | - | - | 50% of TDF use; 57% of TDF plus FTC use at 5 yr |
| **Tolerability** | Poor | Poor | Excellent | Excellent | Good Nephrototoxicity (3%) | Excellent | Good | Good |
| **Major adverse events** | Leukopenia, depression | Leukopenia, depression | Low (50% at 2 yr and 90% at 4 yr) | Intermediate (18% at 2 yr) | Good | High | High | High |
| **HBV resistance mutations** | M204/I/V | M204/I/V | M204/I/V | M204/I/V | M204/I/V | M204/I/V | M204/I/V | M204/I/V |
| **Cross-resistance to LAM** | No | No | No | No | No | No | Yes | No |
| **Interaction with other antiretrovirals** | No | No | No | No | No | No | Zidovudine; stavudine | Didanosine; atazanavir |

*1HBeAg positive subjects with CD4 cell counts of > 350 cells/μL and aminotransferase levels elevated to at least twice the upper limit of normal would probably achieve the greatest benefit from IFN-alfa therapy. While ADV (20 mg/d) does have minimal HIV-1 activity, the development of HIV-1 resistance mutations has not been demonstrated at low dose adefovir (10 mg/d). TDF mutations have not been clearly associated with decreased anti-HBV efficacy. Presence of several mutations is necessary to decrease efficacy for ETV at a dose of 1 mg/d; 1 mg/d for LAM-resistant HBV infection; 1LdT is a thymidine analogue that might interact with zidovudine or stavudine.

14% of them seroconverted to anti-HBe at 4 years of FTC treatment. In a prospective randomized, double-blind, placebo-controlled trial of 10 mg/d ADV vs 300 mg/d of TDF in subjects with HBV and HIV coinfection on stable ART, with serum HBV DNA < 10000 copies/mL, and plasma HIV-1 RNA < 10000 copies/mL, the mean time-weighted average change in serum HBV DNA from baseline to week 48 was -4.44log copies/mL for TDF and -3.21log copies/mL for ADV. In a small cohort of 13 patients with positive HBeAg and detectable HBV DNA who had received > 6 mo of TDF/FTC therapy, add-on ETV to TDF/FTC-experienced patients achieved undetectable HBV DNA load in 38% and normal ALT levels in 8 (62%). ADV: Adefovir dipivoxil; ETV: Entecavir; FTC: Emtricitabine; HBV: Hepatitis B virus; HBeAg: HBV envelope antigen; IM: Intramuscularly; LAM: Lamivudine; LdT: Telbivudine; SC: Subcutaneously; TDF: Tenofovir disoproxil fumarate.
Adefovir dipivoxil

ADV had sustained antiviral activity against LAM-resistant HBV strains in 29 HIV/HBV-coinfected patients throughout 144 wk of treatment, with 25% achieving undetectable HBV DNA and 9% HBeAg seroconversion. In a prospective randomized controlled study of 52 HBV/HIV-coinfected patients, the anti-HBV activity of ADV was comparable to TDF (average change in serum HBV DNA from baseline to week 48, -4.44 log copies/mL for TDF and -3.21 log copies/mL for ADV). The incidence of HBV resistant to ADV is less frequent than that to LAM. Mutations at rtN236T and rtA181V, which confer resistance to ADV, occurred in 29% of the patients receiving 5 years of ADV treatment. These mutations are potentially cross-resistant to TDF, and rtA181V is partially cross-resistant to LAM. The rate of ADV resistance is markedly reduced when ADV is added to LAM rather than used as sequential monotherapy in patients with LAM-resistant HBV infection. In addition, no genotypic resistance
of HIV to ADV was found after 3 years of therapy[108].

**Tenoforvar disopropil fumarate**

TDF is a potent agent and effective against LAM-resistant HBV[108] and ADV-resistant HBV[109]. In a study that included 110 HIV/HBV-coinfected patients with 57% being HBeAg-positive at baseline, TDF-containing cART led to high rates of HBeAg seroconversion after 5 years of treatment: 21% in the LAM group, 50% in the TDF group and in 57% in the TDF plus FTC group[104]. During a median observation period of 83 mo, 91% achieved suppression of HBV replication[108]. In a meta-analysis of available data from 23 studies that included 550 HBV/HIV-coinfected patients treated with TDF[111], the overall proportion achieving suppression of HBV replication was 57.4%, 79.0% and 85.6% at 1, 2 and 3 years, respectively, and prior or concomitant 3TC or FTC did not impact the virologic response of HBV infection to TDF; furthermore, virologic rebound on TDF treatment was rare. Those findings of dual anti-HBV and anti-HIV activity and a high genetic barrier to resistance have made TDF an attractive option for the treatment of both viruses in patients with HIV/HBV coinfection. However, TDF may cause renal impairment (1%-3%), which includes Fanconi's syndrome, tubular dysfunction, increases in serum creatinine, and, in rare cases, acute renal failure. Therefore, regular monitoring of renal function in patients receiving TDF-containing regimens is advised[112].

**Entecavir**

ETV is a guanosine analogue that is highly active against wild-type HBV at a daily dose of 0.5 mg and LAM-resistant HBV at 1 mg. It has been demonstrated that ETV reduced HBV DNA by 4.20log copies/mL in HIV/HBV-coinfected patients with HBV resistant to LAM at 48 wk of therapy[119]. ETV has been found to be associated with a 1-log10 reduction of plasma HIV RNA load and mutation in HIV polymerase (rtM184V) that confers resistance to both LAM and FTC[114]. ETV resistance is the result of 3 major mutations, rtL180M, rtM204V and either rtT184G/S, rtS202I or rtM250V. The first 2 mutations also confer resistance to LAM[113]. Therefore, ETV is not recommended as monotherapy in HIV/HBV-coinfected patients.

**Telmivudine**

Data on the antiviral effect of LdT against HIV in HIV/HBV-coinfected patients are sparse. In HIV-monoinfected patients, LdT decreased HBV DNA levels by 6.45 log10 copies/mL in HBeAg-positive and by 5.23 log10 copies/mL in HBeAg-negative patients[116,117]. LdT has greater anti-HBV efficacy than LAM or ADV, and selects for resistance mutations at an intermediate rate. Resistant mutations were selected in 11% of HBeAg-negative and 25% of HBeAg-positive patients after 2 years of treatment with LdT[116]. In an in vitro and human study, LdT was not shown to exert antiviral activity against HIV-1[17], while a transient reduction in HIV-1 RNA between 2 and 3 log10 copies/mL after 24 wk of telbivudine therapy was seen in 2 of 3 patients without showing genotypic resistance mutations to antiretrovirals[81].

**Impact on progression to end-stage liver diseases or regression of cirrhosis and reduced risk of recurrent HCC**

Serum HBV DNA level is a marker of viral replication and efficacy of antiviral treatment in individuals with chronic HBV infection. Maintaining suppression of HBV replication using anti-HBV therapy may reduce the progression of liver fibrosis, reverse advanced fibrosis, reduce the development of cirrhosis, and prevent hepatic decompensation and HCC in patients with advanced fibrosis or cirrhosis. In a prospective cohort study of 3653 HBeAg-positive participants (aged 30-65 years) in Taiwan[110], the incidence of HCC increased with increasing serum HBV DNA levels at study entry in a dose-response relationship, from 108 per 10000 person-years for patients with an HBV DNA level of < 300 copies/mL to 1152 per 10000 person-years for those with an HBV DNA level of 1 million copies/mL or greater; the corresponding cumulative incidence rates of HCC were 1.3% and 14.9%, respectively. A high serum HBV DNA level (≥ 10000 copies/mL) is a significant risk predictor of HCC independent of HBeAg, serum alanine aminotransferase level, and cirrhosis of the liver[118].

In a systemic review of 21 studies conducted among 3881 anti-HBV NRTI-treated (for at least 24 mo or more) and 534 untreated patients, HCC developed less frequently in anti-HBV NRTI-treated patients (2.8% vs 6.4%, P = 0.003) during a 46 mo (range, 32-108 mo) observation period[119]; furthermore, HCC developed significantly less frequently in patients remaining in virologic remission than in those with virologic breakthrough or no response (2.3% vs 7.5%, P < 0.001)[119]. In a recent report conducted in an HIV-uninfected population, long-term ETV treatment reduced the incidence of HCC in HBV-infected patients and the treatment effect was greater in patients at higher risk of HCC[120]. These findings provide supportive evidence to the well-known association between the biologic gradients of HBV DNA levels and risk of HCC[118].

**Management of lamivudine resistance**

If LAM-resistant HBV is present, LAM can be continued for the management of HIV as LAM-resistant HIV has reduced viral fitness in vitro and slower progression in vivo. TDF, ADV and ETV are active against LAM-resistant HBV[108,109,113,121]. A previous study comparing the efficacy of TDF and LAM combination therapy vs TDF after LAM failure for the treatment of HBV in HIV/HBV-coinfected patients revealed no statistically significant difference in terms of HBeAg loss or HBV suppression[122]. ETV is less preferred because LAM resistance predisposes to ETV resistance[113]. However, a small cohort of 13 patients with positive HBeAg and detect-
able HBV DNA who had received > 6 mo of TDF/FTC therapy, add-on ETV to TDF/FTC-experienced patients achieved undetectable HBV DNA load in 4 (30%) and normal ALT levels in 8 (62%)\[70\].

During anti-HBV treatment, monitoring of liver functions (alanine aminotransferase, aspartate aminotransferase, and total bilirubin) is advised every 3 to 6 mo and serum HBV DNA levels every 6 to 12 mo\[83\]. The presence of detectable serum HBV DNA with the use of sensitive assays after 24 wk of therapy suggests a suboptimal response or treatment failure, and add-on therapy with agents without cross-resistance should be considered at this stage\[102\].

Management of end-stage liver disease

The advances in therapy for HIV infection have prolonged the life expectancy of HIV-infected patients receiving cART\[123\], which has led to a greater need for treating HBV-related chronic complications. The 2 major adverse outcomes in patients with chronic HBV infection are cirrhosis and HCC, both of which can lead to liver-related death\[124\]. A low CD4 cell count in HIV/HBV-coinfected patients has been associated with increased risk of cirrhosis and HCC\[10,125,126\]. Overall, less treatable cases and lower survival rates have been described in HIV-infected patients following the diagnosis of HCC\[49\]. New treatment strategies are available for advanced HCC, but data are limited for HIV/HBV-coinfected patients. Case reports suggest some benefit from sorafenib treatment in HIV/HBV-coinfected patients with newly diagnosed HCC\[127-130\]. For most patients with end-stage liver disease, orthotopic liver transplantation remains the only therapeutic option. Accumulated experience in North America and Europe indicated that the patient and graft survival rates in selected HIV-infected recipients of liver transplants were almost similar to those of HIV-uninfected recipients\[131,132\]. Therefore, HIV infection by itself is not a contraindication to liver transplantation. Together with screening of patients at risk and an early diagnosis, aggressive treatment of HCC, including treatment of relapses and maintenance of HIV and HBV suppression, are the best management strategies for HCC in people living with HIV. All patients should receive anti-HBV NRTIs, and hepatitis B immune globulin indefinitely post-transplantation with a decrease in dose frequency after 12 mo\[133\]. It is recommended that patients with liver disease should start referral and workup for liver transplantation if they become symptomatic with liver disease\[133\], which includes the development of hepatic encephalopathy, ascites, variceal bleeding, or liver dysfunction with albumin < 3 g/dL and prolongation of prothrombin time by > 5 s\[133\].

PREVENTION OF HBV INFECTION AMONG HIV-INFECTED PATIENTS

Although the modes of transmission of HBV are the same as those for HIV, HBV is transmitted more efficiently than HIV\[134,135\]. Other than adoption of safe sex practices and avoidance of sharing needles and diluent, HBV vaccination remains the most effective approach to prevent against HBV infection and its chronic consequences. According to the HIV treatment guidelines by the US Department of Health and Human Services\[82\], pre-vaccination screening should include HBsAg, anti-HBsAg antibody (anti-HBs), and anti-HBc. Serological markers may be time-dependent variables in HBV-infected patients, which are associated with host immunity and viral activities; and, therefore, periodic measurements are recommended\[10\]. The presence of anti-HBs at levels of > 10 international units/L (IU/L) is consistent with seroprotection and at levels of > 100 IU/L is associated with long-term protection\[136,137\]. Anti-HBs antibody titers decrease over time and can fall below protective concentrations.

HBV vaccine series should be administered on the standard schedule (3 × 20-μg doses, administered intramuscularly at 0, 1, and 6 mo) if HBsAg, anti-HBs antibody, and anti-HBc antibody are all negative. Approximately 90% to 95% of healthy adults have protective anti-HBs titers after standard doses of HBV vaccines\[138,139\]. However, only 17.5% to 71% of HIV-infected patients could retain protective anti-HBs\[137,139-141\] (Table 3). In HIV-infected patients, variable immune responses to HBV vaccine have been shown to be associated with dysfunction of CD4 T cells, specific B-cell defects, and hyper-immune activation status and genes within the human leukocyte antigen complex\[140-151\].

In HIV-infected patients, those with CD4 cell counts ≥ 350 cells/μL had a higher seroconversion rate (anti-HBs ≥ 10 IU/L) than those with CD4 cell counts < 350 cells/μL (39.3% vs 26.3%)\[140\]. Failure of anti-HBs seroconversion and lower anti-HBs titers after HBV vaccination in HIV-infected patients have been shown to be associated with detectable plasma HIV RNA, lower CD4 cell counts\[142-147,152,153\], age, HCV coinfection, occult HBV infection, alcohol abuse, and the general health status of the host\[144,148,154,155\]. A favorable response to cART may improve serological response\[137,139\] (Table 3).

Based on these data, early vaccination is recommended in HIV-infected patients before CD4 cell counts declines. This also strengthens the arguments for universal HBV vaccination of individuals at risk for HIV infection before they become HIV-infected and their immunosuppression worsens. Post-vaccination testing is recommended 1 to 2 mo after administration of the final dose of the primary vaccine series to determine the response to the vaccine. The height of the antibody titers is associated with the durability of effective antibody\[156\].

To improve the response rate and long-term persistence of antibodies, numerous studies have tried to use a variety of strategies such as increased doses, intradermal vaccination, and co-administration of immunomodulators. A fundamental strategy is to ensure that patients have optimal adherence to the vaccination schedule. A study conducted in a clinic specializing in the care of
HIV-infected adults revealed that 7.5% had evidence or documentation of prior HBV vaccination at screening, and only 49% of those eligible for vaccination completed the standard vaccination schedule\(^\text{[157]}\). Other studies have also reported completion rates ranging from 29% to 62%\(^\text{[139,140]}\).

**Dosing, vaccination schedules, and administration**

For patients undergoing hemodialysis and for adults with general immune suppression, higher vaccine doses given on a standard schedule (3 × 40-μg doses administered intramuscularly at 0, 1, 6 mo) are recommended\(^\text{[160,161]}\). However, appropriate vaccine dosage has not been well defined in HIV-infected patients. In 1 double-blinded, randomized, controlled trial in 210 HIV-infected adults, 94 in the standard-dose group (3 × 20-μg doses at 0, 1, 6 mo) and 98 in the double-dose group (3 × 40-μg doses at 0, 1, 6 mo) completed the study\(^\text{[148]}\). There was no overall benefit in the double-dose group (seroconversion rate 47% vs 34%, \(P = 0.07\)) but a statistically significant higher seroconversion rate was found in patients with CD4 cell counts ≥ 350 cells/μL and receiving double doses (64.3% vs 39.3%, \(P = 0.008\)). The double-dose strategy also improved seroconversion compared with standard-dose strategy in patients with an HIV viral load < 10000 copies/mL (58.3% vs 37.3%, \(P = 0.01\)). In a small double-blinded, randomized controlled trial comparing a 40-μg dose to a 10-μg dose in 3 administrations\(^\text{[149]}\), the increased dose of HBV vaccine did not increase the response rate in HIV-infected subjects (60.0% vs 40.3%, \(P = 0.89\)). Stratified by CD4 cell count or viral load, CD4 cell count ≥ 200 cells/μL was the only significant factor associated with the response rate and no difference was observed between the 2 different vaccine doses.

For travelers or subjects exposed to HBV, an accelerated vaccination schedule of 3 doses at 0, 1, and 2 mo, followed by a booster at 12 mo, can be given to achieve rapid protection\(^\text{[162,163]}\). A randomized study was designed to evaluate the protective efficacy of an accelerated vaccination schedule (\(n = 407\); 3 × 10-μg doses administered intramuscularly at 0, 1, and 2 mo, followed by a booster at 12 mo) and compared it with a standard regimen (3 × 20-μg doses administered at 0, 1, and 6 mo). The accelerated schedule was associated with a higher seroconversion rate (31.9% vs 19.8%, \(P = 0.001\)), but no difference was noted in the safety profile. Overall, these data suggest that an accelerated vaccination schedule may be more convenient and effective for travelers and subjects exposed to HBV.
circularly at 0, 1 and 3 wk) in comparison to a standard schedule ($n = 434$; $3 \times 10 \mu$g doses at 0, 4 and 24 wk) in HIV-infected individuals$^{[16]}$. The study showed that compliance to the accelerated schedule was better than that to the standard schedule (91.8% vs 82.7%), but the overall response rate was higher in the accelerated schedule arm [50% vs 38.7% difference, 11.3% (95%CI: 4.3-18.3)]. Noninferiority was demonstrated only in patients with CD4 cell counts $> 500$ cells/μL.

Potsch and colleagues reported a higher response rate (89%) using a modified HBV vaccination schedule that administered $4 \times 40$-μg doses intramuscularly at 0, 4, and 24 wk, with 79% achieving antibody titers above 100 IU/L$^{[146]}$. A subsequent study confirmed these results with response rates of 83% and 91% following vaccination with 3 and 4 double doses, respectively$^{[166]}$

An alternative vaccine delivery method, the intradermal route, driven by the fact that the dermis and epidermis of human skin are rich in antigen-presenting cells, could permit vaccine dose sparing, as 20% of the antigen dose has elicited good vaccine responses. It has shown improved immunogenicity in patients with chronic kidney disease$^{[166]}$. However, there are significant operational challenges, such as reformulation, changing from a single- to a multiple-dose presentation, development of intradermal delivery devices and training health workers. An open-label, multicenter, 1:1:1 parallel-group, randomized trial compared the standard HBV vaccination schedule ($3 \times 20$-μg doses administered intramuscularly at 0, 4, and 24 wk; $n = 145$), 4 double doses ($4 \times 40$-μg doses administered intramuscularly at 0, 4, 8 and 24 wk; $n = 148$), and 4 intradermal low-doses ($4 \times 4$-μg doses administered intradermally at 0, 4, 8 and 24 wk; $n = 144$) in HIV-infected adults with CD4 cell counts $\geq 200$ cells/μL$^{[146]}$. At week 28, both the 4 intramuscular double-dose group (82%) and the 4 intradermal low-dose group (77%) showed statistically significant higher response rates than the standard regimen. The four-dose schedule allowed for the possibility of overcoming age, a negative predictor for response in the standard schedule. However, data on long-term persistence of immunity are yet to be seen, and patients with CD4 cell counts of < 200 cells/μL were not evaluated.

**Vaccine safety**

HBV vaccination appeared to be safe in HIV-infected patients compared with HIV-uninfected persons and has no effect on HIV viral load, progression to AIDS or depletion of CD4 cell counts$^{[16,14,146,167]}$. In the study by Launay et al$^{[166]}$, 1 serious hepatic cytolysis event possibly related to the vaccine was reported in the 4 intramuscular double-dose group. A higher incidence of injection site adverse events was reported in the 4 intramuscular double-dose group compared with the standard group, but these adverse events were generally mild.

The use of newer adjuvants may also augment hepatitis B vaccine efficacy. Standard hepatitis B vaccines contain aluminum adjuvants. Two new adjuvants in addition to a commercial HBV vaccine have been evaluated in randomized trials in HIV-infected patients$^{[167-170]}$. The granulocyte macrophage colony-stimulating factor (GM-CSF), a cytokine produced primarily by activated T and B lymphocytes that increases neutrophil count, improves APC function, and is involved in the development and perpetuation of cellular immune responses, has been studied as an adjuvant in HIV-infected individuals$^{[167,169]}$. GM-CSF is safe with expected side effects in HIV-infected subjects when administered as an adjuvant. While 1 study showed promise for the role of adjuvant to augment immune response$^{[169]}$, no additive benefits were noted in the 2 other trials$^{[167,168]}$. CPG 7909, is an oligodeoxy nucleotide containing immunostimulatory CpG motifs, which activates human B and plasmacytoid dendritic cells via Toll-like receptor 9. A randomized, double-blind controlled trial was conducted in HIV-infected adults on effective antiretroviral therapy who underwent HBV vaccination ($3 \times 40$-μg administered intramuscularly at 0, 1, and 2 mo) with/without 1 mg CPG 7909$^{[170]}$. The study showed that significantly more CPG 7909 recipients than control subjects maintained seroprotective titers for up to 60 mo in vaccine-naive participants and in those who had previously experienced vaccine failure$^{[170]}$. While more studies are warranted to determine optimal vaccination strategies in patients with advanced immunosuppression, the vaccination series should be initiated at first visit regardless of CD4 cell count.

**TREATMENT WITH COMBINATION ANTIRETROVIRAL THERAPY FOR THE PREVENTION OF HBV INFECTION**

Some health-care practitioners may weigh the risk of vaccination delay and the likelihood of HBV infection in patients when making decisions to postpone vaccination until cART is started and virologic suppression is achieved to improve serologic response to vaccination. A cohort study in Japan examined the prophylactic effect against HBV in HIV-infected patients who had not received HBV vaccination and were negative for HBsAg, anti-HBs, and anti-HBe at baseline$^{[171]}$. The incidence rate of HBV infection was lower during LAM- or TDF-containing cART (0.669 incident infections in 100 person-years) than during no antiretroviral therapy (5.263 incident infections in 100 person-years) and other antiretroviral therapy (5.263 incident infections in 100 person-years) ($P < 0.001$). A similar trend was also noted in Taiwan$^{[172]}$.

**CONCLUSION**

In this review, we have found in the published data that the prevalence or incidence of HBV infection among HIV-infected patients is likely to decrease in areas where HBV vaccination programs are implemented and the coverage of cART containing TDF plus LAM or FTC is...
high. The challenges in the prevention of HBV transmission are to ensure that HIV-monoinfected patients have optimal adherence to protected sex and an HBV vaccination schedule, and to identify novel approaches or novel adjuvants to improve vaccination effectiveness. While the experience with management of HBV/HIV-coinfected patients using cART containing TDF plus LAM or FTC is accumulating in clinical practice, early diagnosis of HIV infection and initiation of cART to achieve durable suppression of both HIV and HBV replication in those with coinfection are warranted to ensure long-term success in the prevention of HBV-related chronic complications. With the progress made in liver transplantation over the past decades, early referral for workup for liver transplantation is advised when HIV/HBV-coinfected patients become symptomatic with liver disease.

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