

Invited Review

Chronic Hepatitis B and HIV Coinfection

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Hepatitis B virus (HBV) infection is common among people with HIV owing to shared modes of viral transmission. Compared with individuals with HBV infection alone, people with HIV/HBV coinfection experience an accelerated progression of liver disease, including increased risks for hepatocellular carcinoma, liver-related mortality, and all-cause mortality. Therefore, HBV screening and appropriate treatment are crucial for people with HIV. This article reviews the epidemiology, natural history, and management of HIV/HBV coinfection, as well as recommendations for prevention of HBV infection among people with HIV.

Keywords: HIV, HBV, HIV/HBV coinfection, hepatitis B virus, coinfection

Introduction

Hepatitis B virus (HBV) is a partially double-stranded DNA virus that can be transmitted through blood and bodily fluids.¹ HBV infection can cause acute and chronic hepatitis and over time can lead to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease (ESLD).² In 2019, the World Health Organization estimated that 296 million people, or 3.8% of the global population, had chronic HBV infection, with most residing in low- and middle-income countries.³ Despite the availability of effective treatment with antiviral medications and prevention by vaccination, HBV infection remains a

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major driver of morbidity and mortality around the world, with an estimated 820,000 related deaths in 2019.⁴

Owing to shared modes of transmission, chronic coinfection with HBV is common among people with HIV. In the era of antiretroviral therapy, cirrhosis, ESLD, and HCC account for an increasing proportion of deaths among individuals with HIV.⁵⁻⁸ In this article we outline key epidemiologic and natural history features of HIV/HBV coinfection and review important principles in the management and prevention of HBV infection among people with HIV.

Epidemiology of HIV/HBV Coinfection

Globally, an estimated 8% to 10% of people with HIV have chronic HBV infection, although the prevalence of coinfection varies significantly by region.⁹⁻¹⁴ A recent meta-analysis of HBV infection among people with HIV reported the prevalence of HIV/HBV coinfection as highest in the World Health Organization Western Pacific region (11.4%) and sub-Saharan Africa region (10.0%) and lowest in the regions of Europe (6.7%) and the Americas (5.3%).⁹ Modes of transmission for HBV also vary significantly by region. In high-prevalence countries, HBV is most commonly transmitted perinatally, from mother to child, and rates of HIV/HBV coinfection are broadly similar across different HIV risk groups, including individuals engaging in heterosexual sex, pregnant persons, men who have sex with men (MSM), and children.¹⁴ In low-prevalence countries, including the US, sex and injection drug use are more common modes of transmission, with few reported cases of perinatal transmission.^{1,15}

In the US, the prevalence of chronic HBV infection in the general population is estimated to be 0.3% to 0.7%, with most infections occurring among foreign-born individuals.¹⁶⁻¹⁹ In contrast, an estimated

5% to 10% of people with HIV in the US have chronic coinfection with HBV.^{11,20} In a large US-based observational cohort study of people with HIV from 1996 to 2007, the prevalence of HBV coinfection was higher among MSM than in other subgroups, including heterosexual individuals and people who inject drugs. However, these data were collected largely before the opioid epidemic in the US, and newer data from the Centers for Disease Control and Prevention suggest that injection drug use is the most common risk factor for HBV infection among the general US population, followed by having multiple sexual partners.^{11,21}

Natural History of HIV/HBV Coinfection

Compared with individuals with HBV infection alone, people with HIV/HBV coinfection can experience an accelerated progression of liver disease, including increased risks for HCC, liver-related mortality, and all-cause mortality.²²⁻²⁶ In a large US-based cohort study of MSM from the era before and shortly after the advent of antiretroviral therapy, liver-related mortality among individuals with HIV/HBV coinfection was 8 and 18 times higher than in those with HIV or HBV infection alone, respectively.²² Among individuals with coinfection in this study, liver-related mortality was highest among those with a low nadir CD4+ cell count, a finding that was replicated in this same cohort later in the antiretroviral therapy era.²⁶ Although antiretroviral therapy has been shown to improve liver fibrosis among persons coinfecting with HIV and HBV,^{27,28} HBV infection remains a major contributor to ESLD well into the modern antiretroviral therapy era. In a large observational study of 12 clinical cohorts in the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design), investigators evaluated incident ESLD outcomes among more than 34,000 people with HIV from 1996 through 2010.²⁹ Despite substantial increases in the use of antiretroviral therapy active against both HIV and HBV, as well as high rates of HIV viral suppression among those receiving antiretroviral therapy in this cohort, there were no differences in the incident rates of ESLD in individuals with HIV/

HBV coinfection among the early (1996-2000), middle (2001-2005), and modern (2006-2010) antiretroviral therapy eras. The authors hypothesized that this surprising finding might be due to the fact that 35% of the cohort was not receiving optimal anti-HBV therapy with tenofovir, or perhaps to insufficient power and follow-up time.²⁹

The impact of HBV infection on the natural history of HIV infection is less clear. Although some studies have indicated that people coinfecting with HIV and HBV experience lower CD4+ cell counts,^{30,31} HIV/HBV coinfection has not been associated with an increased risk of AIDS progression or mortality in large cohort studies.³²⁻³⁴

Management of HBV Infection in People Coinfected With HIV

Given the high prevalence of chronic HBV infection among people with HIV, and the elevated risk of liver-related complications among individuals with coinfection, it is crucial that all individuals with HIV are screened for HBV. Screening identifies not only individuals who need treatment for HBV infection but also those who would benefit from HBV vaccination.³⁵ For people with HIV, the American Association for the Study of Liver Disease (AASLD) recommends screening with the following tests: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs).³⁵ People with HIV who test positive for HBsAg should undergo further testing with an HBV DNA level to determine the magnitude of HBV replication, as well as testing for hepatitis B e antigen (HBeAg) and hepatitis B e antibody (anti-HBe).³⁶

Major guideline committees recommend initiating antiviral therapy for the treatment of HBV infection in all HIV/HBV-coinfecting persons regardless of CD4+ cell count or HBV-related factors (such as viral level or liver aminotransferase elevation). The immediate goal of therapy is to reduce necroinflammation and HBV DNA replication, and the ultimate goal is to avert or delay the development of cirrhosis, ESLD, and HCC, and improve overall survival (Table 1).³⁵⁻³⁸ There are 6 oral antiviral agents and 2 injectable interferon alfa formulations

Table 1. Summary of Guideline-Based Treatment Recommendations for HIV and HBV Coinfection

Guidelines	When to initiate	What to initiate
AASLD HBV update, 2018 ³⁵	All patients with HIV/ HBV, regardless of CD4+ cell count	2 HBV-active agents: tenofovir (TAF or TDF) with lamivudine or emtricitabine
DHHS antiretroviral guidelines, 2022 ³⁶	All patients with HIV/ HBV, regardless of CD4+ cell count	Tenofovir (TAF or TDF) with emtricitabine; chronic administration of lamivudine or emtricitabine as the only HBV-active agent as part of ART should be avoided.
EASL HBV guidelines, 2017 ³⁷	All patients with HIV/ HBV, regardless of CD4+ cell count	Tenofovir (TAF or TDF)-containing ART regimen
APASL HBV update, 2015 ³⁸	All patients with HIV/ HBV, “irrespective of immunologic, virologic, or histologic considerations”	2 HBV-active agents: tenofovir with lamivudine or emtricitabine

Abbreviations: AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; ART, antiretroviral therapy; DHHS, US Department of Health and Human Services; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

that have been approved for the treatment of HBV infection by the US Food and Drug Administration (Table 2). However, only 3 oral agents—entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF)—are considered first-line, because of their potency against HBV, high barrier to resistance, and favorable adverse effect profile.³⁵ Although lamivudine was the first oral antiviral agent approved for the treatment of HBV, and the first to show a reduction in disease progression and incidence of HCC, its use as HBV monotherapy is no longer recommended because of the substantial risk of developing drug resistance, with a 5-year cumulative resistance rate of 70%.^{37,39,40} The use of adefovir is similarly not favored owing to its toxicity, relatively low potency, and moderate risk of resistance. Telbivudine is no longer manufactured in the US, and interferon alfa is generally not used as a first-line agent because of significant adverse effects.

For individuals with HIV/HBV coinfection, the Panel on Antiretroviral

Guidelines for Adults and Adolescents recommends initiation of an antiretroviral therapy regimen that contains a nucleoside reverse transcriptase inhibitor backbone of TDF or TAF plus emtricitabine (FTC) or lamivudine.³⁶ Although combination antiviral therapy is generally not used in HBV mono-infection, dual therapy with a combination of TDF or TAF plus FTC or lamivudine is recommended in individuals with coinfection, as these agents provide activity against both HIV and HBV and are generally coformulated. Individuals with HIV being considered for a tenofovir-sparing regimen, including the 2-drug regimens of dolutegravir-lamivudine and cabotegravir-rilpivirine, should first be evaluated for HBV to confirm the absence of coinfection. Entecavir, although highly active against HBV, has only partial activity against HIV and can produce an M184V mutation in people with HIV infection if it is not given in conjunction with a fully suppressive antiretroviral therapy regimen.³⁶

For tenofovir, in addition to being highly active against HBV and HIV, data suggest that long-term use can lead to improvements in liver necroinflammation and to regression of fibrosis. In an open-label study of TDF for the treatment of patients with HBV mono-infection, 304 of 348 (87%) had histologic improvement on liver biopsy and 176 (51%) had regression of fibrosis by year 5 of treatment.⁴¹ Despite these encouraging findings for HBV mono-infection, similar results have not been replicated in HIV/HBV coinfection.⁴²

Table 2. US Food and Drug Administration–Approved Oral Antiviral Therapy for HBV Infection

Medication	Potency against HBV	Barrier to HBV resistance	HIV activity	Selection of HIV resistance
Lamivudine	Moderate	Low	Yes	Yes
Adefovir	Low	Moderate	No ^a	No
Entecavir	High	High ^b	Partial	Yes
Emtricitabine	Moderate	Low	Yes	Yes
Telbivudine	High	Low	Partial ^c	No
Tenofovir ^d	High	High	Yes	Yes

Abbreviation: HBV, hepatitis B virus.

^aAnti-HIV activity at higher doses; more potent against HBV.

^bIn patients without lamivudine resistance.

^cNo in vitro activity observed against HIV, but HIV RNA decline reported.

^dEither tenofovir disoproxil fumarate or tenofovir alafenamide.

Although there are several short- and long-term health benefits of treatment for HBV infection, the key limitation of antiviral therapy is that it does not offer a functional cure, defined by the sustained loss of HBsAg and control of HBV viremia, even in the absence of antiviral therapy. Studies performed in individuals without HIV suggest that after 2 to 3 years of therapy, HBsAg loss ranges from 1% to 8% for entecavir, TDF, and TAF despite high rates of viral suppression with these antiviral agents (Table 3).³⁵

Among individuals with HIV/HBV coinfection, there is emerging evidence suggesting a possible advantage to TAF over TDF with regard to HBV viral endpoints. In an international multicenter trial of 234 individuals with HIV/HBV coinfection, participants were randomly assigned to receive either TAF/FTC/bictegravir or TDF/FTC plus dolutegravir for treatment of HIV and HBV infection.⁴³ Participants were followed for 48 weeks and monitored for key HIV and HBV virologic endpoints. Compared with those receiving TDF/FTC plus dolutegravir, the group receiving TAF/FTC/bictegravir had a higher proportion of HBsAg loss (12.6% vs 5.8%), HBsAb seroconversion (8.4% vs 3.3%), HBeAg loss (25.6% vs 14.4%), and alanine aminotransferase normalization (73.3% vs 55.3%). HIV viral suppression and mean CD4+ cell gains were comparable across both groups.⁴³ Interestingly, aside from alanine aminotransferase normalization, similar findings have not been seen in studies of HBV-monoinfected individuals, and replication of these results in larger-cohort studies is needed to establish whether there is indeed an advantage to TAF over TDF in individuals with HIV/HBV coinfection.

Staging of Liver Disease

Because treatment for HBV infection is indicated in all individuals with HIV/HBV coinfection, fibrosis staging does not affect treatment decisions as it does for HBV-monoinfected individuals.

Table 3. Antiviral Efficacy for HBV Infection in Persons Without HIV

Endpoint	Peginterferon alfa ^a	Entecavir ^b	Tenofovir disoproxil fumarate ^b	Tenofovir alafenamide ^c
Viral suppression, %	30-42	61	76	73
HBeAg loss +/- seroconversion, %	29-36	21-25	21	22
ALT normalization, %	34-52	68-81	68	—
HBsAg loss, %	2-7	4-5	8	1

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

^aAssessed 6 months after completion of 12 months of therapy.

^bAfter 3 years of therapy.

^cAfter 2 years of therapy.

Nevertheless, determining whether a patient has cirrhosis remains important for their overall medical care and for making decisions surrounding the need for HCC screening. Although hepatic ultrasound may provide clues to the diagnosis (eg, splenomegaly, nodular hepatic contour), it is not sufficient for making the diagnosis of cirrhosis, and sensitivity may be as low as 40%.⁴⁴ Other noninvasive tests, including the aspartate aminotransferase-to-platelet ratio index and fibrosis-4 scores, have been well validated in patients coinfecting with HIV and hepatitis C virus, but they have a limited ability to discriminate between fibrosis stages in individuals with HBV receiving antiviral therapy, and therefore have limited utility in the management of HIV/HBV coinfection.⁴⁵

Transient elastography is an office-based, non-invasive method for determining liver stiffness in persons with chronic viral hepatitis and fatty liver disease. It propagates an elastic shear wave throughout the liver tissue and uses pulse-echo ultrasound to measure the shear wave velocity, which correlates with liver stiffness.⁴⁶ Although liver biopsy remains the gold standard for fibrosis assessment, transient elastography has emerged as the most accurate noninvasive modality for fibrosis staging among persons with HBV infection. Transient elastography has also been validated in patients with HIV/HBV coinfection and has been shown to have an accuracy of approximately 85% compared with liver biopsy.⁴⁷ The main disadvantages of transient

elastography are its expense and limited availability, as it requires a specific ultrasound machine that is not accessible in many medical practices.

Screening for HCC

Liver disease, including HCC, is one of the leading causes of non–AIDS-related death among people with HIV,⁴⁸ and people with HIV/HBV coinfection are at risk for developing HCC at an earlier age.^{22–26} Cirrhosis is a major risk factor for HCC, with 70% to 90% of HBV-related HCC occurring in persons with underlying cirrhosis.⁴⁹ HBV DNA level has also been shown to be a major predictor of HCC incidence. In a retrospective analysis of 8354 individuals with HIV/HBV coinfection in the US and Canada, the risk of HCC was 1.77 times higher for those with an HBV DNA level of 201 to 200,000 IU/mL and 4.34 times higher for those with an HBV DNA level of more than 200,000 IU/mL compared with those with an HBV DNA level of 200 IU/mL or lower.⁵⁰ In this same study, sustained HBV suppression for 1 year or more was associated with a 58% reduction in HCC risk, with a dose-response relationship with duration of viral suppression.⁵⁰

Because of the markedly elevated risk of HCC among people with cirrhosis, the American Association for the Study of Liver Disease recommends HCC screening for all individuals with HIV/HBV coinfection with cirrhosis, regardless of age.³⁵ In addition, HCC screening is indicated in the following groups with HBV infection irrespective of the presence or absence of cirrhosis³⁵:

- Black men older than 40 years of age
- Asian men older than 40 years of age
- Asian women older than 50 years of age
- Persons with a first-degree family member with a history of HCC
- Persons with hepatitis D virus infection

Considering the faster progression of liver disease among HIV/HBV coinfecting individuals, some experts would recommend HCC screening in all coinfecting persons over the age of 40 years, although there is no standardized approach. Screening for HCC should be performed using hepatic ultrasound, with or without serum α -fetoprotein, every 6 months.³⁵

Individuals with suspected HCC should undergo further testing with multiphasic abdominal imaging, via either computed tomography or magnetic resonance imaging.³⁵

HBV Vaccination for People With HIV

For people with HIV who do not have HBV coinfection, vaccination is a key pillar of prevention. HBV immunization is now universally recommended for infants, children, and adults aged 0 through 59 years, as well as select groups of adults aged 60 years and older, including people with HIV.⁵¹ Although HBV vaccine recommendations have been simplified over time, HBV immunization has been recommended for MSM, people who inject drugs, and heterosexual individuals with multiple sexual partners since the 1980s, and for all individuals with HIV since 2006.⁵² Nevertheless, HBV vaccination rates remain low for people with HIV. For example, in a nationally representative cohort of more than 18,000 adults receiving care for HIV infection between 2009 and 2012, more than one-third of individuals did not have documentation of HBV infection, immunity, or vaccination, and less than 10% of individuals eligible for the HBV vaccination received it during the study period.⁵³ In addition, almost 8% of this cohort had evidence of natural infection during the study period, an indication of ongoing risk for HBV infection in this population.⁵³

The US Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (OI Guidelines) outline the following indications for HBV vaccination among people with HIV⁵⁴:

1. Individuals without chronic HBV infection (HBsAg negative), immunity to HBV (HBsAb <10 mIU/mL), or evidence of past exposure (anti-HBc negative)
2. Individuals with isolated anti-HBc (eg, anti-HBc positive, but anti-HBs and HBsAg negative)

The OI Guidelines offer several vaccine options for HBV, including the following⁵⁴:

1. A double dose of hepatitis B vaccine intramuscularly (Engerix-B or Recombivax HB) at 0, 1, and 6 months; or


2. Combined hepatitis A and hepatitis B vaccine (Twinrix) at 0, 1, and 6 months; or
3. Vaccine conjugated to CpG (Heplisav-B) at 0 and 1 months

Because HIV infection is associated with suboptimal response rates to HBV vaccination, particularly among those with a low CD4+ cell count,⁵⁵ the OI Guidelines recommend checking an anti-HBs titer 1 to 2 months after completion of the vaccine series to document an immunologic response to vaccination.⁵⁴ Although vaccine response is better in persons with higher CD4+ cell counts, particularly those with CD4+ cell counts greater than 350/cell mm³, the OI Guidelines do not recommend delay or deferral of HBV immunization until CD4+ cell recovery on antiretroviral therapy, as some individuals will respond to vaccination despite a lower CD4+ cell count.⁵⁴ Those patients who do not mount a seroprotective antibody response after immunization should undergo another complete vaccine series. In individuals with isolated anti-HBc, in lieu of providing a full vaccination series, it is reasonable to provide 1 standard dose of the HBV vaccine followed by an anti-HBs titer in 1 to 2 months. If the titer is less than 100 mIU/mL, then the complete vaccine series should be provided.⁵⁴

Several strategies, including double dosing, have been studied to improve the immunogenic response to HBV vaccine; however, historically none have been consistently effective enough for widespread adoption. Nevertheless, more recently the Heplisav-B vaccine has emerged as a strategy to increase vaccine response rates, in both vaccine-naïve adults and previous nonresponders to HBV vaccine. In phase III registration trials among persons without HIV, Heplisav-B was found to be safe and effective, producing higher rates of seroprotection than Engerix-B.⁵⁶⁻⁵⁹ Furthermore, in studies involving previous vaccine nonresponders, Heplisav-B was shown to induce higher rates of seroprotection than single-antigen 3-dose hepatitis B vaccines (eg, Engerix-B and Recombivax-HB).^{60,61} Similarly, among persons with HIV, there is emerging evidence for the use of Heplisav-B. Previous studies of Engerix-B versus Engerix-B plus a CpG adjuvant, small real-world observational studies,

and preliminary results from an ongoing prospective, open-label study to evaluate immunogenicity of Heplisav-B, all suggest that this vaccine is safe and efficacious in persons with HIV.^{61,62}

Conclusion

HBV infection remains a major contributor to liver-related deaths among people with HIV, despite effective treatment and prevention strategies. Tenofovir, either TDF or TAF, is the mainstay of therapy for coinfecting patients owing to its potency and high barrier to resistance. Antiviral therapy does not offer a functional cure for HBV infection, but sustained HBV suppression with therapy has been shown to reduce the risk of liver-related complications. Because individuals with HIV/HBV coinfection are at increased risk for progression to cirrhosis, ESLD, and HCC, fibrosis staging and routine HCC screening are important interventions to help identify and prevent complications from HBV-related liver disease. For people with HIV without HBV infection, major guidelines recommend universal HBV vaccination, including for those with isolated anti-HBc. 

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