Current HIV/AIDS Reports (2023) 20:451–457
https://doi.org/10.1007/s11904-023-00670-0

Strategies for Hepatitis B Virus Prevention in People Living with HIV

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Accepted: 29 September 2023 / Published online: 14 October 2023

Abstract

Purpose of Review Coinfection with HIV and hepatitis B virus (HBV) is common owing to shared routes of transmission, and persons with HIV-HBV coinfection experience an accelerated progression of liver disease. Despite the widespread availability of HBV vaccination, rates of seroprotection in people living with HIV (PLWH) have historically been low. In this article, we review strategies in HBV prevention among PLWH, focusing specifically on updates in HBV vaccination and chemoprophylaxis.

Recent Findings Vaccination remains the hallmark of HBV prevention, and recent studies suggest that a double dose of HBV vaccine and Heplisav-B can improve rates of seroprotection among PLWH. The use of tenofovir-containing antiretroviral therapy (ART) has similarly been shown to provide some HBV protection in PLWH; however, this protection can be lost when switching to newer tenofovir-sparing regimens, including long-acting injectables.

Summary All HBV-susceptible persons with HIV should be vaccinated against HBV, regardless of ART regimen and CD4 count.

Keywords HIV · HBV · HIV and HBV coinfection · Hepatitis B virus · Prevention

Introduction

Hepatitis B virus (HBV) remains a major public health concern and leading cause of liver-related mortality worldwide. In 2019, the World Health Organization (WHO) estimated that 296 million people had chronic HBV infection globally, only 10% of whom were aware of their diagnosis [1, 2]. Although highly effective vaccines against HBV have been available since the 1980s, vaccine uptake remains low among adults (estimated to be 25–30%), and in many countries birth-dose vaccination for HBV is not universal [2–4]. Treatment coverage for HBV similarly remains low, with an estimated 2.2% of diagnosed persons on antiviral therapy [2].

Coinfection with HIV and HBV is common owing to shared routes of transmission. Globally, an estimated 8–10% of people living with HIV (PLWH) have chronic HBV [5–7]. Data before highly active antiretroviral therapy suggest PLWH are up to sixfold more likely to develop chronic HBV following infection [8, 9]. When compared to persons with HBV infection alone, persons with HIV-HBV coinfection can experience an accelerated progression of liver disease, including increased risk for hepatocellular carcinoma (HCC) and liver-related mortality [10–14]. Although anti-HBV active antiretroviral therapy (ART) (e.g., tenofovir) is now widely used and ART has been shown to improve liver fibrosis among persons with HIV-HBV coinfection, HBV remains a major contributor to end stage liver disease (ESLD) in today's modern ART era [15–17]. Additionally, persons with HIV have lower response rates to traditional HBV vaccine schedules, contributing to increased risk for HBV acquisition in this population [18–20]. As ART shifts towards long-acting injectable formulations and away from tenofovir-containing backbones, HBV vaccination and prevention will become even more paramount among PLWH. In this article, we review strategies for HBV prevention among PLWH, focusing specifically on updates in HBV vaccination and chemoprophylaxis.

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HBV Vaccination in Persons Living with HIV

Vaccination is a key pillar of HBV prevention, and HBV vaccination is now universally recommended for infants, children, and adults, ages 0 to 59 years, as well as adults 60 years of age and older with risk factors for HBV [21, 22]. Although universal adult HBV vaccination recommendations were not issued until 2022, HBV immunization has been recommended for key groups at risk for HIV, including men who have sex with men (MSM), persons who inject drugs (PWID), and heterosexual persons with multiple sexual partners since the 1980s, and for all individuals living with HIV since 2006 [23]. The current U.S. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (OI Guidelines) recommend HBV vaccination in the following PLWH [24]:

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

However, despite these recommendations, HBV vaccine uptake remains suboptimal among PLWH [4], as do rates of seroprotection (defined as an anti-HBs ≥ 10 mIU/mL) and persistence of seroprotection following standard dose recombinant HBV vaccines [18, 19, 25]. Because of this, the OI Guidelines recommend one of the following HBV vaccine strategies for PLWH [24]:

1. A *double* dose of HepB vaccine IM (Engerix-B or Recombivax HB) at 0, 1, and 6 months or
2. Combined HepA and HepB vaccine (Twinrix) at 0, 1, and 6 months or
3. Vaccine conjugated to CpG (Heplisav-B) at 0 and 1 months

In a systematic review and meta-analysis of clinical trials evaluating serologic response rates to standard dose versus double dose HBV recombinant vaccine among PLWH, there was a significantly higher serologic response rate (anti-HBs titer > 10 IU/L) among PLWH who received a double dose of vaccine, both at 4–6 weeks (OR 1.76 [1.36–2.29]) and > 12 months (OR 2.28 [1.73–3.01]) following vaccine completion compared with those who received the standard dose [20]. However, despite better performance of the double dose of recombinant vaccine when compared to single-dose vaccine in this meta-analysis, serologic response rates to the double-dose vaccine were quite variable across studies, ranging from 47 to 88% [20]. This is in comparison to serologic response rates of 95% for healthy infants and 90% for healthy adults under 40 years of age, following receipt of a standard dose HBV recombinant vaccine series [26, 27].

More recently, Heplisav-B, a cytidine-phosphate-guanosine (CpG) adjuvanted recombinant HBV vaccine, has emerged as a strategy to improve serologic response rates in populations of patients with historically less optimal response to standard recombinant vaccine. In registration trials conducted in healthy adults without HIV, Heplisav-B resulted in higher seroprotection rates, including among older adults, when compared to standard dose Engerix-B [28•, 29•]. Specifically, among healthy adults 18 to 55 years of age, 95.1% (95% confidence interval (CI), 94.0–96.1) of those receiving Heplisav-B compared to 81.1% (95% CI, 77.7–84.4) of those receiving standard dose Engerix-B achieved an anti-HBs ≥ 10 mIU/mL 4 weeks after their final dose of vaccine [28•]. Similarly, among healthy adults 40 to 70 years of age, 90.0% of those who received Heplisav-B versus 70.5% of those who received standard dose Engerix-B achieved an anti-HBs ≥ 10 mIU/mL 4 weeks after their final dose of vaccine, yielding a seroprotection rate difference of 19.5% (95% CI, 14.7–24.7) [29•]. In this same cohort of persons 40 to 70 years of age, 91.9% in the Heplisav-B arm versus 59.0% of those in the Engerix-B arm maintained anti-HBs levels ≥ 10 mIU/mL at 1 year following initiation of their vaccine series (difference in seroprotection rate of 32.9% (95% CI, 27.6 38.3)) [29•].

Among PLWH, Heplisav-B has similarly been shown to produce robust rates of seroprotection. The Bee-HIVe trial (ACTG 5379) was an international, multicenter open-label study of 3 doses of Heplisav-B, given at 0, 4, and 24 months, in HBV vaccine-naïve PLWH [30••]. PLWH were eligible for the study if they had been on ART for greater than 56 days, had a CD4 count > 100 cells/mm^3, had an HIV RNA level < 1000 copies/mL, had no prior exposure to HBV (HBsAg and anti-HBc negative), and had no other immunocompromising conditions [30••]. The study enrolled 74 HBV vaccine naïve PLWH, 46% of whom were male sex, and 73% of whom enrolled at sites outside of the United States. The median age was 47 years, the median CD4 count was 625 cell/mm^3, and 96% was virally suppressed on ART. After excluding 6 people who did not complete necessary follow-up visits or whose follow-up visits fell outside of the study window, 68 people were included in the primary analysis. Four weeks after the third dose of Heplisav-B, all PLWH achieved seroprotection, defined as an anti-HBs ≥ 10 mIU/mL, with 83.8% of individuals having anti-HBs levels > 1000 mIU/mL (Fig. 1) [30••]. Interestingly at week 24, prior to receipt of the third dose of vaccine, 98.5% of PLWH had already achieved seroprotection, with 27.9% having an anti-HBs level > 1000 mIU/mL [30••]. Real-world

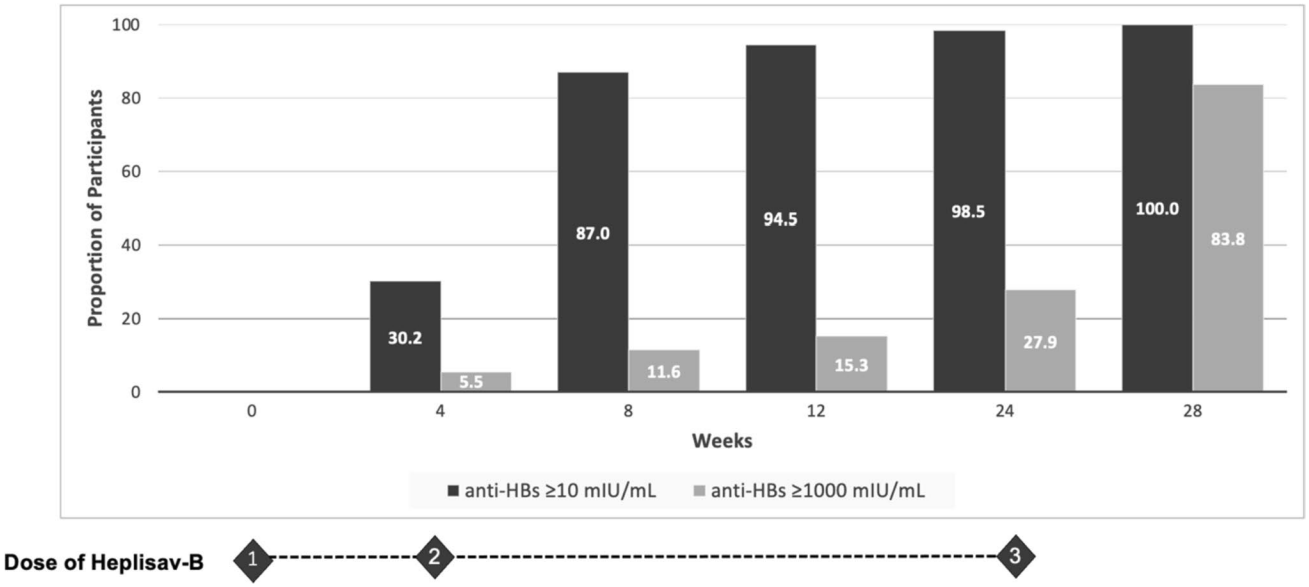

Fig. 1 Proportion of participants with anti-HBs levels ≥ 10 mIU/mL and ≥ 1000 mIU/mL following vaccination with Heplisav-B in the Bee-HIVe trial (ACTG 5379)

retrospective studies have similarly shown high rates of seroprotection following Heplisav-B in PLWH. Among 64 PLWH who received Heplisav-B in San Francisco (63 received 2 doses; 1 received 1 dose), 81% achieved seroprotection, with no difference in seroprotection rates between those undergoing primary vaccination and those with a history of prior HBV vaccination [31]. Similarly, in a retrospective cohort of 120 HBV nonimmune PLWH in Phoenix, Arizona, 93.4% of those who received 2 doses of Heplisav-B ($n = 61$) achieved seroprotection, compared to 57.6% of those who received 3 doses of recombinant HBV vaccine [32]. Among all these studies, the Heplisav-B vaccine was well tolerated among PLWH without major safety concerns.

PreHevbrio is a triple-antigen HBV vaccine, containing 3 recombinant HBV surface antigens, approved for use in adults 18 years of age and older. In a phase 3, double-blind, randomized controlled trial (PROTECT Trial) that included 1607 adults without HIV in the United States, Finland, Canada, and Belgium, participants were randomized to receive 3 doses of PreHevbrio or 3 doses of Engerix-B, both given at 0, 1, and 6 months [33•]. In this study, the primary endpoint of HBV seroprotection 4 weeks after the final dose of vaccine was achieved by 91.4% (95% CI, 89.1–93.3) of persons in the PreHevbrio arm versus 76.5% (95% CI, 73.2–79.5) in the Engerix-B arm (mean seroprotection difference of 14.9% (95% CI, 11.2–18.6)) [33•]. In this trial, rates of seroprotection were higher in the PreHevbrio arm for all age groups, including those 65 years of age and older, in whom 83.6% achieved seroprotection following PreHevbrio versus 64.7% following Engerix-B (mean seroprotection difference of 18.9% (95% CI, 11.6–26.1)) [33•]. However, PLWH were not included in the PROTECT Trial, nor in a similar phase 3 double-blind randomized trial evaluating lot-to-lot consistency and immunogenicity of PreHevbrio versus Engerix-B (CONSTANT Trial) [34]. Currently, there are no randomized clinical trials evaluating the safety or efficacy of PreHevbrio in PLWH and no current recommendations for its use in this population. However, a small prospective cohort study in Israel evaluated the immunogenicity of PreHevbrio in 31 PLWH, the majority of whom were male (90%), with a median CD4 count of 503 cells/mm^3 [35]. In this study, 84% of individuals had an HBsAg ≥ 10 mIU/mL following the third dose of vaccine, and no systemic reactions were reported [35].

Although the use of double-dose recombinant HBV vaccination and Heplisav-B are strategies to improve seroprotection in PLWH, vaccine efficacy among persons with a low CD4 count remains a concern. Indeed, lower HBV vaccine response rates have been linked to a recent or nadir CD4 less than 200 cell/mm^3, as well as a detectable HIV RNA [18, 36, 37]. In one study of PLWH who received 4 double doses of recombinant HBV vaccine, a CD4 count > 200 cells/mm^3 was associated with a serologic response to vaccination (anti-HBs ≥ 10 mIU/mL), as well as a robust antibody response, defined as anti-HBs ≥ 100 mIU/mL [38]. Similarly, single-center retrospective studies evaluating the effectiveness of Heplisav-B among PLWH, suggest that rates of seroprotection are lower among persons with lower current and nadir CD4 counts, as well as for those who are not virally suppressed [31, 39]. Despite decreased response rates to HBV vaccination among persons with lower CD4 counts, the OI Guidelines state that HBV vaccination should not be

delayed or deferred in persons with a lower CD4 count, as many will still respond [24]. However, in the case of vaccine non-responders, some experts would delay revaccination until after a patient's CD4 count is greater than 200 cell/mm^3 or greater; nevertheless, in this situation, the OI Guidelines do recommend revaccination with a double dose of the 3-dose recombinant HBV vaccine series or revaccination with the 2-dose Heplisav-B series [24].

HBV Chemoprophylaxis in PLWH

There are no controlled clinical trial data to support the use of tenofovir as chemoprophylaxis for HBV. However, there are several observational studies among men who have sex with men (MSM) that examined the role of tenofovir containing ART for HIV treatment or HIV pre-exposure prophylaxis (PrEP) for preventing HBV infection, suggesting a protective effect against HBV acquisition (Table 1) [40–44]. Among 2375 HBV-uninfected MSM in the Multicenter AIDS Cohort Study, Falade-Nwulia et al. observed a significantly lower incidence rate of HBV among HIV-positive MSM in the highly active antiretroviral therapy (HAART) era, when compared to the pre-HAART era (incidence rate ratio (IRR) 0.2) [42]. In this same study, being on ART with an HIV RNA level less than 400 copies/mL was associated with protection against incident HBV (IRR 0.2); however, being on ART with an HIV RNA of ≥ 400 copies/mL (suggesting suboptimal adherence) was not [42]. Similarly in a study of 1716 HIV-positive persons in the Swiss HIV Cohort Study, being on dual active antiviral therapy (e.g., tenofovir plus emtricitabine or lamivudine) was associated with a lower incidence of HBV infection, when compared to those on other ART, with an adjusted hazard ratio (HR) of 0.3 [43]. In a Dutch study of 381 MSM with HIV, the overall incidence rate of HBV was 1.10 per 100 person years (PY), but was 2.85/100 PY when no HBV-active ART was used, 1.36/100 PY with use of lamivudine only, and 0.14/100 in the presence of tenofovir use, suggesting that the protective effect of lamivudine, in the absence of tenofovir, is not robust [41]. Analogously, there are reports of PLWH acquiring acute HBV, or developing HBV reactivation, following a switch off of tenofovir containing ART, including long-acting injectable ART [45, 46]. These reports, paired with the observational studies above, clearly signal that clinicians must be mindful of HBV history and risk factors when making changes in ART regimens.

The best data for HBV prevention with antiviral therapy comes from trials that examined perinatal transmission where the model is treatment as prevention in contrast to the aforementioned studies where antiviral therapy is given to the susceptible individual. In a randomized controlled trial of 200 mothers with HBV and hepatitis B e antigen (HBeAg) positivity and an HBV DNA level > 200,000 IU/mL, mothers were randomized to receive either tenofovir disoproxil fumarate (TDF) or usual care without antiviral therapy starting at 30 to 32 weeks of gestation until postpartum week 4 [47••]. All infant received standard immunoprophylaxis. At 28 weeks postpartum, the rate of perinatal HBV transmission was significantly lower in the TDF arm when compared to the standard of care arm (5% vs. 18%) [47••]. Similar results were seen in a systematic review and meta-analysis of antiviral therapy to prevent mother to child transmission (MTCT) of HBV, where authors found a 70%

Table 1 Summary of observational studies demonstrating protective effect of tenofovir as HBV preventive agent in setting of HIV pre-exposure prophylaxis or antiretroviral therapy

Author	Population setting	HBV risk estimates
Gatanaga et al. (2013)[40]	*N* = 354 HIV-infected MSM from a single clinic, Japan	No ART: 6.7/100 p-yr 3TC or TDF in ART: 0.7/100 p-yr
Heuft et al. (2014)[41]	*N* = 381 HIV-infected MSM in a hospital, Netherlands	HBV incidence: 1.1% No HBV-active ART: 2.85/100 p-yr 3TC in ART: 1.36/100 p-yr TDF in ART: 0.14/100 p-yr
Falade-Nwulia et al. (2015)[42]	*N* = 2375 MSM in Multicenter AIDS Cohort Study, United States	HBV incidence: 0.96 per 100 p-yr Suppressed on ART: IRR 0.1
Shilaih et al. (2016)[43]	*N* = 1716 persons with HIV (MSM, heterosexual, PWID) in Swiss HIV cohort *Included those with isolated core Ab*	HBV incidence: 1.6% TDF + 3TC or FTC in ART: HR 0.4
Mizushima et al. (2020)[44]	*N* = 591 MSM in sexual health clinics, Japan	HBV incidence 3.6% One event in PrEP; 14 in non-PrEP HR 0.11 (adjusted HR 0.12)

All patients in these analyses were hepatitis B (HBV) susceptible at baseline and had follow-up serologic testing

MSM men who have sex with men, *ART* antiretroviral therapy, *3TC* lamivudine, *TDF* tenofovir disoproxil fumarate, *p-yr* person-years, *IRR* incidence rate ratio, *PWID* persons who inject drugs, *HR* hazard ratio, *PrEP* pre-exposure prophylaxis for HIV

reduction in MTCT with the use of antivirals [48]. Given this evidence supporting antiviral therapy to reduce the risk of MTCT of HBV, the American Association for the Study of Liver Disease (AASLD) guidelines recommend antiviral therapy in all pregnant persons who otherwise have an indication for HBV treatment, and in pregnant persons with an HBV DNA level > 200,000 IU/mL in the third trimester of pregnancy [49].

Management of Patient with and Isolated Hepatitis B Core Antibody (Anti-HBc)

The presence of hepatitis B core antibody (anti-HBc) indicates that an individual has been previously exposed to HBV. It can be seen during active infection, when present with HBsAg, and it can be seen in settings of immune protection from natural infection, when present with anti-HBs. There are several clinical scenarios that can be present in the setting of an isolate anti-HBc, including occult HBV, false positive anti-HBc, and acute HBV infection; however, overwhelmingly the most common scenario is resolved HBV infection with waning anti-HBs. Among HIV-negative individuals, data indicate that most individuals with waning anti-HBs following vaccination will mount an amnestic response to HBV, which has been correlated in vitro with ongoing immune protection, even after anti-HBs levels fall below 10 mIU/mL [50, 51]. However, it is not clear if the same holds true for PLWH. In several small studies of PLWH with resolved natural infection, only a minority mounted an anamnestic response to a single dose of recombinant vaccine, suggesting a lack of immune protection after loss of anti-HBs [52–54]. In this setting, the OI Guidelines do recommend the PLWH who have an isolated anti-HBc receive one standard dose of HBV vaccine, followed by an anti-HBs titer in 1–2 months [24]. If the titer is > 100 mIU/mL, then no further vaccination is needed; however, if the titer is < 100 mIU/mL, then a complete HBV vaccine series should be completed, followed by repeat serologic testing [24].

Conclusion

In this review, we summarized major strategies for the prevention of HBV among PLWH, including vaccination, chemoprophylaxis, and approaches to improve seroprotection among persons with low CD4 count and those with an isolated anti-HBc. As discussed, vaccination remains the cornerstone of HBV prevention among both people living with and without HIV, and newer vaccines, including Heplisav-B, represent opportunities to improve seroprotective response rates among PLWH. The use of tenofovir-containing antiviral regimens similarly provide some degree of protection against incident HBV in PLWH and in MSM on PrEP; however, the degree of protection provided has not been systematically studied in prospective clinical trials. Nevertheless, as HIV treatment modalities move toward long-acting injectables, and away from tenofovir-containing regimens, the loss of HBV protection afforded by tenofovir when switching ART will become an increasingly important detail to be taken into consideration. Future investigation should explore the efficacy of newer immunizations in PLWH with more advanced HIV and lower CD4 counts who are HBV-susceptible.

Author contributions M.A.C and H.N.K. wrote the main manuscript text, M.A.C prepared the figure, H.N.K. prepared the table. All authors reviewed the manuscript.

Declarations

Competing interests The authors declare no competing interests.

Conflict of Interest Dr. Maria Corcorran declares no conflicts of interest. Dr. Nina Kim is an investigator on a grant where funding is paid to the University of Washington by Gilead Sciences.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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