Current HIV/AIDS Reports (2019) 16:395–403
https://doi.org/10.1007/s11904-019-00461-6

CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Hepatitis B Vaccination and Waning Hepatitis B Immunity in Persons Living with HIV

Priya D. Farooq[1] · Kenneth E. Sherman[1]

Published online: 29 August 2019

Abstract

Purpose of Review Persons with HIV are at a higher risk for acquiring HBV (hepatitis B virus) than the general population due to shared modes of transmission and are significantly more likely to develop and die from sequelae of chronic HBV infection. Early vaccination is key to achieving HBV protective immunity, but response rates are still much lower than in the general population, ranging from 35 to 70%. Individuals with HIV also experience more rapidly waning immunity than those without HIV. Strategies to augment initial response and improve long-term immunity in individuals with HIV include alterations in dose, frequency, and the use of immune adjuvants.

Recent Findings Recent studies have focused on the use of different vaccine formulations, the use of vaccine adjuvants, increased number and strength of vaccine dosages, increased dose frequency, alternative routes of administration, dual vaccinations, and the use of booster vaccines. Although no consensus has been reached on the use of certain vaccination regimens, three and four double-dose vaccine schedules via the intramuscular route have demonstrated higher initial response rates. Early vaccination when CD4 cell counts are greater than 350/mm^3 with low viral loads has been shown to improve initial response, along with completion of immunization series. Adjuvants such as TLR4 and TLR9 agonists appear to improve response to HBV vaccination, but further research is needed in individuals with HIV.

Summary Persons with HIV have significant lower initial and long-term seroresponse rates after HBV vaccination than immunocompetent individuals. Recent and ongoing studies continue to evaluate multiple strategies to improve these rates within a uniquely susceptible population.

Keywords HBV · HIV · Anti-HBs · Protective immunity

Introduction

Individuals with HIV are at a higher risk for acquiring HBV (hepatitis B virus) than the general population due to shared modes of transmission, namely intravenous drug use and sexual contact [1, 2]. Patients with HIV are significantly more likely to develop chronic HBV infection after an acute infection than those without HIV [3]. Chronic HBV infection remains a leading cause of chronic viral hepatitis, cirrhosis, and hepatocellular carcinoma. In particular, individuals coinfected with HBV have a more rapid and severe progression of chronic HBV sequelae, leading to further morbidity and mortality in this vulnerable population [1, 4, 5]. Individuals with HIV/HBV coinfection are 8 times more likely to die from liver disease than those infected with HIV alone, and 19 times more likely than those with HBV alone [6]. In addition to interventions such as safe sex practices and use of clean needles, the most important method of prevention is HBV vaccination, which is recommended by the Centers for Disease Control (CDC) for all persons with HIV [7]. However, for multiple reasons, achieving and maintaining adequate HBV immunity in HIV-infected patients is complex and new strategies have emerged to address these barriers.

This article is part of the Topical Collection on *Co-infections and Comorbidity*

✉ Kenneth E. Sherman
Kenneth.sherman@uc.edu

[1] Division of Digestive Diseases, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0595, USA

Hepatitis B Vaccine Formulations and Schedules

There are multiple HBV vaccine formulations currently approved for use in adults in the USA. Engerix-B® is a single-antigen recombinant vaccine; it is manufactured as a 20-mcg HBsAg (hepatitis B surface antigen) dose that is given on a 0-, 4-, and 24-week schedule, but has been approved for double-dose (40 mcg) vaccination on a 0-, 4-, 8-, and 24-week schedule for chronic dialysis and other immunocompromised patients. This requires administration as two doses of 20 mcg. Recombivax-HB® is also a single-antigen recombinant vaccine and is given as a 10-mcg antigen dose on a 0-, 4-, and 24-week schedule; there is also an approved dialysis dose of 40 mcg given on a 0-, 4-, 8-, and 24-week schedule. HEPLISAV-B® combines 20 mcg HBsAg with a cytosine phosphoguanine oligonucleotide (CPG 1018) adjuvant, a Toll-like receptor 9 (TLR9) agonist, and is given as two doses on a 0- and 4-week schedule. Finally, Twinrix® is a combined HBV and HAV (hepatitis A virus) vaccination with 20 mcg HBsAg and 720 ELISA units of inactivated HAV, administered on a 0-, 4-, and 24-week schedule (Table 1) [8, 9]. Following a complete immunization series, serum anti-HBs (hepatitis B surface antibody) concentration ≥ 10 mIU/ml is considered a seroprotective response (SPR) [10, 11]. Additionally, an initial anti-HBs level > 100 mIU/ml has been associated with a more robust and durable response over time.

There are other formulations of hepatitis B vaccines used outside of the USA (Table 1). These will be discussed in the context of use in people with impaired responses, including those with HIV.

Hepatitis B Vaccination Response in Immunocompetent Persons

In order to appreciate the unique challenges of HBV immunization in persons with HIV, it is important to review responses to vaccination within the general population. In the USA, adult HBV coverage rates are suboptimal, at least in part from low rates of vaccine adherence and series completion. A large retrospective database study found that just over 30% completed the third dose in a HBV series by month 28 after the initial dose [12]. If vaccine series are completed, overall responses are quite good.

Multiple studies examining response rates and long-term immunity have been conducted in the Alaska Native population, which is known to have a high prevalence of both incident and prevalent HBV infection.

Dentinger et al. followed a cohort of 334 Alaska Native children who received a three-dose HBV vaccine series starting at birth and demonstrated anti-HBs concentration ≥ 10 mIU/ml; they were followed for 3151 person-years and had anti-HBs levels checked every other year. Although levels of anti-HBs dropped precipitously on subsequent samples, only 1.8% acquired anti-HBc (hepatitis B core antigen), half of whom had breakthrough infections [13]. This suggests that although baseline levels of anti-HBs decline over time, vaccination still provides durable immunity in most but not all vaccinated children.

In a similar prospective cohort study from McMahon et al., 1578 Alaska Natives vaccinated at age 6 months and older with a three-dose series were followed with annual serologic testing for 11 years. At the 15-year mark, 53% of the original cohort had repeat anti-HBs titers checked. Of those tested, 84% still had detectable anti-HBs levels, including 88% of the subset that responded to the initial series. Initial anti-HBs level, older age at time of initial vaccination, and male sex were also associated with a more durable response [14].

In a 22-year follow-up study of this cohort, 493 persons vaccinated at age 6 months and older had anti-HBs levels checked; 60% demonstrated seroprotection with levels ≥ 10 mIU/ml. A booster dose was given to 164 participants and 81% responded by 60 days. SPR was demonstrated in 87% and no new acute or chronic infections were reported [15]. Another study conducted in this cohort at the 30-year follow-up mark by Bruce et al. demonstrated ≥ 90% protection in this population [16•]. These studies have demonstrated high response rates to initial vaccination and long-term immunity, as well as strong anamnestic response with booster vaccine.

Hepatitis B Serologies in Patients with HIV

HBV screening is recommended in all persons with HIV. Testing should include HBsAg, anti-HBs, and total anti-HBc. Patients with positive anti-HBc and anti-HBs represent those with prior cleared infection and do not require vaccination. Patients with anti-HBs positivity and titer ≥ 10 mIU/ml are considered immune and do not need further immunization at that time. Patients with negative HBsAg, negative anti-HBc, and negative anti-HBs should all be vaccinated. Anti-HBs levels should be checked 4 weeks after the last dose in a vaccinations series. The timing of retesting, particularly in high-risk individuals, has not been established. In the general population, retesting is not recommended but many experts would consider yearly testing and revaccination in those with HIV and ongoing risk profiles.

HIV-Infected Patients and Isolated Hepatitis B Core Antibody

Patients with anti-HBc positivity alone are less straightforward, as this can potentially represent remote infection with

Table 1 Current US and international adult HBV vaccine formulations

Vaccine brand name[a]	Composition/dosage[b]	Schedule(s)	Special indication or alternate schedule(s)
Approved in the USA			
Engerix-B®	20 mcg HBsAg	0, 1, 6 months	3-dose accelerated schedule with booster
	40 mcg HBsAg (two doses)	0, 1, 2, 12 months	
		0, 1, 2, 6 months	Dialysis patients
Recombivax-HB®	10 mcg HBsAg	0, 1, 6 months	Pre-dialysis, dialysis patients
	40 mcg HBsAg	0, 1, 6 months	
HEPLISAV-B®	20 mcg HBsAg and 3000 mcg CpG 1018 adjuvant	0 and 1 month	
Twinrix®	20 mcg HBsAg and 720 units inactivated HAV	0, 1, 6 months	3-dose rapid schedule with booster
		0, 7, 21 days, 12 months	
International formulations (country/countries of origin)			
Bilive™ (China)	10 mcg HBsAg and 500 units HAV	0, 1, 6 months	
Bimmugen® (Japan)	10 mcg HBsAg	0, 1, 6 months	
Enivac-HB™ (Cuba)	20 mcg HBsAg	0, 1, 6 months	
Euvax-B (South Korea)	20 mcg HBsAg	0, 1, 6 months	
Fendrix® (Europe)	20 mcg HBsAg and 50 mcg ASO4 adjuvant	0, 1, 2, 6 months	Pre-dialysis, dialysis patients
GenHevac B™ (France)	20 mcg HBsAg	0, 1, 6 months	Pre-dialysis, dialysis patients
		0, 1, 2, 4, 12 months	
GeneVac-B™ (India)	20 mcg HBsAg	0, 1, 6 months	3-dose rapid schedule
		0, 1, 2 months	
H-B-Vax II® (Australia)	10 mcg HBsAg	0, 1, 6 months	Pre-dialysis, dialysis patients
	40 mcg HBsAg	0, 1, 6 months	
HBvaxPro® (Europe)	10 mcg HBsAg	0, 1, 6 months	Pre-dialysis, dialysis patients
	40 mcg HBsAg	0, 1, 6 months	
Heberbiovac HB (Cuba)	20 mcg HBsAg	0, 1, 6 months	3-dose rapid schedule
		0, 1, 2 months	
Hepavax-B (South Korea)	20 mcg HBsAg	0, 1, 6 months	3-dose accelerated schedule with booster
		0, 1, 2, 12 months	
Hepavax-Gene® (South Korea)	20 mcg HBsAg	0, 1, 6 months	
Hepativax (Argentina)	20 mcg HBsAg	0, 1, 6 months	
Probivac-B® (Mexico)	20 mcg HBsAg	0, 1, 6 months	3-dose accelerated schedule with booster
		0, 1, 2, 12 months	
		0, 7, 21 days, 12 months	3-dose rapid schedule with booster
Shanvac-B® (India)	20 mcg HBsAg	0, 1, 6 months	3-dose accelerated schedule with booster
		0, 1, 2, 12 months	
Viralinte (Mexico)	20 mcg HBsAg	0, 1, 6 months	

[a] Brand name may vary by country of origin or distribution

[b] All vaccines contained recombinant hepatitis B surface antigen (HBsAg)

loss of anti-HBs vs. patients with occult HBV, defined as HBV DNA positive [17]. There is a lack of consensus on the optimal management of patients with HIV and isolated anti-core antibody. Some experts will try booster vaccination, while others will test for serum HBV DNA prior to booster consideration.

In a prospective multicenter study by Piroth et al., 54 patients with CD4 cell count > 200/mm^3 and isolated anti-HBc were evaluated for response to HBV vaccination. Patients were vaccinated with 20 mcg of recombinant HBV vaccine; anti-HBs level was checked 4 weeks later. Those with anti-HBs level < 10 mIU/ml were given three additional double doses (40 mcg) at weeks 5, 9, and 24. Forty-six percent had an anamnestic response; immunity was retained in 58% at week 28 and 50% at month 18. In those who did not respond initially and received additional vaccination, 89% maintained immunity at week 28 and 81% at month 18. The authors concluded that patients with isolated anti-HBc and anti-HBs ≤ 100 mIU/ml after single HBV vaccine should be further vaccinated with three double-dose vaccinations [18•]. Similar findings were reported in two small prospective cohorts of HIV patients with isolated anti-HBc, with low

anamnestic responses of 22–33% and primary response rate of 60–74% following 3–6 vaccine doses. Both studies reported poor long-term immunity, prompting further discussion of long-term monitoring and repeat vaccination in these patients [19, 20]. These findings also support the safety of vaccination in these patients, as none of these patients were identified as having occult HBV infection and there were limited and only minor side effects reported.

Diminished Immunogenicity of Hepatitis B Vaccination in Patients with HIV

Immune response following HBV vaccination is lower in patients with HIV when compared with those without HIV. In contrast to the > 90% seroprotection rate seen in both the vaccine registration trials, and in the Alaska Native population, seroprotection in HIV patients varies widely with a range of 18 to 89% [1]. Variables affecting response following vaccination include age, gender, CD4 cell count, HIV RNA level, combination antiretroviral therapy (cART), coinfection with hepatitis C virus (HCV), other chronic medical conditions, human leukocyte antigen (HLA) alleles, impaired antigen presentation and processing, and poor T and B memory cell function leading to impaired humoral immunity [21–29]. Retrospective data has shown that individuals with HIV vaccinated prior to HIV diagnosis had higher rates of seroprotection when compared with those who were vaccinated after diagnosis, which argues in favor of aggressive adult vaccination in high-risk non-infected patients [30].

An observational study of a large US military cohort by Landrum et al. demonstrated that receiving three or more vaccines, higher CD4 cell count at time of vaccination, and use of cART were all associated with a higher likelihood of HBV vaccine response. In particular, patients on cART with CD4 cell count ≥ 350/mm^3 were more likely to response than those not on cART with CD4 cell count ≥ 350/mm^3. Overall rates of response were still low, even in the cART group, with 49% response in those on cART at the time of the last vaccination and 62% response in patients on cART with CD4 cell count ≥ 350/mm^3 and HIV RNA < 400 copies/ml [24]. Similar findings were reported in a randomized controlled trial by Fonseca et al. Patients with HIV were immunized with three-dose 20-mcg or 40-mcg regimens, with response rates only significantly different in the subgroup analysis of CD4 cell count with a cut-off value of 350/mm^3 and HIV viral load with a cut-off value of 10,000 copies/ml [26]. Comparable results were also reported in a large observational study by Mena et al. [31]. In patients who are not vaccinated prior to contracting HIV, early HBV vaccination when CD4 cell count is ≥ 350/mm^3 and HIV viral load is low can improve overall immune response.

New Strategies to Improve Host Seroresponse and Vaccine Immunogenicity

A number of different vaccinations strategies have been employed to improve immunogenicity of HBV vaccines in patients with HIV, as well as to augment long-term response. These include different vaccine formulations, the use of adjuvants, increased number and strength of doses, increased dose frequency, alternative routes of administration, dual vaccination, and use of booster vaccines (Fig. 1). This review will focus on recent randomized controlled trials (RCT), prospective cohort studies, and well-designed retrospective and observational studies within the past 10 years.

A randomized trial of HBV vaccination in HIV-infected adolescents (ages 12–25) by Flynn et al. assessed the response rates to three-dose regimens of 20 mcg and 40 mcg (double-dose) Engerix-B® and Twinrix®. In the Engerix-B® 20-mcg arm, response rate was 60% at week 28. Response was significantly higher in the double dose and Twinrix® groups, 73% and 75% respectively at week 28. On multivariate analysis, baseline CD4 cell count was an independent predictor of response [23]. It is not clear why those receiving dual vaccination also had improved response rates, although this has been previously demonstrated in HIV-negative adolescents and represents another avenue for future study.

Cruciani et al. evaluated the use of double-dose HBV vaccination at 1-month intervals in patients with HIV with CD4 cell count > 200/mm^3. After a series of three vaccines, the rate of response was 60%. Non-responders (anti-HBs < 10 mIU/ml) were given 1–3 additional booster vaccinations, with total response of 89.2%. However, long-term immunity decreased dramatically, with 63% and 33% seroprotection at 12 and 24 months respectively. Sex, CD4 cell count, and HIV viral load were all significant predictors of response. The authors of the study suggested additional monitoring of anti-HBs levels, especially in those with low levels at initial response [25].

Launay et al. assessed multiple parallel strategies aimed at increasing immunogenicity of HBV vaccination in patients with HIV. In an open-label, multicenter trial, 437 patients were randomized to receive recombinant HBV vaccine on one of three schedules with variable doses, number of doses, and sites of injection—three doses of standard dose at 0-, 4-, and 24-week intervals, four doses of intramuscular (IM) double-dose at 0, 4, 8, and 24 weeks, and four doses of intradermal (ID) low dose (4 mcg) at 0, 4, 8, and 24 weeks. 426 patients were vaccinated; 396 had anti-HBs checked at week 28, with a statistically significant difference among the groups—65% response in the standard arm, 82% response in the four-dose IM double-dose arm, and 77% in the four-dose ID arm [32]. A follow-up study published in 2016 looked at immunity at month 42, with 41% response in the standard arm, 71% in the four-dose IM double-dose arm, and 44% in the four-dose ID arm, demonstrating improved long-term immunity with the 4 dose IM double-dose vaccine

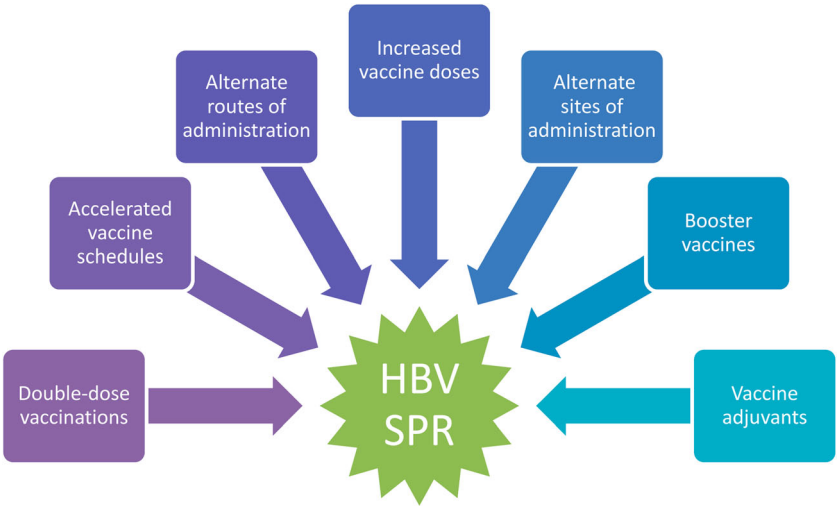

Fig. 1 Strategies to improve seroprotective response to HBV vaccination in persons with HIV

regimen [33•]. A randomized controlled trial by Bunupuradah et al. of children 1–18 years of age with CD4 cell count > 200/mm^3 compared ID with IM administration. Patients were randomized to three doses of HBV vaccine by ID (2 mcg) or IM route (10 mcg). Seroprotective response rates were similar between groups, but anti-HBs were higher in the IM group at all time points [34]. This supports IM administration to optimize long-term immunity.

Two studies by Potsch et al. also evaluated the use of four-dose IM double-dose regimens in individuals with HIV. In the 2010 prospective cohort study, 47 patients underwent vaccination with anti-HBs levels checked 1 month after the last dose—89% responded with anti-HBs ≥ 10 mIU/ml, 78% with levels over 100 mIU/ml, and 60% with levels greater than 1000 mIU/ml. Undetectable HIV viral load was a predictor of response [35]. The 2012 study compared response rates with three- and four-dose IM double-dose regimens; 163 patients underwent a four-dose series with anti-HBs checked 1 month after the third and fourth doses. Response rates were seen in 83% after three doses and 91% after four doses; the same trend (62% and 80%) was observed with strong responses (anti-HBs ≥ 100 mIU/ml) [36]. Similar findings are reported in other prospective cohort studies [37]. This further supports the use of a four-dose series with 40-mcg dosing at initial vaccination to improve overall response in this difficult to vaccinate population.

An observational study by Mena et al. also demonstrated poorer response in patients receiving fewer than three HBV vaccinations or receiving vaccinations on a rapidly accelerated schedule (0, 1, and 2–3 weeks) when compared with an accelerated schedule (0, 4, and 8 weeks) [31]. A randomized control trial by de Vries-Sluijs et al. designed to investigate non-inferiority of standard-dose HBvaxPro®, a European recombinant HBV vaccine, on an accelerated schedule (0, 1, and 3 weeks) compared with standard intervals (0, 4, 24 weeks). Compliance was better in the accelerated group. Patients were stratified by CD4 cell count, and the accelerated schedule was only non-inferior in the CD4 cell count > 500/mm^3 group [38]. There may be a role for accelerated dosing schedules to improve adherence and completion in patients with high CD4 cell counts, likely early in the course of disease or among those with good response to cART.

In addition to choice of initial vaccination regimen, there has been significant discussion regarding the use of single-dose or double-dose series for revaccination in non-responders or hypo-responders. A prospective study by Irungu et al. from Kenya reported a response rate of 86% in initial non-responders after revaccination with standard-dose regimen, with total response rate of 95%; quantitative titers were not obtained and long-term response was not assessed [39]. Rey et al. carried out an open-label, randomized controlled trial to further address this question. 178 HIV-infected adults with CD4 cell count ≥ 200/mm^3 that had previously not responded to HBV vaccination were randomized to either three standard-dose or double-dose HBV vaccinations at weeks 0, 4, and 24. There was no significant difference between groups when assessing for overall response at week 28, although the double-dose group did have higher anti-HBs levels overall with longer durability of response seen at week 72 [40]. A randomized trial of 132 patients by Chaiklang et al. did not find a significant difference among response rates with three- or four-dose 20-mcg and 40-mcg regimens, but also found that higher and more frequent vaccine doses were associated with higher anti-HBs levels [41]. These findings may support using this augmented dose strategy for revaccination. Although initial response rates were similar in single-dose and double-dose regimens, higher anti-HBs levels, as seen in the double-dose groups, can be associated with improved long-term immunity.

A meta-analysis from 2013 by Ni et al. identified five studies of HBV vaccination in patients with HIV, with data supporting the use of increased vaccine dosage to improve immune response [42].

The utilization of various adjuvants to improve vaccine immunogenicity has also been investigated. Cooper et al. evaluated the safety profile and use of adjuvant CPG 7909, which contains TLR9 agonists, to enhance HBV vaccination seroresponse in patients with HIV. A randomized, double-blind controlled trial published in 2005 compared double-dose Engerix-B® with and without CPG 7909. Anti-HBs levels were significantly higher in the CPG 7909 group, with levels > 10 mIU/ml in 89%, 89%, and 100% at 6, 8, and 48 weeks respectively, compared with 53%, 42%, and 63% in the control group. Approximately 50% of the intervention arm participants had failed prior vaccination. The safety profile of the adjuvant was favorable [43]. Follow-up anti-HBs titers measured at 6-month intervals up to 60 months showed higher rates of seroprotection and higher anti-HBs titers at all time points in the CPG 7909 group [44]. A smaller double-blind, placebo-controlled trial by Angel et al. assessed lymphoproliferative response in patients with HIV after HBV vaccine with and without CPG 7909, with significantly enhanced response noted in the intervention arm at weeks 8 and 48, which suggests improved cellular immunity with CPG 7909 in this poorly responsive group [45].

Fendrix® is an HBV vaccine currently approved in Europe for patients with chronic renal disease. It contains 20 mcg of recombinant HBsAg and adjuvant AS04, which contains a Toll-like receptor 4 (TLR4) agonist and aluminum salt. It is given at 0, 1, 2, and 6 months. TLR4 agonists increase antigen-specific T cell activation. de Silva et al. identified 22 patients with HIV who had previously failed HBV vaccination, some with double-dose regimens. Of 22 patients, 18 had a strong response with anti-HBs > 100 mIU/ml and 3 of 22 had anti-HBs 10–100 mIU/ml, with an overall response rate of 95% [46]. Although this was a small trial with possible confounders, the results were promising and warrant further investigation.

HEPLISAV-B® is an adjuvant-enhanced HBV vaccine commercially available in the USA since 2017. As previously described, it contains 20 mcg of recombinant HBsAg and CPG 1018 adjuvant, a Toll-like receptor 9 (TLR9) agonist, and is given as a two-dose regimen on a 0- and 4-week schedule. Three large clinical trials, one randomized, observer-blind trial in Canada and Germany and two US-based phase 3, multicenter, randomized double-blind, controlled trials, were conducted to assess the safety and immunogenicity of HEPLISAV-B® when compared with standard-dose Engerix-B®. The first trial by Halperin et al. published in 2012 identified 2415 healthy participants 18–55 years of age who were randomized in a 3:1 ratio to receive HEPSILAV-B® or Engerix-B®. Patients were followed until week 28 after initial injection. Superior seroprotective rates (SPR) and higher geometric mean concentrations were demonstrated at almost all time points [47]. The second trial by Heyward et al., published in 2013, enrolled 2452 healthy adults 40–70 years of age; they were randomized in a 4:1 ratio to receive HEPLISAV-B® or Engerix-B® and were followed until week 52 after initial injection. Similarly, the SPR were higher at all time points in the HEPLISAV-B® group, with similar safety profiles [48]. Jackson et al. enrolled 8374 participants 18–70 years of age, with a subset of 961 patients with type 2 diabetes mellitus, with results published in 2018. Patients were randomized to HEPLISAV-B® or Engerix-B® in a 2:1 ratio and followed until week 28 after first injection. In both the total population and per-protocol population, SPR was significantly higher with HEPSILAV-B® compared with Engerix-B®, 90% and 65% in the diabetes mellitus group. SPR was > 95% in all other HEPSILAV-B® subgroups [49]. Another observer-blind, randomized controlled, multicenter trial by Janssen et al. recruited 521 patients 18–75 years of age with chronic kidney disease; patients were randomized to HEPLISAV-B® for three doses or double-dose Engerix-B® for four doses and followed for 52 weeks. Patients in the HEPLISAV-B® arm achieved earlier SPR with higher geometric mean anti-HBs concentrations and more durable response over time. Comparing the intervention and standard arms, 89% and 82% had SPR at week 28 and 84% and 77% at week 52 [50].

HEPLISAV-B® is already being administered to some patients with HIV, with the original data extrapolated for use in this population. Benefits include a two-dose vaccination schedule with better adherence, as well as a more robust and durable response in patients immunosuppressed due to chronic kidney disease when compared with standard vaccination. Patients with HIV were not included in the original trials and could have unique adverse effects after exposure to the CPG 1018 adjuvant, although this has not so far been reported in the literature. Further study in individuals with HIV is warranted to elucidate the risks and benefits of administering HEPLISAV-B® to these patients.

Waning Hepatitis B Immunity in Patients with HIV

In addition to poor initial response, patients with HIV also have difficulty maintaining HBV immunity over time. A systematic review and meta-analysis from 2014 by Kernéis et al., which included twelve relevant studies, supported impaired long-term immunity in this patient population and did not find any significant difference between double-dose and standard-dose vaccination with regard to long-term humoral response [51].

Retrospective studies have identified multiple factors affecting long-term immune response, including maximal anti-HBs level following primary vaccination, CD4 cell count,

both current and nadir, HIV viral load, and CD19 cell percentage, indicative of impaired humoral function [40, 52, 53]. A retrospective cohort study by Lara et al. found that booster vaccinations triggered seroconversion in initial non-responders, although it did not have an association with persistent levels of anti-HBs when measured 11 years after primary vaccination. The study also corroborated the association between high anti-HBs titers > 100 mIU/ml and persistent immunity [54].

Guidance for Individuals with HIV

Patients with initial seroprotective response and ongoing risk factors for HBV exposure should have anti-HBs levels checked annually [7]. Booster vaccines or a complete series should be reinitiated if levels decrease below 10 mIU/ml. Evidence is lacking for management of patients vaccinated with low CD4 cell counts given their poor immune response. In patients who were vaccinated when CD4 cell count was < 350/mm^3, we recommend repeat vaccination after initiation of cART and CD4 cell count ≥ 350/mm^3 for at least 3 months [24]. In patients who do not fully recover CD4 cell counts to this level, we recommend revaccination after 1 year with an undetectable viral load [55]. Initial vaccination can be performed with standard-dose or double-dose regimens, although we support use of double-dose vaccination in this population despite mixed results regarding improved response. The role of adjuvant vaccines including HEPLISAV-B® and Fendrix® remains to be elucidated.

Conclusion

Seroprotective response and durable immunity after HBV vaccination in individuals with HIV is a complex subject with numerous variables. Ongoing research is evaluating the use of novel strategies to improve response in this highly susceptible population. Vaccination early in the course of HIV infection, preferably when CD4 cell counts are greater than 350/mm^3 with low viral loads, is key to improve initial response, along with a focus on adherence to a full series of immunizations. Double-dose recombinant vaccination via the intramuscular route has been shown to augment initial response and improve long-term immunity due to improved initial anti-HBs titers. High-risk individuals should have anti-HBs levels checked every year to ensure continued seroprotection and should be re-immunized based on results, preferably with a double-dose regimen. Use of adjuvants, particularly TLR4 and TLR9 agonists, with HBV vaccination appears promising, but further investigation in the HIV-infected population will be needed prior to standardized recommendation.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

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.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Sun HY, Sheng WH, Tsai MS, Lee KY, Chang SY, Hung CC. Hepatitis B virus coinfection in human immunodeficiency virus-infected patients: a review. World J Gastroenterol. 2014;20(40):14598–614. https://doi.org/10.3748/wjg.v20.i40.14598.
2. Crum-Cianflone NF, Sullivan E. Vaccinations for the HIV-infected adult: a review of the current recommendations. Part I Infect Dis Ther. 2017;6(3):303–31. https://doi.org/10.1007/s40121-017-0166-x.
3. Phung BC, Sogni P, Launay O. Hepatitis B and human immunodeficiency virus co-infection. World J Gastroenterol. 2014;20(46):17360–7. https://doi.org/10.3748/wjg.v20.i46.17360.
4. Tang LSY, Covert E, Wilson E, Kottilil S. Chronic hepatitis B infection: a review. JAMA. 2018;319(17):1802–13. https://doi.org/10.1001/jama.2018.3795.
5. Soriano V, Poveda E, Vispo E, Barreiro P. Hepatitis B in HIV-infected patients. Clin Liver Dis. 2013;17(3):489–501. https://doi.org/10.1016/j.cld.2013.05.008.
6. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Muñoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002;360(9349):1921–6. https://doi.org/10.1016/S0140-6736(02)11913-1.
7. HIV Infection and Adult Vaccination. Centers for Disease Control. https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/hiv.html. Accessed March 1, 2019.
8. Table 1. Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2019. Centers for Disease Control. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Accessed March 1, 2019.
9. Table 2. Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2019. Centers for Disease Control. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html. Accessed March 1, 2019.
10. Hadler SC, Francis DP, Maynard JE, Thompson SE, Judson FN, Echenberg DF, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med. 1986;315(4):209–14. https://doi.org/10.1056/NEJM198607243150401.
11. Landrum ML, Hullsiek KH, Ganesan A, Weintrob AC, Crum-Cianflone NF, Barthel RV, et al. Hepatitis B vaccination and risk of hepatitis B infection in HIV-infected individuals. AIDS. 2010;24(4):545–55. https://doi.org/10.1097/QAD.0b013e32832cd99e.
12. Trantham L, Kurosky SK, Zhang D, Johnson KD. Adherence with and completion of recommended hepatitis vaccination schedules among adults in the United States. Vaccine. 2018;36(5):5333–9. https://doi.org/10.1016/j.vaccine.2018.05.111.
13. Dentinger CM, McMahon BJ, Butler JC, Dunaway CE, Zanis CL, Bulkow LR, et al. Persistence of antibody to hepatitis B and

protection from disease among Alaska natives immunized at birth. Pediatr Infect Dis J. 2005;24(9):786–92. https://doi.org/10.1097/01.inf.0000176617.63457.9f.

14. McMahon BJ, Bruden DL, Petersen KM, Bulkow LR, Parkinson AJ, Nainan O, et al. Antibody levels and protection after hepatitis B vaccination: results of a 15-year follow-up. Ann Intern Med. 2005;142(5):333–41. https://doi.org/10.7326/0003-4819-142-5-200503010-00008.
15. McMahon BJ, Dentinger CM, Bruden D, Zanis C, Peters H, Hurlburt D, et al. Antibody levels and protection after hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose. J Infect Dis. 2009;200(9):1390–6. https://doi.org/10.1086/606119.
16• Bruce MG, Bruden D, Hurlburt D, Zanis C, Thompson G, Rea L, et al. Antibody levels and protection after hepatitis B vaccine: results of a 30-year follow-up study and response to a booster dose. J Infect Dis. 2016;214(1):16–22. https://doi.org/10.1093/infdis/jiv748 **This study provided 30-year data on a large cohort of HBV-vaccinated Alaska natives and demonstrated ≥ 90% HBV seroprotection in an immunocompetent population**.
17. Panel on opportunistic infections in HIV-infected adults and adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed March 1, 2019.
18• Piroth L, Launay O, Michel M, Bourredjem A, Miailhes P, Ajana F, et al. Vaccination against hepatitis B virus (HBV) in HIV-1-infected patients with isolated anti-HBV core antibody: the ANRS HB EP03 CISOVAC prospective study. J Infect Dis. 2016;213(11):1735–42. https://doi.org/10.1093/infdis/jiw011 **This prospective cohort study of patients with HIV and isolated anti-HBc found benefit in double-dose revaccination if initial vaccine elicited anti-HBs ≤ 100 mIU/ml**.
19. Chakvetadze C, Bani-Sadr F, Pendeven CL, Lescure FX, Fontaine C, Galperine T, et al. Serologic response to hepatitis B vaccination in HIV-infected patients with isolated positivity for antibodies to hepatitis B core antigen. Clin Infect Dis. 2010;50(8):1184–886. https://doi.org/10.1086/651422.
20. Kaech C, Pache I, Bürgisser P, Elzi L, Darling KEA, Cavassini M. Immune response to hepatitis B vaccination in HIV-positive adults with isolated antibodies to HBV core antigen. J Inf Secur. 2012;65(2):157–64. https://doi.org/10.1016/j.jinf.2012.03.009.
21. Fuster F, Vargas JI, Jensen D, Sarmiento V, Acuña P, Peirano F, et al. CD4/CD8 ratio as a predictor of the response to HBV vaccination in HIV-positive patients: a prospective cohort study. Vaccine. 2016;34(16):1889–95. https://doi.org/10.1016/j.vaccine.2016.02.055.
22. Whitaker JA, Rouphael NG, Edupuganti S, Lai L, Mulligan MJ. Strategies to increase responsiveness to hepatitis B vaccination in adults with HIV-1. Lancet Infect Dis. 2012;12(12):966–76. https://doi.org/10.1016/S1473-3099(12)70243-8.
23. Flynn PM, Cunningham CK, Rudy B, Wilson CM, Kapogiannis B, Worrell C, et al. Hepatitis B vaccination in HIV-infected youth: a randomized trial of three regimens. J Acquir Immune Defic Syndr. 2011;56(4):325–32. https://doi.org/10.1097/QAI.0b013e318203e9f2.
24. Landrum ML, Hullsiek KH, Ganesan A, Weintrob AC, Crum-Cianflone NF, Barthel RV, et al. Hepatitis B vaccine responses in a large U.S. military cohort of HIV-infected individuals: another benefit of HAART in those with preserved CD4 count. Vaccine. 2009;27(34):4731–8. https://doi.org/10.1016/j.vaccine.2009.04.016.
25. Cruciani M, Mengoli C, Serpelloni G, Lanza A, Gomma M, Nardi S, et al. Serologic response to hepatitis B vaccine with high dose and increasing number of injections in HIV infected adult patients. Vaccine. 2009;27(1):17–22. https://doi.org/10.1016/j.vaccine.2008.10.040.
26. Fonseca MO, Pang LW, de Paula CN, Barone AA, Heloisa LM. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. Vaccine. 2005;23(22):2902–8. https://doi.org/10.1016/j.vaccine.2004.11.057.
27. Pessoa SD, Miyamoto M, Ono E, Gouvêa AF, de Moraes-Pinto MI, Succi RC. Persistence of vaccine immunity against hepatitis B virus and response to revaccination in vertically HIV-infected adolescents on HAART. Vaccine. 2010;28(6):1606–12. https://doi.org/10.1016/j.vaccine.2009.11.045.
28. del Pozo Balado MdM, Leal M, Méndez Lagares G, Mata RC, López-Cortés LF, Viciana P et al. Increased regulatory T cell counts in HIV-infected nonresponders to hepatitis B virus vaccine. J Infect Dis 2010;202(3):362–369. doi:https://doi.org/10.1086/653707.
29. Mehta N, Cunningham CK, Flynn P, Pepe J, Obaro S, Kapogiannis BG, et al. Impaired generation of hepatitis B virus-specific memory B cells in HIV infected individuals following vaccination. Vaccine. 2010;28(21):3672–8. https://doi.org/10.1016/j.vaccine.2010.03.022.
30. Landrum ML, Hullsiek KH, Chun HM, Crum-Cianflone NF, Ganesan A, Weintrob AC, et al. The timing of hepatitis B virus (HBV) immunization relative to human immunodeficiency virus (HIV) diagnosis and the risk of HBV infection following HIV diagnosis. Am J Epidemiol. 2011;173(1):84–93. https://doi.org/10.1093/aje/kwq326.
31. Mena G, Llupià A, García-Basteiro AL, Díez C, León A, García F, et al. Assessing the immunological response to hepatitis B vaccination in HIV-infected patients in clinical practice. Vaccine. 2012;30(24):3703–9. https://doi.org/10.1016/j.vaccine.2012.03.018.
32. Launay O, van der Vliet D, Rosenberg AR, Michel ML, Piroth L, Rey D, et al. ANRS HB03 VIHVAC-B Trial. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. JAMA. 2011;305(14):1432–40. https://doi.org/10.1001/jama.2011.351.
33• Launay O, Rosenberg AR, Rey D, Pouget N, Michel ML, Reynes J et al. Long-term immune response to hepatitis B virus vaccination regimens in adults with human immunodeficiency virus 1: secondary analysis of a randomized clinical trial. JAMA Intern Med. 2016;176(5):603-10. doi:https://doi.org/10.1001/jamainternmed.2016.0741. **This follow-up study of a randomized controlled trial demonstrated improved long-term immunity in patients with HIV following an intramuscular double-dose vaccine regimen**.
34. Bunupuradah T, Ananworanich J, Pancharoen C, Petoumenos K, Prasitsuebsai W, Wongngam W, et al. Randomized study of intradermal compared to intramuscular hepatitis B vaccination in HIV-infected children without severe immunosuppression. Vaccine. 2011;29(16):2962–7. https://doi.org/10.1016/j.vaccine.2011.01.114.
35. Potsch DV, Oliveira MLA, Ginuíno C, Miguel JC, Oliveira SAN, Silva EF, et al. High rates of serological response to a modified hepatitis B vaccination schedule in HIV-infected adults subjects. Vaccine. 2010;28(6):1447–50. https://doi.org/10.1016/j.vaccine.2009.11.066.
36. Potsch DV, Camacho LAB, Tuboi S, Villar LM, Miguel C, Ginuíno C, et al. Vaccination against hepatitis B with 4-double doses increases response rates and antibodies titers in HIV-infected adults. Vaccine. 2012;30(41):5973–7. https://doi.org/10.1016/j.vaccine.2012.07.028.
37. Kourkounti S, Retsas T, Paparizos V, Tsimpidakis A, Kapsimali V, Rigopoulos D. Evaluation of a convenient vaccination schedule against hepatitis B in HIV-patients with undetectable HIV viral

load. Vaccine. 2018;36(12):1533–6. https://doi.org/10.1016/j.vaccine.2018.02.018.
38. de Vries-Sluijs TE, Hansen BE, van Doornum GJ, Kauffmann RH, Leyten EM, Mudrikova T, et al. A randomized controlled study of accelerated versus standard hepatitis B vaccination in HIV-positive patients. J Infect Dis. 2011;203(7):984–91, de Vrie. https://doi.org/10.1093/infdis/jiq137.
39. Irungu E, Mugo N, Ngure K, Njuguna R, Celum C, Farquhar C, et al. Immune response to hepatitis B virus vaccination among HIV-1 infected and uninfected adults in Kenya. J Infect Dis. 2013;207(3):402–10. https://doi.org/10.1093/infdis/jis695.
40. Rey D, Piroth L, Wendling MJ, Miailhes P, Michel ML, Dufour C, et al. Safety and immunogenicity of double-dose versus standard-dose hepatitis B revaccination in non-responding adults with HIV-1 (ANRS HB04 B-BOOST): a multicentre, open-label, randomised controlled trial. Lancet Infect Dis. 2015;15(11):1283–91. https://doi.org/10.1016/S1473-3099(15)00220-0.
41. Chaiklang K, Wipasa J, Chaiwarith R, Praparattanapan J, Supparatpinyo K. Comparison of immunogenicity and safety of four doses and four double doses vs. standard doses of hepatitis B vaccination in HIV-infected adults: a randomized, controlled trial. PLoS One. 2013;8(11):e80409. https://doi.org/10.1371/journal.pone.0080409.
42. Ni JD, Xiong YZ, Wang XJ, Xiu LC. Does increased hepatitis B vaccination dose lead to a better immune response in HIV-infected patients than standard dose vaccination: a meta-analysis? Int J STD AIDS. 2013;24(2):117–22. https://doi.org/10.1177/0956462412472309.
43. Cooper CL, Davis HL, Angel JB, Morris ML, Elfer SM, Seguin I, et al. CPG 7909 adjuvant improves hepatitis B virus vaccine seroprotection in antiretroviral-treated HIV-infected adults. AIDS. 2005;19(14):1473–9. https://doi.org/10.1097/01.aids.0000183514.37513.d2.
44. Cooper CL, Angel JB, Seguin I, Davis HL, Cameron DW. CPG 7909 adjuvant plus hepatitis B virus vaccination in HIV-infected adults achieves long-term seroprotection for up to 5 years. Clin Infect Dis. 2008;46(8):1310–4. https://doi.org/10.1086/533467.
45. Angel JB, Cooper CL, Clinch J, Young CD, Chenier A, Parato KG, et al. CpG increases vaccine antigen-specific cell-mediated immunity when administered with hepatitis B vaccine in HIV infection. J Immune Based Ther Vaccines. 2008;6:4. https://doi.org/10.1186/1476-8518-6-4.
46. de Silva TI, Green ST, Cole J, Stone BJ, Dockrell DH, Vedio AB. Successful use of Fendrix in HIV-infected non-responders to standard hepatitis B vaccines. J Inf Secur. 2014;68(4):397–9. https://doi.org/10.1016/j.jinf.2013.12.009.
47. Halperin SA, Ward B, Cooper C, Predy G, Diaz-Mitoma F, Dionne M, et al. Comparison of safety and immunogenicity of two doses of investigational hepatitis B virus surface antigen co-administered with an immunostimulatory phosphorothioate oligodeoxyribonucleotide and three doses of a licensed hepatitis B vaccine in healthy adults 18–55 years of age. Vaccine. 2012;30(15):2556–63.
48. Heyward WL, Kyle M, Blumenau J, Davis M, Reisinger K, Kabongo ML, et al. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared to a licensed hepatitis B vaccine in healthy adults 40–70 years of age. Vaccine. 2013;31(46):5300–5. https://doi.org/10.1016/j.vaccine.2013.05.068.
49. Jackson S, Lentino J, Kopp J, Murray L, Ellison W, Rhee M, et al. Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. Vaccine. 2018;36(5):668–74. https://doi.org/10.1016/j.vaccine.2017.12.038.
50. Janssen RS, Mangoo-Karim R, Pergola PE, Girndt M, Namini H, Rahman S, et al. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a licensed hepatitis B vaccine in patients with chronic kidney disease. Vaccine. 2013;31(46):5306–13. https://doi.org/10.1016/j.vaccine.2013.05.067.
51. Kernéis S, Launay O, Turbelin C, Batteux F, Hanslik T, Boëlle PY. Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis. Clin Infect Dis. 2014;58(8):1130–9. https://doi.org/10.1093/cid/cit937.
52. Lopes VB, Hassing RJ, de Vries-Sluijs TE, El Barzouhi A, Hansen BE, Schutten M, et al. Long-term response rates of successful hepatitis B vaccination in HIV-infected patients. Vaccine. 2013;31(7):1040–4. https://doi.org/10.1016/j.vaccine.2012.12.047.
53. Abzug MJ, Warshaw M, Rosenblatt HM, Levin MJ, Nachman SA, Pelton SI, et al. Immunogenicity and immunologic memory after hepatitis B virus booster vaccination in HIV-infected children receiving highly active antiretroviral therapy. J Infect Dis. 2009;200(6):935–46. https://doi.org/10.1086/605448.
54. Lara AN, Sartori AM, Fonseca MO, Lopes MH. Long-term protection after hepatitis B vaccination in people living with HIV. Vaccine. 2017;35(33):4155–61. https://doi.org/10.1016/j.vaccine.2017.06.040.
55. Geretti AM, Doyle T. Immunization for HIV-positive individuals. Curr Opin Infect Dis. 2010;23(1):32–8. https://doi.org/10.1097/QCO.0b013e328334fec4.