Open Forum Infectious Diseases

BRIEF REPORT

Hepatitis B Virus Screening and Vaccination in Patients With HIV: A Survey of Clinicians' Current Practices

Elizabeth Hastie[1,ID] and Darcy Wooten[2]

[1]PGY-3, University of California San Diego, San Diego, California, USA, and [2]University of California San Diego, La Jolla, California, USA

This survey study evaluates how clinicians approach hepatitis B virus (HBV) vaccination and monitoring in patients with HIV. Providers have clinical practices that vary greatly from one another and from current guidelines, especially for patients who do not seroconvert after initial HBV vaccination and for patients with isolated hepatitis B core antibody.

Keywords. antiretrovirals; isolated HBcAb; HBV monitoring; HBV vaccination; PWH.

People with HIV (PWH) are at increased risk of both acquiring hepatitis B virus (HBV) and developing the severe outcomes of the disease. Of the estimated 40 million PWH worldwide in 2009, about 2–4 million (5%–10%) had a chronic HBV infection [1–4]. Overall, HBV infection is about 10 times more common in PWH than those without HIV in Western countries [1, 5].

PWH who acquire HBV are less likely to clear the infection spontaneously [6, 7]. Co-infected patients are more likely to develop cirrhosis and hepatocellular carcinoma, and death due to liver-related causes is estimated to be 17 times more common [2, 6, 8, 9].

The importance of preventing HBV infection in PWH through vaccination is universally accepted; however, guidelines vary in terms of the best HBV vaccination practices, especially as PWH are less likely to develop protective antibody titers after standard HBV vaccination [2, 10–16]. Engerix-B, Recombivax-HB, and Heplisav-B are the 3 single-antigen HBV vaccines available in the United States. They all consist of recombinant hepatitis B surface antigen (HBsAg). Engerix-B and Recombivax-HB are routinely administered in 3 doses at 0, 1, and 6 months. Heplisav-B, which links recombinant surface antigen to a highly immunogenic adjuvant, is administered in 2 doses, 1 month apart [4, 11].

Multiple studies have evaluated the efficacy and safety of a variety of vaccine regimens to boost HBV immunity in PWH (ie, double dosages, fourth dose), but the results of these studies have been mixed and guidelines remain inconsistent [2, 12–14, 16–20].

In addition, a low CD4 cell count and high HIV viral load have been associated with decreased rates of seroconversion, raising questions about the optimal timing of HBV vaccination in PWH. Concurrently, low anti-HBs titers may not be accurate indicators of loss of protection [2, 20–22].

Management of patients with an isolated hepatis B core antibody is also challenging. Despite 7%–20% of PWH having this serological finding, its clinical significance is unclear, and an approach to vaccination and antibody monitoring is not well defined [2, 4].

Given the lack of data and clear guidance, we evaluated how clinicians are currently approaching HBV vaccination and monitoring in PWH.

METHODS

A web-based survey was developed focusing on 2 clinical vignettes; it was distributed in May 2020 (Supplementary Data). The first vignette explored the approach to HBV vaccination and antibody monitoring in a patient with ongoing risk factors for HBV including sex with multiple male partners and monthly injection drug use, a CD4 cell count >200 cell/μL, an HIV viral load of 500 000, and not having been started on ART. Survey participants were asked to specify when they would start an HBV vaccination series, what vaccine formulation they would use, and at what dosage and frequency. The case continued 1 month after the patient completed the vaccination series, when he was found to have a nonprotective hepatitis B surface antibody titer. Participants were then asked what, if any, intervention and/or monitoring they would pursue.

The second clinical vignette described a patient with well-controlled HIV (CD4 of 472 and an undetectable HIV viral load) on bictegravir/emtricitabine/tenofovir alafenamide who had an isolated hepatitis B core antibody. Participants were asked to choose between no additional workup, initiating a full vaccination HBV series, giving a single dose of a vaccine with subsequent titer monitoring, or checking the HBV DNA level.

The survey was distributed to the University of California San Diego (UCSD) Infectious Diseases division via the UCSD ID listserv, to the Infectious Disease Society of America (IDSA) members via the IDea Exchange (IDSA) listserv, and to ID

Received 15 March 2021; editorial decision 19 May 2021; accepted 24 May 2021.

Correspondence: Elizabeth Hastie, MD, PGY-3, University of California San Diego, (513) 260–2469, 2330 Murray Ridge Rd., San Diego, CA 92123 (ehastie@health.ucsd.edu).

Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab270

and HIV social network members via Twitter and Facebook. Results were stratified by all participants and by only those participants who were members of the UCSD ID division of the IDSA listserv (excluding participants who accessed the survey via Twitter or Facebook).

RESULTS

Demographics

A total of 74 clinicians from 26 states completed the survey between May 18, 2020, and June 15, 2020 (Table 1). The majority practice in an academic setting (55/74), and 53% (39/74) have a postgraduate year of ≥11. Forty-one clinicians (55%) provide care to >20 PWH per month. The most common practice location was California (27/74). Two-thirds of participants (49/74) were members of the UCSD ID division or IDSA's listserv.

Approach to Initial HBV Vaccination

In response to the first clinical vignette, the majority of physicians (78%) would administer an HBV vaccine immediately, while 19% (14/74) would defer HBV vaccination until HIV virological suppression had been achieved. For the initial vaccination, 31 clinicians (42%) would use Heplisav-B, and 21 (29%) would use Energix-B or Recombivax-HB. If using Energix-B or Recombivax-HB for immediate vaccination, the standard dosing and schedule at 0, 1, and 6 months was vastly preferred (90%) over a double dose (10%). No clinicians chose a 4-dose regimen for initial vaccination.

If the patient did not seroconvert 1 month after a standard HBV vaccination regimen, the majority (94%) of clinicians would repeat a vaccination series; 15 clinicians (22%) would repeat vaccination with a standard dose series of Energix-B or Recombivax-HB, 19 (28%) with a double dose series of Energix-B or Recombivax-HB, and 29 (42%) would use Heplisav-B for revaccination. Only 2 clinicians preferred a 4-dose regimen on repeat vaccination. The majority of clinicians (83%) would not routinely monitor for HBV immunity after seroconversion was achieved.

Approach to Isolated Hepatitis B Core Antibody

The approach to management of a PWH with a positive isolated hepatitis B core antibody was varied. For most clinicians (45%), the next step would be to check the patient's HBV DNA level. Eighteen clinicians (24%) would initiate a vaccination series, 7 (9%) would give a single dose of Engerix-B or Recombivax-HB with titer monitoring 1 month later, and 16 (22%) would not pursue further intervention (Table 2).

Table 1. Baseline Demographics of Survey Participants Stratified by Survey Source

ID Fellowship & Postgraduate Year	All Participants, No. (%)	Excluding Twitter & Facebook, No. (%)
Completed or in ID fellowship	62 (84)	41 (84)
PGY 1–5	11 (15)	4 (8)
PGY 6–10	19 (26)	9 (18)
PGY ≥11	39 (53)	35 (71)
No answer	5 (7)	1 (2)
Source of survey link		
UCSD email	18 (24)	18 (37)
EIN email	12 (16)	12 (24)
IDSA IDea exchange email	19 (26)	19 (39)
Twitter	21 (28)	-
Facebook	4 (5)	-
No. of PWH seen/mo		
0	3 (4)	1 (2)
1–5	6 (8)	3 (6)
6–10	12 (16)	7 (14)
11–20	12 (16)	10 (20)
>20	41 (55)	28 (57)
Practice type		
Academic	55 (74)	39 (80)
Private practice	6 (8)	5 (10)
Federally qualified health center	6 (8)	2 (4)
Public health department	0 (0)	0 (0)
Other	8 (12)	4 (8)
Practice location		
Most prevalent state: California	27 (36)	27 (55)
2nd most prevalent state: New York	6 (8)	4 (8)
3rd most prevalent state: Maryland	4 (5)	4 (8)
Other	37 (51)	14 (29)

Abbreviations: EIN, Emerging Infections Network; ID, infectious diseases; IDSA, Infectious Diseases of America; PGY, postgraduate year; PWH, people with HIV; UCSD, University of California San Diego.

DISCUSSION

This survey study provides insight into the current HBV vaccination and monitoring practices of clinicians who care for PWH. Practice preferences for all the clinical vignettes we studied were varied. Survey responses from 2 scenarios were particularly discrepant. First, for the management of a patient who does not seroconvert after initial vaccination, clinicians were equally split between repeating a standard dose of Engerix-B or Recombivax-HB, administering a double dose regimen of Engerix-B or Recombivax-HB, and repeating vaccination with Heplisav-B. Second, for the management of a patient with an isolated hepatitis B core antibody, clinicians were about equally divided between pursuing no further intervention, initiating an HBV vaccination series, and checking an HBV viral load.

After this survey study was completed, the IDSA updated their guidelines for HIV primary care management in 2020, including proposed HBV monitoring and vaccination management. They recommend standard HBV vaccination followed by HBsAb testing 1–2 months later in PWH who are not HBV-immune. Revaccination with a second series at a higher dose or with an additional fourth dose is recommended if the patient does not seroconvert (HBsAb <100 mIU/mL or <10 IU/L at 1–2 months postvaccination). Recommended timing of revaccination is after a patient achieves HIV viral load suppression and improvement in their CD4 cell count.

Table 2. Participants' Practice Preferences for HBV Monitoring and Vaccination Prompted by Clinical Vignettes Stratified by Survey Source

Preferred Timing of HBV Vaccination in a Patient Newly Diagnosed With HIV Getting Started on ART	All Participants, No. (%)	Excluding Twitter & Facebook, No. (%)
Vaccinate immediately	58 (78)	37 (76)
Postpone vaccination until HIV VL is suppressed	14 (19)	10 (20)
Defer vaccination since the patient is on ART	1 (1)	1 (2)
Other	1 (1)	1 (2)
Preferred initial HBV vaccination series for susceptible individuals with HIV		
Energix-B or Recombivax-HB	21 (29)	11 (23)
Heplisav-B	31 (42)	23 (48)
Any of the above	21 (29)	14 (29)
Preferred dose & schedule if using Engerix-B or Recombivax-HB for initial vaccine series		
Standard dose at 0, 1, and 6 mo	62 (90)	41 (91)
Double dose at 0, 1, and 6 mo	7 (10)	4 (9)
Standard or double dose at 0, 1, 2, and 6 mo	0 (0)	0 (0)
Preferred intervention if patient does not seroconvert after first vaccination series		
No further intervention	4 (6)	1 (2)
Repeat with Engerix-B or Recombivax-HB at standard dose at 0, 1, and 6 mo	15 (22)	9 (20)
Repeat with Engerix-B or Recombivax-HB at double dose at 0, 1, and 6 mo	19 (28)	14 (31)
Repeat with Engerix-B or Recombivax-HB at standard dose at 0, 1, 2, and 6 mo	2 (3)	2 (4)
Repeat with Engerix-B or Recombivax-HB at double dose at 0, 1, 2, and 6 mo	0 (0)	0 (0)
Repeat with Heplisav-B	29 (42)	19 (42)
Preferred hepatitis B immunity monitoring after successful vaccination with seroconversion		
No further monitoring	57 (83)	38 (84)
Check HBsAb yearly, and repeat series if titer drops below 10 mIU/mL	12 (17)	7 (16)
Preferred management of positive isolated hepatitis B core antibody		
No further intervention	16 (22)	11 (22)
Initiate hepatitis B vaccination	18 (24)	14 (29)
Give a single dose of Engerix-B or Recombivax-HB with HBsAb titer; check 1 mo later	7 (9)	6 (12)
Check HBV DNA level	33 (45)	18 (37)

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; VL, viral load.

Patients with isolated HBcAb are recommended to have an HBV DNA level checked and be vaccinated if they do not have evidence of HBV infection [12]. Notably, many clinical scenarios are not encompassed by these guidelines, and they lack clear directions for monitoring and follow-up after vaccine administration.

This survey study reveals that clinicians have practices that vary greatly from one another and the guidelines that currently exist. The implications of these varying practices are unknown.

CONCLUSIONS

The limitations of this study include its small study size and inability to verify participant credentials. One-third (25/74) of participants accessed the survey via social media; however, when we compared all responses with those of individuals who accessed the survey via the UCSD ID or IDSA listservs, there was not a substantial difference in the results. Twelve clinicians (16%) had no ID fellowship training, and 9 (12%) cared for ≤5 PWH a month. While not all respondents were ID-trained, their responses are of value, as more non-ID-trained clinicians will provide care for PWH in the future. A final limitation is that we did not ask respondents whether they were aware of or referenced any guidelines while completing the survey.

Despite these limitations, the results highlight the opportunities that exist for improvement of hepatitis B monitoring and vaccination in PWH through standardization. Additional research is necessary to evaluate the impact these practices have on patient outcomes and health care expenditures and to ultimately elucidate the most efficacious strategy of monitoring and vaccination. As recommendations for preferred antiretroviral therapies evolve and some regimens, such as dolutegravir/lamivudine and long-acting cabotegravir and rilpivirine, no longer include tenofovir, the importance of establishing standardized HBV vaccination practices arguably becomes more relevant.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Financial support. The authors received no funding for this work.

Potential conflicts of interest. The authors have no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. This study did not include factors necessitating patient consent. The study was reviewed by UCSD's Human Research Protections Program and approved by the Institutional Review Board.

References

1. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. J Hepatol **2006**; 44:S6–9.
2. Catherine FX, Piroth L. Hepatitis B virus vaccination in HIV-infected people: a review. Hum Vaccin Immunother **2017**; 13:1304–13.
3. Kellerman SE, Hanson DL, McNaghten AD, Fleming PL. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. J Infect Dis **2003**; 188:571–7.
4. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep **2018**; 67:1–31.
5. Attia KA, Eholié S, Messou E, et al. Prevalence and virological profiles of hepatitis B infection in human immunodeficiency virus patients. World J Hepatol **2012**; 4:218–23.
6. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. Hepatology **2009**; 49:S138–45.
7. Chun HM, Roediger MP, Hullsiek KH, et al; Infectious Disease Clinical Research Program HIV Working Group. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. J Infect Dis **2012**; 205:185–93.
8. Mallet V, Vallet-Pichard A, Pol S. The impact of human immunodeficiency virus on viral hepatitis. Liver Int **2011**; 31(Suppl 1):135–9.
9. Thio CL, Seaberg EC, Skolasky R Jr, et al; Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet **2002**; 360:1921–6.
10. Wilkins E, Nelson M, Agarwal K, et al. British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. HIV Med **2013**; 14(Suppl 4):1–71.
11. Schillie S, Harris A, Link-Gelles R, et al. Recommendations of the Advisory Committee on Immunization Practices for use of a hepatitis B vaccine with a novel adjuvant. MMWR Morb Mortal Wkly Rep **2018**; 67:455–8.
12. Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. **In press**.
13. Mena G, García-Basteiro AL, Bayas JM. Hepatitis B and A vaccination in HIV-infected adults: a review. Hum Vaccin Immunother **2015**; 11:2582–98.
14. van den Berg R, van Hoogstraten I, van Agtmael M. Non-responsiveness to hepatitis B vaccination in HIV seropositive patients; possible causes and solutions. AIDS Rev **2009**; 11:157–64.
15. Chaiklang K, Wipasa J, Chaiwarith R, et al. 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:e80409.
16. Kalinowska-Nowak A, Bociaga-Jasik M, Garlicki A, Mach T. Efficacy of vaccination against hepatitis B in adult with HIV infection. Przegl Epidemiol **2007**; 61:339–47.
17. Potsch DV, Camacho LA, Tuboi S, et al. Vaccination against hepatitis B with 4-double doses increases response rates and antibodies titers in HIV-infected adults. Vaccine **2012**; 30:5973–7.
18. Okwen MP, Reid S, Njei B, Mbuagbaw L. Hepatitis B vaccination for reducing morbidity and mortality in persons with HIV infection. Cochrane Database Syst Rev **2014**; 10:CD009886.
19. Launay O, van der Vliet D, Rosenberg AR, 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**; 305:1432–40.
20. 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**; 24:117–22.
21. O'Bryan TA, Rini EA, Okulicz J, et al. HIV viraemia during hepatitis B vaccination shortens the duration of protective antibody levels. HIV Med **2015**; 16:161–7.
22. Nicolini LA, Magne F, Signori A, et al. Hepatitis B virus vaccination in HIV: immunogenicity and persistence of seroprotection up to 7 years following a primary immunization course. AIDS Res Hum Retroviruses **2018**; 34:922–8.