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

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Abstract

This survey study evaluates how clinicians approach HBV vaccination and monitoring in patients living 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

PLWH, HBV vaccination, HBV monitoring, antiretrovirals, isolated HBcAb

Topic

PLWH, HBV vaccination, HBV monitoring, antiretrovirals, isolated HBcAb, Engerix-B or Recombivax HB, Heplisav-B
Introduction

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

PLWH 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 seventeen times more common [2, 6, 8, 9].

The importance of preventing HBV infection in PLWH through vaccination is universally accepted; however, guidelines vary in terms of the best HBV vaccination practices, especially since PLWH are less likely to develop protective antibody titers after standard HBV vaccination [2, 10-16]. Engerix-B, Recombivax HB, and Heplisav-B are the three 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 three doses at 0-, 1-, and 6-months. Heplisav-B, which links recombinant surface antigen to a highly immunogenic adjuvant, is administered in two doses, one month apart [4, 11].

Multiple studies have evaluated the efficacy and safety of a variety of vaccine regimens to boost HBV immunity in PLWH (i.e. double dosages, fourth dose), but 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 PLWH. Concurrently, low anti-HBs titers may not be accurate indicators of loss of protection [2, 20-22].

Management of patients with an isolated hepatitis B core antibody is also challenging. Despite 7-20% of PLWH 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 PLWH.
Methods

A Web-based survey was developed focusing around two clinical vignettes and distributed in May 2020 (see supplementary material). 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/ul, an HIV viral load of 500,000, and who had not yet 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 one month after the patient completed the vaccination series when he was found to have a non-protective 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 work-up, initiating a full vaccination HBV series, giving a single dose of a vaccine with subsequent titer monitoring, or checking an HBV DNA level.

The survey was distributed to the University of California San Diego (UCSD) Infectious Diseases division via the UCSD ID listserv; Infectious Disease Society of America (IDSA) members via the ID Exchange (IDSA) listserv; and to ID 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 or 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 18th, 2020 and June 15th, 2020 (Table 1). The majority practice in an academic setting (55/74) and 53% (39/74) have a postgraduate year of eleven or more. Forty-one clinicians (55%) provide care to more than twenty PLWH 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, thirty-one clinicians (42%) would use Heplisav-B and twenty-one (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 four-dose regimen for initial vaccination.
If the patient did not seroconvert one month after a standard HBV vaccination regimen, the majority (94%) of clinicians would repeat a vaccination series; fifteen clinicians (22%) would repeat vaccination with a standard dose series of Energix-B or Recombivax-HB, nineteen (28%) with a double dose series of Energix-B or Recombivax-HB, and twenty-nine (42%) would use Heplisav-B for revaccination. Only two clinicians preferred a four-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**

Approach to management of a PLWH and with a positive isolated hepatitis B core antibody was varied. For most clinicians (45%), the next step would be to check an HBV DNA level. Eighteen clinicians (24%) would initiate a vaccination series, seven (9%) would give a single dose of Engerix-B or Recombivax HB with titer monitoring one month later, and sixteen (22%) would not pursue further intervention (Table 2).

**Discussion**

This survey study provides insight into the current HBV vaccination and monitoring practices of clinicians who care for PLWH. Practice preferences for all the clinical vignettes we studied were varied. Survey responses from two 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 one to two months later in PLWH 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 1-2 months post-vaccination). Recommended timing of revaccination is after a patient achieves HIV viral load suppression and improvement in their CD4 cell count. 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 is unknown.
Conclusions

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 to just those 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 nine (12%) cared for five or fewer PLWH a month. While not all respondents were ID trained, their responses are of value as more non-ID trained clinicians provide care for PLWH 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 PLWH through standardization. Additional research is necessary to evaluate the impact these practices have on patient outcomes and healthcare expenditure 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.

Patient Consent Statement

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.

Potential Conflict of Interest

The authors have no reported conflicts of interest.
References

1. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol.* 2006;44(1 Suppl):S6-S9. doi:10.1016/j.jhep.2005.11.004

2. Catherine FX, Piroth L. Hepatitis B virus vaccination in HIV-infected people: A review. *Hum Vaccin Immunother.* 2017;13(6):1-10. doi:10.1080/21645515.2016.1277844

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(4):571-577. doi:10.1086/377135

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):1-31. Published 2018 Jan 12. doi:10.15585/mmwr.rr6701a1

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(7):218-223. doi:10.4254/wjh.v4.i7.218

6. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. *Hepatology.* 2009;49(5 Suppl):S138-S145. doi:10.1002/hep.22883

7. Chun HM, Roediger MP, Hullsiek KH, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. *J Infect Dis.* 2012;205(2):185-193. doi:10.1093/infdis/jir720

8. Mallet V, Vallet-Pichard A, Pol S. The impact of human immunodeficiency virus on viral hepatitis. *Liver Int.* 2011;31 Suppl 1:135-139. doi:10.1111/j.1478-3231.2010.02394.x

9. Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet.* 2002;360(9349):1921-1926. doi:10.1016/s0140-6736(02)11913-1

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. doi:10.1111/hiv.12106

11. Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. 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(15):455-458. Published 2018 Apr 20. doi:10.15585/mmwr.mm6715a5

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 [published online ahead of print, 2020 Nov 6]. *Clin Infect Dis.* 2020;ciaa1391. doi:10.1093/cid/ciaa1391

13. Mena G, Garcia-Basteiro AL, Bayas JM. Hepatitis B and A vaccination in HIV-infected adults: A review. *Hum Vaccin Immunother.* 2015;11(11):2582-2598. doi:10.1080/21645515.2015.1055424

14. van den Berg R, van Hoogstraten I, van Agtmel M. Non-responsiveness to hepatitis B vaccination in HIV seropositive patients; possible causes and solutions. *AIDS Rev.* 2009;11(3):157-164.

15. Chaiklang K, Wipasa J, Chaivarith R, Praparatpanan 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. Published 2013 Nov 12. doi:10.1371/journal.pone.0080409

16. Kalinowska-Nowak A, Bociaga-Jasik M, Garlicki A, Mach T. Skuteczność szczepienia przeciwko wirusowemu zapaleniu watroby typu B u dorosłych osób zakazonych HIV [Efficacy of vaccination against hepatitis B in adult with HIV infection]. *Przegl Epidemiol*. 2007;61(2):339-347.

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(41):5973-5977. doi:10.1016/j.vaccine.2012.07.028

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(10):CD009886. Published 2014 Oct 9. doi:10.1002/14651858.CD009886.pub2

19. Launay O, van der Vliet D, Rosenberg AR, et al. 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):1432-1440. doi:10.1001/jama.2011.351

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(2):117-122. doi:10.1177/0956462412472309

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(3):161-167. doi:10.1111/hiv.12189

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(11):922-928. doi:10.1089/AID.2017.0070
Table 1: Baseline demographics of survey participants stratified by survey source

| ID Fellowship & Post Graduate Year | All Participants | Excluding Twitter & Facebook |
|-----------------------------------|-----------------|------------------------------|
| 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**

| Source of Survey Link          | All Participants | Excluding Twitter & Facebook |
|--------------------------------|------------------|------------------------------|
| 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%)           | -                            |

**Number of PLWH Seen per Month**

| Number of PLWH Seen per Month | All Participants | Excluding Twitter & Facebook |
|-------------------------------|------------------|------------------------------|
| 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**

| Practice Type                                    | All Participants | Excluding Twitter & Facebook |
|-------------------------------------------------|------------------|------------------------------|
| 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**

| Practice Location                              | All Participants | Excluding Twitter & Facebook |
|------------------------------------------------|------------------|------------------------------|
| 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%)                     |
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 | Excluding Twitter & Facebook |
|-----------------------------------------------------------------------------------------------|-----------------|-----------------------------|
| 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 living 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 months                                                            | 62 (90%)        | 41 (91%)                    |
| Double dose at 0, 1, and 6 months                                                             | 7 (10%)         | 4 (9%)                      |
| Standard or double dose at 0, 1, 2, and 6 months                                              | 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 months                  | 15 (22%)        | 9 (20%)                     |
| Repeat with Engerix-B or Recombivax-HB at double dose at 0, 1, and 6 months                   | 19 (28%)        | 14 (31%)                    |
| Repeat with Engerix-B or Recombivax-HB at standard dose at 0, 1, 2, and 6 months               | 2 (3%)          | 2 (4%)                      |
| Repeat with Engerix-B or Recombivax-HB at double dose at 0, 1, 2, and 6 months                 | 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 10mIU/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 month later         | 7 (9%)          | 6 (12%)                     |
| Check HBV DNA level                                                                            | 33 (45%)        | 18 (37%)                    |