HEPATITIS B IMMUNIZATION DATA OF PATIENTS LIVING WITH HIV/AIDS: A MULTI-CENTRE STUDY

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SUMMARY

Objectives: Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are the two leading viruses that cause the greatest number of virus-related morbidities in the world. HIV/HBV coinfection is correlated with high morbidity and mortality. For this particular reason hepatitis B vaccination is crucial for people living with HIV.

Methods: Patients who are being followed-up for HIV/AIDS and who have received a hepatitis B vaccine in 4 HIV clinics over a 5-year time period have been studied. Our multi-centered, retrospective, cross-sectional and observational study investigates factors that affect hepatitis B vaccination immune response of individuals living with HIV. The patients have been studied for the parameters such as age, sex, CD4 count at the time of diagnosis or vaccination, HIV-RNA levels, comorbidities, vaccine dosage, success of immunization after vaccination, and the demographics of the patients who have and have not developed immunity.

Results: Of 645 patients that are being followed-up in our clinics, 158 received hepatitis B vaccine; 39 of these 158 patients have been excluded from the study because they did not fulfil the inclusion criteria. Finally, 119 patients were evaluated in the study, 17 of the patients (14.3%) were females and 102 (85.7%) were males. The median age was 41.11 ± 10.09 (min–max: 18–75). Twenty-three of the patients (19.3%) were at the stage of AIDS during diagnosis while 80.7% were at the stage of HIV infection. Ninety-one of the patients (76.5%) have been administered a single dose hepatitis B vaccine on the standard 0, 1st, 6th month vaccination schedule, whereas 23.5% were administered a double dose on the same vaccination schedule. When further evaluated to find whether the patient was able to develop sufficient immunity (anti-HBs ≥ 10), it was found that the immune response was statistically significantly higher in the patients whose CD4 count was greater than 200 at the time of the first diagnosis and vaccination ($p = 0.05$ and $p = 0.001$, respectively). The patients have also been evaluated according to the number of doses they received (1 vs. 2). The immune response of the patients who received two doses was statistically significantly higher ($p = 0.041$).

Conclusion: We can conclude that in the patients with CD4 count less than 200 at the time of their diagnosis and vaccination a high dose recombinant hepatitis B vaccine should definitely be administered as the normal dose and higher dose have similar side effect profiles and the higher dose provides greater immunity.

Key words: HIV/AIDS, hepatitis B vaccine, vaccination, Turkey

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INTRODUCTION

Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are among the viruses that lead to severe morbidity and mortality. According to data from the World Health Organization, currently, there are approximately 300 million patients with chronic hepatitis infection, and every year this number increases by 1.5 million despite the vaccination programmes being rigorously carried out worldwide (1). It is estimated that there are 37 million HIV/AIDS patients globally and that 5–20% of these patients are coinfected with HBV. Due to standard modes of transmission for the two viruses (parenterally, sexually, and vertically), HBV coinfection rates of the patients living with HIV are 40% higher compared to the healthy population (2, 3). The active use of antiviral regimens effective for HBV to treat HIV decreases HBV-related complications (4). However, antiretroviral (ART) drugs significantly decrease HIV-related mortality and morbidity, HBV-related morbidity remains high in patients with HIV/HBV coinfection. Thus, this creates the necessity for patients who are coinfected with HBV to use effective antivirals.

The probability of liver-related mortality of individuals with HIV/HBV coinfection is 8 times higher than those infected only with HIV and is 19 times higher than those infected only with HBV (5). HIV/HBV coinfection is correlated with an increase in HBV-

DNA levels, a deterioration of the natural progression of the chronic HBV infection, and an increase in liver-related mortality (4).

The most effective and cost-effective way of protection against infectious diseases is vaccination. Hepatitis B vaccine alongside human papilloma virus (HPV) vaccine is one of the two vaccines in the routine vaccination that have been proven to prevent cancer. There are five licensed vaccines for hepatitis B, and their administration schedules have been standardized. However, there is no consensus on the dosage or the vaccination schedule for people living with HIV who are HBV seronegative. This is because the cellular immune deficiency caused by chronic infection and inflammation showed that the vaccination schedule which is effective for the healthy population may be insufficient for those living with HIV (3, 6).

It is controversial whether the hepatitis B vaccine should be administered to individuals living with HIV at the time of diagnosis or in the period when HIV viremia is suppressed and CD4 count increases after antiretroviral therapy. Additionally, the dosage of the vaccine is debatable. It was indicated that a high dose of HBV vaccine could be administered for the patients who have been unresponsive to the standard dose and have ongoing HIV viremia with a low CD4 count. The European AIDS Clinical Society (EACS) recommends vaccination during the period in which the CD4 count increased, and HIV viremia regressed after the antiretroviral treatment. The Infectious Diseases Society of America (IDSA) recommends administering a high dose of the hepatitis B vaccine to individuals living with HIV, like immunosuppressed patients (7, 8). The British HIV Association (BHIVA) recommends that all individuals living with HIV should be vaccinated four times on 0, 1st, 2nd, 6th month schedules with a high dose of hepatitis B vaccine (9).

In this article the authors aimed to evaluate factors that affect the antibody responses of patients who are living with HIV who have been vaccinated for hepatitis B in our multi-centered study.

Table 1 summarizes the contradictions of different guidelines regarding hepatitis B vaccination for individuals living with HIV.

MATERIALS AND METHODS

Four different centres participated in our multi-centered, retrospective, observational study to evaluate the factors that affect the vaccine response rates of people living with HIV.

The inclusion criteria for the study: patients ≥ 18 years diagnosed with HIV/AIDS were included in the study. Patients tested for hepatitis B serology at the time of diagnosis and who were HBsAg negative, anti-HBs negative, and anti-HBc IgG negative were evaluated. Patients whose hepatitis B vaccination was completed and who were tested for anti-HBs after 4–8 weeks after the last dose, and who have CD4 count and HIV RNA results at

Table 1. *Guidelines regarding hepatitis B vaccination for individuals living with HIV*

	European AIDS Clinical Society 2021 Guidelines (EACS 2021)	**Infectious Diseases Society of America 2020 Guidelines (IDSA 2020)**	**British HIV Association 2015 Guidelines (BHIVA 2015)**
What should be the C4 count at the time of vaccination?	Vaccination should be recommended to all patients regardless of the CD4 count unless CD4 < 200. If CD4 < 200 the patient should be prescribed HAART first. The vaccination should start once CD4 > 200.	Until there is an immunological and virological response with HAART, the decision to postpone vaccination should be personalized with the likelihood of exposure to HBV infection of the patient.	No recommendation
What should the hepatitis B vaccine schedule look like?	0, 1st, 6th month	0, 1st, 6th month	4 doses regardless of the type of the vaccine (0, 1st, 2nd, 6th month)
When should anti-Hbs levels be checked after vaccination?	No recommendation	4–8 weeks after the last vaccine	4–8 weeks after the last vaccine
What to do when there is no response?	Revaccination with the standard dose on the 0, 1, 6 schedule. If CD4 count is low, and the HIV RNA is high, 3 or 4 doses of high dose vaccination could be considered (0, 1st, 2nd, 6th month)	If the standard dose series have been followed, one dose rappel can be administered in the case of unresponsiveness.	3 doses of yeast-based vaccine (0, 1st, 2nd month) or normal dose adjuvant vaccine (0, 1st, 2nd month) (20 mcg Fendrix)
High-dose vaccine recommendation	Only if the first series of standard vaccination was unsuccessful and if CD4 count is low, and the HIV RNA is high, 3 or 4 doses of high-dose vaccine could be considered (0, 1st, 2nd, 6th month)	Recombivax 40 mcg Enerix 20 mcg Hepsilav-B 20 mcg (0–1st month 2 doses) (CpG adjuvant recombinant vaccine)	Yeast-based vaccines high dose Engerix 40mcg, HBvaxPRO 40 mcg or normal dose adjuvant vaccine (20 mcg Fendrix)
Is periodical follow-up necessary post vaccination?	If anti-Hbs < 10 there should be annual controls. No recommendation if vaccine response developed.	In the case of suspicion of exposure and if the level of transaminase is high, hepatitis serology can be checked.	If Anti-HBs < 10, continue screening for HBsAg as risk of infection remains. Annual anti-HBs follow-up if anti-HBs is between 10–100. Anti-HBs follow-up every 2 years if anti-HBs > 100.

the time of diagnosis and the start of vaccination were included in the study.

The exclusion criteria for the study: the presence of a defect in the vaccination procedure, or incompleteness of the patient information, data about the vaccine type, dose, or the test results.

The standard and double doses of vaccination were administered in the 0, 1st, 6th month with recombinant hepatitis B vaccine. Post-vaccination, patients with anti-HBs results ≥ 10mlU/ml were considered successful, whereas patients with results < 10 mlU/ml were considered nonresponsive in vaccine response effectiveness. An anti-HBs test was performed with Architect i2000 (Abbott, USA) chemiluminescent microparticle immunoassay (CMIA) (2nd generation) and an Architect anti-HBs reactive kit (Abbott, Germany) was used. The patients' age, sex, CD4 count at the time of diagnosis or vaccination, HIV-RNA levels, comorbidities, vaccine dosage, the success of immunization after vaccination, and the typical characteristics of the ones who have and have not developed immunity was recorded. Patient information was acquired from patient follow-up files and the hospitals', data processing systems. Patients with positive anti-HIV test, positive Western-blot confirmation test and/or positive HIV-RNA results were considered HIV-infected patients, while patients with CD4 count < 200 at the time of diagnosis and/or AIDS-defining diseases were considered patients with AIDS. For patients whose CD4 counts are < 200 at the time of diagnosis, like the other vaccines, hepatitis B vaccines are generally administered after antiretroviral treatment once CD4 count increases > 200 and HIV viremia gets suppressed. Some patients considered at high risk of hepatitis B transmission were vaccinated without viral suppression at the time of diagnosis. That is why this study evaluates patients for CD4 counts and HIV RNA levels not only at the time of their vaccination but also at the time of their diagnosis.

Statistics

Statistical analyses of the obtained clinical and demographic data were performed using Statistical Package for the Social Sciences (SPSS) v.25 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation, median (minimum and maximum values), while categorical variables were number and percentage. The feasibility of the data for normal distribution was examined by the Shapiro-Wilk and Kolmogorov Smirnov tests. Independent samples t-test was used when the parametric test assumptions were provided, and the Mann-Whitney U test was used when the parametric test assumptions were not provided. Differences between categorical variables were analysed by chi-square and Fisher's exact tests. Spearman's correlation analysis was used for analysing the relationships between continuous variables. Binary logistic regression analysis was used for determining which variables affected the immunization. In all statistical analyses, $p < 0.05$ was accepted as statistically significant.

RESULTS

This study examines 158 HIV/AIDS patients who received hepatitis B vaccines from 1 January 2015 until 1 January 2020. Thirty-nine patients were excluded from the study because their vaccination schedules were not standard, and their antibody levels were not checked 4–8 weeks after the last dose; 119 patients vaccinated according to the proper schedule were studied for their anti-HBs levels 4–8 weeks after the completion of vaccination, and whose CD4 counts, HIV RNA levels, and comorbidities were recorded at the time of diagnosis and vaccination. Seventeen of 119 people (14.3%) were females and 102 (85.7%) were males. The mean age was 41.11 ± 10.09 (min–max:18–75), 11 patients (9%) had a history of HIV-related opportunistic infection, seven patients (7.5%) had additional comorbidities (e.g., diabetes mellitus, malignity).

Twenty-three of the patients (19.3%) were at the stage of AIDS diagnosis, while 80.7% were at the stage of HIV infection. Ninety-one of the patients (76.5%) were administered a single dose hepatitis B vaccine on the standard 0, 1st, 6th month vaccination schedule, whereas 23.5% were administered a double dose on the same vaccination schedule.

The mean CD4 count for patients who had Anti-HBs < 10 mlU/ml (nonresponsive) was 307.85 ± 236 cell/mm^3; meanwhile, the mean for those who had Anti-HBs ≥ 10 mIU/ml (successful) was 468.74 ± 275.19 cell/mm^3.

There was a statistically significant, positive but weak correlation between post-vaccination anti-HBs antibody levels and CD4 count at diagnosis ($r = 0.226$; $p = 0.013$). We did not find a statistically significant correlation between age and the level of antibodies.

When factors that affected the immunization (Anti-HBs ≥ 10 mIU/ml) were examined, it was observed that sex, age, presence of comorbidities, HIV RNA levels at the time of diagnosis, CD4 count and HIV RNA levels at the time of vaccination, timing of vaccination (at the time of diagnosis or after the start of ART), and vaccination schedule had no effect. When factors that affect the development of vaccine response were examined, it was observed that CD4 count ≥ 200 at the time of diagnosis compared to < 200 increases the vaccine response significantly (OR = 3.015, $p = 0.043$). Similarly, it was observed that CD4 count < 200 at the time of diagnosis decreases the presence of vaccine response significantly (OR = 0.178, $p = 0.006$). It is also evident that the vaccine response is significantly higher (anti-HBs ≥ 10 mlU/ml) in vaccinated patients when CD4 > 200 (Table 3).

When evaluating according to the development of a sufficient immune response with the vaccine (anti-HBs ≥ 10), it was detected that the response rates of the patients with CD4 count > 200 at the time of diagnosis and vaccination are statistically significantly high ($p = 0.05$, $p = 0.001$, respectively). The patients were evaluated as receiving a single standard dose and double doses. In the vaccination schedule, 91 patients received one dose of the hepatitis B vaccine, while 28 received two. It was detected that the correlation between successful vaccine response and two doses is statistically significantly higher ($p = 0.041$); 79% (72/91) of those who received a single dose have reached a sufficient level of antibodies, while this ratio is 96% (27/28) among the patients who received double doses (Table 3).

It can be observed that CD4 count at the time of diagnosis and vaccination, concerning anti-HBs antibody levels, makes a statistically significant difference ($p = 0.016$, $p = 0.044$, respectively). When there is a response, CD4 count at the time of diagnosis and vaccination is significantly higher than when there is no response (Table 2).

Table 2. *Hepatitis B vaccine responses and factors affecting vaccine response in patients living with HIV*

	No response		Response		p-value
	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	
Age	43.05 ± 8.01	43.5 (31–60)	40.72 ± 10.45	38 (18–75)	0.192 (z = −1.305)
CD4 count at diagnosis	307.85 ± 236.93	254 (16–900)	468.74 ± 275.19	429 (5–1222)	0.016* (t = −2.437)
HIV RNA at diagnosis	1200972.25 ± 2747766.97	252840 (5165–12224758)	2454609.95 ± 10222308.92	150000 (2476–72688254)	0.265 (z = −1.116)
CD4 at vaccination	541.45 ± 385.27	432.5 (50–1470)	669.85 ± 306.13	638 (252–2390)	0.044* (z = −2.018)
HIV RNA at vaccination	118399.05 ± 385214.79	0 (0–1718809)	206412.54 ± 1047208.96	0 (0–10000000)	0.688 (z = −0.402)
Antibodies	2.1 ± 3.34	0 (0–9)	409.97 ± 380.41	239 (11–1000)	0.0001* (z = −7.053)

*p < 0.05 statistically significant; SD – standard deviation; t – independent samples t-test; z – Mann-Whitney U test

Table 3. *Effects of CD4 count and vaccine dose on hepatitis B vaccine response*

		Vaccine response		p-value
		No response n (%)	Response n (%)	
CD4 at diagnosis	< 200	7 (35)	15 (15.15)	0.05* a
	≥ 200	13 (65)	84 (84.85)	
CD4 at vaccination	< 200	5 (25)	0 (0.00)	0.0001* b
	≥ 200	15 (75)	99 (100.00)	
Vaccination schedule	Single dose	19 (95)	72 (72.73)	0.041* b
	Double doses	1 (5)	27 (27.27)	

*p < 0.05 statistically significant; a – Chi-square test; b – Fisher's exact test

DISCUSSION

The deterioration of the bowel epithelia due to the fast depletion of memory T cells at the bowel and the increased translocation of microbial products are shown as reasons for the progression of the HIV infection. The release of bacterial products in the circulation triggers inflammation and persistent, systemic activation of the immune system (10). Moreover, the production of solid pro-inflammatory cytokines like IL-2, IL-6, and tumor necrosis factor (TNF)-a tends to remain at high rates despite a decrease after the start of antiretroviral treatments (11). Besides, the HIV viremia that exists at low levels remains responsible for this permanent inflammation (12).

This immune aging manifests with a minimal or insufficient immune response even though CD4 levels increase after antiretroviral treatment. In our study, the vaccination response rates of the patients whose CD4 count was low at the time of diagnosis and whose CD4 count increased after antiretroviral treatment were low. This situation increases concerns around the timing of vaccination. It should be investigated if it is more appropriate to vaccinate for hepatitis B when HIV viremia decreases and the CD4 count comparatively increases or to vaccinate at the time of diagnosis without losing time. Another point of contradiction is around the dosage of the vaccine, that is, if it should be a standard dose or a high dose.

The HBV vaccine response rates of individuals living with HIV, similar to other immunosuppressed patients, are lower than expected population rates. In a study conducted in Poland, it was demonstrated that the HBV vaccine success rate was 63% for people living with HIV, while the rate was 93% for the healthy control group (13). Chatkittikunwong et al. demonstrated that the vaccine response rate is 70% when vaccinated with one dose while 97% with a double dose (14). This study determined the factors that affect the vaccine response as low CD4 count and advanced age. The advanced age affects the vaccine response negatively (15).

The fact that our patients were clustered in the middle age group can explain why no correlation was detected between age and vaccine response in our study (Fig. 1). In our study, the vaccine response rate of individuals who received a single dose is 79%, lower than the healthy population rate. It was observed that this rate is 96% for those who received double doses. This rate matches the hepatitis B vaccination response rate of the healthy population. The anti-HBs > 100, which is considered a good indicator of HBV immunity, was detected two times more in the healthy control group. In this study, like many others, a significant correlation was detected between CD4 counts and vaccination success (13, 16). The number of patients who received a single dose and had anti-HBs > 100 was 46/91 (50.5%), which is at considerably low level compared to the healthy population. In a prospective randomized study, it was shown that the serological

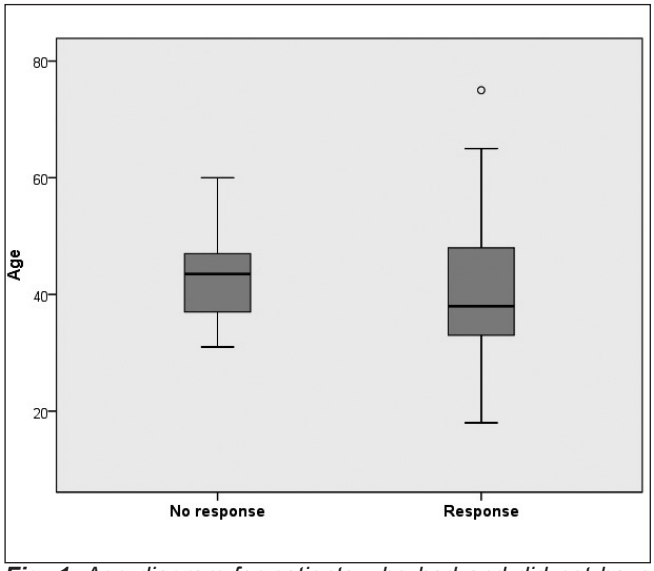

Fig. 1. *Age diagram for patients who had and did not have vaccine response.*

response rate of those who received the high dose was 72%, while the rate of those who received the standard dose was 50% (17).

The fact that the hepatitis B vaccine response rate of the individuals that have HCV infection is low compared to the healthy population, similar to HIV, suggests that the chronic viremia causes immunodeficiency and immune aging (18).

In the study by Laurence, it was found that the development of protective levels of antibodies is correlated with high levels of CD4 and low viral load (19). In our study, a positive correlation between CD4 levels at the time of diagnosis and vaccination and the development of protective levels of antibodies was detected. Following literature data, the antibody levels related to the vaccination increase as the CD4 count increases. However, a correlation between HIV RNA levels at the time of diagnosis and vaccination and antibody response was not detected.

In a study conducted in Brazil, with the standard dose HBV vaccination schedule applied to patients living with HIV, the immune response rate was detected as 80%. However, the vaccine response rate in this study is not correlated with age, CD4 count, and viral load. The comparatively high antibody levels in the study can be related to the exclusion of patients who had CD4 count <200 and to the fact that the CD4 count before vaccination was not taken into consideration. The CD4 count of the patients at the time of the first diagnosis was not evaluated in this study (20).

As demonstrated in some studies, although CD4 levels of the patients ameliorate after antiretroviral treatment, a decrease in cellular immune activities, immune deficiency, and the development of opportunistic infections can be observed. This can explain why the HBV vaccine effectiveness is low in HIV-positive patients compared to the healthy population.

Furthermore, some studies show that genetic factors (high genetic variance related to gene polymorphism) decrease HBV vaccine effectivity, alongside the common risk factors affecting vaccine effectivity like male sex, advanced age, tobacco use, and immune deficiency (21).

In a randomized controlled study, it was shown that in patients living with HIV who did not develop a vaccine response to the first series of hepatitis B vaccines, the administration of the revaccination series in high dose increases the vaccine response rate and antibody levels significantly (17).

Even though the CD4 count increases after the successful ART treatment, the hepatitis B vaccine response of the patients whose CD4 counts were low at the time of diagnosis, were significantly low compared to those whose CD4 counts were high at the time of diagnosis. The fact that there is no difference in local and systemic side effects between the standard and the double dose of the hepatitis B vaccine advances the double-dose vaccination because of its high effectiveness (22).

CONCLUSION

The hepatitis B vaccine response rates of the patients living with HIV are low compared to the rates of the healthy population, especially if the CD4 count is low. The administration of a double dose of the hepatitis B vaccine after an effective ART regimen for patients with CD4 count <200 at the time of diagnosis can increase the immune response. The choice of a high dose of the hepatitis B vaccine for the individuals living with HIV would be the right decision since the low-cost nature of the hepatitis B vaccine and the evidence that shows that the side effects of a high dose are no different from those of a standard dose.

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Conflict of Interests

None declared

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