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Hepatitis B vaccination in human immunodeficiency virus-infected adults receiving hemodialysis

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Background. The Centers for Disease Control and Prevention (CDC) recommends hepatitis B virus (HBV) immunization for all hemodialysis (HD) patients because they are at high risk of infection. Several studies have shown that the development of protective antibody titers after HBV vaccination is much lower in HD patients. We hypothesized that human immunodeficiency virus (HIV) infection in patients with end-stage renal disease (ESRD) would further impair the immune response to hepatitis B vaccination.

Methods. We performed a retrospective cohort study of patients undergoing long-term hemodialysis from 1990 to 2002 at the United States-based dialysis facilities of Gambro Corporation, North America. The response rate defined as an increase in anti-HBs levels ≥10 mIU/L after a month of the third dose of HBV vaccination was determined in HIV-infected and a randomly selected group of ESRD patients. The demographic information, laboratory data, and hepatitis B surface antibody (anti-HBs) titers were recorded from the Gambro Corporation database on these patients.

Results. Of the 347 adult HIV ESRD patients, 116 received three doses of recombinant hepatitis B vaccination. Seventy percent were male, and the majority (86%) were black. Of the 116 patients who received three doses of HBV vaccination, 62 (53.4%) developed protective antibody titers. This was comparable to the response rate of 50.4% in the randomly selected 220 non-HIV hemodialysis patients. Among HIV ESRD patients, the mean hemoglobin (Hgb) was higher in patients who developed protective antibody titers (Hgb 11.61 ± 2 vs. 10.55 ± 1.86, P value <0.01). On multivariate logistic regression analysis, higher Hgb was associated with protective antibody titers (odds ratio: 1.34, 95% CI 0.99–1.72). Seventy percent of the HIV-infected responders maintained protective antibody titers 6 months after vaccination.

Conclusion. Hepatitis B vaccination should be offered to all HIV-infected ESRD patients because over half of the patients with HIV and ESRD can develop protective antibodies.

Key words: human immunodeficiency virus, hepatitis B, vaccination, chronic kidney disease, hemodialysis.

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Hepatitis B virus (HBV) is acquired primarily as a blood-borne infection. Patients with end-stage renal disease (ESRD) on hemodialysis (HD) are at high risk of HBV infection. Despite marked decrease in incidence of newly acquired HBV infection among chronic hemodialysis patients in the United States after implementation of recommendations for the control of hepatitis B in dialysis centers in 1977, outbreaks of HBV continue to occur in these patients due to deficiencies in recommended infection control practices [1–5]. Unlike healthy individuals, those with ESRD and HBV infection usually have mild asymptomatic infections, but a large proportion become chronic carriers, probably due to an immune defect, and remain highly infectious [6]. Therefore, hepatitis B vaccine has been recommended for both hemodialysis patients and staff members since the vaccine became available in 1982 [7]. However, compared with adults with normal immune status, the proportion of hemodialysis patients who develop a protective antibody response after vaccination (even with higher doses) is lower [8–15]. Immune dysfunction caused by a metabolic monocyte defect related to ESRD is thought to be the reason for this unresponsiveness [16, 17].

Human immunodeficiency virus (HIV) infection continues to be an important cause of ESRD. Recent information from the United States Renal Data System database and CDC surveillance data suggests that 1.4% to 1.5% of all HD patients are infected with HIV [4, 18]. Immunization for hepatitis B in HIV-infected HD patients is more important because not only does HBV infection occur more frequently with HIV infection due to common route of infection, but it is much more likely to result in chronic infection [19]. However, some small studies have reported a suboptimal response to HBV vaccination in HIV-infected patients [20–28]. To determine

if the suboptimal response to HBV vaccination in HD patients is further exacerbated by HIV infection, we evaluated development of protective antibodies to HBV vaccination in these patients.

METHODS

We performed a retrospective cohort study of patients undergoing long-term HD at the U.S.-based dialysis facilities of Gambro Corporation, North America, from January 1990 to December 2002. The primary study population consisted of all adult (>18 years) HD patients that were infected with HIV. A random sample of 1000 hemodialysis patients during the same period was also identified from Gambro Corporation database and served as control patients. Only patients who received three doses of HBV vaccination were selected for further analysis. Demographic and laboratory information obtained closest to the time of vaccination was recorded. The date of starting dialysis and the date of death (if prior to January 2002) were recorded. Information on hepatitis B surface antibodies (anti-HBs) was noted one or more months after the third dose of hepatitis vaccination. Anti-HBs levels were measured using in vitro enzyme immunoassay (EIA) ET1-AB-AUK PLUS (DiaSorin Diagnostics, Still Water, MN, USA) Follow-up information on anti-HBs titers was also obtained on patients who developed a positive response. For survival analyses, the data were censored on December 31, 2002.

Statistical analysis

Patients who had an increase in anti-HBs titers ≥10 mIU/L after one month of receiving three doses of hepatitis vaccination were considered as responders. The nominal variables were converted to binary variables to indicate presence or absence. A descriptive analysis was used to graph all variables. The summary statistics and correlations were computed to continuous variables. The association of protective antibodies for hepatitis B was then estimated with a logistic regression model based on maximum likelihood estimation. The chi-square and Fisher exact test to associate protective antibodies with discrete variables were computed. Student *t* test was used to compare mean values between patients with and without protective antibodies. The Kaplan-Meier method was used to estimate the survival of HIV-infected dialysis patients. The log-rank test was used to compare cumulative survival among these patients stratified by response to HBV vaccination. A Cox proportional hazards model was used to evaluate effect of age, gender, race, hemoglobin, serum albumin, urea reduction ratio, and response to HBV vaccination on survival in HIV-infected patients. The reported *P* values in the Cox model are based on the Wald test. All reported *P* values are two-sided, and the significant difference was defined as $P < 0.05$. All values reported are mean ± SD unless otherwise specified. The data analysis was done using SAS system for Windows, version 8e (SAS Institute, Cary, NC, USA). The Human Subject Research Committee of the University of Texas Medical Branch, Galveston institutional review board, approved the study.

Table 1. Characteristics of HIV ESRD patients (HBV vaccination ≥3 doses)

Total ($N = 116$)	
Age	44.7 ± 12
Sex	
Males	81 (69.8%)
Females	35 (30.2%)
Race	
White	10 (8.7%)
Black	99 (86.1%)
Hispanic	6 (5.2%)
Hemoglobin *mg/dL*	11.11 ± 1.99
URR%	67 ± 12
Albumin *g/dL*	3.63 ± 0.53
Year of vaccination	
≤1996	26 (22.4%)
>1996	90 (77.6%)

Mean ± SD.

RESULTS

We identified 347 HIV-infected HD patients. Of these, 171 received ≥3 doses of HBV vaccination. The vaccination protocol used was Engerix-B™ (SmithKline Beecham Biologicals, Philadelphia, PA, USA) 40 μg/2 mL given intramuscularly (60% patients), or Recombivax HB™ (Merck & Company, Inc., West Point, PA, USA) 40 μg intramuscularly (40% patients) on a schedule of 0, 1, 6 months. Of these 171 patients, complete information on anti-HBs was available in 116 patients. The majority of the HIV-infected patients were black (86%), and 70% were males. Table 1 shows the demographic characteristics and laboratory data at the time of vaccination of these 116 patients. Sixty-two of these 116 patients developed anti-HBs levels ≥10 IU/L, accounting for a response rate of 53.4%. In the control (non-HIV) group, 362 received three doses of HBV vaccination (25% Engerix- B™ and 75% Recombivax HB™); however, complete information on follow-up Anti-HBs was available in only 220 patients. Of these 220 patients, 111 (50.5%) responded to the vaccination. The control group of patients was older than HIV ESRD patients (mean age 56.4 ± 14.6 vs. 44.7 ± 12.03, respectively, P value < 0.03).

Among HIV ESRD patients, the hemoglobin level of responders was significantly higher compared with patients who did not respond (11.6 ± 2 vs. 10.5 ± 1.86 mg/dL, respectively; Table 2). On multivariate logistic regression analysis, a higher hemoglobin level was the only variable associated with anti-HBs levels ≥10 mIU/L (Table 3). Sex, race, age, urea reduction ratio, and albumin levels

Table 2. Comparison of HIV and non-HIV ESRD responders and nonresponders to HBV vaccination

	HIV+ ($N = 116$)			Non-HIV ($N = 220$)		
Total	Nonresponders ($N = 54$)	Responders ($N = 62$)	*P* value	Nonresponders	Responders	*P* value
Age *years*	43. 9 ± 11.8	45. 39 ± 12.3	0.54	58.44 ± 14.3	54.37 ± 14.74	0.03
Sex						
Male	40 (74.1%)	41 (66.1%)		57 (52.3%)	54 (48.6%)	
Female	14 (25.9%)	21 (33.9%)	0.27	52 (47.7%)	57 (51.4%)	0.58
Race						
White	6 (11.3%)	4 (6.5%)	0.38	28 (25.7%)	20 (18%)	0.11
Black	43 (81.1%)	56 (90.3%)		51 (46.8%)	64 (57.7%)	
Hispanic	4 (7.5%)	2 (3.2%)		12 (11%)	17 (15.3%)	
Other	1 (0.1%)	0		18 (16.5%)	10 (9%)	
Hemoglobin *mg/dL*	10.55 ± 1.86	11.6 ± 2	0.01	11.66 ± 1.41	11.60 ± 1.43	0.96
URR%	67 ± 0.14	67 ± 0.09	0.72	73 ± 0.07	72 ± 0.07	0.41
Albumin *g/dL*	3.59 ± 0.48	3.66 ± 0.56	0.55	3.80 ± 0.36	3.88 ± 0.43	0.11
Year of vaccination						
Pre-HAART (≤1996)	11 (20.4%)	15 (24.2%)	0.62	N/A	N/A	
Post-HAART (>1996)	43 (79.6%)	47 (75.8%)				

N/A, not applicable. Mean ± SD.

Table 3. Univariate and multivariate logistic regression analysis showing association of responders (anti-HBS ≥10/mIU) with various covariates in HIV-infected hemodialysis patients

Total	Univariate (95% CI)	*P* value	Multivariate (95% CI)	*P* value
Age *year increase*	1.01 (0.98 1.04)	0.53	1.02 (0.98–1.07)	0.36
Sex				
Male	1.00	0.27	1.00	0.67
Female	1.58 (0.70–3.57)		1.26 (0.43–3.71)	
Race				
Black	1.00	0.16	1.00	0.09
Non-black	0.46 (0.16–1.37)		0.30 (0.07–1.26)	
Year of vaccination				
≤1996	1.00	0.62		
>1996	0.80 (0.33–1.94)			
Hemoglobin *g/dL increase*	1.34 (1.04–1.71)	0.02	1.31 (0.99–1.72)	0.05
URR% *increase*	0.93 (0.02–5.38)	0.97		
Albumin *g/dL increase*	1.29 (0.55–3.03)	0.55	0.92 (0.33–2.56)	0.87

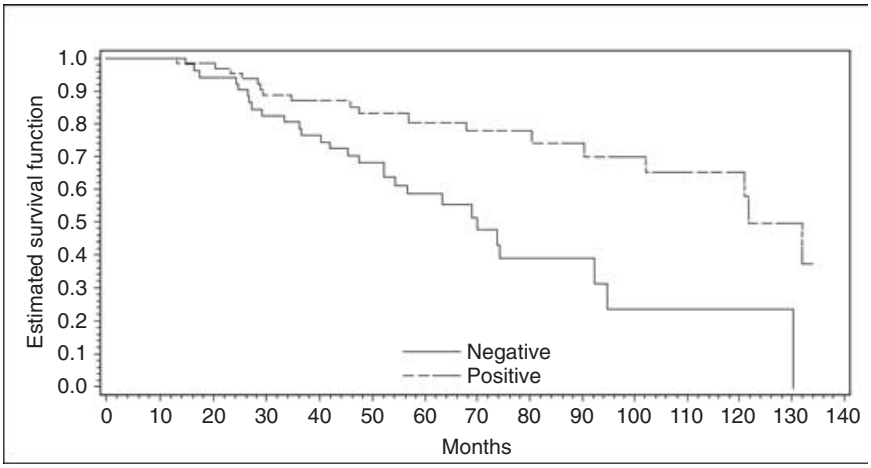
were not associated with response rate to HBV vaccination. We also compared the response rate of HIV ESRD patients prior to ≤1996 and after 1996 when highly active antiretroviral therapy (HAART) became available. Surprisingly, the response rate to HBV vaccination in the pre-HAART era was better than the HAART era [57.6% (15/26) vs. 47% (47/99), respectively] (Table 2). However, the number of patients who received HBV vaccination prior to 1996 was small. Of the 62 HIV-infected patients that responded to HBV vaccination, the follow-up titers of anti-HBs at 6 months or more were available in 34 patients. Ten (29.5%) of these 34 patients had a decline in the titers to unprotective levels, but 24 (70.5%) maintained titers ≥10 mIU/L at 6 months. The rate of decline of protective antibody titers was slower in 80 control responders, for whom follow-up titers were available after 6 months. Sixty-five (81.2%) of these 80 patients had protective anti-HBs levels 6 or more months after completing vaccination.

Of the 116-HIV infected patients, hepatitis C antibody was checked in 43, and 13 (30%) were positive. Twelve (40%) of the HCV-negative patients and 7 (54%) of the HCV-positive patients had protective levels of anti-HBs. The association between hepatitis C and anti-HBs was not statistically significant.

Interestingly, Kaplan-Meier analysis revealed that HIV ESRD responders to HBV vaccination had a better survival than nonresponders (Fig. 1). However, in Cox-proportional hazard analysis, only younger age and high serum albumin levels were associated with better survival. Although there was a trend towards better survival of HIV ESRD responders compared to nonresponders (hazard ratio: 0.42, 95% CI 0.17–1.07), this was not statistically significant (*P* value = 0.07).

DISCUSSION

To our knowledge, no prior study has addressed the important issue of the efficacy of vaccination in HIV-infected ESRD patients. Interestingly, a response rate of 54% in HIV-infected HD patients was better compared with response rate of 50% in a randomly selected group of HD patients who received the same regimen of vaccination. This response rate of 50% in control (non-HIV)



Negative	54	51	40	20	7	1
Positive	62	62	51	31	20	9

Fig. 1. Kaplan-Meier estimates of survival of HIV-infected hemodialysis (HD) responders (positive) and nonresponders (negative) to hepatitis B vaccination (log-rank *P* value = 0.0006). Number of patients at various time periods is shown in the table below. However, on Cox-proportional hazard analysis this finding was not statistically significant (hazard ratio: responders vs. nonresponders 0.42, 95% confidence interval 0.17–1.07, *P* value 0.07).

HD patients is consistent with several other studies that have also reported that only 34% to 88% of patients who receive the three doses of HBV develop protective antibodies [8–11].

Several factors could account for an almost equal response to HBV vaccination in HIV and non-HIV ESRD patients in our study. Most, but not all studies on HIV-infected patients without renal failure have reported impaired immune response to vaccination [20–28]. Huang et al found that HIV-infected homosexual men, asymptomatic or with persistent generalized lymphadenopathy, were able to mount appropriate antibody responses to influenza and pneumococcal vaccine similar to HIV-seronegative men [28]. Reports of the influence of CD4 cell count on the response to HBV vaccination in HIV-infected patients have also been inconsistent. Rey et al found a positive correlation of anti-HBs titers following HBV vaccination with CD4 count [24]. In contrast, Wong et al found a trend toward lower CD4 counts among HIV-infected patients who responded to HBV vaccination [20]. Little is known about the basic immunologic response to HBs Ag following vaccination, apart from expected cooperation between the two areas of the human immune response [29]. Therefore, relatively crude index of T-cell phenotype enumeration may not be the best predictor of response. Although the information on total CD4 count at the time of vaccination was not available to us, a better response rate to HBV vaccination in pre-HAART (57.6%) than HAART (47%) era supports that total CD4 count may not be very important in the response to HBV vaccination.

More importantly, the better response rate in HIV ESRD patients compared with randomly selected control patients could be due to the fact that HIV ESRD patients were significantly younger (mean age HIV-infected vs. control patients: 44.6 ± 12.0 vs. 56.4 ± 14.6, *P* value < 0.04). Several studies have shown that major determinant of HBV vaccine response is age, with the proportion of persons developing a protective antibody response declining to 84% among adults aged >40 years and 75% by age 60 years [31, 32]. Similarly, Peces et al, in a prospective study with 80 HD patients, found that 100% of the patients (younger than 40 years) developed protective antibodies to HBV vaccination compared with only 74% in patients older than 60 years [33].

Some, but not all, studies have suggested that protective antibody titers may fall rapidly after vaccination in HIV-infected patients [27, 34]. Ray et al obtained a total response rate of 90% in HIV-infected patients after giving three additional doses of HBV vaccination to nonresponders. However, only 10/17 (58.8%) patients had protective antibodies after a year [27]. Manicalgi reported a response rate of 62% in 21 young HIV-infected heroin addicts. However, 70% of these patients maintained protective antibody titers after one year of follow-up [35]. We found that 70% of the responders maintained protective anti-HBs titers 6 or more of months after HBV vaccination. The difference in the decline in the protective antibodies in the above studies could be due to different HBV vaccines and regimens used, and/or the peak level of anti-HBs obtained.

It is well know that hemodialysis patients on erythropoietin with higher hemoglobin have a better response rate to HBV vaccination [36–38]. Although we did not have information on erythropoietin doses in our patients, we did find that patients with higher (mg/dL) hemoglobin levels had a 34% greater chance of having protective antibody levels. Because the prevalence of anemia is higher in patients with AIDS compared to patients with early stage of HIV infection, hemoglobin levels may also reflect stage

Table 4. Cox-proportional hazard analysis of survival of HIV ESRD patients

Risk factor	Adjusted Hazard Ratio (95% CI)	*P* value
Anti-HBs		0.068
Negative	1.00	
Positive	0.42 (0.17–1.07)	
Age *per year increase*	1.04 (1.00–1.08)	0.03
Gender		
Female	1.00	
Male	1.05 (0.42–2.64)	0.91
Race		
Other	1.00	
Black	1.44 (0.42–5.00)	0.56
Hemoglobin *mg/dL change*	1.14 (0.91–1.42)	0.24
Serum albumin *g/dL increase*	0.30 (0.12–0.75)	0.009
URR% *increase*	0.53 (0.22–1.29)	0.16

and severity of HIV infection and, henceforth, immune response to HBV vaccination.

Interestingly, we found that HBV vaccine responders had a better survival than nonresponders. This survival benefit was partially lost in the final Cox-proportional hazard model; the responders had a 58% better survival rate (Table 4). Although we did not have information on CD4 counts, the better survival could be due the fact that response to HBV vaccination may reflect the degree of immunosuppression in these patients. Several studies have shown that the stage of HIV infection and albumin levels are predictors of long-term survival of HIV-infected patients [39, 40]. Consistent with these studies, we also found that hypoalbuminemia was associated with higher risk of death (Table 4).

The major shortcomings of our study is that the information on CD4 counts, plasma viral loads, and antiretroviral therapy were not available to us in these patients to determine if immune response to HBV vaccination was related to these factors. The effect of these factors, however, is attenuated by the fact that renal disease in HIV infection develops in advanced stage of HIV infection [41]. The other factor that could have altered results in our study is that patients with severe immunosuppression and advanced AIDS may not have been offered or completed a full course of vaccination due to high mortality rate. This could have lead to overestimation of response rate to HBV vaccination. The reasons for underutilization of HBV vaccination in control patients compared with HIV infected patients (36% vs. 50%) were not available from the database. CDC surveillance of hemodialysis facilities found that, although during 1983 to 2001 the percentage of patients who received at least three doses of HBV increased from 5.4% to 59.8%, the underutilization of HBV vaccination was common, as only 42.8% to 69.5% of patients among various ESRD networks received HBV vaccination [42]. We can only speculate that nephrologists may have utilized HBV vaccination more frequently in HIV-infected patients, realizing that these patients are at a higher risk of hepatitis B.

CONCLUSION

Over half of the HIV-infected patients on HD can develop and maintain protective antibody titers to HBV vaccination. Therefore, HBV vaccination should be offered to these patients, although more frequent screening for anti-HBs titer may be required than the annual testing recommended for hemodialysis patients. Future prospective studies are required to determine predictors of immune response and strategies such as intradermal administration, concomitant administration of erythropoietin or granulocyte colony stimulating factor, and triple antigen recombinant HBV vaccines to enhance the development of protective antibodies in response to HBV vaccination in this high-risk group of patients.

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