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CD4/CD8 ratio as a predictor of the response to HBV vaccination in HIV-positive patients: A prospective cohort study

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ABSTRACT

Background: Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) share transmission mechanisms and thus coinfection is frequent. Active immunization against HBV is essential in HIV patients. Reports using standard and reinforced HBV vaccination schedules vary widely in seroconversion rates depending on the characteristics of the included patients. Regional data concerning HBV vaccination in HIV patients are scarce. We aim to determine the serological response to HBV vaccination using standard schedule in HIV-positive patients and to evaluate characteristics that predict seroconversion.
Materials and methods: We performed a single centre prospective study of HBV vaccination with standard schedule in HIV-positive patients. Adults with negative markers of HBV infection were included between November 2012 and December 2014. Anti-HBs titres were measured 4–8 weeks after completion of vaccination schedule. Clinical, laboratory values and HIV characteristics were analyzed to determine their association with seroconversion and adherence to the HBV vaccination schedule.
Results: The study included 245 HIV-positive patients, 68.9% were male and the mean age was 42.1 years. A total of 80.7% of the patients had undetectable HIV viral loads, 86.1% had CD4 counts >200, and 94.7% were on HAART. The response to vaccination was positive in 62% (95% CI, 56–68%) and mean anti-HBs titres of 646 IU/ml. 85.5% of the responders had anti-HBs titres >100 IU/ml. An age less than 45 years, no tobacco use and a CD4/CD8 ratio >0.4 were associated with seroconversion in multivariate analysis. The seroconversion rates were 86% in the subgroup of patients who met these criteria. A total of 97.9% of the study population completed the vaccination schedule.
Conclusion: The CD4/CD8 ratio was the primary factor associated with positive serological conversion in the multivariate analysis. The seroconversion rates were higher in a selected group of patients who were particularly suitable for the use of the standard HBV vaccination schedule.
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1. Introduction

Hepatitis B virus infection is one of the most prevalent infectious diseases worldwide [1]. Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) share transmission mechanisms and therefore co-infection is frequent [2]. The natural history of HBV in HIV patients is characterized by a more aggressive course with a higher incidence of chronic infection and a higher HBV viral load, more HBV reactivation episodes, a higher incidence of cirrhosis

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and hepatocellular carcinoma [3] and more liver-related mortality [4]; thus, HBV co-infection is currently considered a reason to initiate HAART among patients living with HIV [5]. Similarly, HBV affects the evolution of HIV disease, resulting in earlier initiation and more adverse events associated with HAART [6,7]. Therefore, active immunization against HBV in HIV patients is essential and recommended in clinical practice guidelines [8–10]. The serological response rates to HBV vaccination in HIV patients vary from 17 to 85% in different reports [11–25]. The wide reported seroconversion range could be attributable to differences in the methodological design, such as the administration schedule, vaccine type, administration route, characteristics of the population studied, and the relatively small sample size in prospective studies. Additionally, data from Latin American regions are scarce. CD4/CD8 ratio, an old biomarker for HIV, has been recently associated to morbidity and mortality that is unrelated to AIDS [38,39].

Completion of the vaccination schedule is essential to achieve seroconversion and is an important issue in HIV-positive individuals in whom completion of the indicated schedule is frequently rare (range from 49.6 to 75.5%) [11,26–28]; moreover, completion of the schedule is especially low in drug users [29]. Consequently, measurement of the response after vaccination completion is even lower [26,27].

Therefore, we aim to determine the serological response to HBV vaccination with a standard schedule in HIV patients and evaluate the variables that predict positive seroconversion. We also examine adherence and the factors associated with completion and attendance at vaccination visits.

2. Materials and methods

2.1. Study design

A prospective cohort study was conducted among patients with HIV to provide immunization against HBV in Gustavo Fricke Hospital in Viña del Mar, Chile, between November 2012 and December 2014. This report was conducted in compliance with recommendations established in the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [30].

The inclusion criteria were as follows: adult patients, negative test for HBsAg prior to initiating the vaccination, and no previous history of HBV immunization. Attendance at 2 of the last 3 HIV control programmes was required. Informed consent was provided, and the local ethics committee approved the study.

A blood sample was taken to determine the anti-HBc status (ELECSYS Anti-HBc 2010 Reagent Kit, Electrochemiluminescence immunoassay "ECLIA", Cobas e602, Roche Diagnostics, IN, USA), and positive individuals were excluded from the study. Patients negative for markers of HBV infection were vaccinated with a standard schedule for HBV using 20 μg of Engerix-B® (GlaxoSmithKline, Brentford, United Kingdom) administered intramuscularly at 0, 1 and 6 months. Then, a new blood samples was collected 4–8 weeks after completion of the vaccination schedule to measure the Hepatitis B surface antibody (anti-HBs) levels in the serum (ELECSYS Anti-HBs Reagent Kit, Electrochemiluminescence immunoassay "ECLIA", Cobas e602, Roche Diagnostics, IN, USA). Positive seroconversion was defined as anti-HBs titres >10 IU/ml according to current recommendations [31]. Demographic and clinical variables were assessed (age, gender, education level, men who have sex with men, drug use, alcohol consumption, tobacco use, weight, BMI, waist circumference, presence of hypertension, diabetes mellitus and dyslipidaemia). Laboratory values were collected (total cholesterol, triglycerides, HDL, LDL, liver function tests, haematocrit, white cell count, platelet count, serum creatinine, fasting glucose and serum TSH), and HIV history and characteristics were evaluated, including CDC staging, time since HIV diagnosis, HIV viral load, present and nadir CD4 counts, CD8 count, CD4/CD8 ratio, use of HAART and time receiving it, and HAART active against HBV. Additionally, a history of abandonment of HIV programme appointments defined as spontaneous sustained absences from an HIV programme longer than 6 months was considered. Immediate adverse reactions were monitored by health personnel at the time of vaccination, and a survey of more delayed adverse reactions was administered after completion of the vaccination schedule together with surveillance at hospital admission to determine potential serious adverse effects attributable to the intervention. Adherence to vaccination was evaluated at the end of the planned schedule, including measurement of the vaccination response. Patients who met the inclusion criteria and were willing to initiate vaccination were repeatedly scheduled, whereas the patients who failed to attend at least three scheduled appointments were categorized as absentee.

2.2. Statistical analysis

Descriptive statistics (i.e., means, standard deviations, and proportions) were calculated to assess the characteristics of the study sample. Analyses to determine factors associated with the serological response was performed using a two-step strategy. Bivariate analyses were conducted first using Fisher's exact test for categorical variables and Mann–Whitney's or Student's T test for quantitative data. Furthermore, 95% confidence intervals were calculated whenever appropriate.

Variables that had potential associations with the outcome ($p < 0.15$) were selected for inclusion in the multivariate logistic regression model (age, gender, tobacco use, weight, waist circumference, arterial hypertension, CDC HIV category, detectable HIV viral load, actual CD4 count, nadir CD4 count, actual CD8 count, CD4/CD8 ratio, time using HAART, triglyceride level, HDL level, total bilirubin, serum albumin level and haematocrit percentage). Candidate models were constructed using maximum likelihood methods and considered based on their potential for interactions between independent predictors in their development. Model accuracy was assessed using receiver operating characteristics (ROC) curves, and the overall goodness of fit was established using Hosmer and Lemeshow's statistic. A two-tailed p-value less than 0.05 was considered statistically significant. All patients who started the vaccination schedule were included in the analysis.

3. Results

At the beginning of study, 780 individuals from an HIV ambulatory clinic were eligible according to the selection criteria and received an open invitation to enter the protocol. A total of 458 patients showed interest in enrolling, provided informed consent and were scheduled for an initial visit; however, only 405 arrived to initiate the vaccination schedule. A total of 160 patients tested positive for anti-HBc and were excluded. A total of 245 patients initiated the vaccination schedule, but 5 were lost to follow up prior to the determination of the serological response. Ultimately, 240 patients completed the study protocol (Fig. 1).

Out of the 245 patients who initiated vaccination, the mean age was 42.1 years and 68.1% were male gender. Drug use was infrequent (11.4%), and only 3 patients were IV drugs users; in contrast, alcohol consumption (33.2%) and tobacco use (37.5%) were more prevalent. An important proportion of patients had altered BMIs and waist circumferences (means 26.5 and 89.7 cm, respectively); additionally, near half of the sampled individuals (46.8%) had dyslipidaemia. Regarding the characteristics of HIV infection, 80.7% of the patients had an undetectable HIV viral load, 86.1% had a CD4 count higher than 200 cells/mm^3 and 94.7% used HAART at the beginning of the vaccination scheme. There were no

relevant alterations in laboratory values, including liver function tests, haematological counts, and serum creatinine. The general characteristics of the study sample are provided in detail in Table 1.

In response to the HBV vaccination, 62% (152/245) of the individuals who started the vaccination schedule were positive responders (95% CI, 56–68) with a mean anti-HBs titre of 626 IU/ml (SD 391.5) (Table 1). In patients who responded to the vaccination, 85.5% had anti-HBs titres higher that 100 IU/ml.

The bivariate analysis to evaluate variables associated with seroconversion found that a younger age (40.7 vs. 44.4 years, $p = 0.009$), feminine gender (36.2% vs. 22.6%, $p = 0.025$), no tobacco use (31.1% vs. 47.8%, $p = 0.010$) and metabolic variables such as lower weight (69.8 vs. 72.3 kg, $p = 0.050$) and waist circumference (88.3 vs. 91.9 cm, $p = 0.031$) were predictors of the serological response to vaccination. We found differences in serum albumin levels (4.6 vs. 4.2 mg/dl, $p = 0.005$) and HDL levels (52.1 vs. 45.7 mg/dl, $p = 0.013$), which were higher in the group with positive seroconversion. No other differences were observed in the haematological count, hepatic function, thyroid or renal function test. Details of the bivariate analysis are provided in Table 1.

The multivariate analysis showed that the variables age and weight were co-linear in the correlation test ($r = 0.66$, $p < 0.01$) as were a CD4 count higher than 200 cell/mm^3 with the CD4 count ($r = 0.63$, $p = 0.04$) and CD4/CD8 ratio ($r = 0.6$, $p < 0.01$). We performed separate analyses using the CD4 count as a quantitative variable with several thresholds. However, none of these analyses were superior to the CD4/CD8 ratio. Therefore, the variable CD4/CD8 ratio was chosen for use in the model instead of the other aforementioned variables. Separate analyses using different cut-off ratios (0.4, 0.5 and 1) were conducted. A CD4/CD8 ratio cut-off >0.4 provided a higher discrimination capacity for the multivariate model. Based on this analysis, iterative multivariate models

Table 1
Characteristics of the study sample and bivariate analysis of serological response to HBV vaccination schedule ($n = 245$).

Serological response to vaccination	Total sample 245	Seroconversion (−) 93/245 38%	Seroconversion (+) 152/245 62% (95% CI, 56–68)	
Variable	Total sample	Seroconversion (−)	Seroconversion (+)	*p* value
Age (years)	42.1 (SD 11.8)	44.4 (SD 11.7)	40.7 (SD 11.6)	0.009
Gender (%)				
Feminine	31.1	22.6	36.2	
Masculine	68.9	77.4	63.8	0.025
Educational level (%)				
Primary	29.3%	29.3%	29.3%	
Secondary	38.1%	36.6%	39.1%	
Superior	32.6%	34.2%	31.6%	0.907
Men-sex-men (%)	41.9	42.2%	41.7%	0.942
Drugs use (%)	11.4%	11.9%	11.2%	0.870
Alcohol consumption (%)	33.2%	35.6%	31.7%	0.544
Tobacco use (%)	37.5%	47.8%	31.1%	0.010
Weight (mean, kg)	70.7 (SD 11.5)	72.3 (SD 11.9)	69.8 (SD 11.1)	0.051
BMI	26.5	27.1 (SD 4.3)	26.1 (SD 4.1)	0.185
Waist circumference (cm)	89.7 (SD 9.7)	91.9 (SD 8.7)	88.3 (SD 10.2)	0.031
Arterial hypertension (%)	8.62	2.17	12.9	0.086
Diabetes (%)	11.2	8.24	12.8	0.293
Dyslipidaemia (%)	46.8	45.6	47.6	0.757
CDC HIV category				
A	40.4%	32.9%	44.9%	
B	29.8%	29.6%	29.9%	
C	29.8%	37.5%	25.2%	0.097
Time since HIV diagnosis (months)	85.8 (SD 60.7)	81.1 (SD 59.8)	88.6 (SD 61)	0.177
Detectable HIV viral load (%)	80.7	25.8	15.4	0.049
Actual CD4 count	406.3 (SD 190.8)	338.2 (SD 165)	447.6 (SD 194)	<0.001
CD4 >200 (cell/mm^3)	86.1%	76.1%	92.1%	<0.001
Nadir CD4 count (cell/mm^3)	159.9 (SD 135.6)	136.1 (SD 113)	174.1 (SD 146)	0.019
Actual CD8 count (cell/mm^3)	908.1 (SD 446.8)	955.9 (SD 453)	881.3 (SD 442)	0.108
CD4/CD8 ratio	0.54 (SD 0.36)	0.42 (SD 0.26)	0.62 (SD 0.37)	<0.001
Present use of HAART (%)	94.7	94.6	94.7	0.954
HAART active against HBV (%)	97.4	98.8	96.5	0.414
Time using HAART (months)	61.4	56.1 (SD 50.5)	64.6 (SD 51.2)	0.125
History of abandonment to HIV programme controls (%)	16.7	17.9	16.1	0.719
Reactive VDRL	7.7	10.7	5.8	0.181
Total cholesterol (mg/dl)	200.5 (SD 41.9)	201.1 (SD 43.6)	200.1 (SD 41.1)	0.432
Triglycerides (mg/dl)	172.8 (SD 80.2)	181.3 (SD 78.3)	167.8 (SD 81.1)	0.113
HDL (mg/dl)	49.5 (SD 15.5)	45.7 (SD 14.8)	52.1 (SD 15.5)	0.013
LDL (mg/dl)	114.3 (SD 43.2)	114.9 (SD 40.4)	113.9 (SD 43.2)	0.453
Bilirubin total (mg/dl)	0.86 (SD 0.47)	0.78 (SD 0.66)	0.91 (SD 0.75)	0.094
SGOT (mg/dl)	32.5 (SD 15.8)	32.9 (SD 14.7)	32.2 (16.4)	0.352
SGPT (mg/dl)	41.9 (SD 35.7)	44.4 (SD 47.3)	40.6 (26.4)	0.213
Alkaline phosphatases (mg/dl)	114.4 (SD 65.7)	114.1 (SD 43.6)	114.6 (SD 75.9)	0.478
GGTP (mg/dl)	49.7 (SD 38.2)	54.3 (SD 41.8)	47.1 (SD 36.1)	0.195
Prothrombin time (%)	93.3 (SD 14.1)	95.4 (SD 9.1)	91.7 (SD 16.9)	0.184
Albumin (g/dl)	4.45 (SD 0.52)	4.2 (SD 0.56)	4.6 (SD 0.44)	0.005
Haematocrit (%)	41.3 (SD 4.2)	41.7 (SD 4.0)	40.9 (SD 4.3)	0.099
WBC count (cells/μl)	5791 (SD 2040)	5698 (SD 2264)	5845 (SD 1907)	0.327
Platelet count ($\times 10^3$/mm^3)	243.9 (SD 60.2)	239.6 (SD 63.6)	246.5 (SD 58.1)	0.199
Serum creatinine (mg/dl)	1.03 (SD 2.99)	0.78 (SD 0.15)	1.17 (SD 3.78)	0.169
Fasting glucose (mg/dl)	91.5 (SD 18.3)	90.8 (SD 17.8)	91.9 (18.6)	0.332
TSH (μU/ml)	3.2 (SD 2.45)	3.6 (SD 3.1)	3.1 (SD 2.2)	0.292

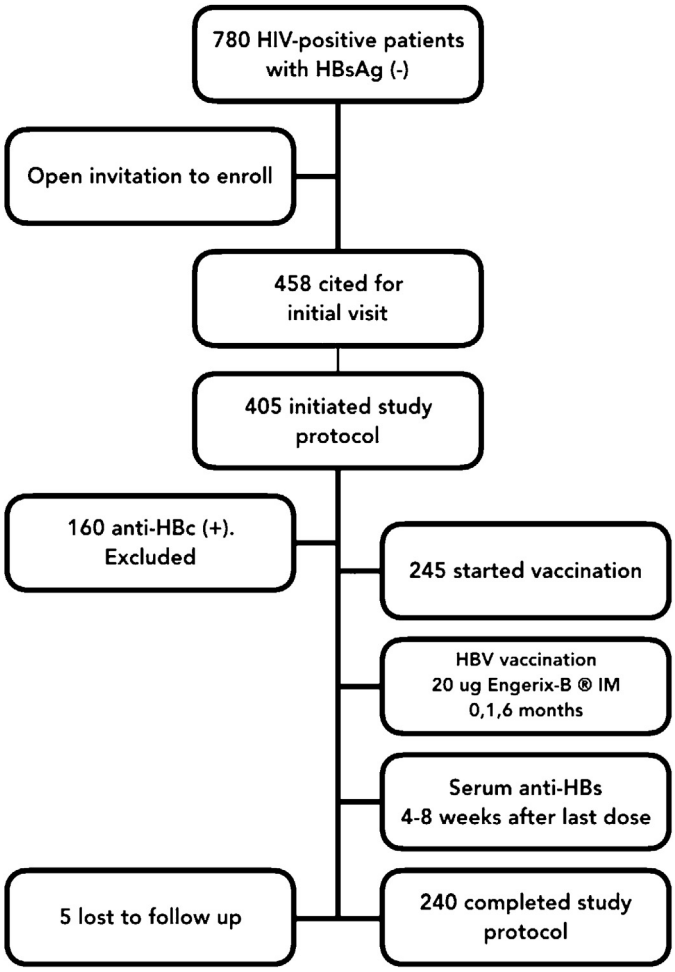

Fig. 1. Flow chart. A total of 780 individuals from an HIV ambulatory clinic were eligible according to the selection criteria and received an open invitation to enter the study. A total of 458 patients showed interest in entering the study, provided informed consent and were scheduled for the initial visit. However, only 405 patients arrived to initiate the study protocol. A total of 160 patients tested positive for anti-HBc and were excluded. A total of 245 patients initiated the vaccination schedule, but 5 were lost to follow up prior to the determination of the serological response. Ultimately, 240 patients completed the study protocol.

were constructed; the final results are shown in Table 2. This model was constructed with data from 228 patients and had a determinacy coefficient of 10%. The model's area under the ROC curve was 0.70 (95% CI, 0.63–0.77), and the Hosmer and Lemeshow statistic showed appropriate goodness of fit with a p-value = 0.99 (Fig. 2).

Based on the bivariate and multivariate analysis results, a subgroup analysis was performed to evaluate the serological response to HBV vaccination. In the subgroup of HIV patients with CD4 counts less than 200 cells/mm^3 (n = 34) the serological response was 35% (95% CI, 19.7–53.5). Seroconversion was achieved in 68% of the patients who did not use tobacco (n = 100, 95% CI, 64–72). When analysing the group of patients who fulfilled favourable factors for seroconversion (younger than 45 years, non-smokers and

Table 2
Multivariate model: serologic response to HBV vaccination.

Variable	β Coefficient (95% CI)	aOR (95% CI)	p value
Age >45 years	−1.0 (−1.61, −0.40)	0.36 (0.20, 0.67)	0.001
Detectable HIV viral load	−0.49 (−1.23, 0.25)	0.62 (0.29, 1.29)	0.198
CD4:CD8 ratio >0.4	1.02 (0.43, 1.60)	2.76 (1.54, 4.95)	<0.001
Tobacco use	−0.83 (−1.4, −0.22)	0.44 (0.24, 0.80)	0.007
Constant (α)	0.80 (0.23, 1.37)	1.11 (0.52, 2.37)	0.006

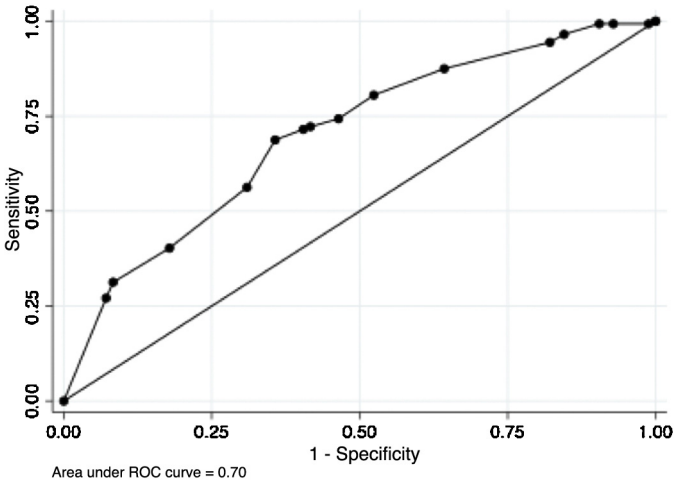

Fig. 2. Receiver operating characteristic curve (ROC curve) of the multivariate model for seroconversion. This model was constructed with data from 228 patients and had a determinacy coefficient (pseudo R^2) of 10%. However, its area under the ROC curve was 0.70 (95% CI, 0.63–0.77). The Hosmer and Lemeshow statistic showed an appropriate goodness of fit with a p-value = 0.99.

possessing a CD4/CD8 ratio higher than 0.4; n = 44), the serological response to HBV vaccination was 86% (95% CI, 81–90) (Fig. 3).

Data concerning adverse reactions were available for 203 patients, and an absence of adverse reactions was reported in 76.8% of these patients (156/203). Local adverse reactions at the vaccination site were infrequent (10.3%). The main systemic reactions included flu-like symptoms (4.9%), headache (6.4%), asthenia (6.4%) and myalgia (5.4%). No serious adverse events were attributable to HBV vaccine during the study period.

We also addressed adherence and completion of the vaccination schedule, which reached 97.9% once the first dose of the vaccine was administered. Very few patients were lost to follow upon completion of the study. Nonetheless, there was a group of patients (n = 53) who did not attend the first visit to start the vaccination schedule despite fulfilling the inclusion criteria, providing informed consent and scheduling the visit to enrol in the study. These patients were newly scheduled at least three times without attendance. In this group of absentees, clinical and demographical characteristics

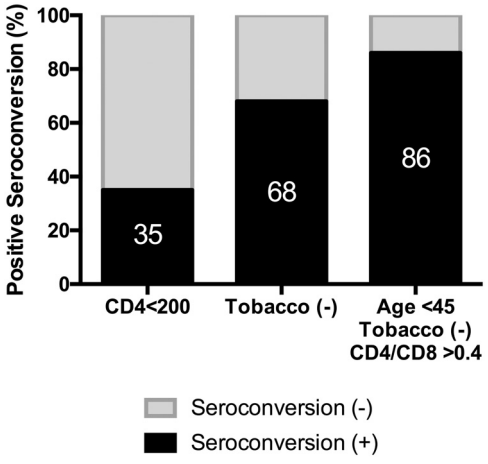

Fig. 3. Serological response to HBV vaccination subgroup analysis. In the subgroup of HIV patients with CD4 counts less than 200 cell/mm^3 (n = 34), the serologic response was 35% (95% CI, 20–54). In the subgroup with the absence of tobacco use (n = 100), seroconversion was achieved in 68% (95% CI, 62–74). Patients who were younger than 45 years, were non-smokers and had a CD4:CD8 ratio higher than 0.4 (n = 44) achieved a serological response to HBV vaccination of 86% (95% CI, 81–90).

Table 3
Multivariate analysis for attendance and completion of vaccination schedule.

Variable	aOR (95% CI)	*p* value
Drugs use	0.40 (0.17–0.94)	0.037
History of HIV programme abandon	0.41 (0.20–0.84)	0.016
Superior education	0.64 (0.42–0.99)	0.045

were identified and associated with the lack of attendance. The multivariate analysis model was constructed through multiple logistic regressions with the maximum-likelihood principle; the details are provided in Table 3. Drug use (aOR 0.40, $p = 0.037$), history of abandonment of HIV programmes (aOR 0.41, $p = 0.020$) and superior education level (aOR 0.64, $p = 0.045$) were predictors of the lack of attendance to the vaccination schedule.

4. Discussion

To the best of our knowledge, this study is the first evaluation of the serological responses to HBV vaccination in a south Latin American HIV carrier population. The closest previous studies were conducted in Mexico and Brazil. The administration of standard doses of the Engerix-B® (GlaxoSmithKline) vaccine by Fonseca et al. [13] in Brazil obtained a response of 34%, and Cornejo-Juarez et al. [15] reported a 62% response in Mexico using Recombivax HB® (Merck).

In our study, a serological response of 62% (95% CI, 56–68) was obtained with the standard schedule using Engerix-B® in HIV-positive individuals controlled in an outpatient HIV clinic. Notably, no significant adverse reactions were observed.

Concerning the heterogeneity of studies investigating HBV vaccination in adult subjects with HIV, we found that most reports on the use of the Engerix-B® vaccine with a standard schedule in HIV subjects were retrospective. For instance, Overton et al. [12], Kim et al. [18], Bailey et al. [26] and Petit et al. [21] in the USA described responses of 17.5%, 44%, 47.5% and 46.5%, respectively. Evidence from prospective studies is limited and includes the aforementioned report by Fonseca et al. [13] and the study by Paitoonpong et al. [17] in Thailand, which reports a 71.4% response. Prospective studies on the use of the standard schedule with other recombinant HBV vaccines (GenHevac B®, Recombivax HB, and HBvaxPro®) have shown serological responses between 50 and 65% [15,23,24].

The average response titres from individuals who responded to the vaccine in our study were 646 IU/ml. The majority of the responders (85.5%) had anti-HBs levels greater than 100 IU/ml, which was associated with long-term protection [32]. Anti-HBs levels greater than 100 IU/ml after vaccination has been described as a pivotal factor associated with sustained long-term seroprotection because 70% of subjects with levels below 100 IU/ml after vaccination have non-protective anti-HBs titres (<10 IU/ml) at two years of follow-up [33].

The findings of the bivariate analysis of the association with a positive serological response were similar to those described in previous reports, where a younger age ($p = 0.009$) [21,24], female gender ($p = 0.025$) [20,23], non-smoker condition ($p = 0.01$) [24,34], undetectable HIV viral load ($p = 0.049$) [11,12,18,22,23,25], higher historical nadir CD4 count ($p = 0.019$) [11,18] and CD4 count greater than 200 cells/mm^3 when starting the vaccination series ($p < 0.001$) [11,15–17,19,21–24] were determinants of a positive response to vaccination. We also observed a lower waist circumference ($p = 0.031$) in the group that achieved seroconversion, which was a condition that was not reported in previous studies and might reveal a need to adjust vaccine doses in relation to anthropometric measurements; this subject should be explored in a targeted manner. Higher HDL ($p = 0.013$) and serum albumin values ($p = 0.005$) were also associated with a favourable response, which could imply the involvement of metabolic factors in seroconversion.

The CD4 count when starting vaccination has been largely described in studies evaluating the response to HBV vaccination in HIV patients [11,15–17,19,21–24]. However, to the best of our knowledge the significance of the CD4/CD8 ratio as a predictor of the response has not been described. A low CD4/CD8 ratio is considered a marker of immune senescence and an independent predictor of mortality in elderly non-HIV patients [35]. Individuals carrying HIV are hypothesized to be in a state of accelerated ageing secondary to persistent inflammation despite adequate viral suppression [36]. Hence, a low CD4/CD8 ratio in HIV-positive patients with good immunovirological responses has been independently associated with the clinical phenomena of ageing [37] and with an increased risk of morbidity and mortality that is unrelated to AIDS in this group [38]. Recently, CD4/CD8 ratio normalization after HAART initiation was associated with a lower risk of non-AIDS related events [39].

In our study, the CD4/CD8 ratio was of paramount importance as a predictor of the response in the bivariate analysis ($p < 0.001$), was the main predictor of the response in the multivariate analysis ($p < 0.001$) and was more relevant than the CD4 count at the time of vaccination. This finding is particularly important because most of the individuals included in this study were HIV patients with good control of their HIV infection; indeed, 80.7% had an undetectable viral load, 94.7% were receiving antiretroviral therapy (HAART) and 86.1% had CD4 counts greater than 200 cells/mm^3. These characteristics of the sample were similar to previous reports, where great variability existed in the immunovirological characteristics of the included patients, with average CD4 counts ranging from 225 to 516 cells/mm^3, HAART use reported in the range of 0–91% of the population, and a variable proportion of patients with a detectable HIV viral load [40].

In this scenario, a largely under-represented group consists of HIV-infected patients with CD4 counts less than 200 cells/mm^3. Indeed, most studies are conducted with relatively small sample sizes and included a meagre number of individuals with low CD4 counts despite this variable representing a major factor in the response to vaccination. Our study had a sample size of 245 patients and included 34 subjects with CD4 counts less than 200 cells/mm^3 in whom the serological response was only 35% (95% CI, 20–54).

Based on the lower seroconversion response to HBV vaccination in HIV-positive individuals, various strategies have been explored to increase the serological response, including the use of vaccine adjuvants [34,41], different routes of administration [24], development of new vaccine formulations [42], and increasing the doses of the vaccine administered [22,24,25]. In this way, current guidelines have been changing to recommend the use of intensified vaccination schedules in the HIV carrier population [8,9,43] because this strategy has shown a higher percentage of seroconversion (close to 80–91%). However, a recent report by Chaikland et al. [44] in Thailand demonstrated that the use of schedules with more doses of the vaccine did not significantly increase the seroconversion rate in individuals with more than 200 CD4 cells/mm^3; instead, this approach induced higher levels of anti-HBs titres after vaccination.

In our study, we found that individuals carrying HIV who were under 45 years of age, who were non-smokers and who had a CD4/CD8 ratio greater than 0.4 had a positive serological response of 86% (95% CI, 81–90). In this manner, we believe that the use of the standard vaccination schedule (HBV vaccine single dose IM at 0, 1 and 6 months) could still play a role in this subgroup of patients, which constituted 18% (44/245) of the study sample. This finding could help reduce the economic impact of using schedules with more doses in the HIV carrier population at risk for HBV infection and could augment adherence to vaccination and completion rates.

Only a small percentage of patients was lost to follow up (2.1%) once the vaccine series was initiated, demonstrating excellent adherence to and completion of the vaccination schedule that was superior to previous data [26–28]. This result could be due to the impact of the inclusion criteria in selecting patients for the study prior to vaccination, which required the individuals to have a history of at least 2/3 assistance visits to an HIV programme. An interesting group to analyze are patients who did not attend the start of the vaccination programme despite being scheduled at least three times. It was not surprising to discover that drug abuse ($p = 0.037$) and a history of poor adherence to HIV control programmes ($p = 0.016$) were determinants of non-attendance to vaccination. However, the association with a higher education level ($p = 0.045$) seemed to be novel. Therefore, these characteristics appear to be of importance if we want to improve the level of compliance for the proposed schedule, which is essential to achieve seroconversion [9].

In conclusion, this study of HBV vaccination with the standard schedule in HIV patients conducted in a public hospital in Chile reports that the serological response is 62% (95% CI, 56–68). This response is coincident with some of the highest response rates described in the literature and confirms the association between seroconversion and the immunovirological status of the patient at the beginning of the vaccination programme as the main determinants of the response. We observed the importance of the CD4 count based on the very low serological response in subjects who had less than 200 CD4 cells/mm^3. Moreover, we describe the CD4/CD8 ratio as a more accurate indicator of the response. We believe that patients with a previous history of drug abuse or HIV treatment dropouts should receive special reinforcement of adherence once the vaccination process is initiated. Similarly, individuals with a higher education level should be subjects of intensified information regarding the benefits of vaccination against HBV towards achieving their vaccination programme assistance.

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Appendix A. Core HIV Study Group

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