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Response to a reinforced hepatitis B vaccination scheme in HIV-infected patients under real-life conditions

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ABSTRACT

Background: HIV-infected patients are at risk of hepatitis B virus (HBV) coinfection, however, respond worse to HBV vaccination (HBV-V) than immunocompetent adults. This study aimed to determine the response to reinforced HBV-V in HIV-infected subjects under real-life conditions.
Methods: HIV-infected patients followed at a Spanish University Hospital who were seronegative for HBV and who received three double-doses (40 μL) of HBV-V at 0, 1 and 2 months were included. Response to HBV-V was defined as HBV surface antibody concentration of ≥10 IU/L 1–12 months after the last HBV-V dose.
Results: Of 332 patients included in the study, 256 (77.1%) showed response to HBV-V. Median (interquartile range) $CD4^+/CD8^+$ ratio among the responders was 0.75 (0.52–1.01) versus 0.61 (0.38–0.84) among the non-responders (p = 0.002). Independent predictors for HBV-V response were: female gender [adjusted odds ratio (AOR): 6.240; 95% confidence interval (95%CI): 1.954–19.925; p = 0.002]; non-smoking [AOR: 2.151; 95%CI: 1.243–3.721; p = 0.006]; a $CD4^+/CD8^+$ ratio ≥0.67 [AOR: 2.580; 95% CI: 1.209–5.505; p = 0.014] and baseline HIV-RNA ≤50 copies/mL [AOR: 2.049; 95%CI: 1.098–3.824; p = 0.024].
Conclusion: Accelerated administration of three double-doses results in considerable high, however still suboptimal, response rates to HBV-V in HIV-infected patients in the clinical practice. A fourth dose should be considered.

1. Introduction

Chronic hepatitis after hepatitis B virus (HBV) represents a major health concern worldwide [1–2]. Major complications of hepatitis B are the development of cirrhosis and hepatocellular carcinoma [3] and 887,000 deaths were attributed to hepatitis B in 2015 [1]. HBV infection still affects over 250 million people worldwide [1] despite the fact that since the early 1980 s, an effective, yeast-derived recombinant hepatitis B vaccine is available [4–5]. The standard vaccination scheme comprises three injections of 10 μg or 20 μg HBsAg at 0, 1 and 6 months [6–7], yielding >95% seroprotection in immunocompetent adults [8–9]. While children are routinely vaccinated in Western countries nowadays, adult vaccination is only recommended for people at risk of HBV infection [10].

HIV-infected patients show an elevated prevalence of HBV infection due to the shared route of transmission and a higher rate of chronicity [11–13], with an increased liver-related morbidity and mortality [14–15]. Additionally, a considerable number of HIV-infected patients show coinfection by hepatitis C virus (HCV), which further promotes liver disease progression [16]. Thus, non-immune HIV-infected individuals clearly benefit from HBV immunization and expert panels recommend vaccination in this population [17–19]. Unfortunately, the rate of seroprotection achieved in HIV-positive patients is sub-optimal and response rates as low as 18% have been described [20]. To overcome this problem, intensified schemes for vaccination have been studied in this population [21]. Indeed, for immunocompromised patients, some guidelines endorse reinforced HBV vaccination (HBV-V) that includes doubling the antigenic load and re-vaccination [17–19]. However, with regards to the HIV-infected population, the application of standard regimens remains the predominant recommendation. In this context, while the Spanish Agency for Medicines and Sanitary Products recommends double dose in patients with renal

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impairment, in HIV positive patients only standard doses are recommended [22]. It does however note that due to insufficient response, additional doses may be warranted. Despite the use of reinforced HBV-V, optimum response rates have not been achieved yet [21].

The aim of this study was to determine the response rates to reinforced HBV-V in HIV-infected patients under real-life conditions, as well as to identify factors associated with response.

2. Patients and Methods

2.1. Study population and vaccination schemes

This is a retrospective cohort analysis conducted at the infectious diseases unit of the Virgen del Rocío University Hospital in Seville, Spain, where clinical data of HIV-infected patients are prospectively recorded in electronic medical records (ACyH1, Betek 43 SL, Spain). All patients were included in the analysis if they (i) were tested seronegative for HBsAg, anti-HBs and anti-HBc; (ii) received three double doses (40 μg HBsAg) of vaccine against HBV (Engerix B, GlaxoSmithKline, S.A., Madrid, Spain) at 0, 1 and 2 months and (iii) had at least one determination of anti-HBs between 1 and 12 months after the last vaccination dose. According to inclusion criterion (i), patients with isolated positive anti-HBc antibody without detectable anti-HBs were excluded from the study.

2.2. Laboratory determinations

Plasma HIV-RNA was quantified using real-time PCR (COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, Roche Diagnostics, Basel, Switzerland; limit of detection: 20 copies/mL). HBV serological markers (anti-HBs, anti-HBc and HBsAg) were determined using an HBV enzyme-linked immunosorbent assay (ELISA) (Siemens Healthcare Diagnosis, Malvern, Pennsylvania).

2.3. Statistical analysis

The outcome variable was response to intensified HBV vaccination between 1 and 12 months after the last dose. A threshold of 10 IU/L for anti-HBs was used to define successful vaccination [23]. A descriptive statistic was conducted where continuous variables were expressed as median, (IQR) and [range], while categorical variables were shown as number (percentage). Categorical factors that potentially impact on response were analysed using the χ^2 test or the Fisher's exact test, when applicable and 95% confidence intervals (CI_{95}) were calculated. Continuous variables were analysed using the Student́s *t*-Test or the Mann-Whitney test. In order to determine the most adequate cut-off value of continuous variables to predict the primary outcome, the Youden Index *J* was calculated by means of receiver-operator characteristic (ROC) curves [24]. Finally, a multivariate logistic regression analysis was conducted, adjusting for age, sex, as well as for those factors that were associated with a $p < 0.2$ in the univariate analysis. Statistical analysis was performed using the SPSS statistical software package release 23.0 (IBM, Chicago, IL, USA) and STATA 9.0 (StataCorp LP, College Station, TX, USA).

2.4. Ethical aspects

The study was designed and performed according to the Helsinki declaration and was approved by the Ethics Committee of the Virgen del Rocío University Hospital (Seville, Spain). All patients gave their written informed consent before being included in the study.

3. Results

3.1. Study population

Between May 2006 to January 2017, a total of 3550 patients attended. Of these, 332 patients were eligible for the study. The selection algorithm is displayed in Fig. 1. Serological determination within the first three months after the last HBV-V dose was available in 302 (90.1%) subjects. Two hundred and seventy (81.3%) patients were on antiretroviral therapy (ART), of whom 243 (90%) patients presented HIV-RNA < 50 copies/mL. The remaining 27 patients had a median (IQR) [range] viral load of 84 (67–229) [51–693] copies/mL. Among the patients not on ART, 59 (17.8%) were ART-naïve, showing a median (IQR) [range] HIV-RNA of 24800 (6350–5540) [467–384000] copies/mL. Baseline characteristics are displayed in Table 1.

3.2. Response to reinforced HBV-V

Two hundred and fifty-six patients (77.1%; CI_{95}: 72.2%-81.5%) responded to reinforced vaccine against HBV. Median (IQR) [range] anti-HBs titre was 252 (71–1000) [8–44] IU/L among those who showed response. The response rates according to different baseline characteristics were: 61 (93.8%; CI_{95}: 85%-98.3%) women versus 195 (73%; CI_{95}: 67.2%-78.3%) men, $p < 0.000$; 159 (82.8%; CI_{95}: 76.7%-87.9%) non-smokers versus 97 (69.3%; CI_{95}: 60.9%-76.8%) smokers, $p = 0.004$; 197 (80.4%; CI_{95}: 74.8%-85.2%) of those who presented HIV viral load (VL) $\leq$ 50 copies/mL at baseline versus 59 (67.8%; CI_{95}: 56.9%-77.4%) who did not, $p = 0.016$, and 234 (77.2%; CI_{95}: 72.1%-81.8%) versus 22 (75.2%; CI_{95}: 56.5%-89.7%) of those with a $CD4^+$ T-cell count $\geq$ versus < 350 cells/μL, respectively, $p = 0.867$. A total of 176 (53%) subjects showed undetectable HIV viral load during 12 months prior to the first vaccine dose. Of these, 144 (81.8%; CI_{95}: 75.3%-87.2%) showed response to HBV-V as compared to 112 (71.8%; CI_{95}: 64%-78.7%) who did not, $p = 0.03$. The median (IQR) [range] $CD4^+$ cell count of those who responded to HBV-V was 611 (475–817) [105–1646] cells/μL versus 542 (426–729) [85–1231] cells/μL among those who did not respond, $p = 0.022$. The corresponding figures for the $CD4^+/CD8^+$ ratio were 0.75 (0.52–1.01) [0.16–3.96] versus 0.61 (0.38–0.84) [0.08–1.81], $p = 0.002$.

Among those patients who showed response, 13 (5%; CI_{95}: 2.7%-8.46%) had a subsequent negative anti-HBs determination before reaching 12 months after the last dose. According to HIV viral load at first dose of their immunization, 8/61 (13.1%; CI_{95}: 5.8%-24.2%) patients with detectable HIV viremia versus 5/197 (2.6%; CI_{95}: 0.83%-5.8%) individuals with undetectable HIV viral load lost the protection against HBV. Neither the baseline $CD4^+$ T-cell count nor the $CD4^+/CD8^+$ ratio reached the pre-defined cut-off for statistical significance ($p < 0.05$) when associated with loss of protection.

The area under the ROC (AUROC) curve for the capacity of the $CD4^+$ T-cell count to predict response to HBV-V was 0.587 (CI_{95}: 0.515–0.658; $p = 0.022$). The corresponding AUROC for the $CD4^+/CD8^+$ ratio was 0.617 (CI_{95}: 0.544–0.658; $p = 0.002$). Due to the higher association to response as compared to the $CD4^+$ T-cell count, the $CD4^+/CD8^+$ ratio was used for further analysis. This parameter yielded a maximum *J* of 0.195 according to a $CD4^+/CD8^+$ ratio of 0.67. Response rates according to this cut-off value were 82.9% (CI_{95}: 76.6%-88.1%) among the 181 patients with a $CD4^+/CD8^+$ ratio $\geq$ 0.67 and 70.2% (CI_{95}: 62.2%-77.4%) among the 151 subjects with a $CD4^+/CD8^+$ ratio < 0.67, respectively ($p = 0.006$). Response rates to HBV-V considering $CD4^+/CD8^+$ ratio in combination with further predictors of response are displayed in Fig. 2. Detailed univariate and multivariate analyses of the predictors for response to HBV-V are shown in Table 2 and anti-HBs titres according to predictive parameters are shown in Fig. 3.

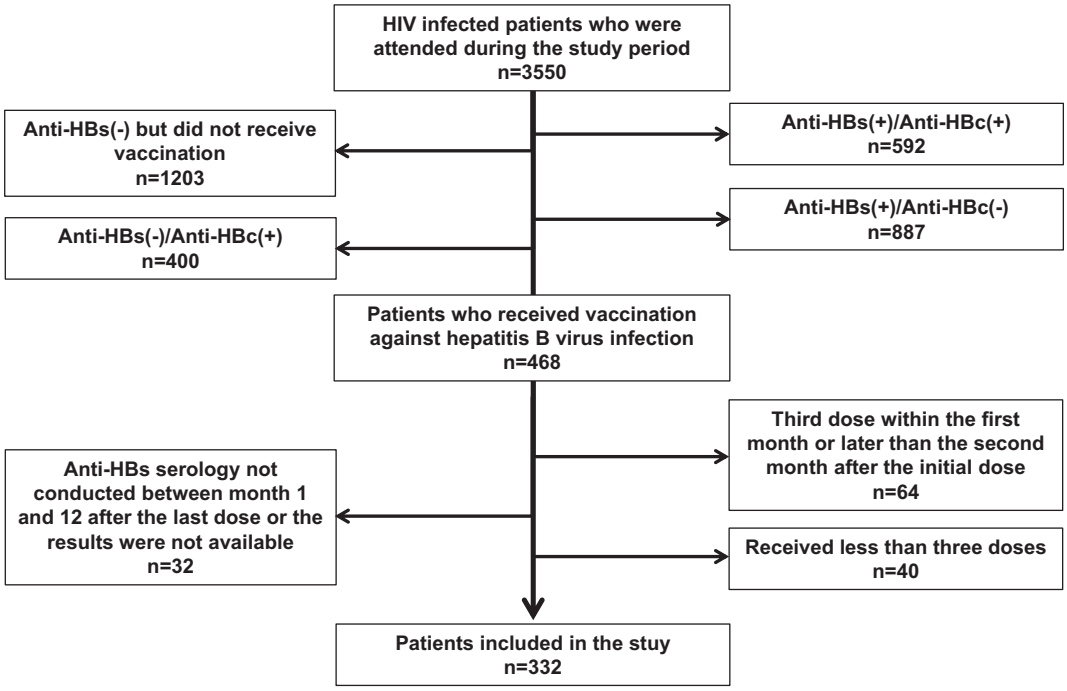

Fig. 1. Flow chart for recruitment of the patients attended during the study period.

Table 1
Baseline characteristics of the patients vaccinated against hepatitis B virus (n = 332).

Parameter	Value
Age (years)[a]	40 (33–46) [16–44]
Male gender, no. (%)	267 (80)
Caucasians, no. (%)	315 (95)
Transmission route, no. (%)	
Homo- or bisexual contact	194 (58)
Heterosexual contact	100 (30)
Injecting drug use	23 (6.9)
Others or unknown	15 (5.1)
Anti-HCV (+), no. (%)	29 (8.7)
Detectable HCV-RNA, no. (%)	17 (5.1)
Cirrhosis, no. (%)	6 (1.8)
Creatinine (mg/dL)[a]	0.86 (0.77–0.96) [0.45–1.39]
Tobacco smokers, no. (%)	140 (42)
Alcohol consumption > 45 g/day, n (%)[b]	21 (10)
HIV-RNA < 50 copies/mL, n (%)	245 (74)
$CD4^+$ T-cell count, cells/μL[a]	585 (453–774) [85–1646]
$CD4^+/CD8^+$ ratio[a]	0.73 (0.47–0.97) [0.08–3.96]
Concomitant HAV vaccination, n (%)	57 (17)

[a] Median (interquartile range) [range];
[b] available in 205 patients. HCV: hepatitis C virus; VL: viral load; HAV: hepatitis A virus.

4. Discussion

In the present study, the observed response rate to reinforced HBV-V in a cohort of HIV-infected individuals was considerably high, but still sub-optimal. However, rates of seroprotection substantially increased in subgroups of patients presenting different, in part HIV-related, predictors of response, while patients with an unfavourable profile would likely benefit from additional doses.

In general, response to HBV-V reported in the HIV-coinfected population varies extensively due to the heterogeneous study designs and patient characteristics, as it has been reviewed extensively in recent reports [21,25]. Response rates to three single doses of HBV-V at 0, 1 and 6 months oscillate between 41% and 47% in HIV-infected patients [26–31], and up to 62% in a more recent study [32]. At our center, historic response rates to the standard vaccination scheme were low as confirmed in several cross-sectional internal studies. One of the studies conducted in 2004 found a seroconversion rate of 39.1% in 18 out of 46 patients, of whom 64% received ART. A follow-up study conducted one year later in 103 patients of whom 45% showed undetectable HIV-RNA found a seroconversion rate of 51%; response rates declined drastically in patients with a $CD4^+$ T-cell count below 200 cells/μL (15.4%) and 300 cells/μL (21.5%) [33]. These unacceptable response rates formed the basis of enforcing the vaccination scheme to double-dose at 0, 1 and 2 months as supported by the recommendations for other response-impaired populations, as dialysis patients [34]. This change in patient management lead to an overall response rate of 77% as presented in this work, somewhat higher as reported by Mena et al, who observed 69% of response when administering HBV-V at a schedule of 0, 1 and 2 months. However, it is to note that some, but not all of the patients of the Mena study received a double dose [35]. Enhancing the dose is a recognised strategy to augment response to HBV-V. A meta-analysis of five studies conducted in patients with a heterogeneous $CD4^+$ T-cell count and ART application (65%-90%), a pooled odds ratio of 1.96 (95% CI: 1.47-2-61) for increased response rates was determined when high (40 μL) and low (10–20 μL) doses were compared [36].

Likewise, in a small prospective study, Cruciani et al. report a response rate as low as 60% after a round of vaccination of 40 μg anti-HBs at 0, 1 and 2 months in a population with 80% receiving ART and a median $CD4^+$ T-cell count of 533 cells/μL. Importantly, after a fourth dose, 73% of the initial non-responders showed seroprotection and an overall response of 89% was observed after administration of up to three further doses [37]. Similarly, elevated response rates after three versus four double-doses (83% and 91%) were reported from a cohort study in patients with a mean $CD4^+$ T-cell count of 385 cells/μL of whom 80% received ART [38]. Finally, data from a randomized clinical trial conducted in ART-receiving patients with a median $CD4^+$ T-cell count of 544 cells/μL and where 20–40 μL anti-HBs was administered at 0, 1, 2 and 6 months further support the profit of reinforced vaccination schemes, since response rates of 93–96% are reported [39]. In summary, based

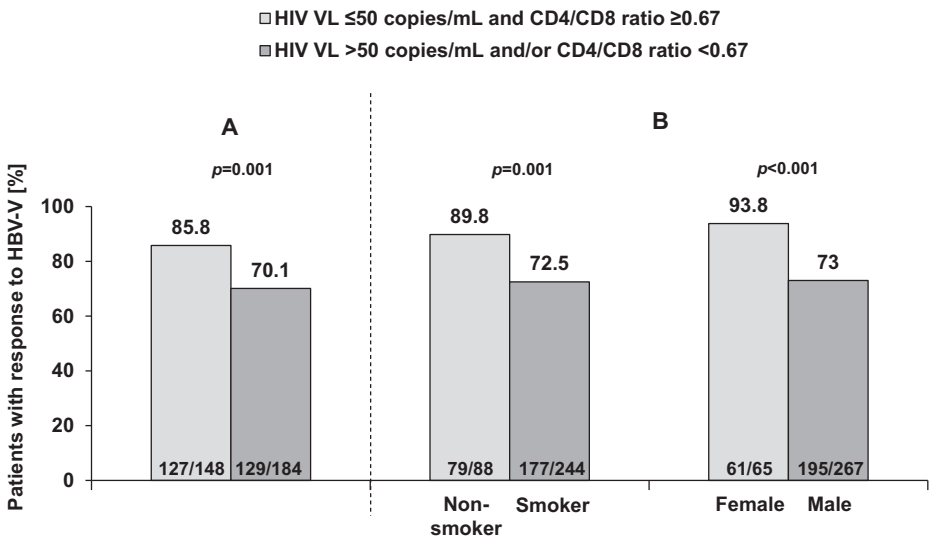

Fig. 2. Response rates to reinforced hepatitis B virus vaccine (HBV-V) according to the $CD4^+/CD8^+$ ratio and the HIV viral load (VL) at the moment of the first dose in the overall population (A) and after further classification according to smoking habit and gender (B).

Table 2
Univariate and multivariate analysis to identify factors associated with response to reinforced hepatitis B virus vaccination (HBV-V) considering either the CD4/CD8 ratio (Model 1) or the total CD4 cell count (Model 2) (n = 332).

				Model 1		Model 2	
Parameter	n	Response,n (%)	*p* univariate	AOR (CI_{95})	*p* multivariate	AOR (CI_{95})	*p* multivariate
Age[a]							
>40 years	166	129 (78)	0.794	0.969(0.939–1)	0.053	0.971 (0.941–1.002)	0.069
≤40 years	166	127 (77)		1		1	
Age (per 10 years increment)	366			0.733 (0.536–1.004)		0.748 (0.547–1.024)	
Gender							
Female	65	61 (94)	<0.001	6.240 (1.954–19.925)	0.002	6.348 (1.990–20.256)	0.002
Male	267	195 (73)		1		1	
Homo- or bisexual contact							
No	133	108 (81)	0.147	1.172 (0.614–2.238)	0.630	1.070 (0.560–2.045)	0.838
Yes	199	148 (74)		1		1	
Anti-HCV positive							
No	303	232 (77)	0.448				
Yes	29	24 (83)					
Cirrhosis							
No	326	251 (77)	1				
Yes	6	5 (83)					
Tobacco smoker							
No	192	159 (83)	0.004	2.151 (1.243–3.721)	0.006	2.187 (1.262–3.791)	0.005
Yes	140	97 (69)		1		1	
Alcohol consumption							
>45 g/day	21	17 (81)	1				
≤45 g/day	184	144 (78)					
Plasma HIV-RNA							
>50 copies/mL	87	59 (69)	0.016	2.049 (1.098–3.824)	0.024	2.180 (1.173–4.049)	0.014
≤50 copies/mL	245	197 (80)		1		1	
$CD4^+/CD8^+$ ratio[a]							
≥0.67	181	150 (83)	0.006	2.580 (1.209–5.505)	0.014		
<0.67	151	106 (70)		1			
$CD4^+/CD8^+$ ratio[a] (per 0.2 increment)				1.209 (1.039–1.407)			
$CD4^+$ T-cell count[a]							
>500 cells/μL	303	179 (80)	0.08			1.002 (1–1.003)	0.017
≤500 cells/μL	29	77 (71)				1	
$CD4^+$ T-cell count[a] (per 100 cells/ μL increment)						1.221 (1.004–1.486)	
Previous HBV-V							
No	270	207 (77)	0.689				
Yes	62	49 (79)					
Concomitant HAV-V							
No	275	215 (78)	0.307				
Yes	57	41 (72)					

AOR: adjusted odds ratio; CI: confidence interval; HCV: hepatitis C virus; HAV-V: hepatitis A virus vaccination [a]entered as continuous variable in the multivariate analysis.

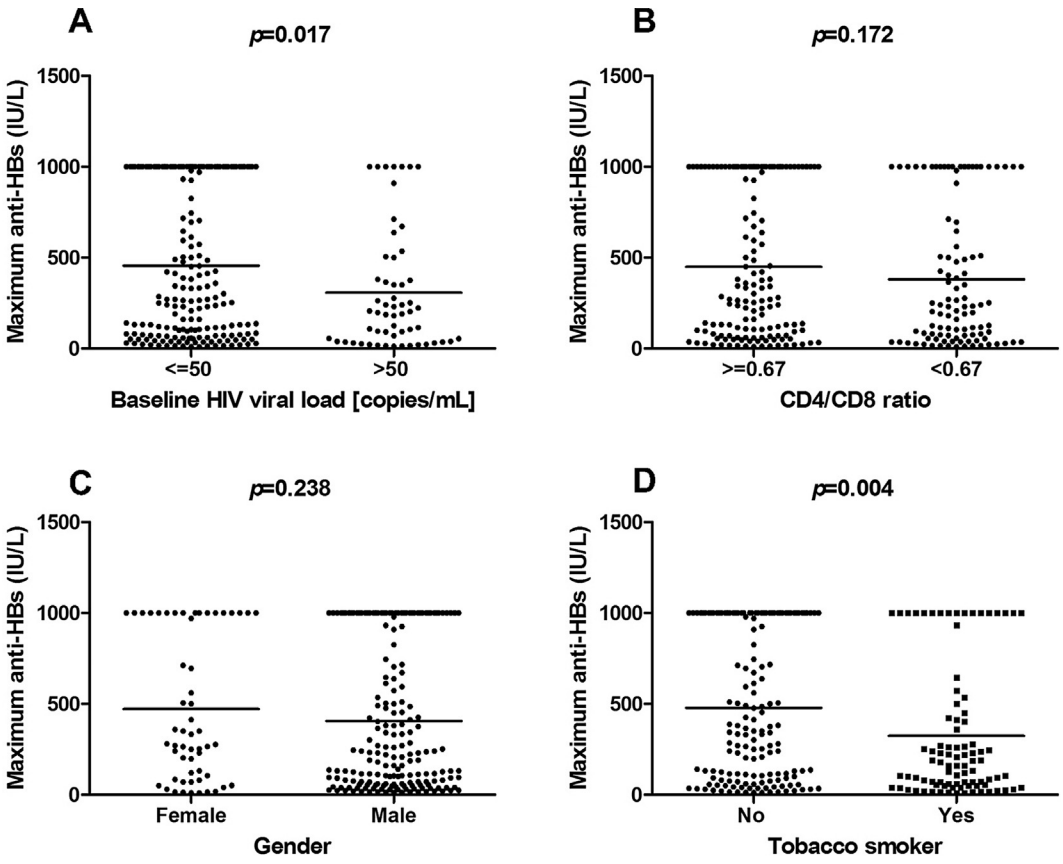

Fig. 3. Maximum anti-HBs levels achieved between 1 month and 12 months after the last vaccination dose in those subjects who showed a response as a function of the baseline HIV viral load (VL) (A), the $CD4^+/CD8^+$ ratio (B), gender (C) and cigarette smoking (D). There was no association between the anti-HBs titre and age (p = 0.520).

on the literature data and confirmed by the present study conducted in the clinical practice, there appears to be a clear benefit of reinforced HBV-V. Furthermore, patients who do not respond to this reinforced HBV-V should be considered for additional doses.

The present study identified several independent predictors for response to reinforced HBV-V. Among the HIV infection-related factors, a low HIV VL and an elevated $CD4^+$ T-cell count was associated with higher response rates. Likewise, higher anti-HBs titres were observed in these subgroups. These results were expected, since HIV viremia and $CD4^+$ T-cell count can be regarded classic predictors of response to HBV-V [21,25] and indeed, these parameters represent the pillars of guidelines for HBV-V strategies in HIV-infected patients [17–18]. Interestingly, the present work found the $CD4^+/CD8^+$ ratio to be more predictive than the $CD4^+$ T-cell count alone. This confirms findings of Fuster and colleagues who recently reported the $CD4^+/CD8^+$ ratio as more accurate predictor for response to HBV-V administered in a standard vaccination scheme [32]. Additionally, in a study conducted by Buggert and colleagues, the $CD4^+/CD8^+$ ratio was found a better surrogate of HIV-induced T-cell pathogenesis as compared to other laboratory parameters, including the CD4 cell count [40]. Thus, the $CD4^+/CD8^+$ appears to be more adequate for the prediction of response to HBV-V and may be considered in future guidelines. Finally, and in accordance with previous studies [30–32,37,41–44], female gender, younger age, as well as no smoking, have been identified as independent predictors of response to reinforced HBV-V. Importantly, almost perfect response rates can be observed when these parameters are combined. Taken these data together, it can be suggested that subjects with favourable HIV-related factors should not be spared vaccination, especially when they present further predictors of response to reinforced HBV-V. In subjects with a low $CD4^+/CD8^+$ ratio in combination with high HIV viremia and/or smoking habit or male gender, i.e. those presenting an unfavourable profile, it is not advisable to defer HBV-V, but rather to vaccinate and monitor anti-HBs response. Furthermore, these patients should be considered candidates for a routine additional dose.

The main limitation of this study is the retrospective design of the analysis. Due to this, no specific follow-up schedule for serological determination was established and patients classified as non-responders could have had an unmeasured but positive response at earlier stages. However, anti-HBs was measured according to the HIV follow-up schedule and patients are routinely cited at least every six months. Indeed, anti-HBs serology was available in more than 90% of the patients within the first three months after the last dose. Still, prospective studies are warranted to support the herein described findings. A further limitation of the present study is that less than 9% of the patients presented levels equal or below 350 cells/μL and although a trend to lower response in these patients was observed, significance was not reached due to the lack of statistical power. This low cut-off value should not be used to condition HBV-V dosage since a considerable proportion of individuals with a $CD4^+$ T-cell count >350 cells/μL did not respond even to reinforced HBV-V, as shown in the present work.

In conclusion, in the HIV-infected population, real-life response to double-dosed, accelerated vaccine against HBV is considerably high, however still improvable. Subjects with favourable HIV viremia and $CD4^+/CD8^+$ cell count should receive this reinforced HBV-V scheme, especially when additional favourable factors are present. All persons should be tested for anti-HBs response one to three months after completion of vaccination, and those with response less 10 mIU/mL should receive a fourth dose. In facilities where

adherence to clinical follow-up is suboptimal, a fourth dose without prior testing may be considered. Especially those patients with an unfavourable profile, a dose at six months is likely to substantially improve seroprotection.

Conflicts of interest

All authors: None to declare.

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