Vaccination against hepatitis B with 4-double doses increases response rates and antibodies titers in HIV-infected adults

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ABSTRACT

Background: Antibody responses to standard regimens of hepatitis B (HBV) vaccination are lower in HIV-infected subjects and the best hepatitis B vaccine schedule in this population is not known.
Objective: To assess the immunogenicity and to evaluate predictors of serologic response of a modified regimen of a HBV recombinant vaccine in a cohort of HIV-infected subjects.
Methods: HIV-infected subjects received 4 doses ($40\,\mu g$) of a recombinant HBV vaccine at 0, 1, 2 and 6 months. Demographic information as well as CD4 cell count and plasma viral load were assessed at baseline. Protective and strong responses were defined as an anti-HBs titer $\geq 10\,mIU/mL$ and $\geq 100\,mIU/mL$, respectively and were evaluated one month after the third and the fourth doses.
Results: 163 HIV-infected individuals were evaluated 67 (40%) were male and median age was 37 years. Median CD4 cell count was 385 cells/mm^3 and 113 (70%) had undetectable HIV-1 viral load. Protective antibody response was observed in 83 and 91% and a strong antibody response was observed in 62 and 80% of the subjects after 3 and 4 doses, respectively.

In a multivariate logistic model undetectable HIV-1 viral load and higher CD4 cell counts were independent predictors of a strong antibody response after 4 doses. Patients with undetectable HIV viral load were almost 3 times more likely to have anti-HBs titers above $100\,mIU/mL$ than those with detectable viral load.
Conclusions: A 4-double-dose regimen of a recombinant HBV vaccine increased response rates and determined higher antibody titers which may translate in prolonged protection agains HBV. Inclusion of a fourth dose of HBV vaccine for HIV-infected subjects should be considered in the public health setting.

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1. Introduction

Hepatitis B virus (HBV) co-infection is responsible for high morbidity and mortality among Human Immunodeficiency Virus-1 (HIV)-infected subjects [1,2]. In recent years, deaths attributable to viral hepatitis complications are among the leading causes in this population [1]. Thus, improving HBV prevention by means of vaccination of people living with HIV/AIDS is of major importance. However, protective antibody responses to standard regimens of hepatitis B vaccination are lower among these subjects than in the general population, particularly in adulthood [3–8]. Moreover, these individuals experience more rapid decline of antibody titers and the clinical implications such as higher carriage rates.

Currently, there are no data to determine the best hepatitis B vaccine schedule for HIV-infected subjects. Several authors reported that a vaccination schedule consisting of 3-doses of $40\,\mu g$ of antigen (double the usual dose for adults) significantly improves the immune response, particularly in patients with higher CD4 cell count [9–12]. Similar approaches have proved effective in patients undergoing hemodyalisis and the other immunocompromised subjects [13].

The aim of this study was to assess the immunogenicity and safety of a 4-dose regimen with $40\,\mu g$ of recombinant vaccine and to evaluate predictors of serologic response and antibody titers in a cohort of HIV-infected subjects in Rio de Janeiro, Brazil.

2. Patients and methods

2.1. Study design, setting and study population

The study was conducted at the School of Medicine and the Hospital Universitário Clementino Fraga Filho (HUCFF-UFRJ) of the

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Universidade Federal do Rio de Janeiro from July 2005 to May 2009. A detailed description of study methods and preliminary data have been published [14] and are briefly presented in this section. An uncontrolled cohort of HIV-1-infected subjects was recruited at the outpatient unit of that hospital. HIV-infected adults subjects, 20–60 years of age, without serological evidence of previous HBV infection or immunization were invited to participate. Subjects were excluded if pregnant or if they had evidence of hepatitis C infection, renal or hepatic chronic disease, malignancy or allergy to vaccine components.

A double dose (40 μg) of a recombinant DNA HB vaccine (EUVAX B – LG Life Sciences, Korea) was given intramuscularly in the deltoid region at study entry and at 1, 2 and 6 months thereafter. Blood samples for hepatitis B serology were collected prior to the first vaccination and 30–60 days after the third and fourth doses. Relevant clinical data were recorded in case report forms designed for the follow-up study. The study protocol was approved by the institutional review board of the School of Medicine and HUCFF-UFRJ and written consent forms were obtained from all participants.

2.2. Study variables and outcome

The following demographic and clinical information were assessed at baseline: age, gender, body mass index – BMI [15], smoking status, CDC Case Definition for HIV Infection Among Adults [16], HAART use, CD4 cell lymphocyte count and HIV-1 plasma viral load (PVL).

Serological assays of previous HBV infection (anti-HBc, anti-HBs and HBsAg) were performed at baseline, according to manufacturers' recommendations. Anti-HBs titers (in mIU/mL) were measured in blood samples using commercial immunoassays (AxSYM® AUSAB® – Abbott, USA) 30–60 days after the third and fourth doses. CD4 cell count, HIV-1 viral load and other laboratory tests for routine follow-up were performed at HUCFF-UFRJ. The detection limit for HIV-1 viral load was 80 copies/mL.

The main analysis assessed the rate and factors associated with seroprotection, defined by anti-HBs titers ≥ 10 mIU/mL [16] after the third and fourth doses. A secondary analysis assessed the rate and factors associated with strong antibody response, defined as anti-HBs ≥ 100 mIU/mL (Hadler, 1986; [17–19]) after the third and fourth doses.

Signs and symptoms, both systemic and on the injection site, were recorded following vaccination to monitor the reactogenicity.

2.3. Statistical analysis

Univariate analyses were performed using x^2 or Fisher exact test for categorical variables, and Student's t test or Wilcoxon test for continuous variables. Reverse cumulative distribution of the logarithm (base 10) of antibody titers based on serological tests after the third and the fourth doses of the vaccine was plotted [20]. Seroconversion rates were estimated and the association with relevant covariates was measured by the odds ratio (OR) and 95% CIs. Variables with a p value <0.10 in the univariate analysis were included in the multivariate analyses. We used a stepwise approach to assess factors independently associated with outcome. All the p values are 2-sided.

3. Results

3.1. Study population

One hundred and seventy four HIV-infected individuals (101 females and 73 males) were evaluated for participation in the study. One subject was excluded due to positive anti-HBc and anti-HBs

Table 1
Baseline characteristic of the 163 patients.

Variables	Median (IQR), n/n (%)
Median age (years)	37 (30–43)
Gender (male)	67/163 (40%)
BMI (kg/m^2)	25 (22–27)
BMI categories (kg/m^2) (%)	
≥ 25 kg/m^2	81 (49%)
<25 kg/m^2	82 (50%)
Smoke	29 (18%)
HAART use (%)	131/163 (80%)
Time on HAART (months)	19 (7–27)
Median CD4 (cells/mm^3) (range)	385 (293–485)
CD4 categories (cells/mm^3) (%)	
<200	5 (3%)
200–349	63 (39%)
350–499	58 (35%)
≥ 500	37 (23%)
HIV viral load below detection limit (≤ 80 copies/mL)	113 (70%)

BMI, body mass index; HAART, highly active antiretroviral therapy.

after re-screening. One woman was found to be pregnant. Nine subjects did not complete the vaccination schedule (5, 1 and 3 subjects received only 3, 2 and 1 doses, respectively) and were excluded from this analysis. We present data on 163 patients who completed the study protocol requirements (Table 1). No withdrawals were attributed to adverse events, and those were mild or moderate pain at the injection site.

Study subjects were predominantly females, median age 37 years, non-smokers, with substantial proportion of overweight or obese individuals. The great majority were on HAART, had CD4 cell counts above 350 cells/mm^3 and HIV load bellow detection limit.

3.2. Serologic response and determinants

Protective antibody response (anti-HBs ≥ 10 mIU/mL) was observed in 136 (83%) and 148 (91%) of the subjects after 3 and 4 doses, respectively. Fig. 1 shows a substantial increase in the proportion of strong immune responses after the fourth dose. Individuals with an adequate serologic response after 4 doses were comparable to non-responders in respect to gender, age, BMI, smoking status, use of HAART, CD4 cell count and PVL. 72% of responders showed HIV-1 viral load below detection limit, compared with 47% non-responders ($p = 0.05$) (data not shown). After adjustment for confounding of relevant covariates in the multivariable model this variable was the only predictor of seroconversion with 4 doses of the vaccine. Patients with undetectable viral load
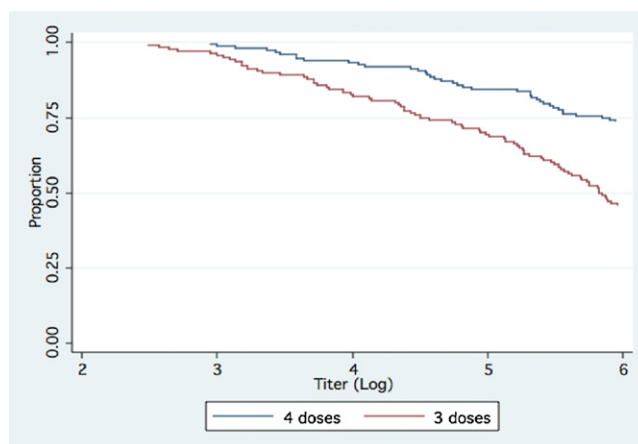

Fig. 1. Reverse cumulative distribution plot of proportion of subjects who showed seroprotection after 3 and 4 doses and antibody titers (log).

Table 2
Predictors of serologic response (anti-HBs titer ≥ 10 mIU/mL) among 163 HIV infected subjects after four doses regimen of HBV vaccination–logistic model.

Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex (male)	1.05 (0.36–3.11)	
Age (years)	0.96 (0.90–1.02)	0.95 (0.89–1.01)
BMI (kg/m^2)	0.93 (0.82–1.06)	
Smoke	0.85 (0.22–3.24)	
Baseline CD4 (cells/mm^3)	1.25 (0.84–1.87)	
HIV viral load ≤ 80 copies/mL	2.88 (0.98–8.45)	3.13 (1.05–9.35)

BMI, body mass index.

at baseline were 3 times more likely to show a protective response than those with detectable viral load (Table 2).

3.3. Strong antibody response and determinants

Strong antibody response (anti-HBs ≥ 100 mIU/mL) was observed in 101 (62%) and 131 (80%) of the subjects after 3 and 4 doses, respectively ($p < 0.001$).

Individuals with a strong antibody response after 4 doses were comparable to non-responders in respect to gender, age, BMI, smoking status, use of HAART, CD4 cell count and PVL. More strong responders showed HIV-1 viral load below detection limit and higher CD4 cell count, compared with non-responders. Study subjects with stronger immune responses to the third dose of the vaccine had on average slightly higher baseline CD4 cell counts (Fig. 2). After the fourth dose of the vaccine the distribuition of CD4 cell counts was very similar in responders and non-responders to the vaccine (Fig. 3).

Adjusting for the effects of relevant covariates in the multivariate model, HIV-1 viral load below detection limit and higher CD4 cell counts were the strongest predictors of strong antibody response (Table 3). Patients with undetectable viral load at baseline were almost 3 times more likely to show anti-HBs titers above 100 mIU/mL than those with detectable viral load. Analogously higher baseline CD4 cell counts were also associated with higher anti-HBs titers.

Among 95 subjects with CD4 ≥ 350 cells/mm^3, 85% and 93% showed protective response, after 3 and 4 doses, respectively. Seventy-three and 85% showed a strong antibody response, after 3 and 4 doses, respectively.
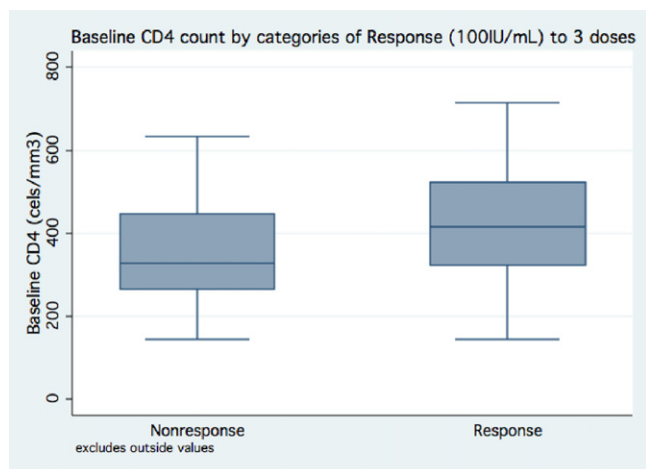

Fig. 2. Baseline CD4 cell count by categories of response (anti-HBs ≥ 100 mIU/mL and no response) to 3 doses.
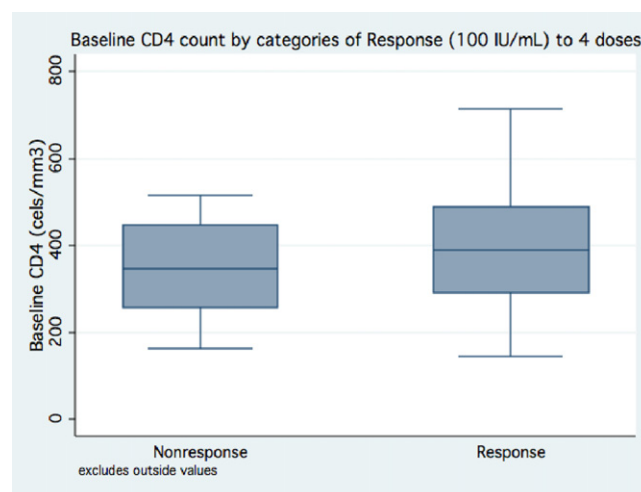

Fig. 3. Baseline CD4 cell count by categories of response (anti-HBs ≥ 100 mIU/mL and no response) to 4 doses.

4. Discussion

Our data showed that higher seroconversion rates were achieved in HIV-infected subjects with 4-double doses of a recombinant HBV vaccine on a 0–1–2–6-month schedule, compared to three-dose schedule. The 4-double-dose regimen also induced higher antibody titers which may result in prolonged protection agains HBV.

The proportion of subjects with evidence of seroprotection obtained in our study was similar to that reported by 2 others groups that also used 4 or more doses and higher antigen dose [21,22], and confirmed results obtained in our pilot study [14]. Moreover the seroprotection rates obtained with the regimen used in this study approached those seen with standard schedules in immunocompetent subjects [18,23,24]. This 4-double-dose-schedule is already recommended for subjects in hemodialysis programmes, based on evidence of HBV seroprotection in high risk populations similar to that obtained in HBV vaccination in healthy adult [13].

Seroprotection rates observed in our study after 3 monthly double doses were effective in getting high rates of response and anti-HBs titers.

After the fourth dose we observed an improvement both in seroprotection and in strong antibody response when compared to what was observed after the third dose. That had also been observed in patients with renal diseases [13,26] and support the recommendation of high anti-HBs titers in specific groups of immunocompromissed patients

As expected, subjects with HIV-1 viral load below detection limits had a higher probability of achieving protective titers (OR = 3.13; 95% IC 1.05–9.35) when compared with those with detectable HIV viral load. The suppression of plasmatic HIV-1 viral load has been

Table 3
Predictors of strong antibody response (anti-HBs titer ≥ 100 mIU/mL) among 163 HIV infected subjects after four doses regimen of HBV vaccination–logistic model.

Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (years)	0.96 (0.92–1.01)	0.96 (0.92–1.00)
Sex (male)	0.87 (0.40–1.90)	0.72 (0.30–1.69)
Baseline CD4 (cells/mm^3)	1.43 (1.05–1.96)	1.44 (1.04–1.99)
HIV viral load ≤ 80 copies/mL	2.85 (1.29–6.32)	2.87 (1.26–6.56)
BMI	0.93 (0.84–1.02)	0.94 (0.84–1.04)

BMI, body mass index.

reported as one of the variables associated with improved vaccination responses [5,6,8,9,12,21,25,27]. Improved immune responses to neoantigens have been observed in HIV individuals after HAART induced viral suppression [6,28]. In addition, restoration of number and function of the T lymphocytes and improved T-cell-mediated response to specific antigens has been reported [27,29]. When we examined seroprotection levels (anti-HBs titer ≥ 10 mIU/mL) our results did not show association of CD4 cell count levels with vaccination responses reported by the others authors [3,5,8–12].

Interestingly, both HIV-1 viral load suppression (OR = 2.87; 95% CI: 1.26–6.56) and higher CD4 cell count (OR = 1.44; 95% CI: 1.04–1.99) were independent predictors of a strong antibody response (anti-HBs titer ≥ 100 mIU/mL) after 4 double doses. Among patients with CD4 cell counts greater than 350 cells/mm^3, a strong antibody response was higher after 4 doses than after 3 doses. This is in line with previous reports of higher anti-HBs titers associated with higher CD4 levels [11,12]. Altogether, there is evidence to support the recommendation to delay HBV vaccination until HIV-1 viral load suppression and CD4 cells count greater than 350 cells/mm^3 are obtained after HAART introduction.

Antibody persistence is correlated with highest anti-HBs levels after vaccination [17,21,23,30,31]. Among immunocompetent subjects the protection against HBV is preserved by means of the subject's immune memory – in whom ever after decrease of antibody detection, or even after antibody loss [32]. Conversely, in immunodeficient subjects such decline may correspond to a loss of protection [17,26,33,34]. Therefore, to assess immunization outcome anti-HBs ≥ 100 mIU/mL titer is often prefered as a correlate of larger and longer protection against infection, specially in high risk subjects [17,19].

The length of follow-up in our study was not long enough to confirm those assumptions. In addition, we did not have a external three-dose HIV-infected group to confirm the differences observed between the 3 and 4 dosis group. Despite those limitations, the high frequency of antibody responses with the proposed regimen in our study suggested that there was in fact an improved response.

In immunocompetent subjects, the third dose of the standard anti-HBV vaccination is necessary to increase response rate and offer long-term protection [35]. For HIV-infected subjects, the US Advisory Committee on Immunization Practices (ACIP) recommends vaccination against HBV with standard schedule (3 doses of 20 mg of hepatitis B virus recombinant vaccine), followed by two or three additional doses for those subjects that do not achieve adequate serologic response [7]. This strategy includes multiple patient visits and laboratory work that may compromise adherence, especially in resource poor settings. In contrast, others guidelines recommend that HIV-positive adults receive a larger dose of HBV recombinant vaccine [35,36].

In summary, our data confirm that a fourth dose, in a 0–1–2–6-month regimen of $40\,\mu g$ per dose significantly improves both response rates and magnitude of immune response to recombinant hepatitis B vaccine in HIV-infected patients, without increasing reactogenicity. This strategy should be considered in the public health setting in order to reduce the burden of hepatitis B virus related disease among people living with HIV.

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