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Independent clinical predictors of impaired response to hepatitis B vaccination in HIV-infected persons

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Summary

Protective response rates to hepatitis B (HB) vaccination have been reported as low as 18-62% in HIV-infected persons. The relative importance of various predictors for this poor response has not been fully characterized. In this retrospective cohort study, we examined the relationship between clinical characteristics and vaccine non-response (HB surface antibody <10 IU/L) among patients attending an urban HIV clinic. Among the 97 patients who met the inclusion criteria, 43 (44%) developed a protective antibody response. In multivariate analyses, age >40 years (odds ratio [OR] 3.03 [95% confidence interval [CI], 1.14-8.06]; $P = 0.026$) and alcohol abuse (OR 4.92 [95% CI, 1.72-20.89]; $P = 0.007$) were independent predictors of failure to develop vaccine response. In addition, CD4 nadir <200 (OR 7.24 [95% CI, 1.91-27.41]; $P = 0.004$), rather than CD4 current to vaccination, remained a strong independent risk factor. Patients with HIV viral suppression on highly active antiretroviral therapy had a significantly lower rate of vaccine failure (OR 0.31 [95% CI, 0.11-0.91]; $P = 0.033$), after adjusting for these other covariates. Our findings underscore the importance of confirming seroconversion after HB vaccination in HIV-infected patients and initiating vaccination early in the course of HIV infection.

Keywords

HIV; hepatitis B vaccination; antibody response

INTRODUCTION

The incidence of acute hepatitis B (HB) infection among HIV-infected persons in the USA is estimated to be as high as 5100-5700 cases/year¹ and the reported prevalence of chronic HB viral infection among HIV-infected cohorts in the USA and Europe ranges between <7 and 9%.^{1,2} HIV-infected persons are also at a greater risk of developing chronic HB and often have higher levels of HB virus (HBV) replication than HIV-negative persons, thus posing a greater risk of HBV transmission.^{1,3,4} Furthermore, HIV/HBV co-infected patients respond less well to therapy than HB mono-infected patients and are at a higher risk for liver-related mortality.⁵

HB vaccination is safe and effective. More than 95% of healthy immunocompetent individuals achieve a protective immune response after a standard three-dose vaccination series.^{6,7} In contrast, response rates in HIV-infected individuals are as low as 18% to 62%.⁸⁻¹³ Previous studies have found an association between various clinical factors that may influence HB

vaccine response, but few studies have examined these factors together. To identify clinical factors independently associated with impaired response to HB vaccination, we conducted a retrospective cohort study among HB-vaccinated HIV-infected patients who received primary care at the University of Washington Harborview Medical Center HIV clinic.

PATIENTS AND METHODS

We conducted the study on the University of Washington (UW) HIV cohort that comprised HIV-infected patients receiving primary continuity care at the UW Harborview Medical Center HIV clinic. The UW HIV clinic is the largest single provider of medical care to HIV-infected individuals in the north-western USA. Patients provide informed consent and are followed until death or relocation from the UW.

The UW HIV information system (UWHIS) captures comprehensive longitudinal data on the UW HIV cohort and was the source of data for this study.¹⁴ The UWHIS integrates clinical data from all outpatient and inpatient encounters including standardized HIV-related information collected at enrolment: demographic, clinical, laboratory, medication and socioeconomic data are downloaded from institutional data sources including the UW electronic medical record. The majority of patients receive all their medications from the on-site pharmacy. Detailed prescription fill/refill data for all outpatient medications and inpatient discharge medications dispensed anywhere in the UW system are downloaded from the UW pharmacy system. Laboratory data are downloaded directly from the UW laboratory medicine system and include results of all tests performed as part of routine clinical care. Medical diagnoses, such as diabetes, renal disease and cirrhosis, and conditions including alcohol, tobacco and substance abuse are recorded prospectively by the treating clinician using a constrained vocabulary of standardized conditions and verified through a systematic review of clinical progress notes and other medical records. This study was approved by the UW institutional review board.

All HIV-infected patients ≥ 18 years of age whose initial clinic visit was between 1 January 1998 and 30 September 2005 were eligible for the study. Patients were required to have prevaccination serologies confirming the absence of current or past HB infection (negative anti-HB surface antibody [HBsAb], HB surface antigen and anti-HB core antibody). They were also required to have received three doses of HB vaccine. The decay rate of HBsAb in HIV-infected HB-vaccinated persons has not been studied; however, declining antibody levels over time have been described in healthy children and adults who undergo HB vaccination.^{7,15, 16} We therefore required that subjects have repeat HBsAb testing within a year of vaccination to account for potential waning antibody levels with more remote repeat testing. Patients who were tested >12 months from vaccination were more likely to have started vaccination in 1998-1999 compared with those who were tested within 12 months (51% versus 18%, $P < 0.001$). This change in practice is consistent with 1991 guidelines that suggested assessment of waning immunity (HBsAb levels) in immunocompromised persons¹⁷ and 2002 guidelines that more clearly recommended confirmation of HB vaccine response one to two months after the last dose.¹⁸

We examined the effect of both current and nadir CD4 cell count values; the latter defined as nadir prior to vaccination and the former defined as the value closest to the time of first HB vaccine within six months before or after vaccination. Patients were considered to be on highly active antiretroviral therapy (HAART) (defined as antiretroviral medication regimens containing ≥ 3 drugs containing a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor) if they received at least three months of treatment at least two months before the first vaccine dose. Patients on HAART were classified as having HIV viral suppression if their HIV-1 RNA level closest to the time of first HB vaccine was <400 copies/mL (limit of detection

was 400 for standard assays in earlier years). Patients who had viral levels >400 copies/mL on the closest date but who were subsequently suppressed to <400 copies/mL within six months of the first HB vaccine dose were also considered to have achieved HIV viral suppression.

The primary outcome measure was a protective antibody response to HB vaccination defined as a postvaccination anti-HB surface antibody (HBsAb) titre ≥ 10 International Units per litre (IU/L). All HBsAb titres were determined using a standardized enzyme immunoassay (Abbott Ausab EIA, Abbott Laboratories, IL, USA) performed by the UW Virology laboratory.

Between 1998-2005, approximately two-thirds of patients seen in UW HIV Clinic were vaccinated with Engerix-B®, a recombinant DNA HB vaccine (GlaxoSmithKline Biologicals, Rixensart, Belgium) and the remaining one-third with Twinrix® a combination of the recombinant HB vaccine and inactivated hepatitis A virus (GlaxoSmithKline Biologicals) - both were administered intramuscularly at a standard adult dose of 20 mcg at zero, one and six months.

We examined the effect of demographic and clinical factors on failure to develop a protective antibody response to HB vaccination. These factors, apart from the lab and medication data outlined above, included age >40 years¹⁹, sex with men and injection drug use (not mutually exclusive), hepatitis C infection (positive hepatitis C antibody and viral RNA) and history of AIDS-defining condition (1993 Centers for Disease Control and Prevention criteria excluding CD4 count <200) and other medical conditions.

Continuous variables were compared by using *t*-test or the two sample Mann-Whitney *U* test as appropriate and categorical variables by the χ^2 test with Fisher's exact testing for small cell values (<10) for 2×2 tables. Logistic regression was used to calculate univariate and multivariate odds ratios. Two-sided *P* values <0.05 were considered significant. Covariates that had *P* values <0.1 on univariate analysis or were considered biologically relevant (i.e. HIV viral suppression) were included in the multivariate model. All statistical calculations were performed using Stata software, version 8.2 (Stata, College Station, TX, USA).

RESULTS

Of the 2048 individuals who had their first visit to UW HIV clinic between 1 January 1998 and 30 September 2005, 1638 (80%) had baseline HB serological testing performed. Of the 400 patients determined to be negative for all HB serologies (HBsAb, HB surface antigen and HB core antibody) prior to vaccination and who had two or more HB vaccines recorded, 157 (39%) underwent postvaccination HBsAb testing. The 243 who did not undergo postvaccination testing were comparable to the 157 tested subjects with respect to the baseline characteristics outlined in Table 1 but did have a slightly lower proportion with AIDS-defining conditions (36% versus 47%, *P* = 0.04). The untested group also differed from the tested group by having later year of vaccination (45% versus 16% for 2006, *P* < 0.001) and fewer vaccine doses (mean 2.6 versus 3.5, *P* < 0.001).

The time from the last vaccine dose to the first postvaccination HBsAb testing ranged from 0.5 month to 6.9 years for the 157 patients who underwent postvaccination testing. Ninety-seven patients (62% of 157) were included in the final analysis and met the predefined criteria of receiving three vaccine doses and postvaccination testing at more than one month and within one year after the last vaccine dose (median 3.2 months, range 1-12). The remaining 60 patients comprised nine patients who received two doses, nine who received four doses, one who received five doses and one who received six doses before testing within a year of vaccination and another 40 vaccinated patients who were tested more than a year after their last vaccine dose. These 60 excluded patients were similar to the 97 analysed in baseline characteristics but was a younger group overall (18% versus 44% were older than 40 years, *P* < 0.001).

Patient characteristics and vaccine response

The clinical and demographic characteristics of the study subjects are shown in Table 1. The median age was 39 years (range, 21-53 years). Fifty-four (56%) patients were white, 23 (24%) were black and 20 (20%) belonged to other racial groups. Thirty-seven (38%) patients had an AIDS diagnosis and 19 (20%) patients were co-infected with hepatitis C.

The overall response rate to HB vaccination was 44%. In univariate analysis, vaccine non-responders were more likely to be over 40 years of age (54% versus 33%, $P = 0.04$) and African-American (35% versus 9%, $P = 0.003$) compared with vaccine responders. Non-responders were also more likely to have a CD4 nadir <200 cells/mm³ (59% versus 23%, $P < 0.001$) or to have abused alcohol (43% versus 19%, $P = 0.01$). CD4 cell counts near the time of first HB vaccine dose were lower for vaccine non-responders (median value of 261 cells/mm³, range, 2-994 cells/mm³) compared with vaccine responders (390 cells/mm³, range, 42-780 cells/mm³, $P = 0.02$). The proportion of patients who achieved HIV viral suppression on HAART at the time of their first HB vaccine tended to be greater among vaccine responders compared with non-responders (28% versus 20%, $P = 0.39$).

Figure 1 shows the proportion of HB vaccine responders stratified by CD4 nadir (categorized as ≤ 100 , 101-200, >200) and HIV viral suppression. Only 15.8% of patients with a CD4 nadir <100 and evidence of viraemia at the time of vaccination had a protective antibody response compared with 80% of patients with a CD4 nadir >200 who achieved viral suppression.

Gender, hepatitis C infection, sex with men, injection drug use, tobacco or overall substance abuse were not associated with vaccine response. We had very few patients with renal disease, diabetes or cirrhosis to determine the effect of these factors.

Predictors of impaired vaccine response

The results of univariate and multivariate analyses are shown in Table 2. Patients with a CD4 nadir <200 had over seven times the odds of non-response compared with those whose CD4 nadir >200 (OR 7.24 [95% CI, 1.91-27.41]; $P = 0.004$), whereas the current CD4 count was no longer significant in the multivariate model. Age >40 years (OR 3.03 [95% CI, 1.14-8.06]; $P = 0.026$), African-American race (OR 6.0 [95% CI, 1.55-15.6]; $P = 0.005$) and alcohol abuse (OR 4.92 [95% CI, 1.72-20.89]; $P = 0.007$) were also independent risk factors for lack of vaccine response. Patients with HIV viral suppression on HAART had a significantly lower rate of vaccine failure compared with patients who were either not taking HAART or not suppressed on HAART - an association that appeared to be independent of the current CD4 count (OR 0.31 [95% CI, 0.11-0.91]; $P = 0.033$).

A sensitivity analysis of all 157 patients who received at least two vaccines and were tested postvaccination up to seven years yielded similar results (data not shown).

DISCUSSION

The overall response rate to HB vaccination in our study population was 44%, which is consistent with rates previously reported in HIV-infected patients.⁸⁻¹² Older age, CD4 nadir <200 cells/mm³, alcohol abuse and African-American race were independent risk factors associated with failure to develop a protective antibody response. In contrast, patients with HIV viral suppression on HAART were more likely to develop a protective antibody response to HB vaccination.

A decreased response to HB vaccination with increasing age has been previously reported in HIV-uninfected populations.¹⁹ Our study confirms this as a robust finding in HIV-infected

patients, even after adjustment for other clinical factors and has important practical implications regarding the timing of HB vaccination in HIV-infected patients.

We found that nadir CD4, rather than CD4 current to the first vaccine dose, remained an independent predictor of vaccine response. The effect of current CD4 was attenuated and no longer statistically significant once disease severity as measured by CD4 nadir was taken into account in the multivariate analysis. The association between nadir CD4 count and response to HB vaccine was previously observed in a small study of the HIV Outpatient Study cohort, which demonstrated that 84.2% of 19 patients who responded to HB vaccination had nadir CD4 counts ≥ 200 cells/mm³ compared with only 46.9% of 32 patients who did not respond to vaccination ($P = 0.008$).²⁰ Others have reported associations between nadir CD4 counts and the humoral response to pneumococcal vaccination.²¹ Another study showed that functional responses to immunization (as measured by antibody response, lymphocyte proliferation and delayed-type hyper-sensitivity responses to tetanus and diphtheria toxoids) were better predicted by nadir CD4 cell counts than by CD4 cell count at the time of immunization.²² Our data are consistent with these results as well as current understanding that HAART-induced immune restoration may be less complete in patients who initiate therapy later in their HIV disease course.^{23,24}

We show that suppressive HAART may improve HB vaccine response and confirm the results of studies showing greater HB vaccine response rates in patients suppressed on HAART.^{8, 20} We demonstrate furthermore that this effect may be independent of an increase in CD4 count,⁸ a finding that will need to be confirmed. HIV replication has been shown to impair functional immune responses indirectly by increasing immune activation and proinflammatory cytokines.^{9,25} In fact, control of viral replication with HAART, which leads to reduced levels of soluble and cell-associated markers of immune activation, has been shown to improve cell-mediated and humoral responses to immunization.^{26,27} The extent to which HAART can restore response to immunization, particularly in patients with advanced HIV disease and low CD4 nadir, remains unclear.²⁸

Previous studies have reported decreased HB vaccine responses among alcoholics who were otherwise considered immunocompetent with seroconversion rates after standard vaccination schedules ranging from 43% to 70%.²⁹⁻³¹ Our study suggests that alcohol may additionally impact HB vaccine response rates in patients whose immunity is already compromised by HIV infection. We were unable to distinguish between current and past alcohol abuse in our study. Proposed mechanisms for alcohol-related immunodeficiency include direct inhibition of T-cell-mediated antibody production by alcohol consumption³² as well as indirect effects of malnutrition and underlying liver disease.

The association between African-American race and impaired response to HB vaccination is surprising. Early large-scale placebo, controlled randomized trials on HB vaccination in health-care workers^{6,7} and men who have sex with men^{33,34} did not report differences in frequency of vaccine response by race. In our study population, African-American patients tended to have lower current CD4 counts (mean 288 versus 377 cells/mm³, $P = 0.12$) and lower nadir CD4 counts (mean 185 versus 265 cells/mm³, $P = 0.08$) compared with non-African-American patients but adjustment for these factors did not change the risk estimate or P values in the multivariate model. A possible biological explanation for our findings is the presence of unbalanced HLA polymorphisms across races that modulate the immune response to HB vaccination.^{35,36} Although our finding of the effect of race on immune response is interesting, it should be interpreted with caution given the small sample size and the potential for unknown or unmeasured confounding factors that may have mediated the effect.

Postvaccination HB surface antibody testing is not a consistent or widespread practice in our study population; only 39% of vaccinated patients underwent testing and 29% tested within a year of vaccination. Patients who did not undergo postvaccination testing were comparable with patients who did with the exception of having later calendar year of vaccination, fewer vaccinations and a slightly lower proportion of patients with AIDS-defining conditions. These differences most likely reflect shorter follow-up time and are unlikely to have distorted our effect estimates. More patients were tested for HBsAb within a year of vaccination during later years, in keeping with the emergence of sexually transmitted diseases guidelines in 2002 that clearly recommended confirmation of HBsAb seroconversion in HIV-infected HB-vaccinated patients.¹⁸ To address potential selection bias introduced by restricting our analysis to those patients who received only three vaccine doses and were tested within a year of vaccination, we conducted a sensitivity analysis of all 157 patients who received at least two vaccinations and were tested postvaccination up to seven years and found similar results.

In summary, advancing age and lower CD4 nadir (but not current CD4) appear to predict vaccine failure - results that suggest that HB vaccination should be initiated soon after patients enter care, preferably early in the course of HIV infection before more profound immunosuppression occurs. In addition, delaying HB vaccination to await CD4 recovery on HAART may not be warranted; viral suppression independent of the current CD4 count may improve rates of HBsAb seroconversion. Those who do not respond to an initial HB series should be re-vaccinated, preferably after complete suppression of HIV replication on HAART. Our findings underscore the importance of identifying strategies that optimize the timing, delivery and effectiveness of HB vaccination in this high-risk population.

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REFERENCES

1. Kellerman SE, Hanson DL, McNaghten AD, Fleming PL. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. *J Infect Dis* 2003;188:571–7. [PubMed: 12898445]
2. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005;19:593–601. [PubMed: 15802978]
3. Hadler SC, Judson FN, O'Malley PM, et al. Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. *J Infect Dis* 1991;163:454–9. [PubMed: 1825315]
4. Colin JF, Cazals-Hatem D, Lioriot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* 1999;29:1306–10. [PubMed: 10094979]
5. Thio CL, Seaberg EC, Skolasky J, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *The Lancet* 2002;360:1921–6.
6. Szmunn W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine in medical staff of hemodialysis units: efficacy and subtype cross-protection. *N Engl J Med* 1982;307:1481–6. [PubMed: 6755247]
7. Dienstag JL, Werner BG, Polk BF, et al. Hepatitis B vaccine in health care personnel: safety, immunogenicity, and indicators of efficacy. *Ann Intern Med* 1984;101:34–40. [PubMed: 6233921]
8. Overton ET, Sungkanuparph S, Powderly WG, Seyfried W, Groger RK, Aberg JA. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. *Clin Infect Dis* 2005;41:1045–8. [PubMed: 16142673]

9. Wilson CM, Ellenberg JH, Sawyer MK, et al. Serologic response to hepatitis B vaccine in HIV infected and high-risk HIV uninfected adolescents in the REACH cohort. Reaching for excellence in adolescent care and health. *J Adolesc Health* 2001;29:123–9. [PubMed: 11530313]
10. Wong EK, Bodsworth NJ, Slade MA, Mulhall BP, Donovan B. Response to hepatitis B vaccination in a primary care setting: influence of HIV infection, CD4+ lymphocyte count and vaccination schedule. *Int J STD AIDS* 1996;7:490–4. [PubMed: 9116065]
11. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load. *Vaccine* 2000;18:1161–5. [PubMed: 10649616]
12. Collier AC, Corey L, Murphy VL, Handsfield HH. Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. *Ann Intern Med* 1988;109:101–5. [PubMed: 2968064]
13. Gandhi RT, Wurcel A, Lee H, et al. Response to hepatitis B vaccine in HIV-1-positive subjects who test positive for isolated antibody to hepatitis B core antigen: implications for hepatitis B vaccine strategies. *J Infect Dis* 2005;191:1435–41. [PubMed: 15809901]
14. Kitahata MM, Dillingham PW, Chaiyakunapruk N, et al. Electronic human immunodeficiency virus (HIV) clinical reminder system improves adherence to practice guidelines among the University of Washington HIV Study Cohort. *Clin Infect Dis* 2003;36:803–11. [PubMed: 12627367]
15. Zanetti AR, Mariano A, Romano L, et al. Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. *Lancet* 2005;366:1379–84. [PubMed: 16226616]
16. Horowitz MM, Ershler WB, McKinney WP, Battiola RJ. Duration of immunity after hepatitis B vaccination: efficacy of low-dose booster vaccine. *Ann Intern Med* 1988;108:185–9. [PubMed: 2963570]
17. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep* 1991;40:1–25.
18. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *MMWR Recomm Rep* 2002;51:1–78.
19. Fisman DN, Agrawal D, Leder K. The effect of age on immunologic response to recombinant hepatitis B vaccine: a meta-analysis. *Clin Infect Dis* 2002;35:1368–75. [PubMed: 12439800]
20. Tedaldi EM, Baker RK, Moorman AC, et al. Hepatitis A and B vaccination practices for ambulatory patients infected with HIV. *Clin Infect Dis* 2004;38:1478–84. [PubMed: 15156488]
21. Subramaniam KS, Segal R, Lyles RH, Rodriguez-Barradas MC, Pirofski LA. Qualitative change in antibody responses of human immunodeficiency virus-infected individuals to pneumococcal capsular polysaccharide vaccination associated with highly active antiretroviral therapy. *J Infect Dis* 2003;187:758–68. [PubMed: 12599049]
22. Lange CG, Lederman MM, Medvik K, et al. Nadir CD4+ T-cell count and numbers of CD28+ CD4+ T-cells predict functional responses to immunizations in chronic HIV-1 infection. *AIDS* 2003;17:2015–23. [PubMed: 14502004]
23. Lange CG, Valdez H, Medvik K, Asaad R, Lederman MM. CD4+ T-lymphocyte nadir and the effect of highly active antiretroviral therapy on phenotypic and functional immune restoration in HIV-1 infection. *Clin Immunol* 2002;102:154–61. [PubMed: 11846457]
24. D'Amico R, Yang Y, Mildvan D, et al. Lower CD4+ T lymphocyte nadirs may indicate limited immune reconstitution in HIV-1 infected individuals on potent antiretroviral therapy: analysis of immunophenotypic marker results of AACTG 5067. *J Clin Immunol* 2005;25:106–15. [PubMed: 15821887]
25. Lane HC, Depper JM, Greene WC, Whalen G, Waldmann TA, Fauci AS. Qualitative analysis of immune function in patients with the acquired immunodeficiency syndrome. Evidence for a selective defect in soluble antigen recognition. *N Engl J Med* 1985;313:79–84. [PubMed: 2582258]
26. Kroon FP, Rimmelzwaan GF, Roos MT, et al. Restored humoral immune response to influenza vaccination in HIV-infected adults treated with highly active antiretroviral therapy. *AIDS* 1998;12:F217–23. [PubMed: 9863863]

27. Valdez H, Smith KY, Landay A, et al. Response to immunization with recall and neoantigens after prolonged administration of an HIV-1 protease inhibitor-containing regimen. ACTG 375 team. AIDS Clinical Trials Group. AIDS 2000;14:11–21. [PubMed: 10714563]
28. Elrefaei M, McElroy MD, Preas CP, et al. Central memory CD4+ T cell responses in chronic HIV infection are not restored by antiretroviral therapy. J Immunol 2004;173:2184–9. [PubMed: 15265956]
29. Mendenhall C, Roselle GA, Lybecker LA, et al. Hepatitis B vaccination. Response of alcoholic with and without liver injury. Dig Dis Sci 1988;33:263–9. [PubMed: 2856849]
30. Villanueva C, Enriquez J, Just J, Teixido M, Mendez C, Rodrigo O. Vaccination against the hepatitis B virus in alcoholics. Med Clin (Barc) 1991;96:211–4. [PubMed: 2041386]
31. Nalpas B, Thepot V, Driss F, et al. Secondary immune response to hepatitis B virus vaccine in alcoholics. Alcohol Clin Exp Res 1993;17:295–8. [PubMed: 8488971]
32. Szabo G. Consequences of alcohol consumption on host defence. Alcohol Alcohol 1999;34:830–41. [PubMed: 10659718]
33. Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med 1986;315:209–14. [PubMed: 2941687]
34. Francis DP, Hadler SC, Thompson SE, et al. The prevention of hepatitis B with vaccine. Report of the centers for disease control multi-center efficacy trial among homosexual men. Ann Intern Med 1982;97:362–6. [PubMed: 6810736]
35. Alper CA, Kruskall MS, Marcus-Bagley D, et al. Genetic prediction of nonresponse to hepatitis B vaccine. N Engl J Med 1989;321:708–12. [PubMed: 2528067]
36. Craven DE, Awdeh ZL, Kunches LM, et al. Nonresponsiveness to hepatitis B vaccine in health care workers. Results of revaccination and genetic typings. Ann Intern Med 1986;105:356–60. [PubMed: 2943202]

Figure 1. Proportion of patients with protective HB vaccine response, by CD4 nadir and HIV viral suppression $P = 0.02$ for viraemia, $P = 0.04$ for suppressed patients

Table 1

Baseline characteristics of patients, by response to hepatitis B vaccination

**No. (%) Characteristics	Vaccine responders (n = 43)	Vaccine non-responders (n = 54)	Total (n = 97)	P
Age, median years (range)	35 (21-53)	41 (22-52)	39 (21-53)	0.005
Sex, male, no. (%)	30 (70)	41 (76)	71 (73)	0.50
Race				
White	31 (72)	23 (43)	54 (56)	0.004
Black	4 (9)	19 (35)	23 (24)	
Other	8 (19)	12 (22)	20 (20)	
MSM	26 (60)	23 (43)	49 (51)	0.08
Injection drug use	9 (21)	14 (26)	23 (24)	0.57
AIDS-defining condition*	11 (26)	26 (48)	37 (38)	0.02
Hepatitis C coinfection	9 (21)	10 (19)	19 (20)	0.77
HAART use [†]	15 (35)	15 (28)	30 (31)	0.45
HIV viral suppression [‡]	12 (28)	11 (20)	23 (24)	0.39
CD4 cells/uL, median (range)				
Nadir	240 (1-740)	150 (1-670)	240 (1-740)	0.001
Current to first vaccine dose [§]	390 (42-780)	261 (2-994)	325 (2-994)	0.02
Substance dependence	16 (37)	29 (54)	45 (46)	0.11
Tobacco dependence	23 (53)	33 (61)	56 (58)	0.45
Alcohol dependence	8 (19)	23 (43)	31 (32)	0.01
Renal disease	1 (2)	4 (7)	5 (5)	0.26
Diabetes mellitus	1 (2)	3 (6)	4 (4)	0.43
Cirrhosis	1 (2)	1 (2)	2 (2)	0.87

MSM = men who have sex with men; AIDS = acquired immunodeficiency virus

* Includes the 1993 expanded list of conditions outlined by the Centers for Disease Control and Prevention, not including CD4 count <200

[†] HAART = highly active antiretroviral therapy containing ≥1 protease inhibitor or non-nucleoside reverse transcriptase inhibitor for at least three months duration at time of vaccination[‡] HIV RNA <400 copies/mL closest to first hepatitis B (HB) vaccine dose[§] CD4 measured closest to first HB vaccine dose (within 6 months before or after) - or first available if none documented prior to vaccination

** Unless otherwise indicated

Table 2

Factors associated with lack of response to hepatitis B vaccination

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P [*]
Age >40 years	2.4 (1.04, 5.55)	3.03 (1.14, 8.06)	0.026
CD4 nadir <200	4.8 (1.96, 11.76)	7.24 (1.91, 27.41)	0.004
HIV viral suppression [†]	0.66 (0.24, 1.70)	0.31 (0.11, 0.91)	0.033
CD4 current <200	4.84 (1.63, 14.34)	0.71 (0.15, 3.41)	0.674
African-American race	5.29 (1.63, 17.17)	6.00 (1.55, 15.62)	0.005
Alcohol abuse	3.25 (1.26, 8.34)	4.92 (1.72, 20.89)	0.007

CI = confidence interval; OR = odds ratio

^{*} P values for multivariate model[†] HIV RNA < 400 copies/mL closes to first vaccine dose