Original Investigation

Long-term Immune Response to Hepatitis B Virus Vaccination Regimens in Adults With Human Immunodeficiency Virus 1
Secondary Analysis of a Randomized Clinical Trial

Odile Launay, MD, PhD; Arielle R. Rosenberg, MD, PhD; David Rey, MD; Noelle Pouget, PhD; Marie-Louise Michel, PhD; Jacques Reynes, MD, PhD; Didier Neau, MD, PhD; Francois Raffi, MD, PhD; Lionel Piroth, MD, PhD; Fabrice Carrat, MD, PhD; for the ANRS HB03 VIHVAC-B (Trial Comparing 3 Strategies of Vaccination Against the Virus of Hepatitis B in HIV-Infected Patients) Group

IMPORTANCE Data on long-term immune responses to hepatitis B virus (HBV) vaccination in adults with human immunodeficiency virus 1 (HIV-1) infection are scarce.

OBJECTIVE To compare long-term (up to month 42) immune responses to the standard HBV vaccination regimen with a 4-injection intramuscular double-dose regimen and a 4-injection intradermal low-dose regimen.

DESIGN, SETTING, AND PARTICIPANTS The phase 3, open-label, multicenter parallel-group (1:1:1 allocation ratio) randomized clinical trial was conducted from June 28, 2007, to October 23, 2008, at 33 centers in France. Participants included 437 HBV-seronegative adults with HIV-1 and CD4 cell counts of more than 200/μL. Follow-up was extended to September 12, 2012, and data were assessed from February 13, 2015, to January 22, 2016. The analysis was imputed for an intention-to-treat population.

INTERVENTIONS Patients were randomly assigned to receive 3 intramuscular standard-dose (20-μg) injections of recombinant HBV vaccine at weeks 0, 4, and 24 (IM20 × 3 group) (145 participants), 4 intramuscular double-dose (40-μg) injections at weeks 0, 4, 8, and 24 (IM40 × 4 group) (148 participants), or 4 intradermal low-dose (4-μg) injections at weeks 0, 4, 8, and 24 (ID4 × 4 group) (144 participants).

MAIN OUTCOMES AND MEASURES The previously published primary trial end point was the percentage of responders at week 28, defined as patients with hepatitis B surface antibody (HBsAb) levels of at least 10 mIU/mL among patients who received at least 1 vaccine dose. The secondary trial end points included the percentage of responders at months 18, 30, and 42 and the duration of response from week 28. Multiple imputation was used to address missing measurements during the follow-up.

RESULTS Among the 437 patients randomized, 426 received at least 1 dose of vaccine. Of these, 287 were men (67.4%) and they had a mean (SD) age of 42.9 (9.7) years. The percentage of responders at month 42 was 41% (95% CI, 33%-49%) in the IM20 × 3 group, 71% (95% CI, 64%-79%) in the IM40 × 4 group ($P < .001$ vs the IM20 × 3 group), and 44% (95% CI, 35%-53%) in the ID4 × 4 group ($P = .64$ vs IM20 × 3 group). Fifteen percent of the patients had HBsAb titers of less than 10 mIU/mL at 33.1 months in the IM40 × 4 group, 8.7 months in the IM20 × 3 group, and 6.8 months in the ID4 × 4 group.

CONCLUSIONS AND RELEVANCE In this follow-up of a trial of adults with HIV-1 infection, the IM40 × 4 regimen of recombinant HBV vaccine improved long-term immune response compared with the standard regimen.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00480792

JAMA Intern Med. 2016;176(5):603-610. doi:10.1001/jamainternmed.2016.0741
Published online April 11, 2016.

Supplemental content at jamainternalmedicine.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the ANRS HB03 VIHVAC-B Group are listed at the end of the article.

Corresponding Author: Odile Launay, MD, PhD, 27 rue du Faubourg St Jacques, 75679 Paris, CEDEX 14, France (odile.launay@aphp.fr).

Although guidelines recommend hepatitis B virus (HBV) vaccination in patients with human immunodeficiency virus 1 (HIV-1) infection without evidence of previous HBV exposure, responses to standard HBV vaccination regimens remain suboptimal compared with responses in HIV-seronegative individuals.[1] A 2011 study reported the results of the French National Agency for Research on AIDS and Viral Hepatitis–sponsored HB03 Trial Comparing Three Strategies of Vaccination Against the Virus of Hepatitis B in HIV-Infected Patients (ANRS HB03 VIHVAC-B). The ANRS HB03 VIHVAC-B compared the safety and immunogenicity of different schedules of HBV vaccination in adults with HIV-1 (4-injection intramuscular double-dose and 4-injection intradermal low-dose regimens vs the standard HBV vaccination regimen).[2,3] At week 28 (primary trial end point at 4 weeks after the last dose), the 4-injection intramuscular double-dose regimen and the 4-injection intradermal low-dose regimen improved antibody response compared with the standard HBV vaccination regimen.

The low seroconversion rate after HBV vaccination in immunocompromised patients is further complicated by a rapid decrease in antibody titers for those who had a response.[4-9] Further precision on the duration of response achieved with alternative HBV vaccination regimens is needed. We report herein the results from the ANRS HB03 VIHVAC-B follow-up of the long-term immune response to these 3 regimens (≤3 years after vaccination).

Methods

Study Design

This phase 3, open-label, multicenter, parallel-group (1:1:1 allocation ratio) randomized clinical trial was performed in 33 sites in France among patients enrolled in the ANRS HB03 VIHVAC-B Trial from June 28, 2007, to October 23, 2008, for assessment of immunogenicity and safety.[2] Follow-up was extended to September 12, 2012, for long-term (month 42) assessment of immune response. The protocol was conducted in accordance with the Declaration of Helsinki and the French law for biomedical research. The study was approved by the Ile-de-France III Ethics Committee, Paris, and the French Regulatory Authority. Written informed consent was obtained from each patient before enrollment.

Patients included in the initial trial were adults with HIV-1, a CD4 count of more than 200/μL (to convert to number of cells ×10^9 per liter, multiply by 0.001), no HBV serologic marker (ie, seronegative for hepatitis B surface antigen, hepatitis B surface antibody [HBsAb], and hepatitis B core antibody). Other inclusion and exclusion criteria have been detailed previously.[2] Patients had been centrally randomized to receive 3 intramuscular injections of the standard dose (20 μg) of recombinant HBV vaccine (GenHevac B Pasteur; Sanofi Pasteur) at weeks 0, 4, and 24 (IM20 × 3 group) (145 participants); 4 intramuscular injections of double doses (40 μg [2 injections of 20 μg]) of recombinant HBV vaccine (GenHevac B Pasteur; Sanofi Pasteur) at weeks 0, 4, 8, and 24 (IM40 × 4 group) (148 participants); or 4 intradermal injections of low doses (4 μg [one-fifth of 20-μg]) of recombinant HBV vaccine (GenHevac B Pasteur; Sanofi Pasteur) at weeks 0, 4, 8, and 24 (ID4 × 4 group) (144 participants). As per the protocol (eFigure 1 in the Supplement), patients who responded were followed up at months 18, 30, and 42 to study the duration of response and the kinetics of HBsAb titers.

Primary and Secondary End Points

The primary trial end point was the percentage of responders at week 28, defined as patients with HBsAb titers of at least 10 mIU/mL among patients who received at least 1 vaccine dose.[2] The secondary end points included the percentage of responders, the percentage of high-level responders (patients with HBsAb titers ≥100 mIU/mL, which are levels considered to have increased and to provide long-term protection against infection in an otherwise healthy population), and the geometric mean titer (GMT) of HBsAb at months 18, 30, and 42. Adverse events were reported at each visit. An independent adjudication committee consisting of an internist, a neurologist, and a hepatologist reviewed blinded safety data.

Laboratory Assays

The quantification of HBsAb titers on serum samples was performed in a central laboratory (Cochin Hospital) using a standardized assay (Monolisa Anti-HBs Plus; Bio-Rad Laboratories, Inc). Each sample was tested by technical staff blinded to vaccine group allocation. Samples with titers of more than the upper linearity limit of the assay underwent retesting after being diluted as recommended by the manufacturer.

Statistical Analysis

Data were analyzed from February 13, 2015, to January 22, 2016. We first explored the percentages of responders and high-level responders at months 18, 30, and 42 among all participants who received at least 1 dose of study vaccine (modified intention-to-treat analysis set; eFigure 1 in the Supplement). Second, we focused specifically on participants who responded at week 28 to explore the duration of response and kinetics of HBsAb titers.

We used 2 different methods to handle missing titers in the analyses of follow-up secondary end points (eTable in the Supplement). When the last observed titer was a nonresponse (as in all nonresponders and in most patients with a missing end point at week 28), we imputed each subsequent missing following titer as a nonresponse. The complete case data set was composed of these imputed nonresponses in addition to the observed titers. For other missing titers, we used multiple imputation (MI) by chained equations that included available measurements, vaccination arm, age, sex, smoking status, CD4 count, HIV-1 RNA status, and time elapsed since HIV-1 diagnosis as predictors. The final inference for MI was combined from 5 sets of imputed samples.

In the modified intention-to-treat analysis, we calculated the mean proportional values derived from observed and imputed values. The differences of percentages of responders or high-level responders between groups at specific points were tested against using a 2-sided *t* test.

Exploratory logistic regression analyses were used to identify the variables associated with a sustained response at month 18 among responders at week 28. We performed 2 separate analyses on the complete case and MI data. The first analysis considered only variables measured at trial inclusion; the second considered the high-level response status at week 28 to account for differences in HBsAb titers at start of the follow-up. Variables with $P < .15$ in likelihood ratio testing in bivariable analysis were included in a multivariable model, and selection of independent variables was based on a backward elimination procedure that retained variables with $P < .05$. To quantify the duration of the response (or the high-level response), we used a nonparametric method for interval-censored data to deal with the lack of information on the exact time when the response (or the high-level response) loss could have occurred between 2 visits.[10] The analysis used complete case data with missing measurements treated as censored data. Time was calculated from week 28 until the last observed response because some patients may have an observed response after a nonresponse during the follow-up visits. We used the generalized log-rank test to compare the duration of response between groups.[11]

To describe the kinetics of HBsAb titer, we used a linear mixed model on complete case data as recommended.[12] The linear mixed model included group, time, and interaction between group and time as fixed effects and patient as a random effect; a first-order autoregressive covariance matrix was used to handle within-patient correlation between successive titers. We used the *F* test of the interaction between time and group to explore a difference in kinetic profiles between groups and *t* tests to explore differences in GMTs between groups at specific points.

In all pairwise comparisons, the IM20 × 3 group was considered a control for the IM40 × 4 and ID4 × 4 groups. All statistical tests were 2 sided. Multiple comparisons of percentages of responders or GMTs between groups at specific points were adjusted using the Bonferroni procedure such that the *P* value for statistical significance was .0083 (.05/6) or .0063 (.05/8). Other tests were performed at a 5% level of significance. Confidence intervals for the proportion of responders were calculated using the normal approximation. All statistical computations were performed using SAS software (version 9.4; SAS Institute Inc).

Results

Study Patients

Among the 437 patients randomized, 426 (139 women [32.6%]; 287 men [67.4%]; mean [SD] age, 42.9 [9.7] years) received at least 1 dose of vaccine. Three hundred eighteen patients (74.6%) were responders at week 28; 78 (18.3%) were nonresponders; and 30 (7.0%) did not undergo testing (eFigure 1 in the Supplement). Patients' characteristics according to vaccination response are described in **Table 1**.

Follow-up of Response and High-Level Response

Using MI data, the percentage of responders by month 42 was 41% (95% CI, 33%-49%) in the IM20 × 3 group, 71% (95% CI, 64%-79%) in the IM40 × 4 group, and 44% (95% CI, 35%-53%) in the ID4 × 4 group (**Table 2**). The percentages of responders and high-level responders were greater in the IM40 × 4 group than in the IM20 × 3 group at months 18, 30, and 42 ($P < .001$ for all comparisons). Notably, 6 patients who missed the visit and did not undergo evaluation at week 28 (thus considered to have vaccination failure in the intention-to-treat analysis) were responders at month 18 without any supplementary vaccination. We noticed no difference in the percentages of responders or high-level responders between the ID4 × 4 and the IM20 × 3 groups at each of the follow-up points.

Duration of Immune Response and Kinetics of HBsAb Among Responders at Week 28

Using complete case data, a sustained response at month 18 was observed in 62 of 81 patients (76.5%) in the IM20 × 3 group, 103 of 112 patients (92.0%) in the IM40 × 4 group, and 68 of 92 patients (73.9%) in the ID4 × 4 group. Using MI data, the proportions of sustained response were 74% (95% CI, 65%-84%) in the IM20 × 3 group, 91% (95% CI, 86%-96%) in the IM40 × 4 group, and 74% (95% CI, 66%-83%) in the ID4 × 4 group at month 18. Similarly, by month 42, a sustained response was observed in 46 of 72 patients (63.9%) in the IM20 × 3 group, 81 of 98 patients (82.7%) in the IM40 × 4 group, and 49 of 87 patients (56.3%) in the ID4 × 4 group; the proportions of sustained response were 62% (95% CI, 52%-73%) in the IM20 × 3 group, 83% (95% CI, 76%-90%) in the IM40 × 4 group, and 57% (95% CI, 46%-68%) in the ID4 × 4 group.

Considering only variables at trial inclusion, the IM40 × 4 regimen was associated with a sustained response at month 18 (**Table 3**). Other independent variables were the time elapsed since the HIV-1 diagnosis, CD4 count of more than 350/μL, and active smoking. Using complete case data, a sustained response at month 18 was observed in 204 of 216 high-level responders (94.4%) at week 28 vs 29 of 69 patients (42.0%) who were not high-level responders (bivariable odds ratio [OR], 23.4 [95% CI, 11.0-49.8]). Using MI data, analysis including high-level response status at week 28, high-level responders (adjusted OR for yes vs no, 25.8 [95% CI, 11.3-59.0]), and time elapsed since the HIV-1 diagnosis (adjusted OR per 1-year increment, 1.07 [95% CI, 1.00-1.14]) remained the only 2 variables significantly associated with sustained response at month 18.

The duration of the response was higher in the IM40 × 4 group than in the IM20 × 3 group ($P = .003$) but did not differ between the ID4 × 4 group and the IM20 × 3 group ($P = .39$) (**Figure 1**); 15% of the patients had HBsAb titers of less than 10 mIU/mL at 33.1 months in the IM40 × 4 group, 8.7 months in the IM20 × 3 group, and 6.8 months in the ID4 × 4 group. The duration of a high-level response also differed between the IM40 × 4 and IM20 × 3 groups ($P = .02$) but not between the ID4 × 4 and IM20 × 3 groups ($P = .22$) (eFigure 2 in the Supplement). The estimated median time of the persistence of a high-level response was 10.5 months in the IM20 × 3 group and 8.7 months in the ID4 × 4 group, whereas it was longer than 35 months in the IM40 × 4 group.

At week 28, the GMT of HBsAb was 395 (95% CI, 255-609) mIU/mL in the IM20 × 3 group, 2311 (95% CI, 1580-3380) mIU/mL in the IM40 × 4 group ($P < .001$ compared with IM20 × 3;

Table 1. Demographic and Clinical Characteristics of Patients Who Received at Least 1 Dose of HBV Vaccine According to the Week 28 Response[a]

Characteristic of Recombinant HBV Vaccine	IM20 × 3 Group (n = 141)		IM40 × 4 Group (n = 145)		ID4 × 4 Group (n = 140)	
	Responders (n = 91)	Nonresponders or Not Tested (n = 50)	Responders (n = 119)	Nonresponder or Not Tested (n = 26)	Responders (n = 108)	Nonresponder or Not Tested (n = 32)
Women, No. (%)	32 (35.2)	8 (16.0)	41 (34.5)	8 (30.8)	44 (40.7)	6 (18.8)
Age, median (range), y	41 (19-60)	45 (22-74)	43 (19-65)	40 (31-61)	43 (19-70)	42 (21-60)
BMI, median (range)	23 (17-36)	23 (18-36)	24 (18-56)	24 (19-33)	23 (16-39)	24 (17-37)
Active smoking, No. (%)[b]	27 (29.7)	22 (44.0)	31 (26.1)	13 (50.0)	34 (31.5)	17 (53.1)
Excessive alcohol use, No. (%)[c]	8 (8.8)	3 (6.0)	5 (4.2)	2 (7.7)	10 (9.3)	2 (6.3)
Anti-HCV antibodies present, No. (%)	2 (2.2)	3 (6.0)	4 (3.4)	2 (7.7)	3 (2.8)	2 (6.3)
Time elapsed since HIV-1 diagnosis, median (range), y	6.5 (0.2-21.5)	8.8 (0.2-23.4)	8.3 (0.2-21.1)	7.2 (0.7-21.3)	8.9 (0.5-22.9)	3.8 (0.3-20.2)
CDC stage C HIV disease, No. (%)[d]	9 (9.9)	5 (10.0)	18 (15.1)	1 (3.8)	15 (13.9)	3 (9.4)
Nadir CD4 count/μL, median (range)	197 (0-800)	272 (3-908)	206 (3-754)	311 (39-779)	180 (0-601)	218 (13-534)
Antiretroviral therapy, No. (%)	81 (89.0)	39 (78.0)	100 (84.0)	15 (57.7)	98 (90.7)	23 (71.9)
Baseline CD4 count/μL, median (range)	510 (243-1632)	520 (180-1342)	507 (219-1679)	509 (278-1232)	491 (213-1340)	456 (234-708)
CD4 count ≤350/μL, No. (%)	12 (13.2)	9 (18.0)	18 (15.1)	3 (11.5)	17 (15.7)	4 (12.5)
HIV-1 RNA <50 copies/mL, No. (%)	74 (81.3)	37 (74.0)	98 (82.4)	13 (50.0)	90 (83.3)	20 (62.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus 1; ID4 × 4, 4-injection intradermal low-dose (4-μg [one-fifth of 20 μg]) recombinant HBV vaccine; IM20 × 3, 3-injection intramuscular 20-μg standard-dose recombinant HBV vaccine; IM40 × 4, 4-injection intramuscular double-dose (40-μg [2 injections of 20 μg]) recombinant HBV vaccine.

[a] Patients were randomized according to vaccination regimen and are presented according to response (titer of hepatitis B surface antibodies [HBsAb], ≥10 mIU/mL) at week 28. Nonresponders were participants with an HBsAb titer less than 10 mIU/mL at week 28.

[b] Defined as smoking at least 5 cigarettes per day.

[c] Defined as at least 15 alcoholic drinks per week for a woman or 22 alcoholic drinks per week for a man, or at least 6 consecutive alcoholic drinks on at least 1 occasion per week.

[d] Defined in the 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults (http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm).

Table 2. Response at Months 18, 30, and 42 for Patients Who Received at Least 1 Dose of Vaccine (Modified Intention-to-Treat Analysis)[a]

Time of Assessment	Complete Case Analysis, No. of Responders/No. Undergoing Testing (%)			Multiple Imputation Analysis				
				Response, % of Patients (95% CI)[b]			P Value[c]	
	IM20 × 3 Group (n = 141)	IM40 × 4 Group (n = 145)	ID4 × 4 Group (n = 140)	IM20 × 3 Group (n = 141)	IM40 × 4 Group (n = 145)	ID4 × 4 Group (n = 140)	IM40 × 4 vs IM20 × 3 Groups	ID4 × 4 vs IM20 × 3 Groups
Month 18								
Response	63/131 (48.1)	107/138 (77.5)	69/124 (55.6)	49 (40-57)	78 (71-84)	58 (50-66)	1.48×10^{-7}	.11
High-level response	26/131 (19.8)	76/138 (55.1)	20/124 (16.1)	20 (13-27)	56 (48-64)	17 (11-24)	2.87×10^{-11}	.57
Month 30								
Response	54/126 (42.9)	92/127 (72.4)	55/122 (45.1)	43 (35-52)	74 (67-81)	48 (39-56)	5.78×10^{-8}	.44
High-level response	20/126 (15.9)	58/127 (45.7)	18/122 (14.8)	15 (9-21)	46 (38-55)	16 (10-22)	1.74×10^{-9}	.93
Month 42								
Response	47/122 (38.5)	85/124 (68.5)	49/119 (41.2)	41 (33-49)	71 (64-79)	44 (35-53)	8.80×10^{-8}	.64
High-level response	20/122 (16.4)	49/124 (39.5)	18/119 (15.1)	16 (10-22)	42 (34-50)	16 (9-23)	5.10×10^{-7}	.99

Abbreviations: ID4 × 4, 4-injection intradermal low-dose (4-μg [one-fifth of 20 μg]) recombinant hepatitis V virus (HBV) vaccine; IM20 × 3, 3-injection intramuscular 20-μg standard-dose recombinant HBV vaccine; IM40 × 4, 4-injection intramuscular double-dose (40-μg [2 injections of 20 μg]) recombinant HBV vaccine.

[a] Measured by response group. Response indicates hepatitis B surface antibody titers of 10 mIU/mL or greater; high-level response, 100 mIU/mL or greater. Details on observed and imputed titers at each of the follow-up points are described in the eTable in the Supplement.

[b] Calculated mean proportional values are derived from complete case data and 5 sets of imputed values for missing titers in responders.

[c] Calculated using a 2-tailed *t* test. $P < .0083$ indicates statistical significance.

α risk, 0.00625), and 322 (95% CI, 216-479) mIU/mL in the ID4 × 4 group ($P = .50$ compared with IM20 × 3) (**Figure 2**). The kinetic profile was similar across the groups ($P = .22$) and showed a marked decrease of more than 90% of the GMT at month 18 to reach 36 (95% CI, 24-57) mIU/mL in the IM20 × 3 group, 178 (95% CI, 121-260) mIU/mL in the IM40 × 4 group ($P < .001$ compared

Table 3. Variables Associated With Persistence of Immune Response at Month 18 in Patients With a Response at Week 28[a]

Variables	Complete Case Analysis		Multiple Imputation Analysis, OR (95% CI)	
	No. of Responders/ No. Undergoing Testing (%)	Bivariable OR (95% CI)	Bivariable	Adjusted[b]
Recombinant HBV vaccination regimen				
IM20 × 3	62/81 (76.5)	1 [Reference]	1 [Reference]	1 [Reference]
IM40 × 4	103/112 (92.0)	3.51 (1.49-8.23)	3.54 (1.59-7.86)	3.79 (1.65-8.73)
ID4 × 4	68/92 (73.9)	0.87 (0.43-1.74)	1.01 (0.52-1.94)	0.98 (0.49-1.95)
Active smoking[c]				
No	175/206 (85)	1 [Reference]	1 [Reference]	1 [Reference]
Yes	58/79 (73)	0.49 (0.26-0.92)	0.41(0.23-0.74)	0.34 (0.18-0.63)
CD4 count >350/μL				
No	30/44 (68)	1 [Reference]	1 [Reference]	1 [Reference]
Yes	203/241 (84)	2.49 (1.21-5.14)	2.26 (1.13-4.51)	2.64 (1.25-5.61)
Baseline HIV-RNA level, copies/mL				
<50	196/234 (84)	1 [Reference]	1 [Reference]	[d]
≥50	37/51 (73)	0.51 (0.25-1.04)	0.51 (0.26-1.02)	[d]
Time elapsed since HIV diagnosis, y	NA	1.07 (1.01-1.12)	1.06 (1.01-1.12)	1.07 (1.02-1.13)

Abbreviations: HBV, hepatitis B virus; HIV, human immunodeficiency virus; ID4 × 4, 4-injection intradermal low-dose (4-μg [one-fifth of 20 μg]) recombinant HBV vaccine; IM20 × 3, 3-injection intramuscular 20-μg standard-dose recombinant HBV vaccine; IM40 × 4, 4-injection intramuscular double-dose (40-μg [2 injections of 20 μg]) recombinant HBV vaccine; NA, not applicable; OR, odds ratio.

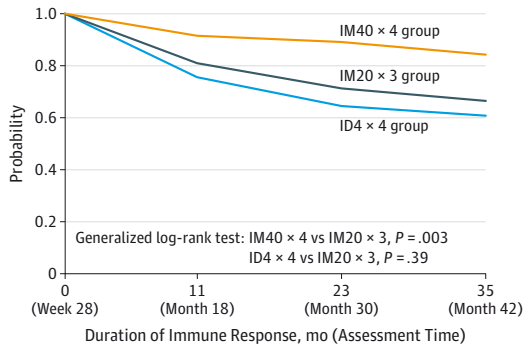
[a] Complete case data included 285 patients and multiple imputation data included 318 patients (see the Statistical Analysis subsection of the Methods section). Response indicates hepatitis B surface antibody titers of 10 mIU/mL or greater.

[b] Adjusted by vaccination group, active smoking, CD4 count, and time elapsed since HIV diagnosis.

[c] Defined as smoking at least 5 cigarettes per day.

[d] Indicates not included in the multivariable model ($P > .15$ in bivariable analysis) or eliminated from the multivariable model by backward selection procedure.

Figure 1. Duration of Immune Response

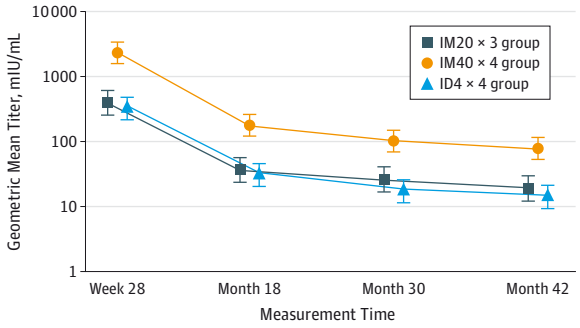


No. at risk

IM20 × 3 group	91	68	56	46
IM40 × 4 group	119	106	95	81
ID4 × 4 group	108	77	60	49

Response indicates hepatitis B surface antibody titers of 10 mUI/mL or higher. Responses are given according to vaccination regimen. ID4 × 4 indicates 4-injection intradermal low-dose (4-μg [one-fifth of 20 μg]) recombinant hepatitis B virus (HBV) vaccine; IM20 × 3, 3-injection intramuscular 20-μg standard-dose recombinant HBV vaccine; IM40 × 4, 4-injection intramuscular double-dose (40-μg [2 injections of 20 μg]) recombinant HBV vaccine.

Figure 2. Kinetics of Geometric Mean Titers of Hepatitis B Surface Antibodies (HBsAb)



Titers are reported for patients who responded to treatment (HBsAb titer, ≥10 mIU/mL) at week 28 by vaccination regimen. ID4 × 4 indicates 4-injection intradermal low-dose (4-μg [one-fifth of 20 μg]) recombinant hepatitis B virus (HBV) vaccine; IM20 × 3, 3-injection intramuscular 20-μg standard-dose recombinant HBV vaccine; IM40 × 4, 4-injection intramuscular double-dose (40-μg [2 injections of 20 μg]) recombinant HBV vaccine. Error bars indicate 95% CIs.

with IM20 × 3; α risk, 0.00625), and 30 (95% CI, 20-46) mIU/mL in the ID4 × 4 group ($P = .55$ compared with IM20 × 3). In the following 2 years, a constant linear decrease of approximately 50% was observed. The GMT of HBsAb at month 42 reached 19 (95% CI, 12-30) mIU/mL in the IM20 × 3 group, 78 (95% CI, 53-115) mIU/mL in the IM40 × 4 group ($P < .001$ compared with IM20 × 3; α risk, 0.00625), and 14 (95% CI, 9-21) mIU/mL in the ID4 × 4 group ($P = .33$ compared with IM20 × 3). No adverse event related to vaccination was reported during the long-term follow-up.

Discussion

This vaccination trial is the first, to our knowledge, to report a long-term immune response with a randomized design for

2 alternative strategies of vaccination to the standard HBV vaccination schedule in adults with HIV-1. The IM4 × 4 regimen significantly improved the long-term immune response compared with the standard (IM20 × 3) regimen. The percentage of responders at month 42 was 71% in the IM40 × 4 group and 41% in the IM20 × 3 group. Among patients who were responders at week 28, a sustained immune response at month 42 was obtained in 83% in the IM40 × 4 group and 62% in the IM20 × 3 group.

In immunocompetent individuals, a decrease in the HBsAb titer to less than 10 mIU/mL is not considered a loss of protection.[13] Despite waning of HBsAb titers, the cellular immune response is supposed to enable rapid production of HBsAb in case of HBV exposure and to avoid chronic infection, which is the reason why no long-term follow-up of HBsAb titer is needed in this population. By contrast, the clinical meaning of a loss of HBsAb in HIV-1–infected individuals is unclear. Their cellular immune response may be impaired and the production of HBsAb in case of exposure to HBV may be insufficient to avoid chronic infection. The study by Landrum et al[14] showed that HBV vaccination before HIV diagnosis was associated with a reduced risk for HBV infection, whereas no significant reduction in HBV infection risk was observed in patients vaccinated after HIV diagnosis. That study[14] also showed that responders to vaccination had a lower risk for HBV infection irrespective of the timing of vaccination. Moreover, the risk for HBV infection is higher in HIV-infected patients who have an increased risk for development of chronic infection and complications.[15,16] In a highly exposed population of men who have sex with men and had been vaccinated, the 2-year attack rates of HBV events, including seroconversion with hepatitis B core antibodies, were 0.23% in those with titers of greater than 10 mIU/mL, 11.11% in those with titers from 2.1 to 10 mIU/mL, and 33.33% in those with titers of less than 2.1 mIU/mL.[17] For all these reasons, maintenance of an HBsAb titer of at least 10 mIU/mL is recommended in HIV-infected patients.[18,19] Taken together, the data support the systematic vaccination of all HIV-infected patients by selecting the vaccination schedules that lead to the highest rates of response and the highest GMT of HBsAb after primary immunization.

A recent systematic review[9] included 12 studies conducted in HIV-infected patients with follow-up times ranging from 12 to 115 months. After three 40-µg doses of HBV vaccine, 71% of the primary responders retained antibody titers of at least 10 mIU/mL at year 1; 33% to 61%, at year 2; and 40%, at year 5. These results show that despite relatively high rates of response after primary immunization, the immune response is rapidly lost in HIV-infected patients compared with healthy individuals.[20] In the recent study by Lopes et al[7] in HIV-infected patients, the mean time to loss of an HBsAb titer of at least 10 mIU/mL was 2.0, 3.7, and 4.4 years for patients with an HBsAb titer of 10 to 100, greater than 100 to 1000, and greater than 1000 mIU/mL, respectively, at primary vaccination.

In a multivariable analysis in our previous report,[2] the variables associated with a response after primary immunization (in addition to regimen group) were female sex, being younger, no active smoking, a higher baseline CD4 count, and an undetectable plasma HIV-1 RNA. In the present analysis, the variables associated with a sustained response at month 18 were a high response at week 28 and a longer time elapsed since HIV-1 diagnosis. In the study by Lopes et al,[7] a high HBsAb titer at primary vaccination was the strongest predictor for the duration of an HBsAb titer of at least 10 mUI/mL. Taken together, these results suggest that an HBsAb titer of at least 10 mIU/mL after hepatitis B surface antigen immunization in immunocompromised patients can be obtained with higher doses of antigen in patients with a controlled HIV viral load. A longer time elapsed since HIV-1 diagnosis was also associated with a sustained response at month 18. This finding is counter to what would be expected, with no clear explanation. Our results add to the evidence that HBV vaccination with higher doses of antigen in immunocompromised patients is important to increase not only response rates but also the durability of seroprotective HBsAb titers.

Immunization with the ID4 × 4 regimen significantly improved the serologic response at week 28, although it did not have the response rates obtained with the IM40 × 4 regimen.[2] The intradermal regimen gave the possibility of reducing the antigen dose compared with intramuscular delivery. However, the advantage in terms of immune response compared with the classic regimen was rapidly lost after primary immunization.

The purpose of the ANRS HB03 VIHVAC-B trial was to explore alternative schedules that might increase immunogenicity to a greater extent than the standard HBV vaccination regimen in adults with HIV-1. Indeed, inducing protection against HBV infection is critical in patients with HIV-1, given the increased risk for HBV infection and the increased risk for liver-related morbidity and mortality.[15,16] Our results indicate that alternative vaccination schedules can be useful to improve long-term immune response to hepatitis B surface antigen and should encourage other attempts of alternative schedules.

Our study of immune response to month 42 has some limitations. First, a relative high rate of loss to follow-up is unavoidable in such a study. Nevertheless, by comparison, this rate was limited among the 318 patients who were responders, because HBsAb titer measurements were available in 292 patients (91.8%) at month 18, 255 patients (80.2%) at month 30, and 227 patients (71.4%) at month 42. Second, because only responders were included in the follow-up, HBV markers in nonresponders are missing and we cannot study whether nonresponders and patients with a loss of HBsAb were equally protected against HBV. In addition, the sample size of the study is too small to evaluate clinical protection.

Conclusions

In a large randomized clinical trial, the IM40 × 4 regimen of recombinant HBV vaccine improved immune response to month 42 in adults with HIV-1. The clinical importance of this finding is unknown at this time. Further studies are needed to evaluate the clinical protection conferred by higher immune response to HBV vaccination.

ARTICLE INFORMATION

Accepted for Publication: February 16, 2016.

Published Online: April 11, 2016. doi:10.1001/jamainternmed.2016.0741.

Author Affiliations: Université Paris Descartes, Sorbonne Paris Cité, Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpital Cochin, Paris, France (Launay, Rosenberg); Institut National de la Santé et de la Recherche Medicale (INSERM), Clinical Investigation Center 1417, Paris, France (Launay); INSERM French Clinical Research Infrastructure Network, Innovative Clinical Research Network in Vaccinology, France (Launay, Reynes, Raffi, Piroth); Hôpitaux Universitaires, Strasbourg, France (Rey); Sorbonne Universités, Université Pierre-et-Marie-Curie, Université Paris 06, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique (Unité Mixte de Recherche en Santé 1136), Paris, France (Pouget, Carrat); Institut Pasteur, INSERM U994, Paris, France (Michel); Centre Hospitalier Universitaire de Montpellier, Hôpital Gui de Chauliac, Université de Montpellier, Unité Mixte Internationale 233, Montpellier, France (Reynes); Service des Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire (CHU) Bordeaux, Unité Mixte de Recherche–Centre National de la Recherche Scientifique 5234, Bordeaux, France (Neau); Collège des Universitaires des Maladies Infectieuses et Tropicales, Paris, France (Raffi); CHU and UMR 1347, Université de Bourgogne, Dijon, France (Piroth); AP-HP, Hôpital Saint Antoine, Unité de Santé Publique, Paris, France (Carrat).

Author Contributions: Dr Carrat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Launay, Rosenberg, Rey, Michel, Piroth, Carrat.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Launay, Carrat.
Critical revision of the manuscript for important intellectual content: Launay, Rosenberg, Rey, Pouget, Michel, Reynes, Neau, Raffi, Piroth, Carrat.
Statistical analysis: Carrat.
Obtained funding: Launay, Carrat.
Administrative, technical, or material support: Launay, Rosenberg, Michel, Carrat.
Study supervision: Launay, Carrat.

Conflict of Interest Disclosures: Dr Launay reports being an investigator for vaccine studies sponsored by Sanofi Pasteur-MSD, MSD, Sanofi Pasteur, GlaxoSmithKline, and Novartis Foundation and receiving travel support to attend scientific meetings from Sanofi Pasteur-MSD, MSD, Sanofi Pasteur, GlaxoSmithKline, and Pfizer. Dr Piroth reports receiving honoraria from GlaxoSmithKline, Gilead, and Bristol-Myers Squibb. Dr Raffi reports receiving honoraria from Bristol-Myers Squibb and Merck Sharp and Dohme and receiving travel support to attend scientific meetings from Bristol-Myers Squibb and GlaxoSmithKline. Dr Carrat reports receiving honoraria from Astra Zeneca and GlaxoSmithKline outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS). Sanofi Pasteur-MSD contributed the vaccines.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: Members of the ANRS HB03 VIHVAC-B Study Group include Anne Frésard, MD (Hôpital Bellevue, Saint-Etienne); Caroline Lascoux, MD (Hôpital Saint-Louis, Paris); Olivier Lortholary, MD (Hôpital Necker–Enfants Malades, Paris); ElinaTeicher, MD (Hôpital Bicêtre, Le Kremlin-Bicêtre); Agathe Rami, MD (Hôpital Lariboisière, Paris); Alain Lafeuillade, MD (Hôpital Font-Pré, Toulon); Pierre de Truchis, MD (Hôpital Raymond Poincaré, Garches); Vincent Jeantils, MD (Hôpital Jean Verdier, Bondy); Daniel Vittecocq, MD (Hôpital Paul Brousse, Villejuif); Laurence Slama, MD, and Gilles Pialoux, MD (Hôpital Tenon, Paris); Sophie Abgrall, MD (Hôpital Avicenne, Avicenne); Yves Levy, MD (Hôpital Henri Mondor, Créteil); Marc-Antoine Valantin, MD (Hôpital Pitié-Salpêtrière, Paris); Pierre-Marie Girard, MD (Hôpital Saint-Antoine, Assistance Publique Hôpitaux de Paris [AP-HP], Paris); Jean-Michel Molina, MD (Hôpital St-Louis, Paris); Didier Neau, MD (Hôpital Pellegrin, Bordeaux); Patrick Miailhes, MD (Hôpital Hôtel-Dieu, Lyon); Isabelle Poizot-Martin, MD (Hôpital Ste Marguerite, Marseille); Sophie Matheron, MD (Hôpital Bichat, Paris); Jacques Reynes, MD (Hôpital Gui de Chauliac, Montpellier); Bénédicte Bonnet, MD (Hôpital Hôtel-Dieu, Nantes); Eric Rosenthal, MD (Hôpital de l'Archet, Nice); David Rey, MD, and Patricia Fischer, MD (Hôpital Civil, Strasbourg); LiseCuzin, MD (Hôpital Purpan, Toulouse); Renaud Verdon, MD (Hôpital Côte de Nacre, Caen); Lionel Piroth, MD (Hôpital du Bocage, Dijon); Pascale Leclercq, MD (Hôpital A. Michallon, Grenoble); Faiza Ajana, MD (Hôpital Gustave Dron, Tourcoing); Thierry May, MD (Hôpital Brabois, Nancy); Agnès Lefort, MD (Hôpital Beaujon, Clichy); Brigitte Elharrar, MD (Centre Hospitalier Intercommunal, Créteil); Odile Launay, MD, PhD (Hôpital Cochin, Paris); and Jean-Paul Viard, MD (Hôpital Hôtel-Dieu, Paris). Members of the Scientific Committee include Dr Launay (coordinator; Université Paris Descartes, Hôpital Cochin, Institut National de la Santé et de la Recherche Medicale [INSERM], Paris); Fabrice Carrat, MD, PhD (Université Pierre-et-Marie-Curie, INSERM, Hôpital Saint-Antoine, Paris); Pascaline Rabiega (INSERM, Paris); Arielle Rosenberg, MD (Université Paris Descartes, Hôpital Cochin, Paris); Marie-Louise Michel, MD (Institut Pasteur, INSERM, Paris); Olivier Lortholary, MD (Hôpital Necker–Enfants Malades, Paris); Lionel Piroth, MD (Centre Hospitalier Universitaire, Dijon); David Rey, MD (Hôpitaux Universitaires, Strasbourg); Philippe Sogni, MD (Université Paris Descartes, Hôpital Cochin, Paris); Isabelle Poizot-Martin, MD (Hôpital Sainte Marguerite, Marseille); Lise Cuzin (Hôpital Purpan, Toulouse); and Ventzislava Petrov-Sanchez, MD (INSERM-ANRS, Paris). Members of the independent adjudication committee include Thomas Hanslik, MD, François Bailly, MD, and Emmanuel Touzé, MD. Members of the independent data monitoring committee include Marie-Lise Gougeon, MD, Stanislas Pol, MD, Jean-Pierre Aboulker, MD, MSc, and Marie-Laure Chaix, MD. Members of the methodology and coordinating center include Dr Carrat (coordinator), Pascaline Rabiega, MD, Noëlle Pouget, PhD, Grégory Pannetier, BA, Wenceslas Yaba, PhD, Céline Kutala-Pires, MPH, Théo Duran, MPH, Cendrine Chevallot, MPH, Frédéric Chau, MCS, and Sylvain Bitschiné, MCS (INSERM U1136, Université Pierre et Marie Curie). The ANRS HB03 VIHVAC-B Study was sponsored by Ventzislava Petrov-Sanchez and Aurélie Pailhé (Agence Nationale pour la Recherche sur le SIDA et les Hépatites Virales, INSERM-ANRS, Paris).

Additional Contributions: We thank the study participants and the participating health care professionals at each site. Jean-Francois Meritet, MD, AP-HP, Hôpital Cochin, Service de Virologie, Paris, France, contributed to the serologic testing. He received no compensation for this role. Francis Beauvais, MD, PhD, helped to prepare the manuscript, for which he was compensated.

REFERENCES

1. Geretti AM, Doyle T. Immunization for HIV-positive individuals. *Curr Opin Infect Dis*. 2010;23(1):32-38.

2. Launay O, van der Vliet D, Rosenberg AR, et al; ANRS HB03 VIHVAC-B Trial. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA*. 2011;305(14):1432-1440.

3. ClinicalTrials.gov. Trial Comparing Three Strategies of Vaccination Against the Virus of Hepatitis B in HIV-Infected Patients. NCT00480792. https://clinicaltrials.gov/ct2/show/NCT00480792. Accessed January 20. 2016.

4. Cooper CL, Angel JB, Seguin I, Davis HL, Cameron DW. CPG 7909 adjuvant plus hepatitis B virus vaccination in HIV-infected adults achieves long-term seroprotection for up to 5 years. *Clin Infect Dis*. 2008;46(8):1310-1314.

5. Cruciani M, Mengoli C, Serpelloni G, et al. Serologic response to hepatitis B vaccine with high dose and increasing number of injections in HIV infected adult patients. *Vaccine*. 2009;27(1):17-22.

6. Kaech C, Pache I, Bürgisser P, Elzi L, Darling KE, Cavassini M. Immune response to hepatitis B vaccination in HIV-positive adults with isolated antibodies to HBV core antigen. *J Infect*. 2012;65(2):157-164.

7. Lopes VB, Hassing RJ, de Vries-Sluijs TE, et al. Long-term response rates of successful hepatitis B vaccination in HIV-infected patients. *Vaccine*. 2013;31(7):1040-1044.

8. O'Bryan TA, Rini EA, Okulicz J, et al. HIV viraemia during hepatitis B vaccination shortens the duration of protective antibody levels. *HIV Med*. 2015;16(3):161-167.

9. Kernéis S, Launay O, Turbelin C, Batteux F, Hanslik T, Boëlle PY. Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis. *Clin Infect Dis*. 2014;58(8):1130-1139.

10. Wellner JA, Zhan Z. A hybrid algorithm for computation of the nonparametric maximum likelihood estimator from censored data. *J Am Stat Assoc*. 1997;92(439):945-959.

11. Zhao Q, Sun J. Generalized log-rank test for mixed interval-censored failure time data. *Stat Med*. 2004;23(10):1621-1629.

12. Twisk J, de Boer M, de Vente W, Heymans M. Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis. *J Clin Epidemiol*. 2013;66(9):1022-1028.

13. FitzSimons D, Hendrickx G, Vorsters A, Van Damme P. Hepatitis B vaccination: a completed schedule enough to control HBV lifelong? Milan, Italy, 17-18 November 2011. *Vaccine*. 2013;31(4):584-590.

14. Landrum ML, Hullsiek KH, Chun HM, et al. The timing of hepatitis B virus (HBV) immunization relative to human immunodeficiency virus (HIV) diagnosis and the risk of HBV infection following HIV diagnosis. *Am J Epidemiol*. 2011;173(1):84-93.

15. Konopnicki D, Mocroft A, de Wit S, et al; EuroSIDA Group. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS*. 2005;19(6):593-601.

16. Thio CL, Seaberg EC, Skolasky R Jr, et al; Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360(9349):1921-1926.

17. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): a final report. *Hepatology*. 1981;1(5):377-385.

18. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58(RR-4):1-207.

19. Geretti AM, Brook G, Cameron C, et al; BHIVA Immunization Writing Committee. British HIV Association guidelines for immunization of HIV-infected adults 2008. *HIV Med*. 2008;9(10):795-848.

20. Alavian SM, Mansouri S, Abouzari M, Assari S, Bonab MS, Miri SM. Long-term efficacy of hepatitis B vaccination in healthcare workers of Oil Company Hospital, Tehran, Iran (1989-2005). *Eur J Gastroenterol Hepatol*. 2008;20(2):131-134.