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

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**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
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 ×10⁹ 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.5 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.\(^\text{10}\) 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.\(^\text{11}\)

To describe the kinetics of HBsAb titer, we used a linear mixed model on complete case data as recommended.\(^\text{12}\) 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 titer. 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 (bi vari ables odd 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 Responsea

<table>
<thead>
<tr>
<th>Characteristic of Recombinant HBV Vaccine</th>
<th>IM20 × 3 Group (n = 141)</th>
<th>Nonresponders or Not Tested (n = 50)</th>
<th>IM40 × 4 Group (n = 145)</th>
<th>Nonresponders or Not Tested (n = 26)</th>
<th>ID4 × 4 Group (n = 140)</th>
<th>Nonresponders or Not Tested (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, No. (%)</td>
<td>32 (35.2)</td>
<td>8 (16.0)</td>
<td>41 (34.5)</td>
<td>8 (30.8)</td>
<td>44 (40.7)</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>41 (19-60)</td>
<td>45 (22-74)</td>
<td>43 (19-65)</td>
<td>40 (31-61)</td>
<td>43 (19-70)</td>
<td>42 (21-60)</td>
</tr>
<tr>
<td>BMI, median (range)</td>
<td>23 (17-36)</td>
<td>23 (18-36)</td>
<td>24 (18-56)</td>
<td>24 (19-33)</td>
<td>23 (16-39)</td>
<td>24 (17-37)</td>
</tr>
<tr>
<td>Active smoking, No. (%)</td>
<td>27 (29.7)</td>
<td>22 (44.0)</td>
<td>31 (26.1)</td>
<td>13 (50.0)</td>
<td>34 (31.5)</td>
<td>17 (53.1)</td>
</tr>
<tr>
<td>Excessive alcohol use, No. (%)</td>
<td>8 (8.8)</td>
<td>3 (6.0)</td>
<td>5 (4.2)</td>
<td>2 (7.7)</td>
<td>10 (9.3)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Anti-HCV antibodies present, No. (%)</td>
<td>2 (2.2)</td>
<td>3 (6.0)</td>
<td>4 (3.4)</td>
<td>2 (7.7)</td>
<td>3 (2.8)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Time elapsed since HIV-1 diagnosis, median (range), y</td>
<td>6.5 (0.2-21.5)</td>
<td>8.8 (0.2-23.4)</td>
<td>8.3 (0.2-21.1)</td>
<td>7.2 (0.7-21.3)</td>
<td>8.9 (0.5-22.9)</td>
<td>3.8 (0.3-20.2)</td>
</tr>
<tr>
<td>CDC stage C HIV disease, No. (%)</td>
<td>9 (9.9)</td>
<td>5 (10.0)</td>
<td>18 (15.1)</td>
<td>1 (3.8)</td>
<td>15 (13.9)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Nadir CD4 count/μL, median (range)</td>
<td>197 (0-800)</td>
<td>272 (3-908)</td>
<td>206 (3-754)</td>
<td>311 (39-779)</td>
<td>180 (0-601)</td>
<td>218 (13-534)</td>
</tr>
<tr>
<td>Antiretroviral therapy, No. (%)</td>
<td>81 (89.0)</td>
<td>39 (78.0)</td>
<td>100 (84.0)</td>
<td>15 (57.7)</td>
<td>98 (90.7)</td>
<td>23 (71.9)</td>
</tr>
<tr>
<td>Baseline CD4 count/μL, median (range)</td>
<td>510 (243-1632)</td>
<td>520 (180-1342)</td>
<td>507 (219-1679)</td>
<td>509 (278-1323)</td>
<td>491 (213-1340)</td>
<td>456 (234-708)</td>
</tr>
<tr>
<td>CD4 count ≤350/μL, No. (%)</td>
<td>12 (13.2)</td>
<td>9 (18.0)</td>
<td>18 (15.1)</td>
<td>3 (11.5)</td>
<td>17 (15.7)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt;50 copies/mL, No. (%)</td>
<td>74 (81.3)</td>
<td>37 (74.0)</td>
<td>98 (82.4)</td>
<td>13 (50.0)</td>
<td>90 (83.3)</td>
<td>20 (62.5)</td>
</tr>
</tbody>
</table>

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; IM20 × 3, 4-injection intramuscular low-dose (4-μg [one-fifth of 20 μg]) recombinant HBV vaccine; IM40 × 4, 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.

* Defined as smoking at least 5 cigarettes per day.
† 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.
‡ 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)*

<table>
<thead>
<tr>
<th>Time of Assessment</th>
<th>Complete Case Analysis, No. of Responders/No. Undergoing Testing (%)</th>
<th>Multiple Imputation Analysis Response, % of Patients (95% CI)b</th>
<th>P Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM20 × 3 Group (n = 141)</td>
<td>IM40 × 4 Group (n = 145)</td>
<td>IM40 × 4 Group (n = 140)</td>
</tr>
<tr>
<td>Month 18</td>
<td>Response</td>
<td>63/131 (48.1)</td>
<td>107/138 (77.5)</td>
</tr>
<tr>
<td></td>
<td>High-level response</td>
<td>26/131 (19.8)</td>
<td>76/138 (55.1)</td>
</tr>
<tr>
<td>Month 30</td>
<td>Response</td>
<td>54/126 (42.9)</td>
<td>92/127 (72.4)</td>
</tr>
<tr>
<td></td>
<td>High-level response</td>
<td>20/126 (15.9)</td>
<td>58/127 (45.7)</td>
</tr>
<tr>
<td>Month 42</td>
<td>Response</td>
<td>47/122 (38.5)</td>
<td>85/124 (68.5)</td>
</tr>
<tr>
<td></td>
<td>High-level response</td>
<td>20/122 (16.4)</td>
<td>49/124 (39.5)</td>
</tr>
</tbody>
</table>

Abbreviations: IM40 × 4, 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.

* 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.

α risk, 0.00625, and 322 (95% CI, 216-479) mIU/mL in the IM40 × 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...
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...
to evaluate the clinical protection conferred by higher 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 respondents, 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.
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