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

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PATIENTS COINFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS 1 (HIV-1) and hepatitis B virus (HBV) are at increased risk for liver-related morbidity and mortality.1,2 Because both viruses share similar modes of transmission, HIV-HBV coinfection rate is high.1,3 Therefore, guidelines recommend that all patients with HIV infection who are negative for HBV markers should be immunized for HBV.4,5 However, the immunogenicity of hepatitis B vaccination in adults with HIV infection is between 17.5% and 72%6-10 and is lower than in HIV-seronegative healthy adults, in whom seroconversion rates are more than 90%.11 Previous studies suggested that modification of the standard HBV vaccination schedule (higher hepatitis B vaccine doses, prolongation of the vaccination schedule, or both) or addition of a vaccine adjuvant may increase response rate.6,8,12-17 Another possible approach to increasing response to HBV antigen is the use of the intradermal route.18 Both high hepatitis B vacc...
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Cine doses and use of the intradermal route are well tolerated.6,14,18 However, available data on alternative HBV vaccination schedules remain insufficient to support changes in current guidelines in the HIV setting.

The goal of the Agence Nationale de Recherches sur le SIDA et les hépatites virales (French National Agency for Research on AIDS and Viral Hepatitis) HB03 VIHVAC-B trial was to compare in a randomized trial the immunogenicity and safety of 2 alternative vaccination protocols (4 double-dose intramuscular injections and 4 low-dose intradermal injections) with the standard HBV vaccine schedule in patients with HIV infection with a CD4 cell count of more than 200 cells/µL.

METHODS

Study Design

A phase 3, multicenter, randomized, open-label, parallel-group, 1:1:1 allocation ratio, clinical trial was performed in 33 centers with patients enrolled in French National Agency for Research on AIDS and Viral Hepatitis trials in France between June 28, 2007, and October 23, 2008. Patients were eligible to participate if they were adults with HIV-1 infection, had a CD4 cell count of more than 200 cells/µL, had no HBV serological marker (ie, negative for hepatitis B surface antigen [anti-HBs], and hepatitis B core antibody), had unchanged antiretroviral treatment for the last 2 months for patients who were receiving antiretroviral treatment at the time of the screening visit (patients with a CD4 cell count of less than 350 cells/µL were required to have received antiretroviral therapy for the last 6 months in conjunction with an undetectable plasma HIV-1 RNA level [<50 copies/µL]), and had a negative pregnancy test at screening and inclusion visits.

Main exclusion criteria included any history of hepatitis B vaccination, acute cytolyis in the last 3 months (alanine aminotransferase, aspartate aminotransferase, or both ≥5 times the upper normal range), any vaccination during the month preceding inclusion, intolerance to any component of the vaccine, ongoing opportunistic infection or hemopathy or solid organ cancer, unexplained fever the week before inclusion, prothrombin ratio equal to or less than 50%, number of platelets equal to or less than 50,000 cells/µL, immunosuppressive or immunomodulating treatment in the last 6 months before the screening visit, splenectomy, compensated cirrhosis (Child-Pugh class B or C [based on the classification system for liver disease severity]), renal function insufficiency (creatinine clearance <50 ml/min [to convert to milliliters per second, multiply by 0.0167]), or other immunocompromised condition not related to HIV infection (eg, solid organ transplantation).

Patients were centrally randomized (1:1:1) into 3 groups. Patients received 3 intramuscular injections of the standard dose (20 µg) of recombinant HBV vaccine (GenHevac B Pasteur 20 µg, Sanofi Pasteur, Lyon, France) at weeks 0, 4, and 24 (group IM20 × 3, n=145); 4 intramuscular injections of double doses (40 µg [2 injections of 20 µg of GenHevac B Pasteur 20 µg, Sanofi Pasteur]) of recombinant HBV vaccine at weeks 0, 4, 8, and 24 (group IM40 × 4, n=148); or 4 intradermal injections of low doses (4 µg [1/5 of GenHevac B Pasteur 20 µg, Sanofi Pasteur]) of recombinant HBV vaccine at weeks 0, 4, 8, and 24 (group ID4 × 4, n=144).

Randomization was stratified according to baseline CD4 cell count (200-349 cells/µL vs ≥350 cells/µL), baseline plasma HIV-1 RNA level (<50 vs ≥50 copies/µL), and the presence of anti-hepatitis C virus (HCV) antibodies, as these factors were suspected to impair the immune response to HBV vaccination.7,8,19 Randomization was managed by the central data center (Inserm U707, Paris, France). The randomization code was developed using a computerized random number generator to select random permuted block sizes of 3 and 6. The randomization list was concealed from the investigators who assigned participants to the vaccination groups through a dedicated Web site after validating the eligibility and stratification criteria. Instructions were given to the center to perform the randomization of the patients on the day of the first vaccine injection (if possible) to minimize delay between randomization and administration of vaccine (decreasing the number of randomized patients excluded from the analysis because of not receiving vaccine).

Blood samples were planned for quantification of anti-HBs titers at weeks 0, 4, 8, 12, 24, and 28. Assessment of standard biochemical tests (including alanine aminotransferase and aspartate aminotransferase levels), CD4/CD8 cell counts, and serum HIV-1 RNA levels were planned at screening/baseline and at weeks 4, 8, 12, 24, and 28.

In addition to the trial, as prespecified in the protocol, patients who achieved a response would be followed up until months 18, 30, and 42 to study the durability and the dynamics of response (which is under investigation), and patients who did not respond will be offered a maximum of 3 supplementary intramuscular injections of standard vaccine dose (20 µg) at months 8, 9, and 10.

Written informed consent was obtained from each patient before enrollment. The protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the “Ile-de-France III” Ethics Committee (Paris, France). An independent adjudication committee consisting of an independent internist, neurologist, and hepatologist reviewed blinded safety data. Blinding was maintained with the use of a devoted reporting adverse event form describing clinical events that did not contain any information regarding the group, the route, the number, or the dose of vaccine injection. An independent data monitoring committee consisting of an independent statistician, immunologist, hepatologist, and virologist reviewed unblinded safety and efficacy data every 6 months during the trial. The committee was particularly mandated to make a determin-
nation regarding the continuation of the trial based on safety data and the presence of any immunologic response in the ID4 × 4 group. These committees had no role in the decision to submit the manuscript.

Safety Assessment

Patients were provided with diary cards explicitly specifying a fixed list of local and general reactions for use in recording whether the reactions were present or absent after each injection. The forms were used by patients for recording the occurrence and severity of the solicited local reactions at the injection site (erythema, edema, pain, induration, pruritus, discoloration, and nodule [ie, local reactions usually observed after intradermal immunization]) during 7 days after vaccination, solicited systemic (general) reactions (fever, headache, asthenia, cutaneous eruption, vertigo, malaise, nausea, vomiting, abdominal pain, diarrhea, myalgia, and arthralgia [ie, general reactions previously reported during HBV vaccine trials]), and any unsolicited adverse events during 28 days after vaccination.

Laboratory Assays

The quantification of anti-HBs titers on serum samples was performed in a central laboratory (Hospital Cochin, Paris, France) using a standardized assay (Monolisa Anti-HBs PLUS Assay; Bio-Rad Laboratories Inc, Marnes-la-Coquette, France). 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 were retested after being diluted as recommended by the manufacturer.

Statistical Analysis

The primary end point was the percentage of responders (patients with anti-HBs titers ≥10 mIU/mL, levels consistent with seroprotection) 4 weeks after the last planned vaccination (week 28), as specified in the protocol. Other prespecified immunological efficacy end points were the percentage of patients with anti-HBs titers of at least 10 mIU/mL at weeks 4, 8, 12, and 24; the percentage of high-level responders (patients with anti-HBs titers ≥100 mIU/mL, levels considered to confer higher and long-term protection against infection23); and the geometric mean titer of anti-HBs at weeks 4, 8, 12, 24, and 28. Special attention was paid to the proportion and intensity of general and local adverse events.

The hypothesis tested in our trial in the HIV setting was that the immunogenicity of 2 alternative vaccination protocols (4 intramuscular double doses and 4 intradermal low doses) was higher than the immunogenicity of the standard vaccination protocol. In addition, because intradermal immunization requires lower antigen doses, significant cost savings could be of interest in limited resource settings with high HBV prevalence.

Our trial was designed to have a power of 80% to detect a difference of 20% (55% vs 35%) of responders in the IM40 × 4 and ID4 × 4 vaccination groups in comparison with the IM20 × 3 group. The level of significance was set to 2.5% 2-sided to account for multiple comparisons with the IM20 × 3 group. Taking into account early study discontinuations, 140 patients had to be enrolled in each group.
As prespecified in the protocol, the modified intention-to-treat analysis population data set was defined as all patients receiving at least 1 dose of vaccine (n = 426). Eleven randomized patients who did not receive any vaccine were not included (Figure 1). The same modified intention-to-treat analysis population data set was considered for the primary analysis and the secondary analyses, but the primary and secondary analyses differed in the method used for handling missing measurements. In the primary (efficacy) analysis, patients who missed the final follow-up visit at week 28 were considered to be nonresponders (n = 8 for IM20 × 3 group; n = 16 for IM40 × 4 group; and n = 6 for ID4 × 4 group) (Table 1; available at http://www.jama.com). In secondary analyses of the percentage of responders, percentage of high-level responders, and geometric mean titer by vaccination group at the specified points, as well as the analysis of predictive covariates for response, missing titer values were handled using last observation carried forward, this approach being the most conservative. Of 2556 measurements, 104 (4%) were missing in 52 patients (12%). The multiple imputation method could not be considered because missingness was related to the level of missing measurement (missingness was not at random) in patients who discontinued the vaccination, and the number of patients in this category was too low for valid inference. All patients with at least 1 dose of vaccine and 1 postvaccination safety measure (n = 424) were included in the safety analyses.

The Cochran-Mantel Haenszel test was used with stratification on CD4 cell count at baseline, plasma HIV-1 RNA level, and HCV coinfection status to compare the percentage of responders in the IM40 × 4 and ID4 × 4 vaccination groups with the standard vaccination schedule (IM20 × 3) (α risk, 2.5%). All other comparisons of baseline characteristics or secondary immunogenicity or safety criteria were performed at 5% level of significance. Proportions were compared using the Fisher exact test for independent samples and the McNemar χ2 test for matched pairs; continuous outcomes were compared using the Mann-Whitney test for independent samples and the Wilcoxon signed rank test for matched pairs. Confidence limits for proportions were calculated using the exact Clopper-Pearson method, and 95% confidence limits for proportions were calculated using the exact Clopper-Pearson method. All patients with at least 15 glasses per week for a woman or 22 glasses per week for a man, or at least 6 consecutive glasses on at least 1 occasion per week.

### Table 1. Demographic and Clinical Characteristics of Patients by Vaccination Regimen

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IM20 × 3 (n = 145)</th>
<th>IM40 × 4 (n = 148)</th>
<th>ID4 × 4 (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>41 (28)</td>
<td>50 (34)</td>
<td>52 (36)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>43 (19-74)</td>
<td>42 (19-65)</td>
<td>43 (19-70)</td>
</tr>
<tr>
<td>BMI, median (range)</td>
<td>23 (17-36)</td>
<td>24 (18-56)</td>
<td>23 (16-39)</td>
</tr>
<tr>
<td>Active smoking&lt;sup&gt;a&lt;/sup&gt;</td>
<td>52 (36)</td>
<td>45 (30)</td>
<td>50 (35)</td>
</tr>
<tr>
<td>Excessive alcohol use&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11 (8)</td>
<td>7 (5)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Anti-HCV antibodies</td>
<td>5 (3)</td>
<td>7 (5)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Time elapsed since HIV diagnosis, median (range), y</td>
<td>7.0 (0.2-23.4)</td>
<td>8.1 (0.2-21.3)</td>
<td>7.3 (0.3-22.9)</td>
</tr>
<tr>
<td>CDC stage C&lt;sup&gt;d&lt;/sup&gt;</td>
<td>15 (10)</td>
<td>19 (12)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Nadir CD4 cell count, median (range), cells/µL</td>
<td>211 (90-908)</td>
<td>217 (3-779)</td>
<td>191 (0-601)</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td>124 (86)</td>
<td>118 (80)</td>
<td>124 (86)</td>
</tr>
<tr>
<td>Baseline CD4 cell count, median (range), cells/µL</td>
<td>516 (180-1632)</td>
<td>509 (219-1679)</td>
<td>482 (213-1340)</td>
</tr>
<tr>
<td>HIV-RNA level &lt;50 copies/mL</td>
<td>114 (79)</td>
<td>114 (77)</td>
<td>113 (78)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Abnormal laboratory values, including low CD4 count (<200/µL) or high HIV-RNA level (>5000 copies/mL) were recorded. The median age was 42 years (range, 19-74 years); 41% were women. Younger patients were more likely to have received the 10 µg dose, and women were more likely to have received the 20 µg dose. A comparison of baseline characteristics or secondary immunogenicity or safety criteria were performed at 5% level of significance. All patients with at least 1 dose of vaccine and 1 postvaccination safety measure (n = 424) were included in the safety analyses. All patients with at least 15 glasses per week for a woman or 22 glasses per week for a man, or at least 6 consecutive glasses on at least 1 occasion per week.

<sup>b</sup>Defined as smoking at least 5 cigarettes per day.

<sup>c</sup>Defined as drinking at least 12 drinks per week for a woman or 17 drinks per week for a man, or at least 5 consecutive drinks on at least 1 occasion per week.

<sup>d</sup>Category of disease as defined in http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm.

### Figure 2. Percentages of Responders and High-Level Responders by Vaccination Regimen

![Graph showing percentages of responders and high-level responders by vaccination regimen](http://www.jama.com).
Pearson methods. Age was categorized using quartiles of the empirical distribution for graphical purpose and proportions of responders across age groups were compared using the Cochran-Armitage $\chi^2$ for trend. All statistical tests were 2-sided.

A list of covariates anticipated to be associated with the antibody response was compiled in the protocol; namely, vaccination group, CD4 cell count, HCV status, HIV-1 RNA detectability, age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), smoking, excessive alcohol use, time elapsed since HIV diagnosis, nadir CD4 cell count, and US Centers for Disease Control and Prevention stage. Logistic regression analyses were used to identify the predictive covariates for response; assumptions were tested and met. Covariates with $P < .25$ in likelihood ratio testing in univariate analysis were included in a multivariate model, and selection of independent covariates was based on a backward elimination procedure, retaining covariates with $P < .05$. All statistical computations were performed using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

### Results

#### Study Patients

A total of 437 adults infected with HIV-1 (145 in IM20 × 3 group, 148 in IM40 × 4 group, and 144 in ID4 × 4 group) were randomized (Figure 1) between June 28, 2007, and October 23, 2008. No differences in baseline characteristics across the study groups were observed (Table 1). Eleven patients did not receive the vaccine and were not included in the analysis. Overall, 141 patients in the IM20 × 3 group, 145 patients in the IM40 × 4 group, and 140 patients in the ID4 × 4 group were vaccinated and were included in the analyses (Figure 1). The proportion of patients who discontinued the vaccination did not differ between groups ($P = .26$). Patients were followed up in the trial for primary comparison during 28 weeks, ending on July 3, 2009. Anti-HBs titer at final measurement was missing in 8 patients (6%) in the IM20 × 3 group, 16 (11%) in the IM40 × 4 group, and 6 (4%) in the ID4 × 4 group ($P = .06$).

#### Immunogenicity

In the primary (efficacy) analysis, a response was observed in 91 patients (65%; 95% confidence interval [CI], 56%-72%) in the IM20 × 3 group; 119 patients (82%; 95% CI, 77%-88%) in the IM40 × 4 group ($P < .001$ vs IM20 × 3 group); and 108 patients (77%; 95% CI, 69%-84%) in the ID4 × 4 group ($P = .02$ vs IM20 × 3 group). Using the last observation carried forward–imputed missing measurements, a response occurred in 93 patients (66%; 95% CI, 58%-74%) in the IM20 × 3 group; in 125 patients (86%; 95% CI, 80%-91%) in the IM40 × 4 group ($P < .001$ vs IM20 × 3 group); and in 110 patients (79%; 95% CI, 71%-85%) in the ID4 × 4 group ($P = .02$ vs IM20 × 3 group) (Figure 2). A high-level response was obtained in 58 patients (41%; 95% CI, 33%-50%) in the IM20 × 3 group, in 107 patients (74%; 95% CI, 66%-81%) in the IM40 × 4 group ($P < .001$ vs IM20 × 3 group), and in 74 patients (53%; 95% CI, 44%-61%) in the ID4 × 4 group ($P = .06$ vs IM20 × 3 group). With the 40-µg intramuscular × 4 and the 4-µg intradermal × 4 regimens, 92% (95% CI, 86%-96%) reported 3 positive responses. Anti-HBs indicates hepatitis B surface antibody; HBV, hepatitis B virus. Last observation carried forward (LOCF) rule applied for missing values. Because the calculations were performed on LOCF-imputed data, the denominators are the number of patients receiving at least 1 vaccine dose at each time point. Error bars represent 95% confidence intervals.
intradermal \( \times 4 \) vaccination schedules, protective anti-HBs titers were also obtained more rapidly than with the standard 20-µg intramuscular \( \times 3 \) schedule (Figure 2).

At week 28, the geometric mean titer of anti-HBs was 55 mIU/mL (95% CI, 31-96 mIU/mL) in the IM20 \( \times 3 \) group, 795 mIU/mL (95% CI, 471-1341 mIU/mL) in the IM40 \( \times 4 \) group (P < .001 vs IM20 \( \times 3 \) group), and 104 mIU/mL (95% CI, 66-162 mIU/mL) in the ID4 \( \times 4 \) group (P = .05 vs IM20 \( \times 3 \) group) (Figure 3).

Age was associated with response in the IM20 \( \times 3 \) group (P = .003) (Figure 4), but not in the IM40 \( \times 4 \) (P = .86) and ID4 \( \times 4 \) (P = .95) groups. The responses differed according to HIV-1 RNA detectability and CD4 cell count in the IM40 \( \times 4 \) group (P = .04), but not in the IM20 \( \times 3 \) group (P = .39) and was not statistically significant in the ID4 \( \times 4 \) group (P = .09) (Figure 4).

In a multivariate analysis, vaccination with the 40-µg intramuscular \( \times 4 \) schedule and the 4-µg intradermal \( \times 4 \) schedule induced higher response rates than the standard 20-µg intramuscular \( \times 3 \) schedule (Table 2). Other predictive factors for response at week 28 were female sex, lower age, no active smoking (defined as smoking \( \geq 5 \) cigarettes per day), higher baseline CD4 cell count, and undetectable plasma HIV-1 RNA (Table 2).

### Safety

Vaccination was discontinued in 6 patients (4%) in the IM20 \( \times 3 \) group, 12 patients (8%) in the IM40 \( \times 4 \) group (P = .22 vs IM20 \( \times 3 \) group), and 6 patients (4%) in the ID4 \( \times 4 \) group (P > .99 vs IM20 \( \times 3 \) group). Vaccine discontinuation was associated with clinical or biological events in 5 patients, all of which were possibly related to vaccination (1 patient had osteoarthritis, 1 patient had headaches, and 1 patient had severe cytolysis in the IM40 \( \times 4 \) group; and 1 patient had dysesthesia and 1 patient had vertigo in the ID4 \( \times 4 \) group). The severe cytolysis event was a unique report of a serious adverse event possibly related to vaccination. An increase in serum levels of liver enzymes alanine aminotransferase and aspartate aminotransferase of more than 10 times the upper limit of normal was observed 4 weeks after the first vaccine administration in a woman (IM40 \( \times 4 \) group) who had received mifepristone for pregnancy termination 5 weeks before the first vaccine dose. Cytolysis resolved 4 weeks after the second vaccination without sequelae. Although a likely explanation for hepatic cytolysis was mifepristone, this event was coded as possibly linked to vaccination, and coding was confirmed by the adjudication committee.

Twenty-one other serious adverse events were reported for 8 patients in the IM20 \( \times 3 \) group, 4 patients in the IM40 \( \times 4 \) group, and 9 patients in the ID4 \( \times 4 \) group (Table 3). None of them was considered as being related or possibly related to vaccination or associated with vaccine discontinuation.

One patient in the IM20 \( \times 3 \) group (lost to follow-up) and 1 in the IM40 \( \times 4 \) group (incarcerated) were not considered in the safety analysis. Overall, 1781 general or local adverse events or laboratory abnormalities were reported (eTable 2; available at http://www.jama.com), and the proportion of patients experiencing at least 1 event did not differ between the IM20 \( \times 3 \) and IM40 \( \times 4 \) group (P = .73) groups or the ID4 \( \times 4 \) group (P = .37) (Table 3). However, patients in the IM40 \( \times 4 \) group experienced a higher rate of fever, nausea, or edema, and patients in the ID4 \( \times 4 \) group experienced a higher rate of local adverse reactions (except pain, which was less frequent) than did patients in the IM20 \( \times 3 \) group. An increase in levels of liver enzymes alanine aminotransferase, aspartate aminotransferase, or both of more than the upper limit of normal occurred in 76 patients (18%), more frequently associated with HCV coinfection (6/16 [38%] HIV-HCV coinfected patients vs 70/408 [17%] HIV monoinfected patients; P = .05), and remained less than 2.5 times the upper limit of normal in 66 patients (87%). No threshold for increase of liver enzyme aminotransferase levels was stipulated in the protocol for withholding vaccine.

No significant variation was observed in the CD4 cell count between day 0 and week 28 (mean difference, −6.8 cells/µL; 95% CI, −32.1 to 18.4 cells/µL; P = .55 for comparison be-

### Table 2. Significant Predictive Factors for Response at Week 28 (Multivariate Analysis)a

<table>
<thead>
<tr>
<th>Factors</th>
<th>No. of Responders/No. of Participants (%)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>206/287 (72)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Female</td>
<td>122/139 (88)</td>
<td>2.03 (1.11-3.73)</td>
</tr>
<tr>
<td><strong>Age, per 10-yr increase</strong></td>
<td></td>
<td>0.70 (0.54-0.92)</td>
</tr>
<tr>
<td><strong>Recombinant HBV vaccination regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM20 ( \times 3 )</td>
<td>93/141 (66)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>IM40 ( \times 4 )</td>
<td>125/145 (86)</td>
<td>3.58 (1.92-6.67)</td>
</tr>
<tr>
<td>ID4 ( \times 4 )</td>
<td>110/140 (79)</td>
<td>2.09 (1.18-3.68)</td>
</tr>
<tr>
<td><strong>Active smokinga</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>231/282 (82)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>97/144 (67)</td>
<td>0.46 (0.27-0.77)</td>
</tr>
<tr>
<td><strong>Baseline CD4 cell count, per 100 cells/µL</strong></td>
<td></td>
<td>1.12 (1.00-1.26)</td>
</tr>
<tr>
<td><strong>Baseline HIV-RNA level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 copies/mL</td>
<td>267/332 (80)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>( \geq 50 ) copies/mL</td>
<td>61/94 (65)</td>
<td>0.40 (0.23-0.71)</td>
</tr>
</tbody>
</table>

aAbbreviations: CI, confidence interval; HBV, hepatitis B virus; HIV, human immunodeficiency virus; OR, odds ratio; IM20 \( \times 3 \), 3 intramuscular injections of 20-µg standard dose of recombinant HBV vaccine; IM40 \( \times 4 \), 4 intramuscular double doses [40 µg (2 injections of 20 µg) of recombinant HBV vaccine; and ID4 \( \times 4 \), 4 intradermal injections of low doses (4 µg [1/5 of 20 µg]) of recombinant HBV vaccine.

bMissing week 28 hepatitis B surface antibody titer measurements were imputed using the last observation carried forward method.

cDefined as smoking at least 5 cigarettes per day.

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The proportion of patients with at least 50 copies/mL of HIV-1 RNA did not differ significantly between day 0 and week 28 in those with paired samples (28 patients [21%] at day 0 vs 23 patients [18%] at week 28, \( P = .20 \) in 131 patients in the IM20 \( \times 3 \) group; 28 patients [21%] at day 0 vs 35 patients [26%] at week 28, \( P = .09 \) in 133 patients in the IM40 \( \times 4 \) group; and 25 patients [19%] at day 0 vs 24 patients [18%] at week 28, \( P = .74 \) in 134 patients in the ID4 \( \times 4 \) group). There was no significant variation in plasma HIV-1 RNA level in those patients with at least 50 copies/mL of HIV-1 RNA between day 0 and week 28 (mean difference, 0.26 log10 copies/mL; 95% CI, −0.13 to 0.66 log10 copies/mL; \( P = .34 \) in the IM20 \( \times 3 \) group; −0.01 log10 copies/mL; 95% CI, −0.28 to 0.27 log10 copies/mL; \( P = .99 \) in the IM40 \( \times 4 \) group; and 0.19 log10 copies/mL; 95% CI, −0.17 to 0.56 log10 copies/mL; \( P = .16 \) in the ID4 \( \times 4 \) group).

Instruction was not provided for antiretroviral therapy initiation or maintenance during the trial; 2 of 20 patients (10%) not receiving antiretroviral therapy at baseline started antiretroviral therapy in the IM20 \( \times 3 \) group, 3 of 30 patients (10%) in the IM40 \( \times 4 \) group (\( P > .99 \) vs IM20 \( \times 3 \) group), and 1 of 19 patients (5%) in the ID4 \( \times 4 \) group (\( P > .99 \) vs IM20 \( \times 3 \) group). Antiretroviral treatment was modified in 17 of 120 patients (14%) of those receiving the treatment at baseline in the IM20 \( \times 3 \) group, 21 of 114 patients (18%) in the IM40 \( \times 4 \) group (\( P = .48 \) vs IM20 \( \times 3 \) group), and 19 of 121 patients (16%) in the ID4 \( \times 4 \) group (\( P = .86 \) vs IM20 \( \times 3 \) group).

### COMMENT

Our study is the first randomized trial to our knowledge evaluating 2 alternative strategies of vaccination vs the standard HBV vaccine schedule in adults with HIV. We observed a significant increase in the response rate 1 month after the last dose of HBV vaccine in patients who received 4 intramuscular doses of 40 µg compared with the 3 standard 20-µg doses (82% vs 65%, respectively). Moreover, with the 40-µg intramuscular \( \times 4 \) schedule, a high seroconversion rate was achieved as soon as 12 weeks (72%; 95% CI, 64%–79%). The proportion of responders at week 28 with the 4-µg intradermal \( \times 4 \) schedule was also higher in comparison with standard immunization (77% vs 65%, respectively).

The results with the 40-µg intramuscular \( \times 4 \) schedule are in agreement with recent pilot studies. In the study by Potsch et al,\(^2\) patients with HIV vaccine received 4 doses (40 µg) of HBV vaccine.
at 0, 1, 2, and 6 months. An antibody response of at least 10 mIU/mL and at least 100 mIU/mL was observed in 89% and 78% of patients, respectively. In the study by Cruciani et al., patients with HIV received 3 high doses (40 µg) of HBV vaccine at 0, 1, and 2 months, and nonresponders to the initial immunization received 1 to 3 boosters. The response rates were 60% after the primary vaccination and 89.2% after the boosters.14

With the 40-µg intramuscular × 4 vaccination schedule, we observed that protective anti-HBs titers were obtained more rapidly than with the standard 20-µg intramuscular × 3 schedule. Therefore, in “real life,” even without completion of the recommended 4-dose schedule, good levels of protection could nevertheless be achieved with only 3 doses. With the standard 20-µg intramuscular × 3 schedule, response to immunization decreased with age as previously reported.23 Of interest, the 40-µg intramuscular × 4 vaccination schedule allowed for the possibility of overcoming this limitation and high rates of immunization were obtained independently of age.

The intradermal route has been tested in several clinical trials, particularly in patients with dialysis who have suboptimal response to HBV vaccine.15 In patients with HIV infection, few data exist regarding HBV immunization using the intradermal route. Our data indicate that the 4-µg intradermal × 4 administration is significantly more efficient than the standard 20-µg intramuscular × 3 administration. Interestingly, the response to the intradermal immunization appeared to be independent of age.

It has been shown that the long-term persistence of the anti-HBs response was associated with the anti-HBs titer after vaccination.14,20,23 In our study, 74% of patients in the IM40 × 4 group had anti-HBs titers of at least 100 mIU/mL, which is considered to be fully protective and associated with long-term response.20,24 In the IM20 × 3 and ID4 × 4 groups, these percentages were 41% and 53%, respectively.

Only 1 serious adverse event possibly related to the vaccine was reported in the IM40 × 4 group. A higher incidence of injection site adverse events was reported in the ID4 × 4 group compared with the IM20 × 3 group. Rates of solicited systemic reactions were generally similar among all 3 groups. Although patterns observed after subsequent injections were similar to those observed after the first injection, the percentages of adverse events in all groups were higher after the first injection than after the following injections. However, these adverse events remained generally mild. Despite these relative drawbacks, the results show the potential for intradermal vaccination to reduce antigen dose compared with intramuscular delivery. New intradermal delivery methods such as micro-injection or needle-free systems are in development.25,26 Such devices could facilitate vaccination campaigns after an evaluation of new vaccine schedules in controlled clinical trials.

In conclusion, in a large randomized controlled trial, both the 4 intramuscular double-dose regimen and the 4 intradermal low-dose regimen improved serological response in comparison with a standard schedule of HBV vaccine in adults with HIV infection with CD4 cell counts of more than 200 cells/µL.

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In conclusion, in a large randomized controlled trial, both the 4 intramuscular double-dose regimen and the 4 intradermal low-dose regimen improved serological response in comparison with a standard schedule of HBV vaccine in adults with HIV infection with CD4 cell counts of more than 200 cells/µL.

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