Safety and Immunogenicity of Hepatitis A Vaccine in Human Immunodeficiency Virus–Infected Patients: A Double-Blind, Randomized, Placebo-Controlled Trial

Carol A. Kemper,1,2 Richard Haubrich,3 Ian Frank,4 Gary Dubin,5 Charles Buscarino,6 J. Allen McCutchan,7 and Stanley C. Deresinski,1,2 for the California Collaborative Treatment Group

1Division of Infectious Diseases, Department of Medicine, Santa Clara Valley Medical Center, San Jose; 2Stanford University School of Medicine, Stanford, and 3Antiviral Research Center, University of California San Diego, San Diego; 4Department of Medicine, University of Pennsylvania, Philadelphia, and 5GlaxoSmithKline Biologicals, Collegeville

The safety and immunogenicity of inactivated hepatitis A (HepA) vaccine was assessed in 133 hepatitis A virus–seronegative, human immunodeficiency virus (HIV)–infected adults. Patients were randomly assigned to receive, in a blinded fashion, either 2 doses of vaccine (1440 enzyme-linked immunosorbent assay units) or placebo 6 months apart. Seroconversion at month 9 was observed in 68% of those with CD4 cell counts ≥200 cells/mm3 but in only 9% of those with lower CD4 cell counts (P = .004). HepA vaccine was well tolerated and had no effect on the course of HIV infection or plasma HIV RNA load.

Infection due to hepatitis A virus (HAV) remains a significant risk for homosexual men. In addition to safe sex practices, the use of an inactivated hepatitis A (HepA) vaccine provides affordable protection against HAV infection, which may be especially important in those who are infected with human immunodeficiency virus (HIV). Acute HAV infection may be more severe in HIV-infected individuals and has caused prolonged increases in HIV load [1]. HAVRIX (GlaxoSmithKline Beecham Biologicals), one of the inactivated HepA vaccines currently licensed in the United States, is highly immunogenic in non–HIV-infected adults, resulting in seroconversion in up to 90%–94% and 100% of persons after the first and second doses, respectively, of vaccine (1440 ELISA units [EIU]) [2]. However, antibody responses to HepA vaccine are diminished in patients with HIV infection [3–6]. In addition, several reports suggest that HIV replication may be transiently up-regulated by certain vaccines, such as influenza vaccines [7, 8] or others [9]. Whether HepA vaccine has a similar effect on HIV RNA levels has not been examined previously, to our knowledge.

We determined the safety and immunogenicity of 2 doses of HepA vaccine (HAVRIX; 1440 EIU) in a group of HIV-infected adults with varying levels of immunodeficiency who were seronegative for anti-HAV antibodies. Whether 2 doses of vaccine, administered 6 months apart, adversely affected CD4 cell counts, plasma HIV RNA levels, or the clinical course of HIV infection was examined.

Patients, materials, and methods. This prospective, double-blind, placebo-controlled study assessed a group of HIV-infected adults (≥18 years old) who were prescreened for the lack of anti-HAV antibody (HAVAB assay; Abbott Laboratories). Patients were enrolled at 1 public hospital and 2 university clinic sites (Santa Clara Valley Medical Center, San Jose; University of California San Diego; and University of Pennsylvania, Philadelphia) between October 1995 and December 1997. Criteria for inclusion in the study were receipt of stable antiretroviral therapy or no therapy for at least 1 month prior to entry, Karnofsky score ≥80, no signs or symptoms of active infection, no fever ≥37.8°C, and no active HIV-related opportunistic infection or malignancy. Patients who had received other vaccines within 4 weeks or who were receiving systemic corticosteroids, immunoglobulin, or immune modulatory agents were excluded.

At entry to the study, information was collected about age, sex, history of antiretroviral therapy, and stage of HIV infection (as defined using the 1993 Centers for Disease Control and Prevention [CDC] classification system [10]). Blood specimens were collected for assessment of anti-HAV antibody, CD4 cell counts, and plasma HIV RNA levels. Approximately 1 week after the screening visit, eligible HAV-seronegative subjects were stratified on the basis of CD4 cell count at the time of entry to the study (<200, 200–499, or ≥500 cells/mm3) and were
randomly assigned (1:1) to receive either 2 doses of HepA vaccine containing 1440 ELU or 2 doses of placebo intramuscularly at 0 and 6 months. Study visits were conducted at 1, 6, 6.5, 7, and 9 months to assess anti-HAV titer, CD4 cell counts, plasma HIV RNA loads, and adverse events. The second dose of vaccine was administered after blood specimen collection at month 6. To evaluate the tolerability of vaccination, subjects were asked to record the occurrence of solicited symptoms (e.g., fever, injection-site tenderness, headache, fatigue, nausea, and vomiting), as well as any other symptoms, for 4 days after each dose of vaccine or placebo. Seroconversion was defined as anti–hepatitis A virus antibody \( \geq 33 \text{ mIU/mL} \) (determined by the University of Miami Hepatology Laboratory by use of an ELISA [Enzymun; Boehringer Mannheim]). The use of antiretroviral therapy was unrestricted during the study.

Descriptive statistics (mean, median, and range) were used to examine the baseline characteristics. The frequency of seroconversion and geometric mean anti–hepatitis A virus titer (GMTs) were determined 1, 6, 7, and 9 months after the first vaccination. Differences among the 3 baseline CD4 groups were assessed by use of the \( \chi^2 \) test (2-tailed \( P < .05 \) was considered to be significant). The primary analyses of vaccine safety were the comparisons of markers of HIV infection (CD4 cell counts and plasma HIV RNA levels) in vaccine and placebo groups 1, 6, 6.5, 7, and 9 months after vaccination. Comparisons of mean CD4 cell counts in both groups were performed using 2-way analysis of variance (ANOVA), with CD4 cell count subgroups and treatment group as factors. Analysis of covariance (ANCOVA) was used to assess differences between treatment groups, with baseline CD4 cell counts as a covariate. In addition, mean log_{10} HIV RNA levels were compared using ANOVA and ANCOVA, with baseline HIV RNA levels as the covariate to be controlled, baseline CD4 cell count group as one factor, and treatment group as another factor. HIV RNA levels were log_{10} transformed for analysis. Data analyses were performed in an intent-to-treat fashion for patients receiving at least 1 dose of vaccine.

Vaccine safety was also evaluated by comparison of the frequency of solicited and unsolicited adverse events reported, as well as the number of patients whose clinical CDC category changed during the study. Between-group comparisons were based on \( \chi^2 \) or Fisher’s exact test for categorical variables and on 2-sample Student’s \( t \) tests for continuous variables.

**Results.** A total of 270 adults were screened, 133 of whom were HAV seronegative and enrolled in the study (mean age, 38 years; range, 22–65 years). Eight (10.7%) were female. Of the 68 subjects (51.1%) who were randomly assigned to receive HepA vaccine, 48 (70.6%) completed the 9-month study. Of the 65 (48.9%) who received placebo, 51 (78.5%) completed the study. The reasons for discontinuation were similar for both groups (loss to follow-up was the most frequent reason). Baseline demographics were similar between treatment groups, although CD4 cell counts were somewhat higher at baseline in vaccine recipients, compared with placebo recipients (376 vs. 327 CD4 cells/mm\(^3\); \( P \) not significant). Mean HIV RNA levels were also similar (3.29 vs. 3.39 log_{10} copies/mL). Sixty-two patients (91%) in the vaccine group were receiving antiretroviral therapy at the time of entry to the study, compared with 60 (92%) in the placebo group. Half the patients were receiving \( \geq 2 \) agents, reflecting the pattern of antiretroviral use at the time of enrollment.

The overall frequency of seroconversion among subjects receiving vaccine was 49% at month 7 and 52% at month 9. Among patients with baseline CD4 cell counts of 200–499 or \( \geq 500 \) cells/mm\(^3\), seroconversion was observed in 53% and 73% at month 7 and in 69% and 67% at month 9, respectively (table 1). When all 3 groups were compared, the frequency of seroconversion among patients with CD4 cell counts <200 cells/mm\(^3\) was significantly lower at month 7 (11%; \( P = .023 \)) and at month 9 (9%; \( P = .004 \)). After the first dose of vaccine, seroconversion at month 6 was observed in only 4 (13%) of 31 subjects with CD4 cell counts \( \geq 200 \) cells/mm\(^3\) and in no subjects with CD4 cell counts <200 cells/mm\(^3\).

Subjects with higher baseline CD4 cell counts had significantly higher GMTs at both month 7 and month 9. For example, GMTs at month 9 were 23, 82, and 145 in patients with <200, 200–499, and \( \geq 500 \) CD4 cells/mm\(^3\), respectively (\( P = .016 \)). Two patients in the placebo group experienced seroconversion during the study, presumably from naturally occurring HAV infection, and both events were associated with the development of very high anti–hepatitis A virus titers (>75,000 mIU/mL).

No significant differences in the frequency of solicited or unsolicited reports of signs and symptoms were observed within 4 days of administration of either the first or second dose of vaccine.

<table>
<thead>
<tr>
<th>Month after first vaccination</th>
<th>Baseline CD4 cell count, cells/mm(^3)</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;200 ((n = 19))</td>
<td>200–499 ((n = 32))</td>
</tr>
<tr>
<td>1</td>
<td>0/13 (0)</td>
<td>4/22 (18.2)</td>
</tr>
<tr>
<td>6</td>
<td>0/13 (0)</td>
<td>2/20 (10.0)</td>
</tr>
<tr>
<td>( \gamma^b )</td>
<td>1/9 (11.1)</td>
<td>8/15 (55.3)</td>
</tr>
<tr>
<td>( \delta^b )</td>
<td>1/11 (9.1)</td>
<td>11/16 (68.8)</td>
</tr>
</tbody>
</table>

**Note.** Data are no. of patients who seroconverted/no. of patients with evaluable specimens (%). Seroconversion was defined as achieving an anti–hepatitis A virus antibody titer \( \geq 33 \text{ mIU/mL} \).

\( a \) Calculated by the \( \chi^2 \) test for differences among the 3 baseline CD4 groups.

\( b \) The month 7 and 9 visits occurred 1 month and 3 months after the second dose of vaccine.
between the vaccine and placebo groups or within the CD4 cell count subgroups. Severe vaccine-related adverse effects were uncommon. Within 4 days of vaccination, 1 subject (1.6%) in each of the vaccine and placebo groups experienced severe headache, and 1 subject (1.6%) in the vaccine group experienced severe fatigue. The only statistically significant HepA vaccine–related event was minor injection-site soreness, which was seen after 35% (39/112) of the doses administered, which was similar for each of the 2 doses, compared with 8% (9/108) of the placebo doses (P < .01). Of interest, the frequency of reported bacterial, viral, or fungal infections (e.g., thrush, herpes simplex, or upper respiratory infections) occurring within 4 days of vaccination was similar for patients receiving vaccine or placebo (24% vs. 26%, respectively; P > .20). The frequency of HIV-related events during the study was also similar between vaccine recipients and those receiving placebo. Within each of the 3 CD4 cell count groups, there was no apparent difference in the proportion of patients whose CDC category changed between the baseline and final visits.

CD4 cell counts increased and plasma HIV RNA levels decreased throughout the study period in both groups (figure 1). Within-subject changes from baseline were significant at some time points for placebo recipients but not for vaccine recipients. For example, the mean change in CD4 cell count from baseline to month 9 for placebo recipients was +52 cells/mm³ (P < .001), compared with +31 cells/mm³ for vaccine recipients (P = .27). The mean decrease in HIV RNA levels from baseline to month 9 for placebo recipients was 0.35 log₁₀ copies/mL (P < .025), compared with 0.18 log₁₀ copies/mL for vaccine recipients (P = .27). However, both ANOVA and ANCOVA analyses showed no statistically significant differences in CD4 cell counts or HIV RNA levels between the 2 treatment groups at any visit, even after we controlled for differences in CD4 cell counts at baseline. Thus, HIV load did not increase 1 month after the first vaccination or 2 or 4 weeks after the second.

**Discussion.** HIV infection impairs the response to a variety of vaccines, including tetanus toxoid [11, 12], pneumococcal polysaccharide [11, 12], influenza virus [11], and HepA and hepatitis B virus vaccines [13–16]. In addition, certain vaccines, such as influenza, have resulted in transient increases in plasma HIV loads within weeks of administration [7, 8]. We found no such effect of HepA vaccine on HIV RNA levels. Increases in CD4 cell counts and decreases in HIV loads were observed in both groups throughout the study, although none of the differences between the groups was significant. Two additional studies of HepA vaccine in HIV infection also found no adverse effect of vaccination on CD4 cell counts or disease progression [3, 6, 17], although HIV RNA levels were not assessed in these earlier studies. The relatively less beneficial changes seen in the vaccine group in our study could have been due to a subtle effect of vaccination, although the immunologic and virologic improvement observed for both groups was more likely related to improvements in antiretroviral therapy during the course of the study. For example, the first of the protease inhibitors, saquinavir, was introduced through expanded access in June 1995 and received US Food and Drug Administration approval in December 1995, just as this study was getting under way. The groups were otherwise well balanced, with a similar frequency of use of antiretroviral therapy at entry to study (data on the use of antiretrovirals during the study were not available for analysis).

Furthermore, our study demonstrated that the frequency of

![Figure 1](https://example.com/figure1.png)
seroconversion and the magnitude of the resulting antibody titer varied significantly, depending on the initial CD4 cell count. Patients with less immune system impairment, as reflected by higher CD4 cell counts at entry to the study, were more likely to seroconvert and to have higher antibody titers. Two-thirds of those with CD4 cell counts ≥200 cells/mm³ responded to 2 doses of vaccine, although only 9% of those with lower CD4 cell counts responded (table 1). Responses to a single dose of vaccine were lower, with only 13% of patients with CD4 cell counts >200 cells/mm³ and no patients with lower CD4 cell counts responding (although the lowest titer needed to confer protection has not been determined).

These results suggest that a success rate of response to HepA vaccine is somewhat lower than those found in earlier studies of HIV infection [3–6]. In one of the earlier studies, in which 90 HIV-infected adults received 2 doses of a HepA vaccine similar to that used in our study, seroconversion occurred in 78% and 88% of subjects after the first and second doses, respectively, of vaccine [3]. Similar to our findings, higher CD4 cell counts at entry to the study were associated with a greater likelihood of seroconversion, and GMTs were significantly higher among patients with CD4 cell counts ≥200 cells/mm³, compared with those with lower CD4 cell counts (130 vs. 20 cells/mm³; P = .0001). Three additional studies of HepA vaccine in HIV infection examined the response to 3 injections of a lower dose of vaccine (HAVRIX; 720 EU) administered at 0, 1, and 6 months [4–6]. In each of these 3 studies (all of which used a seroconversion cutoff anti-HAV antibody titer ≥20 IU/mL), the proportion of patients who responded after a second and third dose of vaccine varied from 50% to 78% and from 76% to 85%, respectively. Of these, the best results were reported by Santagostino et al. [4], who studied 47 HIV-infected patients with hemophilia, 19 of whom had CD4 cell counts <200 cells/mm³. After 3 doses of HepA vaccine, 100% of subjects with CD4 cell counts ≥200 cells/mm³ responded, whereas only 57% of subjects with CD4 cell counts <200 cells/mm³ did.

The reason for the lower frequency of seroconversion to HepA vaccine in our study, compared with the frequencies found in the earlier studies, is not clear. Two of these studies involved HIV-infected patients with hemophilia, who are generally younger than patients studied in other clinical trials of HIV infection; thus, their younger age may have improved their rates of response. Seroconversion in our study was defined as anti-HAV antibody titer ≥33 mIU/mL, whereas a lower cutoff anti-HAV antibody titer, ≥20 mIU/mL, was used in other studies [3–6]. Using the lower cutoff value would have had only a modest effect on our overall results (only 1 patient in our study would have been reclassified as a responder at month 9, and 3 other patients, all of whom eventually responded, would have been thus classified at an earlier visit). Because patients in our study were stratified on the basis of their CD4 cell counts at entry to study and not the nadir value, the immunocompetence of our patients, which was judged on the basis of treatment-enhanced CD4 cell counts, may have been overestimated. Defects in immune responsiveness to vaccination could persist, despite improvement in CD4 cell counts due to more-potent antiretroviral therapy. This possibility is, however, inconsistent with the results of a recent study in which 94% of patients, most of whom had access to highly active antiretroviral therapy, responded to another, similar HepA vaccine [18]. Response rates remained high (87%), even in patients with CD4 cell counts <300 cells/mm³.

In conclusion, HepA vaccine was well tolerated and had no apparent effect on the course of HIV infection or plasma HIV RNA levels. Approximately two-thirds of our patients responded to 2 doses of vaccine administered 6 months apart. Compared with uninfected persons and with the results of other studies of HIV-infected persons [3–6], this relatively lower response rate was unexpected and remains unexplained. The likelihood of response and the resultant antibody titer were clearly increased in patients with higher CD4 cell counts.

The diminished anti-HAV antibody titer response following a single dose of HepA vaccine has implications for HIV-infected travelers. Such patients may also receive serum immunoglobulin in addition to vaccine for imminent travel, although there are some data suggesting that the coadministration of serum immunoglobulin may further blunt the antibody response to vaccination. Furthermore, clinicians may wish to counsel patients that vaccination may not provide uniform protection against HAV. Whether vaccine response can be improved by the use of adjuvants or a third dose of vaccine or by delaying vaccination until there is evidence of improvement in the immune system in response to more highly active antiretroviral therapy, deserves further study.

Acknowledgments

We thank the following individuals for their contributions to this project: Edward Janoff (Veterans Affairs Medical Center, Infectious Disease Section, Minneapolis), William Lang (VirX, San Francisco), Rebecca Sutton and Carol A. Kane (Division of Infectious Diseases and AIDS Program, Santa Clara Valley Medical Center, San Jose, California), and Edward L. Seeffried (University of California, San Diego, Antiviral Research Center).

References


