Response to Hepatitis A Vaccination in Human Immunodeficiency Virus–Infected and –Uninfected Homosexual Men

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The influence of human immunodeficiency virus (HIV) infection and vaccination schedule on the immunogenicity of a hepatitis A vaccine was examined. Ninety HIV-infected homosexual men received two vaccinations with hepatitis A vaccine (each 2 mL of 720 ELISA units/mL) either 1 or 6 months apart; 44 HIV-uninfected men received vaccine at study entry and at 6 months. Anti–hepatitis A virus (HAV) titer after vaccination was measured in 83 HIV-positive and 39 HIV-negative men. Seroconversion (anti-HAV antibody ≥20 IU/L) after two vaccinations occurred more frequently in HIV-negative men (100% vs. 88.2%; P = .03). Anti-HAV titer after two vaccinations was also significantly greater in HIV-negative men (1086 vs. 101 IU/L; P = .0001). HIV-positive men who responded to vaccination had significantly more CD4 lymphocytes (mean, 540/μL) at baseline than those who did not (280/μL; P = .033). Vaccine schedule did not affect response. Vaccination of susceptible patients against HAV should be recommended early in HIV infection using the shorter course to encourage compliance.

In the past 6 years, significant epidemics of hepatitis A have occurred in the homosexual communities of New York, San Francisco, Toronto, Melbourne, Sydney, and elsewhere [1–3]. For homosexual men, the risk of infection with hepatitis A virus (HAV) is increased by higher numbers of sex partners and by certain sex practices that facilitate the ingestion of feces. These practices, such as oroanal contact, are often adopted to reduce the risk of acquiring the human immunodeficiency virus (HIV) but may be particularly efficient for the transmission of HAV. In 1991, a safe and effective whole virion vaccine for hepatitis A became available [4]. This vaccine induces protective levels of anti–HAV antibody in virtually 100% of immunocompetent adults when given according to the recommended schedule of 720 ELISA units (ELU) at 0, 1, and 6 months [4].

However, many other vaccines, including those against influenza [5], tetanus [5, 6], pneumococcal infection [5, 6], and hepatitis B [7, 8], have been shown to be less effective in HIV-infected persons, thereby potentially limiting their utility for homosexual men who are also at increased risk of HIV. Among homosexual men with acute hepatitis A during the Sydney epidemic of 1991, 27% were coinfected with HIV [3].

In order to examine the influence of HIV infection, HIV-related immune depression, and vaccine schedule on the immunogenicity of an inactivated hepatitis A vaccine, a double dose (2 mL of 720 ELU/mL) was administered to 90 HIV-positive and 44 HIV-negative homosexual men. The study was conducted between August 1993 and June 1995.

Methods

Study population. Subjects were homosexual men with known HIV antibody status attending one of two sexually transmitted disease clinics in Sydney. Excluded were men who tested positive for anti-HAV antibody at screening, had received human immunoglobulin in the previous 9 months, or were receiving immunosuppressive medication.

Vaccine. The vaccine used was a double dose of the licensed inactivated whole virion hepatitis A vaccine (Havrix; SmithKline Beecham Biologicals, Rixensart, Belgium). Two 1-mL vials each containing 720 ELU were mixed, and the contents were administered by the same injection into the deltoid muscle.

Study procedure. HIV-positive volunteers were randomly assigned to receive two vaccinations, either 1 month or 6 months apart. All HIV-negative men received the longer treatment schedule, with vaccination at study entry and 6 months later (0, 6–month course). Prior to vaccination, clinical assessment was done and blood was drawn for anti-HAV serology, liver function, HIV serology, and CD4 cell count (HIV-positive men only). Follow-up HIV testing was performed on initially negative subjects.

Subjects receiving vaccination at study entry and 1 month later (0, 1–month course) were assessed at months 1, 2, and 6 for anti-
Table 1. Baseline demographic, clinical, and immunologic characteristics by HIV status and vaccine schedule.

<table>
<thead>
<tr>
<th>Vaccine schedule*</th>
<th>HIV-negative patients</th>
<th>HIV-positive patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0, 6 months</td>
<td>0, 1 months</td>
</tr>
<tr>
<td>n</td>
<td>46</td>
<td>48</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.0</td>
<td>33.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
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<tr>
<td>HIV stage</td>
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<td></td>
</tr>
<tr>
<td>Asymptomatic (%)</td>
<td>—</td>
<td>75</td>
</tr>
<tr>
<td>ARC (%)</td>
<td>—</td>
<td>19</td>
</tr>
<tr>
<td>AIDS (%)</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>CD4 cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (/μL)</td>
<td>—</td>
<td>569</td>
</tr>
<tr>
<td>Range (/μL)</td>
<td>—</td>
<td>28–1500</td>
</tr>
<tr>
<td>CD4 %</td>
<td>—</td>
<td>23.9</td>
</tr>
<tr>
<td>CD8 cells (/μL)</td>
<td>—</td>
<td>1356</td>
</tr>
<tr>
<td>Lymphocytes (/μL)</td>
<td>—</td>
<td>2348</td>
</tr>
</tbody>
</table>

NOTE. Data are means. ARC = AIDS-related complex (non-AIDS CDC group IV disease).
* 0, 1 = at study entry and 1 month later; 0, 6 = at study entry and 6 months later.

HAV titer, liver function, and tolerance of the vaccine. Subjects receiving the 0, 6–month course were similarly assessed at months 1, 6, and 7.

Laboratory. Titer of anti-HAV antibody following vaccination was determined using a commercial competitive enzyme immunoassay (Enzymun-Test Anti-HAV; Boehringer Mannheim, Mannheim, Germany). Quantitation of this colorimetric assay is achieved by comparing optical density to cutoff ratios against standard curves. Previous studies of passive immunization with serum immune globulin have suggested an anti-HAV titer of ≥20 IU/L to be protective against hepatitis A in most cases [9].

Statistics. The proportion of subjects developing protective antibody were compared using χ² or, where inappropriate, Fisher’s exact method. Antibody titers were compared using the Mann-Whitney U test. Calculation of geometric mean titer (GMT) included subjects with no antibody response. Other continuous variables were compared using a 2-tailed t test.

Results

Study subjects. We recruited 136 homosexual men; 90 were HIV-positive and 46 were HIV-negative. Of these, 134 (90 HIV-positive) received vaccine at least once, and 121 (82 HIV-positive) received vaccine twice. Anti-HAV titer after vaccination was obtained for 122 participants (83 HIV-positive and 39 HIV-negative). HIV-negative men were similar in age and weight to their HIV-positive counterparts. There were no significant differences among HIV-positive men on different vaccine schedules with respect to age, weight, clinical status, or CD4 cell count (table 1).

Anti-HAV response. Among HIV-negative men, seroconversion occurred 1 month after the first and second vaccinations in 90.2% and 100% of cases, respectively. Among HIV-positive men, seroconversion occurred in 77.9% and 88.2%, respectively (table 2).

HIV-positive men who seroconverted to anti-HAV at any time during the study had a significantly higher mean CD4 cell count (540/μL) at baseline than those who did not seroconvert (280/μL; P = .033). Only 9 (64%) of 14 HIV-positive subjects with CD4 cell counts ≤200/μL responded. Baseline mean CD4 cell percents were also higher in those who responded (23.2% vs. 12.2%; P = .019). Otherwise, men who did and did not respond were similar with respect to age, weight, and study site (data not shown).

The GMT of anti-HAV antibody was also greater in HIV-negative men than in HIV-positive men (table 2). HIV-positive men with ≥200 CD4 cells/μL at baseline had higher GMTs (130 IU/L) after two vaccinations than subjects with <200 CD4 cells/μL (20 IU/L; P = .0001). Vaccine schedule did not significantly affect response. Seroconversion was observed in 93.3% of HIV-infected men assigned the shorter 0, 1–month dose compared with 81.8% assigned the longer 0, 6–month schedule.

Safety. The vaccine was generally well tolerated. Local soreness was the most common side effect, reported by 10% of HIV-positive and 9% of HIV-negative men. Mild systemic symptoms such as headache, rash, nausea, lightheadedness, and myalgia were reported by a further 33% of HIV-positive and 15% of HIV-negative men.

Discussion

In this study, vaccination with two double doses of vaccine (720 ELU) resulted in a protective serologic response in 88% of
HIV-infected homosexual men. These results reflect somewhat greater success than was reported for the single dose in HIV-infected hemophiliacs (76%) [10] and homosexual men (77%) [11] and far greater success than the 30%–50% response rates usually reported for hepatitis B vaccination in HIV-infected adults [7, 8]. Although this study did not directly compare the 720 and 1440 ELU doses, these findings suggest a greater immunogenicity with the larger dose in HIV-infected adults than has been seen in immunocompetent populations [12, 13].

Published data assessing the association of CD4 cell count with the response to vaccination against other pathogens in HIV-positive study participants have reflected disparate results. In some studies, vaccination against hepatitis B [7], influenza [5], tetanus [5, 6], and Streptococcus pneumoniae [5] was more successful in participants with higher CD4 cell counts, but this association was not seen in other studies of hepatitis B [8] and hepatitis A [11] vaccines. In our population of HIV-infected homosexual men, a high CD4 cell count correlated with both an increased chance of seroconversion and a higher mean titer of anti-HAV antibody. A similar association was observed by Wilde et al. [14] in HIV-infected hemophiliacs but not in the homosexual men studied by Hess et al. [11]. However, the small number (n = 14) of HIV-infected homosexual men in the latter study would have limited detection of such an association. Although Wilde et al. recommended that vaccination against hepatitis A not be undertaken in persons with <200 CD4 cells/µL, we found that 64% of men with this degree of immune depression could still produce protective levels of antibody. Vaccination should therefore be offered as early as possible to all HIV-positive homosexual men with a clinical need.

The GMTs of anti-HAV antibody in HIV-infected men after two doses of vaccine (101 IU/L) was much lower than in their HIV-negative counterparts (1086 IU/L). This study did not examine antibody decline; however, if anti-HAV is lost more quickly with HIV infection (as has been observed following vaccination against hepatitis B [15]), then the titer of anti-HAV might rapidly decline to below protective levels. Further research on the rate of antibody decline in HIV infection is needed before any recommendations for booster vaccinations can be made. Meanwhile, anti-HAV titer should be estimated regularly for HIV-positive persons following vaccination.

A nonsignificant trend towards a better response was seen with the shorter course (93% vs. 82%), but this may be due in part to a greater mean baseline CD4 cell count (569 vs. 454/µL). Dose-response studies in larger populations are needed before the 0, 1–month schedule can be recommended to encourage compliance and to provide earlier protection.

The 1440 ELU dose was very well tolerated in this population, with no novel, severe, or unusual reactions reported. Headache, myalgia, and nausea were all reported more frequently by HIV-infected persons but probably represent the underlying disease.

Acknowledgment

Vaccine for this study was provided by SmithKline Beecham Biologicals.

References


