Determinants of Hepatitis A Vaccine Immunity in a Cohort of Human Immunodeficiency Virus-Infected Children Living in Switzerland

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Vaccination in HIV-infected children is often less effective than in healthy children. The goal of this study was to assess vaccine responses to hepatitis A virus (HAV) in HIV-infected children. Children of the Swiss Mother and Child HIV Cohort Study (MoCHiV) were enrolled prospectively. Recommendations for initial, catch-up, and additional HAV immunizations were based upon baseline antibody concentrations and vaccine history. HAV IgG was assessed by enzyme-linked immunosorbent assay (ELISA) with a protective cutoff value defined as ≥10 mIU/ml. Eighty-seven patients were included (median age, 11 years; range, 3.4 to 21.2 years). Forty-two patients were seropositive (48.3%) for HAV. Among 45 (51.7%) seronegative patients, 36 had not received any HAV vaccine dose and were considered naïve. Vaccine responses were assessed after the first dose in 29/35 naïve patients and after the second dose in 33/39 children (25 initially naïve patients, 4 seronegative patients, and 4 seropositive patients that had already received 1 dose of vaccine). Seroconversion was 86% after 1 dose and 97% after 2 doses, with a geometric mean concentration of 962 mIU/ml after the second dose. A baseline CD4+ T cell count below 750 cells/μl significantly reduced the post-2nd-dose response (P = 0.005). Despite a high rate of seroconversion, patients with CD4+ T cell counts of <750/μl had lower anti-HAV antibody concentrations. This may translate into a shorter protection time. Hence, monitoring humoral immunity may be necessary to provide supplementary doses as needed.

Liver diseases are among the three primary causes of non-AIDS-related deaths in adult patients with HIV infection through hepatotropic viral coinfection, liver toxicity of antiretroviral therapy, and emerging liver diseases, such as nodular regenerative hyperplasia (19). It has been shown that HIV infection does not alter the clinical course of hepatitis A in adults (9); however, this infection may have adverse effects in patients with liver disease and impair adherence to treatment, which can favor the appearance of resistance (13, 23, 36). Thus, HIV-infected adult patients are at increasing risk of liver disease (15) and may thus have a benefit from protection against hepatitis A virus (HAV). Data on HAV infection in HIV-infected children are missing. HAV infection runs a more benign course in healthy children (especially in those aged less than 6 years) (2), and major drug hepatotoxicity is far less frequent in HIV-infected children than adults, although severe side effects may occur (26). Nevertheless, a significant proportion of HIV-infected children may still be at risk of HAV infection when reaching adulthood (4), conferring long-term benefits to HAV immunization.

Studies have demonstrated that HAV vaccines are safe, clinically well tolerated, and highly immunogenic in all age groups (6). While seroconversion reaches 100% in healthy adult and pediatric individuals after 2 doses of Havrix (GlaxoSmithKline Biologicals, Rixensart, Belgium) (2), studies with adult HIV-positive patients showed significantly lower percentages (48.5 to 94%) (16, 21, 22, 24, 33, 35, 39). Duration of protection, currently estimated to be more than 20 years in healthy individuals (12), also seems to be shorter in HIV-positive patients (35). Studies with HIV-infected children are scarce and heterogeneous. Nevertheless, available data suggest a much better immune response than in adults (11, 28, 30, 37). We present here the results of a prospective study with HIV-infected children enrolled in the Swiss Mother and Child HIV Cohort (MoCHiV) cohort. The primary objective was to determine the parameters influencing the antibody response to vaccination against HAV in HIV-infected children.

MATERIALS AND METHODS

Population. Patients enrolled in this study were prospectively monitored in the MoCHiV cohort (32), which includes children diagnosed with HIV infection and records clinical and biologic data biannually. The MoCHiV database also provides information concerning patient demographics, history of HIV disease, viral load upon enrollment in this study, evolution of immunologic status—including CD4 cell nadir—and antiretroviral treatment history (introduction of highly active antiretroviral treatment [HAART], defined by at least 3 antiretroviral drugs, including either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor). Patients were recruited in all five Swiss pediatric university hospitals, in an additional tertiary children’s hospital, and from the Italian-speaking part.
of Switzerland (canton of Ticino), which all together monitor most HIV-infected children in Switzerland. There were no exclusion criteria, including age, apart from refusal to participate. Patients older than 18 years but still treated in HIV pediatric clinics were also included. Informed consent was obtained from the child and/or his legal guardian according to age. This study was approved by the institutional ethics committee and conducted in accordance with the principles of the Declaration of Helsinki, the standards of good clinical practice, and Swiss regulatory requirements. Vaccination history was retrieved from vaccination cards and/or medical records, as previously described (20).

Categorization of HAV vaccine response. Our study population consisted of two groups of HAV-seropositive and -seronegative patients, according to baseline antibody status against HAV (Fig. 1). HAV vaccine history then allowed the constitution of 3 subgroups called unimmunized (1 vaccine dose), and fully immunized children (≥2 vaccine doses) (Fig. 1). Seronegative unimmunized patients are referred to as naïve. We used a 2-dose immunization schema with a minimum of 4 months between the first and second doses. Recommendations for initial, catch-up, and additional HAV immunizations (Havrix; 720 enzyme-linked immunosorbent assay [ELISA] units [20] or Twinrix (720 ELISA units [≥19 years old]) were based upon baseline antibody concentrations and vaccine history; two doses were recommended for naïve children, one catch-up dose for primed children (one previous immunization, even if seropositive at baseline), and one additional boosting dose to fully immunized but seronegative patients. Twinrix (720 ELISA units of inactivated hepatitis A virus and 20 µg recombinant HBsAg protein; GlaxoSmithKline Biologicals) was used instead of Havrix if catch-up or full immunization was also necessary for hepatitis B.

Analysis of vaccine-induced humoral immunity. HAV IgG antibodies were assessed in the Laboratory of Vaccinology (HUG) by ELISA (Enzygnost Anti-HAV; Dade Behring Marburg GmbH, Marburg, Germany), according to the manufacturer’s instructions. We defined seroconversion by measurement of an anti-HAV antibody concentration of ≥10 mIU/ml, which has been considered protective against HAV (2). Results below the assay’s cutoff were arbitrarily given half the cutoff value to allow computation of geometric mean concentration (GMC).

Statistical methods. Demographics and biologic variables, such as gender, ethnicity, age, baseline CD4 cell count, nadir of CD4 cell count, HIV load, HAART, and previously administered HAV vaccine doses, were compared between HAV-positive and -negative children using the Student t test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. All variables with a P value of <0.25 were then included in a multivariable logistic regression model, for which the adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated. The same variables were then evaluated individually as potential determinants of HAV vaccine responses, using linear regression for continuous variables and the chi-square test or Fisher’s exact test for categorical variables, as appropriate. After this, all the variables with a P value of <0.25 were included in a multivariable linear regression model. All tests were two tailed, and a P value of ≤0.05 was considered statistically significant. Sample size was not calculated, as all HIV-infected children of Switzerland included in the MoCHiv cohort were offered the opportunity to participate in the study. Statistical analyses were computed using the SPSS 16.0 statistical package (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of the subgroups of patients. Eighty-seven patients were included in the study (median age, 11 years; range, 3.4 to 21.2 years) between June 2006 and August 2007. Four patients were older than 18 years at enrollment. Forty-five patients were seronegative (51.7%) and 42 seropositive (48.3%) for HAV (Fig. 1). Genders were similarly distributed in both groups. Seventy-nine percent of patients were on HAART, with a median CD4+ T cell count of 756/µl (>50% of patients with CD4+ T cell levels of ≥15%); 60% were fully suppressed, with an undetectable viral load (Table 1).

Among 45 HAV-seronegative patients, 36 (80%) patients were naïve, 5 (11.1%) had already received one dose of vaccine, and 4 (8.9%) were fully vaccinated (≥2 vaccine doses) (Fig. 1). Among 42 HAV-seropositive patients, 17 (40.5%) had no records of past HAV immunization and were considered to have immunity following infection, 7 (16.7%) received only one dose of vaccine, and 18 (42.8%) were fully vaccinated. HAV-positive patients were significantly older (median age, 12.2 versus 10 years; P = 0.01), had lower baseline (median of 686 versus 887 cells/µl; P = 0.02) and nadir (median of 23 versus 407 cells/µl; P < 0.01) CD4+ T cell counts, and had higher HIV loads (median of 1.9 versus 1.3 log10 HIV RNA copies/ml; P = 0.02 [Table 1]). More HAV-seropositive patients had received HAV immunizations (59.5% were known as partially or fully immunized) than HAV-seronegative patients (20% were known as partially or fully immunized; P < 0.01). Thus, a history of HAV immunization (≥1 dose of vaccine) was a reliable predictor of HAV seropositivity (OR, 5.1; 95% CI, 1.8 to 14.4). This factor remained the only statistically significant variable in a multivariate analysis (P = 0.02). All four fully immunized but HAV-seronegative patients had their last vaccine dose between 3.5 and 7 years before enrollment.

Seroresponses to HAV vaccine. Vaccine HAV seroresponses were assessed after the first dose in 29/35 naïve patients (6 Havrix and 23 Twinrix) (Fig. 1). Age, gender, baseline CD4+ T cell count, HAART, and viral load data were similar between patients assessed and not assessed by serology. Seroconversion occurred in...
24/29 naïve patients (86%), with a slight trend toward higher GMCs with Twinrix than with Havrix (58 mIU/ml and 95% CI of 34 to 98 versus 51 mIU/ml and 95% CI of 29 to 91; \( P \) value, not significant [NS]). Responses to the second dose were assessed in 33/39 children, among whom 25 were initially naïve patients. Significant differences were not identified between patients assessed and not assessed by serology. Ten received Havrix as the second dose (6 primed [first dose] with Havrix and 4 with Twinrix), and 23 received Twinrix (3 primed with Havrix and 20 with Twinrix). All but 1 (97%) patient seroconverted after the second dose, with a GMC of 962 mIU/ml (95% CI, 503 to 1,838) (Fig. 2). Again, responses to Twinrix were slightly but not significantly higher than responses to Havrix (983 mIU/ml and 95% CI of 488 to 1,981 versus 912 mIU/ml and 95% CI of 509 to 1,636). This difference was higher following 2 doses of Twinrix (1,247 mIU/ml; 95% CI, 829 to 1,878) than following 2 doses of Havrix or mixed regimens (644 mIU/ml; 95% CI, 316 to 1,312) but did not reach statistical significance. The median interval between the first and second doses was 7 months (interquartile range [IQR], 6 to 12 months). The median interval between vaccination and serology was 3 months (IQR, 2 to 3.3 months) for post-1st-dose serology and 3.2 months (IQR, 2.5 to 3.6 months) for post-2nd-dose serology, with no significant influence on antibody concentrations (details not shown).

In a post-1st-dose analysis, none of the tested variables significantly influenced anti-HAV GMCs. Baseline CD4\(^+\) T cell counts significantly influenced post-2nd-dose responses in univariate analyses \( (P < 0.001) \), and this influence remained significant in a multivariate model \( (P = 0.005) \) including baseline viral load, nadir CD4\(^+\) T cell count, and HAART. Using the median baseline CD4\(^+\) T cell count (750/\( \mu \)l) as a cutoff, we found that only about
60% of patients with CD4+ T cell counts below 750/μl had anti-HAV antibody concentrations higher than 250 mIU/ml, compared to 100% of children with CD4+ T cell counts of 750/μl or more (Fig. 3). When we performed our analysis with exclusion of children below 5 years (physiologically higher lymphocyte and CD4+ T cell counts), the result remained the same (data not shown). An increase of more than 1.5 log10 in anti-HAV antibody concentration between the first and second doses was observed in 8/23 patients with available data and was also associated with a higher CD4+ T cell count (median [IQR] of 1,212 cells/μl [908 to 1,653] versus 807 cells/μl [634 to 1,018]; P = 0.04 [Fig. 4]).

**DISCUSSION**

Immunocompetent children and adults reach nearly 100% seroconversion rates and high GMCs after HAV immunization (6). We demonstrate here that HIV infection reduces the magnitude of vaccine responses, resulting in lower GMCs. However, in our study, the seroconversion rate reached 97% after the second dose of vaccine. We attribute this good result to the favorable immune profile of our patients who were essentially subjected to HAART, with a median CD4+ T cell count of 887/μl (>50% of patients with CD4+ T cell levels of ≥15%) and mostly undetectable HIV-1 RNA. In a population of pediatric patients (median age of 5.5 years) without severe symptoms or immunosuppression (all with T cell levels of >15%), Gouvea et al. showed a 100% seroconversion rate (11). Otherwise, due to heterogeneity of study populations (27), results can differ, with seroconversion rates following HAV vaccination ranging from 48.5 to 94% in HIV-infected adults (16, 21, 22, 24, 33, 35, 39) and from 84.5 to 100% in HIV-infected children (11, 25, 28, 30, 37).

In our study, the only determinant of the antibody response was the CD4+ T cell count. The age of our patients could have had an impact on our results. But, only 4 out of 29 children that had post-1st-dose analyses and only 2 out of 33 children who had post-2nd-dose analyses were below 5 years of age. Thus, their physiologically higher lymphocyte and CD4+ T cell counts were quite unlikely to have influenced our results. The role of CD4+ T cells has already been demonstrated in several adult (16, 21, 24, 35, 39) and pediatric (25, 28, 30, 37) studies. Weinberg et al., in a

![FIG 3](http://cvi.asm.org) Serum antibody concentrations according to CD4+ T cell count after the second HAV vaccine dose. Individual results are displayed as reverse cumulative distribution curves.

![FIG 4](http://cvi.asm.org) Correlation of antibody concentrations after the first (priming) and second (boosting) vaccine doses. Solid line, linear correlation fit line; P, Pearson coefficient; dashed line, separation between patients (8/23) with a ≥1.5-log increase in antibody concentration between the first (priming) and second (boosting) doses.
pediatric population, and Overton et al., in an adult population, identified the viral load as a determinant of response to vaccination (22, 37). Over 50% of the population in the study by Weinberg et al. had a detectable viral load (cutoff, 400 HIV RNA copies/ml) (37), while 73% of our HIV-seronegative population had an undetectable viral load (cutoff, 40 HIV RNA copies/ml). This difference may explain why viral load does not appear as a significant factor of vaccine response in our population. Other determinants such as male gender (22) and tobacco use (17) in adult populations and female gender and age of <12 years in pediatric populations were identified by others (30) but did not play a role in our study.

Although the CD4+ T cell count was a significant determinant of post-2nd-dose response, its influence on anti-HAV antibody concentrations after the first dose was not statistically significant. This may be essentially due to a smaller sample size, or it may highlight the need for sufficient CD4+ T cells to establish and maintain an immune memory (3). Few studies reported an association of CD4+ T cell count with the primary response after the first HAV vaccination (16, 25). Sakawad et al. showed, in a pediatric population quite similar to ours in terms of sample size (38) and immunological profile (mean CD4+ T cell count of 749 cells/μl), that CD4+ T cell count was a significant predictor of seroconversion after the first dose of an HAV vaccine. Their vaccine, however, was virosomal, which could explain the difference in results (25). The influence of the CD4+ T cell count on the magnitude of the post-2nd-dose GMC increase suggests that it is important for the induction and reactivation of the memory response. In another study, CD4+ T cell count measured at different times after primary vaccination did not impact the quality of boosting responses (38). During primary vaccination with T cell-dependent vaccines, the extrafollicular reaction precedes the development of germinal centers. Production of antibodies at this stage is limited, until B cells expressing the CXCR5 receptor migrate toward CXCL13 (CXCR5 ligand) produced by follicular dendritic cells and initiate the germinal center reaction with class switch, somatic hypermutation, and affinity maturation (29). In an adult HIV-positive population, CD4+ T cell counts of less than 350/μl were associated with a diminution of expression of CXCR5 on naive and memory B cells as well as on preplasma cells (5). This impacted migration patterns of B cells and may limit germinal center reactions. Weinberg et al. recently demonstrated the role of B cells per se in HAV vaccine responses (38). They showed that the boosting response of HIV-infected children on HAART relies mainly on viral load and percentage of B cells and only secondarily on the percentage of CD4+ T cells. Their results suggested that bidirectional cooperation between B and T cells plays a major role in the response to HAV vaccination. Thus, a paucity of functioning B cells and defective CD4+ T cell helper function at priming prevent HIV-infected patients from effectively generating memory B cells and consecutively an effective boosting response. Our results are in accordance with this understanding, despite the lack of association between HIV-1 load and anti-HAV responses.

Even though the rate of seroconversion may approach or even equal the one of healthy populations in HIV-infected populations, the anti-HAV GMCS remain significantly lower. In our study, the GMC was 962 mIU/ml (95% CI, 503 to 1,838), and only about 60% of patients with CD4+ T cell counts below 750 cells/μl had anti-HAV antibody concentrations above 250 mIU/ml, a concentration which is virtually always exceeded in healthy persons (37). In two pediatric studies, Gouvea et al. measured a GMC of 2,180 mIU/ml (95% CI, 1,226.5 to 3,875.5) (11) and Sudjaritruk et al. a GMC of 520.95 mIU/ml (30). This is significantly lower than in healthy children, whose GMCS rose above 5,000 mIU/ml in several studies (1, 12, 18). The issue raised here is the persistence of antibodies and thus long-term protection. It is currently estimated to be more than 20 years in healthy children and adults (12). Weinberg et al. showed that the seroprotection against HAV in HIV-infected children dropped from 97% 2 months after the second dose of vaccine to 90% 20 months after the second dose of vaccine (37). In our study, although a history of previous HAV immunization reliably predicted seropositivity, 4 (44.5%) of the fully immunized patients who had received their last dose of vaccine 3.5 years or more before enrollment were seronegative for HAV. Launay et al. monitored the temporal evolution of antibody levels in HIV-infected adults (17). At 48 weeks after the last dose of vaccine, GMCS were equivalent to about 40% and 38% of GMCS measured 1 month after the last doses of a 3-dose schedule (0, 4, and 24 weeks) and a 2-dose schedule (0 and 24 weeks), respectively. This is comparable to what was shown in immunocompetent patients by Van Herck and Van Damme (34). Twelve months after a 2-dose regimen, they measured GMCS corresponding to 31% of those measured 1 month after the second dose of vaccine. In the same study, the annual waning of antibodies after the second dose of vaccine was estimated to be 15%. Recently, Crum-Cianflone et al. reported data about the long-term immunity to HAV among 130 HIV-infected adults (7). After an initial seroconversion rate of 89%, 90% (104 of 116; 95% CI, 83% to 95%) of responders remained seropositive at 3 years and 85% (63 of 74; 95% CI, 75% to 92%) at 6 to 10 years. GMCS were 154, 111, and 64 mIU/ml at 1, 3, and 6 to 10 years, respectively. This corresponds to an annual fall of 12 to 15%, which is similar to what has been described for healthy adults. Higher GMCS over time were associated with a lower viral load. As pediatric HIV-infected populations have comparatively higher GMCS, we can expect that the average persistence of antibody may even be better. However, prediction on an individual basis may not be possible, as underscored in the conclusion of the review by Sutcliffe and Moss (31). These authors conclude that most children respond to vaccination, although immune reconstitution was not sufficient to ensure long-term immunity for some children, but that some children need additional vaccine doses to maintain protective immunity.

Our field study has several limitations. First, serological analyses could only be performed for 29 and 33 of 87 HIV-infected children for post-1st- and post-2nd-dose analyses, respectively. This may have prevented us from identifying other determinants of HAV vaccine responses. However, the conclusions of our study are in accordance with previously published work. Second, we did not include analysis of the CD19 cell count, which was recently shown to impact HAV vaccine response (30). Third, either Havrix or Twinrix vaccine was used, depending upon the need for hepatitis B immunization. Several reports for healthy populations showed that Twinrix immunization results in higher GMCS (8, 10, 14), and this could have positively influenced our results. Fourth, there were 4 seropositive patients at inclusion that were included in the post-2nd-dose analyses. As seropositivity can be explained by previous natural infection, this could have positively influenced our post-2nd-dose results. However, another explanation is the persistence of antibody after the first dose. Clemens et al. showed that antibody titers last ≥12 months after the first vaccine
dose in immunocompetent children (6). We think that this could as well be true for our seropositive patients, who had their first dose of vaccine 7 to 22 months before inclusion, compared to 15 to 121 months in seronegative patients, who also received one dose of vaccine before inclusion. Furthermore, as numbers of these seronegative and seropositive patients are equal (4) in the post-2nd-dose analyses, we do not think that this influenced significantly our results. Finally, the results of our study—like others—may not be readily transposed to other settings and populations with distinct baseline characteristics.

In conclusion, our study indicates that antibody responses elicited by the most immunogenic HAV vaccine available are lower even in HIV-infected children with modestly lower (590 to 731/μL) CD4+ T cell counts who were essentially subjected to HAART. This may predict a shorter period of protection than that in immunocompetent children. Because it is difficult to predict outcome on an individual basis, serological monitoring and additional boosting doses if needed—regardless of immunization history—should be considered for HIV-infected children.

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