Immunogenicity and Tolerability of Hepatitis A Vaccine in HIV-Infected Children

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The immunogenicity and tolerability of hepatitis A virus vaccine was evaluated in a group of 32 children with human immunodeficiency virus (HIV) infection and 27 children with seroreversion. After 2 doses of vaccine, 100% of children experienced seroconversion with good toleration of the vaccine. There were no differences in variation of virus load between immunized HIV-positive children and a group of 31 nonimmunized HIV-positive children with similar characteristics.

The use of HAART has altered the natural history of AIDS, increasing the survival and the quality of life of HIV-infected patients [1, 2]. In parallel, one can observe the emergence of liver disease as one of the major causes of death in HIV-infected patients [3, 4].

Today, many HIV-infected patients have biochemical evidence of liver disease [3], sometimes with a fatal outcome [5]. The full extent and causes of liver disease in children with AIDS are unknown, but such causes include injury from drug therapy and nonspecific abnormalities that occur in patients with chronic illness, neoplasm, and opportunistic infection [4, 5].

In 1998, a seroepidemiologic study estimated the prevalence of hepatitis A virus (HAV) infection as 66.6% in the general population in the city of São Paulo, Brazil, with prevalences of 12.1% in those aged 2–4 years, 28.1% in those aged 5–7 years, and 35.8% in those aged 10–14 years [6].

Although hepatitis A vaccine is recommended for children living in regions with elevated rates of hepatitis A [7], no data on immune response to and tolerability of the vaccine in HIV-infected children have been available until now. The existence of a large population of HAV-seronegative children at risk of infection in the city of São Paulo prompted us to assess the immunogenicity and tolerability of hepatitis A vaccine in HIV-infected children.

Patients and methods. This study was approved by the ethics committee of the Federal University of São Paulo, Brazil (UNIFESP). Before enrolment, written informed consent was obtained from parents or guardians. Between March 2002 and September 2003, 32 HIV-infected children (mean age, 5.5 years) and 27 seroreverted children (mean age, 5.1 years) were vaccinated at the Pediatric AIDS Clinic of UNIFESP. The HIV-infected children were classified into clinical categories as follows: category N, 18.7%; category A, 43.7%; and category B, 37.6%. They were classified into immunologic categories as follows: category 1, 31.2%; and category 2, 68.8%. Of 32 HIV-infected and immunized children, 29 were receiving HAART for a mean duration of 3.5 years; 12.9% of these children were receiving their first regime of HAART. In this group, there were 11 patients with undetectable HIV RNA levels (<400 copies/mL).

All of the HIV-infected children were exposed by vertical transmission. To be enrolled in the study, the children in both groups had to be HAV-seronegative (HAV antibody titer, <20 mIU/mL) before vaccination, have no history of any previous viral hepatitis, not be a chronic carrier of hepatitis B or C, not have recent contact with patients with viral hepatitis, present with normal aspartate aminotransferase and alanine aminotransferase serum levels, and not have any acute disease at study entry. To assess the probability of a decline in $CD4^+$ T cell count associated with vaccination, a control group of 31 HIV-infected, non–HAV-vaccinated children (mean age, 5.8 years), divided into similar clinical and immunologic categories, was included.

Two intramuscular doses of hepatitis A vaccine (Havrix; Glaxo SmithKline Beecham) were administered with a 6-month interval between doses. Blood samples were obtained before and 4–8 weeks after the first and second doses. Serum samples were stored at −80°C until tested for antibody levels.

HAV antibodies were assessed with use of a competitive ELISA kit (Adaltis). Seroconversion was defined as having occurred if the HAV antibody titer was >20 mIU/mL. For HIV-infected children, peripheral $CD4^+$ T lymphocyte counts and HIV load were assessed before and 4–8 weeks after the first and second doses. T cell counts were determined by means of flow cytometry, and HIV load was determined by means of

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Table 1. Demographic and clinical characteristics of HIV-infected children (HIV group) and children with seroreversion (SR group) who received hepatitis A vaccination and nonvaccinated HIV-infected children (HIV NV group).

Characteristic	HIV group (n = 32)	SR group (n = 27)	HIV NV group (n = 31)	P
Age, mean years (range)	5.5 (1.9–9.3)	5.1 (1.6–9.4)	5.8 (3.3–10.5)	.51[a]
Receiving HAART, % of subjects	90.6	…	80.6	.53[b]
Initial HIV load, mean log copies/mL (range)	3.26 (<400–5.4)	…	3.33 (<400–5.3)	.76[c]
Initial CD4$^+$ T cell count, mean cells/mm^3 (range)	1483 (572–2717)	…	1275 (405–2730)	.18[c]

[a] By analysis of variance.
[b] By the χ^2 test.
[c] By Student's t test.

Amplicor (Roche). To measure vaccine safety and tolerability, parents were asked to record the occurrence of local and systemic symptoms.

The χ^2 test and Fisher's exact test were used for categorical variables, and the Student's t test was used for continuous variables. For variables measured in the course of time, analysis of variance (ANOVA) with repeated measures was used.

Results. The demographic characteristics of children enrolled in the study are summarized in table 1. Twenty-seven (87.1%) of 31 HIV-positive children and 18 (72.0%) of 25 children with seroreversion experienced seroconversion after the first vaccine dose ($P = .157$, by the χ^2 test). After the second dose, 100% of children from both groups had HAV antibody titers >20 mIU/mL.

The geometric mean HAV antibody titers did not differ between the HIV-positive group and the seroreversion group. ANOVA with repeated measures showed that HAV antibody titers had the same variability over time in the same way for both groups ($P = .122$), with an increase in antibody values (figure 1 and table 2).

Few vaccinated children experienced adverse events, and most adverse events were experienced after the first dose. Six children in the HIV-positive group and 3 in the seroreversion group presented with systemic adverse events. Local adverse events were seen in 2 children from the seroreversion group and in 1 child from the HIV-positive group (table 3).

Mean HIV load did not vary in the HIV-positive vaccinated children ($P = .635$, by ANOVA) (figure 2). Four to 8 weeks after the first vaccine dose, 2 of 11 children with undetectable HIV loads presented with a transient detectable level of HIV RNA (2.9 and 2.7 log copies/mL). However, HIV load immediately before the second dose was undetectable again in both children. CD4$^+$ T cell counts varied during the study, with a decrease in CD4$^+$ T cell count between the sample obtained before the first vaccine dose and that obtained after the first dose ($P = .016$, by ANOVA). No significant variation was noticed in the other time intervals of the study ($P > .20$, by ANOVA) (figure 3).

To better investigate the variation in CD4$^+$ T cell count observed in the HIV-positive group, another group of HIV-infected children with similar characteristics was evaluated. A similar decrease in CD4$^+$ T cell count (in terms of both absolute numbers and percentages) was observed in both groups during the 7 months of the study. Of interest, mean HIV load was also comparable between the 2 groups, and there was no variation in mean HIV load during the study period (figure 4).

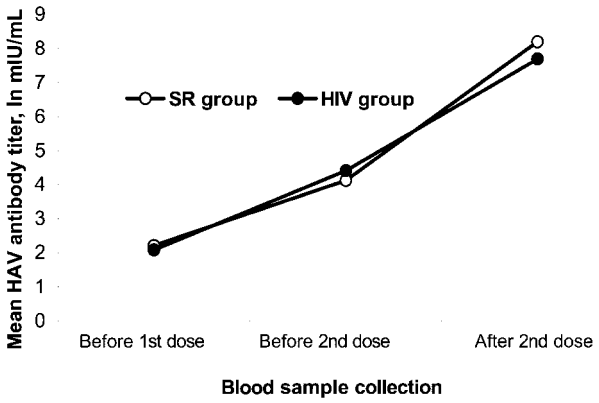

Figure 1. Mean hepatitis A virus (HAV) antibody titers over time in HIV-positive children (HIV group) and children with seroreversion (SR group) who received hepatitis A vaccine.

Table 2. Geometic mean titers of hepatitis A virus antibody in HIV-infected children (HIV group) and children with seroreversion (SR group) who received hepatitis A vaccination, by blood sample collection time.

Patient group	Geometric mean titer, mIU/mL (95% CI)		
	Before first dose	Before second dose	After second dose
HIV group	8.0 (7.0–9.1)	82.4 (50.0–135.7)	2180.2 (1226.5–3875.5)
SR group	9.1 (7.7–10.7)	62.0 (32.0–120.1)	3627.6 (2144.4–6136.5)

Discussion. We have assessed the antibody response to hepatitis A vaccine in HIV-infected children. Most of these children were receiving HAART and had $CD4^+$ T cell levels that were normal for their age. We have deliberately excluded those children who had presented with severe symptoms (clinical category C) or low $CD4^+$ T cell levels sometime in their lives (immunologic category 3). The decision to exclude these children was based on previous studies [8] and on our own experience [9] (A. P. Prancanica, personal correspondence), which suggested that children belonging to immunologic categories 2 and 3 did not respond to immunization as well as those belonging to immunologic category 1. Lange et al. [10] have also noticed that the nadir $CD4^+$ cell count was positively associated with antibody levels.

Moreover, we had already noticed that the vaccine antigen was also a strong determinant of antibody response. In the children we followed up, tetanus antigen proved to be the antigen that provided the best antibody response, whereas measles antigen was the antigen with the poorest response.

However, response to hepatitis A vaccine was even better. We found no differences between the groups in terms of their response after the first vaccine dose or after the second vaccine dose. Moreover, geometric mean antibody values were also very similar in the HIV-positive and seroreversion groups.

Table 3. Adverse events occurring after administration of hepatitis A vaccine in HIV-infected children (HIV group) and children with seroreversion (SR group).

Adverse events	No. (%) of subjects	
	HIV group	SR group
Local events: pain	1 (3.1)	2 (7.4)
Systemic events		
Fever	1 (3.1)	2 (7.4)
Erythema	1[a] (3.1)	1[a] (3.7)
Fatigue	2 (6.3)	…
Headache	1 (3.1)	…
Vomit or diarrhea	3 (9.4)	1 (3.7)
Arthralgia	2 (6.3)	…
Myalgia	3[a] (9.4)	1 (3.7)

NOTE. The same child may have experienced >1 adverse event.
[a] One episode occurred after administration of the second dose.

When we compared our results with findings in the literature, we found the same antibody response to hepatitis A vaccine administered to healthy children [11, 12]. By contrast, HIV-infected adults responded very weakly to hepatitis A vaccine, compared with HIV-seronegative control subjects (seroconversion rate, 77% vs. 100%; geometric mean antibody titer, 636 mIU/mL vs. 1687 mIU/mL) [13]. Neilsen et al. [14] found a similar trend in HIV-infected adults, compared with HIV-seronegative individuals (seroconversion rate, 75.6% vs. 90.2%; geometric mean antibody titer, 100.7 IU/L vs. 1086.2 IU/L). More recently, Kemper et al. [15], in a study involving HIV-infected adults, also showed a low seroconversion rate for all individuals, but the seroconversion rate was even lower in those with low $CD4^+$ T cell counts. We do not have an explanation for the difference in response to hepatitis A vaccine between HIV-positive adults and children.

Of interest, we had a low incidence of adverse events, similar to that observed by others in studies involving healthy children [11].

Finally, we did not detect variations in mean HIV load during the study, with only 2 transient increases after the first dose was administered; both increases reverted to previous levels just before the second vaccine dose was administered. However, we did notice a decrease in $CD4^+$ T cell count after administration of the first dose. Others have documented a transient decrease in $CD4^+$ T cell counts after vaccination with other antigens [8],

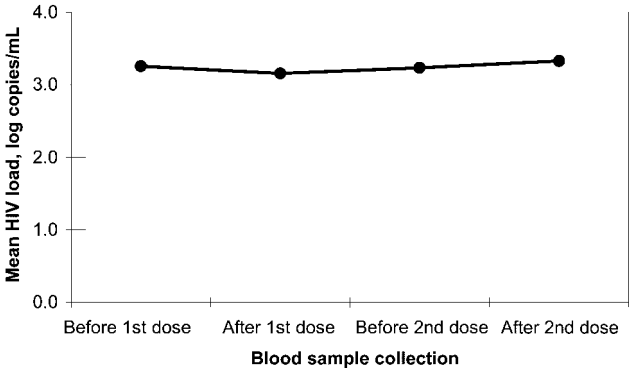

Figure 2. Variation in mean HIV load over time in HIV-positive children who received hepatitis A vaccine.

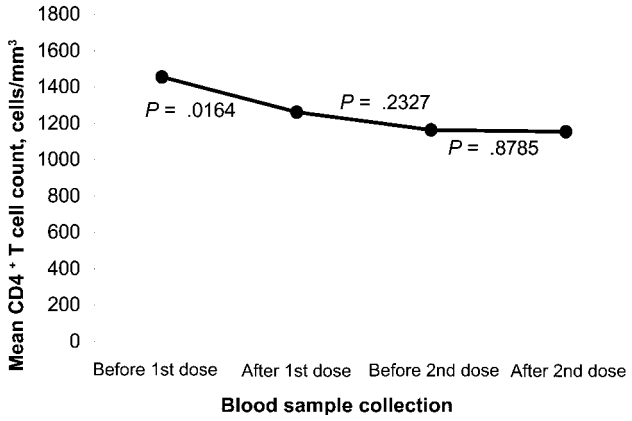

Figure 3. Variation in CD4⁺ T cell count over time in HIV-positive children who received hepatitis A vaccine.

but such decreases were always associated with an increase in HIV load and were attributed to an activation of latent HIV infection in lymphocytes. We did not find such an association in the children in our study.

To further investigate the decrease in CD4⁺ T cell count, we have compared HIV-infected children immunized with hepatitis A vaccine with a group of non-vaccinated HIV-infected children of similar age: both groups showed the same decrease in CD4⁺ T cell count (expressed both as percentages and as absolute numbers). This suggests that the observed decrease in CD4⁺ T cell count was a product of the physiologic decay of CD4⁺ T cells [16] but was also due to HIV infection [17].

In summary, we have shown that HIV-infected children without severe symptoms or immunosuppression can respond to hepatitis A vaccine as well as non–HIV-infected children, with a low rate of adverse events. In view of this finding, we would recommend that hepatitis A vaccine be administered to children who live in areas where HAV infection is prevalent. Hepatitis A vaccination would help to prevent a further burden to the liver of those children and adolescents already exposed to a variety of hepatotoxic drugs.

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Potential conflicts of interest. All authors: no conflicts.

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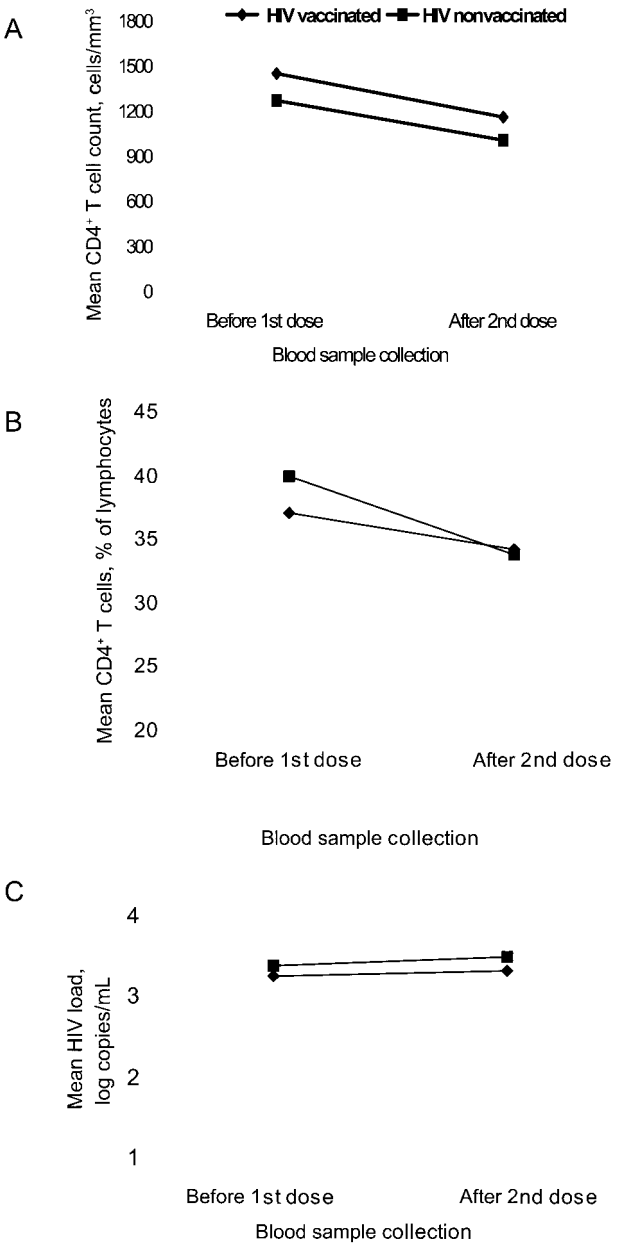

Figure 4. Variation in mean CD4⁺ T cell count expressed in absolute numbers (*A*) and in percentage of lymphocytes (*B*) and of HIV load (*C*) in HIV-infected children vaccinated against hepatitis A virus (HIV vaccinated) and in nonvaccinated HIV-infected children (HIV nonvaccinated) during the 7 months of study.

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