Boletín Médico del
Hospital Infantil de México

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RESEARCH ARTICLE

Antibody persistence 7 years after hepatitis-A vaccine in children with human immunodeficiency virus infection

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Abstract

Background: *HIV-infected children have a higher risk of presenting infections, including the hepatitis A virus (HAV). The inactivated HAV vaccine is immunogenic in immunocompetent hosts; however, there are insufficient studies on the duration of seroprotection in HIV-infected children.* **Methods:** *An analytical cohort study was conducted. HIV-1-infected children who received the inactivated HAV vaccine (2 doses) were included. Blood samples were taken for antibody measurement, the first one 28 days after the second dose and another 7 years after the vaccination schedule. Information on viral load, immunological category, weight, height, and response to antiretroviral treatment from diagnosis to the last assessment was obtained.* **Results:** *19 patients were included, with a mean age of 12.6 years (SD ± 2.29). 58% were male. 80% of the patients presented protective immunoglobulin G antibodies against HAV 7-year post-vaccination. The antibody concentration was found to be between 13 and 80 mIU/mL (median of 80 mIU/mL). 52% showed some degree of immunosuppression. There was no statistically significant relationship between the presence of seroprotection and viral load, treatment failure, immunological category, and malnutrition. Twelve patients presented with antiretroviral treatment failure, and in 33% of them, the antibodies did not offer satisfactory seroprotection.* **Conclusion:** *7-year post-vaccination, 80% of HIV-infected children maintain seroprotection titers against HAV.*

Keywords: *Human immunodeficiency virus. Children. Vaccine. Hepatitis A. Antibodies.*

Persistencia de anticuerpos siete años después de la vacuna de la hepatitis A en niños con infección por el virus de la inmunodeficiencia humana

Resumen

Introducción: *Los niños infectados por el virus de la inmunodeficiencia humana (VIH) tienen mayor riesgo de presentar infecciones, incluyendo hepatitis por virus A (VHA). La vacuna inactivada contra el VHA es inmunógena en el huésped inmunocompetente. No hay estudios suficientes sobre el tiempo de seroprotección en niños infectados por el VIH.* **Método:** *Estudio de cohorte, analítico. Se incluyeron niños con infección por VIH-1 que recibieron la vacuna inactivada contra el VHA (dos dosis). Se les tomaron muestras sanguíneas para medición de anticuerpos, una 28 días después de la segunda dosis y otra 7 años después del esquema de vacunación. Se obtuvo información de carga viral, categoría inmunológica, peso y talla, y respuesta al tratamiento antirretroviral desde el diagnóstico hasta la última valoración.*

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Date of reception: 22-08-2023
Date of acceptance: 18-01-2024
DOI: 10.24875/BMHIM.23000125

Available online: 25-06-2024
Bol Med Hosp Infant Mex. 2024;81(3):176-181
www.bmhim.com

Resultados: *Se incluyeron 19 pacientes con una edad media de 12.6 años (± 2.29). El 58% fueron del sexo masculino. El 80% de los pacientes presentaron anticuerpos immunoglobulin G (IgG) contra el VHA protectores a los 7 años de la vacunación. La concentración de anticuerpos se encontró entre 13 y 80 mUI/ml (mediana: 80 mUI/ml). El 52% mostraron algún grado de inmunosupresión. No existe relación estadísticamente significativa entre la presencia de seroprotección y la carga viral, la falla al tratamiento, la categoría inmunológica ni la desnutrición. Doce pacientes presentaron falla al tratamiento antirretroviral; en el 33% de ellos los anticuerpos no ofrecían seroprotección satisfactoria.* **Conclusiones:** *A 7 años posvacunación, el 80% de los niños con VIH mantienen títulos de seroprotección frente al VHA.*

Palabras clave: *Virus de la inmunodeficiencia humana. Niños. Vacuna. Hepatitis A. Anticuerpos.*

Introduction

Pediatric patients living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) require the same care in their growth, development control, and vaccination schedule as seronegative children. Some studies have found that patients with HIV infection may have a lower immunological response to administered vaccines, probably due to lower or altered production of antibodies after primary immunization and early loss of memory cells[1,2].

Hepatitis A virus (HAV) infection is generally asymptomatic or can cause an acute hepatitis syndrome with varying degrees of severity. The host's response to infection is related to the patient's age and immunological status and can lead to significant morbidity and mortality rates[3]. Hepatitis A in HIV patients does not seem to be more severe, but it may require the suspension of antiretroviral treatment. In children with hepatitis, the duration of viremia is more prolonged with prolonged transaminasemia[4].

The inactivated HVA vaccine is highly immunogenic and safe for normal subjects. It is recommended for use in high-risk groups, including children older than 1 year of age with HIV infection[5]. In the immunocompetent host, with the HAV vaccine, in children under 16 years of age, 97% achieve protective antibody titers (> 20 mIU/mL) 24 days after the first dose, reaching up to 100% after the second dose[6]. Studies conducted in HIV-1-infected adults have shown its safety; however, only 40% of them achieve protective antibody titers, especially in the advanced stages of the disease. Patients with CD4+ cell counts > 20% respond better to the HAV vaccine if they do not have detectable viral load; likewise, a third dose of vaccine increases antibody titers, suggesting increased protection for these patients. In a multicenter study, Kemper found that at the end of the schedule, there is a seroconversion of 68% in patients with counts ≥ 200 cells/mm^3 and only 9% in those with counts ≤ 200 cells/mm^3[3,7-9].

The HVA vaccine in children is safe and effective, even in patients exposed to HIV. It is much more effective when the CD4+ count is ≥ 20% and the viral load is undetectable, although the usual two-dose schedule seems to be insufficient in HIV-infected patients[10]. In a study conducted at a pediatric hospital in Mexico, the application of an inactivated HAV vaccine in two doses to children with HIV produced seroprotection in 96% of patients[11]. There is little information on the duration of serum antibody levels considered seroprotective for the vaccine. Therefore, this study explored the percentage of children infected with HIV vaccinated against HAV who remained seroprotected (levels > 20 mIU/mL) 7-year post-vaccination.

Methods

An analytical study was conducted on a cohort of patients treated at the HIV Clinic in the Infectology Service and Virology Laboratory of a tertiary-level pediatric hospital.

The study included HIV-infected patients who had been immunized with a complete HAV vaccine schedule and had complete paraclinical studies (viral load, CD4+ cell count) at the beginning of the schedule and from whom a sample could be taken 7 years after primary immunization. Patients who had suffered from the disease or had been revaccinated during the 7 years, and those patients older than 17 years at the end of the 7-year follow-up, were excluded. The included patients had received a primary schedule of 2 doses of inactivated HAV vaccine (Havrix®), each of 0.5 mL in the deltoid region, with a 6-month difference between each application. A blood sample was taken for antibody measurement 28 days after the second dose (first determination) and 7 years after the vaccination schedule (second determination). Antibody determination was performed using an ELISA technique (ENZYGNOST® ANTI-HAV from DADE BEHRING). The titers were expressed in mIU/mL, with protective titers considered

> 20 mIU/mL, and the maximum antibody titer level measured was 80 mIU/mL.

Data on viral load, immunological category, weight, and height (to determine nutritional status) at the time of completion of the vaccination schedule and whether they had presented treatment failure at any point during the evolution were collected from the records; the same information was collected at the 7-year follow-up.

The immunological category (used at the time of study planning) was established according to the percentage of CD4+ of the total lymphocyte count as (1) no suppression, a percentage > 25%, (2) moderate suppression between 15% and 24%, and (3) severe suppression < 15%. Nutritional status was established considering a weight or age index below the 3rd percentile, according to the 2000 CDC charts (https://www.cdc.gov/growthcharts/data/spanishpdf97/co06l029.pdf).

Viral load measurement was performed by measuring the concentration of viral RNA in plasma using a reverse transcription polymerase chain reaction. A concentration of <1.68 log^{10} copies/mL was considered the lower detection limit.

In all cases, informed consent was obtained from the parent or guardian.

The study was authorized by the hospital's Research and Bioethics Committee.

For statistical analysis, central tendency and dispersion measures were used according to the variables analyzed. For quantitative variables, the Kolmogorov-Smirnov test was applied. For qualitative variables, frequencies and proportions were calculated. Chi-square was used to test the difference between these proportions, with statistical significance considered at $p < 0.05$ with 95% confidence intervals. Spearman's correlation was performed. Statistical analysis was performed using the SPSS version 20.0 statistical program for Windows.

Results

The study included 20 pediatric patients infected with HIV-1 with a complete vaccination schedule against HAV who continued their follow-up at the HIV clinic. One patient who was revaccinated was excluded, leaving 19 patients for the analysis. The average age of the patients after 7 years of follow-up was 12.6 years (SD ± 2.3, range 9-17 years). 58% were male. All were infected perinatally, receiving treatment from 1 year of age with highly active antiretroviral therapy (HAART), of which 63% (12/19) required a change of regimen due to treatment failure at some point in their evolution.

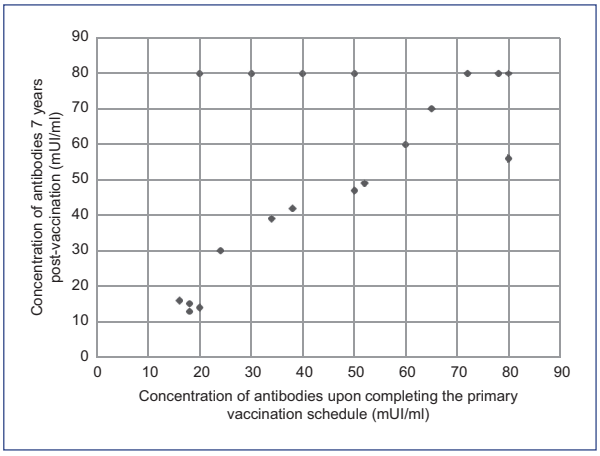

Figure 1. Correlation of HAV antibody concentration at the end of the vaccination schedule and at 7-year post-vaccination.

When classified according to nutritional status, (13/19) 68.4% were found to have normal weight, and 6/19 (31.6%) had grade I malnutrition. At the time of the last dose of the vaccine, according to the CD4+ lymphocyte count, 10/19 (52.6%) were found without suppression, 7/19 (36.8%) with moderate suppression, and 2/19 (10.5%) with severe suppression. At 7 years after vaccination, according to the CD4+ lymphocyte count, it was distributed as follows: 12/19 (63.2%) without suppression, 6/19 (31.6%) with moderate suppression, and 1/19 (5.3%) with severe suppression. The viral load detected 7-year post-vaccination was a minimum of 1.68 log10 copies/mL and a maximum of 4.86 log10 copies/mL, with a median of 1.68 log10 copies/mL.

Anti-HAV antibody levels in the first determination reached a median of 40 mIU/mL (16-80 mIU/mL), and 16/19 (84%) had a concentration ≥ 20 mIU/mL. In 3/19 (16%), the concentration was < 20 mIU/mL; these patients had severe CD4+ suppression (two cases), and one had moderate suppression. At 7-year post-vaccination, antibody levels were found with a median of 56 mIU/mL (13-80 mIU/mL); in 15/19 (79%), the levels were > 20 mIU/mL; and in 4/19 (21%), the levels were < 20 mIU/mL. The levels lower than 20 mIU/mL (13-16 mIU/mL) corresponded to one case with severe CD4+ suppression and three cases with moderate suppression.

A positive correlation was found with a Spearman's r of 0.64 between the level of antibodies against HAV at the end of the primary vaccination schedule and the level of antibodies 7 years later (Fig. 1).

Table 1. Characteristics of HIV-infected pediatric patients who were vaccinated against HAV

	With seroprotection	Without seroprotection	p-value
Treatment failure			
Yes	8	4	0.128
No	7	0	
Malnutrition			
Yes	6	0	0.184
No	9	4	
Immunological category (end of scheme)			
No suppression ($CD4^+$ > 25%)	9	1	0.249
Moderate suppression ($CD4^+$15-24%)	6	1	
Severe suppression ($CD4^+$ < 15%)	0	2	
Immunological Category (7 years)			
No suppression ($CD4^+$ > 25%)	10	2	0.475
Moderate suppression ($CD4^+$15-24%)	5	1	
Severe suppression ($CD4^+$ < 15%)	0	1	
Decrease in immunological category			
Yes	1	0	0.789
No	14	4	
Viral load			
< 1.68 log10*	10	1	0.177
> 1.68 log10	5	3	

*< 1.68 log10 = detection limit.
HIV: human immunodeficiency virus; HAV: hepatitis A virus.

No statistically significant difference (p > 0.05) was found when analyzing the possible association of seroprotection with antiretroviral treatment failure, malnutrition, immunological category, decrease in immunological category, and viral load (Table 1). Those patients who presented a percentage of CD4+ lymphocytes lower than 25% had more frequent antibody levels lower than 40 mIU/m (p = 0.04).

Discussion

Children infected with HIV type 1 are particularly vulnerable to severe, recurrent, and unusual infections, some of which are caused by pathogens preventable by vaccination[12]. In general, the vaccines included in the vaccination program are generally safe for this group of children, but sometimes, the protection response is suboptimal. The safety of the HAV vaccine and its immune response has been evaluated since 1997, initially in adults[13], which is why its application has continued. The immunosuppressed state associated with HIV viral replication can particularly interfere with the development of the immunological response. Although early control of viral replication through effective treatment can preserve immune function, the routine response of children to vaccines may be uncertain over time[14], with a better response observed in children under HAART treatment in whom viral load is controlled[15]. In HIV-infected subjects, the level of antibodies may be lower than that achieved by uninfected subjects[7-9]. In our study, we observed that in children 7-year post-vaccination, almost 80% retain a sufficient amount of protective IgG antibodies (levels > 20 mIU/mL) against HAV. Children with severe immunosuppression (CD4+ lymphocyte count < 25%) at the end of the vaccination schedule did not reach protective levels or were < 40 mIU/mL, and at 7 years, their antibody concentration did not change. Different authors have found that CD4+ counts > 25% in adult and child populations, which is a significant factor for a better response to the HAV vaccine[15-20].

Although it was more consistent that patients with viral loads > 1.68 log^{10} (3/4) did not have seroprotection levels, 5/15 with more than 1.68 log^{10} did reach seroprotective antibody levels. It has been suggested that a higher persistent viral load indicates poor control and, therefore, immune system failure.

Usually, nutritional status directly influences cellular and humoral immunity, which, together with acquired immunodeficiency due to HIV, make patients more susceptible to infectious processes and perhaps an inadequate response to immunization schedules; however,

in this study, it is not possible to evaluate the influence of nutritional status since only 31% had a grade I malnutrition status.

There is minimal information regarding the duration of protective antibody levels of the HAV vaccine in children with HIV, so in this study, the evaluation of antibody levels was performed at 7-year post-vaccination to be compared with the previously published study in children with HIV[10]. It will be necessary to make evaluations in future years to know if the behavior in children with HIV is similar to that found in healthy children, as observed in Alaska, where at 25 years of follow-up, 78% maintained seroprotection levels[21].

HAV infection remains a common infection in our country. A change in its epidemiological behavior has been observed over the years, shifting from being more frequent in younger age groups to more frequent in adolescents and young adults. At 10 years of age, the seroprevalence of infection is only 46%; at 15 years, it is 52%; and at 25 years, it is 93%[22-24], suggesting that given the changes in public health measures, the risk of infection has shifted. The application of the inactivated HVA vaccine aims to reduce the number of subjects who may develop severe complications secondary to the infection, such as fulminant hepatitis and persistent hepatitis.

If we take into account the changes in the behavior of HAV infection in our country as well as the increase in the number of susceptible subjects, it becomes necessary to establish immunization strategies against HAV openly, particularly in patients who have some type of immunodeficiency, such as those infected with HIV. According to the existing information in children with HIV, a marker to ensure a better response to vaccines will be a good level of CD4+ lymphocytes.

One of the limitations of this study is the small sample size, which is due to the decreasing number of cases of vertical transmission in our hospital. In addition, the HAV vaccine is not part of the national vaccination program, so there is limited information available on the population seeking medical care.

In recent years, advances in the diagnosis, treatment, and clinical and laboratory monitoring of HIV infection in children have allowed for greater survival and a better quality of life for this population. It is important to vaccinate HIV-infected children who will reach adulthood and monitor the maintenance of antibodies after vaccination.

We believe that worldwide, information on the HAV vaccine and other vaccines for children with HIV/AIDS should be increased.

Funding

Instituto Mexicano del Seguro Social.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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