Response to Immunization With Measles, Tetanus, and Haemophilus influenzae Type b Vaccines in Children Who Have Human Immunodeficiency Virus Type 1 Infection and Are Treated With Highly Active Antiretroviral Therapy

Ann J. Melvin, MD, MPH, and Kathleen M. Mohan, ARNP

ABSTRACT. **Objective.** To assess the level of immunity to measles, tetanus, and Haemophilus influenzae type b (Hib) in previously immunized children who have human immunodeficiency virus (HIV) infection and were treated with highly active antiretroviral therapy (HAART) and to determine the response to reimmunization.

**Methods.** Retrospective review of clinical data from children who have HIV-1 infection and were treated with HAART. Children were included in the analysis when they had a history of immunizations before treatment with HAART; had specific immunoglobulin G levels to measles, tetanus, or Hib measured after starting HAART but before the receipt of additional immunizations; were reimmunized while on HAART; and had postimmunization immunoglobulin G levels available.

**Results.** Nineteen children (median age: 7 years; range: 3–14 years) who were treated with 3 to 5 drug HAART regimens for a median of 20 months (range: 8–37) met the criteria for at least 1 antigen and were included in this review. Fifteen (79%) of the 19 had plasma RNA levels <50 copies/mL. The median CD4% before HAART was 26% (range: 1–41) and at the time of immunization, 35% (range: 20–54). Before reimmunization, 1 (5%) of 18 children had detectable antibody levels to measles, 6 (35%) of 17 had detectable antibody levels to tetanus, and 14 (78%) of 18 had detectable antibody levels to Hib. After immunization, 15 (83%) of 18, 10 (90%) of 11, and 3 (75%) of 4 seroconverted to measles, tetanus, and Hib, respectively. Antibody levels remained detectable after 1 year in the majority of children tested.

**Conclusions.** Consideration should be given to readministering childhood immunizations to children who have HIV infection and are treated successfully with combination antiretroviral therapy.

**METHODS**

Children who have human immunodeficiency type 1 (HIV-1) infection demonstrate abnormalities of both the humoral and cell-mediated immune systems. Previous studies in children with HIV-1 infection have shown impaired responses to immunizations, with children with HIV-1 infection demonstrating lower antibody responses and lack of persistence of protective antibody levels compared with uninfected children. In addition, children with HIV-1 infection respond poorly to booster immunizations.

The development of highly active antiretroviral therapy (HAART) has provided the promise of improved virologic and immunologic outcomes in treated children. HAART-treated children demonstrate improved numbers of CD4+ cells, including increased levels of both naïve and memory cells, however, it is unclear whether specific immune responses to vaccine antigens are also restored.

The purpose of this report was to evaluate the level of immunity to measles, tetanus, and Haemophilus influenzae type b (Hib) in previously immunized children who have HIV-1 infection and were treated with combination antiretroviral therapy and to determine the response to reimmunization.

**METHODS**

As part of routine care, children who have HIV-1 infection and are treated with HAART through the pediatric HIV clinic at Children’s Hospital and Regional Medical Center (CHRMC) periodically have antibody levels checked against standard childhood vaccine antigens and are reimmunized when indicated. Postimmunization antibody levels are drawn at least 4 weeks after the repeat immunization. Perinatally infected children who were treated with HAART that consists of at least 3 agents with a history of receiving their primary immunization series before the initiation of HAART were identified through a retrospective chart review. Those who had antibody levels performed against measles, tetanus, or Hib after starting HAART but before receiving additional immunizations and who also had been reimmunized while on HAART were included in this analysis. This review was approved by the CHRMC Institutional Review Board.

Measles, tetanus, and Hib immunoglobulin G (IgG) antibody levels were performed by standard methods in clinical laboratories. Measles IgG levels were determined by enzyme immunoassay at the Nichols Institute (San Juan Capistrano, CA). Tetanus toxoid IgG and Hib IgG antibody levels were performed by enzyme immunoassay at Specialty Laboratories (Santa Monica, CA). Children with undetectable antibody levels to measles, tetanus, or Hib were vaccinated with measles-mumps-rubella (MMR; M-M-R II, Merck), diphtheria-tetanus-acellular-pertussis (Tripeda/Pasteur Méreux Connaught <7 years), or Hib conjugate (HibTiter, Lederle Labs), respectively, according to standard immunization practices.
RESULTS

Nineteen children who met inclusion criteria for at least 1 antigen were identified. The median age was 7 years (range: 3–14), and the median time on HAART was 20 months (range: 8–37) at the time of reimmunization. Median quantitative HIV-1 levels before initiation of HAART and at the time of reimmunization were $4.5 \log_{10}$ (range: 3.3–6.3) and 1.7 $\log_{10}$ (range: 1.7–4.8), respectively. Fifteen (79%) of the 19 children had RNA levels <1.7 $\log_{10}$ (<50 copies/mL) at the time of reimmunization. Median CD4+ T-cell number and percentage were 514 cells/mm$^3$ (range: 7–2137) and 26% (range: 1–41) before initiation of HAART and 944 cells/mm$^3$ (range: 397–3900) and 35% (range: 20–54) at the time of reimmunization. Before the initiation of HAART, 11 children were classified as immune category 2, and 4 as immune category 1 according to immunologic criteria.10 No children had received immunoglobulin products within the previous 24 months.

Antibody Responses

Measles

Immunization response data are detailed in Table 1. The median number of measles vaccines before the initiation of HAART was 1 (range: 0–3; 1 child had not received an MMR before HAART). Only 1 (5%) of the 18 children with levels available at baseline had detectable IgG antibody levels to measles (detectable antibody levels defined as >1.10 immune status ratio [ISR]). Eighteen children were immunized with MMR vaccine (including the 1 child without baseline levels available). Fifteen (83%) of the 18 had detectable antibody levels at least 4 weeks after immunization with a median level of 2.37 ISR (range: 1.18–3.15). Eleven of the 15 children who responded to reimmunization with MMR had measles IgG antibody levels measured 1 year after reimmunization. Measles antibodies remained detectable in 8 (73%) of the 11, with levels not significantly different from what had been measured 4 weeks after immunization (in the 8 with detectable levels, median level 4 weeks after immunization was 2.6 ISR, and median level 1 year after immunization was 3.1 ISR).

Tetanus

The median number of tetanus vaccines before the initiation of HAART was 4 (range: 2–6). Six (35%) of the 17 children with levels available at baseline had detectable IgG antibodies to tetanus. For these children, the median level was 0.26 (range: 0.12–0.72) with detectable levels defined as >0.1 IU/mL. Fourteen children were reimmunized with diptheria-tetanus-acellular-pertussis (or tetanus-diphtheria) vaccine (11 with undetectable levels at baseline, 2 with low baseline levels, and 1 for whom baseline levels were unavailable). Ten (90%) of the 11 children with undetectable levels at baseline developed positive antibody levels (median titer 4 weeks after immunization: 0.9 IU/mL; range: 0.2–10.8), and the 2 with low levels at baseline had a 4-fold rise in titer. The child without levels available at baseline also had detectable levels after immunization. After 1 year, tetanus IgG levels remained measurable in 6 of 7 children tested, with levels somewhat lower than what had been measured 4 weeks after immunization (in the 6 with detectable levels, median level 4 weeks after immunization was 2.14 IU/mL, and median level 1 year after immunization was 0.51 IU/mL).

Hib

The median number of previous Hib vaccines was 2 (range: 1–4). Fourteen (78%) of 18 children had detectable IgG antibody levels to Hib. The median level was 265 nG/mL (range: 102 to >5000) with detectable antibody levels defined as ≥75 nG/mL. Only 4 children required reimmunization with Hib, and 3 of these responded to the vaccine with the development of detectable antibodies (median: 532 nG/mL; range: 134–578). Two of these children were retested and had persistent Hib IgG levels at 1 year after immunization.

DISCUSSION

The number of children with HIV-1 infection in this study with detectable antibody levels against measles and tetanus at baseline was less than described in most previous studies.4,7 This may reflect the older age and more advanced disease status of our population (79% with immune category 2 or 3 disease before HAART), 2 factors associated with loss of measurable immunity.2,6 The number of children who responded to reimmunization with MMR and tetanus toxoid was significantly greater than that reported in untreated children with HIV-1 infection (83% vs 14%–21% and 90% vs 40% for measles and tetanus, respectively,1,2,11) but not as high as the response rate in children without HIV-1 infection7,12. In addition, in contrast to the loss of protective antibody levels over time noted in previous studies of untreated children with HIV-1 infection,2 the majority of HAART-treated children in this report had sustained antibody response against measles for 1 year after immunization. Still, almost 30% of the children had a decline in antibody levels of both measles and tetanus to below detectable levels despite normal numbers of CD4+ T cells and treatment with suppressive HAART for up to 29 months, suggesting that normal immune responses were not completely restored.

It is not clear why the majority of children in this study maintained antibodies to Hib and not to measles and tetanus. Previous studies in children with HIV-1 infection before treatment with HAART have shown that although the majority develop Hib antibodies after immunization,13 the levels decline significantly over time such that in one study only 16% had protective antibodies 36 months after immunization.5 Although none of the children in our cohort had documented Hib disease, it is possible that subclinical infections or community exposure served to maintain immunity in these children. The response to repeat Hib vaccine in this study was high; however, few children required Hib revaccination.
# TABLE 1. Clinical Characteristics; Antibody Status to Measles, Tetanus, and Hib; and Response to Reimmunization in Children Who Have HIV-1 Infection and Are Treated With HAART

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age* (Years)</th>
<th>CDC Class</th>
<th>Pre-HAART</th>
<th>At Immunization</th>
<th>Time on HAART</th>
<th>Measles</th>
<th>Tetanus</th>
<th>HIB</th>
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<td></td>
<td></td>
<td>CD4 (%)</td>
<td>CD4 (%)</td>
<td>RNA log₁₀ Titer</td>
<td>Titer‡ Before</td>
<td>Titer After</td>
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<td>Titer After</td>
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<td>25</td>
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<tr>
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<td>1122 (41)</td>
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<td>3900 (44)</td>
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<td>1.7</td>
<td>35</td>
<td>37</td>
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NA indicates no titer available.

* Age at time of immunization.
† Antibody level preimmunization. Positive antibody level for measles >1.10 ISR; tetanus >0.10 IU/mL and Hib >75 nG/mL.
§ ø = undetectable. Antibody level considered to be undetectable for measles <0.90 ISR; tetanus <0.10 IU/mL, and Hib <75 nG/mL.
∥ This child had not been vaccinated with measles before initiating HAART.
¶ Parents reported that this child received his primary immunization series, but documentation of receipt of immunizations could not be obtained.
Few published studies have investigated the response to vaccines in HAART-treated children. The 1 investigation of response to repeat measles vaccine demonstrated an antibody response in 9 (64%) of 14 HAART-treated children when vaccinated after a mean of 10.7 months of HAART. This response is somewhat less than the response seen in the children in our study, most likely reflecting the small numbers included in both studies but possibly related to the lower HIV plasma RNA levels in our subjects (mean: 145 copies/mL vs 27,700 copies/mL) or a longer time on HAART in our children. There have been no published studies on the results of reimmunization with tetanus and Hib vaccines in HAART-treated children.

Progressive loss of specific antibody response has been seen after repeat immunization with a neo-antigen in adults who had HIV-1 infection and were not treated with HAART, suggesting a potential loss of memory cells with repeated antigen exposure. In contrast, many of the children studied developed robust antibody responses despite receiving multiple immunizations before the initiation of HAART. The child who failed to respond to a repeat tetanus vaccine had received 5 tetanus vaccines before initiation of HAART. She developed measurable tetanus IgG antibodies when vaccinated yet again after an additional 8 months of suppressive HAART (5.7 IU/mL 4 weeks after immunization). One child who failed to develop detectable measles levels after the first repeat vaccine was given another measles vaccine after an additional 15 months of suppressive HAART and also developed detectable antibodies. This suggests that additional improvement in immune function may occur with additional time on HAART.

As the majority of children in this study developed detectable antibody levels after immunization, it was not possible to assess the impact of baseline CD4 count, age, RNA load, or time on HAART on response to reimmunization. However, 2 of the 3 children who failed to respond to their MMR vaccine had been on HAART for only 9 months at the time of immunization. The results of this investigation suggest that many children with HIV-1 infection lack measurable antibodies to common vaccine antigens. Unlike previous studies in untreated children, these HAART-treated children developed detectable antibody levels to measles, tetanus, and Hib after repeat immunizations, which in the majority persisted for at least 1 year. Additional studies to determine the relationship between vaccine response and factors such as time on HAART, CD4 T-cell count, and plasma HIV-1 RNA levels after treatment with HAART are indicated. If these findings are confirmed in other studies with larger numbers of children, then consideration should be given to readministering childhood immunizations to HAART-treated children.

ACKNOWLEDGMENT

This study was supported in part by National Institutes of Health grant AI52910.

REFERENCES

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*Pediatrics* 2003;111:e641

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