Response to Measles, Mumps, and Rubella Revaccination in HIV-Infected Children with Immune Recovery after Highly Active Antiretroviral Therapy

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Background. The low prevalence of measles antibody in human immunodeficiency virus (HIV)-infected children after immune recovery as a result of highly active antiretroviral therapy increases the risk of morbidity and mortality from disease. The objective of our study was to evaluate the efficacy and safety of revaccination with measles, mumps, and rubella (MMR) vaccine in HIV-infected children with immune recovery.

Methods. Inclusion criteria were (1) HIV-infected children aged >5 years, (2) a nadir CD4 lymphocyte percentage ≤15%, (3) immune recovery (defined as a CD4 lymphocyte percentage >15% for ≥3 months after highly active antiretroviral therapy), and (4) no protective antibody against measles. Each child received 1 dose of MMR vaccine, and antibodies were measured at 4 and 24 weeks after vaccination. Protective antibodies were defined as an antimeasles immunoglobulin G (IgG) level ≥320 mIU/mL, an antimumps IgG titer ≥1:500, and an antirubella IgG level ≥10 IU/mL.

Results. There were 51 participants. The mean age (± standard deviation) was 10.2 ± 2.5 years. Prior to revaccination, 28 participants (55%) had baseline protective antibody to mumps, and 11 (20%) had baseline protective antibody to rubella. The prevalence of protective antibody at 4 weeks was 90%, 100%, and 78% for measles, rubella, and mumps, respectively, and then slightly decreased to 80%, 94%, and 61%, respectively, at 24 weeks after revaccination. No serious adverse reactions were attributed to revaccination.

Conclusions. The majority of HIV-infected children with immune recovery can develop protective antibodies after MMR revaccination. Revaccination with MMR vaccine in HIV-infected children with immune recovery should be considered to ensure individual immunity and limit the spread of disease.

The Joint United Nations Programme on HIV/AIDS estimated that there were 2.3 million children living with HIV infection or AIDS worldwide in 2006 [1]. Efforts have been made to provide access to HAART for HIV-infected children in developing countries. In Thailand, the National Access to Antiretroviral Program for People Living with HIV/AIDS was implemented by the Thai Ministry of Public Health in 2002. The program has changed the natural course of HIV infection from that of life-threatening infection to chronic disease. We previously demonstrated the efficacy of HAART on HIV suppression and immune recovery among HIV-infected Thai children [2]. Mortality and hospitalization rates have decreased significantly after the implementation of HAART [3]. HIV-infected children can now attend school, participate in social activities, and enter reproductive age like HIV-uninfected children. Common childhood diseases, such as measles, may be associated with more-severe complications in HIV-infected children than in healthy hosts; the absence of protective antibody in HIV-infected children is a significant concern.

In Thailand, the incidence of measles decreased after inclusion of measles vaccination in the national immunization program in 1977 [4]. With a vaccine coverage rate of 98%, the incidence of measles was 33.6 cases per 100,000 persons among persons aged 0–4
years and 7.9 cases per 100,000 persons among persons aged 15–24 years from 2002 through 2004 [5]. In general, measles vaccination produces protective antibody in 88%–95% of children [6, 7]. However, the efficacy of vaccine in HIV-infected children is lower than that in healthy children because of either primary or secondary vaccine failure. Our previous study involving HIV-infected Thai children after HAART revealed a prevalence of measles antibody of only 42% [8], which was similar to studies from The Netherlands and Kenya, in which only 38%–43% of children had antibodies against measles, mumps, and rubella (MMR) [9, 10]. The low prevalence of protective antimeasles antibody in this population not only increases individual risk of morbidity and mortality from the disease, but also compromises community disease-control efforts, especially because HIV-infected children with measles may have significantly prolonged shedding of the virus, compared with HIV-uninfected children [11]. Given these findings, whether measles revaccination will benefit HIV-infected children after successful antiretroviral treatment is an important research question.

Previous studies reported measles antibody response rates in HIV-infected children of 25%–75% [12–14]. Better response was noted among HIV-infected children treated with HAART [15]. Many questions concerning revaccination in HIV-infected children remain unanswered, including optimal timing, number of doses, efficacy of protective antibody induction, adverse events, and the potential risk of accelerated HIV replication.

The objectives of this study were to evaluate the antibody response to MMR revaccination in HIV-infected children with immune recovery after HAART and to assess adverse events of revaccination.

PATIENTS AND METHODS

Patient population. The study was performed at Chiang Mai University Hospital (Chiang Mai, Thailand). The inclusion criteria were (1) HIV-infected children aged ≥5 years, (2) a nadir CD4 lymphocyte percentage ≤15%, (3) immune recovery (defined as a CD4 lymphocyte percentage >15% for at least 3 months after receiving HAART), and (4) a nonprotective antibody level to measles (defined as an antimeasles IgG level <320 mIU/mL). The study protocol was approved by the research ethics committee of Chiang Mai University. Written informed consent was obtained from each child’s parent or guardian before enrollment.

Past illness and immunization data were collected from medical records and interviews with parents or caregivers. The clinical stage of disease for HIV-infected children was determined according to the 1994 US Centers for Disease Control and Prevention revised classification [16]. CD4 lymphocyte count and plasma HIV RNA level determination was performed before the initiation of HAART and at 24-week intervals after the initiation of HAART as a part of routine care.

Vaccine. All participants were revaccinated with a single subcutaneous dose of MMR vaccine (Priorix; GlaxoSmithKline Biologicals). Each 0.5 mL of reconstituted vaccine contains no less than 10^5 TCID_{50} of the Schwarz measles strain, no less than 10^3 TCID_{50} of RIT 4385 mumps, and no less than 10^3 TCID_{50} of the Wistar RA 27/3 rubella virus strains.

Determination of serostatus. Blood samples were collected for determination of antimeasles IgG antibody level, antirubella antibody level, and antimumps antibody titer at 4 and 24 weeks after MMR revaccination.

Laboratory measurements. Laboratory tests were performed at the National Institute of Health, Department of Medical Sciences, Ministry of Public Health (Bangkok, Thailand). ELISA using Enzygnost reagent (Dade Behring) was performed according to the manufacturer’s instructions. The optical density readings were interpreted as negative if the reading was <0.1, equivocal if the reading was 0.1–0.2, and positive if the reading was >0.2. Positive optical density readings were then converted to EIA units, as reported by Ratnam et al. [17]. Protective antibody levels were defined as an antibody level ≥320 mIU/mL for measles [6], an antibody titer >1:500 for mumps [18], and an antibody level ≥10 mIU/mL for rubella [19].

Statistical analysis. SPSS software, version 11.5 (SPSS), and Stata, version 6.0 for Windows (Stata), were used. Continuous variables were analyzed using Student’s t test, and categorical variables were analyzed using χ^2 test and Fisher’s exact test. Univariate logistic regression analysis was also performed to look for predictors of antibody response. Statistical significance was set at a 2-tailed P value <.05.

RESULTS

Demographic and clinical characteristics. In October 2005, 51 HIV-infected children were enrolled and revaccinated. The mean age (±SD) was 10.2 ± 2.5 years. Fifty-three percent were boys. Of the 51 participants, measles immunization status was documented by medical record for 39 children (76%). Thirty-two children (62%) received a single dose of measles or MMR vaccine before 2 years of age, and 7 (14%) received another dose at 4–6 years of age. There were 12 children (24%) for whom immunization data could not be obtained because of lack of records or change in caregiver or guardian. At the time of revaccination, 28 children (55%) had a protective level of antibody to rubella, and 11 children (20%) had a protective level of antibody to mumps. None had a history of clinical measles, mumps, or rubella infection. Two children were lost to follow-up and missed the study visit at 24 weeks after MMR revaccination.
Approximately one-half of the children (51%) were classified as having HIV infection that was Centers for Disease Control and Prevention clinical category C. Prior to initiation of HAART, the mean CD4 lymphocyte percentage (± SD) was 4.8% ± 4.5%, and the mean plasma HIV RNA level (± SD) was 5.4 ± 0.6 log_{10} copies/mL. The mean age (± SD) at which antiretroviral treatment was initiated was 7.8 ± 2.3 years. At the time of revaccination, subjects had been treated with HAART for a mean duration (± SD) of 127 ± 26 weeks. The mean current CD4 lymphocyte percentage (± SD) was 27.2% ± 5.7%. Forty-seven children (92%) had a plasma HIV RNA level <50 copies/mL. The most common HAART regimen used was a combination of 2 nucleoside reverse-transcriptase inhibitors and 1 nonnucleoside reverse-transcriptase inhibitor (23 children [45%] were treated with nevirapine, and 24 children [47%] were treated with efavirenz). The remaining 4 children (8%) were treated with 2 nucleoside reverse-transcriptase inhibitors and a protease inhibitor.

**Immunogenicity.** Antibodies to measles, rubella, and mumps were evaluated in 51 patients at week 4 and in 49 patients at week 24 after revaccination with a single dose of MMR vaccine. At week 4, the prevalence of protective antibody to measles, rubella, and mumps was 90%, 100%, and 78%, respectively. At week 24 after MMR revaccination, the prevalence of protective antibody to measles, rubella, and mumps was 80%, 94%, and 61%, respectively (tables 1–3). There was no difference in prevalence of protective antibody to measles, rubella, and mumps after revaccination between children with and without confirmed prior vaccination (tables 1–3). However, the mean antirubella IgG level and mean antimumps IgG titer were significantly higher in children with confirmed prior vaccination who had detectable baseline protective antibodies prior to revaccination than in the other 2 groups (tables 2 and 3). Univariate logistic regression analysis revealed no correlation between antibody response and age (P = .516), sex (P = .998), duration of HAART (P = .987), CD4 lymphocyte percentage (P = .842), and HIV RNA level (P = .760) at initiation of HAART or antibody response and CD4 lymphocyte percentage (P = .108) and HIV RNA level (P = .747) at the time of revaccination.

**Reactogenicity.** Pain at the injection site within 1–3 days after injection was reported in 23 patients (45%); it resolved spontaneously without treatment in all patients. The remaining 28 patients (55%) reported no adverse events after revaccination. None of the patients experienced significant swelling or erythema at the injection site. None of the patients developed fever or other systemic symptoms.

**Changes in CD4 lymphocyte and HIV-RNA levels after MMR revaccination.** The median time from revaccination to immunologic and virologic assessment was 13 weeks (range, 4–25 weeks). Assessment was performed for 25 (49%) of 51 patients within 2–12 weeks after revaccination. In all 51 participants, there was no difference in mean (± SD) CD4 lymphocyte percentage (27% ± 6% vs. 27% ± 6%; P = .60), CD4 lymphocyte count (674 ± 247 cells/mm³ vs. 712 ± 240 cells/mm³; P = .19), and HIV RNA level (1.8 ± 0.6 log_{10} copies/mL vs. 1.8 ± 0.3 log_{10} copies/mL; P = .43) before and after revaccination. Subset analysis of the 25 children in whom assessment was performed close to the time of revaccination also revealed no change in CD4 lymphocyte and HIV RNA levels before and after revaccination.

**DISCUSSION**

In this study, the majority of HIV-infected children with immune recovery after HAART developed protective antibodies after MMR revaccination. The prevalence of protective antibody at week 4 was 90%, 100%, and 78% for measles, rubella, and mumps, respectively. These rates slightly decreased to 80%, 94%, and 61%, respectively, at week 24 after revaccination. Our study population consisted of school-age children receiving antiretroviral treatment; this population was different from that of the study population.

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Table 1. Prevalence of immune response to the measles component of measles, mumps, and rubella (MMR) vaccine after revaccination.

<table>
<thead>
<tr>
<th>History of MMR vaccination</th>
<th>No. (%) of children with detectable protective antibody to measles*</th>
<th>Antimeasles IgG level, mean mIU/mL ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 4</td>
<td>Week 24</td>
</tr>
<tr>
<td>Confirmed</td>
<td>35/39 (90)</td>
<td>31/38 (82)</td>
</tr>
<tr>
<td>Not confirmed</td>
<td>11/12 (92)</td>
<td>8/11 (73)</td>
</tr>
<tr>
<td>All</td>
<td>46/51 (90)</td>
<td>39/49 (80)</td>
</tr>
<tr>
<td>P</td>
<td>1.00</td>
<td>.55</td>
</tr>
</tbody>
</table>

* Protective antibody to measles was defined as antimeasles IgG level ≥320 mIU/mL.
of the previous studies involving HIV-infected children, which were performed in the pre-HAART era [13], involved younger age groups [14], and consisted of patients living in developed countries [15].

Measles is the most contagious of the 3 agents and is associated with the highest mortality. A study of measles revaccination involving 14 HIV-infected US children receiving HAART demonstrated a 64% protective antibody response [15]. This study and our study were similar with regard to some characteristics, including mean age at revaccination (6.5 years vs. 10.2 years), CD4 lymphocyte percentage (≥15% for all patients; mean, 33% vs. 27%), and time of antibody measurement after revaccination (once at a mean of 2.3 months vs. twice at weeks 4 and 24). The potentially important differences were mean duration of HAART (10.7 months vs. 31.8 months) and percentage of children with an undetectable HIV RNA level (64% vs. 92%). The lower virus burden at the time of revaccination might explain the higher rate of antibody response in our study.

Antibody response to the rubella component of MMR vaccination is usually excellent; a 100% seroconversion rate among HIV-uninfected Thai infants was reported [7]. A study from Finland also reported that all healthy HIV-uninfected children who received MMR vaccine developed antibody to rubella [22]. Another study from Brazil revealed an 80% seroconversion rate among HIV-infected children after MMR vaccination at 15 months of age, and a 94% seroconversion rate was seen among HIV-uninfected control subjects [19]. The excellent response to rubella revaccination that was demonstrated in our study suggests that revaccination of HIV-infected female teenagers who are entering reproductive age decreases the risk of congenital rubella infection in their offspring.

The prevalence of protective antibody to mumps after MMR revaccination in our study (78% and 61% at 4 and 24 weeks after revaccination, respectively) was lower than that in healthy children in other studies, both as primary immunization or booster effect [7, 21, 22]. A study involving healthy Thai infants in Bangkok demonstrated a mumps seroconversion rate of 97.5% [7]. A study from Finland evaluated seroconversion rates 3 months after MMR vaccination among children from 2 different age groups. The seroconversion rates in the younger group (age, 14–18 months) and older group (age, 6 years) were 86% and 96%, respectively [22]. In England, among healthy children who received a booster dose of MMR vaccine at 3.5–6 years of age, 97.7% developed a protective antibody level to mumps [21]. However, the protective antibody level to mumps does not appear to persist over time. As revealed in our study, the prevalence of protective antibody of 78% at 4 weeks after revaccination decreased to 61% at 24 weeks after revaccination. A similar finding was observed in healthy children, in whom the protective antibody to mumps decreased from 96% to 57%–66% in the group of children who were 6 years of age and from 86% to 73% in the group of children who were 14–18 months of age when measured at 3 and 12 months after vaccination [22].

In our study, we did not find any difference in the response to MMR revaccination between children who had and did not have a confirmed history of prior MMR vaccination. We believe that the majority of the children who did not have confirmed history of prior vaccination may have received the vaccine, but the records may have been misplaced because of frequent change of caregivers. The coverage rate of MMR vaccination in Thailand is 98% [5]. The mean antibody level in the groups who had baseline rubella and/or mumps protective antibody

<table>
<thead>
<tr>
<th>History of MMR vaccination</th>
<th>No. (%) of children with detectable protective antibody to rubella</th>
<th>Antirubella IgG level, mean IU/mL ± SD</th>
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<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 4</td>
</tr>
<tr>
<td>Confirmed</td>
<td></td>
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<tr>
<td>All</td>
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<tr>
<td>Detectable baseline</td>
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<td>protective antibody to rubella</td>
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<tr>
<td>No detectable baseline</td>
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<td>protective antibody to rubella</td>
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<td>Not confirmed</td>
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<tr>
<td>All</td>
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<tr>
<td>Antirubella IgG level, mean IU/mL ± SD</td>
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<tr>
<td>a Protective antibody to rubella was defined as an antirubella IgG level ≥10 IU/mL.</td>
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<tr>
<td>b Comparison of values for confirmed history of MMR vaccination with values for no confirmed history of MMR vaccination.</td>
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<td>c Comparison of values for confirmed history of MMR vaccination and detectable baseline protective antibody to rubella with values for confirmed history of MMR vaccination and no detectable baseline protective antibody to rubella and with values for no confirmed history of MMR vaccination.</td>
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prior to revaccination was higher than that in the group who did not have baseline protective antibody. These increasing antibody levels could most likely be explained by the booster effect of revaccination.

No serious adverse reactions occurred as a result of MMR revaccination. Only 23 patients (45%) reported pain at the injection site. Pain was generally mild and spontaneously resolved within a few days without treatment. None of the patients experienced significant swelling or erythema, and none of the patients developed a fever or other systemic symptoms.

Another potential adverse event is the transient increase in plasma HIV RNA level after vaccination. This was reported before the availability of HAART in HIV-infected children after influenza vaccination [23]. We did not observe significant immunologic or virologic change after MMR revaccination in our study. This is consistent with observations reported in the study of pneumococcal and influenza vaccination in HIV-infected children who were receiving antiretroviral therapy [24].

In conclusion, our results have revealed that children with immune recovery after antiretroviral therapy respond well to MMR revaccination. Revaccination in this population should be considered to ensure individual immunity and limit the spread of preventable disease. Currently, there is no specific guideline for immunization in HIV-infected children after immune recovery. Our data may provide useful information for guideline development.

Acknowledgments

We thank Benjamin Lee for help with the manuscript writing.

Financial support. The Faculty of Medicine at Chiang Mai University and the Thailand Research Fund of the Royal Thai Government.

Potential conflicts of interest. All authors: no conflicts.

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