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Immune Reconstitution Syndrome After Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus-Infected Thai Children

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Abstract

Background— There is little information about the immune reconstitution syndrome (IRS) in children, especially from resource-poor countries.

Objective— To determine the incidence and spectrum of IRS in advanced stage human immunodeficiency virus (HIV)-infected children after initiation of highly active antiretroviral therapy (HAART).

Methods— Between May 2002 and April 2004, 153 symptomatic HIV-infected children who had CD4 lymphocyte percentage $\leq 15\%$ initiated HAART in a national antiretroviral drug access program. All patients were followed for 48 weeks. In this study, IRS was defined as a disease event caused by microorganisms or conditions previously reported to be associated with IRS in patients having immunologic and/or virologic response to HAART.

Results— The incidence of IRS was 19% (95% confidence interval, 13.1–26.1). The median time of onset was 4 weeks after start of HAART (range, 2–31). There were 32 episodes of IRS, including 14 caused by mycobacterial organisms, 7 by varicella-zoster virus, 7 by herpes simplex virus, 3 by *Cryptococcus neoformans* and 1 episode of Guillain-Barré syndrome. Patients who had IRS develop had lower baseline CD4 lymphocyte percentages compared with those who did not ($P = 0.02$).

Conclusions— IRS is common among HIV-infected children who received HAART in their advanced stage of disease. Educational programs for patients and health care workers on recognizing and treating these conditions should be integrated into antiretroviral treatment access programs.

Keywords

highly active antiretroviral therapy; human immunodeficiency virus; immune reconstitution syndrome; immune reconstitution inflammatory syndrome; children

Highly active antiretroviral therapy (HAART) improves the immune function and decreases mortality, morbidity and opportunistic infections of human immunodeficiency virus (HIV)-infected persons.¹ Yet, the introduction of HAART presents new clinical issues, including adverse drug effects and the occurrence of diseases that are a consequence of the restoration of the immune response. These diseases, called immune reconstitution syndrome (IRS), or immune reconstitution inflammatory syndrome or immune restoration diseases, usually occur within a few weeks to months after the start of HAART. The majority of patients present with

unusual manifestations of opportunistic infections, most often while the number of CD4 lymphocytes is increasing and the HIV viral load is decreasing.²⁻⁶ Although in most cases the symptoms of IRS resolve after a few weeks, the syndrome can be severe, and result in significant morbidity and occasional mortality. There have been few reports that studied the incidence of IRS in a cohort of patients started on HAART,⁷⁻⁹ especially in children¹⁰ and patients from resource-poor countries.^{11,12} In this report, we prospectively studied the incidence and spectrum of IRS after the initiation of HAART in advanced stage HIV-infected children in Thailand.

MATERIALS AND METHODS

Patients

The study was conducted at 3 hospitals in Northern Thailand, namely the Chiang Mai University hospital, Lamphun provincial hospital and Sanpatong district hospital. Between May 2002 and April 2004, we prospectively enrolled HIV-infected children to receive HAART in a national antiretroviral drug access program supported by the Thai government. Inclusion criteria were: (1) age 15 years or younger; (2) initial percentage of CD4 lymphocyte $\leq 15\%$; (3) no previous treatment with antiretroviral drugs; and (4) no active opportunistic infection. These children represented all patients commencing HAART at the 3 hospitals during the enrollment period. The Research Ethics Committee of Chiang Mai University approved the study. Written informed consent was obtained from each child's parent or guardian before enrollment.

Procedures

Patients attended study visits at weeks 0 (start of treatment), 2, 4, 8, 12, 18, 24, 32, 40 and 48. During each visit, we reviewed the patient's medical history and did a physical examination. All children and caregivers were counseled initially and at each visit to adhere closely to HAART, and to recognize signs and symptoms indicative of opportunistic infections or an IRS and to seek appropriate care. The symptoms include both systemic (eg, prolonged fever, dyspnea, abdominal pain, diarrhea, headache and weakness) and localized symptoms (eg, lymphadenitis, subcutaneous nodules and abnormal skin lesions). Blood tests for CD4 lymphocytes and plasma HIV RNA titers were performed at weeks 0, 8, 24 and 48 of HAART. In some cases, these tests were also performed at the time suspected IRS occurred. Choices of laboratory investigations were directed by clinical symptoms and were performed as soon as IRS was suspected.

Outcomes of HAART were divided into 4 categories based on responses in the number of CD4 lymphocytes and plasma HIV RNA titers during the first 24 weeks of treatment. Immunologic success was defined as an increase from baseline in CD4 lymphocyte percentage $\geq 5\%$, whereas failure to achieve that concentration was defined as immunologic failure. Viral success was defined as a decrease in plasma HIV RNA titer $> 2 \log_{10}$ or as achieving titer < 50 copies/mL. Viral failure was defined as the failure to achieve this level of suppression. For the purpose of this report, a disease event was defined as IRS if it occurred in a patient with immunologic success and/or viral success, and was caused by microorganisms or conditions previously reported to be associated with IRS.²⁻⁶

Immunologic and Microbiologic Methods

CD4 lymphocyte count was assessed with the FACSCalibur Flow Cytometer (Becton-Dickinson, Mountain View, CA) using 3-color reagents and dual platform format. The Roche Ultrasensitive Amplicor assay version 1.5 (Roche Molecular Systems, Branchburg, NJ) measured plasma HIV RNA titer (viral load). The diagnosis of mycobacterial infection was based on microscopic examination and/or culture of clinical specimens. For blood and

specimens from normally sterile sites, the BACTEC 9000MB (Becton Dickinson, MD) was used to perform cultures using a fluorescence detection system. Positive BACTEC cultures were subcultured on solid media for colony isolation. Conventional methods with Lowenstein-Jensen media were used to perform cultures from other clinical specimens. The polymerase chain reaction (PCR) and restriction enzyme analysis technique were used to perform species identification of *Mycobacterium* spp., as previously described.¹³ *Mycobacterium bovis* Calmette-Guérin bacillus (BCG) strain was identified using a multiplex PCR method to detect the RD1 deletion.¹⁴

Diagnosis of mucocutaneous varicella-zoster virus infection and herpes simplex virus (HSV) infection was based on clinical signs and symptoms. In cases with central nervous system manifestations, blood and cerebrospinal fluid (CSF) were examined for varicella-zoster virus, HSV, and cytomegalovirus using nested PCR assays. Diagnosis of cryptococcal infection was made by positive CSF culture or detection of cryptococcal capsular polysaccharide antigen in the serum and/or CSF.

Statistical Analysis

An independent sample *t* test was used to compare baseline CD4 lymphocyte counts and plasma HIV RNA titers, as well as response to HAART of HIV-infected children with and without IRS. Data were analyzed with the Stata 6.0 software (Stata Corp., College Station, TX). A 2-sided *P* value <0.05 was significant.

RESULTS

Between May 2002 and April 2004, 153 HIV-infected children were enrolled to receive HAART from the national drug access program. The HAART regimens used were the combination of stavudine, lamivudine and nevirapine in 81 patients, and the combination of stavudine, lamivudine and efavirenz in 72 patients. The mean age, gender, mean baseline CD4 lymphocyte percentages and mean baseline HIV RNA titers of these 153 children are shown in Table 1. All patients were followed for 48 weeks after initiation of HAART.

Of the 153 children, 29 (19.0%; 95% confidence interval, 13.1–26.1%) had 32 episodes of IRS (Table 2). The median time of onset was 4 weeks after initiation of HAART (range, 2–31). There were 14 episodes of IRS caused by mycobacterial organisms, 7 episodes by varicella-zoster virus, 7 episodes by HSV, 3 episodes by *Cryptococcus neoformans* and 1 episode of Guillain-Barré syndrome. There was no interruption of HAART in any of the patients, except for patient No. 9, whose treatment was discontinued for 8 weeks during IRS. There were 2 patients (Nos. 9 and 10) who received short course corticosteroids during IRS. Three patients (Nos. 4, 6 and 25) died of IRS or its complication.

Of the 14 episodes of mycobacterial infection, 11 were confirmed by culture. In the other 3 episodes, 2 cases of *Mycobacterium tuberculosis* infection were diagnosed by chest roentgenograms and positive tuberculin skin tests, and 1 case of infection by *M. bovis* BCG strain was diagnosed by typical clinical presentations. Of these 14 episodes, 6 patients presented with subcutaneous abscesses and/or lymphadenitis. There were 5 patients who presented with fever, dyspnea and pulmonary infiltrates on chest roentgenograms. Three patients presented with fever and abdominal pain. The median time from initiation of HAART to the onset of clinical symptoms was 3.5 weeks (range, 2–31). In 11 patients, the mycobacterial infections had not been diagnosed previously. In the remaining 3 patients, the IRS represented a paradoxical worsening of the mycobacterial infections, which were being treated successfully at HAART initiation. Two patients died. One died of acute respiratory distress syndrome attributed to *Mycobacterium avium* complex infection. The other died of *Pseudomonas*

aeruginosa septicemia complicating a prolonged hospitalization for *Mycobacterium scrofulaceum* infection.

All 7 patients with IRS associated with varicella-zoster virus infection had typical dermatomal distribution of vesicular lesions and responded well to treatment with oral acyclovir. The median time from the initiation of HAART to the onset of clinical symptoms was 6 weeks (range, 2–21). Of the 7 patients with HSV infection, 6 presented with herpes simplex labialis. The median time from the initiation of HAART to the onset of herpes simplex labialis was 4 weeks (range, 2–31). The remaining patient presented with altered mental status 18 weeks after commencing HAART. Nested PCR assays of her CSF were positive for HSV, and negative for varicella-zoster virus and cytomegalovirus. Electroencephalogram and magnetic resonance imaging of the brain showed findings strongly suggestive of herpes simplex encephalitis. The patient had had cytomegalovirus retinitis and had been treated with intravenous ganciclovir before HAART initiation. Her cytomegalovirus retinitis remained inactive. Despite treatment with intravenous acyclovir, she died during the fourth week of the encephalitic illness.

All 3 patients with cryptococcal IRS had been treated for cryptococcal meningitis before commencing HAART. They presented with low grade fever and headache at 2, 2 and 7 weeks after starting HAART. One patient (patient 28) admitted that she had not been taking the drug, fluconazole, prescribed for secondary prophylaxis. Microscopic examination of her CSF showed 147 leukocytes/mL³ and the culture grew *C. neoformans*. The remaining 2 patients had been taking fluconazole regularly. Their infection was diagnosed by the presence of cryptococcal antigen in the blood samples. No lumbar puncture was performed. All 3 patients responded favorably to treatment with amphotericin B.

The patient with Guillain-Barré syndrome was diagnosed on the basis of microscopic and biochemical findings of the CSF, as well as magnetic resonance imaging of the spinal cord and the electrodiagnostic study. She presented with subacute onset of progressive leg weakness that occurred 3 weeks after initiation of efavirenz-based HAART. The bacterial, mycobacterial and fungal cultures of the CSF showed no growth. Nested PCR assays of her CSF were negative for varicella-zoster virus, HSV and cytomegalovirus. She gradually improved and had a total recovery in 4 weeks.

Three disease events occurred in the 124 children who did not have IRS (“no” IRS group). One 10-year-old girl presented with fever, cough and severe dyspnea 6 weeks after starting HAART, and died shortly after her admission to the hospital. Her blood culture grew *Staphylococcus aureus* and sputum culture grew *Mycobacterium kansasii*. The second patient presented with similar symptoms 4 weeks after HAART. The parents refused admission, and she died at home 2 weeks later. These 2 patients did not have CD4 lymphocyte count and HIV RNA levels other than those at baseline and, thus, did not satisfy our case definition of IRS. The third patient had an opportunistic infection caused by *Salmonella enteritidis* septicemia 7 weeks after commencing HAART. She responded promptly to a course of parenteral antibiotic.

Table 1 shows mean CD4 lymphocyte percentages and mean plasma HIV RNA levels for the 29 children who had IRS and the 124 children in the “no” IRS group. Average CD4 lymphocyte percentage at initiation of HAART was lower in children who had IRS when compared with those who did not (3.1% versus 5.5%, respectively, $P = 0.02$). Upward changes in CD4 lymphocyte percentage were similar in both groups at 8, 24 and 48 weeks after the initiation of HAART. There was no difference in plasma HIV RNA values between the 2 groups at baseline and 8, 24 and 48 weeks after initiation of HAART.

DISCUSSION

This study showed a high incidence of IRS after initiating HAART in advanced stage HIV-infected children. The spectrum of IRS is similar to previous reports. They involve either exacerbation, often with unusual manifestations, of a previously treated opportunistic infections or unmasking of a previously subclinical infection.^{2–6} Less commonly, IRS can manifest as an occurrence of noninfectious disease, such as Guillain-Barré syndrome.¹⁵ There is no generally accepted case definition for IRS. The definition of IRS used in our report covers HIV-infected patients whose antiretroviral treatment has led to an increase in CD4 lymphocyte count and decrease in plasma HIV RNA titer, and who have a disease event caused by microorganisms or conditions that have previously been associated with IRS in major review articles on the subject.^{2–6} This case definition together with clinical manifestations that are different from manifestations of opportunistic infections in patients not taking HAART, such as localized mycobacterial infections, mild cases of herpes zoster or cases of cryptococcal meningitis with prominent inflammatory response in the CSF, is highly specific for IRS.

Of the 32 episodes of IRS, 14 (43.7%) were caused by *Mycobacterium* spp. All patients presented with localized infection in the lymph nodes, subcutaneous or submucosal tissues or lungs. Two patients who had been vaccinated with *M. bovis* BCG strain several years before commencing HAART presented with localized infection by that organism. *Mycobacterium* spp. are often implicated in IRS, and together they represent about 40% of all reported cases.⁴ The patients usually present with fever, lymphadenitis, subcutaneous abscesses, pulmonary infiltrates or inflammatory masses, usually during the first 3 months of HAART.^{16–19} A case of lymphadenitis caused by *M. bovis* BCG strain had also been reported.²⁰

There were 7 episodes (21.9%) caused by varicella-zoster virus. In all cases, manifestations were mild and uncomplicated. Studies have shown that the incidence of herpes zoster markedly increase in HIV-infected patients treated with HAART versus those not taking HAART.^{10, 21–23} Herpes zoster represents about 22% of all reported cases of IRS.⁴ The majority of cases present during the first 4 months of HAART.

Of the 32 episodes of IRS, 6 (18.7%) were manifestations of herpes simplex labialis. One other patient died of encephalitis caused by HSV. Data from 1 observational study suggested that adult patients responding to HAART had a high incidence of mucocutaneous HSV disease.⁸ The study also showed 1 death from encephalitis caused by HSV after HAART.

Three episodes of IRS in our study were manifestation of cryptococcal meningitis. Cryptococcal IRS is characterized by a more prominent inflammatory response in the CSF than in patients not receiving HAART.²⁴ In our patient, the leukocyte count in the CSF was 147 cells/mL³. We had reported cases of cryptococcal meningitis in 21 children who were not taking HAART from Chiang Mai University Hospital.²⁵ Mean leukocyte count in the CSF was 17.6 cells/mL³ (range, 0–130).

In our study, 29 (19%) of the 153 children had 32 episodes of IRS within the first year of HAART. Three children died of IRS or its complications. Two more deaths occurred in children without IRS. The baseline CD4 lymphocyte percentage was lower in children who had IRS when compared with those who did not. There have been few reports that studied the incidence of IRS in a cohort of patients started on HAART. French et al⁸ did a retrospective study on all adult patients commencing HAART at one hospital in Australia. Of 141 patients, ≥ 1 episodes of IRS developed in 33 (23.4%) during the 30 weeks after commencement of HAART. The most common manifestations were dermatomal zoster, mucocutaneous herpes, cytomegalovirus retinitis and *M. avium* complex lymphadenopathy. Logistic regression analysis showed that low baseline CD4 lymphocyte count was a significant risk factor for IRS. In the only published study in children, IRS developed in 7 (11.5%) of the 61 children started

on HAART, all of which were dermatomal zoster.¹⁰ Average CD4 lymphocyte percentage at initiation of HAART in this study was 21.9% compared with 5.0% in our study. This result could explain the difference in the spectrum of IRS between the 2 studies.

Three studies of the incidence of IRS were reported in specific subsets of patients commencing HAART. In a Thai prospective multicenter study of 60 advanced AIDS patients who had had successful treatment of acute cryptococcal meningitis and were on secondary prophylaxis, 20 episodes of IRS developed in 14 patients (23.3%). The most common causes of IRS were tuberculosis, *M. avium* complex, relapsed cryptococcal meningitis and herpes zoster.¹¹ In a retrospective study from India, IRS caused by *M. tuberculosis* developed in 11 (7.6%) of the 144 HIV and tuberculosis-coinfected patients.¹² Finally Shelburne et al⁹ conducted a retrospective study of patients who received HAART and were coinfecting with *M. tuberculosis*, *M. avium* complex or *C. neoformans*. Of the 180 patients, IRS developed in 57 (31.7%), all from the coinfecting microorganisms.⁹

Thus, between 7.6% and 32% of patients commencing HAART had IRS develop. The difference in incidence among various studies can be explained by the difference in the case definition of IRS used and the risk factors in the population being studied. In addition, the incidence and spectrum of IRS were likely to be different in pediatric cohorts compared with adult cohorts and in patients from developing countries compared with developed countries. For example, the spectrum of opportunistic infections in Thailand had been shown to be unique.²⁶

During the past few years, progress had been made in providing HAART to patients in developing countries.²⁷ These patients often had multiple opportunistic and concomitant infections,²⁸ and started HAART at a low baseline CD4 lymphocyte count.²⁹ Thus, there were many patients at risk for IRS developing. In 1 report on 743 adult patients starting HAART and followed for 2–7 months, 61 patients (8.2%) died.²⁹ In another report from South Africa, 16 (13%) of 122 children died within the first 6 months of HAART.³⁰ The major causes of death in these patients were likely to be opportunistic infections occurring in patients with residual defects of cell-mediated immunity, IRS and adverse drug events. Educational programs for health care workers and patients concentrating on recognizing and treating these conditions should reduce the rate of early deaths after HAART in these resource-poor countries.

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TABLE 1

Characteristics of HIV-Infected Children

Variable	Total	IRS	No IRS	P
Age (yr)	7.9 ± 2.8 [*]	8.2 ± 3.1	7.8 ± 2.7	0.50
Gender male	77 (50) [†]	12 (41)	65 (52)	0.28
Baseline				
% of CD4 lymphocytes	5.0 ± 4.7 [n = 153]	3.1 ± 3.9 [n = 29]	5.5 ± 4.8 [n = 124]	0.02
HIV RNA (log ₁₀ copies/mL)	5.37 ± 0.4 [n = 128]	5.37 ± 0.4 [n = 25]	5.37 ± 0.4 [n = 103]	0.96
At week 8				
% of CD4 lymphocytes	9.8 ± 6.7 [n = 139]	8.2 ± 5.9 [n = 26]	10.2 ± 6.8 [n = 113]	0.16
HIV RNA (log ₁₀ copies/mL)	2.38 ± 0.7 [n = 130]	2.43 ± 0.7 [n = 25]	2.37 ± 0.7 [n = 105]	0.68
At week 24				
% of CD4 lymphocytes	12.6 ± 6.0 [n = 146]	11.2 ± 6.1 [n = 27]	13.0 ± 5.9 [n = 119]	0.17
HIV RNA (log ₁₀)	2.07 ± 0.8 [n = 124]	1.99 ± 0.6 [n = 24]	2.09 ± 0.8 [n = 100]	0.61
At week 48				
% of CD4 lymphocytes	16.2 ± 6.4 [n = 135]	14.0 ± 5.9 [n = 24]	16.6 ± 6.5 [n = 111]	0.07
HIV RNA (log ₁₀)	2.10 ± 0.9 [n = 122]	2.28 ± 1.0 [n = 21]	2.06 ± 0.9 [n = 101]	0.30

* Means ± SD.

[†] Number in parentheses, percent.

TABLE 2
Immune Reconstitution Syndrome in Children After HAART

No.	Age and Gender	Immune Reconstitution Syndrome	Time to Onset (wk)	CD4 %		HIV Load (log ₁₀)		Time of CD4 and HIV RNA Testings (wk)
				Baseline	Nearest to IRS	Baseline	Nearest to IRS	
1	6, F	MAC supraclavicular lymphadenitis	2	4 (97)*	5 (59)	5.56	1.70	8
2	7, M	MAC mesenteric lymphadenitis	2	1 (21)	4 (200)	5.47	2.60	12
3	7, M	MAC subcutaneous abscesses	5	1 (31)	9 (100)	ND	4.78	7
4	9, F	MAC pulmonary infection [†] VZV dermatomal zoster	26 12	6 (44)	19 (214)	5.57	1.70	24
5	10, M	HSV labialis <i>Mycobacterium scrofulaceum</i> mesenteric lymphadenitis	4 2	0 (5)	2 (31)	5.02	1.70	24
6	11, M	<i>Mycobacterium scrofulaceum</i> duodenal submucosal nodules [†]	2	0 (3)	7 (15)	4.86	ND	2
7	9, F	<i>Mycobacterium scrofulaceum</i> subcutaneous abscesses	3	2 (33)	8 (188)	5.40	2.22	8
8	8, M	<i>Mycobacterium kansasii</i> subcutaneous abscesses	3	0 (0)	5 (126)	5.50	2.60	8
9	7, M	<i>Mycobacterium simiae</i> pulmonary infection	18	0 (4)	17 (236)	ND	ND	24
10	5, F	<i>Mycobacterium tuberculosis</i> pulmonary infection	12	2 (42)	6 (171)	5.88	1.70	12
11	12, M	<i>Mycobacterium tuberculosis</i> pulmonary infection	16	4 (39)	14 (135)	ND	1.70	20
12	3, M	<i>Mycobacterium tuberculosis</i> pulmonary infection	31	3 (49)	11 (506)	5.88	2.09	24
13	8, F	<i>Mycobacterium bovis</i> BCG strain lymphadenitis	3	3 (30)	6 (121)	4.38	1.87	8
14	8, F	<i>Mycobacterium bovis</i> BCG strain subcutaneous abscess	4	0 (2)	2 (32)	5.88	2.21	8
15	6, M	VZV dermatomal zoster	2	1 (18)	3 (126)	5.22	2.58	8
16	6, F	VZV dermatomal zoster	2	3 (171)	10 (599)	5.33	2.45	8
17	14, F	VZV dermatomal zoster	4	2 (21)	5 (92)	4.82	1.70	8
18	6, F	VZV dermatomal zoster	6	3 (38)	8 (313)	5.65	2.36	8
19	10, F	VZV dermatomal zoster	15	0 (70)	8 (250)	ND	ND	24
20	6, F	VZV dermatomal zoster	21	2 (34)	6 (264)	4.82	2.39	8
21	5, F	HSV labialis	2					
22	10, F	HSV labialis	2	6 (61)	17 (377)	5.24	2.83	8
23	11, M	HSV labialis	4	15 (430)	14 (322)	5.43	1.88	8
24	7, F	HSV labialis	18	0 (0)	7 (240)	5.88	2.63	24
25	11, F	HSV labialis	31	2 (21)	15 (432)	5.88	2.20	24
26	8, M	HSV encephalitis [†]	18	2 (12)	3 (15)	5.09	1.70	8
27	15, F	Cryptococcal meningitis	2	12 (137)	19 (289)	5.17	2.19	8
28	10, F	Cryptococcal meningitis	2	5 (37)	11 (196)	5.76	2.56	8
29	2, F	Cryptococcal meningitis	7	1 (5)	10 (80)	4.80	1.70	8
30	2, F	Guillain-Barré syndrome	3	12 (448)	26 (1443)	5.88	3.48	8

MAC indicates *Mycobacterium*-avium complex; VZV, varicella-zoster virus; ND, not done.

* Numbers in parentheses, cells per μL .

[†]The patient died during the IRS episode.