

Varicella zoster as a manifestation of immune restoration disease in HIV-infected children

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Background: Exacerbation of opportunistic infections in HIV-infected patients shortly after initiation of highly active antiretroviral therapy (HAART) has been named *immune restoration disease* (IRD). Thus far, IRD has not been reported in children.

Objective: We describe the clinical and immune characteristics of IRD in HIV-infected children treated with HAART.

Methods: A historical cohort study was conducted in a tertiary HIV center in perinatally HIV-infected children who were started on a first stable HAART between January 1996 and July 2002. The incidence of opportunistic infections, newly AIDS-defining events or death after initiation of HAART, and virologic and immunologic information was evaluated at baseline and every 3 months post-HAART.

Results: Sixty-one perinatally HIV-infected children were started and maintained on HAART for >6 months. Seven episodes of IRD occurred. All were cutaneous herpes zoster (HZ). Children who developed HZ had significantly lower baseline CD4⁺ and CD8⁺ T-cell numbers compared with children who did not. HZ occurred only in children (7 of 34 subjects) with virological and immunological success to HAART. In children with a previous history of varicella infection, the risk of developing HZ after HAART was higher in those without a protective level of varicella-specific IgG (50%, or 5 of 10 subjects) compared with those with seroprotection (10%, or 2 of 20).

Conclusion: Herpes zoster is a common manifestation of IRD in HIV-infected children after the initiation of HAART. Risks for developing HZ include no protective varicella-specific antibody despite previous varicella infection, severe immunodeficiency at baseline, and vigorous immunologic and virologic responses to HAART. (*J Allergy Clin Immunol* 2004;113:742-6.)

Key words: Immune restoration disease, HIV-1, highly active antiretroviral therapy, opportunistic infections, Herpes zoster

The advent of highly active antiretroviral therapy (HAART), which allows recovery of CD4⁺ T lymphocytes in treating adults and children, has dramatically changed the landscape of HIV infection and revolution-

Abbreviations used

CDC: Centers for Disease Control and Prevention

HAART: Highly active antiretroviral therapy

HZ: Herpes zoster

IF: Immunologic failure

IRD: Immune restoration disease

IS: Immunologic success

MAC: *Mycobacterium avium* complex

NK: Natural killer

OI: Opportunistic infection

VF: Viral failure

VS: Viral success

ized the care of patients with this disease.¹⁻³ HAART decreases mortality, morbidity,⁴ and opportunistic infections (OIs)^{1,3} and leads to immune reconstitution in HIV-infected persons.⁵⁻⁸ After initiation of HAART, some patients develop inflammatory reactions or exacerbation of OIs.⁹⁻¹¹ These responses are termed *immune restoration disease* (IRD) and usually occur within a few weeks to months after starting HAART, most often while the CD4⁺ T-cell numbers and functions are improving and the HIV viral load is decreasing.¹² Manifestations of IRD include worsening or reactivation of OIs, ie, *Mycobacterium avium* complex (MAC), *Mycobacterium tuberculosis*, cytomegalovirus, cryptococcus, hepatitis B or C, or herpes zoster (HZ).

To date, IRD has been described only in HIV-infected adults. The immunopathogenesis of HIV in adults and children differs,² and whether IRD can occur in HIV-infected children is not yet known. In this report, we describe reactivation of HZ as a manifestation of IRD in HIV-infected children.

METHODS

Patients

A historical cohort study was conducted at All Children's Hospital/University of South Florida, including all vertically HIV-infected children who received the first stable HAART regimen from January 1996 through July 2002. HAART was defined as the use of 3 or more antiretroviral medications containing a nonnucleoside reverse transcriptase inhibitor, a protease inhibitor, or a potent nucleoside reverse transcriptase inhibitor (abacavir). A stable HAART regimen was defined as a single regimen taken continuously for at least 6 months, without a regimen change or treatment interruption of more than 2 months in the first 6 months of treatment. The incidence of new AIDS-defining events or death was based on the revised Centers for Disease Control and Prevention (CDC) 1994

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classification for HIV-infected children.¹³ Standard prophylaxis care was delivered based on guidelines for the treatment of HIV-infected children.¹³ Patients were followed at a minimum of 3-month intervals. Viral load, CD4⁺ counts, complete blood count, metabolic panels, and liver function tests were performed at least every 3 months, or more often if indicated. Chest x-ray, purified protein derivative test, and serology for cytomegalovirus, Epstein-Barr virus, and toxoplasmosis were performed yearly. Children at high risk for cytomegalovirus or toxoplasmosis had periodic ophthalmologic examinations and brain computed tomography scans. If MAC infection was suspected, a blood culture for acid-fast bacilli was performed. Prophylaxis for *Pneumocystis carinii* pneumonia, MAC, and toxoplasmosis was conducted according to OI prevention guidelines.¹³ Varicella-specific IgG antibody was performed by enzyme immunoassay (Diamedix, Miami, FL) as part of yearly screening. Subjects were considered to have seroprotection if varicella-specific IgG levels were >20 U/mL.

Highly active antiretroviral therapy outcomes were divided into 4 categories based on virologic and immunologic response to treatment. Immunologic success (IS) was defined as an increase from baseline in CD4⁺ cells >5% or a total CD4⁺ cell count >250 cells/mL within 6 months of starting HAART, whereas failure to achieve success was defined as immunologic failure (IF). Viral success (VS) was defined as a decrease in plasma of >2 log RNA or as achieving a plasma HIV RNA level <400 copies/mL based on the Roche Amplicor assay (Roche Diagnostic Corporation, Indianapolis, Ind). Viral failure (VF) was defined as the failure to achieve this level of suppression. Total CD4⁺ T cells, naive (CD4⁺45RA⁺62L⁺) T cells, memory (CD4⁺45RO⁺) T cells, CD8⁺ T cells, natural killer (NK; CD16⁺ and CD56⁺) cells, and HIV RNA were enumerated at baseline and every 3 months after initiation of HAART.

Statistical analysis

SPSS for windows (Version 10; SPSS, Chicago, Ill) was used for data management and statistical analysis. Independent-samples *t* test and Mann-Whitney *U* test were used to compare HIV-infected children with and without IRD for normal distribution and non-parametric data, respectively. The χ^2 test was used for analysis of categorical variables. Two-sided tests were used, and *P* values < .05 were considered statistically significant.

RESULTS

A total of 61 perinatally HIV-infected children who started a stable HAART regimen were included in this study. Mean age was 6.9 years $\pm$ 4.7 SD; 15 (25%) of children were boys. Thirty-four (56%) were white, 23 (38%) black, and 4 (7%) Hispanic. Mean CD4⁺ percentage at baseline was 21.9% $\pm$ 13.6%. Mean absolute CD4⁺ counts were 702 $\pm$ 675.5 SD; mean viral load was 3.44 $\pm$ 1.0 SD log RNA.

OIs occurring after HAART

Seven of the 61 children developed OIs after HAART; all were cutaneous HZ. No new OIs occurred, and there was no worsening of or reactivation of hepatitis B or C virus, MAC, *Mycobacterium tuberculosis*, cytomegalovirus, or *Cryptococcus* or *Histoplasma* species. One child died 8 months after treatment initiation from hepatic failure of unknown etiology. This particular patient had both VF and IF to HAART.

Herpes zoster in studied subjects

Herpes zoster was clinically diagnosed based on clinical parameters or characteristic rash with dermatomal distribution, and by response to antiviral therapy. Demographic characteristics, HAART regimen, and immunologic and virologic data before starting HAART and during HZ infection are shown in Table I. In all cases, onset of HZ occurred within 6 months after initiation of HAART, with the average time of onset at 95 days (range, 36-169 days). There was a significant increase in CD4⁺ T-cell numbers and percentages concurrent with HZ episodes, as well as reduction of viral load. At the time of HZ infection, 6 of the 7 children affected had a viral load <400 copies/mL. All 7 children had a history of previous varicella infection; only 1 had a history of HZ before starting HAART. Clinical manifestations of HZ were mild; 3 cases that initially failed to respond to oral acyclovir subsequently improved with intravenous acyclovir. In all other cases, intravenous acyclovir was given as initial therapy with rapid response. No other HZ complications occurred, such as ocular, neurological, or hepatic manifestations. Persistence of chronic atypical skin lesions was not observed.

Varicella history and serology in studied subjects

Both varicella history and varicella-specific IgG antibody of the study subjects are shown in Table II. History or previous serology regarding varicella was unavailable for 9 children. In children with a previous history of HZ infection, the proportion of children with serologic protection was lower in children who developed HZ compared with children who did not develop varicella (29% vs 78%, respectively; *P* < .05). The risk of developing HZ in the first 6 months after HAART in children with a previous history of varicella infection was 50% (5 of 10 subjects) in children without seroprotection compared with 10% in children with seroprotection (2 of 20 subjects).

HAART outcome and risk for HZ

We compared the viral and immune response to HAART and the risk for development of HZ. As shown in Table III, HZ occurred exclusively in the IS/VS group and developed at a significantly higher rate than in patients who were either VFs or IFs to HAART (7 of 34 subjects vs 0 of 27 subjects, respectively; *P* = .014). The incidence of HZ was 41 per 100 patient-years in the first 6 months of therapy in the IS/VS group.

Immunologic and virologic results after HAART were compared between children who developed HZ and children without HZ (Table IV). Children who developed HZ had significantly lower baseline CD4⁺ and naive T-cell percentages and CD4⁺, CD8⁺, and naive T-cell numbers (*P* = .008, .037, .008, .034, .012, respectively). There was no significant difference in age, sex, CDC category, memory T cells, NK cells, CD8⁺ T-cell percentage, type of

TABLE I. Characteristics of HIV-infected children who developed HZ after HAART

Patient	Age, y	CDC	Medications	Baseline		During zoster		Days on therapy	Duration from previous events, y	
				CD4 (cells/mm ³)	RNA (log copies/mL)	CD4 (cells/mm ³)	RNA (log copies/mL)		Varicella	Zoster
1	7.2	B3	AZT, 3TC, EFV	12% (408)	5.21	20% (474)	<2.60	46	1.5	None
2	8.5	A1	d4T, RTV, NVP	39% (829)	3.97	38% (1256)	<1.70	92	2.2	None
3	15.4	C3	AZT, 3TC, EFV, NFV	7% (18)	3.67	15% (136)	<2.60	72	3.5	None
4	1.2	C3	AZT, ddI, RTV	1% (8)	5.88	23% (404)	<2.60	128	0.8	None
5	16.7	C3	T-20, LPV/r, ddI, 3TC, EFV	4% (53)	3.81	36% (301)	<2.60	123	10.0	6.8
6	9.1	B3	AZT, ddI, NVP	1% (5)	4.66	18% (56)	3.34	36	7.2	None
7	10.2	A3	AZT, 3TC, NFV	2% (13)	5.39	4% (53)	<2.60	169	0.3	None
Mean $\pm$ SD				9.4% $\pm$ 13.6% (191 $\pm$ 316.9)	4.66 $\pm$ 0.9	22.0% $\pm$ 11.9%* (383 $\pm$ 419.2)*	<2.60*	95.1 $\pm$ 47.9	3.6 $\pm$ 3.6	NA

AZT, Zidovudine; 3TC, lamivudine; EFV, efavirenz; d4T, stavudine; RTV, ritonavir; NVP, nevirapine; NFV, nelfinavir; ddI, drug-drug interaction; T-20, enfuvirtide; LPV/r, lopinavir.

*P value < .05 comparing value at baseline and during zoster episodes as analyzed by paired *t* test.

TABLE II. History and serology data of varicella in HIV-infected children who received HAART

	History of varicella		NA*
	Yes	No	
Developed HZ			
Total	7	0	0
Seroprotective	2 (29%) [‡]	0	0
Seronegative	5 (71%)	0	0
Categorized by HAART responses			
IS/VS	7	0	0
Seroprotective	2 (29%)	0	0
Did not develop HZ			
Total	23	22	9
Seroprotective	18 (78%) [‡]	2 (9%) [†]	
Seronegative	5 (22%)	20 (91%)	
Categorized by HAART responses			
IS/VS	10	16	1
Seroprotective	8 (80%)	2 [†]	
IS/VF	0	2	1
Seroprotective	0	0	
IF/VS	8	2	2
Seroprotective	6 (75%)	0	
IF/VF	5	2	5
Seroprotective	4 (80%)	0	

*Subjects with no data of varicella history or serology tests available.

[†]Seroprotective from varicella vaccination.

[‡]P value < .05 when compared between HZ and non-HZ groups using χ^2 test.

HAART regimen, or viral load at baseline between the groups.

Three months after initiation of therapy, children who developed HZ had lower CD4⁺, CD8⁺, naive, and memory T-cell numbers as well as lower HIV RNA levels (*P* = .006, .01, .017, .017, .011, respectively). However, those with HZ showed a greater increase in CD4⁺ T-cell percentage and a greater reduction in HIV RNA levels at 3

TABLE III. Baseline demographic data and responses to HAART

	Zoster	No zoster	P value
Number of HAART	7	54	
Age at HAART initiation (y $\pm$ SD)	9.7 $\pm$ 5.17	6.5 $\pm$ 4.55	.088
Male:female ratio (n)	0:7	15:39	.178
CDC category (n)			
A:B:C	2:2:3	33:5:16	.173
1:2:3	1:0:6	15:16:23	.085
Medications			
Abacavir	0	14	.187
Nevirapine	2	11	.634
Efavirenz	3	10	.103
Amprenavir	0	1	1.0
Indinavir	0	8	.579
Nelfinavir	2	10	.615
Response to HAART			
IS/VS (n)	100% (7)	50% (27)	.014
IS/VF (n)	0% (0)	5.6% (3)	
IF/VS (n)	0% (0)	22.2% (12)	
IF/VF (n)	0% (0)	22.2% (12)	

months after initiation of HAART compared with children without HZ (*P* = .003, .017, respectively).

DISCUSSION

Herpes zoster was one of the most commonly encountered OIs in HIV-infected children before administration of HAART, with an incidence of 2.9 cases per 100 person-years,¹⁴ compared with 0.16 cases per 100 person-years among healthy children.¹⁵ Several epidemiologic studies have shown that the incidence of OIs decreases with HAART, even in patients showing incomplete immunologic or virologic responses.^{1,3,9} However, we found a much higher incidence of cutaneous HZ manifesting in perinatally HIV-infected children (22.9 cases per 100 person-years) in the first 6 months after HAART. Between

TABLE IV. Immunologic and virologic characteristic of HIV-infected children before and after HAART

Virologic and immunologic characteristics	Value at baseline		Value at 3 months after HAART		Value changes from baseline at 3 months after HAART	
	Zoster (n = 7)	No zoster (n = 54)	Zoster (n = 7)	No zoster (n = 54)	Zoster (n = 7)	No zoster (n = 54)
CD4 ⁺ cells (%)	9.4 ± 13.6*	23.6 ± 12.8	19.1 ± 9.5	26.1 ± 12.2	9.7 ± 6.7*	2.5 ± 5.7
CD4 ⁺ cell counts (cells/mm ³)	191 ± 316.9*	769 ± 682.7	275 ± 241.7*	907 ± 741.3	84 ± 110.9	139 ± 283.4
CD4 ⁺ 45RA ⁺ 62L ⁺ cells (%)	5.8 ± 12.9*	15.8 ± 10.5	10.5 ± 12.6	17.3 ± 10.6	5.4 ± 5.7	1.1 ± 5.1
CD4 ⁺ 45RA ⁺ 62L ⁺ cell counts (cells/mm ³)	131 ± 271.9*	492 ± 454.4	180 ± 236.7*	588 ± 532.4	57 ± 89.4	82 ± 259.5
CD4 ⁺ 45RO ⁺ cells (%)	4.8 ± 1.3	5.9 ± 3.0	9.0 ± 5.8	7.4 ± 5.8	5.0 ± 7.9	1.5 ± 2.6
CD4 ⁺ 45RO ⁺ cell counts (cells/mm ³)	92 ± 122.1	170 ± 146.7	112 ± 108.6*	228 ± 155.2	14 ± 73.8	55 ± 95.4
CD8 ⁺ cells (%)	43.4 ± 17.8	40.2 ± 11.9	39.7 ± 16.3	40.2 ± 12.9	−2.8 ± 12.2	0.5 ± 11.2
CD8 ⁺ cell counts (cells/mm ³)	590 ± 645.9*	1162 ± 1058.5	523 ± 376.7*	1278 ± 1001.2	−144 ± 362.3	128 ± 994.4
NK cells (%)	8.8 ± 9.7	11.0 ± 16.1	9.5 ± 10.6	4.5 ± 3.9	−3.0 ± 4.2	−7.6 ± 12.9
NK cell counts (cells/mm ³)	53 ± 41.3	121 ± 114.3	50 ± 4.2	116 ± 88.6	−37 ± 21.9	−23 ± 55.2
HIV RNA (log)	4.68 ± 0.3	4.35 ± 0.1	2.55 ± 0.6*	3.56 ± 0.9	−2.10 ± 0.8*	−.97 ± 1.1

*P value < .05 compared between HAART with and without zoster.

4 and 16 weeks after initiation of HAART, the HZ incidence in this study was 26.2 per 100 person-years, which is similar to the HZ incidence in HIV-infected adults treated with HAART (26.9 episodes per 100 person-years) reported by Martinez et al.¹⁰ In addition, HZ occurred exclusively in children with both immunologic and virologic responses to HAART, suggesting that these events are the consequence of IRD.

The pathogenesis of IRD is currently not well understood. However, children who developed HZ in this study have several distinct clinical and immunologic features. Previous studies have shown that having severe immunodeficiency at the time of treatment is a risk factor for the development of IRD.¹⁶ This statement is confirmed by our finding that children who developed HZ had significantly lower CD4⁺ and CD8⁺ T-cell numbers at the time of HAART initiation. Varicella-specific antibodies are known to protect against varicella infection but not HZ.¹⁷ We found that our HZ at-risk (previous varicella infection) children who had protective antibody titers against varicella were less likely to develop HZ. The protective antibody probably represents the immune status of these children at the time of initial varicella infection rather than offering true protection. Several studies suggested that cellular immune response is more important in controlling HZ.¹⁷ We also showed that children who developed HZ had lower CD4⁺ and CD8⁺ T-cell numbers 3 months after initiation of HAART compared with children who did not. This evidence suggests that host immune function plays an important role in IRD.

On the other hand, vigorous immunologic response to HAART may be an important contributory factor for IRD. Cell-mediated immune response, or cytokines such as IL-6 or IFN- α , were previously shown to play important roles in IRD events.^{18–20} This may be the reason that children who

developed HZ in this study also had a marked increase of CD4⁺ T cells during HZ episodes. Previous studies have shown that increased CD8⁺ T cells 1 month after initiation of HAART are a risk factor for developing HZ in HIV-infected adults.^{10,21} However, in our study, we did not find CD8⁺ T-cell changes at 3 months after HAART to be associated with HZ. Last, a marked reduction of HIV viral load in all the children who developed HZ was noted. This change in HIV viral load may interfere with the kinetics of other viruses, as suggested by the increase of hepatitis C viremia during HAART.²²

Herpes zoster in this study appears to be mild and consistent with varicella infection occurring in HIV-infected children.^{23,24} We did not encounter any children with acyclovir-resistant HZ as occasionally reported in HIV-infected patients.²⁵ We did not see a good response to oral acyclovir, as opposed to adults, who usually responded well. Because of limited data on efficacy of oral acyclovir in immunocompromised hosts and poor oral bioavailability in children in general,²⁶ acyclovir is recommended to be given intravenously as a first-line therapy for immunocompromised children.²⁷ All cases in this study responded promptly to intravenous treatment. It is not clear why no other OI or related complication of IRD was seen in our study. This could be a result of the continuation of OI prophylaxis in high-risk children despite initial immune reconstitution, or it could be the result of a generally lower incidence of other OI in children.¹⁴ Perhaps it may even be a result of a difference in the dynamics of immune reconstitution in children compared with adults. The majority of children in our cohort were white girls; thus, IRD seen in this report may not reflect the overall US population of perinatally infected children who are predominantly minority children of equal sexual distribution.²⁸ Even though sex and race may not

be an important variable for lymphocyte subsets,²⁹ the IRD finding in this study needs to be confirmed in larger multicenter studies.

We conclude that HZ is a manifestation of IRD in HIV-infected children. Further, children with negative varicella-specific antibody despite a previous history of varicella, severe immunodeficiency before treatment, and vigorous immunologic and virologic responses to antiretroviral therapy are at risk for developing HZ in conjunction with HAART.

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