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Immune Reconstitution Inflammatory Syndrome in Human Immunodeficiency Virus-Infected Children in Peru

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Abstract

Background—Immune reconstitution inflammatory syndrome (IRIS) after initiating highly active antiretroviral therapy (HAART) has not been widely studied in children, especially in resource-poor settings.

Methods—Retrospective cohort study of HIV-infected children initiating HAART between 2001 and 2006 at a tertiary pediatric hospital in Lima, Peru. Charts were reviewed for 1 year after HAART initiation. IRIS was defined as a HAART-associated adverse event caused by an infectious or inflammatory condition in patients with documented virologic or immunologic success.

Results—Ninety-one children (52% female) received HAART for at least 1 year. Median age at initiation was 5.7 years; 91% were ART naive and 73% had CDC stage C disease. The incidence of IRIS was 19.8 events per 100 person years (95% CI: 11.5–28.0). Median time to IRIS was 6.6 weeks after HAART initiation (range: 2–32 weeks). There were 18 IRIS events, 11 unmasking and 7 paradoxical. These included associations with *Mycobacterium tuberculosis* in 4 cases, Bacillus Calmette Guerin lymphadenitis in 1 case, varicella zoster virus in 6 cases and herpes simplex labialis in 6 cases. Children who developed IRIS had a higher baseline HIV viral load ($P = 0.02$) and an indicator of malnutrition ($P = 0.007$) before HAART initiation.

Conclusion—IRIS occurred in 20% of HIV-infected children starting HAART in Peru and was associated with more advanced disease and malnutrition. Future research is needed to examine specific risk factors associated with pediatric IRIS to allow prompt identification and treatment of IRIS.

Keywords

immune reconstitution inflammatory syndrome; HIV; AIDS; HAART; children

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Since the introduction of highly active antiretroviral therapy (HAART), morbidity and mortality due to HIV infection have decreased considerably.[1] Some patients develop an inflammatory response shortly after starting HAART, despite an increase in CD4 lymphocyte count and decreasing viral load.[2-4] This clinical phenomenon has been called immune reconstitution syndrome, immune reconstitution disease, and immune reconstitution inflammatory syndrome (IRIS). IRIS can produce 2 distinct clinical syndromes: unmasking and paradoxical.[5-8] Unmasking IRIS is an occult infection unmasked by immune system recovery after HAART initiation in patients who had no previous signs or symptoms of the infection. Paradoxical IRIS is the symptomatic recurrence of a successfully treated infection driven by antigen-specific immune activation in the setting of few or no viable organisms; cultures are usually negative due to previous effective treatment.

IRIS has been most often described in adults. Retrospective studies report 17% to 32% of adults initiating HAART develop IRIS.[3,6,9,10] The wide variation in prevalence can be partially explained by different IRIS definitions used, pathogens included, degree of immunosuppression and prevalence of opportunistic infections (OIs) in the cohorts studied. The first prospective study of IRIS in South African adults with AIDS reported a 10% incidence of IRIS during the first 6 months of HAART, with most IRIS events associated with a low morbidity.[11] A variety of pathogens have been associated with IRIS, including varicella zoster virus, *Mycobacterium* spp., *Cryptococcus neoformans, Molluscum contagiosum*, cytomegalovirus, and others.[4]

Few studies have examined incidence and etiologies of IRIS in children, and we are not aware of any reports of pediatric IRIS in Latin America. One retrospective study from the United States described varicella zoster associated with IRIS in 11% of children starting HAART.[12] The only prospective study of incident pediatric IRIS reported an incidence of 19% among Thai children, with the majority associated with Mycobacterial spp.[13] Other case reports have identified *Mycobacterium avium* complex, *C. neoformans*,[13] and sarcoidosis associated with IRIS.[14,15] The objectives of this study were to retrospectively examine the incidence, pathogens and clinical spectrum of IRIS in a cohort of children starting HAART in Peru.

MATERIALS AND METHODS

Patient Population

A retrospective study of HIV-infected children at the Instituto Nacional de Salud del Niño, the main tertiary pediatric referral center in Lima, Peru. Inclusion criteria included starting HAART between July 2001 and December 2006, continuing HAART for at least 1 year, and baseline measures of CD4 counts and HIV viral load before initiating HAART. This study was approved by the Research Ethics Committee at Instituto Nacional de Salud del Niño.

Clinical Histories

Medical charts were abstracted for data regarding demographics, clinical, and virologic data and diagnostic test results. HIV infection was diagnosed by enzyme-linked immunoassay (ELISA, Diagnostic Bio-Probes, Milan, Italy) with confirmation by indirect fluorescent antibody (Instituto Nacional del Salud del Niño, Lima). HIV stage was determined using the Centers for Disease Control Classification for HIV in children.[16] Prior to starting HAART, patients received a physical examination, tuberculin skin test, chest x-ray, CD4 count, HIV viral load, and were screened for opportunistic infections. Treatment was initiated for any infection detected during screening.

After starting HAART, children underwent monthly clinical visits. Medical charts were reviewed for 1 year after HAART initiation. CD4 profiles were measured every 3 months,

and viral load every 6 months. CD4 percentages were calculated using absolute CD4 count divided by absolute lymphocyte count closest to the time CD4 count was measured. CD4 count was assessed using flow cytometry (BD FACSCount, BD Biosciences). Viral load was assessed using the Roche Amplicor assay (Roche Diagnostic, Indianapolis, IN) with a lower detection limit of 400 copies/mL.

IRIS Definition

We first identified HAART-associated adverse events that had previously been associated with IRIS in children with immunologic or virologic success.[4] Immunologic success was defined as an increase in baseline CD4 count greater than 5% or a total CD4 cell count greater than 250 cells/mL closest to the time of the IRIS event.[12,13] Virologic success was defined as a decrease in plasma HIV RNA titer >1 $\log_{10}$ or achieving a titer of <400 copies/mL closest to the time of the IRIS event.[12,13] Suspected IRIS cases were verified against the pediatric IRIS case definition and suspected TB-IRIS cases were verified against the pediatric TB-IRIS definition established by the International Network of the Study of HIV-associated IRIS.[5,17] We subsequently defined adverse infectious or inflammatory events as either: (1) paradoxical IRIS if the child had a prior documented history of the OI or as (2) unmasking IRIS if the event was a new onset OI associated with HAART.

Diagnoses of varicella zoster virus and mucocutaneous herpes (HSV) infection were based on clinical signs and symptoms. Tuberculosis was diagnosed by a combination of clinical, radiologic, and microbiologic confirmation using culture or polymerase chain reaction DNA amplification methods. Bacillus Calmette-Guerin (BCG) adenitis was diagnosed from clinical signs and symptoms because the hospital did not have laboratory capability to identify *Mycobacterium bovis*.

Malnutrition was measured using WHO Growth Reference Data.[18] Weight-for-age and height-for-age *z* scores were calculated for each child, and weight-for-height *z* scores were calculated for children ages ≤5 years using WHO Anthro (version 2.02, Geneva, Switzerland). Children with *z* scores less than 2 standard deviations below the mean in any of the 3 categories were classified as having malnutrition. No information on specific nutritional supplementation for malnutrition was collected during this study. Supplemental feeding and micronutrient supplementation for hospitalized children were determined by the patient's physician on a case-by-case basis. Children in the outpatient setting who were 2 years of age or older and receiving HAART, regardless of nutritional state, were given a bag of groceries each month and mothers of infants 6 months of age or younger received formula.

Statistical Analysis

The primary statistical comparison was IRIS cases versus cohort controls. For continuous variables, such as HIV viral load and CD4, independent *t* tests were used. Categorical variables were analyzed using Pearson χ^2 test. Two-sided tests were used with $P < 0.05$ considered statistically significant (SPSS 15.0, Chicago, IL).

RESULTS

Patient Population

Between July 2001 and December 2006, 104 children were started on HAART; 91 (87.5%) met inclusion criteria. Thirteen patients were excluded because of missing baseline CD4 counts or viral load (n = 6), insufficient time receiving HAART (n = 5), or unavailable medical records (n = 2). HAART regimens included zidovudine, lamivudine, and nelfinavir (n = 64); zidovudine, lamivudine, stavudine (n = 26); and stavudine, didanosine, and

nelfinavir (n = 1). Children were predominantly in CDC Category C at HAART initiation (73%) and 91% were ART naive. Fifty-three percent were male and average age at HAART initiation was 6 years (range, 4 months–16 years). Acquisition of HIV was mainly through vertical transmission (90%), but also from transfusion (5%), sexual transmission (1%), and unknown (3%). Baseline demographic data and laboratory data are detailed in Table 1.

IRIS Characteristics

Of the 91 children, 18 (20%, 95% confidence interval: 11.5–28.0) developed an HAART-associated adverse event consistent with IRIS. The median time of IRIS onset was 6.6 weeks (range, 2–34 weeks) after initiating HAART. Of the 18 IRIS events, 12 were unmasking IRIS and 6 paradoxical IRIS. There were 6 cases of varicella zoster, 6 cases of HSV labialis, 5 cases of *M. tuberculosis* and 1 case of BCG adenitis. No IRIS event necessitated HAART interruption. IRIS resolved in all 18 patients. No children died shortly after HAART initiation and there was no IRIS related mortality within 1 year of initiating HAART. Details of patients who developed IRIS are shown in the Table (Supplemental Digital Content 1, http://links.lww.com/INF/A174).

Of the 5 IRIS cases associated with *M. tuberculosis* (TB) infection, there were 2 cases of pulmonary TB, 2 with combined pulmonary and extrapulmonary TB, and 1 with ganglionic TB. Four were confirmed by culture or PCR. The case without culture confirmation was a pulmonary and peritoneal infection diagnosed by chest radiography and abdominal ultrasonography. Of the 5 TB-IRIS events, 1 was paradoxical having been diagnosed with *M. tuberculosis* 3 years previously, while the other 3 were newly diagnosed (unmasking TB-IRIS). Four patients required hospitalization. All patients were treated with anti-TB therapy and had resolution of infection. There was 1 case of BCG adenitis diagnosed clinically in a child who presented with a subcutaneous abscess that resolved without antimicrobial treatment.

There were 6 cases of varicella zoster infection; all with a characteristic dermatomal presentation. Four had a prior episode of varicella zoster infection before starting HAART. All were treated with acyclovir and responded to treatment. Three children required hospitalization. There were 6 cases of herpes simplex labialis. One patient had HSV labialis before starting HAART. Three patients were treated with acyclovir, 3 received no treatment, and symptoms resolved in all patients.

When considering paradoxical versus unmasking IRIS, the 6 cases of paradoxical IRIS were caused by varicella zoster virus (4 cases), *Mycobacterium* spp. (1 case), and herpes simplex labialis (1 case). Unmasking IRIS was caused by *Mycobacterium* spp. (5 cases), herpes simplex labialis (5 cases), and varicella zoster virus (2 cases).

The pre-HAART mean viral load was significantly greater in IRIS cases than in non-IRIS patients ($P = 0.02$). There was no significant difference in CD4 or CD8 count, age, gender, mode of HIV acquisition ($P = 0.9$), or HAART regimen ($P = 0.53$). Although more children with CDC Category C disease had IRIS than children with Category A or B disease, the difference was not significant (24% vs. 8%, OR = 3.68, $P = 0.14$).

Children with IRIS were more likely to have 1 indicator of malnutrition compared with children without IRIS (Table 2, $P = 0.007$). When children ages 0 to 5 and 6 to 17 were analyzed separately, the difference also persisted in the age 6 to 17 group ($P = 0.049$). Logistic regression analysis adjusting for age and sex revealed that malnutrition and baseline viral load were significantly associated with IRIS (beta coefficient and *P* values: 4.73 and 0.015, 1.00 and 0.014, respectively). Baseline CD4 count did not confound this association and was not retained in the final model.

DISCUSSION

IRIS most commonly presents with an infectious etiology, and has been well described after starting HAART.[4] This is the first study to examine pediatric IRIS in Latin America. The 20% incidence found in this study is similar to the 19% prospective IRIS incidence reported among children in Thailand. The range of infectious causes encountered in this study is similar to those reported previously.[12,13,19]

The majority of IRIS cases (67%) were associated with unmasking of infection and only 33% were associated with recurrence of previously treated infection (paradoxical IRIS). Studies of adults in the developing world have noted 50% to 80% of cases resulted from paradoxical IRIS.[3,11] Increased screening at HAART initiation can decrease the number of unmasking infections, as demonstrated by 1 Ugandan study that showed a 50% decrease in unmasking TB infections in children after initiating tuberculin skin test screening before starting the therapy.[20]

The rate of TB-IRIS cases we found was within the wide range reported in the literature for children and adults. Prospective studies have found 10% of IRIS cases associated with TB in children and 41% of IRIS cases associated with TB in adults.[11,13] Herpes viruses have also been commonly implicated in IRIS in children and adults, with varicella zoster virus being one of the most commonly reported causes of IRIS in children.[12,13] The first report of IRIS in children found an incidence of 22.9 cases of varicella zoster virus per 100 person-years in the first 6 months after HAART,[12] and the Thai study found 22% of IRIS cases in children caused by varicella zoster virus.[13] Regarding HSV infections, while they can potentially cause more serious disease such as HSV encephalitis, the cases observed in our study were mild and resolved with treatment. Less severe infection may have been due to easy recognition of HSV labialis and early initiation of treatment. The Thai study showed that 19% of pediatric IRIS cases were related to HSV, including 1 case of HSV encephalitis,[13] and the only prospective study in adults reported 9.1% of IRIS cases associated with HSV infection.[11]

Our study detected an association between IRIS and malnutrition. In children, malnutrition can cause further immunosuppression,[21] and refeeding alone can produce paradoxical IRIS-like reactions.[22] Although we did not collect information regarding nutritional supplementation for each child in this study, all children received monthly groceries and were perhaps at lower risk for this complication. HIV infection can also cause malnutrition through gastrointestinal illness, cachexia, and anemia.[21] Thus, it is plausible that HIV-infected children with underlying malnutrition may develop an exaggerated immune response upon starting HAART. As our study only examined height and weight as indicators of malnutrition, future studies should include more detailed examination of nutrition measures to further examine the relationship between malnutrition and IRIS, as well as the association of refeeding, focusing on children with moderate to extreme malnutrition.

The immunologic mechanism of IRIS is not well defined, but experts suggest it is an antigen-driven process occurring when the immune system becomes dysregulated during the early period of effective antiretroviral therapy. French[23] proposed that immune reconstitution is due to an imbalanced cellular immune response against pathogen-specific antigens, and depending on the pathogen, produces a T_H1, Th17, or $CD8^+$ response. Bonham et al[24] postulated that IRIS occurs during antigen clearance when antigen-specific immunity and homeostatic T-regulatory function is recovering, and that specific cytokines may serve as biomarkers for different forms of IRIS. Given the high prevalence of tuberculosis in Peru, we are not surprised that tuberculosis was a common manifestation of

IRIS. Additional research is needed to further elucidate the immunopathogenesis of IRIS in the developed and developing world—where endemic infections are often different.

The most significant limitation of our study is the lack of an objective definition of IRIS with objective biomarkers for diagnosis. Furthermore, because of the retrospective nature of this study, CD4 lymphocyte counts and HIV viral loads were not consistently available before and after HAART initiation and at the time of the IRIS event. The hospital did not measure CD4 and CD8 lymphocyte percentages so they were calculated from total lymphocyte counts from the nearest date, which provided an approximation of the true CD4 and CD8 lymphocyte percentage. Finally, the number of patients in the study was too small to make firm conclusions about specific risk factors, however, the incidence and clinical spectrum were similar to other publications.

In conclusion, IRIS was a common occurrence in Peruvian HIV-infected children during the first year after initiation of HAART therapy. Clinicians should be aware of both the unmasking of subclinical infections as well as the paradoxical recrudescence of successfully treated infections in children shortly after initiating HAART. Future research should examine specific risk factors associated with IRIS in children so that children who are at highest risk of IRIS can be identified and treated promptly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Baseline Demographic and Laboratory Data of Children Who Initiated HAART

	IRIS		Cohort Controls		*P*
No. children	18		73		
Age at HAART initiation					
Average age	5.6		6.1		0.63
0–2	6	25%	17	75%	0.57
3–5	4	17%	20	83%	
6–7	2	11%	16	89%	
8 and above	6	24%	19	76%	
Sex					
Male	9	19%	38	81%	0.92
Female	9	20%	34	80%	
CDC clinical stage					
A and B	2	8%	23	92%	0.08
C	16	24%	50	76%	
Previous treatment					
ART naïve	18	100%	63	88%	0.29
ART non-naïve	0	0%	7	10%	
Records unavailable	0	0%	2	3%	
Immunologic and virologic parameters					
CD4 count	288	SD ± 95	239	SD ± 247	0.50
CD4%	8.9	SD ± 5.6	5.3	SD ± 9.5	0.15
CD8 count	1256	SD ± 670	1145	SD ± 770	0.58
CD8%	39	SD ± 21	40	SD ± 24	0.83
CD4:CD8	0.27	SD ± 0.20	0.15	SD ± 0.24	0.08
Viral load (log_{10})	5.17	SD ± 0.64	5.52	SD ± 0.56	0.02

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TABLE 2

Percentage of Children With an Indicator of Malnutrition

	IRIS N = 18	Cohort Controls N = 72	*P*
Stunting *	64%	29%	0.09
Underweight †	40%	29%	0.7
Wasting ‡	40%	18%	0.5
Any indicator of malnutrition §	78%	42%	0.007

* Stunting—Height-for-age *z* score >2 SD below the mean.

† Underweight—Weight-for-age *z* score >2 SD below the mean.

‡ Wasted—Weight-for-height *z* score >2 SD below the mean, only calculated for ages 0–5.

§ Indicators of malnutrition measure included stunting, being underweight, or wasting (defined above).